

Michelle Heck

THE SIGN-TRACKER/GOAL-TRACKER PARADIGM AS A BEHAVIORAL MODEL FOR EXPLORING ADDICTION VULNERABILITY

A Translational Perspective

FACULTY OF PSYCHOLOGY, SPEECH THERAPY, AND EDUCATIONAL SCIENCES



THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PSYCHOLOGICAL
SCIENCES

UNDER THE SUPERVISION OF
Etienne Quertemont & Patrick Anselme

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BY

Michelle Heck

UNDER THE SUPERVISION OF

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EXAMINATION PANEL

Dr. Patrick Anselme - Ruhr-University Bochum

Prof. Salvatore Campanella - Université Libre de Bruxelles

Prof. Christel Devue (President) - Université de Liège

Prof. Etienne Quertemont - Université de Liège

Dr. Jessica Simon (Secretary) - Université de Liège

Prof. Reinout Wiers - University of Amsterdam

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*Michelle Heck
Liège, Mai 2026*

**“Always Remember: Your Focus Determines
Your Reality”**

— Qui-Gon Jinn, *Star Wars Episode I: The Phantom Menace*

George Lucas, 1999

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Foreword

Abstract

Through Pavlovian learning, cues associated with rewards can acquire incentive salience, becoming motivationally significant stimuli that may rival or even exceed the value of the rewards they predict. Evidence from animal research indicates that individuals differ in the extent to which they attribute incentive salience to such cues, reflecting variability in cue-reactivity and inter-individual differences in vulnerability to addictive behaviors.

When such cues acquire strong incentive salience, they can trigger approach behaviors that override self-control. Within behavioral paradigms, two distinct phenotypes can be reliably identified during the presentation of a reward-predictive cue: sign-trackers, who preferentially approach and interact with the cue, and goal-trackers, who instead approach and inspect the location where the reward will be delivered. These behavioral patterns do not seem to reflect learning differences; they are thought to index stable neurobehavioral traits governing how individuals prioritize and respond to environmental cues. Importantly, parallels have been proposed between sign-tracking in animals and cue-reactivity processes observed in humans, including phenomena such as attentional bias and value-modulated attentional capture.

Despite these conceptual parallels, there is currently no widely validated method for measuring sign- and goal-tracking in humans. To address this gap, a novel behavioral paradigm was implemented within the framework of this thesis. The paradigm was designed to closely approximate the procedures used in animal research while remaining cost-effective and suitable for human experimental settings.

The present thesis aims to investigate the applicability of the sign-tracker/goal-tracker framework in humans, with the objective of advancing our understanding of individual vulnerability to addiction based on cue-reactivity profiles, and assessing whether this model can be meaningfully translated from animal research to human populations.

Résumé

Par apprentissage pavlovien, les stimuli associés à des récompenses peuvent acquérir une saillance incitatrice, devenant des stimuli motivationnellement significatifs susceptibles d'égaliser, voire de dépasser, la valeur des récompenses qu'ils prédisent. Des données issues de la recherche animale indiquent que les individus diffèrent quant au degré de saillance incitatrice qu'ils attribuent à ces stimuli. Cette variabilité reflète des différences interindividuelles dans la réactivité aux stimuli environnementaux et est associée à une vulnérabilité aux comportements addictifs.

Lorsque ces stimuli acquièrent une forte saillance incitatrice, ils sont susceptibles de déclencher des comportements d'approche, pouvant court-circuiter les mécanismes d'auto-contrôle. Dans les études animales, deux phénotypes distincts peuvent être identifiés lors de la présentation d'un stimulus prédictif de récompense : les *sign-trackers*, qui approchent et interagissent avec le stimulus conditionné, et les *goal-trackers*, qui se dirigent plutôt vers le lieu où la récompense sera délivrée et l'inspectent. Ces différences comportementales ne semblent pas refléter des variations dans les capacités d'apprentissage; elles sont plutôt considérées comme l'expression de traits neurocomportementaux relativement stables, gouvernant la manière dont les individus hiérarchisent les informations motivationnelles et réagissent aux stimuli. Récemment, des parallèles ont été proposés entre le *sign-tracking* observé chez l'animal et les processus de réactivité aux stimuli décrits chez l'humain, incluant notamment des phénomènes tels que les biais attentionnels et la capture attentionnelle modulée par la valeur.

Malgré ces parallèles, il n'existe à ce jour aucune méthode largement validée permettant d'évaluer de façon directe les comportements de *sign-tracking* et de *goal-tracking* chez l'humain. Afin de combler cette lacune, un nouveau paradigme a été développé dans le cadre de cette thèse. Ce paradigme a été conçu afin de transposer les procédures employées en recherche animale, tout en restant compatible avec les contraintes méthodologiques des études expérimentales humaines.

La présente thèse vise à examiner l'applicabilité du cadre sign-tracker/goal-tracker chez l'humain, dans le but d'approfondir la compréhension des vulnérabilités individuelles à l'addiction à partir des profils de réactivité aux indices, et d'évaluer dans quelle mesure ce modèle peut être transposé de façon pertinente de la recherche animale aux populations humaines.

Thesis Outline

The **first section** of this thesis will present the theoretical background underlying the research. **Chapter 1** delves into fundamental motivational processes, including Pavlovian conditioning and incentive salience. Understanding how rewards and reward-predictive cues normally guide behavior provides important insights into both the adaptive functioning of motivated behavior and its dysregulation in conditions such as addiction. The chapter then briefly reviews major theoretical models of addiction, before focusing more specifically on the incentive sensitization theory of addiction. In this context, key concepts including vulnerability factors, cue reactivity, and attentional biases are discussed.

Given the central role of animal models in developing these concepts, **Chapter 2** examines their importance as well as the challenges associated with translational research. Rather than treating animal and human research as competing approaches, this thesis adopts a translational perspective, identifying points of convergence between species while also highlighting the methodological and conceptual limitations that must be considered.

Chapter 3 focuses on the model of individual differences in sensitivity to conditioned reward cues that lies at the core of this thesis: the sign-tracker/goal-tracker framework. The chapter first defines sign- and goal-tracking as distinct conditioned responses and outlines their theoretical foundations within Pavlovian learning, drawing on the animal research that originally established the model. It then examines evidence for sign-trackers as a vulnerable group, by reviewing key cognitive, behavioral, and psychiatric characteristics associated with the sign- and goal-tracking phenotypes. This is followed by a quick examination of the role of reward uncertainty on sign-tracking as well as the emerging literature on human equivalents of sign-tracking. Finally, **Chapter 4** concludes the theoretical section with a scoping review conducted as part of this thesis, synthesizing the existing evidence on human sign- and goal-tracking.

The **second part** of this thesis presents the experimental research, comprising three empirical studies.

Chapter 5 describes the *first study*, which forms the foundation of the project. This study aimed to develop and validate a novel Pavlovian conditioning task designed to

assess sign-tracking behavior in humans. In addition, the study examined the relationship between human sign-tracker profiles and levels of alcohol consumption. **Chapter 6** presents the *second study*, which aimed to examine the relationship between sign-tracking and attentional bias, while also replicating key findings from the first study to further strengthen the translational validity of the model. **Chapter 7** reports the *third study*, which investigated how acute alcohol intoxication and cue-reward uncertainty shape attentional sign- vs goal-tracking behaviors in humans.

The **third section** of the thesis fulfills a synthesizing and concluding role by integrating main findings of the preceding section, and comprises two main chapters.

Serving as a conceptual bridge between the experimental studies and the general discussion, **Chapter 8** presents a narrative review conducted as part of this thesis. This chapter integrates evidence from both animal and human research to examine the impact of reward uncertainty on cue-triggered motivational and attentional processes. **Chapter 9** contains the general discussion and conclusions. This chapter opens with an integrative discussion of the findings from the three experimental studies, offering a broader synthesis and interpretation beyond that provided in the individual paper discussions. It then concludes by highlighting the original contributions of this research to the study of human sign-tracking, while critically addressing its limitations and identifying directions for future research.

The thesis closes with the **last section**, comprising the lists of abbreviations, figures and tables, as well as the appendices and reference list.

Publications Originating From This Thesis

The scientific content of this manuscript is largely based on original research outputs disseminated through peer-reviewed publications (Chapters 4, 5, 7, and 8, with Chapter 6 currently being submitted). The related publications, arranged below according to the order in which their respective findings are integrated into this thesis, are:

- Heck, M., Durieux, N., Anselme, P., & Quertemont, E. (2025). Implementations of sign- and goal-tracking behavior in humans: A scoping review. *Cognitive, Affective, & Behavioral Neuroscience*, 25(2), 263-290. <https://doi.org/10.3758/s13415-024-01230-8>

- Heck, M., Simon, J., Lesenfants, D., Didone, V., Anselme, P., & Quertemont, E. (2025). Sign tracking and alcohol consumption: A translational computerized task assessing individual differences in humans. *Motivation Science*. <https://doi.org/10.1037/mot0000408>
- Heck, M., Lesenfants, D., Didone, V., Anselme, P., & Quertemont, E. (submitted). *Human Sign-Tracking and its Relationship with Attentional Biases for Alcohol*
- Heck, M., Lesenfants, D., Didone, V., Anselme, P., & Quertemont, E. (2026). The effects of reward uncertainty and alcohol intoxication on human sign- and goal-tracking. *Psychopharmacology*. <https://doi.org/10.1007/s00213-026-07039-2>
- Heck, M., Quertemont, E., & Anselme, P. (2026). Motivation, Attention, and Uncertainty: Insights from Animal and Human Research and Implications for Addiction. *Frontiers in Psychology - Addictive Behaviors*, 17. <https://doi.org/10.3389/fpsyg.2026.1796424>

Additional Publications

Throughout my PhD journey, I also participated in several research projects outside the immediate scope of this thesis. These collaborations resulted in the following publications:

- Simon, J., Grogna, D., Rivard, M.-C., Heck, M., Bouchard, S., & Quertemont, E. (2022). Assessing attentional bias for alcohol-related cues using eye tracking in a virtual reality environment. *Frontiers in Virtual Reality*, 3. <https://www.frontiersin.org/articles/10.3389/frvir.2022.849840>
- Heck, M., Quertemont, E., & Simon, J. (2024). Impact of a pre-test measurement of alcohol craving in cue-exposure studies: Relationship with social desirability and demand effects. *Alcohol*, 115, 41-52. <https://doi.org/10.1016/j.alcohol.2023.08.013>
- Heck, M., Quertemont, E., & Simon, J. (under review). Engagement in cue-exposure: Validation of a French version of the User Engagement Scale with an alcohol-cue video. *Psychologica Belgica*.

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AI Declaration

For the sake of transparency, I disclose the limited use of artificial intelligence (AI) tools in the preparation of this dissertation. ChatGPT (GPT-5, OpenAI) and Microsoft Copilot were consulted at specific stages solely for the purpose of language refinement, under the full supervision and responsibility of the author.

In addition, Canva AI, Microsoft Copilot, and Google Gemini were used to generate certain illustrative materials included on pages 1, 47, 80, 161 (lower panel), and 264 (panel A).

No AI tools were used in the generation, analysis, or interpretation of data, nor in the development of research hypotheses, theoretical arguments, or conclusions. All intellectual and analytical content presented in this dissertation is entirely the original work of the author.

Part I

Theoretical Overview

Chapter 1

Of Rewards, Cues, and Motivation

From Basic Pavlovian Processes to Addiction



“This is what the brain is made for: detecting, seeking, and learning about rewards in the environment by moving around, identifying stimuli, valuing them, and acquiring them through decisions and actions. The brain was not made for enjoying a great meal; it was made for getting the best food for survival, and one of the ways to do that is to make sure that people are attentive and appreciate what they are eating.”

— Wolfram Schultz, *Neuronal Reward and Decision Signals:
From Theories to Data*

Introduction

We all have experiences with things we find “rewarding”; things that, at times, exert a powerful and almost irresistible pull on our behavior. Tasty food, digital distractions, games, or drinking alcohol are everyday examples. Consider the following scenarios: while walking through a market, you catch the unmistakable warm, sweet smell of fresh Liège waffles drifting through the air. Even if you had firmly decided to cut down on high-calorie foods, you may find yourself buying one “on an impulse”. Perhaps you occasionally feel compelled to check your phone the moment you hear the characteristic *ping* of a notification (or even in its absence) although you are meant to stay focused (maybe on writing a thesis...). Or maybe, despite having quit smoking some time ago, you find yourself lighting a cigarette after a meal, fully aware that resisting it would be better for your health.

Most people recognize at least one of these situations. Each illustrates a moment in which we act against our own long-term goals, giving in to the immediate appeal of a rewarding object or behavior. Whether it involves impulsively buying a waffle or staying out later than planned after “just one last drink,” such lapses highlight the phenomenon commonly described as *weakness of will*. More formally, this is referred to as *akrasia*, a state in which individuals act contrary to their better judgment and struggle to fully explain their own actions (Heather, 2017; Wiers et al., 2021).

While these everyday examples are often benign, they have clear parallels with more severe and persistent difficulties, in which resisting certain rewards becomes a long-term struggle despite significant health, interpersonal, or professional consequences. This, of course, lies at the core of addictive disorders. Rather than

interpreting these behaviors simply as failures of self-control, decades of research have shown that they arise from deeper learning and motivational processes.

So, what truly pushes us toward that unplanned sweet food, cigarette, or drink? Hunger, pleasure, and habit may each play a role, but research suggests that these behaviors are more comprehensively understood through a motivational¹ lens. Importantly, motivational processes are not always deliberate or conscious, like goal-directed desires can be. Rather, they are often shaped by the way certain cues in our environment catch our attention and provoke approach tendencies.

This idea is captured by the concept of incentive salience. Through learning, cues that predict rewards can take on a special motivational value. They become attention-grabbing and tempting, and they can initiate approach behavior almost automatically (Berridge, 2001, 2007). Thus, even when we are not hungry or do not intend to drink or smoke, the sight, smell, or context linked to these rewards can trigger powerful motivational states and lead to seemingly automatic approach behavior. Importantly, individuals differ in how strongly they attribute incentive salience to cues; differences that may partly explain why some people develop addictions following initial exposure, while others do not.

As illustrated by the waffle example, reward-driven behavior emerges not only from motivation, but also from the interaction of related psychological processes, including learning and attention. The individual must have learned the association between specific cues (e.g., smell, appearance) and the rewarding outcome, and their attention must be drawn to these cues (sometimes automatically). Human and animal behavior is multifaceted, shaped by the convergence of multiple processes, many of which cannot be elaborated further here. While this thesis focuses primarily on motivation, it also addresses its connections with learning and attention at some points.

Scope of the Chapter

This chapter begins by outlining the foundational concepts needed to understand maladaptive motivational processes such as addiction. It introduces basic ideas related to

¹ Here, *motivation* is understood specifically in its **incentive** form, referring to the way certain cues gain the power to attract and orient behavior. According to Berridge (2007), this occurs when the brain transforms a stimulus from something merely *perceived* into a potent *incentive*, capable of compelling action toward rewards.

motivation, reward, cues, and Pavlovian learning, with particular emphasis on the notion of *incentive salience* as defined by Berridge and Robinson (1998, Berridge, 2007). The following section explores how stimuli associated with rewards come to influence cognitive/attentional processes, a phenomenon known as reward-based “selection history”.

Finally, to prepare the ground for the more specialized sections that follow, the chapter concludes with a brief overview of addiction and alcohol use disorder. This includes a short presentation of major theoretical models, the role of cues in conditioning-based frameworks such as the Incentive-Sensitization Theory, and individual vulnerability factors that may contribute to the development of addictive behavior.

Motivated Behaviors: Theoretical Aspects

To address questions such as “*What drives individuals toward certain objects or actions, even when they did not consciously intend to pursue them?*”, it is necessary to begin with two foundational constructs: motivation and reward learning. These concepts allow us to explore what initiates behavior and how rewards shape behavioral tendencies over time.

Questions of this kind have occupied scientists and philosophers for decades. As a result, numerous theoretical frameworks have emerged and have been refined across fields such as psychology, neuroscience, and behavioral economics. The aim of this section is *not* to provide an exhaustive historical review, but rather to introduce and clarify several core notions that will reappear throughout this manuscript: reward, motivation, and incentive salience. In doing so, it is also important to acknowledge the central role of associative learning theories (Pavlovian and instrumental) in shaping contemporary understandings of motivated behavior, particularly within the study of addiction.

Associative learning encompasses two major forms: Pavlovian (classical) conditioning and instrumental (operant) conditioning. In Pavlovian conditioning, an initially neutral stimulus becomes a conditioned stimulus (CS) after being repeatedly paired with an unconditioned stimulus (US) that elicits an unconditioned (unlearned) response. Through this process, the CS acquires the capacity to evoke a conditioned response. Pavlov’s well-known experiment with dogs (1927), in which the dogs eventually salivated upon hearing a bell that had been consistently associated with food delivery,

remains the typical illustration of this learning mechanism. Pavlovian learning has a critical evolutionary function, enabling individuals to anticipate events and adapt their behavior accordingly to promote survival (Domjan, 2005; Fanselow & Wassum, 2016; Krause & Domjan, 2017). Instrumental or operant conditioning, in contrast, involves learning an association between a specific response and its consequences. For example, an animal may learn to press a lever in order to obtain food. Through repeated pairings, the response becomes more likely because it is reinforced by the rewarding outcome. This process reflects Thorndike's "law of effect" (Thorndike, 1911), which states that behaviors followed by satisfying consequences tend to increase in frequency, whereas those followed by aversive outcomes tend to diminish. In summary, Pavlovian learning is characterized by stimulus-stimulus (S-S) associations, while instrumental learning is characterized by action-outcome associations. This thesis focuses exclusively on Pavlovian, non-instrumental associations, as these are particularly relevant to the motivational (some might say automatic) processes implicated in addictive behaviors.

Although the concept of motivation seems crucial for the learning mechanisms described above, it is important to distinguish motivation from learning. Learning refers to the processes through which past experience shapes behavior (whether through associative mechanisms or reinforcement contingencies for instance) by establishing predictive relationships between events (a certain CS predicts the occurrence of a US). Motivation, by contrast, concerns the forces that initiate, sustain, and direct behavior. Whereas associative learning relies primarily on the *predictive* properties of the CS, motivational processes reflect the *incentive* properties of the US, which can be transferred to the CS through learning. This distinction implies that one can acquire accurate knowledge about the relationship between stimuli without necessarily being driven to act on that knowledge: without motivation, behavior lacks the energizing and directional components required for engagement. As Berridge (2012) succinctly states, "[...] *knowledge by itself, no matter what kind, is never motivation. Something else is required to translate remembered knowledge into motivation that can actually generate and control behavior*" (p.1).

Brief History of Reward Learning and Motivation

Before the term “*motivation*” became widespread in psychology and neuroscience (for an extensive review of the concept see Simpson & Balsam, 2016), earlier scientific traditions proposed other concepts to explain why organisms engage in specific behaviors. Across the twentieth century, several major theoretical frameworks were developed, each highlighting different mechanisms underlying motivated action.

Early behaviorist theories proposed that behavior is primarily shaped by reward learning, in particular through positive and negative reinforcement, as articulated in Thorndike’s law of effect (1911) and later formalized by Skinner (Skinner, 1933/1966). According to this view, behaviors that produce desirable outcomes become more likely to occur again, whereas behaviors followed by negative or aversive outcomes decrease in probability. In this reinforcement-based framework, stimulus-response (S-R) associations are strengthened whenever a response is followed by a rewarding outcome, thereby increasing the likelihood that the same response will be repeated in the presence of the same stimulus².

Another early framework focusing rather on physiological and homeostatic aspects was *drive theory*, which considered that human behavior is driven by an internal “force” that “pushes” individuals towards the stimuli that will reduce their needs, thereby optimizing the organism’s potential for survival (Hull, 1943). The theory posited that human behavior is driven by a need to reduce discomfort, caused by an internal state of imbalance. This need will drive the behavior towards the obtainment of adequate rewards, that will restore balance to the system. For instance, hunger will drive individuals to pursue food (reinforcer), which when consumed, leads to reduced hunger, thus reducing the drive (homeostasis). The reinforcing value of a stimulus, according to this model, lies entirely in its capacity to reduce such drives. While intuitively appealing, drive theory soon faced empirical challenges. For instance, N. E. Miller and Kessen (1952) found that delivering food directly into the stomach did not fully reduce feeding behavior in rats, and that oral consumption was a stronger reinforcer than gastric administration. A range

² S-R associations should be understood here as a strictly learning-based mechanism: the occurrence of a reinforcing US strengthens the S-R link that immediately preceded it. Any stimulus present at the time the behavior occurred can, through repetition, come to elicit that same response automatically, forming an S-R habit. S-R associations reflect associative learning, not motivational processes.

of subsequent findings further showed that reinforcement cannot be explained solely through drive reduction. Sweet-tasting substances, for instance, are readily and strongly consumed even in the absence of homeostatic need (Balasko & Cabanac, 1998), and the modern obesity epidemic illustrates that excessive consumption often arises from factors beyond mere hunger or physiological deficit (Bodor et al., 2010).

In the early seventies an alternative approach was proposed by Bolles (1972), who synthesized several phenomena that challenged purely drive-based or reinforcement-based explanations. These included “autoshaping”, where animals develop operant-like behaviors without any explicit reinforcement (for instance, pigeons pecking at a light that predicts food delivery), and “misbehavior”, reported by Breland & Breland (1961), in which trained raccoons stopped performing a reinforced action (placing coins in a box) and instead engaged in consumption-related behaviors, such as “washing” or gnawing the coins themselves. Crucially, these behaviors emerged without response-contingent reinforcement, contradicting the predictions of strict S-R learning models. These observations shifted attention from S-R associations to S-S associations. Researchers began to recognize that animals learn relationships between conditioned stimuli (such as lights or coins) and biologically significant outcomes (such as food). Through repeated pairings, a conditioned stimulus could acquire both predictive and incentive motivational properties (Bindra, 1974, 1978), meaning it could elicit approach behaviors and even consumption-like responses.

This marked the development of the first *“incentive motivational”* frameworks. In these views, motivation was defined as the *“tendency of the whole animal to produce organized activity”* (Hebb, 1972, cited by Koob & Le Moal, 2008), and behavior was thought to arise from incentive expectancies (i.e. the anticipation of pleasurable outcomes, Bolles, 1972), rather than from the reduction of biological drives. Incentive value was further understood to depend on internal states such as hunger, which modulate how attractive a given cue appears (Toates, 1986) (e.g. the tasty smell of a Liège Waffle may be highly incentive while hungry, but far less while satiated). Priming effects have also been shown in the framework of this first incentive motivational theory: both the CS and pre-exposure to the US could intensify internal states (hunger) and motivation (this is well illustrated through the “peanut” effect: you might not be very hungry at a beginning of a dinner, but after having a few peanuts, your hunger critically intensifies).

A major conceptual shift occurred in the 1990s with the development of the Incentive-Salience Theory by Berridge and Robinson (1998). Their work demonstrated that the hedonic value of a reward (its *liking*) plays a more limited role in behavior than previously assumed. Instead, they proposed that *incentive salience*, or *wanting*, can be dissociated from liking. Crucially, reward-associated cues can evoke robust motivational states even when they elicit little or no subjective pleasure (Wyvell and Berridge, 2000). This dissociation profoundly influenced contemporary theories of motivated behavior, especially in the context of addiction where the wanting and liking components are dissociated (a distinction that will be elaborated in more detail below).

Toward a Comprehensive Understanding of Reward

A central concept across all these frameworks is the notion of *reward*. What does this term actually denote? In everyday language, “reward” is often used interchangeably with “pleasure, yet scientifically the construct is considerably more nuanced. Evolution shaped organisms in a way that they find certain stimuli (such as food, water, or sex) inherently rewarding, because these stimuli promote their survival; these are termed *primary* or *natural rewards* (T. E. Robinson et al., 2014). Such stimuli are used as US in experimental settings because they reliably evoke unconditioned responses and act as positive reinforcers. They actually satisfy all the criteria emphasized across reward-learning theories: they act as positive reinforcers in the sense that they increase the frequency of behaviors that produce them, they have the ability to produce pleasure, and they act as incentives that motivate approach behavior (T. E. Robinson et al., 2014). Obviously, several other stimuli can serve as rewards, so a second category (secondary rewards) exist: these have gained value through learned associations with primary reward, and engage largely overlapping neural circuits (Ulrich et al., 2023). Drugs of abuse would theoretically be considered secondary rewards (since they do not necessarily promote survival), but it has been demonstrated that they share many properties of natural rewards (Nesse and Berridge, 1997).

However, contemporary models also view reward as a *multifaceted psychological process*, and not simply as a particular stimulus. According to Berridge and Robinson (1998, 2003), the process of reward consists of three interacting components, that can be separately identified in behavior: learning, motivation, and emotion/affect (Berridge & Robinson, 1998, 2003). Each component can operate at both explicit (conscious) and

implicit (unconscious) levels (Berridge and Robinson, 2003), although there is currently no evidence that the conscious effects can exist independently of unconscious effects (Anselme & Robinson, 2016). This multidimensional framework has become central to modern discussions of reward processing and its alterations in disorders such as addiction.

Incentive Motivation: Focus on Berridge and Robinson's Incentive Salience Model

As already mentioned, Berridge and Robinson (1998) gave a new perspective on motivated behaviors by putting particular emphasis on the concept of incentive salience. Building upon earlier incentive theories of motivation as well as crucial findings relating to dopamine's role in reward processing, they proposed that the psychological "*reward*" process is not unitary but comprises three distinct components:

- Hedonic activation ("*liking*"), referring to the pleasurable effect triggered by an US,
- Associative learning, which encodes the predictive relationship between the CS and the US, and
- Incentive salience ("*wanting*"), which transforms neutral cues into motivationally significant targets once predictive of reward (these cues become "*wanted*").

Although these processes typically co-occur, Berridge and Robinson emphasized that they rely on distinct neural systems (Berridge, 2001; Berridge & Robinson, 1998), with dopamine systems playing a central role in the attribution of incentive salience only.

What they call incentive motivation, or "*wanting*", is a dopamine-dependent psychological process that renders specific stimuli (e.g., food, sex, money, games) attention-grabbing, attractive, and likely to be approached or contacted (Anselme & Robinson, 2019). Via incentive salience, a neutral representation of a cue is transformed into a motivationally charged signal, a stimulus that captures attention and triggers approach (Berridge & Robinson, 1998).

In contrast, "*liking*" refers to the hedonic pleasure elicited by rewards. While it is generally described in common language as a subjective experience that arises from "*rewarding*" stimuli or experiences, the incentive salience model argues that hedonic

pleasure is only one component of reward (Berridge et al., 2009; Litt et al., 2010). Contrary to “wanting”, “liking” has been shown to be controlled by opiate and endocannabinoid systems, whose receptors (called “hedonic hotspots”) are located in the same brain regions as those of dopamine (e.g., Smith et al., 2010).

The conceptual and neurobiological separation of wanting and liking was based on several influential experimental findings:

First, Berridge and colleagues (1998) found that “liking”, as measured through affective hedonic (pleasure) reactions in rats, was not at all reduced by lesions of ascending dopamine projections. Moreover, increases in extracellular dopamine in mutant mice (dopamine transporter deficient mice) critically increased food intake and performance for sweet rewards, while it did not increase hedonic liking to sucrose (Peciña et al., 2003). Also, cue-triggered “wanting” (incentive motivation in response to a conditioned cue) has been shown to occur without the hedonic “liking” counterpart: Injections into the nucleus accumbens (NAcc) of dopamine agonist amphetamine increased the ability of a sucrose cue to spur performance for sucrose reward, even under extinction conditions, while not increasing hedonic, “liking”, responses (Wyvell & Berridge, 2001).

Taken together, these findings indicated that dopamine modulates motivation rather than hedonic pleasure. As stated by Berridge and Robinson (1998), pleasure is simply a triggered affective state, whereas incentive salience determines what becomes a *motivational target*. Thus, while it was considered by earlier theories, that dopamine was responsible for pleasure (Wise, 1982) or for learning to take place (Schultz et al., 1997), Berridge and Robinson challenged these views by integrating multiple findings suggesting that dopamine’s primary function lies in motivational (*wanting*) modulation. Dopamine-dependent wanting is neurobiologically dissociable from associative learning. For instance, eliminating dopamine does not abolish the ability to acquire predictive CS-US associations, and the incentive value of a lever can be altered (and restored by dopamine) without requiring new learning (M. J. F. Robinson & Berridge, 2013). Similarly, artificially enhancing dopamine can induce an intense motivational attraction toward an electrically charged rod, even when the aversive consequences are fully predictable (Warlow et al., 2020).

Further evidence came from studies on dopamine-deficient (DD) mice, which are unable to synthesize dopamine. These animals consume and enjoy palatable food when

placed directly in their mouths but do not initiate food-seeking behavior and die without intervention (Palmiter, 2008). Because they fail to attribute incentive salience, DD rodents are unable to use hedonic or associative processes to transform the perception or representation of a reward into an attractive, wanted incentive target. As nicely summarized by Berridge and Robinson (1998, p. 350): *“DD rodents still ‘like’ rewards and still know the rewards they ‘like’. They simply fail to ‘want’ rewards they ‘like’.”*

These converging results and many others helped establish the incentive salience theory as a dominant contemporary framework of dopamine’s role in incentive motivation.

Importantly, Berridge and Robinson conceptualized “wanting” and “liking”³ as psychological processes that can operate at implicit, unconscious levels (Berridge, 1996). Their subjective counterparts (conscious craving or wanting) or consciously experienced pleasure (liking) only represent the conscious elaboration of these underlying processes (Berridge, 1996, Berridge & Robinson, 1998).

The phenomenon of incentive motivation and the conceptual (and neurobiological) distinction of wanting and liking is particularly relevant for maladaptive behaviors such as addiction. Early incentive motivation theories, including those developed by Bolles, Bindra, and Toates, provided the conceptual foundation for the work of Robinson and Berridge, whose contributions have been especially influential in shaping contemporary models of substance use disorders (SUDs) (Berridge & Robinson, 2016; Felix & Flagel, 2024; T. E. Robinson & Berridge, 1993, 2025). The application of these ideas to addiction will be examined in detail later in the chapter.

A quick overview of the above-mentioned concepts is provided in Table 1, summarizing key definitions and distinctions.

³ The use of quotation marks indicates that these terms refer to subcognitive motivational processes, distinguishing them from the consciously experienced states of wanting and liking (presented without quotation marks), as has been done by Berridge and Robinson (1998).

Table 1. *Summary of Key Concepts Relating to Incentive Motivation*

Concepts	Definitions	Example
Reward (the thing)	Natural (or primary) Rewards: Things that promote survival and are therefore perceived by organisms as <i>rewarding</i> (from T. E. Robinson et al., 2014, p.1)	Food or sex.
	Other (secondary) Rewards: Things that gained value through learned associations with primary reward (from Ulrich et al., 2023, p.1).	Money or power ⁴ .
"Liking"	<i>"Underlying core process of hedonic evaluation that typically produces conscious pleasure, but that can occur without it"</i> (Berridge & Robinson, 1998, p. 313) ; different from its conscious subjective equivalent of pleasure (liking).	Orofacial mimics in rodents and children (Berridge, 2000).
"Wanting" " (incentive motivation)	The form of desire mediated by mesolimbic processes, spurring approach and contact with an attributed stimulus (T. E. Robinson & Berridge, 2025), different from its conscious counterpart (craving/wanting).	Cue-triggered approach
Reward (the process)	A composite process that contains "liking" (hedonic impact), "wanting" (incentive motivation), and learning (associations and predictions) (Berridge et al., 2010).	Upon arriving at a funfair, an individual experiences pleasurable feelings (liking, arising from "liking") elicited by the visual cues (lights and sounds), which evoke positive memories of past visits (learning). Almost automatically, these cues draw the individual toward their favorite game stands ("wanting").

⁴ Stimuli or actions that fulfill universal needs for competence, autonomy, and relatedness can also be rewarding (e.g. video games, see Przybylski et al., 2010).

How Cues Can Control Actions: Behavioral Manifestations of Incentive Salience

A central claim of the incentive salience hypothesis is that , through learning, conditioned cues can acquire incentive motivational properties as they come to predict reward delivery (T.E. Robinson et al., 2014). This idea emphasizes that behavior in everyday life is not controlled only by primary rewards such as water, food, or sex, which historically dominated motivation research. Behavior is also strongly influenced by stimuli that are initially neutral but that become predictive of natural rewards through Pavlovian conditioning. For example, the sound of a treat bag crinkling may cause a dog not only to salivate but also to orient toward the sound, approach its source, or attempt to interact with the bag, even in the absence of food. Comparable examples can be found in substance use contexts. A person sitting in a bar may experience positive affective reactions or sudden cravings simply upon seeing or smelling their preferred alcoholic drink being consumed nearby. These cue-elicited motivational states might then influence behavior, increasing the likelihood that the individual will order a drink, even if they had no prior intention to do so.

When a stimulus is imbued with incentive salience, it becomes an *incentive stimulus*: a cue endowed with the power to attract, motivate, and energize behavior (Zang et al., 2009, T. E. Robinson et al., 2014). These stimuli acquire *three fundamental properties*⁵ (Berridge, 2001; Flagel et al., 2009; Milton & Everitt, 2010):

1. They capture attention and elicit approach behaviors.
2. They act as conditioned reinforcers, supporting new learning.
3. They invigorate instrumental reward-seeking actions.

The first property states that incentive cues attract and bias attention, thereby inducing approach behaviors. Two very common ways of measuring this aspect in laboratory animals are through the Conditioned Place Preference (CPP) procedure or through Pavlovian Conditioned Approach (PCA). In a traditional CPP procedure, an animal is repeatedly given a drug in an environment A, while another environment is paired with a placebo condition. The measure of interest following conditioning is the respective time spent in both environments, with the animal spending more time in the

⁵ also called “*wanting properties*” (Berridge et al., 2009)

"drug-environment" being interpreted as "a preference" or attraction for the conditioned environment due to the rewarding drug effects experienced there (see McKendrick & Graziane, 2020 for a recent review). On the other hand, in PCA procedures a discrete CS is repeatedly shown before a reward US is delivered, and the measure of interest is cue-approach behavior and interaction (Flagel et al., 2008; Hearst and Jenkins, 1974). Interestingly, individuals can come to approach and interact with the CS (even though this behavior is not needed, i.e. reward obtainment is not response-contingent in this procedure). Uslaner and colleagues (2006) were among the first to test this effect of incentive salience on cue-approach with drug associated cues directly. They found that rats came to approach and investigate a discrete cue that predicted cocaine injections, showing directly that drug-paired cues can be imbued with incentive salience and become "motivational magnets" via Pavlovian learning. This cue-approach and interaction behavior is called *sign-tracking*, and since it is at the core of the present thesis, a whole chapter (Chapter 3) will be devoted to it.

In humans too, conditioned incentive cues can come to exert a powerful pull on behavior. A nice illustration of this "attracting and magnetic" feature comes from a classical anecdote mentioned typically in Berridge and Robinson's work (Rosse et al., 1993; T. E. Robinson & Berridge, 2025) about "*chasing ghosts*". This phenomenon refers to repetitive compulsive behaviors that can be observed in crack cocaine addicts scrabbling and searching after anything that resembles rock cocaine (e.g. pebbles, candle wax, food crumbs, bits of drywall, etc.) (Rosse et al., 1993), even though they know they are not cocaine. Nowadays, extensive empirical evidence demonstrates that reward-associated cues can function as potent attentional and behavioral magnets, producing robust approach tendencies and attentional biases. These mechanisms, and their implications for addiction, will be discussed in more detail later in the chapter.

The second property is about conditioned reinforcement. After a CS has been paired with a rewarding US, animals will often perform new instrumental actions simply to obtain access to the CS. This demonstrates that the cue has acquired reinforcing properties of its own. This is traditionally assessed through instrumental paradigms in which animals acquire novel instrumental responses to gain access to previously conditioned cues (Robbins 1978). This effect of incentive stimuli acting as conditioned reinforcers has been shown with cues associated with cocaine, heroin and sucrose, and persisted over months of repeated, intermittent testing (Di Ciano & Everitt, 2004).

Moreover, it has been found to persist despite US devaluation, as shown in Parkinson et al. (2005), where rats still learned to lever press to get access to the CS (light) even after the US has been associated with aversive lithium chloride injections, suggesting that the CS has gained reinforcing properties that are separate from the value of the US.

The third property of incentive stimuli is that they have the ability to instigate reward seeking, by potentiating or energizing instrumental responding (or as put by Berridge et al., 2009, a reward-related CS can instigate US wanting, which can “*spill over*” to other US).

This effect is traditionally measured through procedures such as the so-called Pavlovian-to-instrumental-Transfer (PIT) tasks (e.g., Dickinson et al., 2000; Wyvell and Berridge, 2000). Shortly, these tasks consist of 3 phases of conditioning: an initial Pavlovian phase where a discrete CS is associated with a rewarding US, while no action is required; then an instrumental phase where the animal must produce an instrumental action to obtain a reward (e.g., pressing a lever for a food pellet), and finally a transfer phase where the Pavlovian CS is briefly presented during instrumental performance (typically under extinction, i.e. no reward is delivered). The phenomenon of interest here is that the Pavlovian CS increases the rate of instrumental responding, even though the CS had never before been associated with that action. PIT is interpreted as evidence that the CS evokes a Pavlovian motivational state that energizes behavior directed toward the reward (T. E. Robinson et al., 2014). In human research also, PIT has gained increasing scientific interest, and a recent meta-analysis by Badioli et al. (2024) documents substantial effect sizes across the existing literature. On a cognitive level, it has been suggested that certain forms of PIT might operate at subconscious levels, with one study showing significant general PIT using subliminal cues (Garofalo et al., 2020).

Although these three properties can be psychologically and neurobiologically dissociable in the laboratory, they typically co-occur in natural environments (Milton and Everitt, 2010; T. E. Robinson et al., 2014). Importantly, the fact that incentive stimuli are able to motivate actions and bias behavior is actually highly adaptive because this will increase the likelihood that an animal will acquire survival-related rewards (e.g., food, water, safety) and for propagation of the species (e.g., a mate) (Krause & Domjan, 2017). However, the same processes can become maladaptive (Flagel et al., 2009). Reward-related cues may also trigger excessive or compulsive behaviors, contributing to overeating (contributing to obesity; Berridge, 2012), substance use (T. E. Robinson et al.,

2014) or gambling (Dixon et al., 2014). In the context of SUDs, these three properties of incentive stimuli have been described as the “*three routes to relapse*” (Milton and Everitt, 2010), as each mechanism can independently (and cumulatively) promote drug seeking.

Behavioral expressions of incentive salience are commonly assessed in cue-reactivity studies, which we will broadly define here as paradigms measuring physiological, affective, cognitive, or behavioral responses to conditioned cues. The upcoming chapter (Chapter 2) will provide an in-depth comparison between animal and human cue-reactivity, including challenges unique to human alcohol research (e.g., in humans, predictive cues, such as glasses, brands, or bar environments, are often tightly embedded within the context of consumption, whereas in animal experiments these elements can be fully dissociated and controlled).

Finally, the degree to which individuals attribute incentive salience to conditioned cues varies substantially. Some individuals show strong cue-triggered attraction and motivation, whereas others do not. Such individual differences in responsiveness to reward-associated cues are thought to contribute to vulnerability toward addiction and related psychopathologies. These differences will be explored in detail in later sections (Chapter 3).

Motivated Attention: Why Do We Attend Certain Cues and How They Drive Our Behavior

What is clear from the theoretical aspects and evidence outlined in the previous sections is that stimuli signaling reward (via mesolimbic dopamine) critically guide an individual's (approach) behavior. As conceptualized by Berridge and Robinson (1998), through the phenomenon of incentive salience, reward-relevant stimuli become attention-grabbing, motivational magnets able to energize and orient behavior.

While the animal-based findings on which incentive motivational theories built upon were rather behavioral in nature (studying the effects of reward on motivated behavior), later on, a more “cognitive/attentional” perspective on the effects of reward was investigated. As a preliminary note (and not surprisingly), reward has been shown to have crucial influence in these processes as well. But first, let's briefly outline how attentional mechanisms function.

In our daily-life, our cognitive processing systems are exposed to a myriad of informational stimuli and it is impossible to attend to all available stimuli at once, so our brain filters out certain aspects of this vast amount of information to be processed (Broadbent, 1958).

This is basically the role of (selective) “attention”, *“a cognitive processes that enable the selection of, focus on, and sustained processing of information”* (Cohen, 2011, p.282). Attentional control is about how we explore the environment and how we parse information (Failing & Theeuwes, 2018). So, when studying how and why individuals approach and interact with certain cues, attention plays a crucial role.

Brief Summary of Selective Attention Processes

Classical models of selective attention have described a dynamic interplay between voluntary top-down (or goal-driven) control of attention and more automatic, bottom-up stimulus-driven control (e.g., Corbetta & Shulman, 2002; Itti & Koch, 2001; Theeuwes, 2010). These processes typically compete, and it has clearly been shown that bottom-up processes can affect our attention independently (and even in spite) from top-down processes, i.e., salient distractors can disrupt top-down control in visual attention tasks, a phenomenon that has been labelled *“attentional capture”* (Theeuwes, 1992), or *“oculomotor capture”* (for eye movements, Theeuwes, et al., 1998; 1999;). In summary, voluntary control of our attention is not always in charge of how we attend to stimuli in our environment.

A bit more than a decade ago, a third category of attentional processes has been suggested (Awh et al., 2012), to account for instances where attention is not controlled by top-down goals or physical salience but rather by previous history of attentional deployments (Failing & Theeuwes, 2018). This third kind has been called *“selection history”*. Selection history can be of several kinds (based on priming or statistical regularities for instance), but the one of interest for us here is *reward-based selection history*, where attention is (involuntarily) drawn toward stimuli that are or have been associated with reward (Failing & Theeuwes, 2018). Importantly, there exist crucial relationships between attentional and reward processes. While it has now long been established that rewards can strengthen behavioral responses (Skinner, 1938/1966) and elicit orienting responses to their preceding stimuli (Pavlov, 1927), it seems that similar principles also apply in attention research on how rewards influence attention. This seems

quite intuitive since the “automatic” attraction caused by reward-associated stimuli (one of the properties of incentive stimuli) has long been acknowledged in animal and human studies (as illustrated above). As nicely pointed out by Chelazzi et al. (2013, p.69), *“given the role of selective attention in guiding behavior and given that behavior itself has long been known to be largely influenced by the delivery of rewards, it might seem logical to predict that selective attention is also sensitive to rewards”*.

How Rewards Affect Attentional Processing

When it comes to the study of how reward affects attentional processes, two major effects can be observed: (1) performance enhancement by rewarding incentives, and (2) performance disruptions by reward-associated distractors⁶.

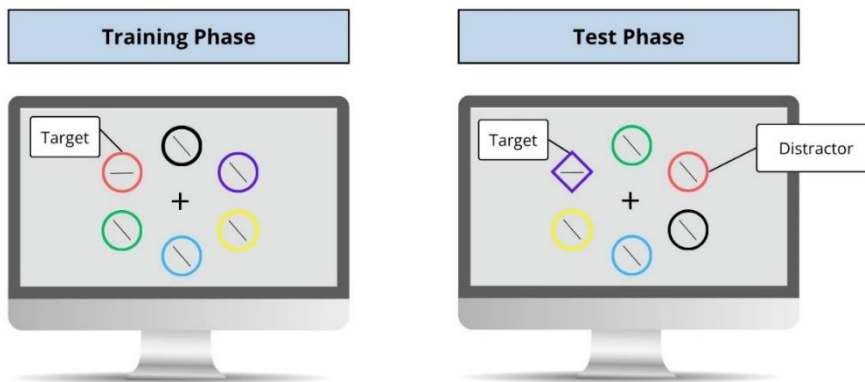
First, rewarding incentives increase task performance. This has been established in several studies on executive functions, such as response preparation and inhibition or adaptation to errors (e.g. Boehler et al., 2014; Mir et al., 2011). Regarding attentional control more specifically, target detection is increased by rewarding trials in spatial cueing and stroop tasks (Engelmann & Pessoa, 2007; Padmala & Pessoa, 2010). It has been suggested that this effect of reward on attention operated in a strategic manner (Chelazzi et al., 2013), using top-down attentional control leading to a beneficial effect on perceptual and attentional processing (Failing & Theeuwes, 2018). But is it indeed top-down control that underlies this performance enhancing effect of reward? Or is it rather a more automatic effect of recent history of reward-driven selection? As argued by Theeuwes (2018, p.1): *“true top-down control of visual selection occurs far less often than what is typically assumed. Most of the time, selection is based on experience and history. It is fast, automatic and occurs without much, if any, effort.”*

The second and more recent line of research has prioritized the latter option by showing disruptive effects: rewards can impede performance when their associated cues are task-irrelevant. Hickey et al. (2010a) investigated this using the additional-singleton paradigm developed by Theeuwes (1991, 1992). In this computerized visual-search task, participants must locate a target shape among distractors, while an irrelevant distractor (the “additional singleton”) appears as a uniquely colored item (e.g., a red among green

⁶ These two effects may seem contradictory, but they operate in the presence of different task conditions: in the first instance, reward-cues are the target stimuli and are relevant for task performance (i.e. the object to which attention should be deployed to improve performance and gain rewards), while in the second task, they are distractors which should be ignored.

shapes). Using this paradigm, Hickey et al. (2010a) identified what they termed “reward-mediated intertrial priming”: attentional capture by a distractor increased when that distractor’s color had recently been associated with reward. Participants were involuntarily drawn to items sharing the color of the previously rewarded target, even when those items no longer had any task relevance. This study also showed that reward-based selection history impacts stimulus representation on a neural level, leading to the conclusion that reward can change the stimulus’ salience to the visual system, prioritizing its perceptual and attentional processing.

Further evidence for such an effect was shown by Anderson and colleagues (B. A. Anderson et al., 2011), who were among the first to describe it as “*value-driven attentional capture*” (VDAC). A typical VDAC paradigm consists of a training phase followed by a test phase. During training, participants search for a color-defined target among various colored items, with one target color associated with high reward and another with low reward. In the subsequent test phase, participants search for a shape singleton presented among randomly colored non-target shapes (similar to the additional-singleton task; Theeuwes, 1992). On half of the trials, one of the non-targets appears in a color that previously signaled reward during training. Anderson et al. observed that search times increased when the non-target item was in a previously high-reward color compared with trials where no previously reward-associated colors were present (B. A. Anderson et al., 2011). See Figure 1 for an illustration of the task.

Figure 1. *Illustration of the VDAC Task*

Note. During the training phase, participants search for a designated color target (e.g., red) and report the orientation of the line contained within the colored shape. Two different target colors are associated with either a high- or a low-reward outcome. In the test phase, the task switches to shape-based search, and the previously reward-associated color appears as an irrelevant distractor to assess its capacity to capture attention.

The VDAC effect persists even over long periods of time (up to 6 months, e.g., B. A. Anderson & Yantis, 2013). Moreover, this effect is thought to occur involuntarily (Pitchford and Arnell, 2025) and does not require participants to be explicitly aware of the stimulus–outcome contingencies that gave rise to it (B. A. Anderson, 2016; Le Pelley et al., 2015; Pearson et al., 2015). This effect of reward-based selection history has also been evidenced at an oculomotor level: objects initially associated with a higher reward elicit stronger oculomotor capture when later presented as task-irrelevant distractors. Such effects have been observed both when participants are free to move their gaze (B. A. Anderson & Yantis, 2012; Bucker et al., 2015) and when they search for targets defined by features unrelated to those that were reward-predictive during training (Theeuwes & Belopolsky, 2012).

On Value-Modulated Attentional Capture (VMAC)

Le Pelley's team (Le Pelley et al., 2015) proposed a new version of the task (which's was now referred to as "*value-modulated attentional capture*", VMAC), to test whether a reward-signaling stimulus competes for attentional selection even if it was never associated with the target and even if responding to it never resulted in reward. In their task, no training phase was present, thus eliminating the "instrumental" aspect that previously characterized the VDAC task (i.e. responding to the high reward-color during training yielded rewards, while this color was used as a distractor in the subsequent test session). Their results showed that attentional capture, measured through reaction time, was stronger when the distractor signaled a high compared to a low reward. The same pattern was also observed in an eye-movement study (Le Pelley et al., 2015, Experiment 3). The VMAC effect also occurred when individuals were not aware of stimulus-reward contingencies and when attending to reward-associated stimuli was detrimental to both task performance and the total reward earned (Le Pelley et al., 2015; Watson, Pearson, Most, et al., 2019). These observations suggest that the VMAC effect is rather automatic (and hence difficult to inhibit), which is very similar to one of the three properties of incentive stimuli mentioned earlier: reward-relevant cues can have a strong and quite automatic impact on behavior (e.g. as observed in PCA, or PIT).

Parallel processes of *reward-driven attention* (such as VMAC) have also recently been obtained in other species. For instance, birds (peafowl, *Pavo cristatus*) exhibited behavior resembling reward-driven attention in human studies (Liao et al., 2023), using a touchscreen-equipped operant-chamber and an attentional task based on the traditional VMAC paradigm (Le Pelley et al., 2015). The bird's attention towards task-relevant stimuli was affected by reward-associated distractor cues. The authors suggest that given the similarity with human behavior (Failing & Theeuwes, 2014, but also non-human primates, see Peck et al., 2009), the attentional/motivational mechanism captured by VMAC may have appeared early in evolution and is preserved across phylogeny, possibly reflecting an adaptive mechanism (B. A. Anderson, 2021; Liao et al., 2023).

The idea of an evolutionary advantage of the attentional prioritization of reward-relevant stimuli (through the facilitation of approach behaviors leading to obtaining resources) has been pointed out by Della Libera & Chelazzi (2006, 2009), as well as Pitchford & Arnell (2025). Recent findings in mice also support the idea of a cross-species,

adaptive mechanism for reward-mediated attentional processing, by showing that mice flexibly allocate spatial attention based on recent reward history (in a “Go/NoGo whisker touch detection task”, Ramamurthy et al., 2025).

At a neurobiological level, empirical evidence is accumulating to suggest that reward-based attentional capture is related to dopamine release in (dorsal) striatum (B. A. Anderson, 2019; B. A. Anderson et al., 2016; 2017). This is a particularly compelling finding given the established role of striatal dopamine in incentive-salience attribution and cue-driven behavior (Berridge, 2001, 2007, 2012, 2018; Berridge & Robinson, 1998). These converging lines of evidence suggest that reward-driven attentional capture may rely on mechanisms that overlap with implicit learning processes governing stimulus-reward associations, rather than on goal-directed attentional selection (B. A. Anderson, 2016; B. A. Anderson et al., 2021 ; Failing & Theeuwes, 2018; Pitchford & Arnell, 2025). Consistent with this view (and also in line with the incentive salience theory), reward-based selection history has been conceptualized as a rapid and involuntary process, operating in a manner analogous to bottom-up, physically driven salience mechanisms (B. A. Anderson & Kim, 2019; Bucker et al., 2015; Failing et al., 2015, Pearson et al., 2022).

At the cognitive level, it has been proposed that reward-based selection history alters the representation of a stimulus through repeated associations, rendering it more salient to the visual system (Failing & Theeuwes, 2018; Theeuwes, 2019). As pointed out by Failing and Theeuwes (2018), this is conceptually highly similar to how Berridge and Robinson proposed incentive salience to operate (Berridge, 2001, 2007; Berridge & Robinson, 1998), i.e., transforming an initially neutral stimulus (by altering its neuronal representation) into an attention-grabbing magnet due to its association with a desired outcome. This claim has indeed been supported by neuroimaging, as well as behavioral studies. Several studies have shown increased neuronal activity in response to reward-associated stimuli in early visual cortex (B. A. Anderson, 2017; Hickey et al., 2010a; Serences & Saproo, 2010). This reward-related modulation of attentional processing at a neural level was also shown in mice (Baruchin et al., 2023). Reward stimuli affected very early stages of visual processing, which might significantly improve visual performance of mice, with the evolutionary advantage of allowing these animals to process reward-relevant stimuli quickly. Behaviorally, it was shown that reward-driven attention increases low-level salience. Qin et al. (2021) showed that along with preferentially capturing

attention, reward-associated stimuli increase the perceived contrast of subsequent stimuli, further supporting the idea that reward-based selection history can indeed impact early visual processing, rendering reward-relevant stimuli more salient (B. A. Anderson, 2013; Awh et al., 2012; Failing & Theeuwes, 2018; Theeuwes, 2019).

A final important aspect is that the degree to which previously reward-associated stimuli affect attentional selection can vary substantially between individuals. Using mainly the VDAC paradigm, several individual differences have been identified that co-vary with the tendency to be attentionally drawn to reward-relevant stimuli. Anderson's team showed decreased VDAC effect in depressed individuals (B. A. Anderson, Leal, et al., 2014), while an increased VDAC effect was shown in individuals exhibiting higher impulsivity (B. A. Anderson et al., 2011), as well as stronger behavioral approach drive (Hickey et al., 2010b) and greater reward responsiveness (Hickey & Peelen, 2015). Importantly, increases of attentional capture have also been documented in individuals with SUDs, for both VDAC (B. A. Anderson et al., 2013), and VMAC (Watson et al., 2024). These findings will be discussed further in Chapter 4.

In summary, motivational, reward- and attentional processes are highly intertwined: reward experience shapes perception and attention largely beyond top-down and bottom-up processes. Stimuli previously associated with reward are prioritized through changes in the neuronal representation of these stimuli, so that they become more salient to the visual system (i.e. reward-based selection history). These perceptual/attentional effects are in line with Berridge and Robinson's theory of incentive salience. They might be considered as attentional consequences of incentive salience attribution. The ability of environmental stimuli (such as conditioned cues associated with rewards) to bias behavior and to guide actions is, in most circumstances, highly adaptive. By directing organisms toward cues that predict biologically significant outcomes, these processes enhance the likelihood of obtaining survival-relevant rewards and support efficient decision-making in complex environments (Corbit & Balleine, 2015; Krause & Domjan, 2017; T. E. Robinson et al., 2014). However, in modern environments saturated with cues signaling the availability of rewarding outcomes, these same mechanisms can become maladaptive. Conditioned cues may evoke intrusive thoughts, excessive emotional responses, or compulsive behaviors—a constellation of effects that falls under the broader concept of *cue reactivity*. Such cue-driven processes are widely believed to contribute to the development and maintenance of psychiatric conditions, including SUDs and over-eating

(Berridge et al., 2010; Corbit & Balleine, 2015). The view that incentive stimuli constitute a key motivational force in drug-seeking behavior traces back several decades (Stewart et al., 1984). Current frameworks of addiction (and of Alcohol Use Disorder (AUD) more specifically) consistently underscore the importance of Pavlovian incentive mechanisms and the attentional biases arising from them.

Addiction

Substance (Ab)Use: From an Ancient Cultural Phenomenon to a Major Burden for Modern Society

Drug (ab)use has been part of human society since the dawn of time (Saah, 2005). Indeed, throughout history, psychoactive substances have been widely used, whether during religious ceremonies, for medicinal purposes or, in more recreational, socially approved ways (Crocq, 2007). All around the world, archaeological data concerning psychoactive substance strongly suggest the great antiquity of humankind's ritual use of these substances (Guerra-Doce, 2015; Hutton, 2020). While their use is ancient, modern molecules of psychoactive substances and routes of administration are evolutionary new features, which are thought to contribute to pathological consumption patterns by acting directly on deep-rooted brain mechanisms of emotion and behavior, thus giving false alarms of fitness to the organisms and acting directly (Nesse & Berridge, 1997).

Despite their ancient cultural and historical ties, the detrimental effects of the misuse of these substances have been recognized for ages, and the concepts of pathological consumption and loss of control for example are still at the heart of public and scientific interest (Crocq, 2007). Addiction and drug (ab)use represent a major health and financial burden for society. In fact, addiction can be considered a worldwide epidemic (Saah, 2005) with ravaging effects in terms of public health. Globally, 35 million people are estimated to suffer from drug use disorders, corresponding to a global prevalence of 0.77 per cent among the population aged 15–64 (United Nations Office on Drugs and Crime, 2023). While the occasional, controlled, and limited use of substances must be distinguished from clinically defined “*addiction*”, professionals agree nowadays that there is a continuum of consumption patterns, ultimately leading to SUDs and “*addiction*” (Koob et al., 2019a). The scientific literature reflects this graded view by employing a variety of terms to denote differing levels of condition severity. A nice work

was done by summarizing increasing levels of condition severity (for AUD), by Heilig and colleagues (Heilig et al., 2021). Figure 2 was directly inspired by Heilig et al.'s paper (2021) and illustrates three successive dimensions of severity that are nested: Risky (or hazardous) substance use, which refers to patterns of consumption that substantially elevate the likelihood of negative physical or psychological outcomes (for the individual or for others) at a level that merits clinical attention or preventive guidance, even though clear harm has not yet manifested (WHO, 2024a)⁷; some of those individuals have a SUD (such as an AUD), but most do not. SUDs are defined in the latest version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), as patterns of symptoms caused by using a substance that an individual continues taking despite its negative effects, with increasing severities are reported: mild moderate and severe (American Psychiatric Association, 2013). Addiction (or dependence) on the other hand, is a term often used in common language (e.g. *"being an addict"*) but also in scientific and clinical usage. It typically refers to individuals at a moderate or high severity of SUD⁸. Thus, not all individuals with a SUD are addicted to the drug in question, but a subgroup are.

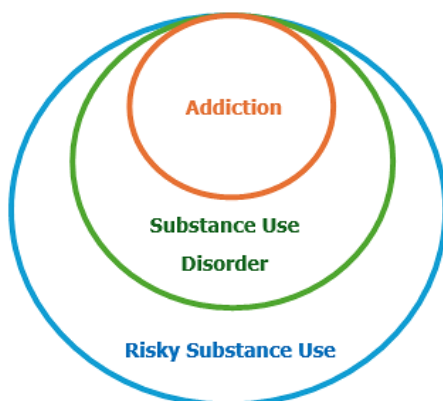
For society, the terms "addiction", or "substance dependence" carry an ancient negative connotation. While, historically, the way addiction was defined and considered has critically evolved between its first "discovery" (end of the 18th century, Rush, 1787, cited by Martin et al., 2016) and now, a certain stigma has persisted when it comes to people with SUD. Two main opposing views can historically be mentioned: a moralizing framework that considers people struggling with "addiction" as weak-willed individuals, that are selfish and chose to let go to pleasurable consumptions instead of contributing to society, and a more "disease" oriented view that (on its extreme end) considers people suffering from SUDs as unfortunate "victims" that cannot be held responsible for their condition, due to a significant loss on control (some even talk about a complete loss of free will) (Davies, 1997 cited by Baumeister & André, 2024 ; Martin et al., 2016, Leshner, 1997). Going in depth considering these conceptual, semantical (and to some extent even philosophical) issues would be out of scope for the present work, but some aspects of this

⁷ The WHO also characterizes "episodes of harmful use", referring to an *"episode of use of a psychoactive substance has caused clinically significant damage to a person's physical health or mental health, or has results in behavior leading to harm to the health of others"* (WHO, 2024a, pp.3-4)

⁸ The WHO defines substance dependence as an *"impaired regulation of use of a psychoactive substance manifested by impaired control over substance use, increasing precedence of substance use over other aspects of life, and specific physiological feature indicative of neuroadaptation to the substance"* (WHO, 2024a, pp.3-4), which closely resembles the DSM-5 definition.

debate will be mentioned again in an upcoming section (General theories of addiction, p.29), since the way we define the condition and how we consider its etiology has a significant impact on how we investigate underlying processes and potential treatments.

Figure 2. *Nested Levels and Terms Related to the Concept of Addiction*



Focus on Alcohol Use Disorder

Alcohol is one of the most commonly consumed psychoactive substance worldwide (Winstock et al., 2021). Yet, it is defined by the World Health Organization (WHO) as *"a toxic, psychoactive substance"* linked to over 200 diseases and conditions, including 7 types of cancer (WHO, 2024b). Surprisingly it is the only psychoactive substance that is clearly and significantly detrimental to global health but is not regulated at the international level by legally-binding regulatory instruments (WHO, 2024a). Again, harmful use should be distinguished from more severe cases, and the WHO defines *"harmful use of alcohol"* as *"drinking that causes detrimental health and social consequences for the drinker, the people around the drinker and society at large, as well as the patterns of drinking that are associated with increased risk of adverse health outcomes"* (WHO, 2010, p.5). According to the WHO's definition, AUD includes two categories of behaviors: alcohol dependence and harmful pattern of alcohol use (the third and fourth types of use described above).

According to the latest estimates from the WHO (WHO, 2024a, Chapter 2), there were 2.5 billion people above 15 years of age who used alcoholic beverages worldwide in 2019, while 400 million people (age 15 and more) had an AUD (representing 7.0% of

adults)⁹. Thus, individuals who consume alcohol (heavily) constitute a readily accessible population for investigating mechanisms underlying SUD, representing a crucial target for scientific investigation to improve current knowledge of vulnerability, treatment, and prevention.

The harmful use of alcohol is the 4th global social burden generated by human beings (Dobbs et al., 2014) and one of the top five risk factors for disease, disability and death throughout the world (Lim et al., 2012). Alcohol consumption resulted in 2.6 million deaths worldwide in 2019 (4.7% of all deaths in that year)¹⁰, and 115.9 million “disability-adjusted life years” (which quantify “*disease burden*”, i.e., “*the gap between current health status and an ideal situation in which everyone lives to old age free from disease and disability*” (WHO, 2024a, p.45). In addition to physical and mental health consequences, alcohol consumption is often associated with socioeconomic consequences such as loss of earnings, unemployment or family problems, stigma and barriers to accessing health care (Klingemann & Gmel, 2001). More specifically in Belgium, 9.7% of the population aged 15 years and older report consuming alcohol on a daily basis, whereas 40.6% report drinking at least once a week but not every day (Gisle et al., 2018). In 2012, the direct costs of alcohol (mis)use in Belgium were estimated at 906.1 million euros while indirect costs amount to 642.6 million euros (Verhaeghe et al., 2017). Furthermore, alcohol was also responsible for 157 500 disability-adjusted life years representing 6.3 billion euros intangible costs (Verhaeghe et al., 2017).

In many contemporary societies, alcohol use is not merely tolerated but often normalized and, in certain contexts, actively promoted (Bartram et al., 2017; J. S. Meyer & Quenzer, 2013). This has led some authors to refer to a prevailing “*culture of intoxication*” (Hutton, 2016). Policy frameworks and commercial practices have further reinforced problematic drinking behaviors, for example through the late-night retail availability of alcohol and the pervasive promotion of drinking via large-scale advertising campaigns, including those on social media (Hutton, 2016). This normalization of alcohol use poses a significant challenge for public health, as it reinforces permissive attitudes toward drinking and complicates efforts aimed at prevention and harm reduction.

⁹ compared to 8.8% in 2016 (WHO, 2018)

¹⁰ Compared to approximately 3 million deaths in 2016 (5.3% of total deaths worldwide that year) (WHO, 2018)

Alcohol's Pharmacological Effects

Acute Effects

Alcohol produces widespread effects in the central nervous system by acting on inhibitory, excitatory, and modulatory neurotransmitter systems (Beck et al., 2025; Volkow & Blanco, 2023). Its most consistent neuropharmacological action is the enhancement of GABAergic inhibition and the suppression of glutamatergic excitation, leading to reduced neuronal activity and contributing to sedation, anxiolysis, and motor impairment (Criswell & Breese, 2005; Cruz et al., 2008; Zhu & Lovinger, 2006).

In the reward system, alcohol indirectly increases dopamine release in the nucleus accumbens by stimulating endogenous opioid and cannabinoid signaling (de Waele et al., 1994; Volkow & Blanco, 2023;). Opioid receptor activation contributes to the hedonic effects of drinking, whereas dopamine is more strongly linked to motivational aspects of drug seeking ("wanting") (Di Chiara, 2002; Heinz et al., 2009). Serotonergic modulation also influences alcohol's rewarding and stimulating effects, and serotonergic dysfunction predicts heightened risk for developing alcohol use disorders (Heinz et al., 2001; Schuckit & Smith, 2000).

At a behavioral level, alcohol (at low blood alcohol concentrations (BAC)), produces a constellation of stimulating and prosocial effects, including elevated mood, euphoria, talkativeness, and reduced negative affect (Ekman et al., 1964; Gilman et al., 2008). With increasing doses, the depressant properties of alcohol dominate, leading to sedation, motor impairment, decreased alertness, and unpleasant symptoms (especially as BAC declines) such as exhaustion, dysphoria, nausea, or hangover (Martin et al., 1993). Alcohol can also produce analgesic effects, mediated by its stimulation of endogenous opioid receptors (Neddenriep et al., 2019).

Cognitively, even at low BAC levels, alcohol impairs attention, vigilance, and neurophysiological markers of sensory processing, effects that increase with dose (e.g., Koelega, 1995; Fairbairn et al., 2021). Moderate consumption can disrupt judgment and promote overconfidence (e.g., Tiplady et al., 2004). Some findings also suggest shifts in moral decision-making, increasing utilitarian choices (H. Karlsson et al., 2022).

Executive functions (including working memory and response inhibition) are significantly impaired at moderate to high doses (A. M. Day et al., 2015). At the emotional level, alcohol distorts emotion recognition, dampening sensitivity to negative expressions

such as anger, fear, or sadness (Eastwood et al., 2020; Khouja et al., 2019). Neuroimaging studies reveal that alcohol also reduces activity in limbic regions, especially the amygdala, when processing threatening stimuli, contributing to its anxiolytic and disinhibiting effects (Gilman et al., 2008; Gorka et al., 2013). These effects are attenuated in heavy drinkers, likely reflecting tolerance (Gilman et al., 2012).

Chronic Effects and Neuroadaptations

Long-term alcohol use leads to persistent neurobiological adaptations that contribute to the chronic and relapsing nature of substance use disorders (Beck et al., 2025; Volkow & Blanco, 2023). Repeated stimulation of the dopaminergic system is followed by compensatory down-regulation of dopamine (D2) receptors, a hallmark neuroadaptation associated with reduced reward sensitivity and increased compulsive use. A meta-analysis confirms a consistent reduction in striatal D2 receptor availability in individuals with alcohol dependence (Kamp et al., 2019).

Chronic alcohol exposure also produces enduring changes in GABAergic and glutamatergic systems, contributing to tolerance, withdrawal symptoms, and dependence (Criswell & Breese, 2005; Roberto et al., 2004). Opioid receptor expression may also be altered; for example, detoxified alcohol-dependent individuals show increased opioid receptor availability in the ventral striatum and medial prefrontal cortex, which correlates with craving (Heinz et al., 2005).

Beyond neurochemical effects, chronic heavy drinking exacerbates mental health issues, impairs social functioning (see Pabst et al., 2024), and reinforces maladaptive patterns, further entrenching the disorder's chronic course (Volkow & Blanco, 2023).

Current Clinical Definition and Symptomatology

According to the DSM-5, AUD is defined by a maladaptive pattern of alcohol use that persists despite its negative consequences (APA, 2013). The DSM-5 outlines eleven diagnostic criteria for AUD, organized into four overarching categories: impaired control, physical dependence, social impairment, and risky use (APA, 2013). These criteria encompass behaviors such as compulsive alcohol-seeking, diminished control over consumption, withdrawal symptoms, negative affect in the absence of alcohol, and an intense craving to drink. A diagnosis is established when at least two of the eleven criteria are met within a 12-month period, with severity (mild, moderate, or severe) determined by the total number of symptoms endorsed.

From the patient's perspective, and of importance for the present work, craving and cue-reactivity (the consequences of exposure to internal or external cues related to alcohol consumption) are often cited as among the most difficult aspects of living with AUD. For example, a friend, who was himself struggling with problematic alcohol use and had sought treatment, once explained to me that he had begun to notice stimuli he had previously overlooked: for instance, the presence of beer cans and other alcoholic beverages at Lunch Garden (a Belgian self-service restaurant chain). He reported that simply seeing these items, and being aware of their availability, was difficult to manage (personal communication, March 2025). This anecdote illustrates how initially trivial and usually unnoticed environmental cues can elicit craving and psychological discomfort in everyday situations. Consistent with some theoretical accounts of addiction, such descriptions strongly suggest that environmental cues can exert a powerful pull, triggering rapid, seemingly automatic processes.

General Theoretical Aspects of Addiction

Chronic Brain Disease vs. Disorder of Choice Debate

Although many experts reached agreement on a general definition of addiction and its core features in the DSM-5 (for diagnostic purposes), this does not imply the existence of a single, unified, theory-driven definition grounded in empirical evidence. Numerous theories have been proposed to account for the development and maintenance of addiction, and the aim here is not to provide an exhaustive review. Despite decades of research, no consensus has emerged, and key aspects of addiction (such as its definition, key mechanisms, etc.) remain the subject of ongoing debate.

Broadly, current dominant addiction theories can be organized around two opposing perspectives. The first conceptualizes addiction as primarily the consequence of neuroadaptive changes, aligning with its definition as a chronic, relapsing brain disease by the National Institute of Drug Addiction (NIDA; Leshner, 1997). This perspective encompasses several frameworks originating from different scientists. While some emphasize automatic processes and a progressive loss of control (Everitt & Robbins, 2005, 2016), others highlight the role of negative reinforcement and allostatic processes (Koob, 2020; Koob & Le Moal, 2008), or heightened incentive motivational processes (T. E. Robinson & Berridge, 1993, 2008, 2025). Regardless of the precise mechanisms proposed, they all have in common that they (broadly speaking) propose that "addiction"

involves (long-lasting) neuroadaptations in reward, motivation, learning and executive control brain circuits (Everitt & Robbins, 2005; Koob & Volkow, 2016b; T. E. Robinson & Berridge, 1993). This framework is often subsumed under the “*Brain Disease Model of Addiction*” (BDMA).

An opposing theoretical view conceptualizes addiction as a disorder of choice, rooted in otherwise normative, but suboptimal, decision-making mechanisms, and according to which behavior remains fully controlled by the individual (Heyman, 2009, cited by Kurti & Dallery, 2012). This view is largely motivated by empirical and conceptual observations that, according to its proponents, are difficult to reconcile with the BDMA (see Blithikioti et al., 2025; Lewis, 2017; Satel & Lilienfeld, 2014). The most frequently cited arguments are as follows:

1. Preserved self-control and evidence for voluntary abstinence: Several studies show that most people with addiction have intact self-control and “free will”, being able to abstain from consuming when sufficiently motivated (e.g. contingency management¹¹ studies, see Phillips-Chantelois et al., 2025 for a recent systematic review and meta-analysis). Moreover, a substantial proportion of individuals cease problematic use without formal treatment, a phenomenon often referred to as “*spontaneous recovery*” or “*maturing out*” (Dawson et al., 2006; Heyman, 2013; Lewis, 2017).
2. Concerns about stigma and learned helplessness: Critics argue that framing addiction as a “*chronic brain disease*” risks reinforcing pessimism by suggesting that individuals are “ill and always will be”, potentially fostering feelings of helplessness and external attribution of control.
3. Limited efficacy of neurobiological treatments: Given that most neurobiological interventions (such as pharmacotherapies or neuromodulation) have not consistently produced robust or lasting remission, critics contend that focusing primarily on the brain may be overly reductionist and insufficient for addressing addiction (BDMA’s “*neurocentrism*”).
4. Neuroplasticity is not unique to addiction: The neurobiological changes observed in people with SUDs resemble forms of neuroplasticity that naturally occur

¹¹ A non-pharmacological treatment for SUDs using monetary rewards to help patients achieve target behaviors such as abstinence (Shirazi et al., 2025)

through learning and personal development, raising questions about whether these changes should be pathologized.

5. Insufficient attention to reasons for use: Critics argue that the BDMA does not adequately account for the psychological or contextual reasons that lead individuals to use substances in the first place (e.g., coping with anxiety, depression, or trauma) (Satel & Lilienfeld, 2014); echoing the self-medication hypothesis (Khantzian, 1997).

Let us briefly sum up the debate between pro-BDMA researchers and the “opposing team” of “pro-disorder of choice” (based on an interesting debate between Nora Volkow and Marc Lewis in Amsterdam, (Drug Policy Week, 2018)). While the former group of researchers (such as Dr. Nora Volkow) have long argued that addiction is a chronic brain disease, using the term “disease” due to the negative consequences of addiction on daily life, the latter group (as nicely represented by Dr. Marc Lewis) argue that “*a bad habit*” would better suit the condition of addiction (and would better serve the people suffering from addiction). Regarding the debate on the “*chronic*” part, BDMA scientists have since loosened up a little their definition by acknowledging that the brain can recover to some extent (but it is still a long-lasting condition in many cases). While the BDMA has faced substantial criticism in recent years (Blithikioti et al., 2025; Heather et al., 2018), it remains widely endorsed within the neuroscience community of addiction research, and certain critiques have recently been incorporated into revised formulations (Heilig et al., 2021). Moreover, BDMA accounts for the paradox central to addiction (*i.e. desiring things that are harmful to our well-being or conscious goals*), a concept closely linked to the phenomenon of *akrasia*¹² (Kraut, 2022) ; or as framed by Satel and Lilienfeld: “*how can the capacity of choice co-exist with self-destructiveness?*” (Satel & Lilienfeld, 2014).

In practice, most critiques addressed to either side of the debate rarely invalidate the alternative view entirely, and an intermediate perspective is likely the most appropriate. This view has recently been articulated, calling it a “*plea for non-competing theories of addiction*” (Epstein, 2020). This paper argues against the consideration that support for one theory is evidence against other theoretical frameworks and considers that many addiction theories can be true (in some circumstances, some individuals, to

¹² In Greek, literally: “*lack of mastery*”

some extent) (Epstein, 2020). Indeed, findings converging with one theoretical point of view does not mean this theory can account for “*addiction as a whole*” and does not impede that the “opposing” theory has some validity too. In short, no single theoretical framework can fully account for the multifaceted nature of addiction.

There are several compelling arguments both for and against these two perspectives, as discussed elsewhere (Hogarth, 2020; Wiers et al., 2025). In the present work, we do not dwell on semantic debates (e.g., is “*chronic brain disease*” the most appropriate label or not?) or the precise definitions of the processes involved in addiction. Likewise, we do not take a position on competing theoretical accounts concerning “*free will*” or the extent to which neurological alterations shape behavior. Instead, we simply adopt the basic premises of Robinson and Berridge’s framework, namely that a number of processes involved in problematic substance use and addiction can occur largely outside individuals’ conscious awareness, are difficult to regulate, and contribute to the maintenance of addictive behavior as well as relapse (theorized under the “Incentive Sensitization Theory (IST) of Addiction” (T. E. Robinson & Berridge, 1993)). Importantly, this perspective does not imply that individuals are entirely devoid of free will. The present work focuses specifically on the IST as it was the first, and the most influential to explicitly highlight the central role of excessive motivational processes and the powerful influence of cues on behavior (T. E. Robinson & Berridge, 1993). But first, let’s have a quick overlook of other historical theories of addiction.

A Quick Look at Major Competing Addiction Theories

Globally, within the broad BDMA, addiction has been historically theorized according to three major visions:

- 1) **The Incentive Sensitization Theory (IST)** (T. E. Robinson & Berridge, 1993, 2016, 2025) posits that addiction results from excessive, aberrant motivational states (i.e., excessive *wanting*), which are a direct consequence of neurobiological changes induced by repeated exposure to psychoactive substances (mostly due to their effects on the brain’s dopaminergic reward systems). This theory will be examined in more detail in the next section.
- 2) **Habit Theory** states that addiction is driven by compulsive habits that form after repeated substance consumption. According to its proponents, over time, voluntary

goal-directed actions are transformed into rigid habits (i.e. compulsive drug-seeking), insensitive to reward devaluation¹³ (Everitt et al., 2001; Everitt & Robbins, 2005, 2016). The neurobiological process proposed to underly this shift is a passage from prefrontal cortical to striatal control over drug-seeking, and a progression from the ventral to the dorsal striatum (Everitt & Robbins, 2005). Compulsive drug-seeking has been theorized to account for impairments of executive control, and an imbalance between neural systems that underly habitual behavior compared to goal-directed behavior systems (Lüscher et al., 2020). While the formation of automatized actions has long been proposed (Tiffany, 1990), several authors nowadays challenge the habit-theory of addiction, arguing that it fails to explain phenomena such as cue-triggered excessive cravings as well as the resourcefulness and flexibility that people suffering from SUDs can display for procuring drugs (M. J. F. Robinson et al., 2022; T. E. Robinson & Berridge, 2025). As nicely put by Heinz and colleagues: *"Individuals with drug addiction are neither automatons that carry out habitual behavior without cognitive control nor are they just individuals with bad choices."* (2024, p.3).

- 3) **Opponent Process (or Allostasis) Theory** suggests that, while substances are first consumed for their pleasurable effects, after prolonged use, an *"opponent"* process counteracts the drug's pharmacological effects (leading to tolerance). Consequently, individuals consume more drugs to avoid the negative effects of withdrawal (Koob & Le Moal, 1997). This theory posits that the primary motivational mechanism underlying drug use is the avoidance of aversive withdrawal symptoms and other distress feelings, a process sustained through negative reinforcement (Koob, 2021). Scientists from competing theories have yet stated that while withdrawal could indeed be a motivation to consume, *it is "neither necessary nor sufficient for inducing compulsive addiction or relapse."* (T. E. Robinson & Berridge, 2025, p.4.8). Later on, building on their initial opponent-process theory, Koob and Volkow formalized a more comprehensive model of addiction (the *"Three-stage Model"*, Koob & Volkow, 2016), incorporating some aspects of habit theory as well as IST. This model is often

¹³ Habits have been characterized as forms of behavior that are rigidly cued by context, enacted independently of conscious goals or intentions, and largely unaffected by outcome devaluation (Keramati et al., 2011; Wood & Neal, 2009).

considered the predominant biomedical model of addiction (Koob, et al., 2019; Koob & Volkow, 2016).

Focus on the IST: Addiction as a State of Aberrant Motivation

The essence of Robinson and Berridge's IST is the observation that after prolonged substance use, meso-cortico-limbic dopamine pathways (more specifically mesolimbic projections to the NAcc, Flagel et al., 2011; T. E. Robinson & Flagel, 2009) become *sensitized* (in vulnerable individuals and under particular circumstances, T. E. Robinson & Berridge, 2008, 1993). This effect is called *incentive sensitization* because it acts on the process that attributes incentive salience to cues (cues become highly *wanted*, they attract attention disproportionately). Through this hypersensitive process, neutral cues are transformed into potent *incentive cues* (portraying the three properties explained above), which exert a powerful (and difficult to resist) influence on behavior. Importantly, sensitization has been shown to be long-lasting, even after prolonged periods of abstinence, which has been interpreted by Berridge and Robinson to account for high relapse rates observed in substance users even long after withdrawal (Berridge & Robinson, 2003; T. E. Robinson & Berridge, 1993, 2001, 2003, 2008, 2016). Unlike "normal" incentive motivation (which fluctuate according to physiological states, e.g., food cues lose their motivational power once hunger is satisfied), sensitized "*wanting*" is proposed to be persistent and largely non-reversible (T. E. Robinson & Berridge, 1993).

"Wanting" relies on the mesolimbic dopamine system, which involves the midbrain, the NAcc (and other parts of the striatum), the amygdala, and the prefrontal neocortex (Berridge & Robinson, 2003; Berridge et al., 2009). In contrast, "*liking*" originates from a more limited brain regions (hedonic "*hotspots*") within the NAcc and the ventral pallidum (Castro & Berridge, 2014a; Berridge & Robinson, 2003, see Castro & Berridge, 2014b for a review of neural substrates of "*liking*" and "*wanting*"). Since "*wanting*" and "*liking*" are dissociable neural processes and the former is more extensively coded by dopamine than the latter, increases in "*wanting*" via drug-induced sensitization do not affect "*liking*" (T. E. Robinson and Berridge, 2008). This asymmetry explains well why people continue to consume addictive substances despite experiencing less and less pleasure associated with it (tolerance of hedonic effects). T. E. Robinson and Berridge (1993, 2025) argue that pleasure might play a role in initial substance consumption, but it has quite a negligible role in addiction.

In their latest comprehensive update on the IST of addiction, T. E. Robinson and Berridge (2025) clarify that the IST does not deny the role of pleasure, habits or withdrawal. Also, they acknowledge that initial consumption motives (e.g., fit in socially, reduce anxiety, etc.) can play a significant role for drug use in some individuals, and that many people are able to quit consuming when they choose to, thus directly addressing common critiques put forward by BDMA opponents. Robinson and Berridge now also specify that robust incentive sensitization does only develop in a subset of (vulnerable) individuals, as it accounts for cases where addiction has become "*compulsive*" (in the sense of continued drug use in spite of negative consequences and a true desire to stop) (T. E. Robinson & Berridge, 2025). This echoes previous theoretical proposals such as the one by Fenton & Wiers (2017), suggesting an intermediate model between BDMA and choice-models. They suggest that severe cases of addiction can be well explained by the BDMA framework (i.e., long-lasting brain modifications), while most instances are better explained by a "*disorder of choice*" model where self-control (or "*free-will*") is intact and people can change if they are sufficiently motivated to. In the same vein, Heilig and colleagues (2021) have also recently acknowledged that people can adapt their behavior in response to incentives (as seen in contingency management). They also suggest that "*addiction as a brain disease*" and "*addiction as a disorder of choice*" are complementary perspectives. In this newly proposed perspective, addiction reflects pathological choice preferences (biased toward immediate drug reinforcement, insensitive to costs, and unstable over time), resulting from brain adaptations that severely constrain, but do not eliminate, choice capacity, which nicely aligns with major tenets of the IST.

Another major theoretical account (one that does not formally position itself within the BDMA framework yet remains highly relevant to the core principles of IST) are Dual-Process theories of addiction (Bickel et al., 2016; Lindgren et al., 2019; McClure & Bickel, 2014; Stacy & Wiers, 2010; Wiers & Stacy, 2006). These models propose that addiction arises from an imbalance between two cognitive systems, consistent with Kahneman's distinction between System 1 and System 2 (Kahneman, 2011). The first is a fast, associative, reflexive (bottom-up) system, while the second is a slower, deliberative, reflective (top-down) system. According to this framework, addiction and relapse emerge through the interaction of a hyperactive System 1, characterized by heightened (one could say "*sensitized*") *cue reactivity* (e.g., automatic approach tendencies and attentional

biases) and a hypoactive System 2, which concurrently impairs the capacity to exert cognitive control over these impulsive tendencies.

This theoretical perspective is conceptually compatible with IST, as the overactivation of the impulsive system can be understood as the behavioral expression of aberrant motivational states driven by drug-induced sensitization of dopamine pathways and long-term alterations in cortical functioning. As a useful complement to IST, dual-process models provide a broader lens by explicitly incorporating not only exaggerated bottom-up reactivity but also deficits in top-down regulatory control.

As a brief illustration of how System 1 processing (impulsive and automatic) connects to incentive salience, consider the following scenario¹⁴. Imagine you enter a supermarket intending to buy bananas. This intention reflects a top-down, goal-directed process guided by System 2, which should, in principle, lead you efficiently to your target. However, as you walk through the aisles, your attention is involuntarily captured by the logo of your favorite drink (despite it being irrelevant to your current goal). If you later find yourself purchasing the drink instead of (or in addition to) the bananas, this shift in behavior reflects the influence of System 1. From the perspective of the IST, the interpretation is that the logo has acquired incentive salience, effectively functioning as a motivational magnet. As a result, the associated behavior (buying the drink) becomes more impulsive and automatically suggested, overriding your original goal.

This example again illustrates how theoretical frameworks emerging from different traditions can, in fact, fit together remarkably well.

On Cue Reactivity, and Automatic, Cue-Triggered Behavior

According to the IST account, through incentive sensitization, individuals with SUDs are more likely to instill incentive motivational properties onto a drug cue, converting it into an incentive stimulus that takes hold of their attention and becomes irresistible (Berridge, 2000). So, central tenets of the IST of addiction are that drug cues will: (1) attract attention, and induce approach behaviors, and (2) lead to significant levels of (drug and cue) “wanting”. These phenomena relate to what is globally called *cue reactivity*, which should be heightened with repeated consumption (i.e., an overactivation of the impulsive system within Dual-Process Models).

¹⁴ Inspired by the “Bob” example in Le Pelley et al. (2024).

On a behavioral level in animal models, direct experimental evidence for incentive sensitization comes from studies showing that past drug treatment facilitates all three features of incentive stimuli (T. E. Robinson & Berridge, 2008): PCA (as indexed by *sign-tracking*, e.g., T. E. Robinson & Flagel, 2009); PIT (e.g., LeBlanc et al., 2013; Shiflett et al., 2013; Wyvell & Berridge, 2001); and conditioned reinforcement (e.g., Taylor & Horger, 1999; Di Ciano, 2008). At a neural level, heightened activation of mesolimbic structures (that encode incentive value of reward stimuli) have been reported following drug exposure (Tindell et al., 2005).

In people also, extensive evidence shows that exposure to alcohol-related conditioned stimuli (cue-exposure paradigms) reliably elicits subjective craving as well as alcohol cue-elicited neural reactivity in individuals with AUD¹⁵ (Carter & Tiffany, 1999; Schacht et al., 2013; Witteman et al., 2015). Increased craving and physiological reactivity to alcohol cues have been documented in non-treatment-seeking heavy drinkers, treatment-enrolled patients, and even abstinent individuals with AUD (Bordnick et al., 2008; Papachristou et al., 2014; Sinha et al., 2011; Witteman et al., 2015). Specific neuronal responses have also been reported in response to alcohol cues in AUD patients compared to controls (Almeida-Antunes et al., 2022; Schacht et al., 2013; Tan et al., 2023; Zeng et al., 2021). These responses can be related to subsequent alcohol use or relapse (Courtney et al., 2016; Miranda Jr. et al., 2020; Vafaie & Kober, 2022), although other studies failed to show such predictive relationships (Witteman et al., 2015).

Attentional and Approach biases

Along craving and neuro-physiological responses, another behavioral output related to incentive salience attribution in general (but also to incentive sensitization) is the phenomenon of *attentional bias* (AB). It refers to the preferential and automatic allocation of attention to specific cues (in this case “drug cues”) (see Field & Cox, 2008 for an initial review).

As illustrated in earlier sections (through mechanisms such as PCA, PIT, or “*reward selection history*”), reward-related cues can attract attention and energize behavior in non-pathological contexts. However, these processes are theorized to become strong, automatic tendencies in people suffering from SUDs, contributing to maintenance of

¹⁵ Although cue-reactivity can differ between treatment seeking and non-treatment seeking individuals with AUD (Venagas & Ray, 2020).

consumption and relapse (Field & Cox, 2008). A mutually reinforcing relationship between craving and AB has been proposed as a potential explanatory mechanism (Bollen et al., 2020; Field et al., 2009; Field & Cox, 2008, although the role of AB has been downplayed a little recently Field et al., 2016, suggesting that AB is not a long-lasting and stable feature). A quite similar phenomenon of an *automatic capture of attention* was delineated previously through the concept of VMAC. As mentioned earlier, prioritization of reward-related cues (such as evidenced in VMAC studies and theorized in the incentive salience hypothesis) has been proposed to reflect an evolutionarily adaptive process in which an organism's history of reward learning shapes the automatic allocation of attention toward stimuli that previously signaled survival-relevant outcomes. In SUDs, however, the same mechanisms can become dysregulated, causing substance-associated cues to dominate behavior even when they never serve adaptive purposes. Even though these phenomena did not originate in the same area of research (motivational vs cognitive/attentional), they actually have proposed quite closely overlapping interpretations of the underlying mechanism of addiction (Le Pelley et al., 2024). Pearson and colleagues (2022) proposed that *"addictive behaviors represent pathological prioritization of reward-related stimuli"* (p.321). This conceptualization aligns closely with the one proposed by the IST. There is thus a link between AB in addiction, and *"naturally occurring"* biases toward reward-relevant cues (such as evidenced in VMAC or PCA to reward cues): substance-related ABs might be the *"sensitized"* version of such mechanisms through repeated substance use.

In addiction research, Abs are traditionally measured through computerized reaction-time tasks such as the Stroop Test or Visual Probe Task (e.g. Pennington et al., 2019; Vollstädt-Klein et al., 2012). However, these methods have been increasingly criticized for their poor internal consistency and limited reliability (Bollen et al., 2022; Field et al., 2016). More *"direct"* techniques based on eye-tracking have emerged, showing ABs not only in heavy drinkers but also in social drinkers, students, and adolescents (Bollen et al., 2020; Ceballos et al., 2009; McGivern et al., 2021; Roy-Charland et al., 2017; Simon et al., 2022). In parallel, more *ecologically valid* paradigms have been introduced¹⁶, such as

¹⁶ In the same vein of using more *"natural"* stimuli in AB tasks, Wiechert et al. (2021) recently introduced a novel dual-probe task that presents competing alcohol-related and neutral advert streams, offering a more reliable attentional-bias measure with excellent internal consistency and meaningful associations with both laboratory and habitual drinking behavior.

so-called “free-viewing” tasks (which do not request participants to pay attention to the cues, McAteer et al., 2018; Soleymani et al., 2020). These have been suggested to be more reliable (Bollen et al., 2022). Evidence at the level of early attentional encoding also suggests that alcohol cues may hold a privileged attentional status for heavy drinkers, who process them more efficiently (Tibboel et al., 2010).

While the IST of addiction seems to point to stable long-lasting effects of sensitization on cue-processing (as indexed through processes such as AB), research has actually shown that AB for alcohol stimuli is not stable, but rather dynamic, fluctuating with factors such as craving state (Bollen et al., 2020), in vivo alcohol exposure (Ramirez et al., 2015), and immediate alcohol expectancies (in social light drinkers, see Field, Hogarth, et al., 2011). Among individuals with AUD, findings are mixed: some studies report attentional disengagement from alcohol cues or even avoidance biases in patients with more severe AUD (Bollen et al., 2021, 2025), and several studies fail to find a robust relationship between AB and drinking severity (Seth et al., 2025; see also Bollen et al.’s systematic review, 2022). Conversely, in subclinical populations (such as heavy, binge, or at-risk social drinkers), AB and its association with drinking severity tend to emerge more consistently (Bollen et al., 2022; e.g. Albery et al., 2015; Luehrig-Jones et al., 2017; Pennington et al., 2020). The clinical relevance of AB also remains debated. While some studies suggest that heightened AB may predict relapse risk (Garland et al., 2012), others report no such association (Snelleman et al., 2015). Another intriguing finding of Bollen et al.’s systematic review (also see Mauraage et al., 2021) was that AB does not appear to be automatic¹⁷ (i.e., not evidenced in early stages of attentional processing contrary to what was expected based on its supposedly “unconscious” origin), but rather arising during later, controlled stages of attention (Bollen et al., 2022, 2025; McAteer et al., 2015). Finally, some evidence suggests a broader AB toward appetitive cues in heavy drinkers, possibly reflecting a spillover of incentive salience from alcohol stimuli to other rewarding stimuli (Bollen et al., 2020; Pennington et al., 2019).

Similar to AB, another cognitive bias relevant to addiction is *approach bias* (ApB) (i.e. implicit motivational tendencies that reflect the extent to which individuals are automatically inclined to move toward alcohol (or drug)-related cues). Numerous studies

¹⁷ This has also been recently shown experimentally (Fuchs-Leitner et al., 2026), although this study used reaction-time based measures within a Dot-Probe task, which have been suggested to have poor reliability (Ataya et al., 2012).

have shown that stronger drug-approach biases are associated with higher levels of substance use (Watson et al., 2012 for a review). Approach tendencies have for instance been observed in heavy (but non-clinical) alcohol users (Wiers et al., 2009, 2010), social drinkers (Field et al., 2005b), and cigarette smokers (Field et al., 2005a; Thewissen et al., 2007). Hazardous drinkers can also display stronger ApB than light drinkers (Field, Caren, et al., 2011).

From an applied perspective, both AB and ApB modification techniques have gained attention as interventions designed to retrain these automatic processes, with several studies reporting promising outcomes (Rinck et al., 2018; Schoenmakers et al., 2010; Wiers et al., 2010, 2011), while ApB modification currently has the strongest empirical support as a potentially valuable adjunct to AUD treatment (Wiers et al., 2025). By repeatedly training avoidance movements away from alcohol cues, ApB modification is thought to reduce relapse risk and reshape underlying motivational processes. Supporting this view, Eberl et al. (2012) reported that ApB modification led to stronger avoidance tendencies and significantly lower relapse rates at one-year follow-up, with changes in ApB mediating treatment effects. Comparable benefits have been observed for smoking cessation (Garey et al., 2024). However, findings are not uniformly consistent. Some studies report reductions in drinking or relapse without corresponding shifts in ApB (Di Lemma & Field, 2017; Rinck et al., 2018), raising questions about the exact mechanisms through which these interventions exert their effects. Similarly, recent work on AB modification indicates that pairing bias-modification with cognitive behavioral therapy (CBT) does not necessarily enhance efficacy: Amano et al. (2025) found no added benefit of AB modification + CBT over CBT alone in reducing relapse risk or cravings in male patients with AUD. Together, these results highlight both the promise and the complexity of bias-modification approaches. Moreover, a systematic review on alcohol AB literature stated that studies are highly heterogeneous and several recommendations should be addressed to enhance the reliability of findings (see Bollen et al., 2022, i.e. using standardized stimuli and questionnaires, appropriate sample sizes, etc.).

Individual Differences in Addiction Vulnerability

Although many individuals are exposed to psychoactive substances (Volkow et al., 2021), only a minority ultimately develop a diagnosable substance use disorder (Anthony et al., 1994; Gowing et al., 2015; F. A. Wagner & Anthony 2002). For most substances,

only about 15% of users transition from recreational use to addiction (Anthony et al., 1994). This pattern is not unique to humans. Experimental studies in animal models have similarly demonstrated that addiction-like behavior emerges in only a small subset of individuals exposed to drugs such as cocaine (Ahmed, 2010, 2012; Deroche Gamonet et al., 2004).

A central aim of addiction neuroscience is therefore to understand why some individuals maintain occasional, non-problematic substance use while others develop persistent patterns of compulsive consumption. Research increasingly focuses on the cellular and molecular mechanisms underlying the transition from controlled drug use to the loss of behavioral control over drug seeking and drug taking that characterizes chronic addiction (Koob & Volkow, 2016). A large body of work has consequently examined individual differences that contribute to addiction vulnerability.

Vulnerability to SUD arises from interactions among genetic, biological, developmental, and psychological factors. Genetic influences account for approximately 40-60% of the risk for developing SUDs (Uhl et al. 1993; Volkow & Blanco 2023)¹⁸. Genome-wide association studies have identified both risk and protective variants, with some of the strongest protective effects linked to genes involved in alcohol metabolism. Some of these variants accelerate the conversion of ethanol into acetaldehyde, producing aversive physiological responses that reduce the likelihood of heavy drinking (Crabb et al., 2004; Quertemont, 2004).

Another critical factor, partly shaped by genetic influences, is the individual variation in subjective responses to alcohol. People differ in their sensitivity to alcohol's stimulating, rewarding, sedative, and unpleasant effects (de Wit et al. 1989; Duka et al. 1998). The *"low level of response hypothesis"* proposes that reduced sensitivity to alcohol's sedative and dysphoric effects increases the risk of AUD (Schuckit, 1994; Schuckit & Smith 1996, 2000; Schuckit et al., 2011). Consistent with this hypothesis, stronger unpleasant responses to alcohol are associated with lower subsequent drinking levels (Ray et al. 2009). A dual-risk model has thus been proposed, in which vulnerability reflects both reduced sensitivity to sedative effects and heightened sensitivity to alcohol's stimulating and rewarding properties. Supporting this view, heavy drinkers show

¹⁸ Although Single Nucleotide Polymorphism-based heritability estimates are lower (5-10%), indicating a highly polygenic profile (Zhou et al. 2020).

enhanced stimulant responses and blunted sedative and cortisol responses to alcohol, patterns that predict future binge drinking (A. C. King et al., 2011). Evidence also suggests that low alcohol sensitivity may be associated with greater attribution of incentive salience to alcohol-related cues (Cofresí, Kohen, et al., 2022).

Developmental and environmental factors further influence AUD risk. Early initiation of alcohol use significantly increases the likelihood of developing alcohol-related problems later in life (Volkow et al., 2021), likely reflecting heightened reward sensitivity and the ongoing maturation of cognitive control systems during adolescence. Exposure to adverse childhood experiences (ACEs) also represents a major risk factor. Longitudinal research indicates that individuals exposed to three or more ACEs have approximately three times higher odds of alcohol dependence compared with those reporting no ACEs, with disruptions in parent and peer relationships partially mediating this association (Mongan et al., 2025).

Personality traits also contribute to addiction vulnerability. In particular, impulsivity has consistently been identified as a robust predictor of SUDs (for a review see Verdejo-Garcia & Albein-Urios, 2021). Similarly, traits such as novelty seeking and sensation seeking have been suggested to play a causal role in the initiation and escalation of substance use (Foulds et al., 2017).

Among the behavioral factors associated with addiction vulnerability, individual differences in sensitivity to conditioned reward cues have received increasing attention. Indeed, individuals do not respond equally to cues that predict rewards or substance availability. Variability in cue responsivity has been documented across several research traditions discussed earlier in this chapter. In the incentive salience literature, for example, studies of *sign-tracking* behavior in animals have demonstrated that individuals differ in their tendency to attribute motivational value to reward-predictive cues. Similarly, research in the human attentional selection literature (particularly on reward-driven attentional capture and reward-selection history) has shown that individuals vary in the extent to which reward-associated stimuli automatically attract attention.

Within the framework of IST, repeated substance use is proposed to enhance the motivational salience of drug-related cues. As a result, individuals with heavier patterns of consumption are expected to develop stronger ABs toward substance-relevant conditioned stimuli. As mentioned earlier, empirical studies have provided some support for this prediction, demonstrating increased AB toward alcohol-related cues in heavy

drinkers (e.g., Pennington et al., 2020; Simon et al., 2020), although several inconsistent findings have also been reported (Bollen et al., 2022, 2025; Field et al., 2016). Moreover, AB is not entirely stable and can fluctuate as a function of situational and motivational factors such as craving or priming (e.g., Bollen et al., 2022). These findings suggest that AB may reflect both state-dependent processes linked to current motivational states and trait-like tendencies that develop through repeated substance use.

Beyond these state and trait aspects of AB (i.e. increased AB as a “trait” following repeated substance exposure and state-dependent fluctuations of AB depending on craving, priming, etc.), a third possibility has been proposed: pre-existing individual differences in sensitivity to conditioned cues may themselves contribute to addiction vulnerability. A growing body of evidence suggests that some individuals are inherently more prone to attribute motivational value to reward-predictive stimuli, a tendency that has been linked to increased risk for addictive behaviors (Albertella et al., 2021; Flagel et al., 2008; Watson et al., 2024; for reviews see Anselme & Robinson, 2020; Felix & Flagel, 2024; Flagel et al., 2009; Le Pelley et al., 2024; A. L. Pearce et al., 2022). Such cue-reactive phenotypes may therefore represent an important behavioral pathway through which vulnerability to substance use disorders emerges. Because the present thesis specifically focuses on these behavioral and attentional individual differences (particularly the distinction between sign-tracking and goal-tracking phenotypes) a more detailed discussion of this literature is provided in Chapter 3. The present section serves only to situate cue sensitivity within the broader framework of addiction vulnerability.

The Role of Animal Research in the Development of Addiction Theories

A substantial proportion of the empirical findings and theoretical frameworks discussed in the preceding sections originate from animal research. Experimental studies in animals have played a central role in advancing knowledge about the motivational processes underlying reward seeking, the neurobiological mechanisms of addiction, and vulnerability factors such as genetic predispositions and cue reactivity. For example, foundational concepts within the BDMA framework (e.g. the distinction between “liking” and “wanting” proposed in the IST) were largely developed through animal studies. Similarly, behavioral phenomena such as incentive salience attribution and sign-tracking were initially characterized in animal models before being investigated in humans.

Distinctions between major theoretical perspectives on addiction often mirror differences in their primary sources of empirical evidence. As outlined earlier in this chapter, one key conceptual divide contrasts proponents of the *BDMA* and advocates of *disorder-of-choice* perspectives. To some extent, this distinction parallels the methodological split between frameworks grounded predominantly in human observational and clinical research versus those emerging from controlled experimental work in animal models.

For instance, theories that rely heavily on human observational data (such as the *disorder-of-choice* framework, (Hyman, 2009, cited in Kurti & Dallery, 2012; Lewis, 2017) typically emphasize voluntary decision-making processes, goal-directed choice, or initial motivation to consume as central to substance use. In contrast, several influential neurobehavioral theories of addiction were initially developed within animal research paradigms, including opponent process theory (Koob & Le Moal, 1997) and IST (T. E. Robinson & Berridge, 1993). Importantly, however, such clear-cut distinctions between theoretical camps are increasingly difficult to maintain. As already illustrated, contemporary models of addiction tend to integrate elements from multiple traditions (neurobiological, psychological, and socio-cultural) into more comprehensive and multidimensional accounts (Heilig et al., 2021; T. E. Robinson & Berridge, 2025; Wiers, 2025).

Despite the major contributions of animal research to addiction science, the use of animal models has also been the subject of ongoing debate. Critics have questioned both the validity and the translational relevance of findings obtained in laboratory animals. While some criticisms stem from ethical or ideological concerns, others highlight methodological challenges that have received increasing attention within the scientific community. Among these are issues related to translational failure, where findings obtained in animal studies do not consistently generalize to humans, as well as broader concerns regarding reproducibility and robustness across experimental contexts. Addressing these challenges has become a key priority in contemporary addiction research, with ongoing efforts aimed at improving experimental rigor and enhancing the translational value of preclinical models (Spanagel, 2017, 2022).

The present work is directly situated within this translational perspective. Specifically, this thesis aims to adapt and translate a behavioral paradigm originally developed in animal research to the study of human behavior. Consequently, evaluating

the role and limitations of animal models in addiction research is essential for contextualizing the current work. Accordingly, the following chapter addresses several core issues central to translational research, including the definition of a scientific model, the importance of translational value, and questions of validity. It further reviews the principal arguments both supporting and challenging the use of animal models in addiction research, as well as the broader challenges inherent to translational approaches that aim to bridge findings across animal and human studies. Particular emphasis will be placed on the field of cue reactivity, where multiple behavioral phenomena first identified in animal models have demonstrated striking and robust parallels in human research.

Chapter Summary

- Reward processes play a central role in directing and energizing behavior.
- Berridge and Robinson's concept of incentive motivation describes a dopamine-dependent "wanting" that emerges from incentive salience and drives approach and reward consumption.
- Through Pavlovian reward learning, neutral cues can acquire incentive value, gaining a strong ability to pull behavior, motivate actions, and bias decision-making.
- Selective attention studies echo this effect: reward-related cues reliably capture attention, reflecting processes thought to be evolutionarily adaptive.
- Many addiction theories recognize incentive stimuli as playing a major role in drug seeking and relapse. Extensive animal and human research shows that drug-paired cues rapidly acquire incentive properties that sustain and reinstate drug-seeking behavior and cue-reactivity.
- Among the factors contributing to addiction vulnerability, individual differences in cue-sensitivity have been repeatedly highlighted.
- While many of these insights stem from animal models, systematic translation and back-translation studies are now a priority to ensure that experimental findings meaningfully inform human addiction research.

Chapter 2

Of Mice & Men: Translational Addiction Research

Modeling Human Addiction Based on Animal
Models



“Questioning the utility of animal models is not specific to addiction, but concerns most animal models of higher brain functions and dysfunctions. Such debate is needed and stimulates progress towards translation.”

— Véronique Deroche-Gamonet, The Relevance
of Animal Models of Addiction

Introduction

At first glance, it may seem counterintuitive (perhaps even surprising) to non-expert readers that many of today’s dominant theories of addiction originate not from clinical observations, but from preclinical research carried out in animals. After all, addictive behaviors in humans often involve complex social and psychological dimensions that have no direct equivalent in the natural behavior of laboratory animals. And, to the best of our knowledge, there are no naturally occurring binge-drinking rats or gambling raccoons in nature. Yet animal models have repeatedly demonstrated their value in clarifying the underlying mechanisms of addiction and in shaping the conceptual frameworks that drive the field forward.

An interesting anecdote shared by Rainer Spanagel during the 2025 RSA (Research Society on Alcohol) Congress in New Orleans (Spanagel, 2025) nicely illustrates how animal models can prove to be crucial for refining and evaluating clinical approaches in the field of addiction. In the 1990s, a procedure known as *ultra-rapid opioid detoxification* was developed, combining opioid antagonists (such as naloxone or naltrexone) with general anesthesia. Early clinical reports suggested that this method could suppress withdrawal symptoms entirely by inducing detoxification while the patient was unconscious. Although these findings generated considerable enthusiasm, others (including Spanagel) remained skeptical. He emphasized that the pharmacological mechanisms underlying the procedure were poorly understood and that the human clinical studies reported to date involved only small patient samples (Spanagel, 1999; Spanagel et al., 1998). When his team subsequently attempted to translate this procedure to animal models, the outcomes proved strikingly different. In rodents, administration of opioid antagonists under anesthesia not only failed to alleviate withdrawal but instead

intensified and prolonged withdrawal symptoms¹⁹ (Spanagel et al., 1998). These preclinical findings underscored the need for rigorously controlled clinical trials before the widespread adoption of this approach in routine medical practice.

In this case, preclinical research played a decisive role in revealing the potential risks and limitations of what had initially appeared to be a promising clinical intervention, ultimately contributing to the reconsideration and decline of the procedure. Although such clear-cut examples are exceptional, they serve as a useful reminder that preclinical and translational research can meaningfully influence the development and evaluation of clinical approaches to addiction.

Scope of the Chapter

The first part of this chapter aims to situate animal research within its broader scientific context. To ground the discussion, this chapter begins by addressing several foundational questions, including the definition of a scientific model, its purpose, and the importance of translational value. It then examines core issues such as face validity, the specific contributions of animal models, and, critically, what aspects of addiction these models can and should represent. These questions are far from trivial. Even among experts, there is no universally accepted consensus on the key mechanisms that underly addiction, and accordingly, the target of modeling remains unclear. Common critiques and challenges will be addressed, all while highlighting the continued relevance and contributions of animal models to our theoretical understanding.

The second part of the chapter will turn toward the phenomenon of *cue reactivity* (in a broad sense). As outlined in the previous chapter, cue reactivity has been proposed as a central feature of addiction in general, and of alcohol use disorder (AUD) in particular. This section will review some key findings that highlight striking translational parallels between human and animal studies, illustrating how cue-driven processes can be successfully investigated across species. Finally, the chapter will conclude by briefly discussing several conceptual and methodological challenges that continue to shape translational addiction research and by outlining a number of considerations and recommendations for future work.

¹⁹ As measured through body weight loss, diarrhea, writhing, teeth chattering and wet dog shakes (Spanagel et al., 1999).

Animal Models in Addiction Research

Defining Models and Their Function

What does it exactly mean to talk about animal models in addiction research? In everyday language, we could define a *model* as something that represents or simulates something else, by mimicking its key characteristics. In general, scientific modelling can be linked to *"a desire to understand, predict, and control life beyond the laboratory"* (Boddez et al., 2023, p.3). Scientific models are the centerpieces of the scientific method, allowing researchers to construct, test, and refine our understanding of the world (Gerlee & Lundh, 2016b).

There is no true meaningful definition of what a scientific model is, since models do not belong to a distinctive ontological category and anything can be a model (Frigg & Hartmann, 2024). There exists a plethora of models, which can be theoretical (mathematical, cognitive, economical, etc.) or physical (live tissues, or living beings), and scientists from different domains might give slightly different definitions of what models are. However, what emerges from the definitions provided by several interviewed scientists across domains is a shared understanding that a model *"describes/represents/reflects a limited part of reality. The goal of a model is (by being a simplified description) to create understanding of a phenomenon, but it is also used in order to make predictions"* (Gerlee & Lundh, 2016a, p.57). In other words, models allow us to grasp aspects of reality that are otherwise complex and difficult to comprehend, implying that they are inevitably incomplete and, in that sense, always wrong (Gerlee & Lundh, 2016b).

Given that nearly anything can function as a model (and that entities considered models in one context may be used otherwise in another), it is important to specify what qualifies something as a model. To this end, the two defining criteria established by Boddez and colleagues (2023) are very useful. According to them, a model is being used (1) when the researchers invoke a target phenomenon that is different from the model. For instance, in a commonly known behavioral test in animal research, the Elevated-Plus-Maze (EPM), the researcher measures the tendency of a rodent to stay in safe spaces on an elevated platform (in a "+" shape, with two open arms and two closed) in order to represent (or *model*) human anxiety. As mentioned earlier, a model is thus, per definition,

imperfect in that it does not entirely represent the target phenomenon. The second defining criterion is that (2) the model allows us to gain information about the target phenomenon (making it a *research model*, Boddez et al., 2023). Taking the EPM example again, by administering an anxiolytic substance and observing the effects on the rodent's tendency to stay safe vs. to explore the edges of the platform, the researchers may gain some insight into the drug's potential anxiolytic effects for actual patients suffering from anxiety disorders. This echoes well what Gerlee and Lundh (2016a) reported to be the purposes of models: creating knowledge, understanding and making predictions.

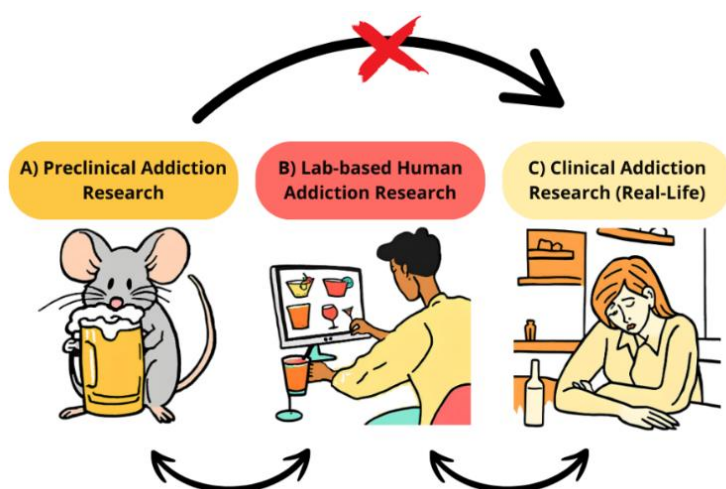
Another important point to mention is that a procedure that serves sometimes as a scientific model can sometimes be used as an experimental procedure (outside of the modelling context) or even become the focus of study itself. For example, the EPM is often used to compare mouse strains to measure baseline anxiety-like behavior. In this case, the procedure serves as a standardized test rather than a model of anxiety. Similarly, if researchers study how changes in lighting or maze design affect EPM performance, the test itself becomes the object of study. Thus, a model (or procedure) is not inherently a model by definition; its status as a model depends entirely on what its purpose is.

The Translational Path

One central aim of any model is to capture the target phenomenon as accurately as possible and to generate insights that are useful for addressing real-world problems. In this sense, a key criterion is its *translational value*—that is, the degree to which findings obtained from the model can be applied to the phenomenon it is intended to represent (Boddez et al., 2023). For animal models, the ideal scenario is that effects observed in the animal fully translate to humans. Figure 3 illustrates this idealized translational continuum linking findings from rodent models to human laboratory paradigms and, eventually, to human clinical experience (Stephens et al., 2013). In practice, however, such smooth translation is uncommon, and research often jumps directly from preclinical findings to clinical context (Figure 3. Path A→C). Yet, the strongest parallels between rodent models and human conditions typically emerge under highly controlled circumstances, such as those found in human laboratory studies (Figure 3. Path A→B) (Stephens et al., 2013). This means that “animal/human” translation is not a single leap but a sequential, multi-step process: findings must first generalize from the animal model to a human laboratory model, and only then to real-world clinical or behavioral contexts.

As Stephens and colleagues (2013, p. 634) note, *“in many cases, the link between the human laboratory findings and the real world is more tenuous, so that the human laboratory findings may be better viewed as analogous to the real-world situation”*. Translational steps involving clinical populations are therefore essential. They allow researchers to evaluate both the diagnostic and prospective validity of experimental paradigms—assessing the degree to which a behavioral model relates to, or can predict, symptoms or behaviors in realistic clinical settings (Lange et al., 2021). Unfortunately, this ideal triad (spanning animal models, human laboratory paradigms, and clinical realities) is often overlooked. Many animal-based studies make direct inferential leaps to real-world human conditions without sufficiently addressing the intermediate translational steps. Moreover, substantial translational failures occur at every level of this pathway. These shortcomings can partly be attributed to the broader reproducibility crisis in the behavioral and biomedical sciences (Spanagel, 2022), but they are also influenced by a range of additional conceptual, methodological, and practical factors (as discussed below).

Figure 3. *The Ideal Translational Path: The “Animal Model - Human Laboratory Model - Human Clinical Practice” Triad*



About Validity

Given that translation from animal models to human clinical phenomena is a multi-step and often imperfect process, assessing an experimental model's overall usefulness becomes far from straightforward. Even when a model aspires to high translational value, determining how to objectively evaluate its validity is a complex challenge. As noted earlier, models serve a dual purpose: they both represent existing knowledge about the world and function as tools to generate new knowledge. This dual role implies that the scientific strategies used to evaluate them inevitably incorporate a degree of subjectivity. As with many concepts in science, model validity can be approached from several perspectives. Detailing all of them is out of the scope of the present work, so here we will only consider what is commonly called *face validity* (i.e., the degree to which the model superficially resembles the target phenomenon) and *construct validity* (i.e., the extent to which the model truly captures the theoretical construct it is intended to).

While face validity is still frequently invoked in scientific modelling, it has long been argued that it should not be the sole criterion for evaluating a model's usefulness. Downing (2006) famously critiqued the concept, noting that *"the term face validity is sloppy at best and fraudulent and misleading at worst"*, and emphasizing that *"substance is far more important than superficial looks"* (p.8). In addiction research, Stephens and colleagues (2013) similarly contended that relying on analogy-based assessments (i.e., relying on face validity) is insufficient, and that *"giving two things the same name does not make them the same thing"* (p. 632). Within the more specific context of preclinical work, Spanagel (2017) further argued that apparent face validity often stems from anthropomorphic interpretations of animal behavior rather than from genuine mechanistic correspondence. This concern about face validity was also echoed by Boddez et al. (2023), who referred to this reliance on surface-level resemblance as *"phenomenological similarity"*, defined as *"similarity in the way in which things appear to us via our senses without bothering about causality"* (p.10). This notion corresponds closely to what is traditionally termed face validity. Boddez and colleagues further argued that focusing solely on phenomenological similarity is insufficient for ensuring high translational value in experimental models.

As an alternative to face validity, Stephens and colleagues (2013) proposed that model evaluation should be grounded in the systematic characterization of behaviors that are theoretically and empirically linked to the underlying mechanisms of addiction; that is, behaviors with demonstrated homology. They reaffirmed this position in their recent update on "*the continuing challenges of studying parallel behaviors in humans and animal models*" (Crombag et al., 2025). Yet (as they also stated), this approach faces a major conceptual challenge: there is currently no universally accepted theory of addiction (and perhaps such a unified theory may never exist).

Instead of face or phenomenological validity, Boddez and colleagues (2023) advocated for a systematic assessment of *functional similarity*, defined as "*the extent to which there is overlap between variables that affect performance in the model and variables that affect the target phenomenon*" (p.12).

This concept aligns to some extent with the notion of construct validity, namely, the extent to which a model truly captures the theoretical construct it is intended to represent. Further, if the same variables systematically influence both the experimental model and the real-world phenomenon of interest, this provides empirical support for what Boddez et al. (2023) describe as *deep similarity*, that is, similarity at the level of underlying mechanisms or processes. Because the mental and neurobiological mechanisms underlying psychological phenomena are not directly observable, deep similarity is inherently difficult to demonstrate. Nevertheless, systematically examining functional similarity offers a pragmatic strategy for approximating it and for strengthening the translational robustness of experimental models.

Even more stringent conceptions of validity have been proposed in the measurement literature. For instance, Borsboom and colleagues (2004) argued that a test is valid only if (1) the attribute it aims to measure exists and (2) variations in that attribute causally produce variations in the measurement outcomes. While this causal conception of validity is frequently discussed in the context of psychometric instruments, it is rarely directly demonstrated in practice. Correlations with other measures or good fit of latent variable models cannot conclusively establish that a latent attribute *causally* generates the observed responses, since these can be influenced by multiple interacting processes.

What Have Laboratory Animals to Offer to Addiction Research?

There are several compelling reasons to use animal models to investigate human conditions such as addiction. A primary rationale is that many research questions cannot be ethically or feasibly addressed in human laboratory settings. Issues such as the long-term consequences of adverse early-life experiences, the effects of first-time exposure to addictive substances, or the impact of prenatal alcohol exposure cannot be experimentally manipulated in humans for obvious ethical reasons; laboratory animals therefore provide an indispensable solution. Fortunately, extensive neurobiological evidence has shown that mammals (and even more distantly related species such as invertebrates) share fundamental morphological, connectivity and biochemical principles underlying brain function (Assaf et al., 2020; Scaplen & Kaun, 2016), even though important physiological differences do exist and must be acknowledged. This cross-species continuity provides a robust rationale for comparative investigations aimed at uncovering general principles of neural organization and behavior. Rodent models in particular, offer the added advantage of cost-effectiveness, as they allow for the systematic implementation of large numbers of experimental tests at reasonable societal cost (Kuhn et al., 2019).

Although animal models in addiction research face several criticisms (discussed below), they have nonetheless generated critical insights into the study of substance use disorders (SUDs). Researchers widely acknowledge their role in advancing theoretical models of addiction, supporting the development of pharmacological and behavioral treatments, and serving as highly informative tools for elucidating pathological mechanisms and identifying therapeutic targets in AUD and other SUDs (Fields, 2024; Fuchs et al., 2019; Gardner, 2021; Lamontagne & Olmstead, 2019; Spanagel, 2017). Importantly, animal models enable the study of causal relationships under highly controlled conditions (Fields, 2024; Olmstead, 2006), making them particularly valuable for investigating complex, multifactorial diseases such as addiction.

A key question that naturally follows is: *Which aspects of AUD can be modeled using animal paradigms?* A brief survey of the literature shows that virtually every major component of problematic alcohol use (and each stage of the addiction cycle) can be reproduced to some degree in animal models, from the initiation of alcohol consumption to relapse-like behavior. Experimental procedures such as operant self-administration,

conditioned place preference (CPP), cue-induced reinstatement (a common proxy for relapse), and drug-seeking under punishment are well-established approaches that allow researchers to probe essential features of addiction. Collectively, these paradigms map onto several of the diagnostic criteria for human AUD, including persistent consumption despite negative consequences, craving-like behavior, tolerance, and withdrawal. They also permit investigation of more mechanistic determinants, such as the role of environmental and contextual cues, or the influence of genetic and experiential predispositions on substance use patterns in rodents. A thorough review of this expansive literature lies beyond the scope of the present thesis. However, a number of recent, comprehensive reviews provide excellent overviews of existing animal models of addiction (or AUD), summarizing, contrasting, and highlighting their translational relevance to human AUD (Becker & Lopez, 2025; Crombag et al., 2025; Fuchs et al., 2019; Gardner, 2021; Lamontagne & Olmstead, 2019; Nieto et al., 2021; Spanagel, 2017; Vanderschuren & Ahmed, 2021). These works collectively underscore both the richness of available experimental tools and the growing sophistication with which they parallel human addictive behaviors.

Common Critiques and Counterarguments

Despite their prominent role in scientific research, debates over the use of animals in science and the validity of animal models are longstanding and periodically re-emerge in the scientific and public discussions. These debates are shaped by multiple perspectives: for activist organizations, the issue often embodies an ethical or ideological struggle, whereas for scientific institutions it constitutes a legal and political concern. The stakes are high: do the scientific benefits and advances derived from animal research outweigh the financial and moral costs (i.e., animal lives)? Should investments in animal research continue? These questions have recently gained renewed attention in the United States. In April 2025, the National Institutes of Health (NIH) announced a new initiative aimed at reducing both animal research and its funding (NIH, 2025). This announcement triggered strong reactions within the scientific community. For instance, the RSA urged its members (via e-mail) to formally oppose the initiative, warning that: *“Widely reducing research projects with animals threatens public health and will greatly stall the development of new therapeutics for not only alcohol use disorders, but all disease”* (personal communication, May 20, 2025). Similar positions have been taken by other

professional organizations. The American Psychological Association (APA), for example, has emphasized that *“animal models remain essential for psychological and biomedical research”* (APA, 2023). Even researchers at our own university have taken a public position. In 2018, a large consortium of researchers published an opinion piece in response to a column by the scientific advisor of the nonprofit organization *“Suppression des expériences sur l’animal”* (Elimination of Animal Testing), which had been published in *La Libre Belgique* (Muraille et al., 2018).

The aim of the following section is not to provide an exhaustive account of the arguments put forward by opponents of animal research or by scientists (a full thesis could probably be dedicated to that) but simply to offer a brief overview of the contemporary debates surrounding the use of animal models in basic research, and more specifically, in behavioral/neuroscience studies of addiction. This overview sets the stage for the final argument of the chapter, highlighting why the careful translation of findings from animal models to human research is critically important.

Four Major Objections Against Animal Research Models

The four major objections to the use of animal models in science that we briefly describe here can be summarized as follows:

- 1) Species differences, or *“We (as humans) are not 70-kg rats.”*
- 2) Scientific reliability and transparency or *“Findings from animal studies are unreliable, often fail to replicate in humans, and many animal-based studies are never published.”*
- 3) Ethical considerations and animal welfare, or *“Scientists are sadistic people who make animals suffer for a living and do not care about their welfare.”*
- 4) Model validity, or *“Studying human diseases in animals that do not naturally develop them is artificial and therefore not valid.”*(which is also intrinsically related to the first argument).

The first argument often raised by critics of animal research can be summarized by the slogan of Antidote Europe²⁰: *“We are not 70-kg rats”*, suggesting that interspecies differences prevent scientifically valid comparisons between lab animals and humans.

²⁰ Antidote Europe is an association that *“opposes animal experimentation for strictly scientific reasons, aiming to inform the public about the harm this practice causes to human health and the environment, and to promote truly scientific methods”*, Antidote Europe, n. d.).

While such differences undoubtedly exist, mice (the most commonly used laboratory animal (European Commission, 2023)) are mammals that share numerous physiological similarities with humans. *"Their evolutionary distance is offset by a short generation time, the possibility of genetic manipulation, and relatively low maintenance costs"* (Muraille et al., 2018, p.3). To illustrate this point, Muraille et al. (2018) refer to Mendel's pea plants, an evolutionarily distant model that nevertheless laid the foundations of modern genetics. Likewise, in the field of addiction research, even simple organisms such as the fruit fly and the earthworm have provided valuable insights into the genetic and cellular mechanisms underlying ethanol's effects. Both species display behaviors reminiscent of ethanol-intoxicated humans (i.e., increased locomotor activity, ethanol-induced sedation, tolerance development, and withdrawal-like symptoms) (Scholz, 2025; Scholz & Mustard, 2013).

The second major line of criticism against the use of animal research models concerns their scientific reliability, and arguments are rather oriented towards the scientific method itself. Indeed, critics frequently point to the so-called *translational gap* (or *"valley of death"*, the limited generalizability of findings from animal studies to humans) as evidence of inherent limitations in these models. They further argue that experiments involving animals are unreliable, noting that outcomes are often influenced by methodological factors such as diet, strain, and housing conditions, etc. In addition, a substantial proportion of animal-based procedures remain unpublished, raising concerns about transparency (Animal Defenders International, 2025). There is no straightforward counterargument to these claims, as many of the issues raised apply broadly to the scientific enterprise rather than uniquely to animal models. These criticisms mirror broader challenges recognized in contemporary research culture, such as translational failure, publication bias (i.e., the non-publication of null or negative findings), and inconsistencies in results arising from heterogeneous methods and poor reporting²¹. Publication bias and methodological shortcomings have recently been identified as major contributors to the translational gap (Spanagel, 2022). In response, researchers have increasingly implemented measures to enhance transparency and reproducibility.

²¹ These issues are particularly well documented in psychology (Nosek et al., 2022), but they extend more broadly to science as a whole (Bausell, 2021). Consequently, some literature referenced in this thesis is very likely to be affected by these concerns. A systematic evaluation of the intrinsic methodological quality of each primary study would nevertheless have required a dedicated meta-research effort and therefore clearly exceeds the scope of the present work.

Among these, the ARRIVE guidelines (Sert et al., 2020) provide standardized recommendations for reporting animal research and include best-practice principles for experimental design and conduct. Building on these initiatives, Meinhardt et al. (2025) recently proposed the STRINGENCY²² framework, derived from Spanagel's (2022) "ten recommendations", as "*an integrative approach to good practice guidelines for preclinical alcohol research which can also apply to behavioral research in general and which aims to improve preclinical research to better prepare it for translation and minimize the 'valley of death' in translational research*" (p. 171). From this perspective, many limitations often ascribed to animal models may instead stem from suboptimal scientific practices—issues that the research community is now actively striving to overcome.

The third argument mentioned here is related to ethics and animal welfare, which are obviously important considerations in any experiment involving animals. Opponents of animal research frequently invoke "speciesist" arguments, emphasizing that animals, as sentient beings, have intrinsic rights that should not be subordinated to human interests. The argument based on animal suffering is, by definition, an emotional one (any observer would naturally react emotionally to selected video excerpts circulated by some activist organizations). As a result, people can sometimes react beyond reason: the controversy surrounding animal research can lead to stigma toward professionals in the field (Gircor, 2024) and, in more extreme cases, to criminal attacks on laboratories or companies (Swallow, 2009) as well as severe harassment targeting researchers and research directors (Grimm, 2015). It is therefore important to put these concerns into context and not be carried away by emotion. The use of animals in research is currently subject to strict regulation through multiple legislative frameworks, including European Directives, national laws, and institutional ethical review committees, all of which explicitly emphasize and control animal welfare.

A key component of these regulations is the 3Rs principle: Replacement, Reduction & Refinement (originally formulated by Russell & Burch, 1959). "*Replacement refers to the substitution of conscious, higher-order animals with insentient material whenever possible. Reduction entails using fewer animals to obtain information of a given amount and precision. Refinement involves any modification of experimental procedures that decreases the incidence or severity of inhumane treatment for animals that still must be*

²² See [List of Abbreviations](#) for the full meaning of the acronym.

used” (Russell & Burch, 1959, p. 64, cited by Tannenbaum & Bennett, 2015). Importantly, as emphasized by Tannenbaum & Bennett (2015), the clear aim of the 3Rs, as articulated by Russell and Burch, is to reduce (and, whenever possible, eliminate) animal *distress*, rather than to oppose the use of animals in research per se. More recently, Strech and Dirnagl (2019) have proposed extending this framework by adding three further principles: Robustness, Registration, and Reporting (resulting in 6Rs). These additional “Rs” were introduced in response to broader systemic challenges in science (discussed above), and to issues specific to animal research, including publication bias, inadequate reporting, and poor methodological rigor. Such issues, as Strech and Dirnagl (2019) argue, diminish the scientific and translational value of research findings, contribute to inefficient allocation of public resources, may misguide clinical research, and ultimately result in unnecessary animal use and suffering (also see Spanagel, 2022). Together, these six principles underscore that researchers are responsible not only for scientific integrity but also for minimizing unnecessary animal use. Integrating all six Rs into research practice is therefore essential to advancing both scientific quality and animal welfare.

Finally, another common argument is that human diseases, which do not occur naturally in animals, must be artificially induced. While this claim is essentially accurate, the mere fact that a condition is created artificially does not render it invalid. As noted earlier, the defining feature of a model is precisely its *role to reproduce something that it is not*. Many artificially created models nonetheless yield highly valuable insights; for example: chemically induced models of diabetes to investigate metabolic dysfunction, crash test dummies in automotive safety testing, etc.

Specific Critiques of the Use of Animal Models in Addiction Science

This final argument leads us to critiques directed specifically at animal models of addiction. The two key criticisms that will be considered here can be naively called:

- 1) *“Animals don’t do drugs”!*
- 2) *“No true treatment has emerged from biomedical animal-based research on addiction”!*

Unlike the broader critiques discussed above (which often originate from the general public and target not only animal models in addiction research but animal-based science more generally), the following criticisms are more specific, and typically arise

within the scientific literature, where researchers themselves critically debate the use of animal models in addiction research, with some advocating for their value and others remaining skeptical.

Animals Don't Use Drugs

This argument might seem quite intuitive for non-experts, in the sense that in our day-to-day life, or in nature, we do not encounter drug-addicted or alcohol-consuming animals whatsoever. For non-specialists, this observation can therefore appear to undermine the face validity of animal models of addiction, raising the question of whether behaviors observed in laboratory animals can meaningfully inform our understanding of human substance use disorders. This concern is particularly salient in the context of alcohol research, where it is well known that the great majority of rodents do not readily consume alcohol. To overcome this limitation, researchers have developed a range of experimental strategies designed to increase voluntary alcohol intake. These include procedures such as sucrose fading (i.e., to consume a palatable sucrose solution to which alcohol is progressively added until the animal ultimately consumes alcohol alone), using alcohol vapor exposition or the use of selectively bred rodent lines that display high alcohol preference and consumption. These procedures allow researchers to induce levels of alcohol intake that produce measurable pharmacological and behavioral effects, but they also highlight the extent to which alcohol consumption in laboratory animals is often experimentally facilitated rather than spontaneously occurring (although strictly speaking, alcohol consumption does not occur *spontaneously* in humans either, but it is rather socially and culturally facilitated).

Beyond alcohol specifically, several broader features of laboratory drug self-administration paradigms have been criticized for their limited ecological validity. In many rodent models of substance use and addiction, access to drugs is temporally restricted to a limited number of hours per day, and animals are frequently tested in relatively impoverished environments. In addition, experiments often provide few meaningful alternatives to drug intake. Access to non-drug rewards is frequently absent or limited. This concern was succinctly captured by Hyman and Malenka (2001), who noted that *"although drug self-administration by rodents has provided important information, it is difficult to argue that it truly models compulsion, when the alternative to self-administration is solitude in a shoebox cage"* (cited by Ahmed, 2012). Supporting this view, studies have

shown that, when given the opportunity to choose between cocaine and alternative rewards such as palatable food or wheel-running, most rodents markedly reduce or even cease cocaine intake (Ahmed, 2010, 2012; Cosgrove et al., 2002). Interestingly, however, a small subset of animals continues to prefer the drug despite the availability of alternatives. This observation has been interpreted as potentially mirroring the epidemiological pattern observed in humans, where only a minority of individuals exposed to drugs ultimately develop addiction (Anthony, 2002; Deroche-Gamonet & Piazza, 2004).

Finally, it can be argued that the motivations underlying drug use differ fundamentally between humans and laboratory animals. Human substance use often occurs within rich social and psychological contexts and may serve a variety of instrumental purposes beyond the pharmacological effects of the drug itself. Individuals may consume substances, for example, to facilitate social interaction, reduce anxiety, enhance performance, or modulate mood. This phenomenon has been described as *drug instrumentalization* (Müller, 2018), emphasizing that drug use can be embedded in broader goal-directed behavior. In contrast, drug consumption in laboratory animals typically occurs in simplified environments and is primarily driven by the direct reinforcing properties of the drug.

Consequently, critics argue that the context in which substances are consumed in laboratory settings is highly artificial and may not fully capture the complexity of human substance use.

Yet, there are compelling arguments in favor of using animal models to study alcohol-related behaviors. Alcohol and drug consumption have been proposed to reflect behaviors with deep evolutionary roots, supported by both genetic and archaeological evidence (Carrigan et al., 2015; Sullivan & Hagen, 2002). Archaeological findings suggest that even late prehistoric human populations consumed fermented beverages as early as 13,000 years ago (L. Liu et al., 2018). Field studies have further shown that alcohol consumption is not unique to humans: wild chimpanzees in Côte d'Ivoire and Uganda ingest approximately 14 ± 9 g of ethanol daily from naturally fermented fruit (Maro et al., 2025). Such findings highlight a long-standing biological continuity in alcohol exposure across species and support the relevance of animal models in this research area.

Criticisms regarding the “artificial” nature of animal models overlook a fundamental aspect of scientific modeling: a model is, by definition, a simplified and

distinct representation of the phenomenon it seeks to explain (as mentioned earlier). It is also worth noting that certain experimental procedures, though seemingly artificial and potentially introducing confounding variables, often mirror real-life human behaviors more closely than they appear at first glance. For instance, the sucrose-fading procedure described earlier (commonly used to facilitate alcohol self-administration in animals) shares notable similarities with the way humans typically initiate alcohol consumption. Young people often begin by drinking sweetened alcoholic beverages, such as cocktails or cider, before gradually progressing to stronger or “purer” forms of alcohol (Crombag et al., 2025).

Importantly, the argument here is not that animal models can fully capture multifactorial and complex phenomena such as human addiction. As mentioned in the previous chapter, AUD is profoundly shaped by social and environmental determinants, marked interindividual variability, and the dynamic interplay of biological, psychological, and contextual factors. As such, neither the full complexity of these disorders nor the subjective experiences of those affected can be entirely recreated under controlled laboratory conditions using rodent models (Field & Kersbergen, 2020; Fields, 2024). A clear illustration of this limitation lies in human-specific behaviors (e.g. happy-hour-driven binge drinking, drinking games, or *chemsex*) which are particularly difficult, if not impossible, to model in animals. Nevertheless, significant progress has been made in modeling behaviors once considered uniquely human. For instance, binge drinking (which could initially be regarded as a distinctively human pattern of alcohol consumption) has been successfully reproduced in several validated animal paradigms, including models integrating voluntary alcohol intake, providing valuable insights into its underlying neurobiological and behavioral mechanisms (Jeanblanc, Rolland, et al., 2019; Jeanblanc, Sauton, et al., 2019).

It is evident that no animal model can fully encapsulate the human condition and that a single, unitary model of addiction encompassing all underlying processes is unattainable in laboratory settings (Field & Kersbergen, 2020; Nieto et al., 2021). Though this could be a valid criticism in certain ways, the same applies to human studies, as the disorder manifests heterogeneously across individuals, and capturing “*the whole picture*” is also quite impossible in human laboratory settings (Spanagel, 2017). Rather, it is now widely acknowledged that preclinical research should focus on developing limited but closely homologous behavioral paradigms in animals and humans that rely on objectively

and behaviorally measurable parameters to model key features of the disorder (Spanagel, 2017; Stephens et al., 2013). This perspective has been widely advocated within addiction research (Lamontagne & Olmstead, 2019; Nieto et al., 2021; Spanagel, 2017; Stephens et al., 2013). In other words, as Lamontagne and Olmstead (2019) noted, animal researchers can study *symptoms*, not *disorders*. In the spirit of such a shift in experimental focus, it has been proposed (in the field of animal research for neuropsychiatric disorder in general) to shift the terminology from “*animal models of condition X*” to “*animal models useful in the study of condition X*”²³ (Bale et al., 2019), representing a subtle but meaningful change emphasizing their instrumental rather than mimetic role. Such models can elucidate key psychological and neurobiological mechanisms involved in alcohol use and seeking, allowing for more reliable cross-species predictions. Corresponding human paradigms may serve as biomarkers or intermediate behavioral phenotypes for specific aspects of AUD (Duka et al., 2011). Rather than reproducing the full complexity of addiction, such approaches aim to isolate core behavioral pathologies that contribute to the broader disorder.

Decades of Animal-Based Research Without Breakthrough in Treatments for Addiction

Despite the tremendous advances made over the past decades in understanding the neurobiology of psychiatric disorders (such as AUD), the development of clinically effective treatments has remained limited (Spanagel, 2017). In fact, we appear to be no closer to finding truly effective treatments for addiction than we were 20–30 years ago (Crombag et al., 2025).

However, as stated by Bale and colleagues (2019), the general lack of new psychiatric drugs (not only in the field of SUD) cannot be blamed solely on animal models but reflects broader limitations across all research approaches. This failure largely stems from the exceptional complexity of the human brain and its disorders.

As already mentioned, the translational failure is a well-known phenomenon in the scientific community, and even researchers within the field have pointed out that to date there is no highly efficient treatment for drug addiction that has emerged from decades of animal studies, and that several drugs tested in animals don’t work in humans resulting

²³ Although I agree with the rationale behind this suggestion, I will continue to use the term “*animal models of addiction*” in this manuscript for the sake of clarity.

in a “*huge waste of resources*” (Field & Kersbergen, 2020; Müller, 2018; Spanagel, 2017). However, this obviously does not mean that nothing has been learned since then. As mentioned earlier, animal models have clearly contributed to the development and refinement of theoretical models of addiction as well as pharmacological components (Nieto et al., 2021; Spanagel 2017; Vanderschuren & Ahmed, 2021). There is clearly some predictive value coming from them since two authorized medications for AUD were developed and validated through animal research (acamprosate, naltrexone).

Even though some studies failed to efficiently translate to humans, we must keep in mind that such null findings²⁴ are of great interest for science as they help refine theoretical models, reorient translational efforts, minimize time and resource wasting. Moreover, as emphasized by Crombag and colleagues (Crombag et al., 2025; Stephens et al., 2013), the lack of a unified and comprehensive theoretical framework of addiction also contributes to the limited translational success of animal models. Consequently, future research should prioritize the refinement of theoretical models and the development of robust, theory-driven, and parsimonious behavioral tests, which are crucial for advancing the field.

An Attempt to Bridge the Gap: Parallels Between Animal and Human Cue Reactivity

As underscored at the end of the previous chapter, cue-triggered behaviors are widely considered a central component of addictive disorders. Many experimental methods used to investigate cue reactivity were originally developed in animal models. Looking back at the three properties of incentive stimuli mentioned in Chapter 1, each of them has been proposed to possibly contribute to drug use in different but complementary ways, providing what Milton and Everitt (2010) described as “*three routes to relapse*”. First, the attentional and approach-eliciting properties of incentive cues can draw individuals toward drug-related locations or paraphernalia (modelled for instance by CPP in animals). Second, their capacity to act as conditioned reinforcers can sustain drug-seeking even when the drug itself is unavailable, as shown in instrumental paradigms where animals learn a new response to obtain a drug-paired cue. Third, their

²⁴ i.e., when an experimental outcome does not show the expected effect, including results that don’t match the hypothesis, are negative, contradict previous evidence, or are inconclusive (American Brain Foundation, 2024)

ability to evoke conditioned motivational states can maintain drug-seeking and drug-taking, and during abstinence might precipitate relapse (which can be modelled using PIT tasks). Translational research has examined analogous processes in humans, sometimes using direct adaptations of animal paradigms and sometimes employing conceptually analogous tasks. Cue reactivity therefore represents a particularly informative example of translational research, as many findings appear to converge across species.

Because the following chapter examines in detail one specific form of cue-driven behavior associated with individual vulnerability to addiction (the sign-tracker/goal-tracker (ST/GT) model) this phenomenon will not be discussed further here. Instead, the remaining of the present chapter focuses on two other cue-related processes that have been investigated across species: CPP and PIT. Although CPP has been extensively used in animal research, it has received comparatively little attention in human experiments. In contrast, PIT has become a well-established paradigm in both laboratory rodents and humans and currently provides a quite robust translational framework for studying cue-motivated behavior. Together, these two behaviors nicely illustrate both the strengths and the limitations inherent to translational approaches.

Conditioned Place Preference in Rodents and Humans

As mentioned in Chapter 1, the CPP paradigm provides a behavioral index of reward processes via approach tendencies. It has provided historical insights into addictive properties of substances (Carr et al., 1989). As a brief reminder, typical CPP procedures (McKendrick & Graziane, 2020; Tzschentke, 2007) use two similar but clearly distinguishable chambers to see whether an animal learns to associate one environment with a rewarding experience. The procedure has three steps. First, during habituation, the animal can move around both chambers freely so researchers can note any natural preference. Next, in the conditioning phase, the animal receives a rewarding US (e.g. food or drug) in one chamber, while the other chamber is paired with a placebo or control condition. Finally, in the test phase, the animal is again allowed to explore both chambers without any US. If the conditioning worked, the animal will spend more time in the chamber previously linked with the reward. This behavioral approach or preference for the conditioned chamber is typically interpreted through classical conditioning-derived *incentive motivation*. Yet several authors have cautioned that the mechanisms underlying

CPP may be more complex than this. Huston and colleagues (2013) argued that this classical interpretation may oversimplify the range of learning and motivational processes involved in the paradigm²⁵. Despite methodological and theoretical complexities, a growing body of research in humans has demonstrated that CPP-like paradigms have reported behavioral preferences that closely parallel those observed in animal models. These converging findings suggest that, notwithstanding the potential influence of additional processes, conditioning mechanisms remain a plausible and empirically supported explanation for CPP effects across species.

Several studies have attempted to directly translate the CPP paradigm from animal models to human participants. Such work is valuable not only for the general reasons outlined earlier regarding translational (cross-species) research, but also for more specific methodological and theoretical considerations. Beyond its general translational value, this work is motivated by three key aims (Krishnan et al., 2023):

- Testing cross-species assumptions: In rodents, time spent in a drug-paired environment is taken as evidence of conditioned reward or aversion, though alternative explanations exist (e.g. Huston et al., 2013). Demonstrating similar effects in humans helps clarify whether place preference truly reflects conditioned motivational value.
- Relevance to real-world drug use: Drug-associated environments (e.g., bars) may acquire incentive properties that draw individuals back and increase use or relapse risk.
- Linking subjective and behavioral responses: Human CPP tasks allow researchers to relate subjective drug effects to behavior, clarifying how experienced drug rewards shape conditioned preferences.

Human CPP paradigms use either real rooms or virtual reality environments. Childs and de Wit (2016) developed a procedure closely modeled on animal CPP: after an initial

²⁵ Indeed, these authors have suggested several additional mechanisms that might influence behavior in CPP paradigms. One is the release-reward effect, in which placement into a chamber following potentially aversive handling may itself function as a reinforcing event, thereby confounding interpretations of chamber preference. Also, the test phase constitutes an extinction session, as the previously paired unconditioned stimulus is absent; extinction can elicit behavioral responses such as exploration or escape tendencies that may alter place preference independently of the conditioned association. Moreover, memory-related processes are critical: expression of CPP requires retrieval of the learned context-outcome association, and pharmacological manipulations may disrupt retrieval or induce state-dependent learning, leading to altered performance during the drug-free test.

drug-free exploration session, participants underwent conditioning sessions pairing alcohol or a control beverage with one of two distinct but equally appealing rooms. In a subsequent drug-free test, preference was measured by the time spent in each room. Variants of this design have also been implemented in virtual reality (Childs et al., 2017), offering ecological validity with tight experimental control (Linhardt et al., 2022).

Globally, empirical findings from human studies generally support the presence of place-conditioning effects. CPP has been observed with drugs such as amphetamine, alcohol, and preliminarily, cocaine (Childs & de Wit 2009, 2013, 2016; Lutz & Childs, 2021; Shipman et al., 2006), paralleling robust findings in animals (Cunningham et al., 2000; Tzschentke, 2007). Cross-species convergence also extends to non-drug rewards, including food, money, music, and points in humans, and comparable rewards in rodents (Astur et al., 2015; Childs et al., 2017; Molet et al., 2013; Radell et al., 2016). A recent meta-analysis (Linhardt et al., 2022) confirms that humans, like animals, tend to prefer environments paired with rewarding outcomes. Together, these results indicate that CPP-like procedures produce broadly similar patterns across species. However, the literature remains methodologically heterogeneous, and standardized protocols are needed to improve consistency in future work.

It is important, however, to keep in mind that human and animal CPP paradigms differ in several methodological respects (Krishnan et al., 2023). First, outcome measures vary: animal studies typically assess time spent in the drug-paired environment, whereas human studies may measure either time spent or self-reported liking of the environment. The extent to which such room-liking ratings correspond to time-based preference measures is not yet established. Second, prior drug exposure often differs, as laboratory animals are usually drug-naïve, whereas human participants frequently have previous experience with the substance. Third, the route and mode of drug administration differ: drugs are typically passively administered to animals (e.g., injections), while humans usually ingest them voluntarily (e.g., capsules or beverages), although rare exceptions exist (e.g., Shipman et al., 2006).

Despite these differences, human CPP studies offer a key advantage: the possibility of linking behavioral measures of place preference with verbal reports of subjective drug effects, allowing researchers to examine how experienced drug states contribute to the acquisition of conditioned preferences. Still, the human CPP literature is still quite sparse, leaving significant gaps in current knowledge (Krishnan et al., 2023). This stands in

marked contrast to the vast body of rodent work, comprising thousands of experiments (Tzschentke, 2007).

Pavlovian-to-Instrumental Transfer in Rodents and Humans

As already described in Chapter 1, PIT typically involves three phases. In standard rodent PIT paradigms, animals first learn an instrumental action that earns a reward. Second, in a separate Pavlovian conditioning phase, neutral cues are paired with reward outcomes. Third, during the transfer test, these cues are presented while animals perform the instrumental action, even though the cues are now irrelevant. PIT is shown when reward-predictive cues alter the rate of instrumental responding, indicating that conditioned stimuli can energize reward-seeking behavior. In the literature, two types of PIT effects are typically distinguished: general and outcome-specific PIT (see Cartoni et al., 2016; Corbit & Balleine, 2015, for comprehensive reviews). Specific transfer refers to increased responding for an instrumental action that is associated with the same reward predicted by the cue. In contrast, general transfer reflects a broader motivational effect, whereby a reward-predictive cue increases responding for instrumental actions associated with other types of rewards. Interestingly, on a neuro-anatomic level, there has been suggested to be a double-dissociation between these two forms of PIT, involving different subregions of the NAcc (Corbit & Balleine, 2011).

The PIT phenomenon has been widely studied in animal models, offering key insights into how reward-predictive cues invigorate motivated behavior. From a neuroanatomical perspective, evidence indicates that PIT arises from interactions within amygdala-striatal circuits under modulation of prefrontal regions. In particular, the NAcc shell together with the basolateral amygdala has been implicated in mediating outcome-specific PIT, whereas general PIT appears to depend primarily on the NAcc core and the central amygdala (Cartoni et al., 2016).

Within addiction research, rodent studies show that prior drug exposure can strengthen PIT. Repeated psychostimulant use (e.g., amphetamine, cocaine) enhances cue-triggered motivation, amplifies the impact of reward-predictive cues, and increases cue-evoked dopamine bursts (Berridge & Wyvell, 2001; Leblanc et al., 2012; Ostlund et al., 2014). Drug exposure can also shift PIT toward more generalized responding. For example, cues paired with alcohol have been shown to broadly enhance reward seeking (e.g., sucrose) (Corbit & Janak, 2007; Corbit et al., 2016; Glasner et al., 2005). Together,

these findings indicate that reward-predictive cues (as well as alcohol cues) can strongly influence motivated behavior through both general motivational invigoration and outcome-specific mechanisms. Building on these findings from animal models, researchers have increasingly investigated whether similar PIT effects can be observed in humans and how they may contribute to addictive behaviors.

The PIT paradigm translates relatively easily to humans, typically through computerized tasks preserving the classic three phases. For example, in the task developed by Schad and colleagues (2020), the instrumental conditioning phase required participants to learn to collect or avoid different visual stimuli (shells). They did so by repeatedly pressing a button to move a hidden cursor toward the shell. Some shells were associated with monetary rewards ("good" shells), whereas others produced monetary losses ("bad" shells), and probabilistic feedback guided participants' learning about these contingencies. In the subsequent Pavlovian conditioning phase, abstract fractal images paired with tones served as conditioned stimuli and predicted monetary outcomes ranging from -2€ to +2€. Participants were instructed to observe and memorize the cue-outcome contingencies, without making any responses. Finally, in the transfer phase, participants again performed the instrumental task; however, Pavlovian cues now appeared in the background, and no outcomes were delivered (though participants were informed that outcomes still counted for their final payment). This phase allowed researchers to assess how the previously learned Pavlovian cues influenced ongoing instrumental behavior in the absence of feedback.

In recent decades, human studies consistently demonstrated both general and specific PIT effects (Badioli et al., 2024; Cartoni et al., 2016). A recent meta-analysis reported robust effect sizes for both specific and general PIT effects in humans, supporting the paradigm's translational potential. Neuroimaging work shows recruitment of the amygdala and NAcc, mirroring previous animal findings (Mendelsohn et al., 2014; Prévost et al., 2012; Talmi et al., 2008). PIT has been observed with monetary, food, and social rewards (Lehner, Balsters, Herger, et al., 2017). In addiction contexts, smoking-related cues increase responding for cigarettes even after devaluation (Hogarth, 2012; Hogarth & Chase, 2011), and individuals with AUD show heightened PIT, with NAcc activation predicting relapse (Garbusow et al., 2014; 2016).

Despite strong cross-species parallels, methodological gaps remain. As noted by Amorim et al. (2026), many animal PIT tasks lack a neutral cue baseline, complicating

interpretation. Introducing such baselines reduced PIT in a reverse-translated design, suggesting task parameters strongly shape behavior (Amorim et al., 2026). More broadly, heterogeneity in human task designs, measures, awareness, and clinical profiles makes direct animal-human comparisons challenging (Doñamayor et al., 2021).

Overall, PIT provides a powerful cross-species framework for studying how predictive cues influence motivation but translating animal findings to humans requires careful methodological alignment.

Inherent Limits and Challenges for Translational Addiction Research

As illustrated by the two preceding translational models, efforts to translate experimental paradigms from animal models to humans must address several theoretical, methodological, and species-specific considerations. Fundamental differences between rodents and humans inevitably constrain translational research and shape the interpretation of findings.

The Subjective Experience

In human research, motivational states and subjective feelings are often measured through self-report questionnaires. As highlighted in human CPP studies, this can be a methodological advantage because it provides access to experiential information that cannot be directly obtained in animal models (Linhardt et al., 2022). In human addiction research, for example, the rewarding effects of alcohol, or craving states are frequently evaluated through subjective reports. However, direct measurement of subjective states in non-human animals remains inherently difficult (Crombag et al., 2025). As Ahmed recently emphasized (Ahmed, 2025, p.3), *"unlike humans, animals lack language and, thus, lack what Harriet de Wit and colleagues have aptly called the 'fast lane for intake of abstract knowledge' (de Wit et al., 2018)."* This "language gap" has long been recognized as a barrier to translation between human and animal studies in addiction research (Ahmed, 2018a). Language enables humans to acquire abstract information about drugs and addiction without direct experiential exposure, and it allows us to conceptualize and communicate about our internal drug-related states (Ahmed, 2025). Such linguistic and metacognitive capacities have no clear analogue in non-human animals, creating a

fundamental asymmetry in how subjective experiences can be accessed and measured across species.

To address this limitation, researchers have proposed some behavioral indices intended to index such subjective reactions in animals. For instance, Berridge and colleagues demonstrated that hedonic reactions to tastes delivered into the mouth can be inferred from species-conserved facial expressions (Berridge, 2000; Berridge & Grill, 1983). These findings support the idea that certain affective responses may be measured across mammalian species using objective behavioral markers. Similarly, certain frequencies of ultrasonic vocalizations in rats have been shown to reliably reflect positive emotional states (Burgdorf et al., 2011), providing another potential proxy for affective processes.

On the other hand, reliance on explicit self-report measures in humans also presents limitations. Individuals may lack introspective access to the processes underlying their behavior, and motivational states (particularly those implicated in addiction) may operate largely outside conscious awareness (Berridge et al., 2009). Human studies are additionally influenced by social and contextual factors that are largely absent in animal experiments. One such factor is *"reactivity"*, defined as *"behavioral changes that occur when individuals are aware that they are being observed or studied"* (Jimenez-Buedo & Guala, 2016, p.10). In the behavioral sciences, it has long been recognized that experimental participants are not passive responders to stimuli; rather, they actively interpret the experimental context and attempt to infer the purpose of the study (Orne, 1962). Knowledge or assumptions about the experimental hypothesis can influence participants' responses, sometimes leading them to behave in ways that confirm perceived expectations (Nichols & Maner, 2008). Another important source of bias is social desirability, defined as *"the tendency to provide responses that present oneself in a favorable light"* (Paulhus, 1991, p.17). In addiction research, such biases could substantially affect self-reported measures. For example, Marissen et al. (2006) reported a significant negative correlation between social desirability and self-reported craving in detoxified heroin users, suggesting that individuals with stronger social desirability tendencies may underreport motivational states related to drug seeking.

A further psychological factor influencing human experiments is substance expectancy. Expectancies have been shown to influence outcomes in alcohol studies (e.g., Field, Hogarth, et al., 2011), with some evidence indicating that explicit activation of

reinforcer expectancies is often necessary for conditioned responses to emerge in humans (Watson et al., 2012). This might appear to distinguish human cue-reactivity from similar phenomena observed in animals; however, as Crombag et al. (2025) point out, this difference may be more apparent than real, as we currently have no means of determining whether animals also develop an explicit/causal (or even conscious) awareness of the relationship between a reinforcer and its predictive cue (but see Blaisdell et al., 2006). Finally, initial expectations are also highly different, rendering first drug exposure markedly different between humans and laboratory animals. Humans typically approach their first substance use with some prior knowledge (shaped by education, cultural context, and media for instance) about what the effects might be. In contrast, a laboratory rodent's first drug exposure is neither desired nor intended and cannot be guided by any expectations about anticipated effects; it must be a complete experiential surprise (Ahmed, 2018b, 2025). This creates a profound asymmetry between species: the human first drug experience is cognitively scaffolded by beliefs and expectations, whereas the animal's is not.

Experimental Control Over Conditioning

Another important translational challenge concerns experimental control over the conditioning history of substance-related cues. In animal research, experimenters can precisely control when and how Pavlovian associations happen. In contrast, in human addiction research, conditioning with substance-related cues typically occurs outside the laboratory through real-life experiences. As a result, the learning history underlying cue-reward associations is largely unknown and may be influenced by numerous uncontrolled factors (Doñamayor et al., 2021). Despite this limitation, recent studies have attempted to implement *de novo* Pavlovian conditioning with alcohol in humans, thereby approximating procedures used in preclinical models. For example, Mayo and de Wit (2016) found that neutral cues paired with alcohol subsequently captured more attention than non-reinforced cues, and that this attentional bias (AB) was positively related to participants' self-reported liking of alcohol. Similarly, Oberlin et al. (2018) demonstrated that experimentally pairing neutral cues with low to moderate doses of alcohol can successfully establish conditioned responses, engaging limbic and prefrontal brain regions involved in reward learning.

Evidence also suggests that individual differences shape the acquisition and expression of alcohol-related cue associations: novel visual cues can acquire appetitive properties and elicit neurophysiological responses when paired with naturalistic alcohol-related cues, with stronger effects observed in heavier drinkers (Cofresí, Piasecki, et al., 2022) and in individuals with low alcohol sensitivity (Fleming et al., 2021), i.e., individuals considered at higher vulnerability for alcohol misuse.

Rodents and Humans Don't Live the Same Lives: On Environmental Conditions, Co-Morbidity, and Drug Instrumentalization

Other factors that cannot be controlled in human experiments and that are important to take into account are environmental factors, such as early-life adversity and stress exposure (which have been consistently associated with addiction in animal studies, Levis et al., 2022; Sinha, 2001). Although researchers can include self-report questionnaires to assess such experiences in humans, the true extent, timing, and severity of exposure remain difficult to quantify reliably.

These considerations align closely with the concept of vulnerability factors discussed in the previous chapter. Only a subset of individuals who initially experience psychoactive substances will go on to develop a SUD (Anthony et al., 1994; Gowing et al., 2015). This subset typically exhibits specific predisposing characteristics, including certain personality traits (e.g., impulsivity, Verdejo-Garcia & Albein-Urios, 2021), or co-occurring psychiatric disorders (Puddephatt et al., 2022). Thus, preclinical researchers have increasingly recognized that relying on “naïve animals with average emotional profiles, housed under standard laboratory conditions” may fail to capture the heterogeneity of human vulnerability (Müller, 2018). It is now suggested that more informative translational models will require incorporating animals that represent human-like risk phenotypes, such as those with heightened stress reactivity, impulsivity, or anxiety-related traits (Müller, 2018).

Another important translational consideration is the social context in which drug consumption occurs. In traditional animal models of addiction, rodents typically consume or self-administer drugs while being isolated from their peers (Ahmed, 2010). Indeed, individual housing is frequently used to prevent aggression, despite the inherently social nature of many laboratory species (Török & Bárdos, 2026). By contrast, in humans, substance use often takes place in social settings, and peer influences and environmental

context play a significant role in the initiation and maintenance of drug use (Heilig et al., 2016; Valente et al., 2007). Laboratory housing conditions (such as isolation) might affect rodent behavior. As noted by Arakawa (2018), artificial caging environments and group housing arrangements constitute important ethological factors that can influence a wide range of behavioral processes, including emotional reactivity, learning, memory, and attention. Such constraints may therefore limit the ecological validity of animal models and their translational relevance for understanding human behavior. Early work already highlighted the importance of social and environmental enrichment in drug consumption experiments. The classic Rat Park studies by Alexander and colleagues demonstrated for the first time that rats housed in enriched colony environments with ample social interaction and space consumed significantly less morphine than isolated rats (Alexander et al., 1981; Hadaway et al., 1979). While these findings drew early attention to the substantial impact of social context and environmental conditions on drug-taking behavior, their interpretation is limited by the small numbers of animals included in the analyses (Gage & Sumnall, 2019). Since then, other studies have suggested that social housing in rodents may serve as a protective factor against addiction (Holgate et al., 2017; Van Ingelgom et al., 2024)²⁶.

In response to such limitations, more recent research has begun to develop paradigms that better capture the social and ecological dimensions of substance use. For instance, Peretz-Rivlin et al. (2025) introduced the HOMECAGE system (*"Home-cage Observation and Measurement for Experimental Control and Analysis in a Group-housed Environment"*), a paradigm designed to study oral opioid self-administration in group-housed mice. By allowing animals to remain in a socially interactive and naturalistic environment while monitoring drug intake, this approach provides a more translationally relevant framework for investigating opioid use and the factors that contribute to addiction-related behaviors. Another notable effort in the same vein was the development of *"Souris-City"* by Dr. Philippe Faure and colleagues (Torquet et al., 2018). This paradigm enables extended behavioral monitoring of mice living in stable social groups over long time periods. Within *Souris-City*, it has been shown that stable individual differences emerging from social interactions can be reliably captured. For example, mice

²⁶ However, the picture is not entirely straightforward: while environmental enrichment generally reduces ethanol intake, social enrichment can, in some cases, potentiate it, underscoring the nuanced and sometimes bidirectional influence of social factors on substance use (Fulenwider et al., 2021).

developed consistent, individualized reward-seeking strategies when choosing between water and sucrose, which in turn predicted how they adapted following the introduction of nicotine as a reinforcer. These individual differences were further associated with distinct patterns of spontaneous activity and dopaminergic neuron responses to nicotine (Fayad et al., 2024).

Finally, an additional challenge for translational research concerns the phenomenon of drug instrumentalization, a feature that appears to be particularly characteristic of human substance use. Drug instrumentalization (as already mentioned) refers to the idea that individuals may use psychoactive substances not only for their intrinsic rewarding effects but also as means to achieve other desired goals, such as improving mood, enhancing performance, facilitating social interaction, or coping with stress. Yet, there is currently no formal methodology to directly demonstrate such instrumental motivations in animal models (Ahmed, 2011, 2025; Ahmed et al., 2021). Future animal models may therefore benefit from incorporating paradigms that better capture self-medication-like motivations, in which drug intake serves to alleviate negative emotional or physical states (Müller, 2018).

Recommendations for Better Translation

While significant challenges and unresolved issues continue to complicate translational addiction research, recent findings (particularly in the domain of *cue reactivity*) have revealed striking parallels between animal and human behavior and have contributed to increasingly refined theoretical accounts. Building on this progress, several recommendations can be formulated to guide and strengthen future translational efforts.

First, researchers should incorporate the three new Rs (Spanagel, 2022; Strech & Dirnagl, 2019) and, more broadly, uphold rigorous standards in methodology, statistics, and reporting (Nieto et al., 2021). In the same spirit, prioritizing validation studies when translating animal-based findings to humans, and directly assessing functional similarity across species, should be considered essential.

A second important avenue for improving translational research is reverse (or back) translation, defined as approaches that identify patterns of human behavior observed in experimental tasks and use them to develop laboratory assays with maximal formal similarity in animal models (Kangas, 2025). This strategy could strengthen the continuity between human and animal research by designing paradigms that capture comparable

behavioral processes across species (Venniro et al., 2020). At the same time, effective reverse translation requires careful consideration of species-specific biological and sensory characteristics. Task structures cannot simply be transferred from humans to animals without modification; rather, they should be adapted to the perceptual and behavioral capacities of the species under study. For example, rats rely far less on visual information than humans and instead rely more heavily on olfactory and tactile inputs. As Genzel (2021, p.4) aptly reminds us: *"a rat is not a little human, a mouse is not a little rat, and flies are not cheap mice"*, highlighting a key principle of translational science: animal models provide valuable insights, but cross-species differences must always be taken into account when designing experiments and when interpreting or translating findings.

Third, and of key importance, studies should focus on specific components of addiction, rather than attempting to model the disorder in its entirety, which has limited conceptual value (Lamontagne & Olmstead, 2019; Nieto et al., 2021; Spanagel, 2017; Stephens, 2013; Venniro et al., 2020). Moreover, selecting animals with traits that confer vulnerability to addiction in humans, such as anxiety, sensation seeking, or impulsivity (Müller, 2018), and that exhibit DSM-5-relevant addiction-like behaviors, including voluntary substance use over the long term despite negative consequences (Ahmed, 2010, 2012; Vanderschuren & Ahmed, 2021), is essential. Overall, research should focus on those vulnerable individuals who persist in substance use, as they provide the most translationally relevant insights into compulsive addiction (Ahmed, 2012; Nieto et al., 2021).

Concluding Remarks

Considering the purpose of animal models in research, the potential causes of translational failures, and the ethical considerations inherent to animal experimentation, the effective translation of findings from animal models of addiction to human research (and ultimately to clinical practice) remains crucial. Achieving this translation is essential not only from a scientific perspective, but also from an ethical one. The use of animal models in research is justified largely by the expectation that it will generate knowledge relevant to human health. When translational value is limited, both the scientific rationale and the ethical legitimacy of such work are called into question.

Although translational addiction research faces a number of important challenges and criticisms (some of which reflect broader structural issues currently affecting the scientific enterprise), it remains crucial to continue efforts aimed at bridging the gap between preclinical and human research. As nicely put by Deroche-Gamonet (2020): “*The bathwater is cloudy, but throwing the baby out with it, i.e. rejecting animal models as a whole, is detrimental*”. Rather than abandoning these models, the challenge lies in refining them and improving the frameworks through which their findings are interpreted and translated.

As researchers, we have the responsibility to contribute to the refinement of scientific models to ensure that they can generate testable predictions. Accordingly, hypotheses and insights derived from animal models of addiction should be implemented and systematically tested in human laboratory studies (see Figure 3). Future research should place greater emphasis on rigorous validation studies, reverse-translational approaches, and the identification of vulnerable subgroups of individuals. Without demonstrating functional similarity between the animal model and the human phenomenon, further investment of time, resources, and animals is difficult to justify, as the core purpose of these models is to generate meaningful insights into the processes underlying problematic substance use/addiction.

One prominent example of a model aimed at capturing individual vulnerability factors is the *ST/GT framework*, which originated in animal research and is grounded in differential conditioned responses to reward-associated cues. This model has recently begun to gain traction in human studies and appears to offer promising opportunities for cross-species investigations into behavioral markers of addiction vulnerability (Crombag et al., 2025), even though it remains an emerging area. The following chapter will explore this model more in depth.

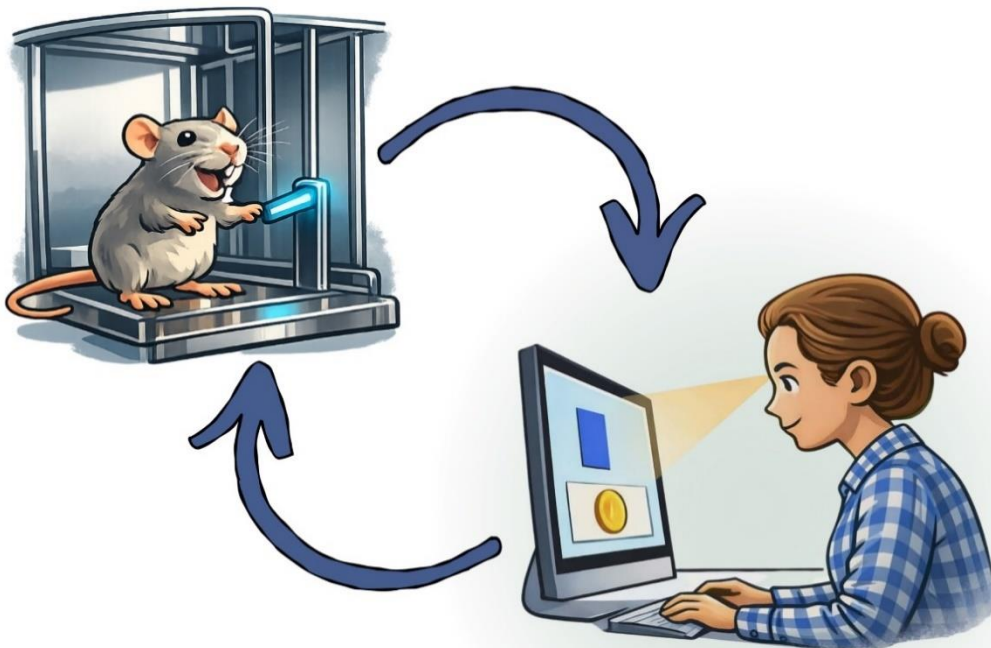
Chapter Summary

- Animal models are inherently simplified representations of complex human phenomena. Their goal is not to replicate every detail but to capture essential mechanisms in ways that generate insights relevant to real-world problems.
- Despite frequent criticism (both scientific and public), animal models have been central to addiction research. Most researchers agree that they have provided foundational contributions to addiction theory and treatment development.
- Some concerns stem from emotional or ethical objections, but others reflect legitimate scientific issues. Problems related to reproducibility, methodological rigor, and reporting standards have increasingly been recognized and must be addressed to reduce the translational gap.
- Nevertheless, several findings originating from animal research have translated successfully to humans. Robust evidence from paradigms such as CPP and PIT shows meaningful cross-species convergence.
- Translational addiction research still faces inherent challenges. Rodents cannot self-report, human experiences and environments cannot be experimentally controlled, and the motivations and contexts of drug use differ across species. Yet continued methodological innovations and scientific advances offer grounds for optimism.
- Among conditioning-based translational models, the Sign-tracker/Goal-tracker framework has recently gained substantial interest for application in human research and will be the focus of the next chapter.

Chapter 3

Of Signs and Goals:

Focus on the Sign-Tracker/Goal-Tracker Model



“...the animal may lick the electric lamp [CS], or appear to take the air into its mouth, or to eat the sound, —that is, licking his lips and making the noise of chewing with his teeth as though it were a matter of having the food itself.”

— Pavlov, *The Reply of a Physiologist to Psychologists* (1932, p. 95)

Introduction

The preceding chapters have underscored the central role of reward-predicting cues and incentive-motivational processes in addiction, particularly through the lens of motivational theories such as the Incentive Sensitization Theory (IST) framework. Across both human and animal studies, we have seen that environmental cues associated with reward can acquire powerful motivational properties, drawing attention and eliciting approach behaviors. Chapter 2 further introduced the field of translational addiction research, illustrating how cue-driven behaviors first identified in animal paradigms can be successfully modeled in humans. This translational approach is crucial not only for scientific advancement but also for ethical and methodological integrity, although it bears several challenges.

Among cue-driven behaviors, sign-tracking has recently emerged as a central focus in contemporary addiction research. As previously discussed, *sign-tracking* (typically measured within Pavlovian Conditioned Approach (PCA) paradigms) refers to the tendency to approach and interact with a cue that predicts reward delivery. In animal research, this behavior has been robustly linked to enhanced vulnerability to addiction-related processes. However, an important challenge for the field concerns the translation of these insights from animal models to human populations. As noted by Crombag et al. (2024, p.568),

“the ST/GT model is potentially an important insight when it comes to preclinical addiction models, but it will be essential (and potentially fruitful) from a translational, model validation perspective that research in this area using human subjects is promoted and expanded.”

Scope of the Chapter

Addressing this translational gap constitutes a central motivation for the present thesis. To situate these objectives within the broader literature, it is essential to first review the theoretical and empirical foundations underlying sign- and goal-tracking.

The first section of this chapter clarifies the range of concepts encompassed by “*sign-tracking*” in the scientific literature. First, sign-tracking refers to a specific conditioned response observed in PCA paradigms (that has been investigated since the 1970s). Later, it was proposed as a theoretical framework for understanding the etiology of addiction, notably through Tomie’s sign-tracking model of addiction. Most relevant to this thesis, however, is the growing recognition that sign-tracking may characterize a subgroup of individuals who are particularly vulnerable to addictive behaviors.

The next section will review the major characteristics that differentiate sign-tracker (ST) and goal-tracker (GT) individuals, as well as traits and processes that tend to co-occur with these behavioral phenotypes. We begin by presenting findings that link sign- and goal-tracking tendencies to addiction vulnerability. We will then delve into other core features that differentiate STs from GTs, highlighting key behavioral and cognitive findings with clear relevance to addiction research. A crucial factor known to significantly modify sign-tracking behaviors, reward uncertainty, will also be briefly described.

Finally, the last section will (very briefly) outline the main paradigms that have been implemented in humans to model sign- and goal-tracking behaviors. Since the primary objective of the scoping review conducted within the framework of this thesis was to address this very topic, this chapter will not delve further into the description of the paradigms. Instead, the scoping review follows as the concluding chapter of the theoretical section (Chapter 4), before transitioning to the experimental section of this thesis.

What Do We Study When We Talk About Sign-And Goal-Tracking?

Sign-tracking has been employed to investigate a wide range of phenomena across the literature, and researchers do not always share the same theoretical objectives when using this paradigm. First, sign-tracking has been conceptualized primarily as a *Pavlovian conditioned response*, used to identify the neurobiological mechanisms through which environmental cues acquire conditioned motivational properties (Fuchs et al., 2019). It thus can serve as an index of cue reactivity, measuring *attraction and incentive motivation attributed to a reward-related cue* (Anselme & Robinson, 2019). Since the emphasis is placed on the behavior itself, this constitutes a rather quantitative approach, with behavioral indices varying along a continuum. Second, sign-tracking has been proposed as a central component of a broader theoretical framework for addiction development, offering explanations for the transition from voluntary, controlled drug use to compulsive, poorly regulated drug taking based on the increasing influence of conditioned cues (Tomie, 2016, 2018). Finally, sign-tracking measurements have served as a *behavioral marker of individual differences in vulnerability to addiction as well as propensity for relapse* (Kuhn et al., 2019). In this context, its measurement serves to differentiate groups of individuals supposed to be more or less vulnerable towards addiction, being a more categorical approach.

The Very Basis: A Conditioned Response

As mentioned in the previous chapter, PCA refers to cue-triggered behavior, largely studied in animals. By measuring the extent to which animals approach (and interact with) cues that are predictive of reward, PCA paradigms typically reveal behaviors of *sign-tracking*²⁷ (Hearst & Jenkins, 1974). To get an integrated understanding of what we are talking about when studying sign-tracking, we must briefly go back to the initial experiments dating back to the late 20th century that shed light on this phenomenon: Pavlovian autoshaping²⁸ studies.

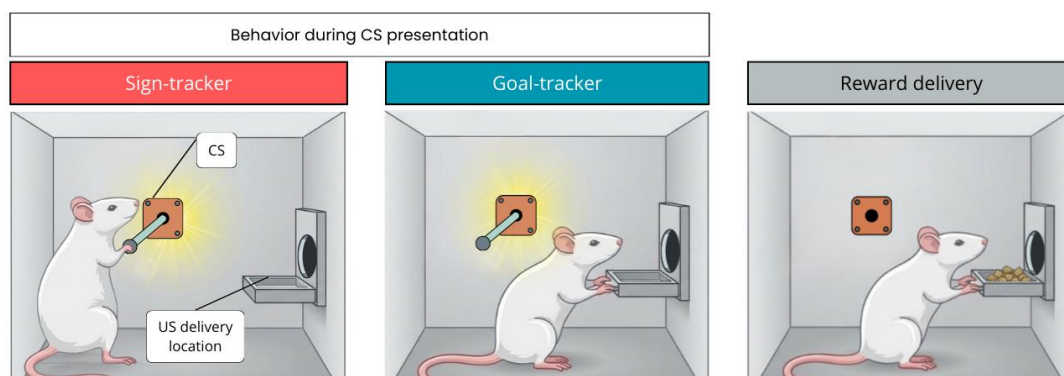
²⁷ Some authors consider PCA as a synonym of sign-tracking (Tomie, 2018).

²⁸ Note that the word « *autoshaping* » is sometimes incorrectly used as a synonym of sign-tracking in the literature (reflecting a confusion between the procedure and the behavior itself), as previously pointed out by others (Crombag et al., 2025; Stephens et al., 2013).

The Pavlovian Autoshaping Procedure

Pavlovian autoshaping procedures consist in repeated trials in which a cue serving as a CS (commonly a retractable metal lever in rodent studies) is briefly presented, and as soon as it disappears, food pellets (US) are automatically delivered (in a near, separate location). Importantly, the animal does not have to perform any specific behavior to obtain the reward (i.e. it is “response-independent”). Yet, after repeated exposure to a CS-US association, different behavioral conditioned responses emerge: some animals, referred to as STs, are drawn toward the lever cue and will engage with (sniffing, pressing, or gnawing) it, because this cue acquired incentive value through learning (Flagel et al., 2007; T. E. Robinson & Flagel, 2009). In contrast, GTs approach and inspect the location where the reward will appear during the lever cue presentation (Boakes, 1977). A third, mixed group (called “intermediates”, INT), displays a combination of both tendencies, approaching either the cue or the food site from one trial to the next (Flagel et al., 2008). Figure 4 illustrates sign- and goal-tracking behaviors in a classical autoshaping task.

Figure 4. *Illustration of Sign- and Goal-Tracking Behaviors in a Rodent PCA Task*



Note. During CS presentation, ST animals orient toward the retractable lever and may approach, touch, or gnaw it. In contrast, GT animals orient toward the location of impending reward delivery (the food tray).

When using PCA tasks to characterize sign- and goal-tracking behaviors, researchers typically take several measurements that together lead to a composite index quantifying individual differences in cue-directed behavior: the PCA index (P.J. Meyer, Lovic, et al., 2012). This index relies on three behavioral metrics recorded during CS

presentation: a probability difference score, calculated by subtracting the probability of food-cup entry from the probability of lever contact; a response bias score (RBS), obtained by subtracting the number of food-cup entries from the number of lever contacts and dividing this value by their total; and a latency difference score, defined as the latency to food-cup entry minus the latency to lever contact, divided by cue duration. The PCA Index is computed as the average of these three scores and ranges from -1 to +1, with more positive values indicating stronger sign-tracking behavior, more negative values reflecting stronger goal-tracking behavior, and values near zero representing theoretically intermediate behavior.

An important factor in eliciting sign- and goal-tracking behaviors in PCA tasks is the nature of the CS. As noted by P.J. Meyer et al. (2014), *"variation in the ability of CSs to acquire incentive salience, and thus their ability to act as incentive stimuli capable of motivating behavior, is determined in part by properties of the CS itself."* (p.1). Supporting this, Beckmann and Chow (2015) demonstrated that visual features of a stimulus are necessary (but not sufficient) to evoke sign-tracking: even when a lever and a nosepoke were positioned identically, the lever reliably produced sign-tracking, whereas the nosepoke produced predominantly goal-tracking. Other work further shows that certain CS modalities, such as auditory tones, fail to induce sign-tracking and instead elicit only goal-tracking, functioning as relatively weak incentive stimuli (P. J. Meyer et al., 2014; J. J. Chow et al., 2016). Similarly, when an extendable lever CS is covered so that it can be heard but not seen, animals shift from sign-tracking toward more intermediate behavioral patterns (Singer, Bryan, et al., 2016). Together, these findings underscore that for sign-tracking to emerge, the cue must be discrete, highly localizable, and perceptually salient.

Conceptualization of Sign-Tracking

Sign-tracking has been conceptualized as an *"an involuntary Pavlovian reflexive response, over which the subject has little or no control"* (Tomie et al., 2016, p.3). Experimentally, this phenomenon was first demonstrated in the classic long-box studies by Hearst and Jenkins (1974), where pigeons came to approach and peck an illuminated

key light CS that signaled forthcoming food US access²⁹. Again, no response whatsoever was needed to receive the US. Yet, pigeons persisted in this pecking behavior even when doing so reduced or prevented food access. Such behavior clearly appears as “aberrant”, since it has no purpose and, like here, may lead to (self-imposed) reward omissions. Thus, sign-tracking was suggested being an “automatic”/involuntary/reflexive behavior, as stated by Tomie and colleagues (2016) “it serves no purpose and is a complete waste of time and energy” (p.9).

A phenomenon closely resembling sign-tracking was reported decades earlier by Breland and Breland (1961), who were professional animal trainers testing operant conditioning in many different species (pigs, chickens, whales, etc.). In their report, called *The Misbehavior of Organisms*, they mention strange behavior patterns that emerged in trained raccoons and other animals, and which could not be explained by classic behaviorist theories. One well-known example involved raccoons that had been trained to deposit coins into a box in order to receive a food reward. Although the animals initially performed the task successfully, their behavior gradually changed: instead of completing the instrumental action efficiently, they began to interact increasingly with the coin itself (rubbing, chewing, and manipulating it) often at the expense of obtaining the food reward³⁰. This pattern suggested the emergence of an involuntary and seemingly maladaptive attraction toward the reward-associated object. Although at the time, the authors interpreted these behaviors not in terms of *sign-tracking* per se, but rather in terms of “*instinctive drift*”³¹, it bears a striking resemblance to sign-tracking, as it reflects a strong motivational attraction toward a reward-associated cue. For this reason, the example has frequently been cited in later discussions of sign-tracking, particularly by Tomie and colleagues (Tomie et al., 2016; Tomie & Morrow, 2018). An important difference from classical sign-tracking paradigms should nevertheless be noted. In the raccoon training task, the coin served an instrumental function in obtaining the food reward and was therefore not a purely Pavlovian CS. Despite this distinction, the example

²⁹ The “long” box means there was a relatively long distance from the cue to the food tray, so that approaching the cue resulted in less or no access to the food.

³⁰ A very cute video illustrating these raccoon experiments is available on the following link: <https://www.youtube.com/watch?v=D52sQJEQI0Y&t=78s>.

³¹ “Instinctive drift” refers to the tendency for a learned, conditioned response to gradually be replaced or disrupted by the animal’s innate behaviors related to that context, such that over time the organism’s performance “drifts” toward instinctive patterns (even when doing so hinders the conditioned response or delays reinforcement) (Breland & Breland, 1961).

remains widely referenced in the literature because it vividly illustrates the powerful and sometimes maladaptive attraction that reward-associated cues can exert over behavior.

As sign-tracking behavior or PCA represent a relatively “simple” form of Pavlovian CRs, it is a powerful tool for assessing the incentive properties of conditioned cues (T. E. Robinson et al., 2014; Stephens et al., 2013), and more specifically its ability to attract behavior (first incentive cue property discussed in Chapter 1). In Chapter 2, we described another widely used method for examining the motivational significance of Pavlovian conditioned stimuli: conditioned place preference (CPP). Notably, several authors have proposed conceptual parallels between sign-tracking and CPP (Cunningham & Patel 2007; McKendrick & Maziane, 2020; Newlin, 1992;). Specifically, some authors suggested that the approach toward the drug-paired context observed in CPP can be viewed as a particular form of sign-tracking, insofar as the drug-associated environment is thought to acquire incentive motivational properties and thereby become attractive (Flagel et al., 2009; Huston et al., 2013; although Cunningham et al., 2006 argued that CPP is not due to Pavlovian approach).

Sign-Tracking With Drug Cues

Because substances of abuse possess strong rewarding properties, the cues that predict them can readily acquire incentive salience (as discussed in Chapter 1). It is therefore not surprising that numerous studies have shown that alcohol cues can also support sign-tracking behavior (Cunningham & Patel, 2007; Krank et al., 2008; Villaruel & Chaudhri, 2016). For example, when a light CS was paired with alcohol, Krank (2003) observed that some rats approached the cue itself, which subsequently altered their operant responding to alcohol. Similarly, using alcohol as the US, Cunningham and Patel (2007) demonstrated that only three pairings of a visual CS were sufficient to produce robust PCA behavior in mice.

Robust sign-tracking responses have also been documented with cues associated with other substances, such as cocaine (Uslaner et al., 2006; Yager & Robinson, 2013) and opioids (Yager, et al., 2015), indicating that the phenomenon generalizes across multiple classes of addictive substances. A later section will examine in more detail the broader implications of sign- and goal-tracking for addiction vulnerability, and therefore this overview is kept intentionally brief here.

Properties and Neurobiological Underpinnings of Sign-Tracking Behavior

Sign-Tracking Persists Despite Non-Reinforcement

A striking aspect of sign-tracking is its persistence even when the reward is no longer available. In animal studies, sign-tracking behavior has been shown to resist reward omission (i.e., withholding the reward when individuals interact with the CS), Pavlovian extinction (i.e. absence of US delivery), and outcome devaluation (i.e. reducing the value of the US through satiation or illness), and individuals classified as STs are more prone to spontaneous recovery than GTs (Ahrens et al., 2016; Beckman & Chow, 2015; Chang & Smith, 2016; Fitzpatrick et al., 2019; Morrison, et al., 2015; Stringfield et al., 2018). These patterns support the view that sign-tracking reflects a form of behavior that is relatively compulsive, persistent, and inflexible (Tomie et al., 2008, 2016).

Consistent with this interpretation, sign-tracking rats even persist in approaching the cue when doing so produces aversive consequences. In a study by Saunders and colleagues, rats continued to approach a cocaine-predictive cue despite needing to cross an electrified grid to reach it, and despite the absence of cocaine delivery during the punishment phase (B. T. Saunders et al., 2013). This persistence in the face of punishment and the absence of the US suggests that sign-tracking is driven by the strong incentive motivational properties acquired by the cue itself, making the behavior difficult to suppress, even under conditions that would normally discourage approach.

Neurobiological Bases

The distinction between sign- and goal-tracking behaviors has contributed to elucidating the neurobiological mechanisms underlying the attribution of incentive salience (a process that, as outlined in Chapter 1, depends heavily on dopaminergic signaling and mesolimbic circuitry). Evidence from multiple studies suggests that these two behavioral phenotypes rely on partially dissociable neural systems (J. J. Clark et al., 2012; Flagel, Clark, et al., 2011; Flagel, Cameron, et al., 2011; B. T. Saunders & Robinson, 2012). This has led researchers to propose that sign- and goal-tracking reflect distinct psychological processes, rooted in the differential engagement of these neural pathways³².

³² this idea will be further developed later from an attentional and learning perspective.

A substantial body of work highlights dopamine's central role in sign-tracking. Dopamine antagonists selectively impair the acquisition of sign-tracking but leave goal-tracking largely unchanged (Flagel, Clark, et al., 2011). Likewise, only STs show a phasic dopaminergic response to the conditioned stimulus in the NAcc core (Flagel, Clark, et al., 2011). They also exhibit activation of the cortico-striatal-thalamic "motive circuit" in response to food- or drug-associated cues (Flagel, Cameron, et al., 2011; Yager et al., 2015), a pattern absent in GTs. Pharmacological evidence further supports this dissociation: after conditioned responding is acquired, intra-accumbens dopamine receptor blockade disrupts the expression of sign-tracking but not goal-tracking (B. T. Saunders & Robinson, 2012). These findings indicate that dopamine in the accumbens core is not required for learning stimulus-reward associations but is essential for attributing incentive salience to reward-predictive cues, consistent with the incentive salience hypothesis.

A more exhaustive review of the neurobiological substrates of sign- and goal-tracking lies beyond the scope of the present work (see Kuhn et al., 2018 for a review).

The Sign-Tracking Model (STM) of Drug Taking

Tomie and colleagues developed the "*Sign-Tracking Model (STM) of loss of self-control of drug-taking*" to explain how initially voluntary, intentional, and seemingly well-controlled drug use gradually becomes automatic, poorly controlled, and addiction-like (Tomie, 1995, 1996; Tomie et al., 2008, 2016, 2018). The model starts with the observation that sign-tracking and addictive behaviors share several important features. According to these authors, both can persist despite negative consequences, and may appear relatively independent of conscious intention or deliberate choice. Tomie was one of the first to explicitly connect these phenomena, suggesting that Pavlovian sign-tracking offers a useful framework for understanding the emergence of compulsive drug taking (Tomie, 1996; Flagel et al., 2009).

The central claim of the STM is that the loss of control over drug taking arises from the development of a Pavlovian sign-tracking conditioned response toward cues associated with drug administration (Tomie et al., 2016). In classical sign-tracking procedures, repeated pairings of a CS with a US cause the cue itself to acquire

motivational properties, such that individuals begin to approach, contact, and engage with that cue. Tomie and colleagues argued that human drug taking naturally contains these same elements, because drugs are typically consumed through small manipulable objects (e.g., a wine glass, beer bottle, syringe, pipe). Repeated pairings between such objects and the rewarding effects of the drug may therefore establish sign-tracking toward the drug-taking conduit itself. In the case of alcohol, they proposed that repeated associations between a specific type of glassware and alcohol reward may lead the glass to acquire excessive control over drinking-related action, thereby contributing to poorly controlled alcohol consumption (Tomie et al., 2016).

Within this framework, addiction is understood as a shift from intentional action to increasingly cue-triggered, reflexive responding. Tomie et al. (2016) describe this as a process whereby a *"thoughtless"* or *"mindless"* form of drug taking emerges: the individual picks up and consumes the drug without having formed a specific conscious intention to do so. This places the STM close to habit-based accounts of addiction (Everitt & Robbins, 2005, 2016), but Tomie's formulation is distinctive in assigning a central causal role to the incentive effects of the drug-taking object itself.

Tomie et al. (2016) further argued that sign-tracking and drug abuse share six common features: both are acquired through CS-US pairings, reflexive³³, triggered by discrete cues, involuntary in the sense that they are difficult to suppress, compulsive in that they may occur despite contrary intentions, and durable, including phenomena resembling relapse. This formulation was intended to capture the way in which cue-controlled behavior may come to dominate action even when the individual explicitly intends not to engage in drug use.

An important precursor to this theory was Tomie's earlier concept of cue-at-the-manipulandum (CAM) (Tomie, 1995, 1996). CAM refers to conditioning setups in which the reward-predictive stimulus is physically located on the object that must be manipulated to obtain reward. Tomie argued that these procedures are especially prone to producing sign-tracking toward the manipulandum itself, because the cue not only predicts reward but is also the very object the organism must approach and contact. As a

³³ understood as *"an acquired reflex, performed automatically without the formation of a specific intention"* (p.18).

result, PCA may become difficult to distinguish from instrumental responding. What looks like goal-directed reward seeking may partially reflect cue-elicited attraction instead.

This concern was extended to rodent alcohol self-administration studies in Tomie et al. (2005, 2006). The authors suggested that typical alcohol self-administration paradigms may unintentionally create a CAM situation when the sipper tube functions both as the means of access and as a salient predictive cue. In such cases, contact with the tube may reflect not only operant alcohol seeking but also Pavlovian sign-tracking. As a result, measured “intake” may be inflated because cue-elicited contacts are counted as voluntary drinking. The sipper tube can act as a cue-bearing manipulandum that enhances intake by eliciting sign-tracking-like behavior. Beyond the methodological point, Tomie argued that CAM conditions model addiction-like behavior. By tightly linking a reward cue to the action device, they promote persistent, stimulus-bound responding—features characteristic of compulsive drug use. Thus, CAM is framed not only as a measurement confound but also as a mechanism through which cues come to dominate behavior.

The role of CAM is further elaborated in Tomie et al.’s (2018) discussion of the “*addiction blind spot*” or “*addiction scotoma*”. Here the emphasis shifts to the user’s failure to recognize that drug taking is becoming cue-driven and no longer fully intentional. According to this view, sign-tracking develops gradually and covertly, so that individuals may continue to experience their behavior as self-chosen even when it has become increasingly automatic. Tomie et al. (2018) link this to an illusion of control: people tend to overestimate their ability to regulate their behavior and may fail to notice when their actions become compulsive and stimulus-driven. The repeated use of a particular drug-taking object is central to this process, as it provides exactly the kind of stable cue-reward pairing that fosters sign-tracking while concealing the transition from voluntary to automatic action.

One of the practical implications of the STM is that interventions could target the cue value of the drug-taking object itself. Tomie and colleagues proposed, for example, that a *broad drinking repertoire* (i.e. drinking alcohol from a wide variety of containers) should reduce the contingency between any one type of glassware and alcohol reward, thereby weakening sign-tracking tendencies. Conversely, a *narrow drinking repertoire*, in which alcohol is repeatedly consumed from the same specialized vessel, should

strengthen the cue-reward relation and therefore be associated with poorly controlled drinking (Tomie et al., 2016). In a similar vein, Tomie et al. (2018) suggested that alcohol-specific glassware could be used for non-alcoholic beverages, or that alcohol could be consumed from unusual containers, in order to break strong cue associations.

A major limit of the STM is that it potentially overstates the extent to which problematic drug taking is purely reflexive, involuntary, or outside intentional control. Contemporary theorists have argued that many behaviors often labeled “*habitual*” or “*automatic*” may still remain sensitive to goals, expectancies, and context, and therefore may not be adequately captured by a simple opposition between voluntary action and cue-driven compulsion (see Buabang et al., 2025; Giannone et al., 2024; Heinz et al., 2024; Hogarth, 2020; Kruglanski & Szumowska, 2020). From this perspective, Tomie’s account may risk underestimating the contribution of goal-directed processes in addiction.

Nevertheless, Tomie’s framework remains valuable for at least two reasons. First, it offers an unusually specific cue-based account of the transition from controlled to poorly controlled drug use, centering on the drug-administration object as a motivationally powerful stimulus. Second, it has also highlighted that individual differences in sign-tracking propensity may index vulnerability to addiction. Indeed, Tomie and colleagues explicitly suggested that a tendency to attribute incentive salience to discrete reward-predictive cues may represent a behavioral trait conferring heightened addiction risk (Tomie et al., 2016, 2018).

Sign-Trackers as A Group of Vulnerable Individuals

As noted earlier, sign-tracking refers to a conditioned response in which an individual approaches and interacts with a cue that predicts reward. Although individuals vary continuously in the strength of this tendency (allowing sign tracking to be quantified dimensionally), in the present section we focus on a categorical approach by comparing individuals who predominantly exhibit sign-tracking or goal-tracking behaviors³⁴.

Individual differences in responses to reward-predictive CSs have played a central role in addiction research, prompting questions such as: *Why do cues acquire such powerful motivational properties in some individuals but not others?* (T. E. Robinson et al.,

³⁴ Mixed profiles also exist (INTs) but are not examined in detail here.

2014). At the core of the ST/GT distinction is the differential attribution of incentive salience to cues. In STs, the CS itself becomes imbued with motivational value; in GTs, it does not (Flagel & Robinson, 2017; T. E. Robinson & Flagel, 2009). Building on this foundation, a large body of work demonstrates consistent differences between STs and GTs across a range of addiction-relevant processes.

As emphasized by Tomie (2018), individuals differ both in their vulnerability to addiction and in their propensity to exhibit sign-tracking, and these tendencies reliably co-vary. Consequently, sign-tracking has been proposed as a behavioral marker of heightened addiction vulnerability (Flagel et al., 2009; Flagel & Robinson, 2017). This aspect will be further developed in the following sections.

STs show markedly stronger approach behaviors toward incentive cues, reflecting the greater motivational significance these cues acquire for them. This has been demonstrated for cues associated with both natural rewards and drugs. For instance, P. J. Meyer, Ma, et al. (2012) showed that STs more readily approached a tactile cue paired with cocaine and emitted more positive ultrasonic vocalizations (USVs), an index of positive affect in rodents. Cocaine itself also elicited stronger and sensitizing USVs in STs, and individuals with the highest initial USV responses were more likely to later be classified as STs (Tripi et al., 2017). Yager and Robinson (2010) also showed that a food-cue is more effective in reinstating food-seeking behavior, following extinction of the instrumental response, in STs than GTs, showing that it has more powerful incentive properties in STs.

Consistent with these findings, reward-paired cues function as more powerful conditioned reinforcers in STs across multiple studies (Lomanowska et al., 2011; P. J. Meyer, Lovic et al., 2012; T. E. Robinson & Flagel, 2009; Yager & Robinson, 2010), a pattern that also extends to drug-associated cues. A clear demonstration comes from Yager and Robinson (2013), who showed that after identical cocaine self-administration histories and subsequent Pavlovian cue pairing, a cocaine-associated light cue reinstated drug-seeking far more robustly in STs than in GTs. Consistent findings have been reported for cues associated with cocaine (B. T. Saunders & Robinson, 2010), nicotine (Versaggi et al., 2016; Yager & Robinson, 2015), alcohol (Villaruel & Chaudhri, 2016), and remifentanyl (Yager et al., 2015).

Finally, and directly echoing with the STM, STs and GTs also differ in their sensitivity to outcome devaluation (as mentioned earlier, suggesting more rigid/compulsive aspects in sign-tracking). Following US devaluation, GTs typically reduce both cue- and outcome-directed behavior, whereas STs continue to respond to the cue (Keefer et al., 2020; Morrison et al., 2015). However, extended autoshaping training can render STs sensitive to outcome devaluation (Derman et al., 2018; Keefer et al., 2020), suggesting they are not as inflexible as originally thought.

Although STs and GTs are often conceptualized as opposing traits, individuals do not rely exclusively on one strategy or the other. Empirical evidence shows that both behaviors can emerge within the same organism, indicating that all individuals possess the capacity to engage in both sign-tracking and goal-tracking (Beckmann & Chow, 2015). As noted earlier, factors such as the sensory properties of the cue can influence which strategy is more likely to be expressed in a given context (Beckmann & Chow, 2015; P. J. Meyer et al., 2014). Several authors have proposed that the neurobehavioral valuation processes underlying sign- and goal-tracking operate as independent yet parallel systems within individuals (Beckmann & Chow, 2015; J. J. Clark et al., 2012). Thus, sign-tracking does not represent an intrinsically abnormal behavioral pattern. Because the attribution of incentive salience supports survival-relevant behaviors (locating food, mates, or other biologically significant resources), sign-tracking can, under appropriate circumstances, represent an adaptive strategy that enhances resource acquisition (Domjan, 2005; Hollis, 1982; 1997). As Hollis (1982) noted, *"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"* (p. 3). Moreover, sign-tracking is far from unique to rodents or humans. It has been observed across a remarkably wide range of species, including primates, horses, birds, and fish (Bullock & Myers, 2009; Burns & Domjan, 2001; Miyashita et al., 1999; Nilsson et al., 2008), and even among invertebrates such as cephalopods (Purdy et al., 1999), suggesting it has deep evolutionary roots.

Characteristics of the ST and GT Endophenotypes

Vulnerability To Addictive Behaviors

The most extensively studied difference between STs and GTs (and the one most relevant to the present work) concerns their respective vulnerability to addictive behaviors. A substantial body of evidence indicates that STs exhibit a range of behavioral characteristics associated with heightened addiction risk.

For instance, STs have been shown to self-administer larger amounts of cocaine at low doses (Beckmann et al., 2011), to prefer drug rewards over non-drug alternatives such as food (Tunstall & Kearns, 2015; but see Vanhille et al., 2015), and to work harder to obtain cocaine (B. T. Saunders & Robinson, 2011). They also exhibit stronger drug-seeking behavior and a heightened propensity for relapse (both drug-induced and cue-induced) following periods of abstinence (B. T. Saunders & Robinson, 2010; B. T. Saunders, Yager, & Robinson, 2013; B. T. Saunders & Robinson, 2011). Additional findings show that STs are more likely than GTs to approach cues predictive of opioid delivery, such as cues signaling intravenous remifentanyl (Yager et al., 2015). Cues paired with cocaine likewise acquire greater motivational value in STs, eliciting more approach behavior and more persistent drug seeking (Yager & Robinson, 2013).

However, not all studies have produced consistent results, and mixed results have also been published. For instance, B. T. Saunders and Robinson (2010) observed no ST/GT differences in the acquisition of cocaine self-administration during Pavlovian approach training, although this may have resulted from the use of a nose-poke rather than a lever-based response. Importantly, after extinction, STs made significantly more responses for the cocaine cue, indicating that the cue functioned as a more potent conditioned reinforcer for STs. Similarly, with nicotine, Yager and Robinson (2015) found that nicotine-predictive cues elicited dose-dependent approach behavior in both STs and GTs. However, as with cocaine cues, nicotine cues acted as more effective conditioned reinforcers in STs.

Additional challenges to the ST-addiction vulnerability hypothesis have emerged. Pohořalá et al. (2021), for example, reported no association between sign-tracking and several addiction-like behaviors in rats. In response, Flagel et al. (2021) argued that

methodological limitations (particularly the presence of contextual cues) made it difficult to detect the specific vulnerabilities predicted by the sign-tracking phenotype in their study.

Yet, STs are recognized in the literature as being more vulnerable than GTs when it comes to addiction. T. E. Robinson et al. (2018) synthesized evidence supporting the view; and key factors include enhanced initial drug motivation in STs, heightened sensitivity to discrete cues, greater resistance to Pavlovian extinction; increased preference for drug over non-drug rewards and greater engagement of incentive motivational neural systems (Ahrens et al., 2016; Flagel et al., 2011; B. T. Saunders and Robinson, 2010, 2011; B. T. Saunders et al., 2013; Singer, Guptaroy et al., 2016; Tunstall and Kearns, 2015; Yager et al., 2015).

Another line of research suggests that the relationship between sign-tracking and substance use may be bidirectional. Several studies report that adolescent alcohol exposure reduces goal-tracking behavior (Madayag et al., 2017) and increases sign-tracking tendencies in adulthood (McClory & Spear, 2014; Spoelder et al., 2015). Alcohol exposure also alters dopaminergic function, including increased phasic dopamine signaling to conditioned stimuli (Fiorenza et al., 2018) and to positive prediction errors (Spoelder et al., 2015). Acute alcohol effects may similarly modulate approach behavior: Duckworth (2017) found that a low alcohol dose (0.3 g/kg) increased sign-tracking, whereas a higher dose (0.6 g/kg) had no effect.

Although many findings converge on the conclusion that STs are, on average, more vulnerable to addiction than GTs, a growing body of evidence indicates that the distinction between the two phenotypes is more nuanced and can shift depending on environmental and experiential factors. For example, prolonged and intermittent cocaine self-administration induces incentive sensitization in both STs and GTs, reducing the behavioral differences that are typically observed early in training (Kawa et al., 2016).

A more complex picture is also supported by the observation that GTs appear particularly sensitive to contextual and auditory cues. Indeed, a tone CS (which is not easily localizable within the operant chamber and cannot be approached *per se*) tends to promote goal-tracking rather than sign-tracking responses (P. J. Meyer et al., 2014). This is noteworthy because contextual cues are well known to play a central role in cue-evoked relapse in addiction (Chaudhri et al., 2008; Crombag et al., 2008; Crombag & Shaham,

2002; Valyear et al., 2017). Thus, GTs may also possess a particular vulnerability to addiction, albeit driven by different types of cues than those affecting STs.

For example, Saunders & Robinson found that GTs exhibit stronger context-conditioned hyperactivity and greater context-induced reinstatement of drug-seeking than STs (B. T. Saunders & Robinson 2012). Additional evidence for heightened contextual sensitivity in GTs comes from studies reporting enhanced context-based fear conditioning in this phenotype (Morrow et al., 2011). Pitchers, Phillips, et al. (2017) provided further mechanistic insight by demonstrating that GTs show increased vulnerability to cocaine-seeking relapse when the drug cue functions as an occasion setter (when it signals drug availability). Interestingly, another study by Pitchers and colleagues reported that a tone CS reinstated cocaine seeking equally in STs and GTs, diverging from the typically observed phenotype differences in cue reactivity (Pitchers, Wood, et al., 2017).

Environmental factors further complicate the ST/GT distinction and align well with known risk and protective factors in addiction. Rats reared in social isolation exhibit elevated sign-tracking behavior relative to controls (Lomanowska et al., 2011), whereas environmental enrichment and positive social interactions tend to buffer against maladaptive cue-elicited responding, reducing sign-tracking tendencies (Beckmann & Bardo, 2012).

Robinson and colleagues propose that STs are not uniformly more susceptible to addiction than GTs; rather, different individuals may follow different pathways into addiction (T. E. Robinson et al., 2014). As suggested by Kawa et al. (2016), it is the constellation of behavioral traits that often accompany the ST phenotype that increases the probability of escalating from casual to compulsive drug use. Tomie and colleagues (2016) similarly argue that sign-tracking reflects *an observable expression of an underlying personality profile associated with heightened addiction vulnerability*.

Taken together, this literature suggests that STs tend to show elevated addiction risk because they exhibit a broader *"trait complex"*, which, alongside heightened cue-triggered motivation, also includes characteristics such as impulsivity and poor executive control (Flagel & Robinson, 2009; Flagel et al., 2021; T. E. Robinson et al., 2018; Sarter & Phillips, 2018). Some of these traits (such as impulsivity) are well-established risk

factors for addiction (Flagel et al., 2010; Molander et al., 2011; Verdejo-Garcia & Albein-Urios, 2021).

Finally, recent studies investigated whether sign- and goal-tracking phenotypes are relevant to human addiction. As will be reviewed in the following chapter (Scoping review, Heck et al., 2025), emerging evidence suggests similar patterns in both non-clinical and clinical human samples. However, compared to the extensive findings in animal models, human research in this area remains limited and is still developing.

Cognitive, Behavioral and Personality Characteristics

Impulsivity

Impulsivity, broadly defined, is a common trait of human behavior. It can be defined as a tendency to act prematurely without foresight (Dalley et al., 2011), but it is a multidimensional construct rather than a unitary trait. Indeed, various forms of impulsivity have been described (Evenden, 1999), encompassing partially dissociable behavioral and neurobiological processes (Dalley & Robbins, 2017). Shortly, in rodents, two major types of impulsivity are often distinguished (Chirinéa & Gouveia, 2019)³⁵: impulsive action ("the inability to withhold from making a response" (Winstanley et al., 2006)) and impulsive choice (referring to decisions that fail to adequately consider alternative outcomes and are therefore suboptimal (Dalley & Roiser, 2012)).

Human studies further fractionate impulsivity into dimensions such as urgency, lack of planning, lack of perseverance, and sensation seeking (Whiteside & Lynam, 2001), which are commonly assessed through self-reports. Unfortunately, several authors have pointed out that impulsivity assessed through behavioral measures (whether in animals or humans) is often difficult to reconcile with impulsivity assessed through self-report instruments (Dick et al., 2010; Reynolds et al., 2006). Yet, there are some behavioral tasks that can be directly translated between these species (see Esteves et al., 2021 for a review of such translational tasks). The concept of impulsive choice can be conceptually related to "*risky decision making*" in humans, with personality traits such as impulsivity predicting risky decision making (Lauriola et al., 2014).

³⁵ but others exist such as reward sensitivity and rash impulsivity in the field of addiction (Dawe and Loxton, 2004).

Impulsivity and risky decision-making have been consistently implicated in alcohol use, gambling disorder, and addiction vulnerability (Herman & Duka, 2019; Kovács et al., 2017; MacKillop et al., 2011). In rodents, individuals with higher alcohol consumption exhibit greater sensitivity to delayed rewards (Beckwith & Czachowski, 2016; Wilhelm & Mitchell, 2008), a phenotype proposed as a predisposing factor for substance use (and other) disorders (Bickel et al., 2012; Gowin et al., 2019). Similarly, in humans, elevated impulsivity is associated with heavier alcohol use, including in non-dependent individuals with a family history of alcohol abuse (Sanchez-Roige et al., 2014, 2016). This relationship appears bidirectional, as alcohol intoxication itself further impairs inhibitory control, thereby promoting continued consumption (Herman & Duka, 2019). Converging evidence from longitudinal and clinical studies suggests that non-planning and affect-driven impulsivity, as well as reward-related valuation processes, are particularly robust predictors of SUD vulnerability (Verdejo-Garcia & Albein-Urios, 2021).

A critical link between impulsivity and sign-tracking has long been suggested (Tomie et al., 1998; 2008), although comparatively few studies have examined this relationship experimentally. Existing evidence indicates that ST rodents exhibit greater action impulsivity, typically measured as premature responding. STs make more premature responses than GTs (C. P. King et al., 2016; Lovic et al., 2011), and Flagel et al. (2010) likewise reported that STs were more impulsive on measures of impulsive action, though not on measures of impulsive choice. Importantly, impulsive action is thought to arise from reduced prefrontal cortical regulation over subcortical motivational impulses (Davis et al., 2013; Schmaal et al., 2012), an aspect that has also been extensively examined in relation to sign- and goal-tracking and will be discussed in the following section.

Other studies however have found differences between STs and GTs specifically on impulsive choice. Tomie et al. (1998) observed that sign-tracking was associated with impulsive choice as a preference for immediate small food reward over delayed large food reward. Olshavsky et al., (2014) also showed that animals orienting to a reward CS (equivalent to sign-tracking behavior) were more impulsive and made more risky decisions. Yet, another study found no difference in risky choice between ST and GT rats (Ferland et al., 2019). Moreover, recent evidence using the rodent gambling task demonstrates that increased sign-tracking is associated with maladaptive decision-

making, including reduced selection of optimal options, increased preference for high-risk/high-reward choices, and elevated premature responding (Swintosky et al., 2021).

In humans also, similar relationships between sign-tracking and impulsivity were suggested (Cope et al., 2023; Garofalo & di Pellegrino, 2015; Schettino, 2022), although they were based on questionnaire-assessed impulsivity. Risky choice has also been examined in relation to ST/GT (Cherkasova et al., 2024), but findings remain inconclusive. A recent well-powered aggregated analysis (Krom et al., 2026) similarly reported no clear evidence for robust links between ST/GT tendencies, and impulsivity or risky decision-making. The few effects that were observed varied across studies and across specific impulsivity subscales. Nonetheless, one recent study provided an experimental demonstration that human sign-trackers may rely on suboptimal decision strategies when irrelevant Pavlovian cues are present, potentially due to less efficient cue-value updating (Degni et al., 2026).

Attentional Control, Cognitive and Learning Styles

Indirectly linked to impulsivity and risky decision making, a consistent body of literature has examined differences in attention control, and more broadly cognitive styles between STs and GTs. Similar and coherent differences are reported, adding to the big picture of the ST phenotype. Attentional processing and selection have been extensively implicated in addiction, with a large body of literature documenting the presence of attentional biases (ABs) toward substance-related cues. These biases may manifest as a preferential allocation of attention or as difficulties in disengaging from substance-related stimuli (Bollen et al., 2020, 2022; Field & Cox, 2008; McGivern et al., 2021; Pennington et al., 2020). Beyond these effects, evidence also suggests that heavy drinkers may exhibit preferential attentional encoding of alcohol-related information (Tibboel et al., 2010), indicating that such biases can operate at multiple stages of information processing. As outlined in Chapter 1, these ABs are thought to arise from the heightened motivational relevance of substance-related cues, a process central to IST (T. E. Robinson & Berridge, 2001, 2003, 2008). In line with this conclusion, correlational and prospective studies have demonstrated that individual differences in reward-driven attentional capture are significantly associated with (and predict subsequent) substance use, suggesting that such mechanisms may play a critical role in the early stages of adolescent substance use initiation (van Hemel-Ruiter et al., 2013, 2015).

Attentional Control

Comparative studies of STs and GTs consistently reveal poorer top-down attentional control in STs, supported by both behavioral and neurobiological findings (Campus et al. 2019; Koshy Cherian et al. 2017; Paolone et al. 2013). As summarized by Sarter and Phillips (2018), reduced attentional control manifests as unstable task performance, reduced compliance, difficulty recovering after distraction, and increased susceptibility to bottom-up attentional capture by salient cues.

Attentional control in rodents is commonly assessed using the Sustained Attention Task (SAT), in which rats report the presence or absence of brief visual signals. STs reliably perform worse than GTs, showing fewer hits and more missed signals (Paolone et al., 2013; Thériault et al., 2025; but see Phillips & Sarter, 2020). Such poorer attentional control has been consistently associated with decreased prefrontal cholinergic function through several experiments (Koshy Cherian et al., 2017; Paolone et al., 2013).

Based on several experimental findings, Sarter and Phillips (2018) proposed that STs and GTs exhibit distinct cognitive-motivational styles that rely on different neurobiological systems: STs engage a “hot,” dopaminergic, salience-driven mode of processing that prioritizes cue attractiveness, whereas GTs employ a “cold,” cholinergic, utility-based mode that supports goal-directed behavior and suppresses cue-driven responding (Kucinski et al., 2022; Pitchers, Kane et al., 2017; Pitchers, Phillips et al., 2017). This conceptualization resonates with Flagel & Robinson (2017), who emphasize that subcortical motivational circuits regulate the ability of reward cues to gain motivational control over behavior (as in STs), while cortical top-down circuits restrain such cue-driven processes (as in GTs). Accordingly, Phillips & Sarter (2020) found that STs rely heavily on bottom-up signal salience during SAT performance. STs’ accuracy depended strongly on signal brightness, while GTs’ accuracy did not, indicating that cholinergic activation in GTs enables stable performance independent of stimulus salience. In contrast, the relative hypoactivation of the cholinergic system in STs biases them toward bottom-up cue detection. However, more recent findings nuance this strong dichotomy. Thériault et al. (2025) reported ST/GT differences in classic SAT performance but not in distractor variants, suggesting that environmental factors (such as lighting) may influence perceptual sensitivity more strongly than ST/GT phenotype. They conclude that cue-

driven distractibility may be shared across phenotypes rather than strictly separated processes.

Broader Executive Functions

Another group of researchers (Enkel et al., 2019) examined whether STs and GTs differ across broader executive functions, revealing mixed results and domain-specific profiles rather than clear-cut differences. For instance, STs outperformed GTs in an attentional set-shifting task (indexing behavioral flexibility). In contrast, no clear group differences were observed in reversal learning (indexing cognitive flexibility), although other findings (e.g., Nasser et al., 2015) point to higher behavioral inflexibility in STs. As expected, GTs showed superior performance in conditional discrimination tasks requiring inhibitory control (Enkel et al., 2019). On the other hand, STs demonstrated enhanced performance in working memory tasks, particularly under conditions involving longer delays.

Taken together, these findings illustrate that STs and GTs differ not only in their motivational responses to cues and impulsive responding, but also in attentional control, cognitive flexibility, and the neurobiological systems supporting these capacities.

Divergent Learning Mechanisms in STs and GTs: The Model-Free/Model-Based Distinction

There is a long-standing tradition in psychology of distinguishing between two broad processes underlying behavior: a more deliberate, cognitively controlled system and a more automatic, stimulus-driven system. This distinction is reflected in influential frameworks such as Kahneman's dual-system account (System 1 and System 2, Kahneman, 2011) and related dual-process models in addiction research (e.g. Stacy & Wiers, 2010). Although such conceptualizations have been debated in the literature (see Evans and Stanovich, 2013 for arguments counteracting critics of dual-process models), they continue to inform contemporary research, and substantial empirical evidence supports their core premises (for a review, see Lindgren et al., 2019). While a detailed discussion falls outside the scope of the present study, the distinction may nonetheless aid in interpreting the ST/GT phenotypes.

A closely related duality has emerged in the computational study of learning and decision-making, where researchers distinguish between model-free and model-based

learning. Briefly, model-free learning operates in a habitual, automatic manner by relying on past experience to assign value to cues or actions. It works by comparing expected rewards with actual outcomes, generating what is known as a reward prediction error (RPE), which is then used to update the stored value of a stimulus. Behavior is guided efficiently, but somewhat rigidly, as the system does not readily adapt when circumstances change. In contrast, model-based learning involves the construction of an internal representation, or “model,” of the environment. This model includes knowledge about how events are connected and the value of potential outcomes. Although model-based learning is more cognitively demanding, it allows for flexible, goal-directed behavior, enabling individuals to rapidly adjust their actions when either outcomes or environmental relationships change.

This framework has been applied to the ST/GT distinction. As Clark and colleagues (2012) describe, sign-tracking behavior is well aligned with a model-free strategy: STs rely on a relatively low-computational process in which incentive value is attributed directly to reward-predictive cues, such that the cue itself becomes attractive and capable of eliciting approach and engagement. Goal-tracking, in contrast, requires representing the spatial and temporal structure of the environment (i.e., approaching the location where the reward will be delivered) and therefore aligns with a model-based, representational process (J. J. Clark et al., 2012). Such a conceptualization is indeed in line with many experimental findings mentioned above, showing differences in attentional control and other executive functions. This distinction also resonates with the cognitive-motivational framework proposed by Sarter and Phillips (2018), who describe STs and GTs as reflecting “hot” versus “cold” modes of cue processing, respectively.

A substantial body of neurobiological evidence supports this functional dissociation. In sign-tracking, dopamine release in the NAcc closely resembles a RPE signal and is critical for acquiring the behavior (Flagel, Clark, et al., 2011; B. T. Saunders & Robinson, 2012). Comparable signals have been observed in human STs using functional magnetic resonance imaging (fMRI) (e.g., Schad et al., 2020), alongside greater engagement of attentional and salience-related networks in response to reward cues rather than outcomes (Duckworth et al., 2022). Converging electroencephalogram (EEG) findings further suggest reduced cortical control in high sign-trackers, as indexed by an elevated mid-frontal theta/beta ratio (Mattioni et al., 2025). Consistently, disrupting

dopamine transmission in rodents prevents the acquisition of sign-tracking behavior, while leaving goal-tracking unaffected (Flagel, Clark, et al., 2011; Iglesias et al., 2023). In line with this, GTs do not attribute incentive salience to the CS (T. E. Robinson & Flagel, 2009), do not show RPE-like dopaminergic signaling, and do not require dopamine for learning cue–outcome relations (Flagel, Clark et al., 2011), indicating that dopamine is not required for predictive learning per se but for attributing incentive salience to cues (a pattern fully consistent with incentive salience theory).

GTs, in contrast, appear to rely on neural systems associated with higher-order, top-down control and flexible representation (J. J. Clark et al., 2012; Schad et al., 2020). In particular, corticothalamic circuitry seems to play a key role in suppressing incentive salience attribution (Campus et al., 2019; Haight et al., 2015): inhibiting these projections in GTs induces sign-tracking, whereas stimulating them in STs reduces it (Campus et al., 2019).

However, this apparent dissociation (interpreted as reflecting a more “cognitive” or model-based learning style in GTs) has recently been challenged. Notably, Derman et al. (2018) questioned both the strict separation between ST and GT mechanisms and the assumption that sign-tracking is insensitive to outcome value. Using outcome devaluation procedures (via illness induction) they found that sign-tracking behavior was in fact sensitive to outcome devaluation, indicating that it is at least partly governed by reward expectancies rather than being purely habitual or compulsive. Furthermore, Derman and colleagues found that sign tracking to a lever CS could block the acquisition of goal tracking to a tone CS, and vice versa. This suggests that ST and GT behavior may depend on a shared prediction error-driven associative process, rather than on entirely distinct computational systems. In a similar vein, Enkel et al. (2019) reported no significant differences between STs and GTs in outcome devaluation sensitivity, further indicating that goal-directed control is not absent in STs.

Summary: STs and GTs as Complex Endophenotypes

In sum, converging behavioral, cognitive, and neurobiological evidence indicates that sign-tracking and goal-tracking represent distinct motivational-cognitive profiles (Kucinski et al., 2022; Sarter & Phillips, 2018). STs predominantly rely on bottom-up, dopaminergic, stimulus-driven processes that enhance the attribution of incentive salience but weaken attentional control and behavioral flexibility (Campus et al., 2019; J.

J. Clark et al., 2012; Flagel, Cameron et al., 2011; Flagel & Robinson 2017; Haight et al., 2015; Lesaint et al. 2014; P. J. Meyer et al. 2012). In contrast, GTs draw more heavily on top-down, cholinergic, corticothalamic mechanisms that support predictive processing, attentional regulation, and resistance to cue-driven responding.

These patterns broadly correspond to distinctions between model-free and model-based learning systems. However, recent critiques (Derman et al., 2018; Enkel et al., 2019) caution against a strict one-to-one mapping of ST and GT phenotypes onto these computational frameworks. Instead, both forms of learning likely arise from interacting and partially overlapping processes, with individual differences reflecting variability in the balance between incentive salience attribution and cognitive control. When considered alongside differences in impulsivity and risky decision-making, it becomes evident that, at a broad level, the ST endophenotype captures many behavioral characteristics that parallel those observed in human addiction (Colaizzi et al., 2020).

Other Co-Occurring Psychiatric Disorders

The ST/GT model has been proposed by several authors to capture a neurobehavioral endophenotype that could be relevant to a number of psychiatric disorders (Colaizzi et al., 2020; Morrow et al., 2011, 2015; Morrow, 2018; T. E. Robinson et al., 2014; B. T. Saunders and Robinson, 2013). It has been further suggested that the overlapping neurobiological mechanisms underlying sign-tracking, general incentive processes, addiction, and other psychiatric conditions may indicate a shared predisposing factor, potentially helping to explain the observed comorbidity among such disorders (Morrow, 2018). From this perspective, sign-tracking behavior may function as a transdiagnostic marker of vulnerability spanning multiple forms of psychopathology (see Morrow, 2018, for a review). Consequently, several research teams have investigated sign- and goal-tracking behaviors or phenotypes in relation to disorders beyond addiction. Below, I provide a few examples to illustrate the breadth of this emerging line of research.

Attention-deficit hyperactivity disorder (ADHD) provides one example of an impulse-control disorder that may share features with sign-tracking (Morrow, 2018). As outlined above, STs show inhibitory and attentional deficits linked to underlying dysfunction in the cholinergic system (Koshy Cherian et al., 2017; Pitchers, Kane, et al.,

2017). Supporting this potential link, a genetic polymorphism of the choline transporter has been associated with ADHD in humans (English et al., 2009, cited by Morrow, 2018). Dinu et al., (2024) directly investigated a potential relationship with sign-tracking in humans by comparing individuals with ADHD to controls. Although they found no significant group differences in sign-tracking, individuals with ADHD showed a trend toward greater sign-tracking propensity. Additionally, the study found no differences in externalizing behaviors between STs and GTs in either sample.

Anxiety-related disorders may also share mechanisms with sign-tracking. Heightened, cue-evoked responding to aversive events can be viewed as the counterpart to the exaggerated motivational value STs attribute to reward cues, and the primary animal model for anxiety (fear conditioning) parallels the PCA procedure (Morrow, 2018). In this paradigm, the reward is replaced by an aversive outcome. As in the ST/GT distinction, individuals vary widely in fear expression following Pavlovian fear conditioning, and STs show greater fear responses to discrete shock-associated cues than GTs (Morrow, et al., 2011). This suggests that the enhanced emotional and motivational value STs attribute to cues is not restricted to reward (Morrow, 2018). Post-traumatic stress disorder (PTSD) has been suggested to exhibit similar patterns of cue reactivity than addiction, with trauma-related cues triggering persistent, excessive fear states analogous to cue-induced craving. Supporting this parallel, Morrow's group found that STs were more susceptible to developing PTSD-like fear responses that intensify ("incubate") over time (Morrow, et al., 2015)."

Obsessive-compulsive disorder (OCD) has likewise been discussed in relation to sign- and goal-tracking phenotypes. From the perspective of the habit theory, researchers have noted phenomenological similarities between addiction and OCD: both involve stereotyped rituals, and "*intrusive, repetitive thoughts*" (related to craving in addiction) (Grassi et al., 2020). However, recent studies have challenged this parallel between addiction and OCD (and compulsive behaviors more generally) (Singer et al., 2018; Heinz et al., 2024). In animal models, sign-tracking has nonetheless been proposed as a predisposition that may facilitate the transition from functional to dysfunctional checking in OCD, especially given shared involvement of dopamine and the NAcc (Eagle et al., 2020). Indeed, two studies reported that ST rats engaged in more dysfunctional checking

than GTs (Eagle et al., 2020; Vousden et al., 2020), suggesting that the ST phenotype may offer a novel model for pathological checking.

Research has also examined **Parkinson's disease** (PD) in relation to sign- and goal-tracking. This interest stems from evidence that STs show poorer attentional control and heightened addiction vulnerability. In PD, both reduced attentional control and cholinergic losses have been linked to increased fall risk (Bohnen et al., 2009; Kim et al., 2019, cited by Kucinski et al., 2018). Sarter's lab (Kucinski et al., 2018) investigated whether STs' attentional deficits extend to complex motor control. They found that STs fell more frequently than GTs when crossing a straight rotating rod or navigating a rotating zig-zag rod. GTs adopted safer, more strategic movement patterns indicative of stronger top-down control. Furthermore, on a neurobiological level, they also showed that GTs, but not STs, activate the basal forebrain projection system to mediate their relatively superior ability for complex movement control (Kucinski et al., 2019). Since complex motor impairments seem to co-occur with the ST phenotype, the authors suggest that sign-tracking may index an endophenotype that elevates risk for diverse neurobehavioral disorders.

The Impact of Uncertainty

Reward uncertainty is a final factor that critically modulates sign- and goal-tracking. The present section briefly introduces the phenomenon, as a dedicated narrative review later in the thesis (Chapter 8) provides a detailed and integrative account of uncertainty effects on motivational and attentional processes, from a translational perspective.

In the context of Pavlovian autoshaping, *reward uncertainty* refers to conditions in which food is delivered only after some CS presentations, on a random basis, such that the animal cannot predict whether a given CS will be followed by reward or by its absence (Anselme & Robinson, 2020). When reinforcement is probabilistic (e.g., when only 50% of trials are rewarded), animals reliably show an increase in sign-tracking behavior, a pattern documented across several species, including rodents, pigeons, and quail (Anselme et al., 2013; Boakes, 1977; Crawford et al., 1985; Glueck et al., 2018; D. A. Gottlieb, 2004; Hellberg et al., 2018; M.J.F. Robinson et al., 2014; see Anselme, 2018 for a review). Under these conditions, goal-tracking decreases, and a larger proportion of animals adopt a ST phenotype compared to animals trained under conditions of certain reward (M. J. F.

Robinson et al., 2015). These effects can be long-lasting, persisting even after uncertainty has disappeared, and might be accompanied by increases in risk-seeking or gambling-like behaviors (M. J. F. Robinson et al., 2014). Beyond probabilistic manipulations, temporal unpredictability (e.g., variable inter-trial intervals) has also been shown to amplify cue-directed responding (Kaneko et al., 2025).

Given that uncertainty is a defining feature of gambling environments, several authors have drawn parallels between uncertainty-driven sign-tracking and gambling-related behaviors. Indeed, gambling settings are thought to maximize cue-driven responding, and uncertainty-enhanced sign-tracking has been proposed as an experimental model of compulsive “*chasing*” in gambling disorder (Zack et al., 2020). Some authors have even suggested that behavioral addictions may constitute “*an extreme, almost pure form of sign-tracking behavior*” (Morrow, 2018, p.165).

At the neurobiological level, reward uncertainty is associated with increased dopaminergic activity in the NAcc (Fiorillo et al., 2003; Hart et al., 2015). Consistent with this, prolonged exposure to uncertain reward schedules can induce drug-like sensitization and persistent “addiction-like” behavioral states across species (Mascia et al., 2019; M. J. F. Robinson et al., 2015; Singer et al., 2012; Swintosky et al., 2021; Zack et al., 2014, 2020), mirroring the effects of psychostimulants that produce enduring behavioral sensitization.

Although the effect of uncertainty on sign-tracking is quite robust, its theoretical interpretation remains unclear. At first glance, the enhancement of sign-tracking under partial reinforcement appears inconsistent with incentive salience theory, which does not explicitly incorporate reward probability and might predict reduced cue attraction when outcomes are less reliable. Anselme (2018) reports: “*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)*” (p.111). However, when considered from an adaptive perspective, the effect is not necessarily irrational. In natural environments, foraging effort increases when resources are scarce, and uncertainty can therefore serve as a potent motivational signal that engages systems supporting persistence and pursuit (Anselme, 2018).

As will be developed in our published narrative review (Chapter 8), the increased dopaminergic activity may provide a plausible mechanism for the amplification of sign-

tracking under uncertainty. Emerging theoretical accounts propose that uncertainty may not enhance incentive salience per se. Instead, uncertainty may be processed as a *challenge* or difficulty signal, thereby engaging broader effort-mobilization systems (Anselme, 2025). In this view, dopaminergic responses interact with other systems to support adaptive responses to environmental unpredictability.

Human Translational Approaches to Sign- and Goal-Tracking

Crombag and colleagues (2024) have recently highlighted a promising translational opportunity for using the ST/GT model to investigate addiction based on conditioning processes. More broadly, it has been argued that *“phenotyping animals and humans based on behaviors that capture incentive salience is a priority for research and clinical frameworks to understand heterogeneity in AUD”* (Nieto et al., 2021, p.3). Establishing a robust and broadly defined addiction-related vulnerability phenotype (which is presumed to underlie the ST profile in humans) therefore represents an important research objective. However, as noted by others (Flagel et al., 2021; Pohořalá et al., 2021), despite recent progress (e.g., Colaizzi et al., 2020; Garofalo & di Pellegrino, 2015; Schad et al., 2020), we still lack the methodological tools necessary to reliably evaluate sign- and goal-tracking behavior in humans. To date, it remains unclear whether a heightened propensity to attribute incentive salience to reward-predictive cues constitutes a genuine vulnerability factor for human addiction.

Accordingly, the primary aim of this thesis was to investigate sign- and goal-tracking in humans using experimental approaches that parallel those employed in animal research. More specifically, the project examined whether a simple computerized PCA task can capture behavioral phenotypes analogous to the sign-tracking and goal-tracking patterns observed in animals. We also sought to identify the variables that meaningfully influence these behaviors.

Looking back at the aims of translational models and the ideal translation path outlined in the previous chapter, the present work represents the second step (Figure 3, path A → B): evaluating whether a model of addiction vulnerability developed in the animal literature can be meaningfully translated to the human laboratory. Ultimately, laboratory models (both animal and human) should generate knowledge and make

predictions that speak to real-world conditions. However, before a model can be expected to do so, it must first be demonstrated under controlled laboratory conditions that it captures the target phenomenon as accurately as possible and that this phenomenon shows the theoretically expected associations with relevant variables. The experiments in this thesis were designed precisely for this purpose.

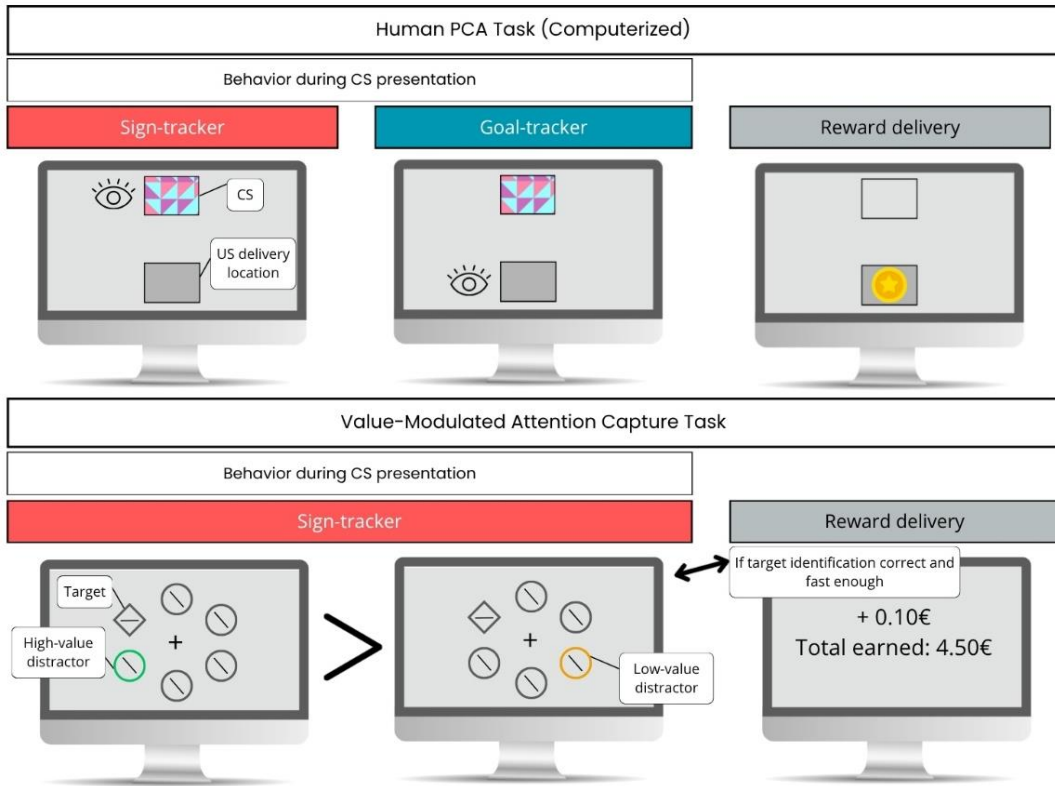
As discussed in the previous chapter, several challenges are inherent to translational research. Human participants may engage strategic cognitive processes to infer the study's aim and adjust their behavior accordingly (Jiménez-Buedo, 2021; Orne, 1962). On the other hand, human studies offer valuable access to subjective reports (feelings, expectations, thoughts) that might provide additional insight into cue-approach behaviors.

A key question, then, concerns how best to implement the ST/GT model in humans. PCA paradigms offer an intuitive translational approach, but they present important practical challenges. Constructing and deploying an apparatus comparable to that used in animal studies is not trivial (see Joyner et al., 2018 for a protocol adapted for children). Moreover, the inherently social nature of human experimentation may impose social norms that discourage participants from freely exploring a room or interacting with objects in a spontaneous manner. Ecological validity also raises questions: what real-world behavior is captured by repeated presentations of a discrete CS preceding a reward in humans? And what stimuli should serve as CS and US? Whereas rodent studies rely on food rewards, these may not be sufficiently motivating for humans depending on hunger state or personal preferences. Computerized PCA tasks address some of these issues by removing the need for physical approach responses, instead inferring sign- and goal-tracking tendencies through eye-gaze patterns (although one might argue that gaze allocation is not strictly equivalent to the physical approach behavior observed in rodents). This approach assumes that allocating more visual attention to the cue versus the reward location reflects the attribution of incentive salience (A. L. Pearce et al., 2022).

Another widely used method for capturing a human analogue of sign-tracking is the Value-modulated-attentional capture task (VMAC) (described in Chapter 1). Several authors have argued that VMAC and sign-tracking share clear conceptual parallels: individuals show an approach-like bias toward a reward-predictive cue, even when doing so is counterproductive (Le Pelley et al., 2015, 2024; A. L. Pearce et al., 2022; Watson,

Pearson, Most, et al., 2019). Figure 5 illustrates human sign-tracking behaviors in both paradigms.

Figure 5. Illustration of Sign- and Goal-tracking Behaviors in Human Tasks



Note. The upper panel illustrates analogous human ST and GT behaviors in a computerized PCA paradigm. While the CS (e.g., a fractal image displayed at the top of the screen) is presented, ST individuals show increased dwell time on the CS itself, whereas GT individuals allocate more gaze time toward the goal location where the reward will subsequently appear (e.g., a coin icon). The bottom panel illustrates sign-tracking-like behavior in a VMAC task. Here, ST tendencies manifest as prolonged reaction times when the search display includes a high-value reward-predicting stimulus relative to a low-value CS. Although this task does not provide a direct behavioral analog of goal-tracking, sign-tracking is generally considered a continuum; thus, reduced sign-tracking-like effects may be interpreted as more GT-like behavior.

In addition to these major paradigms, several alternative approaches have been proposed for indexing human sign (and goal) -tracking (see Heck, Durieux, et al., 2025 hereafter). Neural responses to reward-related (so-called “*sign-tracking-like neural responses*”) have been examined using EEG, particularly through comparisons of brain

responses to food-related versus other appetitive cues (Sege et al., 2025; Versace et al., 2016). The underlying hypothesis is that a human endophenotype resembling sign-tracking would manifest as heightened neural reactivity to food cues (e.g., high-fat/high-sugar foods) relative to other natural rewards. Other more game-like tasks have also been developed to probe human sign-tracking or closely related behaviors (Nelson et al., 2019; Serrano-Barroso et al., 2022).

We do not elaborate further here, as the following chapter presents our scoping review, which provides a detailed overview of these paradigms as well as many recent findings in human sign-tracking research (up to January 2024).

Importantly, and addressing a long-standing gap in the field, several recent studies have examined the psychometric properties of ST/GT identification in humans and the reliability of commonly used tasks such as the VMAC. Badioli et al. (2026) reported that the eye-gaze index commonly used to classify individuals as STs or GTs demonstrates satisfactory test-retest reliability for identifying STs but appears less reliable for identifying GTs—although additional research is needed to substantiate this conclusion. Similarly, Garre-Frutos et al. (2024) investigated reliability issues in VMAC tasks by examining how different preprocessing choices influence reliability estimates. Their findings indicate substantial heterogeneity arising from several preprocessing steps and show that increasing the number of blocks and removing outliers improves the reliability of the VMAC effect. However, they also note that outlier removal may be undesirable when the goal is to preserve individual-difference variability. The authors emphasize the importance of reporting reliability indices when using this task.

Chapter Summary

- Sign-tracking refers to a Pavlovian tendency to approach and interact with a cue that predicts reward delivery, reflecting the cue's acquired incentive value. In PCA tasks, STs approach and engage with the cue itself, whereas GTs approach and inspect the reward location.
- Sign-tracking was also placed at the center of Tomie's Sign-Tracking Model of addiction vulnerability, which argues that loss of control over drug use emerges when sign-tracking CRs develop toward drug-associated cues, with particular emphasis on drinking glassware.
- More importantly, STs form a subgroup especially vulnerable to addiction, displaying co-occurring traits such as heightened impulsivity and impaired attentional control, and have been proposed as complex endophenotypes relevant to addiction and other psychiatric conditions.
- Mechanistically, GTs are thought to rely more on top-down cholinergic, corticothalamic systems supporting prediction, attention, and control, whereas STs rely more on bottom-up dopaminergic, stimulus-driven processes that enhance incentive salience but reduce attentional control and flexibility.
- Several external factors can modify sign-tracking behavior, and reward uncertainty in particular increases sign-tracking (possibly through evolutionarily relevant mechanisms that promote information-seeking and attention to uncertain predictors of reward).
- Although animal research robustly links sign-tracking to addiction vulnerability, translating these findings to humans remains challenging, and is only a relatively recent endeavor.

Chapter 4

Implementations of Sign- and Goal-Tracking Behavior in Humans

A Scoping Review

Michelle Heck

Nancy Durieux

Patrick Anselme

Etienne Quertemont

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Supplementary information for this chapter can be found in [Appendix A](#).

Abstract

Background. Animal research has identified two major phenotypes in the tendency to attribute incentive salience to a reward-associated cue. Individuals called “sign-trackers” (STs) preferentially approach the cue, assigning both predictive and incentive values to it. In contrast, individuals called “goal-trackers” (GTs) preferentially approach the location of the upcoming reward, assigning only a predictive value to the cue. The ST/GT model has been shown to be relevant to understand addiction vulnerability and other pathological behaviors in animals. Therefore, recent studies tried to implement this animal model in the human population.

Objectives. This scoping review aims to identify and map evidence of human sign- and goal-tracking.

Methods. Studies that explicitly measured human sign- and goal-tracking or related phenomena (e.g., attentional bias (AB) induced by reward-related cues), using paradigms in line with the animal model, were eligible for this review. We searched for published, unpublished and grey literature (PhD theses, posters, conference papers) through the following databases: MEDLINE, Scopus, PsycINFO, Embase, Open Science Framework (OSF), and Google Scholar. The Joanna Briggs Institute (JBI) methodology for scoping reviews was adopted. Screening and extraction were carried out by three reviewers, in pairs.

Results. A total of 48 studies were identified. These studies used various experimental paradigms and used the term “sign-tracking” inconsistently, sometimes implicitly or not at all.

Conclusions. We conclude that the literature on human sign-tracking is very heterogeneous on many levels. Overall, evidence supports the existence of sign- and goal-tracking behaviors in humans, although further validated research is crucially needed.

Keywords: Incentive Salience, Pavlovian Conditioned Approach, Animal Model, Eye-Tracking, Addiction, Attention, Motivation

Introduction

Individual differences in the propensity to attribute incentive salience to reward-predictive cues are relevant for the identification of risk profiles in several psychological disorders (Flagel et al., 2010). They may constitute a translational and transdiagnostic model for the etiology and maintenance of a variety of compulsive reward-seeking behaviors (Morrow et al., 2011; Pool & Sander, 2019; B. T. Saunders & Robinson, 2013). Indeed, over the past two decades, animal research has demonstrated that individuals with a higher sensitivity to reward cues are more vulnerable to these cues when related to disorders such as substance use disorders (SUDs) (Hellberg et al., 2019; T. E. Robinson et al., 2014; T. E. Robinson & Flagel, 2009; B. T. Saunders & Robinson, 2011).

In animal research, these effects were identified by means of the so-called “*autoshaping*” procedure, in which the brief presentation of a localizable discrete cue acting as a CS is predictive of the delivery of a food reward (US) immediately after its termination. Although no action is required to obtain the food reward, some individuals approach and interact with the CS (Brown & Jenkins, 1968). Those individuals are called STs, because the predictive cue has become a “*motivational magnet*” following repeated association with the food reward (Anselme & Robinson, 2020; Berridge, 2007; T. E. Robinson & Flagel, 2009). Other individuals, called GTs, only assign a predictive value to the CS; they are not motivationally attracted by the cue, and, during its presentation, they move directly toward the location where the reward is to be delivered. Finally, a portion of individuals are ambivalent, alternating between both types of behaviors (Flagel et al., 2008; P. J. Meyer et al., 2012). This variation in the topography of the conditioned response is not a matter of differences in the strength of Pavlovian learning, as both STs and GTs learn the CS-Food association. It rather reflects differences in the propensity to attribute incentive salience to discrete localizable CS (Flagel et al., 2009; P. J. Meyer et al., 2012; T. E. Robinson & Flagel, 2009; B. T. Saunders & Robinson, 2013), leading to differentiated stable phenotypes. The two phenotypes might be associated with different computational strategies, typically referred to as model-free for STs and model-based for GTs (Huys et al., 2014; Lesaint et al., 2014; Moin Afshar et al., 2023; Schad et al., 2020; Wuensch et al., 2021). Briefly, model-based learning means that the individual is using an explicit cognitive model to produce goal-oriented behaviors, while model-free learning

means that the individual merely reacts to stimuli, based on statistical regularities or associations, and does not implement any cognitive model. This dissociation may therefore imply that GTs approach the reward location due to the previous learning that a reward will be available there (goal-directed), and STs approach and interact with the CS due to its incentive value (e.g., Pellón et al., 2018; Strand et al., 2022).

As outlined above, the propensity to sign-track may predispose individuals to approach and pay attention to cues repeatedly associated with reward. The Incentive Sensitization Theory (IST) of addiction (T. E. Robinson & Berridge, 1993) relies on the evidence that exposure to highly rewarding substances, such as drugs of abuse, induces excessive attraction for their associated cues through permanent sensitization of dopamine neurons in the brain. So, there is a continuum between the incentive salience of a mere food cue (e.g., odor) and incentive sensitization, leading to various pathological behaviors such as overeating and craving—defined as “*a strong desire or compulsion to take the substance*” (WHO, 1992). Incentive sensitization is a source of AB, that is, implicit changes in attentional resource allocation and approach behaviors toward those cues (Field & Cox, 2008).

A growing body of literature has shown that the ST phenotype is associated with a higher vulnerability to drug addiction (Anselme & Robinson, 2020; B. T. Saunders & Robinson, 2011). Indeed, ST rats self-administer addictive substances more frequently and are more prone to relapse (B. T. Saunders & Robinson, 2011; Tomie et al., 2008). Compared to GT rats, they have also been shown to display other behavioral characteristics linked to pathological behaviors in humans, such as greater impulsivity (P. J. Meyer & Tripi, 2018), less top-down control (Paolone et al., 2013), and greater novelty-seeking (Beckmann et al., 2011). Given the predominance of the ST/GT model in the animal literature in the explanation of SUDs and other pathological behaviors (such as ADHD, inhibitory control, maladaptive eating behaviors, etc.), recent studies tried to implement this animal model in the human population.

For several years, researchers have attempted to find appropriate experimental paradigms to implement a human equivalent of sign-tracking behavior such as observed in rats and other species (for reviews see Anselme & Robinson, 2020; Colaizzi et al., 2020), a behavior whose relevance to human addiction is well known (Tomie et al., 2008). One major problem with human experimental settings, is that direct measures of behavioral

approach (such as the time latency before physical contact or the number of lever presses by a rat) are not easily implemented, perhaps in part because human adults have internalized social rules of not touching what does not belong to them. As a direct consequence, a great majority of researchers have created paradigms in which approach is inferred from proximal measures (B. T. Saunders & Robinson, 2013), in particular, visual attention allocated to a CS. This perspective sounds legitimate in the sense that sign-tracking is akin to the Abs observed, for instance, in response to drug cues compared to neutral cues in humans (Anselme & Robinson, 2020; Field & Cox, 2008).

To date, most attempts to measure human sign-tracking behavior were carried out through computerized tasks based on reaction time (Albertella, Le Pelley, et al., 2019; Albertella, Watson, et al., 2019; C. Liu et al., 2021; Watson, Pearson, Most, et al., 2019), sometimes coupled with an eye-tracking device (Garofalo & di Pellegrino, 2015; Schad et al., 2020). However, experimental paradigms that measure actual approach behaviors are also increasingly emerging (Colaizzi et al., 2023; Cope et al., 2019). Another procedure sometimes used in the ST/GT literature is the “Pavlovian-to-Instrumental Transfer” (PIT) task. The principle behind PIT is to induce a cue-reward association through Pavlovian conditioning to alter instrumental responses to the cue (Cartoni et al., 2016; for a recent review of this concept, see Garbusow et al., 2022). In altering the motivational influence of the reward predictive cue, PIT has much in common with sign-tracking (Garbusow et al., 2014). Indeed, individual differences in human PIT have been found to relate to sign- and goal-tracking behavior (Garofalo & di Pellegrino, 2015). The PIT effect has also previously been used to quantify incentive salience attribution (Sebold et al., 2021; Wassum et al., 2013). However, the PIT and the ST/GT paradigms also differ in many respects. In the PIT procedure, the propensity to attribute incentive salience to the CS is not directly tested. What is tested is the ability of the CS to alter the instrumental response for the reward. The standard PIT procedure cannot therefore easily identify ST/GT phenotypes. In the context of sign-tracking studies, only the Pavlovian phase of the PIT procedure may characterize behavioral phenotypes relating to sign- and goal-tracking.

The literature on human sign- and goal-tracking encompasses diverse experimental paradigms, including computerized and real-life tasks. A crucial point for the human study of sign- and goal-tracking is to use a definition of sign-tracking behavior as close as possible to that found in the animal literature. Indeed, inconsistencies and

heterogeneity in the experimental results sometimes originate in differences in the interpretation of the phenomenon. For example, *autoshaping* denotes an experimental procedure and *sign-tracking* a behavior, but both terms are sometimes used as if they were synonyms and hence used interchangeably (Kearns & Gomez-Serrano, 2010; Pithers, 1982; Tomie & Morrow, 2018). In another vein, behaviors akin to sign- and goal-tracking in human participants have also sometimes been defined in very vague ways, such as "*abnormal responses to reward cues*" (Wardle et al., 2018) and "*markers of impulsivity and attentional problems focusing on individual differences*" (Serrano-Barroso et al., 2022).

While many attempts to transpose the animal ST/GT model in humans were published in the last decade, there has so far been no review summarizing the existing experimental paradigms. Gathering the relevant literature is made difficult by significant methodological deviations from the original ST/GT animal paradigm in some studies. Other studies investigate this phenomenon more closely, but without any reference to "*sign-tracking*" and/or "*goal tracking*". Given the broad range of literature to be considered in the present review, precise inclusion criteria had to be defined. For instance, studies investigating attentional capture in relation to rewards were included because of their relevance for human sign-tracking behavior, whereas studies investigating ABs (i.e., the automatic capture of attention by stimuli naturally associated with rewards such as drugs of abuse or fast-food) were not included. Although ABs are clearly related to sign-tracking behavior, the inclusion of such studies would be far beyond the scope of the present review.

A preliminary search was conducted on Medline (OVID), PsycInfo (OVID), and the OSF platform. No planned or published systematic or scoping reviews on human analogs of sign- and goal-tracking behaviors were identified. A systematic review project was published on OSF (McGinley, 2020), but only focuses on the PIT paradigm. Colaizzi et al. (2020), as well as Anselme and Robinson (2020), have reviewed and discussed the neurobiological and behavioral aspects of sign-tracking in animals while describing recent attempts to translate animal research in humans. Colaizzi and colleagues concluded that "*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" (p. 91). Anselme and Robinson stated that *"in humans, sign-tracking can be likened to a form of attentional bias"* (p. 9), and that *"attentional bias in humans and sign-tracking in animals may therefore likely underlie similar phenotypes, both primarily modulated by dopaminergic activity, and could provide a strong translational bridge for addiction and gambling research"* (p. 9). To the best of our knowledge, however, no systematic description of the domain including recommendations for future research has yet been provided. Given the diversity in the ways of implementing the ST/GT model in humans (Colaizzi et al., 2020) and the lack of consensus on the method to be used, the present scoping review aims to identify and map what has been done on this topic. A synthesis of this literature is crucial for future research, as it represents a first step towards a consensus on the human analog of a widely validated paradigm in animal research, potentially relevant for the study of vulnerability factors for several pathological behaviors. The research question of the current review was *"What is known about sign-tracking/goal-tracking in humans? And what methods have been used to implement and measure a human equivalent of sign- and goal-tracking behaviors in animals?"*.

Methods

This review was conducted in accordance with the JBI methodology for scoping reviews (Peters et al., 2020) and was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Scoping Reviews (Tricco et al., 2018).

Inclusion Criteria

Participants

This scoping review considered studies that included human subjects, regardless of gender, age, health status, or ethnicity.

Concept

This scoping review considered studies that implemented and measured sign-tracking and/or goal-tracking behavior in humans. Because there is no unequivocal definition of the human analog of this model, this review included studies that:

- Explicitly mentioned implementing or measuring sign-tracking/goal-tracking behavior in humans, regardless of the method used.
- Did not explicitly mention *human sign- or goal-tracking*, but referred to closely related concepts/methods such as:
 - the "*tendency to attribute incentive salience to reward stimuli*", or "*the vulnerability/susceptibility to the influence of Pavlovian cues*" in humans, with a measure that is equivalent or very close to sign- and goal-tracking behavior in animals,
 - human PIT, and included a measure that is equivalent or very close to sign- and goal-tracking behavior in animals,
 - "*human autoshaping*", with a measure that is equivalent or very close to sign- and goal-tracking behavior in animals,
 - "*reward-related attentional capture*" in human subjects, with a measure that is equivalent or very close to sign- and goal-tracking behavior in animals.

In order to consider only experimental paradigms that were "*equivalent or very close to*" the animal ST/GT model, we needed to establish more specific exclusion criteria. The exclusion procedure was therefore based on 5 sub-criteria, which were used during the whole process. Studies that did not explicitly state implementing or measuring human sign- and goal-tracking were excluded when:

- The CS-US association was not created in the laboratory (within the experimental setup) but occurred in real-life settings (e.g., a well-known logo such as "McDonald's yellow M"). This excluded most AB studies, which were out of the scope of the present review.
- There was no opposition between the attractiveness of the CS and of the reward delivery location (this excluded, for example, studies in which the response to the

CS was recorded under extinction, a scenario unrelated to the Pavlovian autoshaping paradigm).

- Reward delivery required an instrumental response (i.e., the CS-US association was not purely Pavlovian, as it is in the animal model).
- The experiment did not involve a positive outcome (i.e., absence of reward during the task or learning based on aversive conditioning).
- The experiment did not involve a measure of CS attractiveness (this excluded experiments only based on instrumental measures such as invigoration of response rates, pure reaction time measures or physiological measures, as these strongly deviate from the initial animal model).

In brief, this review included: (1) studies that clearly state that they investigate human sign- or goal-tracking, regardless of the methods used; (2) studies that claim to investigate human sign- or goal-tracking (or draw an explicit parallel with it) even though they meet some of the exclusion criteria; and (3) studies that do not explicitly claim to investigate human sign- or goal-tracking but used similar methods described above, with the additional condition that they do not meet one of the exclusion criteria.

Context

This review considered all contexts.

Types of Sources

In this scoping review, we included published or unpublished experimental studies written in English, as well as grey literature (except Undergraduate and Master theses).

Search Strategy

The search strategy aimed to find published, unpublished, and grey literature relevant to the review question. First, an initial limited exploratory search was conducted to help identify relevant search terms. Next, a complete search using all identified keywords and index terms was undertaken on April 26, 2023. The consulted resources were Medline (OVID), PsycInfo (OVID), Embase (Elsevier) and Scopus (Elsevier) (see [Appendix A](#), table A for search strategies). Subsequently, the reference lists of the included studies and of the relevant reviews found during the search process, were hand searched for additional studies. Finally, citing literature (identified through Google

Scholar's "*cited X times*") of the selected studies was scanned for relevance and possibly included. A complementary literature search was completed on November 6, 2023, through Google Scholar and OSF. Citation searching of included sources was performed on November 30, 2023. For any posters or congress papers identified, a search by author was performed to seek for a published version of the studies they present (this was not planned in the registered protocol).

The research was not restricted to a given period, because the first human sign-tracking studies date back to the 1980s.

Study Selection

After the search was completed, all records were uploaded to the Covidence systematic review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), and duplicates were removed. Three reviewers, in pairs, independently screened the title and abstract of studies, and excluded studies that did not meet the inclusion criteria. One reviewer screened all references (MH) and two reviewers, each screened half of the references (PA & EQ). The full-text studies were retrieved and uploaded to Covidence. The selected studies were then assessed independently by three reviewers (same procedure as mentioned above) to determine if they met the predefined inclusion criteria. Any disagreement was resolved by consensus or through discussion with the third reviewer. Quality appraisal of the selected studies was not conducted since the standard procedure and aim of scoping reviews is to provide an overview of the literature (Peters et al., 2020).

Data Extraction

Data were extracted from the included sources by three independent reviewers (same as mentioned above) using a data extraction tool developed by the authors (see [Appendix A](#), Table B) and refined during the process, following the JBI scoping review methodology (Peters et al., 2020). Any disagreements that arose between reviewers were resolved through discussion or with the third reviewer. When necessary, the authors of the selected studies were contacted to request missing or additional data. In case no response was received within the next two weeks, only the available data were extracted (this was not mentioned in the registration but had to be decided during the process for scheduling reasons).

Data Analysis and Presentation

Results are presented graphically or with tables when useful. The accompanying narrative further describes the literature. The findings of the review are presented in five sections, organized according to the experimental paradigms that were identified, and one additional section.

Transparency and Openness

We adhered to the PRISMA 2020 guidelines for systematic reviews (Page et al., 2021). There is no data or code available since this is a theoretical review. Graphical presentations were created using R, version 4.3.3 (R Core Team, 2024). This review project was preregistered on OSF, at <https://osf.io/utfcq/>. Two amendments were made after protocol registration and are already mentioned above. They concern (1) an additional search by author name, for each identified poster/congress paper, and (2) the definition of five precise exclusion criteria, allowing us to consider only experimental paradigms that were “*equivalent or very close to*” to the animal ST/GT model.

Results

Study Inclusion

A total of 2754 references were identified and uploaded to Covidence for screening. Of these, 1602 were duplicates. At the title and abstract phase, 1152 studies were screened, with 925 classified as irrelevant. Five citations were not available as full text, neither in open access, nor through our libraries or after contacting the authors. There were 222 full-text studies assessed for eligibility through full-text screening, and 178 were excluded (see [Appendix A](#), Figure A, for PRISMA flowchart, Page et al., 2021).

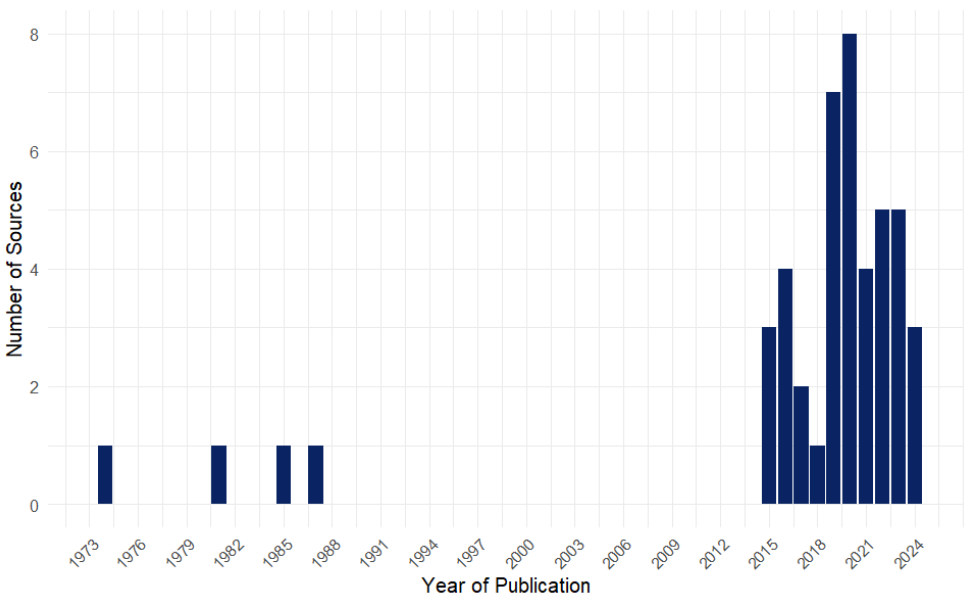
The complementary search resulted in the inclusion of 11 additional reports. Three articles for which we already identified the preprints were published in January 2024 and were thus merged with their preprint (Cherkasova et al., 2024; Dinu et al., 2024; Watson et al., 2024). In total, 46 studies (from 58 reports) were included in the review.

Characteristics of the Included Studies

The characteristics of the included studies are presented in [Appendix A](#) (Tables). Studies were published across the date range 1974 to 2024, showing an early interest for

this topic 50 years ago and a growing interest since 2015 (see figure 6). Thirty-nine studies were reported in journal articles, 3 in PhD theses, 3 in posters or conference abstracts, and 1 in a preprint. One PhD dissertation was subdivided into 3 parts, because 3 very different paradigms were implemented in the research program (Colom, 2023).

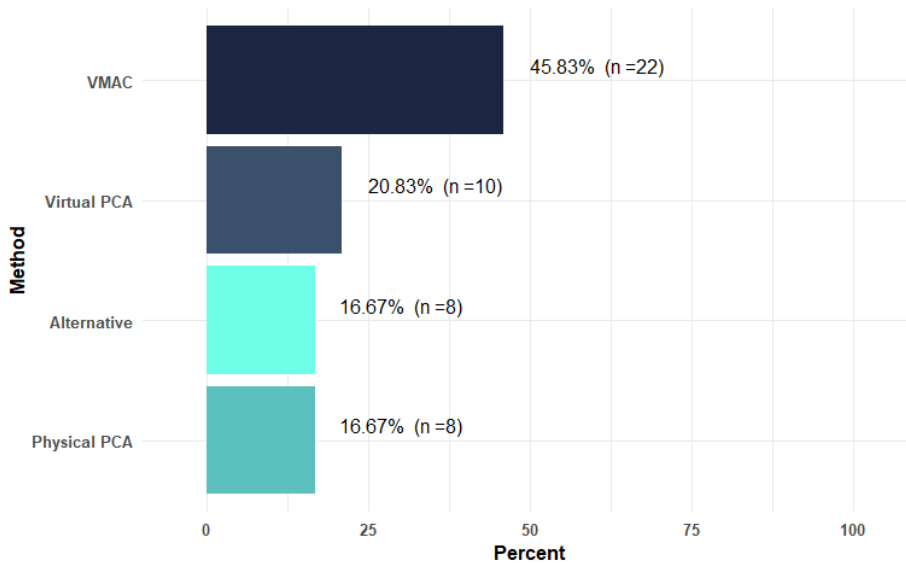
Figure 6. *Number of Studies on Human Sign- and Goal-Tracking or Closely Related Behaviors Over Time*



Review Findings

Studies implementing human sign-tracking (or closely related behaviors) can be classified into four major categories of experimental paradigms: (1) Physical Pavlovian Conditioned Approach (PCA) tasks or similar methods (N=8), (2) Virtual PCA tasks either embedded in a PIT task (N=5) or alone (N=5), (3) Value-modulated attentional capture (VMAC) tasks either with (N=13) or without (N=9) an eye-tracking measure, and (4) "Alternative" tasks (not included in the previous categories, i.e., "game-like tasks", "neuroimaging", "real-life & electrophysiological measures", and "unclassified tasks", N=8). Figure 7 shows the breakdown of studies in four these categories.

Figure 7. *Distribution of Studies in the Four Major Categories of Paradigms Used to Implement/Measure Human Sign-Tracking or Its Analog in Humans, Included in This Review (N= 48)*



Note. VMAC= Value-modulated attentional capture, PCA= Pavlovian conditioned approach

Studies were grouped according to these four major categories, which are described in the next section. For each category, we summarized the task characteristics, type of participants studied and main findings relevant for the present topic, in a narrative way. The first two categories were closer to the animal ST/GT paradigm and were therefore described in more depth. Detailed information about studies (sample description, etc.) is summarized in [Appendix A](#). For studies explicitly implementing or measuring sign- or goal-tracking behavior in humans that were included on that basis, note that some of them met our exclusion criteria and are reported in Appendix A.

Two additional characteristics of major importance were identified and summarized for each category of paradigms in a separate section below: (1) the presence of a ST and GT (and INT) categorization of participants in the study, and (2) the type of rewards used in the different experimental paradigms.

Physical Pavlovian Conditioned Approach Tasks

Few research teams have implemented actual PCA tasks, where the participants can physically interact with a CS (often a lever) and a US (e.g., coin or food dispenser) (n=8). In these tasks, approach behavior and attractiveness of the CS are measured through actual contacts with both stimuli (sign vs. goal), like in animal studies.

Some of these PCA studies (n=4) were published in the 70's and 80's, before the terms "*sign-tracking*" and "*goal-tracking*" became popular. Their goal was to investigate either *autoshaping* behaviors in humans (V. J. Anderson et al., 1981; Pithers, 1985; Wilcove & Miller, 1974), or *superstitious behavior acquisition* in children (G. A. Wagner & Morris, 1987). While two of these studies were conducted on children (V. J. Anderson et al., 1981; G. A. Wagner & Morris, 1987), the two others were conducted on student participants. As precursors of the contemporary study of human sign-tracking, these studies implemented experimental devices, including movable levers (and lights) and coin dispensers, with which the participants could interact. Both studies with children used a device designed as a "clown box" that delivered rewards through its "mouth". The rewards used in these experiments were mainly coins, except in Wagner and Morris (1987), which implemented a marble delivery system (G. A. Wagner & Morris, 1987). Children could exchange collected marbles for preselected toys at the end of the study. Broadly speaking, these studies found no clear evidence of CS-oriented (*sign-tracking-like*) behaviors in humans compared to studies with non-human animals (V. J. Anderson et al., 1981; G. A. Wagner & Morris, 1987; Wilcove & Miller, 1974), except for Pithers (1985) who reported conditioned responses in participants when the CS and the US were paired, but not when they were unpaired, results in line with previous animal findings. Despite their striking methodological similarities with the animal autoshaping procedure, these studies had several major limitations with respect to the ST/GT framework. Many of them provided a descriptive rather than quantitative assessment of CS-oriented behavior (V. J. Anderson et al., 1981; G. A. Wagner & Morris, 1987; Wilcove & Miller, 1974). In other words, they mainly assessed the dominant behaviors occurring following the presentation of a reward-associated cue, without reporting how children/students behaved relative to the cue and the reward location. As a result, the participants could not be classified according to the degree of CS attractiveness using a ST/GT categorization.

After more than two decades of absence in the scientific literature, physical PCA tasks recently benefited from renewed interest with the publication of four studies explicitly investigating human sign-tracking behavior. Two of these sources originate from PhD theses (one type of publication from the grey literature) and developed new and innovative ways to measure sign- and goal-tracking in humans (Colom, 2023, Chapter 9; Joyner, 2019). Again, half of the studies were conducted on children/pre-adolescents (Colaizzi et al., 2023; Joyner, 2019), while the others were conducted on an institutional sample (Colom, Chapter 9), or in emerging adults from a research volunteer database (Cope et al., 2023). The experimental devices of these studies mainly consisted of extendable levers and reward magazines, except for Colom (2023, Chapter 9), where pressable buttons were used as CS. Rewards ranged from food (Joyner (2019) to colorful plastic marbles or tokens, exchangeable for either preselected food items (Colom, 2023, Chapter 9) or money (Cope et al., 2023), or prizes or money (Colaizzi et al., 2023). Participants were mostly classified as STs and GTs on the basis of a complex index score opposing behaviors towards the CS versus the reward location, derived from the animal literature (see P. J. Meyer et al., 2012). The distribution of this score is then typically split in three, leading to three distinct groups, with the “intermediate” (INT) group being sometimes removed from the analyses (Colom, 2023, Chapter 9). Cope et al. (2023) however identified ST, GT, and INT groups using a latent profile analysis on measures of lever presses and gazes. While all four of these studies intended to categorize participants into ST/GT groups, only two of them did identify distinct behavioral profiles in line with sign- and goal-tracking (Colom, 2023, Chapter 9; Cope et al., 2023). Since Joyner’s (2019) and Colaizzi and colleagues’ (2023) participants showed very limited GT behavior, they rather created ST and non-ST groups. Overall, physical PCA studies were able to identify ST and GT phenotypes (or at least non-STs, including INTs) in humans. Based on predictions from animal studies, these ST and GT phenotypes were tested for their differences on impulsivity-related variables, but mixed results were obtained. Two studies found an association between impulsivity and sign-tracking (Colaizzi et al., 2023; Cope et al., 2023), whereas the other two reported negative results (Colom, 2023; Joyner, 2019).

Virtual Pavlovian Conditioned Approach Tasks

The virtual versions of the physical PCA task are more common and remain close to the ST/GT animal model (see Figure 5, upper panel for an illustration). They have been

used alone (N=5) (Colom, 2023, Chapter 7 & 8; Dinu et al., 2024; Doran, 2016; Schettino et al., 2024) or in the context of PIT paradigms (N=5) (Cherkasova et al., 2024; Garofalo & di Pellegrino, 2015; Lehner, Balsters, Bürgler, et al., 2017; Schad et al., 2020, 2023). These tasks consist in associating a visual CS (often a fractal picture) with the delivery of a reward on a computer screen. Briefly, the CS appears at a specific location on the screen for a short amount of time (3 to 5s), followed by the reward on the opposite side of the screen. The task of the participants is usually to collect the reward by pressing a key on a computer keyboard. With one exception (Colom, 2023, Chapter 8), these studies used an eye-tracking device to quantify the amount of gaze fixation on the CS versus the location of reward delivery. Colom (2023, Chapter 8) proposed a novel "*virtual room-based Pavlovian environment*" where participants were allowed to interact with pulling levers and light buttons, in a procedure similar to the ST/GT animal paradigm. The task was therefore based on virtual approach behaviors rather than attentional capture by the CS.

STs or GTs are usually identified based on a contrast between amount of gaze fixation on the CS versus the location of reward delivery (Cherkasova et al., 2024). These studies have used median or tertiary split to discriminate ST/GT phenotypes, sometimes excluding INTs from the analyses (Colom, 2023; Schad et al., 2020; Dinu et al., 2024 used both methods). Schad and colleagues (2020) used a different approach to create ST and GT groups. They computed the influence of CS value on gaze index during the last second of CS presentation per participant. STs and GTs were then defined as those with the most positive and the most negative regression coefficients, respectively. These authors also proposed an alternative way to define STs and GTs through computational modelling.

Most of the studies using a virtual PCA task have been conducted on healthy adult volunteers from the general population (Doran, 2016; Cherkasova et al., 2024; Colom, 2023, Chapter 8; Garofalo & di Pellegrino, 2015; Schettino et al., 2024). Others have been conducted on young males (Schad et al., 2020), or recently detoxified alcohol-dependent patients in comparison to healthy controls (Schad et al., 2023). An institutional sample has also been studied (Colom, 2023, Chapter 7). Since Lehner and colleagues investigated the relationship between sensitivity to rewards and reward-predicting cues and obesity, their sample was constituted of adult volunteers recruited through announcements of the Swiss Adiposity foundation in local clinics, self-help groups, plus-size clothing stores, and the university website (Lehner, Balsters, Bürgler, et al., 2017). The most common kind of

reward used in these studies was money, symbolized through coin or bank note pictures in the experimental task (Doran, 2016; Cherkasova et al., 2024; Garofalo & di Pellegrino, 2015; Schettino et al., 2024; Schad et al., 2020). Virtual money (coin or banknote pictures) that is not converted to actual money at the end of the experiment, has also been used (Colom, 2023, Chapters 8 and 9; Dinu et al., 2024). In line with their study's objective, Lehner et al. materialized rewards through images of sweet or salty snacks, that were accumulated throughout the task and obtained at the end of the experiment (Lehner, Balsters, Bürgler, et al., 2017). While one study showed a positive association between sign-tracking behavior and impulsivity (Garofalo & di Pellegrino, 2015), no association with impulsivity or substance use was found in other studies (Colom, 2023, Chapter 8; Doran, 2016). On a neuronal level using fMRI, Schettino et al. (2024) reported a subcortical control in sign-tracking behavior and a more cortical influence in goal-tracking behavior, while Schad et al. (2020) showed a double dissociation between model-free and model-based learning in human STs vs GTs, with STs showing a neural reward prediction error (RPE) signal that was not detectable in GTs. Moreover, GTs showed lower PIT effects, which might reflect distinct motivational properties of the CS. The same research team investigated human sign-tracking again through a PIT task coupled with an eye-tracking and fMRI imaging, in detoxified alcohol-dependent patients compared to matched healthy controls (Schad et al., 2023). They replicated the distinction between STs and GTs, in relation to model-free and model-based learning, in the patient group, but not in the control group. Contrary to their expectations, they did not find an increase of sign-tracking in the patient group and found that GTs were more prone to relapse. Three other studies also did not confirm their hypotheses. Dinu et al. (2024) and Cherkasova et al. (2024) found no relationship between ADHD and sign-tracking and found goal-tracking to be linked to greater risk-promoting effects of cues, respectively. In one study of the PhD thesis, Colom (2023, Chapter 7) failed to identify consistent ST/GT profiles using a computerized task with eye-tracking. Indeed, participant's behaviors were more related to preexistent attentional biases rather than to individual differences in incentive salience attribution to the reward predicting cues. Regarding the association with obesity, Lehner and colleagues found that fixation style (i.e., sign- or goal-tracking tendencies) had a complex interaction with body weight, notably overweight participants had a significant bias toward the reward location (Lehner, Balsters, Bürgler, et al., 2017).

VMAC Tasks

A parallel has sometimes been established between sign-tracking in animals and value modulated attentional capture or VMAC (Albertella, Watson, et al., 2019; Albertella, Le Pelley, et al., 2020; Byrom & Murphy, 2018; Colaizzi et al., 2020; Le Pelley et al., 2015, 2024; A. L. Pearce et al., 2022; Wiers et al., 2021), sometimes also called “value-driven attentional capture” (A. L. Pearce et al., 2022) in humans. This experimental task, initially developed by Le Pelley et al. (2015), measures the extent to which a signal for reward comes to exert control over behavior through attentional bias (Watson, Pearson, Most, et al., 2019). In the VMAC task, participants are requested to respond to a target stimulus as quickly as possible (e.g., detecting a diamond shape within circles and reporting the orientation of the line inside the target shape), while another visual cue (color distractor) signals the magnitude of a reward opportunity (high vs. low reward) (see Figure 5, bottom panel).

Typically, distractor cues are of two colors (e.g., red and blue), each predicting a specific reward magnitude (e.g., red for high reward, blue for low reward). To get the reward, participants must respond as quickly as possible to the target, and too slow responses lead to reward omission. In that respect, several versions of the VMAC task were used. Sometimes, the procedure is designed to punish gazes to the reward-associated distractor through reward-omission (Albertella et al., 2017; Pearson et al., 2015, 2016, 2020; Pearson & Le Pelley, 2020, 2021; Watson, Pearson, Chow, et al., 2019; Watson, Pearson, & Le Pelley, 2020; Watson et al., 2021, 2022), and sometimes the reward magnitude is dependent on response speed (Albertella, Le Pelley, et al., 2019; Albertella, Watson, et al., 2019; Albertella, Chamberlain, et al., 2020; Albertella, Le Pelley, et al., 2020; Albertella et al., 2021; Duckworth et al., 2022; C. Liu et al., 2021; Watson, Pearson, Most, et al., 2019). Therefore, the most profitable behavior for the participant is to ignore the distractor and only attend to the target stimulus. In spite of the cost of such behavior, participants still tend to look at the distractor and this effect is heightened for distractors predicting higher rewards (Le Pelley et al., 2015; Pearson et al., 2015). This behavior is assumed to be underpinned by the automatic attribution of incentive salience to the reward predicting cue, which makes it similar to sign-tracking behaviors in animals (Albertella, Le Pelley, et al., 2019; Colaizzi et al., 2023; A. L. Pearce et al., 2022). The VMAC task is sometimes coupled with an eye-tracking device, allowing the quantification of the

attentional capture by the reward predicting cue. This component is therefore particularly relevant for the study of sign-tracking behavior in humans. Below, we distinguish VMAC studies with and without eye-tracking. The most commonly used reward in these tasks consists in points, which can be accumulated and converted into money.

VMAC Without Eye-Tracking

Among the VMAC studies without eye-tracking, some of them explicitly draw a parallel with the ST/GT paradigm (Duckworth et al., 2022; C. Liu et al., 2021; Watson et al., 2024), while others do not despite using a very similar procedure and were therefore also included in the present scoping review (Albertella, Chamberlain, et al., 2020; Albertella et al., 2021; Albertella, Le Pelley, et al., 2019, 2020; Albertella, Watson, et al., 2019; Watson, Pearson, Most, et al., 2019).

While most of these studies were conducted on adults from the general population (Albertella, Chamberlain, et al., 2020; Albertella et al., 2021; Albertella, Le Pelley, et al., 2019, 2020; Duckworth et al., 2022; C. Liu et al., 2021) or students (Albertella, Watson, et al., 2019; Watson, Pearson, Most, et al., 2019), one recent study recruited individuals seeking treatment for problematic alcohol use (Watson et al., 2024).

Duckworth et al. (2022) investigated the neural correlates of sign-tracking. According to their results, “sign-tracking is associated with activation of the ‘attention and salience network’ in response to reward cues but not reward feedback”. C. Liu et al. (2021) investigated the association between sign-tracking and alcohol drinking motives in relation to problematic drinking. Although they found no difference in alcohol use between the participants classified as ST and GT, they showed that the ST/GT phenotype was a moderator of the relationship between drinking motives and alcohol consumption. However, there was no direct relationship between sign-tracking and alcohol use.

In a more clinical perspective, Watson et al. (2024) studied human sign-tracking in relation to problematic alcohol use and relapse. Results showed that a VMAC score indicative of sign-tracking positively correlated with the severity of alcohol use, obsessive thoughts about alcohol use and compulsive drinking behavior. Moreover, sign-tracking predicted alcohol relapse at three months.

Several other studies with a very similar VMAC methodology also found a significant relationship between the VMAC scores and compulsive or alcohol drinking behaviors, although they did not express their results in terms of sign-tracking. Albertella

and colleagues (Albertella, Chamberlain, et al., 2020; Albertella, Le Pelley, et al., 2019, 2020; Albertella, Watson, et al., 2019) showed that reward-related attentional capture is significantly related to compulsivity and risky alcohol use. They also showed that people with greater reward related attentional capture (i.e., STs) were more likely to fail a 1-month abstinence challenge (dry January) (Albertella et al., 2021). Finally, Watson, Pearson, Most, et al. (2019) draw a parallel between the VMAC task and the ST/GT paradigm. They showed that participants were significantly slower on trials with a distractor announcing a high reward availability (vs. a low reward availability), and that this effect persisted during an unrewarded extinction phase.

VMAC With Eye-Tracking

Although the VMAC studies coupled with an eye-tracking device (N= 13) do not explicitly refer to the ST/GT paradigm, the addition of a measure of attentional capture by the reward-associated cue makes the results of such studies quite relevant for the investigation of human sign-tracking behavior. All of these studies were conducted on student samples (Albertella et al., 2017; Le Pelley et al., 2015, 2019; Pearson et al., 2015, 2016, 2020; Pearson & Le Pelley, 2020, 2021; Watson, Pearson, Chow, et al., 2019; Watson, Pearson, & Le Pelley, 2020; Watson, Pearson, Theeuwes, et al., 2020; Watson et al., 2021, 2022).

Albertella et al. (2017) found a significant association between the VMAC effect and drug use, and this relationship was modulated by the level of cognitive control. Contrary to students with a high cognitive control, those with a low cognitive control showed a significant positive correlation between their VMAC scores and illicit drug use. Other authors used very similar procedures to study reward-related attentional capture (Le Pelley et al., 2015, 2019; Pearson et al., 2015, 2016, 2020; Pearson & Le Pelley, 2020, 2021; Watson, Pearson, Chow, et al., 2019; Watson, Pearson, & Le Pelley, 2020; Watson, Pearson, Theeuwes, et al., 2020; Watson et al., 2021, 2022). Overall, these studies consistently showed that participants developed an automatic counterproductive AB for high reward signals, which persisted even when looking at the distractor caused reward omission (Le Pelley et al., 2015; Pearson et al., 2020; Watson, Pearson, Theeuwes, et al., 2020), when the reward was devaluated (Watson et al., 2022), when participants were explicitly told that looking at the distractor would lead to reward omission (Pearson et al., 2015), or when both distractor types (low and high reward) were presented

simultaneously (Pearson et al., 2016). Moreover, this AB was more pronounced for rapid eye saccades (Le Pelley et al., 2019) and was increased by a high memory load (Watson, Pearson, Chow, et al., 2019). Interestingly, this AB also occurred with food rewards, and was reduced in individuals scoring higher on eating restraint (Watson et al., 2021). It was also shown to be reduced by an acute alcohol dose (Watson, Pearson, & Le Pelley, 2020). Pearson and Le Pelley (2020, 2021) concluded that the relationship between reward and attentional selection is complex in the sense that the automatic capture of attention by reward-associated cues may be attenuated when attending to the distractor leads to reward omission.

Alternative Tasks

Several other studies explicitly investigated human sign- and goal-tracking behaviors or were relevant for the topic but could not be classified in the previous major categories (N=8). They were classified as (1) "*game-like tasks*" (N=3), (2) "*neuroimaging experiments*" (N=2), "*real-life assessment*" (N=1), and "*unclassified tasks*" (N=2).

Designing game-like tasks to measure human sign- and goal-tracking could be an ingenious way to tackle the issue of ecological translation. Indeed, a videogame could be much more engaging for human participants than a mere piece of food collected after presentation of a touchable lever CS; humans have been playful beings ("*Homo ludens*") since the dawn of time (Huizinga, 1998). Among the papers in this category, Serrano-Barroso et al. (2022) used a "pinky-piggy" videogame application with 4- to 5-year-old children, where two CS (money bag and a colorful pig) were associated with coins (US) appearing on the screen. In this task, a money bag and a grey pig were displayed on a screen. Four seconds later the bag began to shake, and the pig became colored, then coins appeared on the screen. The children had to touch the pig to accumulate virtual money. All touches on the screen were registered throughout the task but had no incidence on reward contingency. Touching the pig produced an *oink* sound, while touching the bag emitted a coin shaking sound. The authors indicate that the app was designed in reference to autoshaping, presented as "*a classical experimental procedure in animal models*" (p. 4). Although the task was very similar to the ST/GT paradigm, the results were not directly interpreted in reference to sign- and goal-tracking behaviors. Accordingly, participants were not categorized as STs or GTs. Instead, the authors used "*high responders*" vs "*low responders*" categories, based on their number of clicks (on the

bag and the pig cues). Their categories were therefore homologous but not equivalent to ST/GT phenotypes. The main result was that high responders had lower scores on neurodevelopmental scales (for non-verbal development, spatial structuring, and visual perception) and showed a lower mean level of attention than low responders.

Two other studies by Nelson et al. (2019, 2022) used a game-like procedure coupled with an eye-tracking device to assess sign- and goal-tracking behaviors in university students and college-aged volunteers. In their videogame, participants had to learn to activate weapons to repel invading spaceships. Eye gazes toward a specific spaceship (the outcome or US) and toward a flashing light cue (CS) predicting this outcome were recorded throughout the task. The two aims of these studies were to assess visual searching for expected outcomes in humans during an associative-learning task (Nelson et al., 2019), which they define as goal-tracking, and to examine the effects of stimulus pre-exposure and conditioning on visual attention (Nelson et al., 2022). In the second study, participants were classified as STs or GTs according to their preference for the CS or the US. A ratio score was computed by dividing the number of gazes in the US zone by the total number of gazes on the last trial. Nelson et al. (2022) defined sign-trackers as *"individuals preferring to look at the signal predicting the upcoming spaceship"*, and goal trackers, as *"preferring to look for the appearance of the predicted ship, at the end of training"*. The results suggested that STs and GTs were differentially sensitive to the effects of pre-exposure to the CS and to context changes.

In a completely different vein, Versace et al. (2016) investigated human sign- and goal-tracking through brain responses to pictures in obese and lean adult individuals. The aim of their study was to dissociate two endophenotypes related to individual differences in the propensity to attribute incentive salience to food-related cues. Participants were exposed to food-related, pleasant, neutral, and unpleasant pictures while recording EEG. STs and GTs were categorized using a latent profile analysis (LPA) based on their late positive potentials (LPPs). STs were individuals with higher responses to food-related cues and lower responses to pleasant cues, contrary to GTs. Obese individuals were more often classified as STs than lean individuals. Members of the same research team also investigated how gut microbiome profiles varied between STs and GTs in obese and lean individuals. They reported preliminary findings in a poster (Schembre et al., 2016)

suggesting that STs and GTs show varying gut microbiota, with STs having a more diverse microbiome compared to GTs.

To study sign- and goal-tracking behaviors in a more ecological way, Schettino et al. (2022) implemented an ecological momentary assessment and ambulatory peripheral autonomic monitoring. In their daily life, adult participants from the general population had to rate the attractiveness of several pre-selected (preferred) rewards and their naturally associated predictive cues. For instance, rewards and their predictive cues could be coffee and the noise of the coffee machine, respectively. At the same time, their electrocardiogram was recorded. The results indicate that, overall, participants rated cues and rewards as equally attractive. However, individuals with higher impulsive, obsessive-compulsive and addiction-prone tendencies rated the predictive cues as more attractive compared to the rewards themselves, and this pattern was also reflected in autonomic measures.

Salmeron (2020) investigated human sign- and goal-tracking in adults with and without SUDs. Participants had to watch a set of pictures (food, drug, positive, and neutral pictures) on a screen. They could push a button to extend the display duration of a picture, but no actual reward was granted to the participants during the task. A sign-tracking score was computed based on their responses to the pictures. Contrary to what the animal literature indicates, healthy controls showed more sign-tracking behavior than substance users. Moreover, sign-tracking correlated negatively with drug consumption in smokers and cocaine users.

Finally, Wardle et al. (2017, 2018) developed a new procedure devised to be a translational paradigm to measure human sign-tracking (2017). In their task, the favorite food reward of a participant was repeatedly paired with an initially neutral picture (CS). More specifically, healthy adult participants were seated in front of a computer screen wearing headphones, with a partition to their side. A rotating tray was in the partition, with one food tray on each side. A research assistant was seated on the other side, manually loading the food cup with the participants' selected food reward. Right after the CS picture was shown on the screen (6s), the assistant rotated the tray to deliver the reward. Participants were instructed to eat the snacks within the 25s after delivery (they were not allowed to keep it for later). Psychophysiological measures (electromyography, skin conductance, and heart rate) were also recorded during the task. After two conditioning

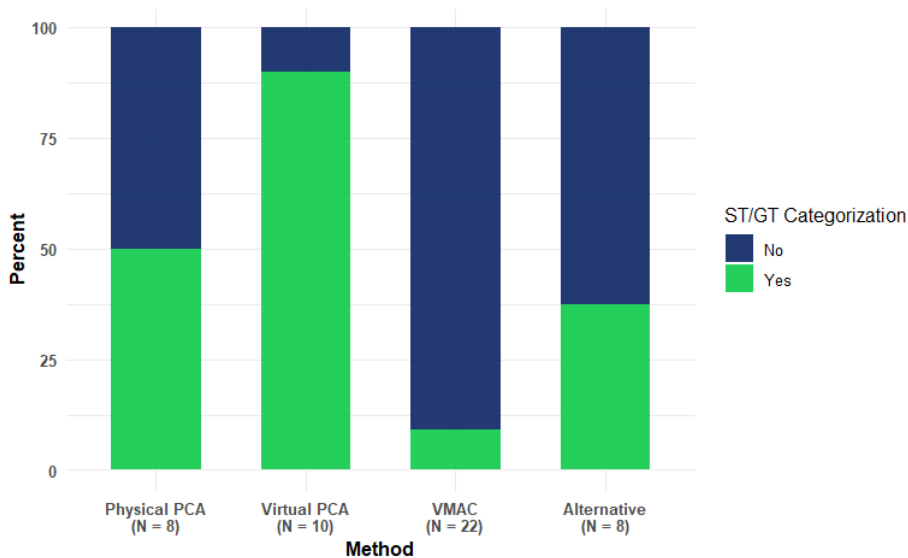
sessions, several measures of appetitive responses to the CS were then performed (i.e., Rating Pictures Task, Chasing Pictures Task, and Dot-Probe Task). The results showed appetitive conditioned responses to the CS picture with some of the measures, especially the psychophysiological recordings, but no significant approach behavior or positive subjective ratings of the CS. Unexpectedly, the various appetitive measures for the CS picture did not strongly correlate with each other (Wardle et al., 2018). Attentional bias for the CS picture (as measured by a Dot-Probe task) was the only indicator of appetitive conditioning that significantly correlated with impulsivity.

Summary of Some Important Divergent Methodological Features of the Reviewed Studies

In addition to the methods used to measure sign- and goal-tracking behaviors in humans, two other aspects were found to be highly heterogeneous in the literature.

First, the various human paradigms greatly differ in their attempts to identify distinct ST and GT phenotypes. As already mentioned, in some of the human paradigms listed above, the “sign” (CS) and the “goal” (reward location) were insufficiently contrasted to allow for such classification of participants. Figure 8 shows the proportion of studies implementing a participant profile classification, for each category of paradigms described previously. Among physical PCA task studies, all contemporary ones have categorized participants into groups of STs/GTs/INTs (Colaizzi et al., 2023; Colom, 2023, Chapter 9; Cope et al., 2023; Joyner, 2019), whereas the oldest physical PCA studies did not. Virtual PCA task studies have all identified different groups of participants based on their sign-or goal-tracking behavior, although Lehner et al. (2017) did not use the terms STs/GTs, but rather categorized participants into two groups according to their predominant eye fixation on the CS or the reward location (“*high eye index*” vs “*low eye index*”; Lehner, Balsters, Bürgler, et al., 2017). Except for two studies (Duckworth et al., 2022; C. Liu et al., 2021), VMAC paradigms did not typically lead to a ST/GT categorization but rather considered a continuous score of biased attentional capture. As for the alternative tasks, only three studies used a ST/GT categorization (Nelson et al., 2022; Schembre et al., 2016; Versace et al., 2016).

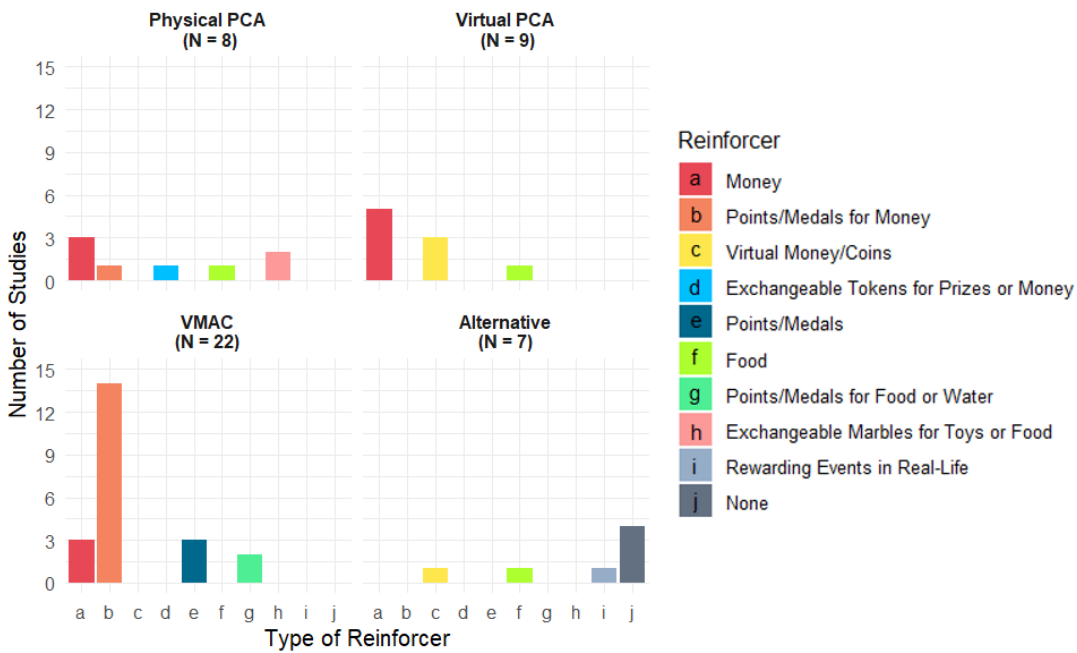
Figure 8. *Percentage of Studies That Categorized ST/GT (or Other) Profiles for Each Subtype of Method*



Note. PCA= Pavlovian conditioned approach; VMAC= Value-modulated attentional capture. Studies that investigated categories of individuals are represented by the bottom bar (green in color version), those that did not, by the top bar (dark blue in color version).

The second major source of disparity between the reviewed studies is the type of reward used. Figure 9 shows the types of rewards used for each category of experimental paradigms identified in the present review (see also [Appendix A](#), for type of reward per study).

Figure 9. *Distribution of Reward Types Used in Each Subtype of Experimental Paradigm Implementing Human Sign- and Goal-Tracking*



Note. PCA= Pavlovian conditioned approach; VMAC= Value-modulated attentional capture. Schad et al., 2023 and Schembre et al., 2016 were not included in this graph, due to missing information about the reward type.

While some studies used actual money as the reward (e.g., V. J. Anderson et al., 1981; Cherkasova et al., 2024; Garofalo & di Pellegrino, 2015), others used a points system, with points being converted into a financial reward at the end of the experiment (sometimes based on task performance, sometimes a fixed amount) (e.g., Cope et al., 2023; Duckworth et al., 2022; Pearson et al., 2016). Purely “virtual rewards”, such as coin pictures, points/medals accumulation along the task, have also been widely used (e.g., Albertella et al., 2021; Serrano-Barroso et al., 2023; Watson, Pearson, Most, et al. 2019). Several food items (or drinks) have also been used as rewards in studies measuring human sign-tracking, either directly delivered (Joyner, 2019; Lehner, Balsters, Bürgler, et al., 2017; Wardle et al., 2018) or exchanged for points accumulated during the experimental task (Watson et al., 2021,2022). Finally, several of the “alternative tasks” did

not implement the opportunity to receive any rewards at all during the task (e.g., Versace et al., 2016; Salmeron, 2020).

Discussion

The purpose of this scoping review was to identify and map what has been done on sign- and goal-tracking in humans, and more specifically, identify what paradigms have been used to implement it. The reviewed studies were presented according to four major categories of experimental paradigms: physical PCA, virtual PCA, VMAC and alternative tasks.

The first attempts to test human “*sign-tracking*” under the term “*autoshaping*” date back to the 1970’s (V. J. Anderson et al., 1981; Pithers, 1985; Wilcove & Miller, 1974). The thematic then seemed to be forgotten until the mid-2010’s, when it has made a significant comeback in the scientific literature (see Figure 6). In recent years, a number of studies have tried different methods to develop a human analog of sign-tracking behavior.

As shown in the present review, there is a huge heterogeneity in the methodologies of the studies claiming to investigate sign- and goal-tracking behaviors in humans. Additionally, some studies investigate behavioral analogs of sign-tracking without reference to the ST/GT literature. Until now, there is no consensus on the best way to measure those behaviors in human participants. To bring some order in this diversity, we have classified the published studies into four major categories: physical PCA tasks, virtual PCA tasks, VMAC tasks, and alternative, non-classified tasks. Overall, physical PCA tasks show the greatest face validity by mimicking CS-triggered approach behavior measured in animals. Accordingly, the findings from these PCA studies are generally in line with the conclusions from the animal literature on sign-tracking. Although they could be considered a gold standard for the translation of the ST/GT model in humans, they require sophisticated materials and resources and may also lack sufficient ecological validity, especially in adult human participants. This is probably why half of these studies were conducted in children, who might be more prone to spontaneous interaction with colorful devices.

As approach behaviors are not easily recorded in humans, several authors developed proximal measures in virtual PCA tasks (e.g., Cherkasova et al., 2024; Colom, 2023; Dinu et al., 2024; Garofalo & di Pellegrino, 2015; Schettino et al., 2024). In most of

these tasks, the measurement of approach behaviors consisted in the recording of attentional capture through eye-tracking devices. In other words, sign-tracking was still interpreted as incentive salience attribution to a cue, but characterized as privileged attention given to the CS versus the reward location. The translational aspect is that eye gaze is an analog or a proxy of approach behavior in humans (Stephens et al., 2010). Except for the use of eye-tracking measurements, virtual PCA tasks are therefore very similar to ST/GT animal models. The results of these studies were disparate, successfully identifying ST/GT groups but not always succeeding in confirming previously reported relationships between sign-tracking and other behaviors (substance use, impulsivity, ADHD, risky choices). Neuroimaging results (Schettino et al., 2024) suggesting a subcortical control in sign-tracking behavior and a more cortical influence in goal-tracking behavior, are consistent with findings from the animal literature (e.g., Flagel et al., 2011).

VMAC tasks have been the most widely used method to investigate human sign- and goal-tracking behaviors, although this purpose is not always explicitly stated. Several versions of this task were published, drawing or not a parallel with the ST/GT paradigm. In contrast to animal studies, in which sign-tracking is measured through direct approach behavior in a Skinner box, the VMAC task measures the extent to which a signal for reward comes to exert control over behavior through attentional bias (Watson, Pearson, Most, et al., 2019). Most VMAC studies used reaction times as the dependent variable to infer attentional capture to a reward-associated CS. This automatic capture of visual attention is supposed to reflect incentive salience attribution, acting outside volitional control (Colaizzi et al., 2020), and hence might be an analog of sign-tracking behavior in humans (Le Pelley et al., 2024). Interestingly, eye-tracking devices were implemented in some versions of the VMAC tasks, making the procedure quite similar to virtual PCA tasks. Several studies have consistently demonstrated the presence of automatic ABs for reward-associated cues. The cognitive mechanisms underlying the VMAC effect are undoubtedly related to the incentive salience attribution involved in sign-tracking behavior. Accordingly, the few VMAC studies which tried to draw a parallel with ST/GT experiments found compatible results with the animal literature (Duckworth et al., 2022; C. Liu et al., 2021; Watson et al., 2024). Overall, VMAC studies have shown that reward-related cues can bias human attentional capture, especially in some individuals, suggesting that humans also show individual variations in the sensitivity to a CS associated

with reward delivery. Moreover, impulsivity, risky alcohol use, and other addiction-related behaviors have been shown to be associated with this reward-related AB (Albertella et al., 2021; Albertella, Watson, et al., 2019; C. Liu et al., 2021; Watson et al., 2024). However, in its usual configuration, the VMAC procedure differs from the ST/GT animal model in several respects (see below).

Miscellaneous alternative paradigms were also devised to measure sign-and goal-tracking in humans. To date, however, those latter models still lack validation studies and replications to properly assess their potential contribution to the study of these behaviors in humans. It is noteworthy, however, that the gamification of the traditional autoshaping procedure might be a thoughtful and innovative way to translate the ST/GT animal model in humans, while maintaining sufficient face validity.

Physical Approach Behaviors vs. Visual Attention Capture

On a strictly translational perspective, measuring sign- and goal-tracking behaviors in humans should involve some kind of approach or contact with a touchable, predictive cue and a reward delivery location. In the standard ST/GT animal paradigm with rodents, a retractable lever is used as the reward-associated cue and physical interactions with it are recorded as sign-tracking behavior (Flagel et al., 2007; P. J. Meyer et al., 2012). However, few of the reviewed human studies used approach behavior or direct contact with the CS as the sign-tracking measure, except for the physical PCA tasks. As already mentioned, it is not easy to implement a task with physical contact in humans without giving specific instructions to the participants. This is probably why most human ST/GT studies replaced direct contact by the recording of visual attention toward the CS, most often using eye-tracking devices. Attentional capture by the reward-associated cue is then considered as a visual analog of approach or sign-tracking behavior. Attentional capture is therefore the strategy underpinning most virtual PCA tasks, all VMAC studies and some of the unclassified experiments. A major advantage of this procedure is that attentional capture is automatic and difficult to control by the participants. Indeed, VMAC studies demonstrated that the AB for high reward-associated cues persists even when looking at it causes reward omission (Le Pelley et al., 2015; Pearson et al., 2020; Watson, Pearson, Theeuwes, et al., 2020).

There is currently little experimental demonstration that attentional capture is a proper equivalent of physical contact to assess sign-tracking behavior. Very few studies have investigated whether these measures are strongly correlated in the context of the ST/GT paradigm. Cope et al. (2023) tested both eye-tracking and behavioral measures to compute ST, GT, and INT profiles. They showed a positive, but non-significant, correlation between lever gazes and lever presses. Joyner (2019) combined measures of direct physical contact, proximity, and head orientation towards a lever CS and food magazine in children. They obtained significant correlations between the measurement indices and significant agreements for the classifications based on these indices. Based on these few findings, attentional capture seems to be an adequate visual analog of approach behaviors to investigate sign-tracking in humans. Given that most human experiments use attentional versions of the ST/GT tasks, further studies are required to validate this measurement procedure.

Translational Assessment of the Human ST/GT Models

From the present review, it was clear that some of the human studies were further away from the ST/GT animal model than others. Five translational exclusion criteria were defined, although all studies claiming to study human sign- and goal-tracking (and not always in agreement with these criteria) were included in the present review ([Appendix A](#)). These translational criteria can therefore be used to assess how comparable these studies are to the ST/GT animal model. A perfectly valid translational human analog of the ST/GT animal model should comply with these criteria. Accordingly, a human ST/GT model should: 1) experimentally establish the association between the CS and the reward, 2) oppose sign- and goal-tracking behaviors or learned strategies, 3) avoid requiring an instrumental behavior to obtain the reward, 4) reward the participant with positive reinforcements and 5) implement a direct measure of the attractiveness or incentive salience of the CS and reward.

When based on attentional capture, sign-tracking results from incentive salience attribution to the reward-associated cues and might therefore be considered as a form of AB. However, AB studies usually investigate the effects of natural cues that were repeatedly associated with rewards in real life, such as alcohol brands, food brands, and drug-related objects. Yet, such previously learned associations between a CS and a

reward are not optimal for detecting ST and GT phenotypes in the laboratory. Indeed, controlling the frequency of exposure to a specific cue-reward association that occurred in real life is virtually impossible. When the goal is to identify ST and GT phenotypes, it is therefore very important to test sign- and goal-tracking behaviors learned in standard experimental conditions. Some of the reviewed human studies, especially from the unclassified category, labelled participants as ST or GT based on their response to a real-life preexisting CS. It is currently unknown if and to what extent such classifications would overlap with categorizations based on the sign-tracking behavior observed in standard experimental conditions. Transposing sign-tracking to real life is certainly an essential step in validating the model in humans. But this step should come after the thorough investigation of the original paradigm.

The need for an actual contrast between a sign (CS) and a goal (reward location) is essential to properly translate the animal ST/GT paradigm in humans. In animal studies, the sign (usually a retractable lever) and the goal (usually a food magazine) are physically distant. They cannot be approached simultaneously, such that the animal must decide which one is the most attractive (Boakes, 1977). The identification of ST and GT phenotypes is precisely based on a competition between the CS and the reward delivery location. In the initial VMAC tasks (Le Pelley et al., 2015), the target stimulus is a discriminative cue indicating which keyboard key is the right instrumental response. Clearly in that procedure, it is possible to determine how attractive the CS is for a specific participant. This is measured through the delayed response time when the CS is shown along with the target stimulus. But the procedure does not directly contrast a sign and a goal and cannot consequently classify participants as true STs or GTs. Furthermore, in many VMAC studies, the effect of the distractor cue is tested under extinction, i.e., when no more reward is available. In those studies, rewards are delivered only during the training phase, whereas the effect of the distractor is measured in a testing phase without reward (A. L. Pearce et al., 2022). This prevents any contrast behaviors between a *"sign"* and a *"goal"*. Moreover, at that point, the *"sign"* has lost its *"signaling"* value, since no reward is delivered. As mentioned in the introduction, this aspect was part of our exclusion criteria. However, this procedure has been extensively used in the literature and has highlighted several connections between the VMAC effect and psychological disorders, such as depression, opioid addiction, ADHD, OCD, and risk-taking in HIV+

individuals (for reviews see B. A. Anderson, 2021; Le Pelley et al., 2024). Moreover, the attractiveness of the “goal” is not directly measured in the initial VMAC task. What is indirectly measured is the attention paid to the distractor, which is inferred from a delayed response time to the target stimulus. It is currently unknown whether sign- and goal-tracking behaviors indirectly inferred from such delayed response time would correspond to more traditional measures based on approach behaviors or direct attentional capture.

The animal ST/GT paradigm relies on Pavlovian conditioning. No response is required from the animals to obtain the reward. Also, sign-tracking behavior has no positive or negative consequences in the standard paradigm. The distinction between Pavlovian and instrumental conditioning is important since they are not driven by the same underlying mechanisms. However, many VMAC studies involve instrumental behaviors, significantly departing from the ST/GT animal model (see [Appendix A](#)). In VMAC studies, the CS-reward relationship is Pavlovian. The colored distractor predicts reward magnitude and no action towards this CS is required to succeed in the task (Le Pelley et al., 2024). However, the VMAC procedure also involves a specific instrumental response towards a target stimulus to obtain the reward. Moreover, the task often includes an additional instrumental component in the form of some punishment for responding to the CS or for too slow responding to the target. All reviewed VMAC studies involve a time limit beyond which no reward is delivered. In eleven of those VMAC studies, a punishment (reward omission) is also administered for looking at the CS. Some other VMAC studies also punish wrong responses or make the reward magnitude dependent on reaction time. The consequences of such methodological decisions are still unknown and would require specific studies to conclude that the VMAC procedure is a genuine human analogue of the ST/GT animal model.

Most ST/GT animal studies are based on positive reinforcement conditioning, using food as a reward. It is theoretically possible to study aversive sign-tracking, especially when approach behavior is replaced by attentional capture. However, we decided to focus on sign-tracking in relation to reward predicting cues since this has been linked to addiction vulnerability. As shown in Figure 9, human sign-tracking studies used several types of rewards: monetary, fictional, or food. Moreover, in some studies, no reward was delivered during the experiment (e.g., Salmeron, 2020; Nelson et al, 2022).

Identification of ST and GT Phenotypes in Humans

One of the major observations resulting from the ST/GT animal model is the individual variability in the tendency to develop sign-tracking behavior (see Flagel et al., 2007, 2008, 2009). On this basis, individual animals have often been classified as STs or GTs, suggesting that these categories reflect stable phenotypes (Gillis & Morrison, 2019). As shown in Figure 8, sixteen studies tried to categorize human participants according to their tendency to develop sign-tracking. Most of these studies (75%) used physical or virtual PCA tasks. The most common procedure to create ST/GT categories was through tertile (or median) split computed on “*response bias scores*” (RBS) toward the CS, although some studies also used alternative methods such as LPA (Cope et al., 2023; Versace et al., 2016). Few studies included a third (INT) category for individuals whose behavior alternated between sign- and goal-tracking. In general, the nature of the RBS from which the categories were defined is highly heterogeneous. In PCA tasks, the categories are typically established from the number and latency of physical contacts with (or gazes to) the CS vs. the reward location (e.g., Colaizzi et al., 2023; Cope et al., 2023; Dinu et al., 2024). However, in VMAC studies, the categories are defined by the differences in reaction times for high vs. low rewards (Duckworth et al., 2022; C. Liu et al., 2021). Some studies also created categories based on behaviors toward a CS without any reward delivered during the task (e.g., Nelson et al., 2022). It is currently unknown whether these various categorizations overlap or even whether they assess the same underlying processes.

The animal literature shows that several experimental parameters may significantly alter sign and goal preferences, and thus the proportion of individuals within the ST, GT, and INT categories. For instance, the type of US (e.g., water vs. food) and the mode of US delivery (e.g., intravenous vs. oral) seem to alter the way individuals approach or interact with the CS, respectively in pigeons (Jenkins & Moore, 1973) and rodents (Uslaner et al., 2006). CS duration and CS-US interval (Holland, 1980), reward predictability (Anselme et al., 2013), inter-trial interval (ITI) (Mahmoudi et al., 2023), as well as the nature of the CS (a lever vs. a tone) (P.J. Meyer et al., 2014), also impact the proportion of STs (and GTs when assessed) in rodents. Unfortunately, few human studies have tested such variations in the parameters. Additionally, there is little consensus and comparability on these parameters between human studies. For instance, we have already pointed out in this review that the

type of reward strongly varies between human ST/GT studies. Another parameter that must be considered is CS duration, for which strong variations in experimental design were noted (e.g., 8.3 s in Colaizzi et al., 2023; 5 s in Garofalo & di Pellegrino, 2015; 3 s in Cope et al., 2023). Examining the impact of these methodological choices in human participants may help to establish a human paradigm able to maximize individual variability in the attribution of incentive salience to reward cues. In summary, there is an obvious lack of replication and validation studies, making it difficult to conclude that stable ST and GT phenotypes exist in humans. In rats also, the idea that the ST and GT phenotypes are stable traits of individuals, insensitive to environmental factors, is controversial (e.g., P. J. Meyer et al., 2014; M. J. F. Robinson et al., 2015). In addition to varying the contexts in which both phenotypes are tested, better consensus on the experimental parameters and on the way to analyze the available data would help clarify the interpretations.

Relationships Between Human Sign-Tracking Behavior and Other Variables

In the animal literature, relationships between sign-tracking behavior and other individual variables have been established, leading to the suggestion that sign-tracking might be a risk factor for several psychological disorders in humans. In rodents, the ST phenotype has been repeatedly associated with addictive behaviors (B. T. Saunders & Robinson, 2011; Tomie & Morrow, 2018). In humans, several studies also show significant associations between sign-tracking and drug or alcohol consumption (Albertella et al., 2017, 2021; Albertella, Watson, et al., 2019; Schettino et al., 2022; Watson et al., 2024), although negative results were also reported (Doran, 2016). Clearly, further research is needed to substantiate the association between sign-tracking and drug or alcohol addiction. Rodent studies also repeatedly showed that the ST phenotype is characterized by higher impulsive tendencies (Lovic et al., 2011; Tomie & Morrow, 2018, although see Flagel et al., 2010). However, in the reviewed human studies, this effect is far from clear. Some studies show a positive correlation between sign-tracking and impulsivity (Colaizzi et al., 2023; Cope et al., 2023; Doran, 2016; Garofalo & di Pellegrino, 2015; Schettino et al., 2022), while others failed to show any association (Colom, 2023, chapter 8 and 9; Doran, 2016; Joyner, 2019). Drawing firm conclusions on impulsivity from current studies

is difficult, given the poor consistency in the methods used to measure sign-tracking. Finally, sign-tracking has been shown to induce poor attentional control in rodents (Paolone et al., 2013). Preliminary evidence suggests similar effects between sign-tracking-like behavior and some aspects of attentional control in humans (Albertella et al., 2017; Serrano-Barroso et al., 2022), although these findings require further investigation.

Limitations

Given the great heterogeneity in definitions, terminology and methodology, searching and summarizing studies on sign-tracking in humans is a challenge. Although several search terms were used in order to get all relevant information, we might have missed potentially relevant studies. Nevertheless, we believe that this review provides a pretty comprehensive map of what has been done on human-sign-tracking.

Conclusion

The ST/GT model and its implications for human addiction date back to several decades (Boakes, 1977; Brown & Jenkins, 1968; Hearst & Jenkins, 1974; Tomie, 1996; Tomie et al., 1998), although its translation to humans is quite recent. Until now, the techniques implemented vary greatly on crucial methodological aspects such as the type of reward used, the existence of a ST/GT categorization or the dependent variable taken into account (physical approach of cues, eye gaze, reaction time measures, etc.). In this review, we identified four major categories of methods used to study human sign-tracking. Their detailed examination indicated the high heterogeneity that characterizes this literature, and we suggested five criteria that we think are important for a good translational ST/GT model. Few replication and validation studies have been published until now and further research is necessary to create a better consensus on how to measure sign- and goal-tracking behaviors in humans.

Funding

Sources of funding of included studies are listed in [Appendix A](#).

The reference list of this article has been incorporated into the [general bibliography of this thesis](#). References marked with an asterisk indicate studies included in the scoping review.

Part II

Experiments

Chapter 5

Sign-Tracking and Alcohol Consumption

A Translational Computerized Task Assessing Individual Differences in Humans

Michelle Heck

Jessica Simon

Damien Lesenfans

Vincent Didone

Patrick Anselme*

Etienne Quertemont*

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Supplementary Information for this chapter can be found in [Appendix B](#).

*Equal contributions.

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Abstract

Background. Individuals differ in their tendency to assign motivational value to reward-predictive cues, conceptualized as sign-tracking versus goal-tracking behaviors in animal models. Sign-trackers (STs) approach a reward-predictive cue, while goal-trackers (GTs) go to the location of reward delivery. An intermediate (INT) phenotype is sometimes identified. These profiles have been linked to addiction vulnerability, because of a higher propensity to sign-track in drug-addicted rats. However, efforts to translate this model to humans have yielded inconsistent findings, partly due to variability in experimental paradigms.

Objectives. The present observational study hypothesized that distinct profiles based on gaze behavior could be identified in humans and that these profiles would differ on addiction-related variables, such as alcohol consumption and impulsivity.

Methods. One hundred six adults completed three computerized tasks: a simple reward task, a Pavlovian conditioned approach (PCA) task, with gaze behavior measured via eye-tracking, and a dot-probe task. Participants were categorized as STs, GTs, or INTs with a latent profile analysis (LPA). Alcohol consumption and personality traits were assessed via questionnaires.

Results. The three profiles significantly differed in alcohol consumption level, with a small-to-medium effect size observed ($\chi^2 = 8.10$, $p = 0.01$, $\eta^2 = 0.059$). STs displayed higher levels of alcohol consumption than GTs ($p = 0.03$). No significant differences emerged for other alcohol-related or personality variables.

Conclusions. These findings demonstrate the feasibility of identifying ST/GT profiles (or analogues) in humans using a simple PCA task. The observed link between sign-tracking and alcohol consumption supports the notion that sign-tracking may serve as a vulnerability marker of alcohol use.

Keywords: Sign-Tracking, Incentive Salience, Individual Differences, Alcohol

Introduction

Drug (ab)use has been part of human society since the dawn of time (Saah, 2005) and its detrimental effects on health have been recognized for ages (Crocq, 2007). Alcohol being one of the most widely used psychoactive substances (Sumantri Oei & Hasking, 2013), alcohol use disorders (AUDs) are among the most prevalent mental disorders worldwide (Grant et al., 2015). In the European countries, 8.8% of the population aged 15 years+ suffer from AUDs (WHO, 2018). Even more alarming, harmful alcohol use results in 3 million deaths each year (5.3% of all deaths around the world) (WHO, 2018).

Given the relatively high prevalence and devastating impact of AUDs on individuals and society, it is important to address the mechanisms that contribute to its development in order to provide the best treatments. Indeed, people are not all equal in the face of AUDs, an observation that suggests the presence of vulnerability markers for this disorder. Impulsivity, for instance, has consistently been shown to be a vulnerability marker for substance use disorders (SUDs, for a review see Verdejo-Garcia & Albein-Urios, 2021). Other personality traits such as novelty or sensation seeking could also play a causal role in the development of SUDs (Foulds et al., 2017). Individual differences in the propensity to attribute incentive salience (a higher motivational value) to reward-predictive stimuli were also shown to be relevant for the identification of risk profiles with respect to SUDs in animal studies (Anselme & Robinson, 2020; Flagel, Clark, et al., 2011; Tomie et al., 2008).

The ST/GT animal model has extensively examined individual differences in cue-triggered behavior in rats and other species (Boakes, 1977; Hearst & Jenkins, 1974). Typically, animals are repeatedly exposed for a few seconds to a CS, such as a lever with rodents, which consistently precedes the delivery of a food reward in a food dish, without any action required by the individuals. Following a few sessions, the animals gradually diverge in their behaviors, leading to the identification of two main behavioral phenotypes. Individuals called STs approach and interact with the CS when available (e.g., rats sniff, nibble, and press the lever), attributing a predictive but also an incentive value to it. In contrast, during the CS presentation, individuals called GTs approach and interact with the location where the reward is to be delivered, attributing only a predictive (no

incentive) value to the CS (Flagel et al., 2009; T. E. Robinson & Flagel, 2009). INT profiles, showing less consistent approach behaviors, have also been reported (Flagel et al., 2009). In other words, the attribution of incentive salience to the CS makes it attractive (or “wanted”), captures attention, and elicits approach behavior.

In the last two decades, the ST phenotype has consistently been linked to a higher vulnerability to drug addiction in animal research (Anselme & Robinson, 2020; Berridge, 2007; Flagel et al., 2008, 2009; T. E. Robinson et al., 2014; B. T. Saunders & Robinson, 2011; Tomie et al., 2008). Moreover, ST individuals are prone to display behavioral characteristics that overlap with human addictive behaviors (Colaizzi et al., 2020), such as a greater impulsivity (Tomie & Morrow, 2018), lower top-down attentional control (Paolone et al., 2013) and greater novelty seeking (Beckmann et al., 2011). The ST/GT model therefore seems appropriate to capture a neurobehavioral endophenotype that could be relevant for the investigation of addiction vulnerability as well as other psychiatric disorders (Colaizzi et al., 2020, p. 84; Lovic et al., 2011; T. E. Robinson et al., 2014; B. T. Saunders & Robinson, 2013). More specifically, this model may constitute a translational and transdiagnostic model for the etiology and maintenance of a variety of compulsive reward-seeking behaviors (Pool & Sander, 2019), including SUDs. However, there is currently no consensus on a valid methodology to translate this animal model to humans (Colaizzi et al., 2020; Heck, Durieux, et al., 2025).

To date, human ST and GT behaviors have mostly been measured through computerized tasks based on reaction time (Albertella, Le Pelley et al., 2019; Albertella, Watson, et al., 2019; Le Pelley et al., 2015; C. Liu et al., 2021; Watson, Pearson, Most, et al., 2019) and eye-tracking (Cherkasova et al., 2024; Dinu et al., 2024; Garofalo & di Pellegrino, 2015; Schad et al., 2020). Physical PCA tasks, using levers and collectable rewards similarly to the animal model, have only been tested in a few studies (Colaizzi et al., 2023; Colom, 2023; Cope et al., 2023).

In a translational perspective close to the animal paradigm, Colaizzi et al. (2023) implemented a setup in which sign- and goal-tracking (defined as non-ST in this study) could be assessed in children. In their paradigm (Joyner et al., 2018), a lever CS predicted monetary reward delivery. As with laboratory rodents, the ST/GT categorization was based on a response bias score (RBS), derived from both the number of physical contacts and the time latency to contact the CS and the reward delivery location. Their results

indicated that children with a propensity to sign-track were prone to externalizing behaviors, adding further evidence to the idea that the ST/GT model represents a translational marker of human vulnerability for impulse-control related disorders. Cope et al. (2023) used a similar paradigm to investigate human sign-tracking behavior, based on both physical approach and eye gaze. They successfully identified three phenotypes (STs, GTs, and INTs) and found a significant association between impulsivity and the ST profile.

A major issue in the emerging literature on the human ST/GT models is the heterogeneity in the methods used to measure the phenotypes. Additionally, critical differences from the animal model are frequent and may prevent a proper translation of the paradigm in humans (Heck, Durieux et al., 2025). For instance, the value-modulated attentional capture (VMAC) task has sometimes been used to investigate ST behaviors in humans. The task aims to measure how a CS delays the identification of a target stimulus, an effect presumably induced by the attribution of incentive salience to the CS (Le Pelley et al., 2015, 2024). However, VMAC tasks differ in many respects from the standard ST/GT paradigm and are not designed to easily classify individuals according to their ST or GT phenotypes (Heck, Durieux, et al., 2025). On the other hand, direct measures of behavioral approach toward reward-predicting cues—such as the lever-directed behaviors commonly observed in laboratory animals—are challenging to implement in humans. This difficulty may arise because such behaviors are less natural for humans, potentially influenced by the internalization of social norms in adulthood that discourage touching objects that do not belong to them (Heck, Durieux, et al., 2025). Moreover, implementing such measures in human studies often requires specialized and potentially costly equipment, as well as trained personnel to manage and operate the apparatus effectively.

In the present study, we sought to create a translational experimental design based on the virtual “*approach*” to a CS versus the reward location, to measure ST and GT in adult humans using a procedure as close as possible to the typical animal paradigm (often referred to as Pavlovian *autoshaping*). Our computerized PCA task was coupled with an eye-tracking device, since eye gaze is sometimes used as an index of approach behavior in humans (Stephens et al., 2010). Moreover, previous studies have successfully used gaze metrics to distinguish between STs and GTs (Garofalo & di Pellegrino, 2015; Schad et al., 2020). Similar tasks have emerged since the development of our experiment (Cherkasova

et al., 2024; Dinu et al., 2024), but they have not been used to investigate the relationship between sign- and goal-tracking and alcohol use. In an exploratory perspective, a dot-probe task was also included to compare the attentional capture by the “*sign*” and the “*goal*” stimuli learned during the former computerized PCA task. Indeed, a parallel has been established between sign-tracking and attentional bias (AB) (Anselme & Robinson, 2020; Stephens et al., 2010), although the occurrence of an AB for the CS in a ST/GT task has never been tested so far. It was predicted that the AB score derived from the dot-probe task would positively correlate with the ST/GT score.

In addition to differentiating participants into STs and GTs, we aimed to determine whether the sign-tracking score (supposed to reflect individual differences in the attribution of incentive salience to a reward-paired cue) correlates with variables directly related to substance misuse, such as individual alcohol consumption levels. Other questionnaires were also used to investigate the relationship between the sign-tracking score and variables indirectly related to alcohol consumption (drinking occasion index, alcohol sensitivity, compulsivity-related problems), as well as factors associated with sign-tracking (such as impulsivity and psychological distress, see Albertella, Le Pelley, et al., 2019). Finally, the present study investigated how the ST and GT phenotypes are influenced by the experience of reward (anticipated pleasure) and the sensitivity to reinforcement (reward interest and reward reactivity). Indeed, pleasure anticipation and reward sensitivity are related to reward motivation (Gard et al., 2006; Geaney et al., 2015) and were suggested being additional risk factors for substance use (Cope et al., 2019). We predicted that sign-tracking would correlate with a higher impulsivity, a greater alcohol consumption and more severe alcohol-related problems, as well as with a greater reactivity to reward and anticipation of pleasure. Measures of subjective liking for conditioned stimuli were also included to assess the breadth of appetitive conditioning. Indeed, after Pavlovian conditioning, subjective liking for reward-paired pictures was shown to increase significantly, when compared to unrewarded cues (Garofalo et al., 2020). Levels of subjective liking were thus predicted to increase following the experimental tasks.

Materials and Methods

Participants

This study involved 106 volunteers (71 females, 34 males and 1 identified as non-binary; mean age = 21.98, sd = 2.73, Table 2). They were invited to complete an online screening questionnaire to check for inclusion criteria. Inclusion required no history of severe neurological diseases, no regular substance use (defined as more than twice in the last two months, except for tobacco and alcohol), no ADHD, no colorblindness, and being at least occasional alcohol consumers (abstinent people were not included). All participants had normal or corrected-to-normal vision. Table 2 shows means and standard deviations for age, education level, alcohol consumption severity score (AUDIT-C) and recent drinking index in the present sample.

Table 2. *Sample Description*

Variable	GTs		INTs		STs	
	Mean (std)	Range	Mean (std)	Range	Mean (std)	Range
Age	22.15 (2.93)	19-31	22.10 (3.08)	18-32	21.69 (2.15)	18-26
Education level	14.45 (2.02)	8-20	14.97 (2.26)	12-20	13.80 (1.35)	12-17
AUDIT-C	4.10 (2.26)	1-10	3.87 (2.11)	1-10	5.37 (2.37)	1-10
Recent Drinking Index	13.88 (17.00)	0-68	21.00 (58.72)	0-315	25.34 (27.63)	0-100
Gender						
Male	N=15		N=10		N=9	
Female	N= 25		N= 20		N= 26	
Non-binary	N= 0		N= 1		N= 0	

Note. Recent drinking index = number of alcoholic drinks consumed during the past 2 weeks x number of drinking occasions during the past 2 weeks.

A minimum of 94 subjects were needed based on an a priori power analysis, with an alpha threshold of .05, power of .80, and an effect size of .085 (between small and medium) for the regression analysis of the ST/GT score on alcohol consumption level. Initially, 126 participants took part in this study. Seven were excluded because they failed the attention check item and were considered careless responders. Thirteen participants were removed from the analysis due to one of the data quality check criteria (see Section “Eye-Tracking”). The final sample therefore included 106 participants.

The study was conducted in accordance with institutional guidelines and the Declaration of Helsinki. It was approved by the local Ethics Committee.

Participants were recruited via word of mouth, social media or advertising posters. The study was initially presented to the participants as investigating the factors that influence fluid intelligence, assessed through reaction time measures. After filling out the online screening, participants meeting the inclusion criteria were contacted to take part in the experimental phase of the study (on-site). All participants gave informed consent to take part in the study and had the chance to participate in a price draw to win a 20-euro gift voucher. Recruitment and testing took place from December 2022 to July 2023, at the university's facilities.

Experiment

Procedure

The in-person testing consisted of three phases: pre-experimental questionnaires (10 minutes), ST/GT task completion (approximately 20 min), and post-experimental questionnaires (15 minutes). Participants were tested in a quiet room. They were allowed to take short breaks between the different steps to avoid fatigue. At the end of the experimental session, the real purpose of the study was revealed to the participants, after which they had the possibility to give a second informed consent.

Stimuli

Before starting the ST/GT task, participants were instructed that they could collect a certain number of points in the next tasks, and that more points collected would unlock more glorious expertise badges. We chose accumulation of points and unlocking of badges to reflect reward amount because this procedure does not impact the participants' motivation to seek rewards (Albertella, Watson, et al., 2019; Watson,

Pearson, Theeuwes, et al., 2020). The stimuli for the PCA task and the dot-probe task were as follows:

- *Goal and sign pictures*: Blue rectangles (11 cm length x 6.5 cm height) filled with either blue squares or blue dots, counterbalanced across participants.
- *Reward*: Either a yellow 5-point coin or a yellow 10-point coin in the design of a casino coin.
- *Expertise badges*: Fancy and colorful badges reflecting performance (ranging from the categories bronze, silver, gold, platinum, diamond, and expert).
- *Dot-probe training pictures*: Five white and blue pictures of pets.
- *Dot-probe new pictures*: The same kind of pictures as used for the goal and sign but filled with triangle or cross shapes.

The stimuli were presented on a computer screen (1920 x 1080 pixels) with a grey background. A battery of three computer tasks was implemented: (1) the simple reward task, (2) the PCA task, and (3) the dot-probe task. The three tasks were run on a homemade custom Matlab software (version R2019b).

Simple Reward Task

The participants had to press a key when a coin was displayed on the goal picture, at the goal location. Goal location was counterbalanced across participants (bottom or upper part of the screen). The coin appeared for 1.5 seconds on the goal shape, and the sound of a falling coin could immediately be heard when the participant pressed the key to collect the reward. There was a 20% chance that the coin was a "10-point coin" to maintain a level of curiosity and avoid monotony during the task.

The aim of this first task was for the participants to learn where to collect the rewards and was designed to mimic the *magazine training phase* in animal models, where rewards are regularly delivered without any CS presentation. The simple reward task consisted of 15 trials, with a variable inter-trial interval (ITI) from 4 to 8 seconds. Prior to starting the task, participants were instructed as follows: "*When you are ready, we will start the first task. It will last approximately 4 minutes. During this task, objects will be displayed in a blue rectangle. These will allow you to earn points. Your objective is to respond as quickly as possible to their presentation by pressing the "enter" key.*" At the end of the task, the earned badge was displayed on the screen.

PCA Task

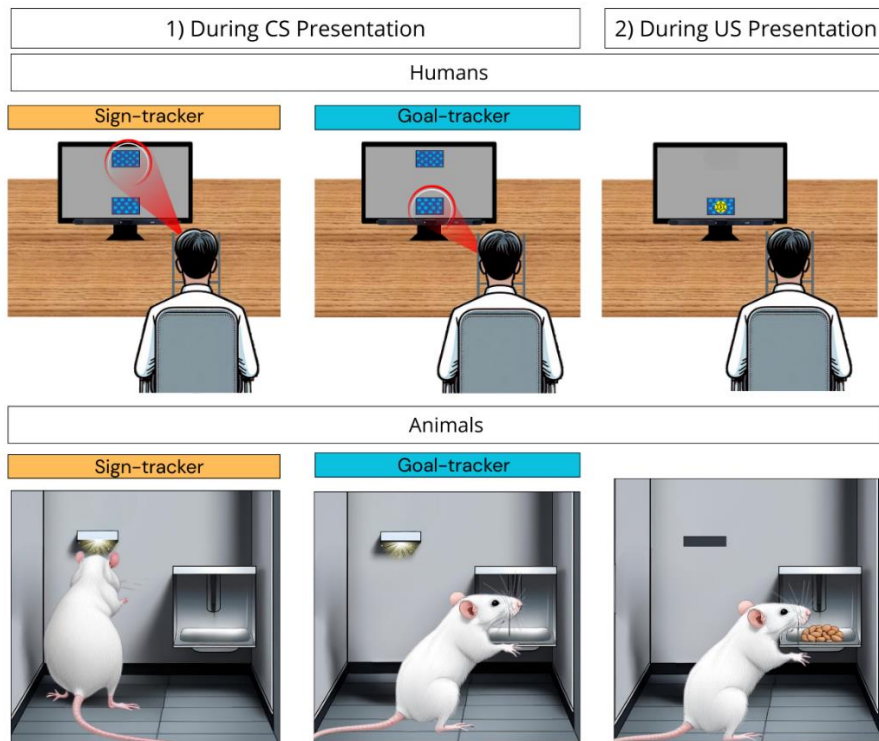
The PCA task was designed to match as much as possible the *autoshaping* procedure used in animal ST/GT studies. The goal and sign cues were the same as in the previous task. The goal shape was permanently present and could be located at the bottom or upper part of the screen (the location being the same as in the simple reward task). The sign shape was displayed on the opposite part of the screen (upper or bottom) for 3 seconds and disappeared just before a coin was presented on the goal shape for 3 seconds. Therefore, the sign shape was defined as a CS announcing reward delivery. Reward delivery followed the CS presentation with an 80% probability, given that probabilistic reward schedules are more effective in generating CS-directed responses than fully predictable ones (Anselme et al., 2013; Glueck et al., 2018; M. J. F. Robinson et al., 2023). We chose 80% rather than a lower probability (e.g., 50% or 25%) because our aim was to stimulate participants' attention to the cue by introducing non-rewarded trials, instead of studying the effects of reward uncertainty per se. We therefore used a relatively low level of uncertainty.

When participants pressed the "enter" key after a coin was displayed, the sound of a falling coin could immediately be heard, informing them that they collected the reward. The reward then disappeared from the goal shape. The task consisted of two blocks of 20 trials with a variable ITI ranging from 4 to 8 seconds. Like in the previous task, there was a 20% chance that a "10-point coin" was obtained.

Prior to starting the PCA task, participants were instructed as follows: *"This task is similar to the first one, except that we are no longer measuring your reaction time here. You can also score points. Use the 'enter' key as before. Please keep your attention on the computer screen and don't look at the keyboard."* At the end of the task, the earned badge was displayed on the screen.

Figure 10 illustrates the layout of our newly created computerized PCA task alongside a reference to the traditional animal PCA paradigm, highlighting the similarities designed to ensure cross-species comparability in assessing sign-tracking behavior.

Figure 10. Layout of the Developed Computerized Pavlovian Conditioning Approach (PCA) Task in Comparison to the Original Animal Task



Note. The lower part of the figure shows the traditional animal PCA paradigm (adapted from Kuhn et al., 2018), while the upper part represents our developed task in humans. The left part represents the typical ST/GT behaviors during CS presentation; the right part represents the US delivery. In the human PCA task, the person is seated in front of a computer screen, with their head in a chinrest. The task consists of multiple presentations of a predicting cue (upper blue rectangle, CS) followed by a reward cue (coin, US). Approach behavior is inferred from eye-gaze behavior. For the animal paradigm, a retractable, illuminated lever (CS) is presented before food pellet delivery (US). (Image created using Canva AI, 2025).

Dot-Probe Task

Training Phase

The training phase consisted of 15 trials, in which two out of five pet pictures were simultaneously shown for 500 ms on each side of a central fixation cross on the screen. Their presentation was randomized. After removal of the two pictures, a single randomized letter (E or F) became immediately visible on the location where one of the two pictures was previously displayed. The location of the letter behind the right or left picture was also randomized. The task of the participants was to press as quickly as possible the corresponding key (E or F) on the keyboard. If the participant failed to answer within 1.5 seconds, the trial was recorded as a time-out. The ITI was variable, between 2 and 4 seconds. Prior to starting the training phase, participants were instructed as follows: *"Here, you will be presented with a fixation cross in the center of the screen, followed by a pair of pictures. Start by fixing the middle cross. Once the pictures have disappeared from the screen, a white letter will appear on the left or right side of the screen. Your task is to press the corresponding key as quickly as possible. For this task, the options are the 'E' key, or the 'F' key. Once you have answered, another cross will appear, followed by a new series of pictures. You will perform several of these trials. Please keep your attention on the computer screen and don't look at the keyboard. You will start with a practice run of 15 trials".*

Test Phase

The task was identical to the training phase, except that the stimuli displayed on the screen were the *"goal shape"* and *"sign shape"* (see section "Experiment" - "Stimuli", p.162) of the PCA task and two additional new shapes. Stimuli display duration was 100 ms (a shorter latency was chosen to minimize the risk of cognitive processing of cues), and the ITI varied between 0.5 and 1.5 seconds. This task consisted of 128 trials. Time-outs were rare, ranging from 0% to 7.81% of trials across participants, and the total number of trials was large. Thus, a fixed number of trials without repetition was used during the task (of note, one participant was excluded due to time-outs exceeding 70% of trials). Prior to starting this task, participants were instructed that they had to proceed as before and that the task would last about 10 minutes. For the correlational analyses, only the trials in which the sign cue was opposed to the goal cue were considered. If a participant had developed

an AB for either the sign or the goal cues, s/he was expected to respond quicker when the letter was displayed behind that cue. For further exploration of the AB scores, trials in which the sign and the goal were opposed to new stimuli were also considered.

Data Collection

Questionnaires

For conciseness, a more detailed description of the questionnaires is provided in ([Appendix B](#)). In the screening phase, all participants completed socio-demographic online questionnaires including the history of neurological problems that could affect cognitive functioning, and regular use of tranquilizers or illicit drugs. They also completed the short version of the alcohol use disorder identification test (AUDIT-C, Bush et al., 1998) and the short version of the UPPS-P Impulsive Behavior Scale (UPPS-P French translation, Billieux et al., 2012).

In the pre-experimental phase, all participants completed electronic versions of the following questionnaires:

- *The Reinforcement Sensitivity Theory of Personality Questionnaire* (RST-PQ, Corr & Cooper, 2016). In the present study, we only measured three dimensions (total number of items = 24): Reward interest (RI), Goal-drive persistence (GDP) and reward reactivity (RR).
- *The Temporal Experience of Pleasure Scale* (TEPS, Gard et al., 2006) Only the anticipatory scale, consisting of 10 items, was measured.
- *Four visual analog scales* ranging from 0 to 100 asked the participants about their level of subjective liking of the four visual stimuli used in the study (sign, goal and the two new items of the dot-probe task).

In the post-experimental phase, participants completed electronic versions of the following questionnaires:

- *The short Depression, Anxiety, Stress Scale* (DASS-21, Lovibond et al., 1995).
- *The Alcohol Sensitivity Questionnaire* (ASQ, O'Neill et al., 2002).
- *Questions about current alcohol consumption.* To gain insight into participants' recent drinking behavior, we included the following two questions into the protocol: "How many drinks have you had in the last 14 days?" and "On how

many occasions have you drunk alcohol in the last 14 days?". A recent drinking index was computed by multiplying these two numbers.

- *The Brief Assessment Tool for Compulsivity Associated Problems (BATCAP, Albertella, Le Pelley, et al., 2019).*

Eye-Tracking

A Tobii 5 eye-tracking system (with an image sampling rate of 133 Hz) was mounted on a 60.5 cm diagonal computer screen. The eye tracker was calibrated using a six-point procedure at the beginning of the experiment. A chinrest was used to standardize the head-screen distance at 70 cm. Tobii Experience software was used to calibrate the eye-tracking system.

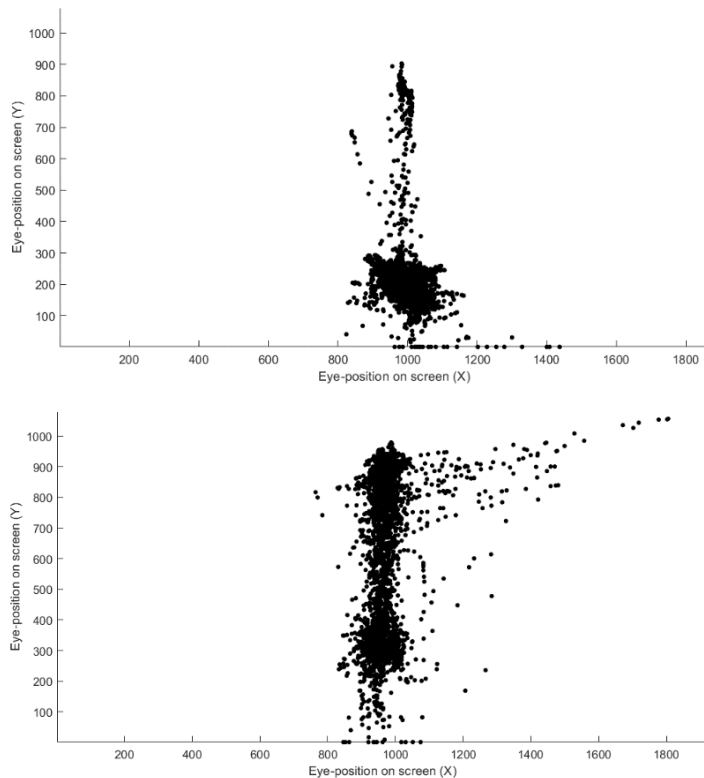
To compute eye gaze-based ST/GT scores, the screen was virtually separated into 9 regions of interest (ROI, 3 equal parts on each axis). Eye gaze position was collected throughout the PCA task. The two main ROIs used to compute the scores were the upper center and the bottom center of the screen, where the goal and the sign stimuli were located (see Figure 11 for a visualization of eye tracking during the task). The in-between region (middle center) was also of interest for later analyses (LPA).

We used a custom implementation of the Velocity Threshold Algorithm for fixation identification. First, eye position in pixels was converted to visual degrees. Then velocity was computed in degrees/sec for axes X and Y. To distinguish fixations from saccades, we used individualized thresholds for each subject based on their gaze velocity during mandatory fixations in the dot-probe task (training phase). Each threshold was computed by adding $1.95 \times \text{standard deviation}$ to their mean gaze velocity during fixations (= confidence interval of 95%). In probability and statistics, the 97.5th percentile point of the standard normal distribution is a number commonly used for statistical calculations. The approximate value of this number is 1.96, meaning that 95% of the area under a normal curve lies within approximately 1.96 standard deviations of the mean. Because of the central limit theorem, this number is used to approximate 95% confidence intervals.

Eye movements were considered fixations when they were strictly below the personalized threshold. Too short fixations (<100 ms) were removed to smoothen eye-gaze data. For each identified fixation, duration and ROI were collected. Two outcome measures were obtained: Fixation count (number of fixations) and dwell time (total

fixation time on each ROI), two classic parameters when working with fixation-based measures (Mahanama et al., 2022).

Figure 11. *Representative Visual Patterns of Eye-Gazes on the Computer Screen During the PCA Task in Two Different Participants.*



Note. Each black dot represents the eye position on the screen, every 50 ms during the task. No filter was applied at this stage; the graph only helps visualize gaze behavior. The sign was in the upper middle zone of the screen for both participants, while the goal was in the bottom middle part.

Three main criteria were used for data quality check and poor quality data exclusions: A participant was excluded (1) if the gaze stagnated in the middle zone throughout the whole task, without variation (perhaps an indicator of poor calibration or other technical problem, $n = 0$), (2) if there were more than 30% of gazes at the outer edge of the screen (5% of the screen) compared to the rest of the screen (poor calibration, $n = 2$), and (3) if on average the individual gazed less than 1 second per CS presentation at

either of the ROI (goal and sign) or at the center of the screen (due to too few data to compute a meaningful sign-tracking score, $n = 11$).

Eye-Tracking Based Sign- and Goal-Tracking Scores

Eye-tracking based ST/GT scores were computed similarly to the RBS classically used in animal research (e.g., P. J. Meyer, Lovic, et al., 2012). Dwell time on the “goal” was subtracted from dwell time on the “sign” and divided by the total dwell time on both ROIs (during the 3s CS presentation). Thus, the ST/GT score ranged from -1 to 1, with negative scores suggesting “goal-tracking” phenotypes, positive scores indicating a “sign-tracking” phenotypes, and scores around 0 meaning a rather “intermediate” tendency. This score was computed for the first and second blocks of the PCA task, the number of fixations, and the total dwell time—leading to 4 ST/GT scores. Distribution of these scores are displayed in [Appendix B](#), Figure B). Since some time was required for the participants to become familiar with the task and for specific conditioned responses to emerge (Colaizzi et al., 2023; Cope et al., 2023; Garofalo & di Pellegrino, 2015), only the second block score was considered in the main analyses. Analyses involving all computed scores (for the first hypothesis) are available in [Appendix B](#) (Tables C-H).

Reaction time

For the dot-probe task, scores were calculated by subtracting the reaction time index (mean reaction time divided by the percentage of correct trials) for the goal picture from the reaction time index for the sign picture. A positive score was therefore indicative of an AB for the sign cue and a negative score for the goal cue. For the computation of the dot-probe task score, only the sign vs. goal trials were considered, although both stimuli were also in competition with new pictures in other trials (see [Appendix B](#), Tables I-J for these analyses).

Data Analysis

Statistical analyses were performed using R 4.3.3 (R Core Team, 2024). Data handling and pre-processing were done using readxl (v1.4.3, Wickham & Bryan, 2025), tidyverse (v2.0.0, Wickham et al., 2019) packages. Visualizations were done using ggplot2 (v3.5.0, Wickham, 2026), and ggpubr (v0.6.0, Kassambara, 2025a) packages. Main analyses (including ANOVA, model assumptions verification, Kruskal-Wallis tests) were

run with *rstatix* (v0.7.2, Kassambara, 2025b). Correlational analyses and internal consistency measures were computed with *psych* package (v2.4.3, Revelle, 2025). Linear mixed effects models for learning analyses were run with *lme4* (v1.1-34, Bates et al., 2015) and *car* (v3.1-2, Fox & Weisberg, 2019) packages. LPA were run with *tidyLPA* package (v1.1.0, Rosenberg et al., 2019). Confirmatory factor analyses (CFA) were run with *lavaan* package (v0.6-19, Rosseel, 2025).

Alpha level was set at 0.05, but corrections for multiple correlations were applied as indicated. Given that the questionnaires were administered electronically, no missing data was recorded, as participants were required to answer all questions to proceed.

LPA was performed to identify whether the 3-profile model of STs, GTs, and INTs fitted our data. LPA is a categorical latent variable modeling approach (Collins & Lanza, 2010) that focuses on identifying latent subpopulations within a population based on a certain set of variables (Collins & Lanza, 2010; Howard & Hoffman, 2018; Spurk et al., 2020). In this analysis, the following variables from the second block of the sign-tracking task were included as indicator variables: Number of fixations on the “goal”, number of fixations on the “sign”, number of fixations on the in-between zone, total dwell time on the “sign”, total dwell time on the “goal”, and total dwell time on the in-between zone. A series of three models was run with each having an additional number of profiles. The final choice of the number of relevant profiles is made on the basis of theoretical assumptions but also several fit indices (Collins & Lanza, 2010), such as the Bayesian Information Criterion (BIC), the Akaike Information Criteria (AIC), and entropy close to 1. When computing the profiles, our model specifications allowed the covariances among the indicator variables to be freely estimated within a profile, but both variances and covariances were constrained to be the same across profiles (Pastor et al., 2007). Once consistent profiles were obtained, a Kruskal-Wallis rank-sum test was run again to test for differences between these groups on alcohol consumption severity (AUDIT-C). Further, we ran a Kruskal-Wallis rank-sum test for significant differences between these groups to test whether the LPA derived profiles were coherent with our ST/GT index.

To examine whether alcohol consumption levels are significantly associated with the ST vs. GT profiles, including the INT subgroup as identified through LPA, we conducted a Kruskal-Wallis rank-sum test. In this analysis, the three profile groups served as the independent variable, while the AUDIT-C score was the dependent variable. This

test was chosen because the AUDIT-C scores failed to meet the normality assumption. Additionally, given that previous studies have categorized participants using a tertile split approach (Cherkasova et al., 2024; Dinu et al., 2024; Duckworth et al., 2022), we conducted the same analysis using groups based on tertile splits of “gaze duration” scores. However, it is important to note that this categorization may be of limited relevance in the present case, as the ST/GT score distribution is left-skewed (results in [Appendix B](#)).

To test the relationship between the ST/GT profile and other alcohol-consumption related variables, Spearman correlation coefficients were computed. A Benjamini & Hochberg (1995) (B-H) correction was applied to adjust the p-values for multiple comparisons. Similarly, Spearman correlation coefficients were calculated to test the relationships between the ST/GT index score and personality related variables (impulsivity, reward reactivity, reward interest, anticipated pleasure, psychological distress). Additionally, we examined whether the ST/GT score differed by gender. This question is particularly relevant given the well-established role of sex in both alcohol consumption and sign-tracking tendencies. Numerous studies have shown that men consume significantly more alcohol, have a greater tendency for solitary drinking, and exhibit a higher prevalence of AUD compared to women (Global Burden of Disease, 2020; Skrzynski & Creswell, 2021; Wilsnack et al., 2000; WHO, 2018). In contrast, recent findings suggest that females exhibit stronger sign-tracking behavior, both in rodent models (Hakus et al., 2025) and in humans (Degni & Garofalo, 2025). In this study, we asked participants to report their gender; therefore, our analyses are based on gender rather than biological sex. Although this was not part of our initial hypotheses, we conducted this exploratory analysis and report the results in [Appendix B](#). It is also important to note that our study may be underpowered to detect potential gender differences in sign-tracking due to limited and unequal sample sizes for each gender (Women, N= 71, Men, N=34).

To test whether subjective liking of the sign and goal stimuli at the end of the experiment differed among the three groups, we performed a mixed model analysis of variance (ANOVA) with the subjective liking scores as dependent variables and group (ST, GT, INT, based on the eye-tracking scores) and cue-type (sign vs. goal) as the independent variables.

Since the dot-probe task was included in an exploratory perspective, we tested whether there was a correlation between the bias score derived from the dot-probe paradigm and the ST/GT index score as well as alcohol-related consumption-related variables ([Appendix B](#), Table K). A positive correlation was expected since both tasks assess a bias for either the “sign” or the “goal”. To further explore the relevance of this task, ST, GT and INT groups were compared (Kruskal-Wallis rank sum tests) regarding the index bias variable when the sign and goal pictures were opposed with new ones.

Finally, we aimed to check the properties of this new ST/GT task through an assessment of the internal consistency. A Cronbach’s alpha was calculated for the 20 trials, in the first and second blocks, using the ST/GT score (see Section “Eye-Tracking Based Sign- and Goal-Tracking Scores” for details on score calculation) based on dwell time. To test whether gaze (towards the sign and the goal) significantly changed across the two experimental blocks (i.e., associative learning took place) for the 3 behavioral profiles, we ran a linear mixed model with participants nested within profiles as the random factor. Since these analyses were not part of the main hypotheses of this experiment, the results are shown in [Appendix B](#).

Results

Hypothesis 1. Differentiating Human Sign- and Goal-Trackers

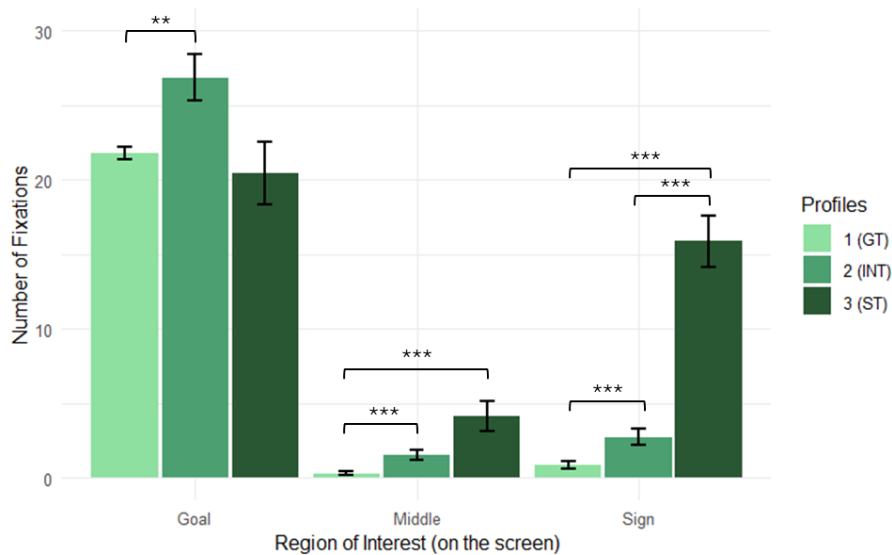
In the LPA, the best model based on fit indices was the 3-profile model (AIC = 1130.96, BIC = 1240.16, entropy = 0.93). Table 3 shows the fit indices for the three models. Posterior probabilities (i.e., probabilities for each participant to belong to each of the three profiles) indicated good confidence in the most likely profile membership. For profile 1, the probabilities ranged from 0.71 to 0.99 (mean = 0.97, sd = 0.06). For profile 2, they ranged from 0.69 to 0.99 (mean = 0.96, sd = 0.08). For profile 3, they ranged from 0.93 to 1.00 (mean = 0.99, sd = 0.01). Figures 12 and 13 show means and standard errors for the indicator variables in the three profiles. Based on the examination of these graphs, groups 1, 2, and 3, were labeled respectively, “GT”, “INT”, and “ST”.

Table 3. *Model Fit Indices for the Three Latent Profile Analyses*

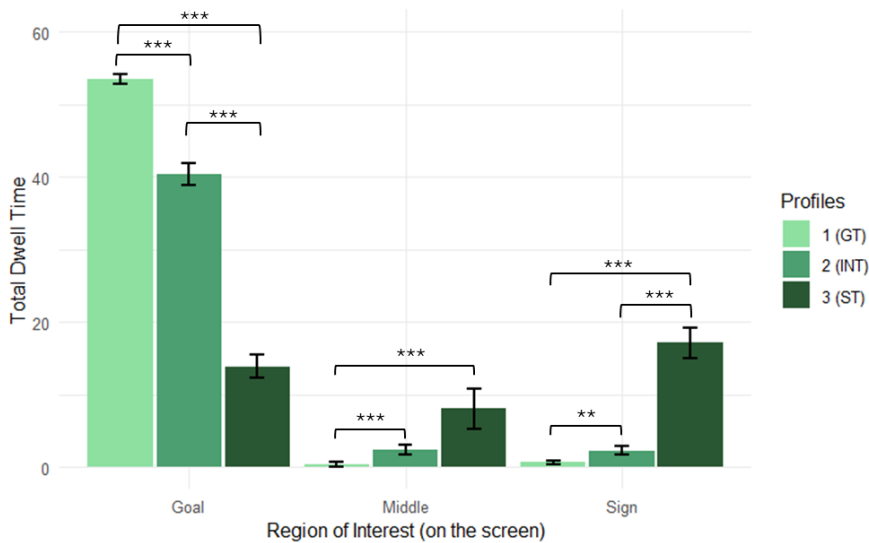
Tested Model	AIC	BIC	Entropy	Profile Sizes	Bootstrapped Likelihood Test (p-value)
1 Profile	1194.52	1266.43	-	-	-
2 Profiles	1184.85	1275.40	0.83	Profile 1: 44% Profile 2: 56%	.05
3 Profiles	1130.96	1240.16	0.93	Profile 1: 38% Profile 2: 29% Profile 3: 33%	.01

Note. AIC= Akaike Information Criterion, BIC= Bayesian Information Criterion

Figure 12. *Number of Fixations on Each Region of Interest in the Three LPA-Extracted Profiles*



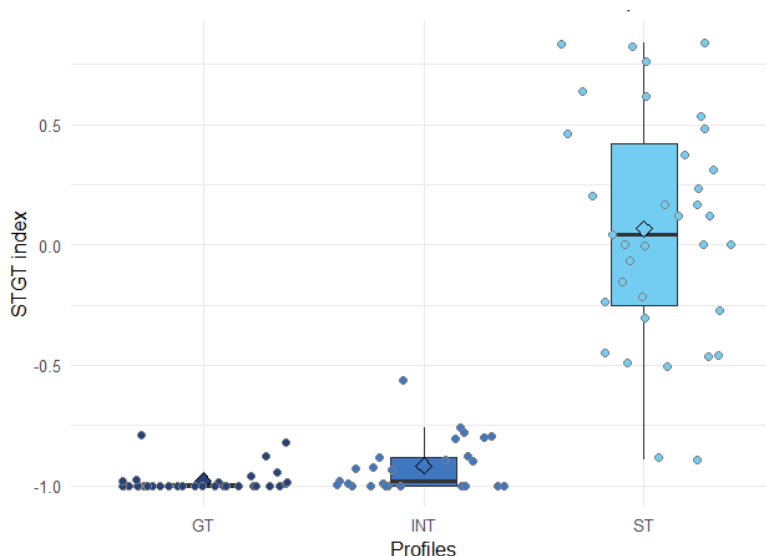
Note. The figure shows the means and standard errors. ***<0.001, **<0.01

Figure 13. *Total Dwell Time on Each Region of Interest in the Three LPA-Extracted Profiles*

Note. The figure shows the means and standard errors. *** $p < 0.001$, ** $p < 0.01$

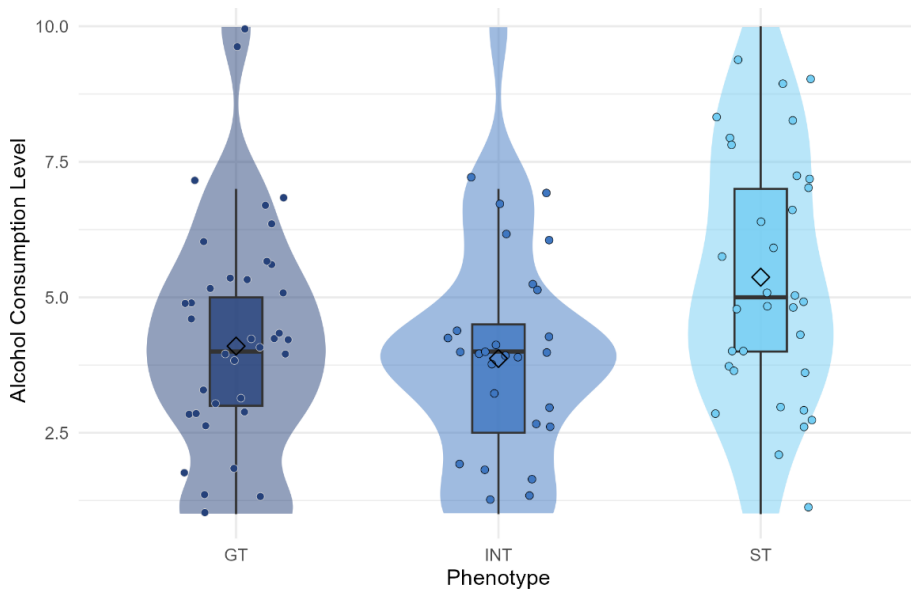
A way to further test the validity for these profiles is to estimate the differences that may exist across profiles in relation to theoretically relevant outcomes (Spurk et al., 2020), i.e., in this context, alcohol consumption levels.

When testing whether the LPA-derived profiles differed with regard to our ST/GT index (RBS based on gaze duration in the second block), the Kruskal-Wallis rank-sum test was significant with a large-sized effect ($\chi^2 = 73.04$, $p < 0.001$, $\eta^2(H) = 0.690$, 95% CI = [0.61, 0.79]). Figure 14 shows the distribution of the ST/GT scores among the three groups created by the LPA. Post hoc pairwise Wilcoxon tests (corrected with a B-H correction for multiple comparisons) indicated that all groups significantly differed from each other (all $p < 0.001$).

Figure 14. *Distribution of ST/GT Scores in the LPA Created Profiles.*

Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes.

A Kruskal-Wallis rank-sum test on these three profiles, aimed to assess differences in alcohol consumption (AUDIT-C), showed a significant effect of small to medium size ($\chi^2 = 8.10$, $p = 0.01$, $\eta^2(H) = 0.059$, 95% CI = [-0.09, 0.13]). Figure 15 shows the distribution of AUDIT-C scores in STs, GTs, and INTs, based on LPA-created profiles. Post hoc pairwise Wilcoxon tests indicated that the differences between STs and GTs ($p = 0.03$) and between STs and INTs ($p = 0.02$) were significant. No significant difference was obtained between GTs and INTs ($p = 0.65$). The same analysis, using ST, GT, and INT groups based on a tertile split (RBS), yielded highly similar results with a medium effect size ($p = 0.004$, $\eta^2(H) = 0.084$, 95% CI = [-0.07, 0.16], [Appendix B](#), Figure C).

Figure 15. AUDIT-C in STs, GTs and INTs, Based on LPA Created Profiles

Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Hypothesis 2. Relationships Between Human Sign-Tracking and Variables Related to Alcohol Consumption

We examined the relationship between the ST/GT scores and other alcohol consumption/addiction related variables—i.e., alcohol-compulsivity related problems (BATCAP-Alc), alcohol sensitivity (ASQ), the recent drinking index, and AUDIT-C. Only the correlation between AUDIT-C and the ST/GT score was significant ($R_s = 0.29$, $p = 0.01$). Table 4 shows correlation coefficients, p-values and confidence intervals for each Spearman correlation coefficient. For the sake of completeness, the full correlation matrix between the ST/GT score and alcohol-related variables is available in [Appendix B](#) (Table L).

Table 4. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Alcohol-Related Variables*

Variable	Spearman Rho	Adjusted P- Value	Raw P- Value	CI Lower (Adjusted)	CI Upper (Adjusted)
ASQ	-0.03	0.795	0.795	-0.27	0.22
BATCAP (Alcohol)	0.10	0.442	0.332	-0.16	0.34
Recent Drinking Index	0.19	0.093	0.047	-0.05	0.42
AUDIT-C	0.29*	0.010	0.003	0.05	0.50

Note. ASQ = Alcohol sensitivity questionnaire, BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test (see 2.6. "Questionnaires"). * $p < 0.05$

Hypothesis 3. Relationships Between Human Sign-Tracking and Personality-Related Variables

Regarding the association between the ST/GT score and personality-related variables, no significant correlations were obtained using the Spearman correlation coefficients, after B-H correction. However, it is noteworthy that the correlation coefficient between the ST/GT score and the "positive urgency" dimension of impulsivity is of medium size even though it did not reach the significance threshold after correction ($RS = 0.25$, raw $p = 0.01$, adjusted $p = 0.064$). Table 5 shows correlation coefficients, p-values and confidence intervals for each Spearman correlation coefficient. For the sake of completeness, the full correlation matrix between the ST/GT scores and personality-related variables is available in [Appendix B](#) (Tables M and N).

Table 5. *Correlation Coefficients, P-Values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Personality-Related Variables*

Variable	Spearman rho	Adjusted <i>p</i>	Raw <i>p</i>	CI Lower (Adjusted)	CI Upper (Adjusted)
Psychological Distress	0.06	0.651	0.54	-0.20	0.31
UPPS-P- Urgency	0.18	0.202	0.07	-0.08	0.42
UPPS-P- Positive Urgency	0.25	0.064	0.01	-0.01	0.48
UPPS-P- Lack of Premeditation	0.14	0.286	0.14	-0.12	0.39
UPPS-P- Lack of Perseverance	0.07	0.651	0.48	-0.19	0.32
UPPS-P- Sensation Seeking	0.00	0.990	0.99	-0.26	0.26

Note. TEPS = temporal experience of pleasure scale, UPPS-P = short version of the UPPS impulsivity scale (see section "Data Collection" - "Questionnaires").

Hypotheses 4 and 5. Subjective Liking and Attentional Bias Score

A mixed model ANOVA on subjective liking for both types of stimuli, did not reveal any statistically significant effect among the three groups (Table 6).

Table 6. *Statistics for Mixed Model ANOVA on Subjective Liking*

Effect	F	p	ges
Group (ST/GT/INT)	0.939	0.394	0.009
Stimulus (Goal vs. Sign)	0.673	0.413	0.003
Group*Stimulus	1.774	0.175	0.016

Note. ges = generalized eta squared

Regarding the ST/GT index that was derived from the reaction times in the Dot-Probe task, there was no significant correlation for any variables tested: Neither the ST/GT index (eye-tracking), nor the alcohol consumption-related variables. Results are shown in [Appendix B](#) (Table K) for the sake of completeness. In the same vein, the goal and sign bias scores when these stimuli were in competition with new ones did not differ between groups of STs, GTs, and INTs ([Appendix B](#), Tables I and J).

Discussion

The main purpose of this study was to implement a new computerized PCA task to determine its relevance at differentiating human ST and GT profiles. This study also aimed to determine whether the sign-tracking profile derived from eye-tracking responses related to alcohol consumption and personality variables, which are typically associated with sign-tracking in animal studies. Finally, a dot-probe task was included to test whether AB could parallel sign-tracking behavior, and thus correlate with the eye-tracking-derived ST/GT score.

Our task successfully identified three distinct behavioral profiles based on visual attention directed toward a conditioned reward-predicting cue and the (virtual) reward delivery location. LPA indicated that the three-profile model provided the best fit to the data, considering the number of fixations and dwell time allocated to the sign, the goal, and the intermediate zone. Based on theoretical frameworks, we classified these profiles as STs, GTs and INTs. Notably, these groups exhibited significant differences in alcohol consumption levels, with STs displaying significantly higher AUDIT-C scores compared to both GTs and INTs. The identification of distinct behavioral profiles—STs, GTs, and INTs—through eye-tracking is consistent with prior findings (Cope et al., 2023; Schettino et al., 2024), although several studies have only distinguished between STs and non-STs (Colaizzi et al., 2023; Joyner, 2019). Given the pronounced left-skew distribution of the RBS in our sample (suggesting a higher prevalence of goal-tracking behavior), a tertile split approach was deemed less appropriate, and a data-driven multivariate method (LPA) was preferred for group classification. However, it is important to note that both methods yielded highly similar results, reinforcing the robustness of our findings. Both approaches converged in showing a significantly higher level of alcohol consumption among STs ([Appendix B](#), Figure C). Furthermore, when testing whether LPA-derived profiles differed

significantly on the ST/GT score, a large and significant effect emerged. The left-skewed distribution of the RBS (towards goal-tracking) may be attributed to the novelty of the task, including the nature of its stimuli, which may not have been sufficiently engaging to elicit strong visual interactions. Alternative explanations include potential variations in attentional capture mechanisms due to the task's low cognitive demands, which may have influenced response tendencies, as well as a sampling bias toward goal-tracking individuals. Given the relatively low RBS scores found even in STs, one could argue that our participants did not exhibit strong sign-tracking tendencies. However, since we conceptualize PCA behavior as a continuum, the group labeled "STs" still represents the upper extreme of sign-tracking tendencies within the distribution observed in our sample.

Nevertheless, the present study identified a significant relationship between alcohol consumption levels and the ST phenotype in humans, as individuals classified as STs exhibited higher AUDIT-C scores than GTs. Regarding the INT profile, the participants exhibited significantly lower alcohol consumption levels compared to the ST group, while their consumption was comparable to that of the GT group. Furthermore, the ST/GT score was positively correlated with AUDIT-C, and a similar trend was observed with the recent drinking index. However, after applying the Benjamini-Hochberg correction, the correlation with the recent drinking index did not reach statistical significance (Table 4). This may reflect the limited timeframe captured by this index, potentially reducing its ability to detect meaningful associations.

These findings are consistent with what has been shown in several studies using the VMAC task to model sign-tracking behavior in humans, in which a significant association with problematic alcohol use and relapse was found (Albertella et al., 2021; Albertella, Watson, et al., 2019; Watson et al., 2024). The direction of this causal relation is still to be uncovered. Animal studies have suggested that STs are predisposed to addiction (and relapse) due to both heightened reward-cue and drug-cue reactivity (Tomie, 2018). It is therefore considered a preexistent vulnerability factor. Indeed, ST individuals are more likely to stay close to or to approach drug-paired cues (P. J. Meyer, Ma, et al., 2012; Yager et al., 2015), they find these cues more rewarding compared to GT individuals (B. T. Saunders & Robinson, 2010), they tend to prefer drugs such as cocaine over food compared to GTs (Tunstall & Kearns, 2015), and they are more likely to relapse following repeated drug consumption (B. T. Saunders et al., 2013; B. T. Saunders & Robinson,

2013). Specifically, alcohol cues are more attractive and act as more efficient conditioned reinforcers in STs compared to GTs (Villaruel & Chaudhri, 2016). However, this relationship could also work the other way round—i.e., increased substance use could render individuals more vulnerable to their predictive cues and thus turn them into STs (Kruse et al., 2017; Madayag et al., 2017; McClory & Spear, 2014). For example, alcohol exposure in adolescent rats increased the probability of developing sign-tracking behavior to reward-predicting cues (Kruse et al., 2017; Madayag et al., 2017 (only in females); McClory & Spear, 2014). However, there is also non-supporting evidence of increased goal-tracking behavior in selectively bred alcohol-preferring rats, and increased sign-tracking in alcohol non-preferring rats (Peña-Oliver et al., 2015). Causal effects might also go both directions and further research is needed to clarify this question.

The eye-gaze indices from which our ST/GT groups were derived differed in their ability to distinguish behavioral profiles. Figures 12 and 13 show that dwell time better differentiates the three profiles than number of fixations. Indeed, when examining dwell time for each region across the profiles (Figure 13), GTs gazed longer to the goal than STs and INTs; STs gazed longer on the sign than the other two groups; and both STs and INTs gazed longer on the middle region than GTs. On the other hand, the number of fixations on the goal (Figure 12) was less effective in differentiating profiles, with INTs showing significantly more gazes on every region compared to GTs. This is consistent with the idea that the intermediate category is more ambivalent and more susceptible to alternate their gazes between the sign and the goal (resulting in more frequent eye-movements), increasing their total number of gazes in the three regions. Interestingly, while INTs did not significantly differ from GTs in terms of alcohol consumption, their distinct eye-gaze pattern suggests a unique attentional profile. This supports the notion that INTs represent a separate subgroup rather than a transitional or indistinct category. Despite some heterogeneity among previous studies using similar eye-gaze indexes to categorize ST/GT groups, dwell time—recorded as total gaze duration for each area of interest—is the most commonly used measure (Cherkasova et al., 2024; Cope et al., 2023; Garofalo & di Pellegrino, 2015; Lehner, Balsters, Bürgler, et al., 2017; Schettino et al., 2024). The number of fixations has less often been used in previous studies (Dinu et al., 2024).

Unlike previous studies on human sign-tracking (Cope et al., 2023; Garofalo & di Pellegrino, 2015), our study did not find a significant association between impulsivity and the ST profile *per se*. However, this divergence may stem from methodological differences, particularly the use of a different self-report measure of impulsivity (Barratt Impulsiveness Scale vs. UPPS-P). These scales likely capture distinct facets of impulsivity, some of which may not be directly reflected in sign-tracking behavior. For instance, self-reported “lack of premeditation” in humans differs conceptually from assessments of impulsive action or impulsive choice in rodent models, such as the 5-choice serial reaction time task (Esteves et al., 2021). Encouragingly, the correlation coefficient between the ST/GT score and the “positive urgency” dimension of impulsivity was of medium size, suggesting a meaningful relationship despite not reaching significance after B-H correction. Moreover, an analysis of the full correlation matrix between impulsivity dimensions and the ST/GT score ([Appendix B](#), Table N) identified this correlation as statistically significant ($RS = 0.25$, adj. $p = 0.023$). While modest, this finding aligns with theoretical expectations and provides additional support for the validity of our paradigm. However, further research is required to confirm and expand upon these findings. Moreover, a consensus on the specific dimensions of impulsivity to assess within the ST/GT paradigm is crucial to ensure a robust translational perspective.

Regarding the relationship between sign-tracking and other personality-related variables, such as anticipatory pleasure (TEPS scale) and reward responsiveness (RST-PQ subscales), the present study did not show any significant correlation. Yet, drive and fun seeking, two subdimensions of the behavioral approach system (BAS), were found significantly related to alcohol use (Ivory & Kambouropoulos, 2012; Loxton & Dawe, 2001), alcohol cue-reactivity (Kambouropoulos & Staiger, 2001), and dysfunctional eating (Loxton & Tipman, 2017; May et al., 2016). Anticipatory pleasure (as measured through TEPS-anticipatory) has been linked to individual differences in reward motivation (Gard et al., 2006; Geaney et al., 2015) and more recently to ST/GT/INT profiles in humans (Schettino et al., 2024). The lack of positive results regarding these aspects in our study could be due to the poor factor structure of our translated versions of these questionnaires. Indeed, model fit indices were mediocre to bad for the TEPS and RST-PQ questionnaires (see [Appendix B](#) for details about CFA). These analyses should therefore be repeated with higher-quality versions of the questionnaires.

In our study, we did not observe statistically significant gender differences in sign- and goal-tracking tendencies ([Appendix B](#), Figure D). Although men exhibited significantly higher AUDIT-C scores compared to women, this difference in alcohol use did not appear to be associated with ST/GT phenotype. However, recent research has suggested that gender may play a role in sign-tracking behavior, with some studies reporting a greater propensity for sign-tracking among females in both human and animal models (e.g., Degni & Garofalo, 2025; Hakus et al., 2025). These findings highlight the importance of further investigating the potential influence of gender—and ideally, assigned sex at birth—on individual differences in cue-triggered behavior in future studies.

The lack of positive findings for the dot-probe task based on an AB score and the subjective liking scores for sign vs. goal pictures might be due to the abstract nature of the stimuli used (blue rectangles filled with different shapes). Moreover, they were visually quite similar and, given the modest number of associations between them and the reward ($n = 40$), they might not have induced a significant AB during the 250ms presentations in the dot-probe task. In most studies using a dot-probe task, stimuli frequently encountered in the real world are typically used (e.g., faces or alcoholic beverages). Another factor that may have disrupted the dot-probe task as an indicator of AB towards one of the two stimuli was the location of the cues on the screen. In the Pavlovian conditioning phase, the two stimuli (sign and goal) were presented in the upper vs. bottom part of the screen (following the task design established by Garofalo and di Pellegrino, 2015). In contrast, the dot-probe task presented stimuli on the left and right sides, in line with standard protocols commonly used to assess AB. Although this change in spatial location may have introduced an attentional shift or distraction, it also helped ensure that attention in the dot-probe task was driven by the motivational properties of the stimuli themselves, rather than by residual spatial associations from the conditioning phase. The absence of an effect in the dot-probe task may also suggest that the attribution of incentive salience, as reflected in sign-tracking approach behavior, is more effectively captured through direct behavioral measures in the Pavlovian conditioning task. This motivational process may not translate well to a subsequent attentional task, such as the dot-probe, especially in the absence of reward or direct contingency with the previously learned associations.

Our study did not question the ecological relevance of using a PCA task in humans. However, this does not represent a real limitation of the study, in the sense that our

objective was to translate the animal ST/GT model. We observed in the literature that obtaining a clear dissociation between STs and GTs with humans is more difficult than with rats. Explaining the origin of these differences is therefore crucial to understand the processes at stake, and perhaps find optimal conditions in which sign- and goal-tracking can reliably be obtained in humans. One option would be to study these behaviors in real-life settings, as already suggested (Schettino et al., 2022). For example, ecological momentary assessments might be useful to assess motivational salience attributed to daily-life reward-predicting cues. This has been investigated by Schettino et al. (2022), who found that people with increased impulsive, obsessive-compulsive, and addiction-prone tendencies were prone to find the cues more attractive than the rewards. Although they did not identify ST or GT phenotypes, this approach may represent a promising step in the translation of the animal model to real life in humans. Developing an ecological approach to sign- and goal-tracking might also help better predict how the ST and GT profiles interact with the use of illicit substances and with their clinical outcomes. At present, only two studies have investigated this question. They found that sign-tracking was predictive of non-abstinence (pseudo-relapse) during a one-month abstinence challenge in a non-clinical sample (Albertella et al., 2021) and of relapse during a 3-month follow-up in AUD patients (Watson et al., 2024). These studies used the VMAC task to model sign-tracking behavior and did not actually compare STs to GTs, but rather correlated the response bias scores related to attentional capture by reward associated cues with alcohol-use variables.

Finally, while our task for classifying behavioral profiles based on gaze behavior is newly developed and requires further validation to confirm its consistency, it was closely modeled on established animal studies and previous human research (Flagel et al., 2008; Garofalo & di Pellegrino, 2015). Additionally, despite the skewed distribution of the RBS score, the strength of our findings – particularly the expected differences in alcohol consumption across profiles, as well as the small yet expected association with impulsivity—supports the relevance of this task, paving the way for future research to further refine and confirm the usefulness of such computerized paradigms. Future research is needed to replicate these findings and further assess the task’s sensitivity and reliability.

In conclusion, this study successfully identified human phenotypes that likely reflect individual differences in reward-cue interaction—classified as STs, GTs, and INTs—which exhibited significant differences in alcohol consumption levels. This finding adds to the growing body of evidence demonstrating that computerized PCA tasks can effectively differentiate human sign- and goal-tracking behaviors based on eye-gaze metrics (Cherkasova et al., 2024; Dinu et al., 2024; Garofalo & di Pellegrino, 2015; Lehner, Balsters, Bürgler, et al., 2017; Schettino et al., 2024). Furthermore, our study underscores the relevance of these individual differences in addictive behaviors (Albertella et al., 2021; Albertella, Le Pelley, et al., 2019; Watson et al., 2024), reinforcing the potential importance of the ST/GT model in understanding how variations in incentive salience attribution to cues may contribute to addiction vulnerability. Identifying sign- vs. goal-tracking phenotypes could not only help target at-risk individuals but also might improve prevention efforts through psychoeducational strategies, akin to the “*scientific short stories*” developed by Tomie’s team (Levitch et al., 2018). Their findings suggest that increasing awareness of how the loss of self-control can lead to addiction could be a promising approach for prevention programs. Despite some limitations, this study was carefully designed to closely align with the animal model of sign- and goal-tracking, providing a robust translational framework. By bridging human and animal research, these findings pave the way for future translational studies aimed at further elucidating the mechanisms underlying incentive salience attribution and its role in addiction.

Declarations

Transparency and Openness

We have reported how the sample size was determined, all data exclusions, all manipulations, and all measures in the study, and we have followed Journal Article Reporting Standards - JARS (Appelbaum et al., 2018). The experimental data are available at <https://osf.io/tn7bv/>.

The code for the experimental task is available upon request from the authors. Data were analyzed using R, version 4.3.3 (R Core Team, 2024). This study’s design and its analysis were not pre-registered. Data analysis code is not available.

Use of IA

Artificial intelligence (AI) was used solely for the creation of Figure 10, which was developed using Canva's AI-based image tool (Canva AI, 2025). No AI tools were used to generate scientific ideas, analyses, or interpretations of this manuscript. The authors take full responsibility for the content and accuracy of the information presented in this article.

The reference list of this article has been incorporated into the [general bibliography of this thesis](#).

Chapter 6

Human Sign-Tracking and its Relationship with Attentional Biases for Alcohol

From Mixed Findings to New Questions

Michelle Heck

Damien Lesenfants

Vincent Didone

Patrick Anselme*

Etienne Quertemont*

The content of this chapter has been submitted for publication.

Supplementary Information for this chapter can be found in [Appendix C](#).

Abstract

Background. Pavlovian sign- and goal-tracking have been proposed as a translational framework for understanding individual vulnerability to addiction. In humans, eye-movement-based Pavlovian Conditioned Approach (PCA) tasks and alcohol-related attentional bias (AB) paradigms may capture complementary facets of cue-driven behavior, yet their relationship remains underexplored.

Objectives. This study (1) tested the hypothesized positive association between sign-tracking and alcohol-related AB, and (2) further evaluated a computerized PCA paradigm for identifying human sign- versus goal-tracking tendencies by attempting to replicate prior evidence linking sign-tracking with higher alcohol use.

Methods. Two experiments were conducted with non-clinical adult samples. Experiment 1 ($n = 138$) used a gaze-contingent, interactable lever as the conditioned stimulus (CS), analogous to animal models. Experiment 2 ($n = 159$) replicated the procedure using a non-interactive CS (static blue rectangles) due to inconclusive results in Experiment 1. Eye movements indexed sign- and goal-oriented attention, and latent profile analysis (LPA) was used to derive PCA behavioral profiles.

Results. Across both experiments, participants predominantly exhibited goal-tracking, limiting the emergence of distinct sign-tracking profiles. We found no robust evidence supporting the predicted association between sign-tracking and alcohol-related AB, and only weak evidence for higher alcohol consumption among sign-trackers in Experiment 2.

Conclusions. Experiment 2 showed patterns broadly consistent with previous findings, whereas the interactive-lever design in Experiment 1 failed to produce meaningful effects. The generally lower size of observed effects likely reflects low reward salience and high task passivity (e.g., fictitious token reinforcement). These findings underscore the need for methodological refinement (particularly regarding CS characteristics, reward type, and task engagement) to better delineate the boundary conditions of human sign- and goal-tracking and strengthen the translational validity of PCA paradigms.

Keywords: Sign-tracking, Attentional Bias, Alcohol, Pavlovian Conditioned Approach

Introduction

In everyday life, we are constantly exposed to cues that predict rewards, such as the sound of a coffee machine signaling an upcoming cup of coffee, the use of a lighter before smoking a cigarette, or the sound of a social media notification suggesting potential “likes” on a recent post. Through Pavlovian learning, these cues acquire incentive salience, enabling them to trigger appetitive behaviors such as reward approach, seeking, and craving (Berridge, 2004; Berridge & Robinson, 2003; T. E. Robinson & Berridge, 1993, 2025).

Animal research has shown individual differences in how these cues are motivating and impact behavior. These differences have extensively been studied in animals using the autoshaping procedure, also known as PCA. In PCA, a discrete CS is presented for a few seconds and is then consistently followed by the delivery of a food reward. During the CS presentation, individuals with a sign-tracking profile (STs) tend to approach and interact with the CS (e.g., a lever in rodent studies), whereas those with a goal-tracking profile (GTs) preferentially approach and inspect the location where the reward is to be delivered (e.g., the food tray). A third, intermediate profile (INTs), alternating between both behaviors, is occasionally reported (Flagel et al., 2009). Sign-tracking behavior is typically quantified using a response bias score (RBS), a numerical index based on the frequency or timing of contacts with the CS and the food dish location.

The ST/GT distinction is thought to reflect differences in incentive salience attribution: STs assign both a predictive and motivational value to the CS, making it highly attractive, whereas GTs attribute only a predictive value (Anselme & Robinson, 2020; Flagel et al., 2009; T. E. Robinson & Flagel, 2009). Although these phenotypes are relatively stable in laboratory animals, with evidence pointing to a genetic basis (e.g., Fitzpatrick et al., 2013; Flagel et al., 2010), they are not immutable. Decades of research indicate that several factors modulate their expression, including the type of CS (e.g., lever vs. tone; P. J. Meyer et al., 2014), CS consistency (e.g., M. J. F. Robinson et al., 2015), and early-life social experiences (Lomanowska et al., 2011).

Animal studies further suggest that the ST/GT profiles have significant implications for addiction vulnerability (Anselme & Robinson, 2020; Flagel et al., 2009). STs acquire drug-taking behaviors (e.g., self-administration) more rapidly and exhibit greater

susceptibility to cue-induced craving and relapse compared to GTs (Anselme & Robinson, 2020; Flagel et al., 2008, 2009, 2010; T. E. Robinson et al., 2014; B. T. Saunders et al., 2013; B. T. Saunders & Robinson, 2010, 2011; Tomie et al., 2008). Moreover, STs display traits overlapping with human addictive behaviors, such as heightened impulsivity and reduced top-down attentional control (Paolone et al., 2013; Pitchers, Kane, et al., 2017; Sarter & Phillips, 2018). Consequently, the ST/GT framework has been proposed as a neurobehavioral endophenotype relevant not only for addiction but also for other psychiatric disorders (Colaizzi et al., 2020).

To establish the clinical utility of this model, robust evidence of its relevance in humans is essential. Over the past decade, numerous studies have adapted the ST/GT framework for human research, employing diverse materials, methods, and analytical strategies (for reviews see Colaizzi et al., 2020; Heck, Durieux, et al., 2025). However, many paradigms deviate substantially from the original *autoshaping* procedure, complicating interpretation and limiting comparability. As a result, no standardized protocol currently exists for assessing sign- and goal-tracking in humans. Among the proposed approaches, eye-tracking during PCA tasks appears particularly promising (Cherkasova et al., 2024; Colaizzi et al., 2023; Cope et al., 2023; Degni & Garofalo, 2025; Dinu et al., 2024; Garofalo & di Pellegrino, 2015; Heck, Simon, et al., 2025). From a translational perspective, this methodology (whether conducted in real-world settings using physical materials or by means of computerized tasks) offers the highest face validity³⁶, by preserving most crucial aspects of Pavlovian conditioning during autoshaping (Heck, Durieux, et al., 2025).

In a previous study, we developed a novel translational computerized task to assess individual differences in human STs and GTs, and examined their association with alcohol consumption (Heck, Simon, et al., 2025). Our findings indicated that individuals classified as STs showed overall higher alcohol use than GTs, a pattern observed using both the RBS and latent profile analysis (LPA, data-driven) to characterize groups. It is important to note, however, that the RBS distribution was strongly skewed toward goal-tracking,

³⁶ Although face validity is insufficient for evaluating a model's validity, as already mentioned (Stephens et al., 2013), and a greater emphasis should be placed on assessing "*functional similarity*", referring to "*the extent to which there is overlap between variables that affect performance in the model and variables that affect the target phenomenon*" (Boddez et al., 2023, p.12). Our studies addressed this criterion also by examining relationships between sign-tracking and alcohol and personality variables.

reducing the robustness of the group contrasts. Moreover, we found no significant relationship between impulsivity measures and sign-tracking magnitude, although a small, non-significant trend emerged between sign-tracking and positive urgency ($r = .25$).

Overall, human studies support the relevance of ST/GT behavioral phenotypes as potential markers of vulnerability to substance use, in line with findings from animal research. Associations have been reported between sign-tracking and drug or alcohol use (Albertella et al., 2017, 2021; Albertella, Watson, et al., 2019; Heck, Simon, et al., 2025; Schettino et al., 2022; Watson et al., 2024), as well as with impulsivity-related traits (Colaizzi et al., 2023; Cope et al., 2023; Doran, 2016; Garofalo & di Pellegrino, 2015; Schettino et al., 2022). Because STs attribute incentive salience to conditioned stimuli associated with reward, they should also differ from GTs in their susceptibility to develop drug-related AB, defined as a disproportionate allocation of attention toward drug-associated cues and theorized to reflect heightened attribution of incentive salience to drug-predictive stimuli.

Alcohol AB is well documented, and research indicates consistent associations with alcohol consumption and craving, particularly in subclinical populations³⁷ (Bollen et al., 2022; Ceballos et al., 2009; McGivern et al., 2021; Roy-Charland et al., 2017; Simon et al., 2022; although see Seth et al., 2025). Notably, this bias is dynamic and fluctuates with factors such as craving state (Bollen et al., 2020), in vivo alcohol exposure (Ramirez et al., 2015), and immediate alcohol expectancies (Field, Hogarth, et al., 2011). One intriguing hypothesis is that the heterogeneous findings observed in alcohol AB research, especially in clinical samples, may reflect individual differences in ST/GT tendencies. Such differences could determine whether AB plays a meaningful role in AUD for some individuals but not others (Bollen et al., 2022). Although AB and sign-tracking may represent distinct phenomena (particularly given the absence of a true animal equivalent for AB studies), they both capture aspects of “automatic” or “irrational” behavior, manifesting as either physical approach or the allocation of attentional resources toward reward-associated cues. Both have been linked to addiction-related processes, yet, to our

³⁷ Notably, results are mixed and less consistent in individuals with severe alcohol use disorder (AUD) (Bollen et al., 2021, 2022, 2025).

knowledge, they have never been examined together to determine if they are significantly associated.

Building on the results of our initial study (Heck, Simon, et al., 2025), the present research aimed to address this gap by examining whether ST, GT, and INT profiles are associated with alcohol-related AB. Specifically, we tested whether individuals displaying stronger sign-tracking tendencies would also exhibit greater AB toward alcohol-related cues. We hypothesized a positive relationship between sign-tracking tendencies and alcohol AB.

Experiment 1 involved administering the computerized PCA task alongside a free-viewing AB task. The PCA task was very similar to that used in our previous study, except for the visual representation of the “*sign*” and “*goal*” stimuli. To better approximate animal paradigms, we used, as a predictive stimulus (sign), the image of a lever that participants could interact with via gaze. The lever moved horizontally in response to gaze direction, reflecting evidence from animal studies that the manipulable and discrete nature of the CS is critical for inducing ST behavior (Beckmann & Chow, 2015; P. J. Meyer et al., 2014, but see Scülfort et al., 2016). The goal stimulus was represented by a simple rectangle. However, we suspect that this methodological change compromised the task’s ability to adequately model sign- vs goal-tracking behavior (as discussed more thoroughly later in this article). Indeed, the interactive lever may have altered participants’ interpretations of the task, as such stimuli are typically associated with contingent outcomes in humans, potentially encouraging an operant-like response in which rewards were inferred to depend on lever manipulation rather than Pavlovian contingencies alone.

Consequently, in Experiment 2 we reverted to the parameters used in our previously published task (Heck, Simon, et al., 2025), employing a non-interactive visual stimulus as the CS. Therefore, the only difference between Experiments 1 and 2 was the representation of the sign and goal stimuli.

Experiment 1

Materials and Methods

Participants

The sample of this study included 138 volunteers (85 females, 50 males and 3 identified as non-binary; mean age = 23.46, sd = 3.60, see Table 7 for sample description). They completed an online screening survey to check for inclusion criteria, which were: no history of severe neurological diseases, no regular substance use (more than twice in the last two months, except for tobacco and alcohol), no colorblindness, no medicated ADHD. All participants had to be aged between 18 and 35 and be at least occasional alcohol consumers (abstinent people were not included). All participants had normal or corrected-to-normal vision.

Based on the effect size of the previous study, a minimum of 138 participants were required to achieve .80 power (with an alpha level of 0.5). However, more participants were recruited, to account for the non-parametric analyses and data loss due to quality check criteria (for eye-tracking data), as well as careless responding. Overall, 180 subjects took part in the whole study. Four were excluded because they failed the attention check item, thus being considered careless responders. One was excluded due to human error. Finally, 37 subjects were excluded from the analysis due to at least one of the data quality check criteria (see Measures – Eye-gaze).

Table 7. *Sample Description of Experiment 1*

Variable	Median (std)	Min-Max
Age	23 (3.60)	18-35
Education Level	15 (2.29)	7-22
AUDIT-C	4 (2.30)	0-10
Recent Drinking Index	6 (70.15)	0-810

Note. Education Level = number of successful school years starting from elementary school; AUDIT-C= short version (consumption) of the Alcohol Use Disorder Identification Test, Recent drinking index = number of alcoholic drinks consumed during the past 2 weeks x number of drinking occasions during the past 2 weeks.

The study was conducted in accordance with institutional guidelines and the Declaration of Helsinki. It was approved by the local Ethics Committee. Subjects were recruited via word of mouth, social media or advertising posters. The study title was a dummy (related to intelligence and reaction time measures), to avoid disrupting behaviors that we wanted to study. After filling out the online screening, participants who met inclusion criteria were contacted to take part in the experimental phase of the study (on-site). All participants gave written informed consent to take part in the study and had the chance to participate in a price draw to win a 20-euro gift voucher. Recruitment and testing took place from February 2024 to August 2024.

Procedure

The testing session consisted of three phases: (1) pre-experimental questionnaires (2 minutes), (2) the battery of experimental tasks (approximately 25 min, this phase was interrupted by a break after the first two blocks of the PCA task, during which subjects completed a questionnaire), and (3) post-experimental questionnaires (10 minutes). Participants were tested in a quiet room. Their head was restrained by a chinrest at a distance of 70 cm from the screen. They were allowed to take short breaks between the different steps to avoid fatigue. At the end of the experimental session, the real purpose of the study was revealed to the participants, after which they had the possibility to give a second written informed consent.

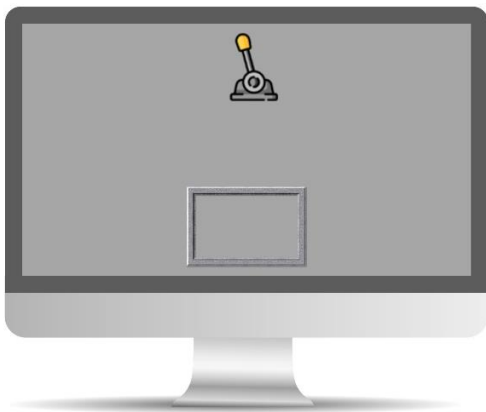
Stimuli

Before starting the ST/GT task, participants were instructed that they could collect a certain number of points in the next tasks, and that more points collected would unlock more glorious expertise badges. We chose accumulation of points and unlocking of badges to reflect reward amount because this procedure does not impact the participants' motivation to seek rewards (Albertella, Watson, et al., 2019; Watson, Pearson, Theeuwes, et al., 2020). The stimuli for the PCA task and the AB task were as follows:

Sign and Goal Pictures

The sign (CS) was a picture of lever, which moved on the opposite direction each time the participants looked at it. The goal was a grey rectangle in which the coin rewards were delivered (a visualization of these stimuli is available in Figure 16). The sign and goal pictures were located on middle top or middle bottom of the screen and counterbalanced for location across participants.

Figure 16. *Illustration of the New Sign and Goal Stimuli on the Computer Screen*



Reward Stimuli

Either a yellow 5-point coin or a yellow 10-point coin in the design of a casino coin.

Expertise Badges

Fancy and colorful badges representing performance (ranging from the categories bronze, silver, gold, platinum, diamond, and expert).

Test Pictures (free-viewing AB task)

Ten pairs of pictures (taken from the royalty-free picture stock "Pixabay") of approximately the same color.

Stimuli Pictures (free-viewing AB task)

Sixty pairs of alcohol and neutral pictures (10 in each of the following categories: beer, wine, champagne, liquor, cocktails, environments). The alcohol pictures were selected from the Wake Forest Alcohol Imagery Set (WFAIS) (Peterson et al., 2019),

through consensus with experts and non-experts among colleagues (PIs and PhD candidates). The neutral pictures were created to resemble each alcohol picture while not being directly associated with alcohol, using either DALL-E (OpenAI), or by taking our own pictures. They were matched on color and brightness (using Adobe Photoshop, version 2024). All the pairs of pictures underwent a pilot validation phase, during which independent participants were asked to rate the alcohol-relatedness of each picture (on a visual analogue scale ranging from 0 to 10), to make sure that the neutral stimuli were considered alcohol-unrelated. Mean score ranges for each category are shown in [Appendix C](#), Table O). One neutral picture, scoring 3.8, was replaced before the experiment. An illustration of two pairs of pictures is available in [Appendix C2](#) (Figure E).

The stimuli were presented on a computer screen (1920 x 1080 pixels) with a grey background. A battery of three computer tasks was implemented: (1) the simple reward task, (2) the PCA task, and (3) the free-viewing AB task. The three tasks were run on a homemade custom Matlab software (version R2019b).

Simple Reward Task

This task involved a permanent rectangle (goal) on the screen, counterbalanced for location across participants (bottom or upper part of the screen). The coin appeared for 1.5 seconds on the goal shape, and the sound of a falling coin could immediately be heard when the participant pressed the key to collect the reward. There was a 20% chance that the coin was a "10-point coin" (instead of a 5-point coin) to maintain curiosity and avoid monotony during the task. The aim of this first task was for the participants to learn where to collect the rewards, and it was designed to mimic the *magazine training phase* in animal models, where rewards are regularly delivered without any CS presentation. The simple reward task consisted of 10 trials, with a variable inter-trial interval (ITI) from 4 to 8 seconds. Prior to starting the task, participants were instructed as follows: "*During this task, objects will be displayed in a blue rectangle. These will allow you to earn points. Your objective is to respond as quickly as possible to their presentation by pressing the "enter" key.*"

PCA Task

This task was developed in (Heck, Simon, et al., 2025) and was designed to match the autoshaping procedure used in animal ST/GT studies. The goal shape was permanently present in the lower or upper part of the screen. In the opposite area of the screen, the interactive lever (sign) appeared for 3 seconds before a coin was shown on the goal shape for 3 seconds. The lever CS and the coin reward were associated with an 80% chance to hold interest in the task.

During CS presentation, any eye movements recorded within the lever zone switched the lever side (left or right), mimicking physical interaction with it.

During reward presentation, pushing the "enter" button produced the sound of a falling coin informing participants that the reward was being collected. The task consisted of 4 blocks of 20 trials with a variable ITI ranging from 4 to 8 seconds. Like in the previous task, there was a 20% chance that a "10-point coin" was obtained.

Prior to starting the task, participants were instructed as follows: *"This task is similar to the first one, except that we're no longer measuring your reaction time here. You can also score points. Use the 'enter' key as before. Please keep your attention on the computer screen and don't look at the keyboard."*

Free-Viewing AB task

The task was divided into two parts, a training phase and a test phase (McAteer et al., 2015).

Training Phase

The training phase consisted of 10 trials, depicting a pair of neutral pictures, for 2500 ms on each side of a central fixation cross on the screen. Order of pairs was randomized. Between image presentations, a fixation cross appeared for 1500 ms. The ITI was variable, between 2 and 4 seconds. The instructions were as follows: *"You will now see pairs of images. We ask you to look at these pairs as if they were pop-ups on your computer. Between each pair of images, you'll see a fixation cross. You must always look at this cross so that the next pair of images arrives. You'll start with 10 practice trials. Press the space bar to start."*

Test Phase

The test phase involved the same task, except that the picture pairs included one alcohol-related image (randomly interspersed with pairs consisting of two neutral images). Stimuli duration was 2500 ms and the ITI varied between 0.5 and 1.5 seconds. This task consisted of 72 trials (60 alcohol and 12 neutral). Prior to starting this task, participants were instructed that they had to proceed as in the training phase and that the task would last about 8 minutes.

Data Collection

Questionnaires

In the screening phase, all participants completed socio-demographic online questionnaires including the history of neurological problems that could affect cognitive functioning, as well as regular use of tranquilizers or illicit drugs. They also completed the short (consumption) version of the alcohol use disorder identification test (AUDIT-C) (Bush et al., 1998) and the short version of the (French translation) Impulsive Behavior Scale (UPPS-P) (Billieux et al., 2012).

In the pre-experimental phase, all participants completed electronic versions of the following questionnaires: *The Edinburgh handedness inventory* (Oldfield, 1971), which assesses handedness through 22 items. The 11-item version was used. And *The Karolinska Sleepiness Scale* (KSS) (Kaida et al., 2006), which measures the subjective level of fatigue at a particular time of day based on a nine-point Likert-type scale (both questionnaires were used, but not included in this report).

During the task-completion phase, the first two and last two blocks of the PCA tasks were separated by a pause to reduce repetitiveness. During this break, participants completed the *The Reinforcement Sensitivity Theory of Personality Questionnaire* (RST-PQ) (Corr & Cooper, 2016), which assesses six dimensions. In the present study, we only measured five dimensions (total number of items = 24): Reward Interest, Goal-Drive Persistence, Reward Reactivity, Impulsivity (which constitute four sub-dimensions of the Behavioral Activation System), and Behavioral Inhibition System (BIS)³⁸. An attention

³⁸ The Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS), as operationalized by Carver and White (1994), derive from Gray's reinforcement sensitivity theory. The BIS reflects sensitivity to aversive cues and is associated with the experience of negative affect such as anxiety and fear, whereas the BAS reflects sensitivity to rewards and is associated with approach motivation, goal-directed behavior, and positive affect.

check item was embedded in this questionnaire in order to identify and exclude careless responders after collecting the data (Maniaci & Rogge, 2014). The item read: "*Please select "completely agree" for this item", on a 6-level scale from "completely disagree" to "completely agree"*".

In the post-experimental phase, participants completed electronic versions of the following questionnaires:

- *The Karolinska Sleepiness Scale (KSS)* (Kaida et al., 2006).
- The short *Depression, Anxiety, Stress Scale (DASS-21)* (Lovibond et al., 1995), which yields three subscale scores (21 items). A total score can be computed, representing general psychological distress.
- The French version (Gache et al., 2005) of the *Alcohol Use Disorders Identification Test (AUDIT)* (J. B. Saunders et al., 1993) consisting of 10 multiple-choice items measuring alcohol consumption, alcohol dependence, and alcohol-related problems. Higher scores reflect a high probability of harmful alcohol use.
- *Questions about recent alcohol consumption*, consisting of the following two questions: "*How many drinks have you had in the last 14 days?*" and "*On how many occasions have you drunk alcohol in the last 14 days?*". A *drinking occasion index* was computed by multiplying these two numbers. We also measured the following item: "*How many times have you engaged in binge drinking in the past month?*" (defined as consuming >5 drinks within 2 hours for men and >4 drinks within 2 hours for women.).
- *The Brief Assessment Tool for Compulsivity Associated Problems (BATCAP)* (Albertella, Le Pelley, et al., 2019), which assesses a range of compulsive symptom types. It covers alcohol use, gambling, binge eating and excessive Internet use (as well as contamination, checking, and ordering compulsions). In this study, we only used addiction-related components. A "*primary addiction score*" was computed (score of the top-scoring domain across addiction behaviors).

Eye-Tracking

A Tobii 5 eye-tracking system (with an image sampling rate of 133 Hz) was mounted on a 60.5 cm diagonal computer screen. The eye tracker was calibrated using a six-point procedure at the beginning of the experiment. A chinrest was used to standardize the head-screen distance at 70 cm. Tobii Experience software was used to calibrate the eye-tracking system.

To compute eye gaze-based ST/GT scores, the screen was virtually separated into 9 regions of interest (ROI, 3 equal parts on each axis). Eye gaze position was collected throughout the PCA task. The two main ROIs used to compute the scores were the upper center and the bottom center of the screen, where the goal and the sign stimuli were located. The in-between region (middle center) was also of interest for LPA.

We used a custom implementation of the Velocity Threshold Algorithm for fixation identification. First, eye position in pixels was converted to visual degrees. Then velocity was computed in degrees/sec for axes X and Y. To distinguish fixations from saccades, we used individualized thresholds for each subject based on their gaze velocity during mandatory fixations in the training phase of the free-viewing task. Each threshold was computed by adding $1.95 \times \text{standard deviation}$ to their mean gaze velocity during fixations (= confidence interval of 95%). In probability and statistics, the 97.5th percentile point of the standard normal distribution is a number commonly used for statistical calculations. The approximate value of this number is 1.96, meaning that 95% of the area under a normal curve lies within approximately 1.96 standard deviations of the mean. Because of the central limit theorem, this number is used to approximate 95% confidence intervals.

Eye movements were considered fixations when they were strictly below the personalized threshold. Too short fixations (<100 ms) were removed to smoothen eye-gaze data. For each identified fixation, duration and ROI were collected. Two outcome measures were obtained: Fixation Count (number of fixations) and Dwell Time (total fixation time on each ROI), two classic parameters when working with fixation-based measures (Mahanama et al., 2022).

Three criteria were used for data quality check and poor quality data exclusions: A participant was excluded (1) if the gaze stagnated in the middle zone throughout the entire task (perhaps an indicator of poor calibration or other technical problem, $n = 0$ in both experiments), (2) if there were more than 30% of gazes at the outer edge of the

screen (5% of the screen) compared to the rest of the screen (poor calibration, $n = 1$ in Experiment 1, $n = 0$ in Experiment 2), and (3) if on average the individual gazed less than 1 second per CS presentation at either the ROI (goal and sign) or the center of the screen (because of too few data to compute a meaningful sign-tracking score, $n = 36$ in Experiment 1, $n = 20$ in Experiment 2).

Eye-Tracking Based Sign- and Goal-Tracking Scores

Eye-tracking based ST/GT scores were computed as follows: dwell time on the "goal" was subtracted from dwell time on the "sign" and divided by the total dwell time on both ROIs (during the 3s CS presentation). Thus, the ST/GT score ranged from -1 to 1, with negative scores corresponding to "goal-tracking" phenotypes, positive scores representing "sign-tracking" phenotypes, and scores close to 0 meaning a rather "intermediate" tendency. This score was computed for all blocks of the PCA task, the number of fixations, and the total dwell time. Since some time was required for the participants to become familiar with the task and for specific conditioned responses to emerge (Colaizzi et al., 2023; Cope et al., 2023; Garofalo & di Pellegrino, 2015), only the second block score was considered in the main analyses. During the testing sessions, it became clear to the research team that the third and fourth blocks came to bore the participants, who became less and less involved in the task. This is why these last two blocks were not included in the present analyses. Groups of STs, INTs, and GTs were created via LPA.

Attentional Bias

For the free-viewing AB task, two bias scores were computed (McAteer et al., 2015), each representing different stages of attentional processing. An automatic attention score, computed as the percentage of first gazes on the alcohol vs neutral pictures, and a sustained attention score, computed as the total percentage of time the gaze was recorded on the alcohol vs neutral picture.

Statistical Analyses

All analyses listed here were planned in the pre-registration (<https://osf.io/f29uz>), and run with R 4.3.3 (R Core Team, 2024). Basic data importation, processing, and plotting were done using readxl (v1.4.5, Wickham & Bryan, 2025), tidyverse (v2.0.0, Wickham et al., 2019), ggpubr (v0.6.1, Kassambara, 2025a), patchwork (v1.3.2, Pedersen, 2025),

ggthemes (v5.2.0, Arnold et al., 2025), ggdist (v3.3.3, Kay & Wiernik, 2025), and ggplot2 (v3.5.0, Wickham, 2026). ANOVAs and related analyses used rstatix (v0.7.2, Kassambara, 2025b), car (v3.1-3, Fox & Weisberg, 2019), and lmerTest (v0.9-40, Hothorn et al., 2022). Effect sizes were computed with lsr (v0.5.2, Navarro, 2021). Mixed effects models and pairwise comparisons were conducted using lme4 (v1.1-37, Bates et al., 2015), lmerTest (v3.1-3, Kuznetsova et al., 2017), and emmeans (v2.0.0, Lenth et al., 2025). Correlations with psych (v2.5.6, Revelle, 2025), and latent profile analyses with tidyLPA (v1.1.0, Rosenberg et al., 2019).

Alpha level was set at 0.05, but corrections for multiple correlations were applied as indicated. Given that the questionnaires were administered electronically, no missing data was recorded, as participants were required to answer all questions to proceed. There was, however, missing data for the AB task due to an insufficient number of trials with gazes recorded in the ROIs (defined as at least one third of trials). Consequently, participants with missing AB data were excluded from the analyses ($N = 7$).

The primary hypothesis examined whether ST/GT profiles were associated with levels of alcohol consumption. To address this, we conducted a LPA to determine whether the previously established three-profile model fit our data. Indicator variables for the LPA were derived from the second block of the PCA task and included: Number of fixations on the goal, sign, and in-between zone, and Total dwell time on the goal, sign, and in-between zone. We estimated a series of models with increasing numbers of profiles. Model selection was guided by both theoretical considerations and multiple fit indices (Collins & Lanza, 2010), including the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and entropy (values approaching 1 indicating better classification). Following some work (Pastor et al., 2007), our model specification allowed covariances among indicator variables to be freely estimated within profiles, while variances and covariances were constrained to equality across profiles.

After establishing consistent profiles, we tested group differences in alcohol consumption severity (AUDIT-C scores, short version of the Alcohol Use Disorder Identification Test) using a Kruskal-Wallis rank-sum test (given that ANOVA assumptions were not met).

Secondary and Tertiary Hypotheses: We further examined whether ST/GT/INT profiles were associated with AB for alcohol cues. Specifically:

- Automatic orienting: A Kruskal-Wallis test assessed differences in the proportion of initial fixations on alcohol-related versus neutral stimuli (calculated as the number of alcohol-first / total trials).
- Controlled attention: Another Kruskal-Wallis test evaluated differences in the percentage of total fixation time allocated to alcohol versus neutral images.

To validate the conceptual integrity of the alcohol AB task, we conducted correlational analyses between alcohol consumption measures and the two attentional bias indices, expecting positive associations as theoretically predicted. To control for multiple comparisons, we applied the Benjamini-Hochberg (B-H) correction (Benjamini & Hochberg, 1995).

Exploratory correlational analyses (Spearman's rho), pre-registered prior to data collection, examined relationships between ST/GT scores and alcohol consumption variables, as well as personality-related constructs (e.g., impulsivity, reward reactivity, psychological distress). B-H correction was also applied (Benjamini & Hochberg, 1995).

Finally, in an exploratory (and non-pre-registered) analysis, we examined whether dwell time directed toward the sign and the goal varied across trials and experimental blocks for the three behavioral profiles identified via LPA. To do so, we fitted a linear mixed-effects model that included fixed effects of profile, trial number, block, and their interactions (profile $\times$ trial and profile $\times$ block). The corresponding results are reported and illustrated in [Appendix C](#) (Figures F-I).

Results

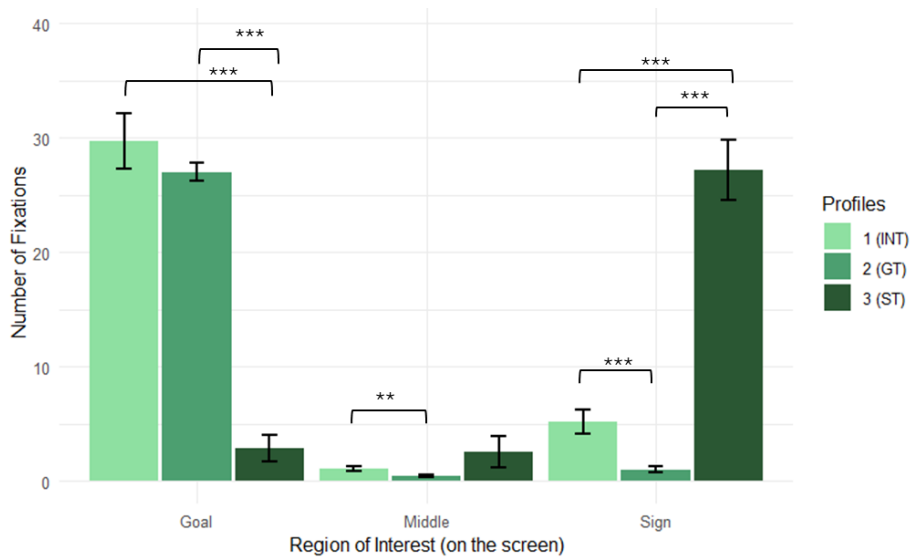
Hypothesis 1. Are the ST/GT Profiles Related to Alcohol Consumption Levels?

The best model based on fit indices was the 3-profile model: AIC = 1357.71, BIC = 1477.73, entropy = 0.95. Table 8 shows the fit indices for the three models. Posterior probabilities (i.e., probabilities for each participant to belong to each of the three profiles) indicated highly mediocre confidence in the most likely profile membership for profiles 1 and 2. For profile 1, the probabilities ranged from 0.52 to 0.99 (mean = 0.95, sd = 0.11). For profile 2, they ranged from 0.57 to 0.99 (mean = 0.98, sd = 0.082). For profile 3, they ranged from 0.99 to 1.00 (mean = 0.99, sd = 0.003). Figures 17 and 18 show means and standard errors for the indicator variables in the three profiles. Based on the examination of these graphs, groups 1, 2, and 3, were labeled respectively, "INT", "GT", and "ST".

Table 8. *Model Fit Indices for the Three Latent Profile Analyses in Experiment 1*

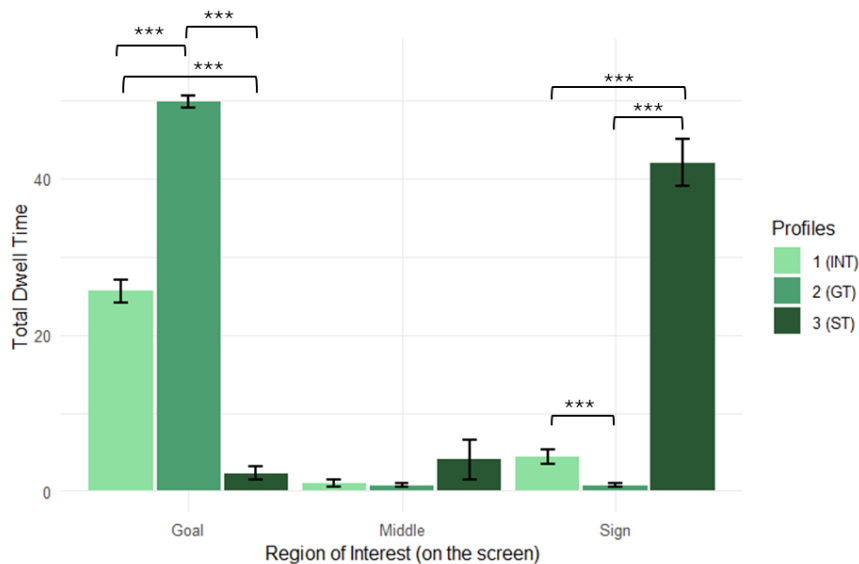
Tested Model	AIC	BIC	Entropy	Profile Sizes	Bootstrapped Likelihood Test (p-value)
1 Profile	1579.92	1658.96	-	-	-
2 Profiles	1530.61	1630.14	0.90	Profile 1: 49% Profile 2: 51%	.01
3 Profiles	1341.31	1461.33	0.95	Profile 1: 31% Profile 2: 50% Profile 3: 19%	.01

Note. AIC=Akaike information criterion; BIC = Bayesian information criterion.

Figure 17. *Number of Fixations on Each Region of Interest in the Three LPA-Extracted Profiles, in Experiment 1*

Note. The figure shows the means and standard errors. ***p<0.001, **p<0.05

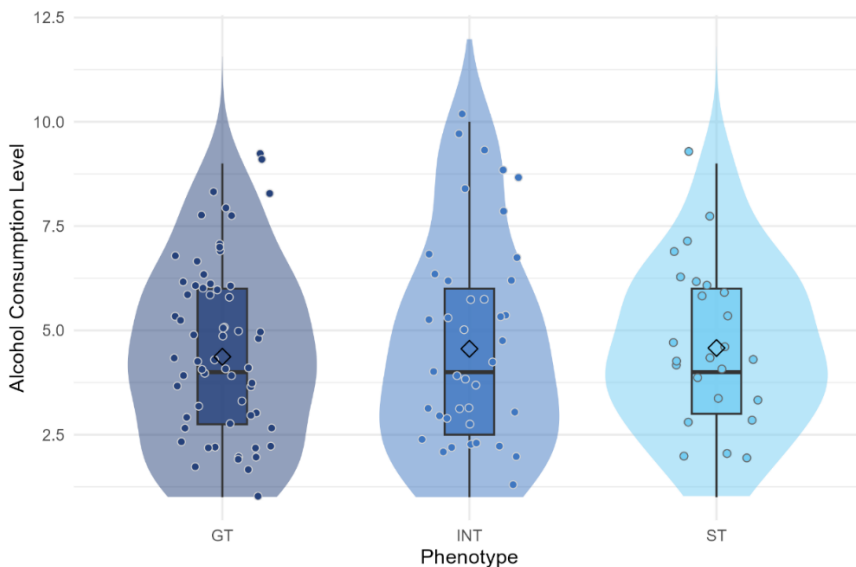
Figure 18. *Dwell Time on Each Region of Interest in the Three LPA-Extracted Profiles, in Experiment 1*



Note. The figure shows the means and standard errors. *** $p < 0.001$, ** $p < 0.05$

The Kruskal-Wallis rank-sum test, assessing the differences in alcohol consumption (measured through AUDIT-C, short version of the AUDIT) in these profiles, did not show any significant effect ($\chi^2 = 0.33$, $p = 0.84$, $\eta^2(H) = -0.001$, 95% CI = [-0.07, -0.01]). Figure 19 shows the distribution of AUDIT-C scores in STs, GTs, and INTs, based on LPA-created profiles.

Figure 19. Alcohol Consumption Level in STs, GTs and INTs based on LPA, in Experiment 1



Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Hypothesis 2. Is There a Relationship Between Human Sign-Tracking and Alcohol Attentional Bias?

To test whether the attentional profiles differed in *automatic orienting* (operationalized as the proportion of trials in which participants initially fixed the alcohol-related image) an ANOVA was conducted. Assumptions of normality and homogeneity of variance were met. The analysis revealed no significant group differences ($F(2,128) = 0.225, p = 0.799$). The effect size was very small ($\eta^2 = 0.004$), indicating that only 0.4% of the variance in initial alcohol fixations was explained by attentional profile.

To examine whether the attentional profiles differed in *controlled attention* (as measured by the proportion of total fixation time on alcohol-related images), a Kruskal-Wallis test was conducted since assumptions for ANOVA were not met. The analysis revealed no statistically significant difference between the three groups ($\chi^2(2) = 0.65, p = 0.723, \eta^2[H] = -0.011$).

Correlational analyses between alcohol consumption measures and alcohol-related AB variables are presented in [Appendix C](#) (Table P). Although a positive correlation was observed between AUDIT-C scores and the total fixation time on alcohol-related stimuli, this association did not remain statistically significant after applying the B-H correction for multiple comparisons.

Exploratory Analyses: Relationships Between Human Sign-Tracking and Personality- and Alcohol Consumption Related Variables

No significant correlation was observed between the ST/GT score and personality-based variables (Table 9).

Table 9. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Impulsivity, Reward Reactivity and Psychological Distress in Experiment 1*

Variable	Spearman Rho	Adjusted P-Value	Raw P-Value	CI Lower (Adjusted)	CI Upper (Adjusted)
Psych.dist	0.03	0.876	0.717	-0.21	0.27
RSTPQ- RR	0.11	0.876	0.184	-0.13	0.34
RSTPQ- Goal	0.05	0.876	0.573	-0.19	0.29
RSTPQ- BIS	0.03	0.876	0.705	-0.21	0.27
RSTPQ- RI	-0.04	0.876	0.625	-0.28	0.20
RSTPQ- IM	0.03	0.876	0.699	-0.21	0.27
UPPSP-UR	-0.01	0.916	0.871	-0.25	0.22
UPPSP-PU	0.009	0.916	0.916	-0.23	0.25
UPPSP-LPre	0.09	0.876	0.312	-0.16	0.32
UPPSP-LPer	-0.04	0.876	0.688	-0.27	0.20
UPPSP-SS	-0.06	0.876	0.483	-0.29	0.18

Note. CI= Confidence Interval, Psych.dist = Psychological distress (depression, anxiety and stress scale DASS-21), RST-PQ = Reinforcement Sensitivity Theory of Personality Questionnaire, subdimensions: RR = reward reactivity, Goal= goal-drive persistence, BIS = behavioral inhibition system, RI = reward interest, IM = impulsivity; UPPS-P = short version of the UPPS impulsivity scale, subdimnesions: UR = urgency, PU = positive urgency, LPre = lack of premeditation, Lper = lack of perseverance, SS = sensation seeking.

No significant correlations were observed between the ST/GT score and alcohol consumption-related variables (Table 10).

Table 10. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Alcohol-Consumption Related Variables in Experiment 1*

Variable	Spearman Rho	Adjusted P- Value	Raw P- Value	CI Lower (Adjusted)	CI Upper (Adjusted)
BATCAP (Alcohol)	0.05	0.598	0.598	-0.17	0.26
DrinkOccas	0.09	0.419	0.280	-0.11	0.29
AUDIT-C	0.13	0.371	0.124	-0.07	0.33

Note. BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test.

Interim Discussion

This study was intended as a follow-up to our previous proof-of-concept (Heck, Simon, et al., 2025) demonstrating human sign-tracking using our novel task, by examining its association with alcohol consumption and AB toward alcohol-related cues. From a translational perspective, we aimed to advance the task further by incorporating an interactive virtual lever (similar to that used in animal studies) into the paradigm. This lever was designed to move in response to participants' gaze, based on evidence from animal research that the type of CS (discrete and manipulable) plays a critical role in sign-tracking behavior (P. J. Meyer et al., 2014; Roughley & Killcross, 2019).

In this pre-registered study, none of our hypotheses were confirmed. Unlike in our previous work, where we successfully identified ST, GT, and INT groups using LPA, the posterior probabilities for group membership in the current study were suboptimal for the "GT" and "INT" profiles. Moreover, the distribution of participants across groups differed from our earlier findings (previous study: GT = 38%, ST = 33%, INT = 29%; current

study: GT = 50%, ST = 19%, INT = 31%). Importantly, these discrepancies do not invalidate the present study, as LPA-based group assignments are task-specific and reflect attentional patterns under the experimental conditions employed (Cope et al., 2023).

No significant associations were observed between sign-tracking and alcohol consumption levels, nor with personality traits theoretically linked to sign-tracking (e.g., impulsivity, reward sensitivity). Likewise, no relationship was observed between sign-tracking and AB. However, given the uncertainty surrounding the accurate identification of STs and GTs due to modifications to the PCA task, strong conclusions based on these null findings cannot be drawn. Also, the AB task did not yield the expected relationships with alcohol-related variables (neither for automatic nor sustained attention) despite theoretical and empirical evidence suggesting such links (Bollen et al., 2022; Field & Cox, 2008). It is further possible that the lever-related interference observed in the PCA task carried over to the subsequent AB task, thereby disrupting participants' visual behavior and obscuring the expected patterns as a function of their alcohol-use levels.

We hypothesize that the modifications implemented in this study may have substantially altered participants' task strategies and overall engagement. Specifically, the use of a gaze-controlled symbolic lever on a screen differs substantially from the physical, manipulable lever commonly employed in rodent studies. This discrepancy may partly explain the null findings observed here. Also, the interactive lever may have prompted an operant-like approach, leading participants to believe that rewards were contingent on moving the lever. Such an interpretation is based on learned human experiences, where manipulating a lever typically produces an outcome (analogous to flipping a switch), unlike naïve rodents for which the lever is initially a neutral object prior to conditioning. In this case, the sign would no longer function as a simple CS signaling the reward, but rather as a manipulandum within an operant framework. Under such conditions, it would no longer be possible to distinguish STs from GTs on the basis of the incentive salience attributed to a CS.

To address this possibility, future studies should incorporate a cognitive interviewing phase at the conclusion of the experiment to assess participants' perceived contingencies, the functional role they attributed to the lever, and the strategies they adopted during the task. Such qualitative data, unavailable in animal studies, could provide valuable insights, while acknowledging that implicit or unconscious processes

may exert effects that diverge from explicitly reported beliefs. As an illustrative anecdote, some participants spontaneously reported that they found it enjoyable to move the lever with their eyes and that triggering the switch made the task less monotonous. This suggests that their interactions with the lever may have been motivated by task engagement or entertainment rather than reflecting genuine *sign-tracking* behavior.

To address these concerns, we conducted a second experiment designed to determine whether the use of an interactive lever was responsible for the unexpected findings. By reverting to our original, semantically neutral CS (blue rectangles), this follow-up study aimed to assess whether reinstating the initial task parameters would restore the anticipated associations.

Experiment 2

Materials and Methods

Participants

The sample of this study included 159 volunteers (102 females, 56 males and 1 identified as non-binary; mean age = 21.70, sd = 2.72, see Table 11 for sample description). Inclusion criteria were strictly the same as in Experiment 1.

Overall, 180 subjects took part in the whole study. 20 subjects were excluded from the analysis due to at least one of the data quality check criteria (see section “Data Collection” – Eye-tracking). One subject was removed since they participated in the previous experiment also.

Table 11. *Sample Description of Experiment 2*

Variable	Median (std)	Min-Max
Age	21 (2.72)	18-33
Education Level	14 (1.81)	9-21
AUDIT-C	5 (2.46)	1-12
Recent Drinking Index	12 (70.60)	0-720

Note. Education Level= number of successful school years starting from elementary school; Recent Drinking Index = number of alcoholic drinks consumed during the past 2 weeks x number of drinking occasions during the past 2 weeks.

Recruitment, consent, and study title were the same as in Experiment 1. Recruitment and testing took place from October 2024 to December 2025. Notably, no prize draw was used for participant compensation in this experiment.

Procedure and Data Collection

The procedure and materials were identical to those used in Experiment 1, with the exception of the visual stimuli for the sign and goal. Specifically, the interactive lever CS was replaced by a blue rectangle patterned with blue dots, while the grey rectangle indicating the goal location was substituted with a blue rectangle patterned with blue squares, following the design in (Heck, Simon, et al., 2025). In other words, the interactable nature of the CS was removed, rendering the current experiment a partial self-replication of the previous study.

Given that the first experiment revealed that two additional experimental blocks were overly demanding for participants, Experiment 2 was adjusted to include only two blocks of 20 trials for the PCA task.

Statistical Analyses

Although Experiment 2 was not planned a priori, it complied with all preregistered procedures and analyses, in the same way as Experiment 1. All analyses were run with R 4.5.1 (R Core Team, 2024). Alpha level was set at 0.05, but corrections for multiple correlations were applied as indicated. Given that the questionnaires were administered electronically, no missing data were expected, as participants were required to answer all questions in order to proceed. However, missing data occurred due to system bugs: one participant had missing data for the KSS and another for the RST-PQ. These participants were excluded from the relevant analyses, as these measures were not part of the primary analyses. There was also missing data for the AB task due to an insufficient number of gazes recorded in the ROIs (defined as at least one third of trials). Participants with missing AB data were excluded from the relevant analyses ($N = 5$).

Results

Hypothesis 1. Are the ST/GT Profiles Related to Alcohol Consumption Levels?

The best model based on fit indices was the 3-profile model (AIC = 1674.33, BIC = 1800.15, entropy = 0.93). Table 12 shows the fit indices for the three models. Posterior probabilities indicated mediocre confidence in the most likely profile membership. For profile 1, the probabilities ranged from 0.63 to 1.00 (mean = 0.94, sd = 0.10). For profile 2, they ranged from 0.52 to 1.00 (mean = 0.95, sd = 0.11). For profile 3, they ranged from 0.55 to 0.99 (mean = 0.98, sd = 0.07). Figures 20 and 21 show means and standard errors for the indicator variables in the three profiles. Based on the examination of these graphs, groups 1, 2, and 3, were labeled respectively, "INT", "ST", and "GT".

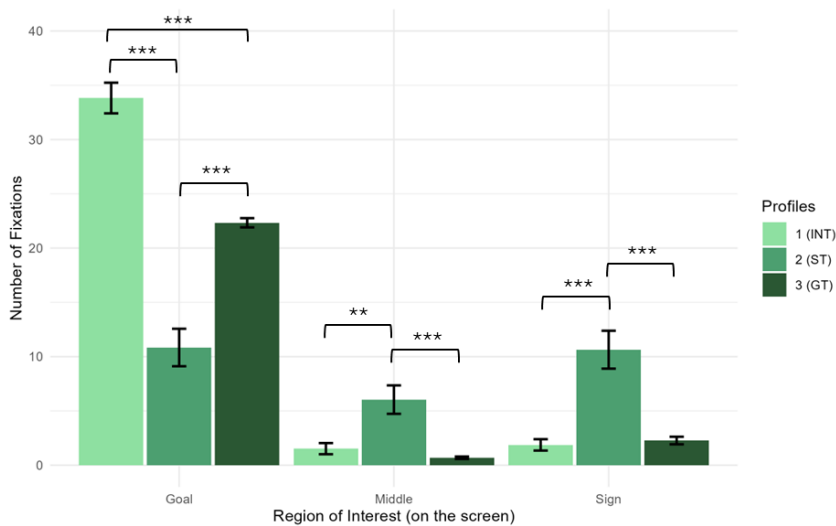
Table 12. *Model Fit Indices for the Three Latent Profile Analyses, Experiment 2*

Tested Model	AIC	BIC	Entropy	Profile Sizes	Bootstrapped
					Likelihood Test (p-value)
1 Profile	1832.49	1915.35	-	-	-
2 Profiles	1805.06	1909.40	0.84	Profile 1: 36% Profile 2: 64%	.01
3 Profiles	1674.33	1800.15	0.93	Profile 1: 14% Profile 2: 16% Profile 3: 70%	.01

Note. AIC=Akaike information criterion; BIC = Bayesian information criterion.

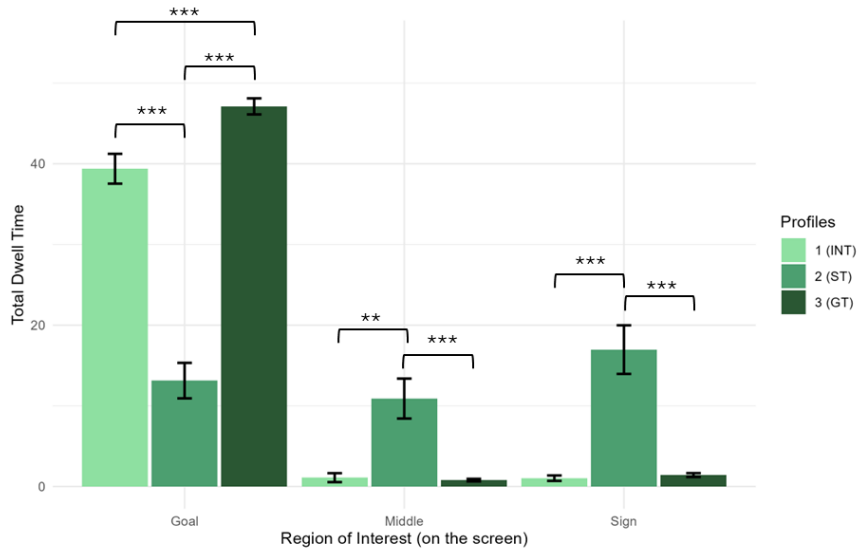
The Kruskal-Wallis rank-sum test, assessing the differences in alcohol consumption (AUDIT-C) in these profiles, did show a statistically significant effect, although its magnitude was very small, likely due to the uneven distribution of participants across groups ($\chi^2 = 6.01$, $p = 0.04$, $\eta^2(H) = 0.03$, 95% CI = [-0.06, 0.06]). Figure 22 shows the distribution of AUDIT-C scores in STs, GTs, and INTs, based on LPA-created profiles. Post hoc pairwise Wilcoxon tests indicated that only the difference between STs and GTs ($p = 0.04$) was significant. No statistically significant difference was observed between GTs and INTs ($p = 0.93$) nor between INTs and STs ($p = 0.13$).

Figure 20. Number of Fixations on Each Region of Interest in the Three LPA-Extracted Profiles, Experiment 2



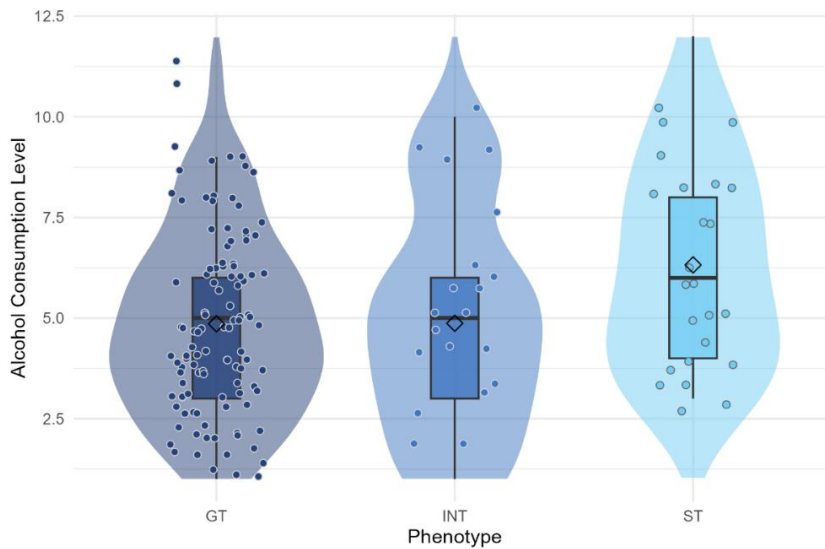
Note. The figure shows the means and standard errors. *** $p < 0.001$, ** $p < 0.01$

Figure 21. Dwell Time on Each Region of Interest in the Three LPA-Extracted Profiles, Experiment 2



Note. The figure shows the means and standard errors. *** $p < 0.001$, ** $p < 0.01$

Figure 22. Alcohol Consumption Level in STs, GTs and INTs based on LPA in Experiment 2



Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Hypothesis 2. Is There a Relationship Between Human Sign-Tracking and Alcohol AB?

To test whether the attentional profiles differed in *automatic orienting* (operationalized as the proportion of trials in which participants initially fixated on the alcohol-related image), a Kruskal-Wallis test was conducted since ANOVA assumptions were not met. The analysis revealed no statistically significant difference between the three groups ($\chi^2(2) = 0.50$, $p = 0.77$, $\eta^2[H] = -0.012$).

We also examined whether the attentional profiles differed in *controlled attention* (as measured by the proportion of total fixation time on alcohol-related images), for which the assumptions of normality and homogeneity of variance were met. The ANOVA revealed no significant group differences ($F(2,130) = 0.225$, $p = 0.87$). The effect size was extremely small ($\eta^2 = 0.002$), indicating that only 0.2% of the variance in initial alcohol fixations was explained by attentional profile.

Correlational analyses examining associations between alcohol consumption measures and alcohol-related AB indices are reported in [Appendix C](#) (Table Q). Small-to-moderate statistically significant positive correlations were observed between all alcohol consumption-related variables and total fixation time on alcohol-related stimuli (Spearman's $\rho = .20-.25$). All associations remained statistically significant following adjustment for multiple comparisons using the B-H method.

Exploratory Analyses: Relationships Between Human Sign-Tracking and Personality-Related Variables

No significant correlation was observed between the ST/GT score and personality-based variables (Table 13).

Table 13. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Impulsivity, Reward Reactivity and Psychological Distress in Experiment 2*

Variable	Spearman Rho	Adjusted P-Value	Raw P-Value	CI Lower (Adjusted)	CI Upper (Adjusted)
Psych.dist	0.02	0.93	0.74	-0.19	0.24
RSTPQ- RR	0.14	0.42	0.07	-0.08	0.35
RSTPQ- Goal	-0.01	0.93	0.84	-0.23	0.20
RSTPQ- BIS	0.007	0.93	0.93	-0.21	0.23
RSTPQ- RI	0.09	0.78	0.28	-0.14	0.30
RSTPQ- IM	0.15	0.42	0.05	-0.07	0.36
UPPSP-UR	0.12	0.42	0.11	-0.10	0.33
UPPSP-PU	0.05	0.93	0.49	-0.17	0.27
UPPSP-LPre	0.01	0.93	0.85	-0.20	0.23
UPPSP-LPer	0.01	0.93	0.81	-0.20	0.24
UPPSP-SS	-0.05	0.93	0.55	-0.26	0.17

Note. Psych.dist = Psychological distress (depression, anxiety and stress scale DASS-21), RST-PQ = Reinforcement Sensitivity Theory of Personality Questionnaire, subdimensions: RR = reward reactivity, Goal = goal-drive persistence, BIS = behavioral inhibition system, RI = reward interest, IM = impulsivity; UPPS-P = short version of the UPPS impulsivity scale,

subdimensions: UR = urgency, PU = positive urgency, Lpre = lack of premeditation, Lper = lack of perseverance, SS = sensation seeking.

No significant correlations were observed between the ST/GT score and alcohol consumption-related variables (Table 14).

Table 14. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Alcohol-Consumption related Variables in Experiment 2*

Variable	Spearman Rho	Adjusted P- Value	Raw P- Value	CI Lower (Adjusted)	CI Upper (Adjusted)
BATCAP (Alcohol)	0.02	0.96	0.83	-0.19	0.22
DrinkOccas	0.00	0.96	0.96	-0.19	0.19
AUDIT-C	-0.06	0.96	0.44	-0.25	0.13

Note. BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test.

Interim Discussion

This second study was initiated in response to concerns regarding the methodological modifications introduced in the previous experiment. Its primary objective was to test whether reverting to the original task stimuli would allow us to identify a link between alcohol AB and sign-tracking, and also replicate the previously observed differences in alcohol consumption across ST, GT, and INT groups (Heck, Simon, et al., 2025). The same hypotheses specified in the original pre-registration were re-examined here using a new sample. LPA-based profiles were again unequally distributed with a great majority of GTs (70%, compared to 14% of INTs and 16% of STs). Similar to Experiment 1, posterior probabilities for group membership were again suboptimal. A statistically significant difference emerged between ST/GT groups in alcohol consumption levels with STs exhibiting a slightly higher AUDIT-C score than the

other profiles (Figure 22). Although this effect was very small and groups highly unbalanced, it is noteworthy that it nonetheless goes in the same direction as in our previous study (Heck, Simon, et al., 2025) as well as the work of others showing a correlation between sign-tracking to monetary rewards and AUDIT scores (Watson et al., 2024).

With regard to the correlational analyses with the ST/GT score, no clear results emerged for alcohol or personality variables. Again, a positive correlation, even though not statistically significant emerged between ST/GT score and impulsivity. Although statistically not conclusive, this is highly in line with previous findings (Cope et al., 2023; Garofalo & di Pellegrino, 2015; Lovic et al., 2011; Schettino et al., 2022, although see Krom et al., 2026). Alcohol consumption as measured by the AUDIT-C was not significantly correlated with the ST/GT score. However, the Kruskal-Wallis test revealed significant differences across the ST/GT latent profiles. This discrepancy likely reflects a limitation of the RBS, which does not consider dwell time in the middle zone (the area between the sign and the goal), whereas our LPA-based classification incorporates all three zones. As illustrated in Figures 20 and 21, participants categorized as “STs” in this sample distributed their attention almost equally across the sign, the goal, and the middle zone, differing from the two other profiles, and mirroring patterns we observed previously (Heck, Simon, et al., 2025). Consequently, LPA-derived classifications provide a richer and more nuanced characterization of attentional patterns than the traditional PCA-based ST/GT score.

Regarding the AB task developed for this study, we found small-to-moderate positive correlations ($r = .20-.25$) between sustained attention to alcohol-related stimuli (total dwell time) and all tested alcohol-related measures. These included: (a) alcohol consumption severity assessed via the AUDIT (consumption subscale and full version), (b) the Brief Assessment Tool for Compulsivity Associated Problems (BATCAP), which captures distress related to drinking behaviors, and (c) a recent consumption index (number of alcoholic drinks consumed during the past two weeks $\times$ number of drinking occasions during the same period) (see [Appendix C](#), Table Q). The absence of significant associations with the measure intended to capture automatic attention (initial orientation) is consistent with prior literature (Bollen et al., 2022, 2025), which demonstrated that ABs tend to manifest later rather than early in processing.

General Discussion

Both experiments in this study produced somewhat ambiguous—yet nonetheless informative—findings. In the first experiment, which implemented an interactive lever as a visual CS, none of the hypothesized effects were observed. This absence of expected results raises the possibility that this methodological modification interfered with the task’s ability to function as intended. In contrast, the second experiment, which reverted to the original cue design, yielded findings more consistent with prior literature. Specifically, STs exhibited a higher median level of alcohol consumption than GTs, and there was a tentative (though not statistically significant) association between sign-tracking and impulsivity. These findings should, however, be interpreted with caution, given the unbalanced distribution of participants across ST, GT, and INT groups. Taken together, these results prompt several methodological and theoretical considerations that warrant further discussion.

Challenges in Measuring Sign- and Goal-Tracking in Humans

These findings raise the question of whether our PCA tasks truly capture sign- and goal-tracking in humans, or whether it might be influenced by additional processes. In the present studies, RBS scores were generally low, with a strong predominance of goal-tracking, a pattern consistent with our previous work (Heck et al., 2025; 2026), but atypical compared to much of the broader literature, which often reports more balanced or varied distributions, enabling more precise examination of individual differences (e.g., Garofalo & di Pellegrino, 2015; Schettino et al., 2024). Conversely, some studies have found the opposite pattern, with STs predominating (Cherkasova et al., 2024; Colaizzi et al., 2023), although one of these was conducted in children (who might represent a very specific population in relation to sign-tracking). Another study employing a physical PCA task and LPA-based profiling reported another unexpected distribution of profiles, with a predominance of INT profiles (and only 20% of ST and 12% of GT; Cope et al., 2023).

Such discrepancies suggest that ST/GT/INT proportions are highly sensitive to experimental context, sample characteristics, and task design. Standardizing paradigms (Heck, Durieux, et al., 2025), and using data-driven classification methods (e.g., clustering) (Godin & Huppé-Gourges, 2025) have been proposed to improve reliability. Moreover,

most human studies rely on single-session PCA tasks, which might reflect momentary tendencies rather than stable traits. This contrasts with animal research, where multiple conditioning sessions are required for stable behavioral phenotypes to emerge, and where early sessions often produce goal-tracking behaviors before sign-tracking develops over time (see Godin & Huppé-Gourges, 2025, P. J. Meyer et al., 2012). Longitudinal designs in humans remain rare but are crucial for assessing the temporal stability of these behaviors. One recent study examining 4-month stability using a food-reward PCA found good temporal stability for sign-tracking but not goal-tracking, suggesting that the GT profile may be either less common or poorly captured by traditional indices (Badioli et al., 2026), going in the opposite direction from what we found.

The predominance of “GTs”, participants who primarily fixated on the reward delivery location, in our design warrants further consideration. Beyond the possibility that our sample simply included more individuals with goal-tracking tendencies, we suggest that features of the task itself may have limited the expression of sign-tracking behaviors. In particular, the paradigm may not have been sufficiently engaging, potentially due to (1) the use of a fictitious reward system (collecting coins to earn a badge) and/or (2) the overall passivity of the task. Both factors may have reduced the motivational salience of the CS, thereby constraining the emergence of sign-tracking behavior.

Although prior work shows that virtual point-based rewards can produce sign- and goal-tracking-like patterns (Albertella, Watson, et al., 2019) comparable to monetary rewards (Watson, Pearson, Theeuwes, et al., 2020), these findings come from Value-Modulated Attentional Capture (VMAC) tasks. VMAC differs substantially from our simplified PCA. VMAC requires performance-contingent responses (e.g., responding correctly to earn points), with clear high- vs. low-reward contrasts, which likely increases motivation. In contrast, our PCA task involved passive viewing with no performance consequences. This low-contingency structure may not have sufficiently engaged participants to elicit robust sign-tracking.

A key difference between our proof-of-concept study (Heck, Simon, et al., 2025) and the replication attempt reported here (Experiment 2) concerns reward salience. In the earlier study, participants had a 1-in-20 chance of winning a €20 voucher, which (although not contingent on performance) likely acted as an extrinsic motivator and

increased attentional engagement. In Experiment 2, this lottery was removed (due to a change in the policy of our faculty ethics committee), potentially meaning participants no longer perceived that “*something was at stake*”. Empirically testing this assumption would be valuable. Directly contrasting food- and money-based incentives could also clarify motivational influences on human sign- and goal-tracking. Finally, adding a post-task cognitive interview could help explain how participants understood task contingencies and how reward expectations shaped their attentional strategies.

Translational Perspectives

Translating animal behavioral paradigms into human research remains challenging (Crombag et al., 2025; Stephens et al., 2013). Beyond practical constraints such as constructing manipulable apparatuses, human participants bring interpretive processes into the experiments (Jimenez-Buedo & Guala, 2016; Nichols & Maner, 2008; Orne, 1962). For example, operating a lever carries pre-existing meaning for humans (typically associated with producing a consequence), and social norms (e.g., do not touch unfamiliar equipment) might reduce interaction with physical experimental devices.

Reward structure is another major species difference in ST/GT studies. Primary reinforcers like food reliably motivate rodents, whereas for humans, food rewards vary in motivational salience depending on satiety, preferences, and daytime. Monetary rewards generally exert stronger influence but might be sensitive to individual factors such as socioeconomic status. Moreover, humans rarely participate for intrinsic reasons; motivations often include payment, course credit, or helping the experimenter, unlike food-restricted animals housed in controlled environments such as Skinner boxes.

When designing experimental tasks of this nature, researchers try to anticipate every detail (e.g. where participants will look, what they might think, or how they will interact with the setup). Yet, the subjective experience of participants during the task largely remains a “black box.” Thus, as mentioned earlier, incorporating brief post-task cognitive interviews could uncover participants’ strategies, misinterpretations, or motivational gaps, thereby informing the development of more engaging and ecologically valid paradigms.

Conclusions and Future Prospects

In summary, the present set of experiments did not provide evidence for a relationship between sign-tracking and AB toward alcohol-related cues. Although these results run counter to theoretical predictions positing an association between these constructs (Anselme & Robinson, 2020), it provides an important first step. However, it is important to acknowledge the methodological variations across studies, which may partly account for the inconclusive findings, as well as the generally small effect sizes and non-significant associations observed.

More broadly, these results raise important questions regarding the design and implementation of translational tasks (particularly PCA paradigms) aimed at assessing sign- and goal-tracking tendencies in humans. Key considerations include the role and magnitude of reward incentives, the structure and clarity of task instructions, and the respective advantages and limitations of using manipulable versus purely visual conditioned stimuli. Careful attention to these factors will be essential for improving both the validity and translational value of such paradigms, and for advancing our understanding of how individual differences in cue reactivity may relate to vulnerability to addictive behaviors.

Based on the current findings, it is not possible to conclude with confidence that the present paradigm represents an optimal tool for measuring these behavioral tendencies. Nevertheless, the task appears to tap into at least a related underlying process. The observed effects, although small in magnitude, were directionally consistent with previous research, and some key hypotheses have recently received empirical support, such as the amplifying effect of uncertainty on sign-tracking tendencies (Heck et al., 2026, next Chapter). Taken together, these converging patterns suggest that the paradigm is not devoid of construct validity, but rather that its sensitivity and reliability may require further refinement.

Declarations

Data Availability and Transparency

The experimental data are available at <https://doi.org/10.17605/OSF.IO/34FAZ>. The code for the experimental task is available upon request from the authors. This study's analysis were pre-registered at <https://osf.io/f29uz>. Data analysis code is not available.

Use of IA

Portions of the manuscript were edited for clarity and flow using Microsoft 365 Copilot (Microsoft, Redmond, WA), a generative AI assistant based on a GPT-5 chat model (version 2.20260108.46.0). Copilot was used solely to improve language, grammar, and readability. All scientific content, interpretations, and conclusions are the responsibility of the authors.

The reference list of this article has been incorporated into the [general bibliography of this thesis](#).

Chapter 7

The Effects of Reward Uncertainty and Alcohol Intoxication on Human Sign- and Goal-Tracking A Randomized Experimental Study

Michelle Heck

Damien Lesenfants

Vincent Didone

Patrick Anselme*

Etienne Quertemont*

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Publication

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Supplementary Information for this chapter can be found in [Appendix D](#).

*equal contributions

Abstract

Background. Sign- and goal-tracking behaviors capture individual differences in reactivity to reward-predictive cues and are increasingly recognized as translational markers of addiction vulnerability. While animal research shows that cue-reward uncertainty (i.e. the inability to predict whether a reward will follow its predictive cue) and alcohol modulate sign-tracking, empirical evidence in humans remains scarce.

Objectives. This experimental study investigated how acute alcohol intoxication and cue-reward uncertainty shape attentional responses to reward cues in humans.

Methods. One hundred eighteen young adult participants were assigned to one of four groups in a 2×2 design: Alcohol (0.5 g/kg) vs. Placebo and Uncertain (50% reinforcement) vs. Certain (100% reinforcement) reward conditions. Eye-tracking during a Pavlovian conditioned approach (PCA) task quantified sign- or goal-tracking tendency, followed by a non-rewarded "*omission*" phase.

Results. Reward uncertainty significantly increased attentional allocation to the reward-predictive cue ($\eta^2p = 0.04$), consistent with animal evidence that uncertain outcomes amplify responses to conditioned cues. Contrary to predictions, alcohol did not produce reliable enhancements of sign-tracking ($\eta^2p = 0.01$). Effects during reward omission were mixed: the groups that previously experienced reward certainty increased their attention towards the sign while decreasing their attention towards the goal. Exploratory analyses incorporating initial ST/GT tendencies as covariates further indicated that cue-attention during omission aligned with participants' initial ST/GT behavior.

Conclusions. Reward uncertainty, but not alcohol intoxication, affected sign-tracking tendencies. By directly translating animal findings to a human paradigm with eye-tracking, these results support the idea that uncertainty affects how individuals orient toward reward-predictive stimuli, a process relevant to theories of addictive behavior.

Keywords: Reward Uncertainty, Alcohol, Sign-tracking, Pavlovian Conditioned Approach

Introduction

Numerous theoretical frameworks of addiction have underscored the central role of Pavlovian conditioning in the development and maintenance of substance use disorders (SUDs) (Everitt et al., 2001; T. E. Robinson & Berridge 1993; Wiers & Stacy, 2006). Reactivity to substance-related cues has mostly been discussed in relation to physiological (Wang et al., 2019), attentional (Ramirez et al., 2015), behavioral (Acker & MacKillop, 2013), subjective (Blaine et al., 2019) and even neural responses (Courtney et al., 2016). All these effects result from the learning of a Pavlovian association between a CS and an US.

Over the past two decades, scientific research, primarily involving animal models, has increasingly focused on the study of "*sign-tracking*" and "*goal-tracking*", two forms of Pavlovian-conditioned responses that are highly relevant to addiction (Flagel et al., 2007; T. E. Robinson & Flagel, 2009). When rats are exposed to the brief presentation of a CS lever reliably followed by the delivery of a reward US (e.g., a food pellet) at a different location, they tend to adopt one of two distinct conditioned response patterns. STs preferentially approach and engage with the CS, which not only predicts the reward but also seems to have acquired its motivational properties. In contrast, GTs direct their behavior toward the location of the expected reward, treating the cue primarily as a predictive signal only and not a motivational stimulus. Finally, some individuals, referred to as INTs, display a mixed response pattern, alternating between sign- and goal-tracking behaviors. These phenotypic differences are thought to reflect differing propensities to attribute incentive salience to reward-predictive cues (T. E. Robinson and Flagel, 2009). The ST and GT phenotypes show stable individual differences in traits such as impulsivity (Lovic et al., 2011), attentional control (Paolone et al., 2013), and dopaminergic reactivity to reward cues (Flagel et al., 2007; Flagel, Clark, et al., 2011; T. E. Robinson & Flagel, 2009).

In rats, the ST phenotype has been associated with increased vulnerability to addiction compared with the GT phenotype, including a higher responsiveness to food and drug cues, enhanced drug self-administration, heightened cue-induced craving, and a greater risk of relapse (Anselme & Robinson, 2020; Berridge, 2007; Flagel et al., 2008, 2009, 2010; T. E. Robinson et al., 2014; B. T. Saunders & Robinson, 2010, 2011; B. T.

Saunders et al., 2013; Tomie et al., 2008). STs have also been shown to be more resistant to appetitive extinction and less behaviorally flexible than GTs (Ahrens et al., 2016; Fitzpatrick et al., 2019). During extinction phases, when the previously rewarded stimulus is no longer paired with reinforcement, GTs rapidly adjust their behavior by ceasing to approach the reward-associated location. In contrast, STs persist in approaching the cue-associated location for a significantly longer period, indicating a stronger cue-driven motivational bias and diminished adaptability to changes in reward contingencies. Although ST and GT phenotypes are considered relatively stable traits, with evidence pointing to a genetic basis (e.g., Flagel et al., 2010), there is also evidence that they are not immutable. The ability to express one or the other profile notably depends on the type of CS (e.g., lever vs. tone; P. J. Meyer et al., 2014) and the consistency of the CS-US association (e.g., M. J. F. Robinson et al., 2015) (see below).

The translation of sign- and goal-tracking to human research is more recent and has only received systematic attention in the last few years (Anselme & Robinson, 2020; Colaizzi et al., 2020; Heck, Durieux, et al., 2025). In human studies of sign- and goal-tracking, a variety of experimental paradigms have been employed to assess individual differences (for a recent comprehensive overview, see Heck, Durieux, et al., 2025). These studies include computerized Pavlovian Conditioned Approach (PCA) tasks paired with eye-tracking to assess attentional patterns (e.g. Cherkasova et al., 2024; Dinu et al., 2024; Garofalo & di Pellegrino, 2015; Heck, Simon, et al., 2025; Schad et al., 2020;), as well as physical PCA tasks, which either incorporate eye-tracking (Cope et al., 2023) or rely on direct behavioral measurements of interaction with the sign (cue) and goal (reward) locations (Colaizzi et al., 2023).

Despite considerable variability in experimental methods and analytical approaches among studies (Heck, Durieux, et al., 2025), human research broadly suggests that it is possible to identify individuals who exhibit ST and GT (and in some cases, INT) behavioral phenotypes. Importantly, these phenotypes have sometimes been linked to translationally relevant variables such as impulsivity (e.g., Colaizzi et al., 2022; Cope et al., 2023; Garofalo & di Pellegrino, 2015) and alcohol use (Albertella et al., 2021; Heck, Simon, et al., 2025; Watson et al., 2024). Recent theoretical work has proposed a direct connection between incentive salience attribution and human sign-tracking, particularly through value-modulated attentional capture (VMAC) tasks, which suggest

that reward-associated cues gain motivational significance and are more likely to capture attention, thereby increasing their influence on behavior (Le Pelley et al., 2024). Supporting this framework, fMRI evidence indicates differential incentive salience attribution in human sign- versus goal-trackers during Pavlovian-to-instrumental transfer (PIT) tasks (Schad et al., 2020). However, empirical studies on human sign- and goal-tracking currently still remain scarce in comparison to animal studies, and null findings have also been reported, emphasizing the need for methodological refinement and conceptual clarity in this emerging field (see Heck, Durieux, et al., 2025).

Given that a CS acquires its incentive salience through its association with the US, one should expect that a fully consistent CS-US association (100% predictive of reward) enhances the CS's incentive salience and approach behavior more than an inconsistent one (only 50% predictive of reward). However, animal research has demonstrated that rats exposed to reward uncertainty increase the strength of sign-tracking, especially when it is combined with uncertainty in reward magnitude (Anselme et al., 2013; Anselme, 2015; M. J. F. Robinson et al., 2014), as well as the number of individuals adopting this profile (M. J. F. Robinson et al., 2015). Other factors that may contribute to increase reward uncertainty, such as long and variable inter-trial intervals (ITI), also increase sign-tracking (Kaneko et al., 2025; Lee et al., 2018). Importantly, dopamine signaling has been suggested being implicated in the effects of uncertainty during Pavlovian conditioning (Hart et al., 2015).

In human research, similar motivational/attentional effects have been obtained under the framework of *Uncertainty-Modulated Attentional Capture* (UMAC). UMAC refers to the tendency for reward-associated distractors to capture attention more strongly when the outcome is uncertain (Cho & Cho, 2021; J. Y. L. Chow et al., 2025; Ju & Cho, 2023; Le Pelley et al., 2019; Massa et al., 2024; Pearson et al., 2024). This effect appears to be both rapid and automatic (Le Pelley et al., 2019) and it persists even when participants are explicitly informed about reward contingencies, suggesting that it does not rely on strategic or goal-directed learning (J. Y. L. Chow et al., 2025).

In addition to uncertainty, pharmacological factors may also influence the propensity to engage in sign-tracking behavior. Among these, alcohol administration has received particular attention, as it has been shown to enhance sign-tracking tendencies in animal models. This effect may be mechanistically linked to alcohol's ability to increase

dopaminergic activity in mesolimbic pathways (Boileau et al., 2003; Didone et al., 2016). For instance, Tomie and colleagues (Tomie, Cunha, et al., 1998) demonstrated that ethanol administration significantly increased sign-tracking behavior in rats across a range of doses. These results support the broader hypothesis that sign-tracking reflects a form of impulsive responding (Tomie, Aguado, et al., 1998), a trait frequently implicated in addictive behaviors. Evidence from both human and rodent research indicates that acute alcohol administration enhances impulsivity, likely through its effects on inhibitory control (Adams et al., 2012; de Wit et al., 2000; Dougherty et al., 2008; Olmstead et al., 2006; Poulos et al., 1998).

In humans, priming doses of alcohol have been shown to heighten attentional biases (ABs) toward alcohol-related cues (M. A. Miller & Fillmore, 2011; Nikolaou et al., 2013), although some studies have reported a decrease in AB following consumption, possibly due to satiation effects (Monem & Fillmore, 2019; Weafer & Fillmore, 2013). Beyond alcohol-specific cues, cross-priming effects have been observed: alcohol administration can enhance ABs toward other substance-related cues, such as those associated with cocaine or nicotine (Field et al., 2005a; Montgomery et al., 2010).

Collectively, these findings suggest that alcohol may not only heighten attention toward alcohol-relevant stimuli, but also amplify a more general reward sensitivity. This may occur through alcohol's capacity to increase impulsive responding, ultimately exacerbating behavioral biases toward salient cues (whether expressed as cue-driven sign-tracking behavior or AB) across both human and nonhuman models.

From an attentional perspective, the Alcohol Myopia Theory³⁹ (Steele & Josephs, 1990) offers two complementary interpretations for the effect of alcohol on cue attention (as pointed out by Watson, Pearson, & Le Pelley, 2020). First, alcohol could narrow attentional capacity globally, reducing processing of peripheral or distracting stimuli such as a CS in a sign-tracking paradigm. Alternatively, alcohol may selectively focus attention on highly salient cues (Steele & Josephs, 1990), which would predict an increase in sign-tracking-like behaviors. This has been examined in a VMAC study in humans. Watson and colleagues tested this bi-directional hypothesis and found that moderate alcohol intoxication enhanced attentional performance in a VMAC task: intoxicated individuals

³⁹ Originally designed to explain extreme social behavior under alcohol intoxication, this theory has expanded to cognitive aspects.

earned more rewards because they were less distracted by high-value predictive stimuli, suggesting that alcohol can alter attentional prioritization in complex ways (Watson, Pearson, & Le Pelley, 2020). It is important to note, however, that the task structure in Watson et al.'s study differed substantially from that of the present investigation. In their paradigm, attending to the reward-predicting cue resulted in reward omission, a contingency that was not present in our design.

The aim of this study was to advance the validation of the ST/GT model in humans by experimentally examining two key modulators of reward processing: reward uncertainty and acute alcohol administration. Building on robust evidence that uncertainty enhances attentional engagement and cue-driven approach behavior, we sought to determine whether it also modulates the tendency to sign-track in our previously developed PCA task (Heck, Simon, et al., 2025). Both factors have been independently linked to dopaminergic signaling, which plays a central role in incentive salience and the tendency to sign-track versus goal-track. Given these converging mechanisms, we hypothesized that alcohol and uncertainty would exert additive effects, jointly amplifying cue-directed attention (sign-tracking) relative to goal-directed attention.

Therefore, this study tested whether either factor (uncertain reward delivery or a moderate alcohol dose [0.5 g/kg]) would enhance attentional allocation to a reward-predictive cue. We hypothesized that participants exposed to both alcohol and uncertainty would exhibit the strongest bias toward the cue compared to those experiencing only one or neither factor. Additionally, we explored whether exposure to uncertainty and/or alcohol would impact behavior under reward omission. This prediction was grounded in three considerations: (1) decades of research demonstrate that partial reinforcement reliably enhances extinction resistance; (2) sign-tracking individuals typically persist longer during extinction, and both manipulations—uncertainty and alcohol—were expected to promote sign-tracking tendencies; and (3) alcohol may further augment extinction resistance through its documented effects on inhibitory control. To assess this, a non-reinforced "*Omission*" phase was included at the end of the PCA task. To our knowledge, this is the first experiment to examine the joint effects of reward-cue uncertainty and alcohol administration on human sign-tracking behavior, representing a preliminary but hypothesis-driven step in this line of research.

Methods

Participants

This study involved 118 young adult volunteers (74 females, 44 males; Table 15). Participants were first invited to complete an online screening questionnaire to assess eligibility. Inclusion criteria required: no history of severe neurological disorders; no regular use of substances (defined as use more than twice in the last two months, excluding tobacco and alcohol); no diagnosis of ADHD currently treated with medication; no color vision deficiency; and being at least occasional alcohol consumers (i.e., individuals who were fully abstinent were excluded). Additional exclusion criteria were specific to the alcohol administration component of the study and included: being pregnant, having medical conditions that contraindicated alcohol consumption, taking medications incompatible with alcohol use, and having experienced allergic or adverse reactions following alcohol consumption. All participants had normal or corrected-to-normal vision. Table 15 shows means and standard deviations for age, education level, alcohol consumption severity score (AUDIT-C), and recent drinking index in the present sample.

Table 15. *Sample Description*

Variable	Median (std)	Min-Max
Age	21.00 (2.93)	18-33
Education Level	14.00 (1.99)	10-23
AUDIT-C	5.00 (2.49)	1-10
Recent Drinking Index	9.00 (55.76)	0-400

Note. Recent drinking index = number of alcoholic drinks consumed during the last 2 weeks x number of drinking occasions during the last 2 weeks.

A priori power analysis for ANOVA, with an alpha level of .05, power of .80, and a medium effect size led to a total of 128 participants (32/group). We added approximately 20% to the projected sample size, due to loss of participants given the data quality criteria for our eye-tracking based ST/GT score (projected N= 152, 38/group).

Initially, 139 participants took part in this study. Eighteen participants were removed from the analysis due to problems with one of the data quality check criteria (see “Eye-Tracking” below). Two were removed because they reported an AUDIT score = 0 at in-person testing. One participant was excluded because this individual also took part in previous studies of the same project. The final sample therefore included 118 participants for the main analysis.

Participants were recruited via word of mouth, social media or advertising posters. The study was initially explained to the participants as investigating “*Individual variability in the impact of alcohol on reaction times*”. After filling out the online screening, participants meeting the inclusion criteria were contacted to take part in the experimental phase of the study (on-site). All participants gave informed consent to take part in the study. Recruitment and testing took place from November 2024 to June 2025, at the university's facilities. The study was conducted in accordance with institutional guidelines and the Declaration of Helsinki. It was approved by the local Ethics Committee.

General Procedure

All participants were informed that they would receive varying quantities of alcohol in a mixed beverage. This approach was selected due to the inherent challenges in achieving effective blinding in completely balanced alcohol administration studies. Specifically, individuals who receive alcohol are likely to experience noticeable physiological and subjective effects, which can lead them to accurately infer their group assignment—thus undermining the credibility of an “*expecting alcohol/receiving placebo*” condition. Several studies have highlighted the difficulty of maintaining successful blinding in alcohol research, even with modest doses (Martin & Sayette, 1993; Ross & Pihl, 1989). Given these constraints, our partially informed design aimed to balance ethical transparency with methodological rigor. Prior to attending the in-person testing session, all participants were provided with the following instructions to ensure safety and data integrity: (1) refrain from consuming alcohol the evening prior to the session, (2) abstain from eating for at least five hours before the session, (3) bring a valid form of identification to allow verification of their age, and (4) bring a personal item (e.g., a book) to occupy themselves at the end of the experiment in case they experienced a waiting period due to excessive intoxication.

In-person testing was conducted in a quiet, private room and consisted of three main phases: (1) informed consent, alcohol/placebo administration, and pre-experimental questionnaires (approximately 15–20 minutes); (2) completion of the PCA task (~20 minutes); and (3) post-experimental questionnaires, a full debriefing, and a second informed consent (~15 minutes). The third phase was followed by a potential washout period, if required. Short breaks were allowed between phases to minimize participant fatigue. At the end of the session, all participants were fully debriefed about the true purpose of the study and their actual group assignment. In total, four groups were tested: Alcohol + Uncertainty, Alcohol + Certainty, Placebo + Uncertainty, and Placebo + Certainty (see below for details). Group comparability regarding alcohol consumption variables was verified, confirming that no confounding factors influenced the outcomes despite randomization (see [Appendix D](#), Table R).

Alcohol/Placebo Administration

The beverage administration procedure was identical for participants in the Alcohol and Placebo groups, the only difference being the presence or absence of alcohol. To begin with, all participants completed a breathalyzer test to ensure a zero baseline blood alcohol concentration (BAC). Participants' IDs were then checked to verify that they were over 18 years of age. Each participant was subsequently weighed—calibrated for light or heavy clothing when necessary—to calculate the beverage volume required to reach a target BAC of 0.5 g/kg. For practical reasons, experimenters were not blinded, as they were responsible for preparing the beverages. However, given the minimal researcher involvement in the experimental protocol, which was largely computerized, this was deemed acceptable.

The alcoholic beverage consisted of Captain Morgan Spiced Gold Rum (35% alcohol by volume), mixed with cola and lime juice. The placebo beverage was prepared identically, using Captain Morgan Spiced Gold 0.0% (non-alcoholic) instead. Following established procedures in alcohol administration research (Rohsenow & Marlatt, 1981), all drinks were prepared in the participant's presence using branded bottles, to enhance the credibility of the placebo. Participants were instructed to consume the entire beverage within five minutes to standardize the timing of alcohol absorption. This was

followed by a 10-minute absorption period during which participants completed questionnaires (see *Questionnaire* section for details).

A second breathalyzer test was conducted after this waiting period, with participants blinded to the results. At the end of the experimental session, a final breath alcohol measurement was taken to ensure that any participant intending to drive was within the legal limit. Mean breath alcohol concentration (BrAC) increased significantly from before the experimental tasks ($M = 0.18$, $SD = 0.06$) to after the PCA tasks and questionnaires ($M = 0.22$, $SD = 0.06$; $t_{(56)} = 4.81$, $p < .001$).

PCA Task

Before starting the ST/GT task, participants were instructed that they could collect a certain number of points in the next tasks, and that more points collected would unlock more glorious expertise badges.

Points corresponded to virtual coins collected on each trial (1- or 10-point coins). Performance was defined as the total number of coins collected and was converted into badge levels using predefined percentage intervals: Bronze (0-25%), Silver (25-40%), Gold (40-55%), Platinum (55-70%), Diamond (70-85%), and Expert (85-100%). The variation of coin magnitude (1 vs. 10 points) was implemented to maintain curiosity and reduce task monotony, rather than induce differential performance.

The stimuli were presented on a computer screen (1920 x 1080 pixels) with a grey background. A battery of two computer tasks was implemented: the simple reward task and the PCA task. The tasks were run on a homemade custom Matlab software (version R2019b).

Briefly, the simple reward task involved a fixed blue rectangle filled with blue squares (goal location) on the screen. Goal location was counterbalanced across participants (bottom or upper part of the screen). The coin appeared for 1.5 seconds on the goal shape, and the sound of a falling coin could immediately be heard when the participant pressed the key to collect the reward. There was a 20% chance that the coin was a "10-point coin" to maintain a level of curiosity and avoid monotony during the task. The aim of this first task was for the participants to learn where to collect the rewards and was designed to mimic the magazine training phase in animal models, where rewards are regularly delivered without any CS presentation. The simple reward task consisted of 10

trials, with a variable ITI from 4 to 8 seconds. Prior to starting the task, participants were instructed as follows: *"During this task, objects will be displayed in a blue rectangle. These will allow you to earn points. Your objective is to respond as quickly as possible to their presentation by pressing the 'enter' key."*

The PCA task was an adapted version of the *autoshaping* procedure used in animal ST/GT studies. It consisted of two blocks of 20 trials with a variable ITI ranging from 4 to 8 seconds. Like in the previous task, there was a 20% chance that a "10-point coin" was obtained. The goal shape was permanently present and could be located at the bottom or upper part of the screen (the location being the same as in the simple reward task). The sign shape was displayed on the opposite part of the screen (upper or bottom) for 3 seconds and disappeared just before a coin was presented on the goal shape for 3 seconds. Therefore, the sign shape was defined as a CS announcing reward delivery with a given probability. Two experimental groups were tested: one experienced a 50% CS-reward probability (uncertainty), the other a 100% probability (certainty). Participants collected rewards by pressing "enter," triggering a coin sound. Prior to starting the PCA task, participants were instructed as follows: *"This task is similar to the first one, except that we are no longer measuring your reaction time here. You can also score points. Use the 'enter' key as before. Please keep your attention on the computer screen and don't look at the keyboard."*

In the PCA task, task parameters ensured that all participants reached the highest (Expert) badge level, irrespective of point magnitude condition, such that no meaningful differences in total badge value were observed between groups. Badges therefore served as a symbolic incentive and were not used as outcome measures. The primary focus of the task was the assessment of attentional allocation between the coin (goal-related) location and the sign (cue) location.

Figure 10 depicts the layout of the newly developed computerized PCA task alongside the traditional animal PCA paradigm, illustrating design elements that were intended to approximate key features relevant to cross-species comparisons of sign-tracking behavior.

Following the PCA task, participants completed a so-called reward "omission" block that closely mirrored the original design but consisted of 15 trials in which the CS was presented for 3 seconds without the opportunity to earn any reward or coin.

Participants were informed only that this task resembled the previous one. No explicit instructions regarding reward omission were provided, as in animal studies, the sudden transition to the omission phase being likely to be surprising.

Questionnaires

In the screening phase, all participants completed socio-demographic online questionnaires including the history of neurological problems that could affect cognitive functioning, and regular use of tranquilizers or illicit drugs. They also completed the short version of the alcohol use disorder identification test (AUDIT-C, Bush et al., 1998).

In the pre-experimental phase, all participants completed electronic versions of the short version of the (French translation of) Impulsive Behavior Scale (UPPS-P, Billieux et al., 2012). Additional questionnaires were included but not relevant to the present analyses: The *Edinburgh Handedness Inventory* (Oldfield, 1971), which assesses handedness through 22 items. The 11-item version was used. The *Karolinska Sleepiness Scale* (KSS, Kaida et al., 2006), which measures the subjective level of fatigue at a particular time of day based on a nine-point Likert-type scale, was also administered.

Between the PCA task and the Omission block, participants completed electronic versions of alcohol subscale of the Drug Effects Questionnaire (DEQ, Morean et al., 2013). A 100 points visual analog scale was used to assess four dimensions of alcohol's subjective effects: "Feel", ("*Do you FEEL any drug effects right now?*"), "High" ("*Are you HIGH right now?*"), "Like" ("*Do you LIKE the effects you are feeling right now?*"), "More" ("*Would you like MORE of what you consumed, right now?*").

In the post-experimental phase, participants completed electronic versions of the following questionnaires:

- *The Brief Assessment Tool for Compulsivity Associated Problems* (BATCAP, Albertella, Le Pelley, et al., 2019), which assesses a range of compulsive symptom types. It covers alcohol use, gambling, binge eating and excessive Internet use (as well as contamination, checking, and ordering compulsions). In this study, we only used the addiction-related aspects.
- *Questions about current alcohol consumption*. To gain insight into participants' recent drinking behavior, we included the following two questions into the protocol: "*How many drinks have you had in the last 14 days?*" and "*On how*

many occasions have you drunk alcohol in the last 14 days?". A recent drinking index was computed by multiplying these two numbers. We also measured the following item: *"How many times have you engaged in binge drinking in the past month?"* (defined as consuming >5 drinks within 2 hours for men and >4 drinks within 2 hours for women).

- *Alcohol Consumption*. The French version (Gache et al. 2005) of the Alcohol Use Disorders Identification Test (AUDIT; J. B. Saunders et al., 1993) consists of 10 multiple-choice items measuring alcohol consumption, alcohol dependence, and alcohol-related problems. Higher scores reflect a high probability of harmful alcohol use.

Eye-Tracking

A Tobii 5 eye-tracking system (with an image sampling rate of 133 Hz) was mounted on a 60.5 cm diagonal computer screen. The eye tracker was calibrated using a six-point procedure at the beginning of the experiment. A chinrest was used to standardize the head-screen distance at 70 cm. Tobii Experience software was used to calibrate the eye-tracking system.

To compute eye gaze-based ST/GT scores, the screen was virtually separated into 9 regions of interest (ROI, 3 equal parts on each axis). Eye gaze position was collected throughout the PCA task. The two main ROIs used to compute the scores were the upper center and the bottom center of the screen, where the goal and the sign stimuli were located. We used a custom implementation of the Velocity Threshold Algorithm for fixation identification. First, eye position in pixels was converted to visual degrees. Then velocity was computed in degrees/sec for axes X and Y. To distinguish fixations from saccades, we used individualized thresholds for each subject based on their gaze velocity during mandatory fixations in an additional training task. Each threshold was computed by adding $1.95 \times \text{standard deviation}$ to their mean gaze velocity during fixations (= confidence interval of 95%). Eye movements were considered fixations when they were strictly below the personalized threshold. Too short fixations (<100 ms) were removed to smoothen eye-gaze data. For each identified fixation, duration and ROI were collected.

As in our previous study (Heck, Simon, et al., 2025), analyses were conducted separately for the first and second blocks of the ST/GT task (each consisting of 20 trials).

To focus on the most sensitive and reliable measure, only scores based on Dwell Time (total time spent looking at the ROI) are reported in the present manuscript. However, the full dataset (including measures such as number of fixations) is openly available and can be consulted by interested readers via our public repository.

Three main criteria were used for data quality check and poor quality data exclusions: A participant was excluded (1) if the gaze stagnated in the middle zone throughout the whole task, without variation (a possible indicator of poor calibration or other technical problem: $n = 0$), (2) if there were more than 30% of gazes at the outer edge of the screen (5% of the screen) compared to the rest of the screen (poor calibration or unfocused participant: $n = 0$ for the main PCA task and $n = 1$ for the Omission Block), and (3) if on average the individual gazed less than 1 second per CS presentation at either of the ROI (goal and sign) or at the center of the screen (due to too few data to compute a meaningful sign-tracking score: $n = 18$ for the main PCA task and $n = 4$ for the Omission Block).

Eye-tracking based ST/GT scores were computed similarly to the response bias scores (RBS) classically used in animal research (e.g., P. J. Meyer, Lovic, et al., 2012). Dwell time on the "goal" was subtracted from dwell time on the "sign" and divided by the total dwell time on both ROIs (during the 3s CS presentation). Thus, the ST/GT score ranged from -1 to 1, with negative scores theoretically suggesting a "*goal-tracking*" behavior, positive scores pointing towards a "*sign-tracking*" behavior, and scores around 0 meaning a rather "*intermediate*" tendency. This score was computed for the first and second blocks of the PCA task using Dwell Times.

Data Analysis

Statistical analyses were performed using R 4.4.1 (R Core Team, 2024). The following packages were used: basic data import, processing, and visualization were performed using readxl (v1.4.5, Wickham & Bryan, 2025), tidyverse (v2.0.0, Wickham et al., 2019), ggpubr (v0.6.1, Kassambara, 2025a), and patchwork (v1.3.2, Pedersen, 2025). ANOVAs and related analyses were conducted with rstatix (v0.7.2, Kassambara, 2025b) and car (v3.1-3, Fox & Weisberg, 2019). Effect sizes were computed using effectsize (v1.0.1, Ben-Shachar et al., 2020). Correlation analyses were carried out with psych (Revelle, 2025). Data transformations were performed using rnomi (v1.0.1.2, McCaw,

2023). Mixed effects models and pairwise comparisons were conducted using lme4 (v1.1-37, Bates et al., 2015), lmerTest (v3.1-3, Kuznetsova et al., 2017), and emmeans (v2.0.0, Lenth et al., 2025).

Alpha level was set at 0.05, but corrections for multiple correlations were applied when needed. Given that the questionnaires were administered electronically, participants were required to answer all questions to proceed—there was no missing data.

As a preliminary step, we compared the Alcohol and Placebo groups on subjective responses to the beverage using the subscales of the Drug Effects Questionnaire (DEQ). Because the DEQ scores were not normally distributed, we conducted non-parametric Mann-Whitney U tests to verify the effectiveness of the experimental manipulations and ensure that the placebo beverage elicited convincing subjective effects.

The first main hypothesis was that both alcohol intoxication and reward uncertainty would significantly influence sign-tracking tendencies, with each factor expected to increase the ST/GT score, and their combination leading to the highest sign-tracking scores. To test this, we conducted a two-way ANOVA including the interaction between alcohol and uncertainty. Since the assumptions of normality and homoscedasticity were not initially met, the ST/GT scores were transformed using an Inverse Normal Transformation (Blom's method). This transformation successfully corrected the distribution, resulting in both normality and homogeneity of variance being satisfied.

The second hypothesis was exploratory and tested whether alcohol intoxication and reward uncertainty would significantly affect cue-attention during a subsequent non-reward (so-called reward omission). During the "*reward omission*" phase, the goal rectangle (the location where coins were previously delivered) remained visible, analogous to the food magazine in rodent studies. We anticipated that "*rational actors*" might continue to monitor the goal location to some extent in expectation of coins, given the absence of explicit instructions about reward omission. For this reason, we focused on dwell time towards the sign as the primary variable of interest: continued attention to the sign despite the absence of reinforcement was interpreted as "*resistance to reward omission*". Thus, during reward omission, we expected a more pronounced reduction in sign-directed attention in the 100%-placebo group, with weaker decreases in the other groups. Additionally, we also examined goal-directed attention, although we did not hold specific a priori predictions regarding the direction of these effects.

- 1) To investigate whether behavioral extinction took place in the non-rewarded phase compared to the acquisition block (Block 1 was chosen here to have the purest effect of uncertainty), we conducted linear mixed-effects analyses examining sign- and goal-directed attention across the three experimental blocks (Block 1, Block 2, and Omission), including Group (Alcohol vs. Placebo), Certainty (50 vs. 100), and their interactions. Pairwise comparisons between blocks were then performed in each group, with p-values adjusted for multiple testing using the Tukey correction.
- 2) We further investigated the relationship between individual differences in sign-tracking tendency and attentional allocation to the sign cue during the reward omission phase. Specifically, we tested whether higher ST/GT scores from Block 1 were associated with increased dwell time on the sign cue during omission, using a Spearman correlation.
- 3) To complement this analysis, we conducted a multiple linear regression including initial ST/GT tendencies (Block 1 scores) as a continuous predictor. The model tested the main and interactive effects of Group (Alcohol vs. Placebo), Probability (50% vs. 100%), and mean-centered ST/GT scores on Sign Dwell Time during reward omission. Mean-centering the continuous predictor reduced multicollinearity and facilitated interpretation of interaction terms. All resulting variance inflation factors were below 5, indicating an acceptable level of multicollinearity. Some degree of multicollinearity was expected by design, as both alcohol intoxication and reward uncertainty were hypothesized to influence directly the third predictor, i.e. the ST/GT score. Thus, the predictors in the model were not fully orthogonal, which reflects the theoretical and experimental rationale behind the manipulation of these variables. Centering ST/GT scores allowed us to isolate more clearly and interpret more carefully the unique and interactive contributions of each factor despite their anticipated overlap.

In line with common practices in the ST/GT literature and to better capture potential interactions between ST/GT behavior and contextual manipulations, participants were also categorized into three discrete phenotypic groups (STs, GTs, and INTs) based on a tertile split of their Block 1 ST/GT scores (entire sample). These analyses are reported for

exploratory and comparative purposes in [Appendix D](#)). Appendix D also presents a linear mixed-effects model assessing trial-by-trial changes in attention allocated to the goal location, included to confirm that participants showed comparable learning of the CS-US contingency.

Additional Exploratory Analyses

In a previous study (Heck, Simon, et al., 2025) using the same PCA task, we observed a significant positive association between AUDIT-C scores and ST/GT scores ($r = .29$), as well as a trend toward significance between ST/GT scores and the positive urgency dimension of impulsivity ($r = .25$). In the present study, replicating these findings is not straightforward due to methodological constraints: the four experimental groups differed not only in terms of beverage content (alcohol vs. placebo), but also in task contingencies (50% vs. 100% reward probability), which are known to impact cue-driven behavior. This experimental heterogeneity limits the interpretability of pooled correlations across the entire sample. However, we conducted exploratory correlation analyses within each subgroup (i.e., 2×2 crossing of beverage and certainty conditions) to provide preliminary insights into whether the relationship between alcohol use severity and ST/GT performance is preserved across task variants. These subgroup-level findings should be interpreted with caution due to limited power and lack of formal hypothesis, as reported in [Appendix D](#) (Table T).

Finally, for completeness and informational purposes, exploratory correlational analyses were conducted separately within the Alcohol and Placebo groups to examine associations between alcohol consumption levels, self-reported subjective effects of intoxication, and measured breath alcohol concentration (in the Alcohol Group). The results of these analyses are presented in [Appendix D](#) (Tables U-V).

Results

Manipulation Check

To confirm that the placebo beverage was effective in eliciting subjective effects, we first assessed whether DEQ subscale scores in the Placebo group were significantly greater than zero. All DEQ subscales showed significant deviations from zero in the expected direction, indicating that participants in the Placebo group did report subjective

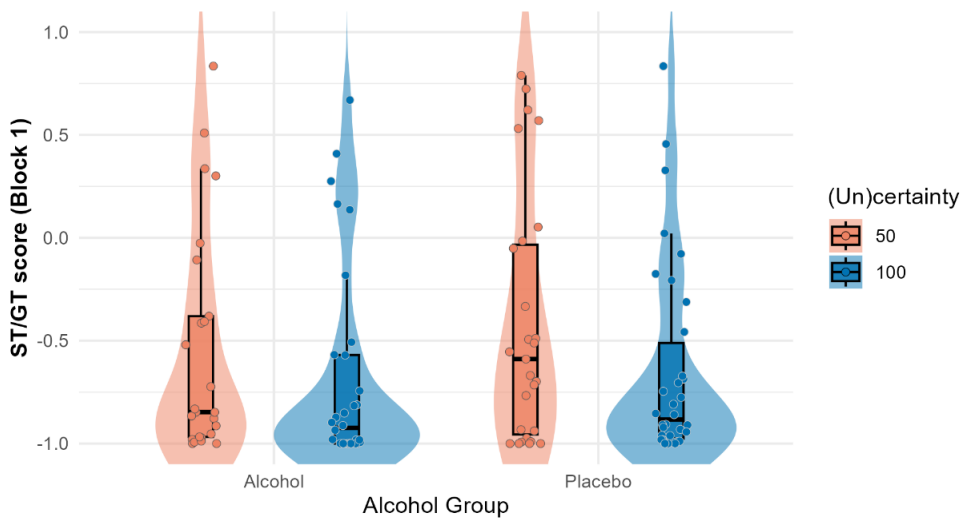
effects despite the absence of alcohol: *"Feel"* ($W = 1128, p < .001, r = .76$), *"High"* ($W = 703, p < .001, r = .68$), *"Like"* ($W = 1891, p < .001, r = .87$), and *"More"* ($W = 1275, p < .001, r = .79$).

To evaluate whether the experimental manipulations produced the expected differences between groups, a series of Mann-Whitney U tests were conducted on the DEQ subscales. As predicted, the Alcohol group reported significantly higher ratings than the Placebo group on the *"Feel"* ($W = 2793, p < .001, r = .52$; Alcohol: $M = 58.93, SD = 28.94$; Placebo: $M = 26.80, SD = 26.20$) and *"High"* ($W = 2679, p < .001, r = .47$; Alcohol: $M = 44.47, SD = 30.39$; Placebo: $M = 15.33, SD = 21.04$) subscales. In contrast, no significant group differences were found for the *"Like"* ($W = 1681, p = .76, r = .03$; Alcohol: $M = 55.09, SD = 21.75$; Placebo: $M = 56.39, SD = 12.64$) or *"More"* subscales ($W = 1448, p = .15, r = .13$; Alcohol: $M = 38.49, SD = 28.98$; Placebo: $M = 47.53, SD = 33.72$), suggesting that these aspects of the subjective responses were not reliably influenced by the presence of alcohol. Violin and box plots with individual data points are available in [Appendix D](#) (Figure K) for each subscale.

Is Sign-tracking Tendency Affected by Alcohol Intoxication and Reward Probability?

Block 1

A two-way ANOVA was conducted to examine the effects of Group (Alcohol vs. Placebo) and Reward Probability (50% vs. 100%) on the ST/GT scores. The analysis revealed a statistically significant main effect of Probability ($F_{(1, 114)} = 4.53, p = 0.03$, partial $\eta^2 = 0.04$), indicating that reward uncertainty significantly influenced participants' sign-tracking responses, in the sense that ST/GT scores were higher in the 50% group. However, the main effect of Group was not statistically significant ($F_{(1, 114)} = 1.61, p = 0.20$, partial $\eta^2 = .01$) suggesting no overall difference between the Alcohol and Placebo conditions. The Group $\times$ Probability interaction was also not statistically significant ($F_{(1, 114)} = 0.34, p = 0.56$, partial $\eta^2 = 0.003$), indicating that the effect of probability did not differ as a function of group. Figure 23 shows the distribution of the ST/GT score across experimental conditions.

Figure 23. *Distribution of ST/GT Scores by Group and (Un)Certainty Level*

Note. Horizontal lines are the medians of the ST/GT scores during the first block of the PCA task. The lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Block 2

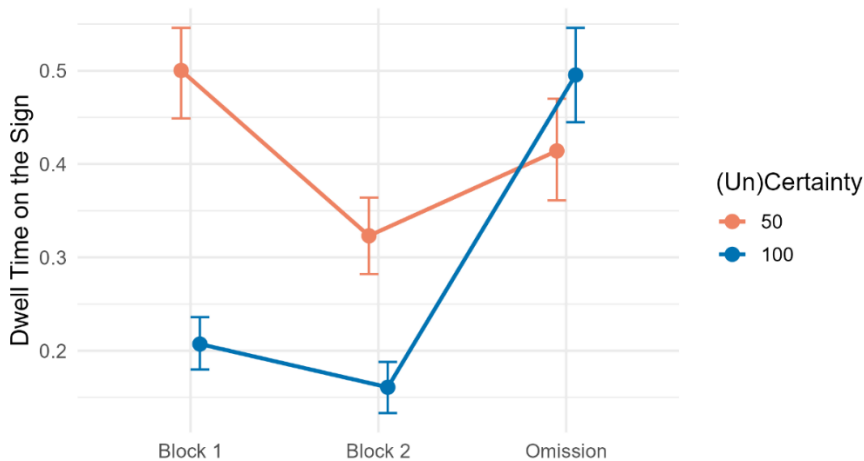
A two-way ANOVA was also conducted to examine the same effects in the second block of the task. The analysis did not reveal any statistically significant main effect: nor for Probability ($F_{(1, 114)} = 1.80$, $p = 0.18$, partial $\eta^2 = 0.02$), neither for Group ($F_{(1, 114)} = 0.74$, $p = 0.39$, partial $\eta^2 = .006$). The Group $\times$ Probability interaction was also not statistically significant ($F_{(1, 114)} = 0.02$, $p = 0.88$, partial $\eta^2 < 0.001$).

To further examine what happened during the first block, specifically regarding participants' attention toward the Sign, we conducted the same analysis using Dwell Time on the Sign only. This analysis is available in [Appendix D](#) (Figure L).

Do Alcohol Intoxication and Reward Uncertainty Increase Resistance to Reward Omission?

For **sign-directed attention**, the mixed effects model (fit by REML) revealed a significant interaction between Block and Certainty on fixation duration. Specifically, the effect of Omission differed depending on certainty level, as indicated by a significant

Omission $\times$ Certainty (100%) interaction (Estimate = 0.38, SE = 0.13, $t(109) = 2.81$, $p = 0.005$). No significant main effect of Omission was observed ($p = 0.110$), nor were the main effects of group ($p = 0.136$) or certainty ($p = 0.164$) significant. The main effect of Block 2 (compared to 1) was however significant ($p=0.007$). Similarly, the interaction between Omission and group ($p = 0.291$), as well as the three-way interaction among Omission, group, and certainty ($p = 0.994$), were not significant. Post-hoc pairwise comparisons (adjusted using Tukey's method) of estimated marginal means revealed that the effect of Block on sign Dwell Time varied across certainty levels. For participants in both 50% certainty groups, the difference between acquisition (Block 1) and reward omission was not significant (estimate = -0.08, SE = 0.07, $z = -1.28$, $p = 0.407$), nor was the difference between Block 2 and omission. However, between block 1 and 2 there was a statistically significant difference with the second block being below the first (estimate = 0.17, SE = 0.05, $z = 3.26$, $p = 0.003$). In contrast, for participants with 100% certainty, Dwell Time to the sign significantly increased during reward omission in both groups when compared to the first acquisition Block (estimate = 0.29, SE = 0.06, $z = 4.58$, $p < 0.001$). The difference between Block 2 and Omission was also statistically significant in these groups (estimate = 0.33, SE = 0.05, $z = 6.19$, $p < 0.001$). Figure 24 shows means and bootstrapped confidence intervals of Sign Dwell Time in Blocks 1 and 2 and "Omission", without considering the alcohol group variable (non-significant) for clarity. For completeness, the complete figure, including also alcohol group is available in [Appendix D](#) (Figures M-N).

Figure 24. *Sign-Directed Dwell Time Across Blocks and Omission by (Un)Certainty*

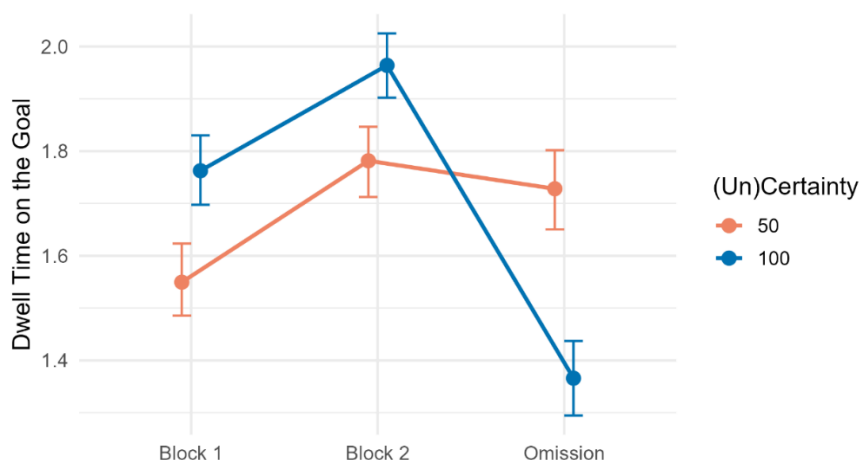
Note. Points represent the means, and vertical error bars indicate the 95% bootstrap-based confidence intervals. Alcohol Group was not included here for clarity in data display, see [Appendix D](#) for the comprehensive Figure.

For **goal-directed attention**, the mixed effects model (fit by REML) revealed a significant interaction between Block and Certainty on Goal fixation duration. Specifically, the effect of Omission differed again depending on certainty level, as indicated by a significant Omission $\times$ Certainty (100%) interaction (Estimate = -0.64, SE = 0.20, $t(109) = -3.29$, $p = 0.001$). No significant main effect of Omission was observed ($p = 0.07$), nor were the main effects of group ($p = 0.73$) or certainty ($p = 0.44$) significant. Similarly, the interactions between Omission and group ($p = 0.42$) and between group and certainty ($p = 0.86$), as well as the three-way interaction among Omission, group, and certainty ($p = 0.60$), were not significant.

Post-hoc pairwise comparisons (corrected using Tukey's method) of estimated marginal means revealed that the effect of Omission on goal Dwell Time varied across certainty levels. For participants in the 50% certainty groups, the difference between acquisition (Block 1) and Omission was not significant (estimate = 0.18, SE = 0.10, $z = 1.78$, $p = 0.175$). The differences between Block 1 and 2 was statistically significant (alcohol and placebo groups pooled, estimate = 0.23, SE = 0.08, $z = 2.84$, $p = 0.012$) while between block 2 and Omission it was not (estimate = 0.05, SE = 0.09, $z = 0.58$, $p = 0.83$). In contrast, for participants with 100% certainty, Dwell Time to the goal significantly

decreased between acquisition (Block 1) and reward omission (both alcohol and placebo groups pooled, estimate = -0.39, SE = 0.09, $z = -4.28$, $p < 0.001$). Both groups also displayed statistically significant differences between Block 2 and Omission ($p < 0.001$), as well as between Block 1 and 2 ($p = 0.015$). Figure 25 shows means and bootstrapped confidence intervals of Goal Dwell Time in Blocks 1, 2 and Omission.

Figure 25. *Goal-Directed Dwell Time Across Blocks and Omission by (Un)Certainty*



Note. Points represent the means, and vertical error bars indicate the 95% bootstrap-based confidence intervals. Alcohol Group was not included here for clarity in data display, see [Appendix D](#) for the comprehensive Figure.

Taking Initial ST/GT Tendency as a Covariate

First, the relationship between initial ST/GT scores (Block 1) and dwell time for the sign during reward omission was tested using Spearman's Rho correlation. A positive and statistically significant correlation of almost large size was found ($\rho_s = 0.47$, $p < 0.001$).

Sign and Goal Dwell Time During Omission

A multiple linear regression was conducted to examine the effects of Group (Alcohol vs. Placebo), Probability (50% vs. 100%), initial ST/GT score (Block 1, centered), and their interactions on **Sign-directed dwell time during the omission phase**. The model accounted for a significant portion of variance ($R^2 = 0.31$, $adj. R^2 = 0.27$, $F_{(7, 105)} = 6.86$, $p < 0.001$).

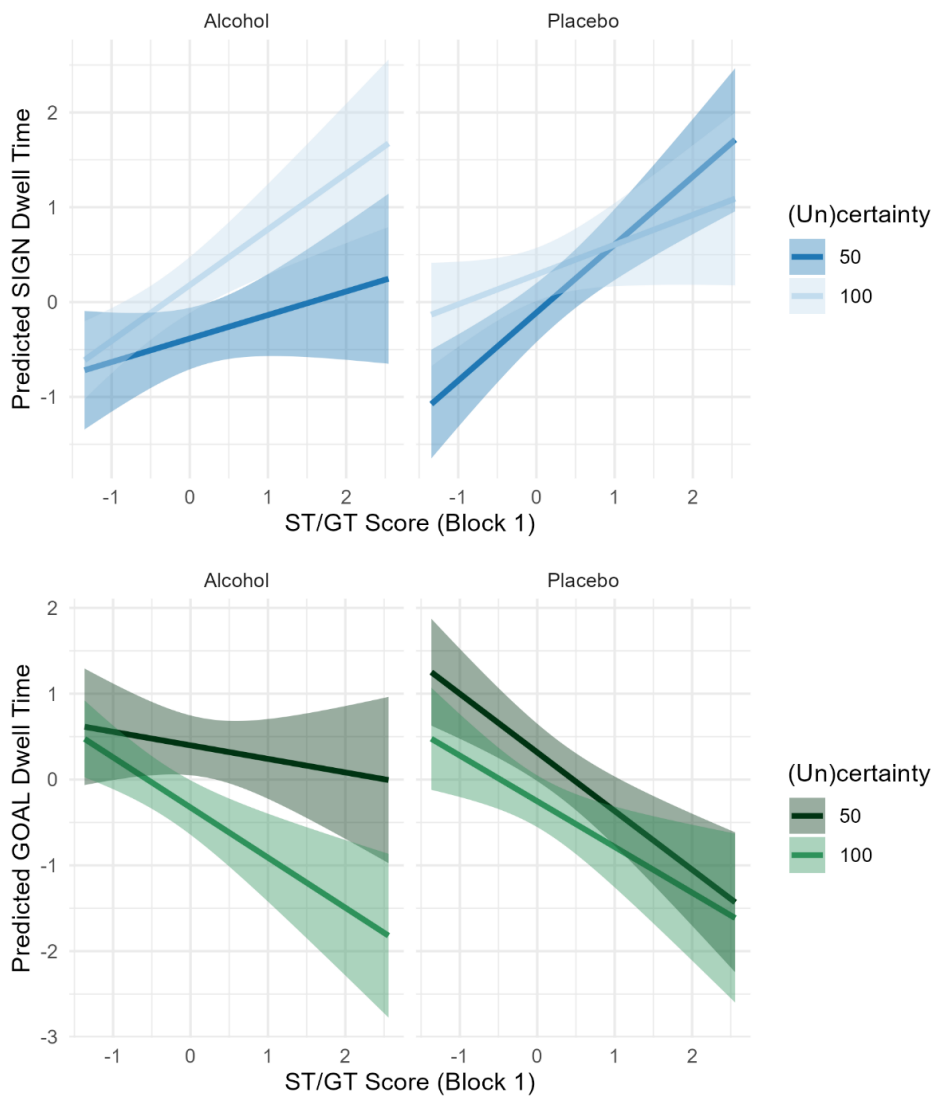
There was a statistically significant interaction between Group and ST/GT score ($b = 11.00$, $SE = 3.55$, $p = 0.002$, partial $\eta^2 = 0.03$), suggesting that higher ST/GT scores predicted longer Dwell Times in the Placebo group, but not in the Alcohol group. Additionally, the three-way interaction between Group, Probability, and ST/GT score was also significant ($b = -13.21$, $SE = 5.15$, $p = 0.012$, partial $\eta^2 = 0.06$), suggesting modulation of the effect by probability. Specifically, the positive association between the ST/GT score and Dwell Time for the Sign cue in the Placebo group was stronger when certainty was minimal (50%), while it was stronger in the Alcohol group when certainty was maximal (100%). Figure 26 (upper panel) illustrates the predicted Sign-directed Dwell Times based on the fitted model, allowing visualization of the interaction between Group, Probability, and ST/GT scores. No significant main effects were observed for Group ($p = 0.116$, partial $\eta^2 = 0.05$) and ST/GT score ($p = 0.478$, partial $\eta^2 = 0.22$), with a non-significant trend for Probability ($p = 0.056$, partial $\eta^2 = 0.008$), when controlling for the other factors. There were also no significant two-way interactions found between Group and Probability ($p = 0.484$, partial $\eta^2 = 0.01$) or between Probability and ST/GT score ($p = 0.239$, partial $\eta^2 = 0.009$). These results suggest that the relationship between initial sign-tracking behavior and Dwell Time to the Sign (during reward omission) is context-dependent, emerging primarily under conditions of uncertainty, in the absence of alcohol.

The same analysis was conducted to examine the effects of Group (Alcohol vs. Placebo), Probability (50% vs. 100%), ST/GT score (Block 1, centered), and their interactions on **Goal-directed dwell time during the omission phase**. The model accounted for a significant portion of variance ($R^2 = 0.29$, $adj. R^2 = 0.25$; $F_{(7, 105)} = 6.23$, $p < 0.001$).

A significant main effect of Probability emerged, with higher predicted Goal-directed Dwell Times in the 50% condition compared to the 100% condition ($p = 0.011$, partial $\eta^2 = 0.07$; Condition 50% (Uncertainty): $M = 30.28$, $SD = 14.71$, Min-Max= 4.20-52.15; Condition 100% (Certainty): $M = 19.98$, $SD = 11.11$, Min-Max= 1.65-43.08). Additionally, the interaction between Group and ST/GT score was statistically significant ($p = 0.026$, partial $\eta^2 = 0.03$), suggesting that the relationship between initial ST/GT score and Goal Dwell Time varied between Alcohol and Placebo conditions. Figure 26 (bottom panel) illustrates predicted Goal Dwell Times during the reward omission block as a function of initial ST/GT scores (Block 1), Group (Alcohol vs. Placebo), and Probability

(50% vs. 100%), based on the fitted linear model. Specifically, in the Placebo group, higher sign-tracking scores were associated with decreased Goal-oriented dwell time, while this relationship was weaker in the Alcohol group. No other main effects or interactions reached statistical significance (all p s < 0.18).

Figure 26. Predicted Dwell Times for Sign and Goal by Group, Probability, and ST/GT Scores during Reward Omission



Note. The upper panel shows dwell times toward the Sign during reward omission, while the bottom panel shows dwell times towards the Goal during reward omission. Both dwell time scores were Inverse Normal Transformed (Blom's Method). Shaded areas represent 95% Confidence Intervals. Lines are split by Probability and panels by Group (Alcohol vs. Placebo).

Discussion

The present study aimed to extend the translational validity of the ST/GT model in humans by examining the impact of two modulators of reward processing—reward uncertainty and acute alcohol administration—on cue-driven behavior. Building on prior animal and human research suggesting that both factors can amplify impulsive responding and enhance attention to reward-predictive cues (e.g., Anselme et al., 2013; Duckworth, 2017), we hypothesized that each of them would increase sign-tracking behavior as measured in a PCA task. Moreover, given that sign-tracking is known to increase resistance to extinction (Ahrens et al., 2016), we expected these effects to persist during a non-rewarded phase.

Consistent with our first hypothesis, we found that reward uncertainty significantly increased the ST/GT score (Block 1), supporting the notion that uncertainty enhances motivation and attention towards reward-predictive cues. This effect was even stronger when examining raw Sign-oriented dwell times, with a medium effect size (partial $\eta^2 = 0.07$).

The motivating effect of uncertainty can be conceptually understood through several complementary explanatory frameworks. From a learning theory perspective, unpredictable rewards generate larger prediction errors (i.e., discrepancies between expected and actual outcomes) which enhance the associability of predictive cues and increase attentional exploration to optimize learning (J. M. Pearce & Hall, 1980). From cognitive and evolutionary viewpoints, exposure to reward uncertainty promotes sign-tracking because the lack of cognitive or predictive control over outcomes encourages organisms to attend to any stimulus that might signal the possibility of reward. This strategy may represent an adaptive mechanism to increase survival in environments where food resources are scarce and unpredictable (Anselme et al., 2013; Anselme and Güntürkün, 2018). Contrary to a consistent cue-reward association, an inconsistent one is not attractive (low incentive salience), but it is assumed to increase effort mobilization to seek—rather than approach—potential rewards in challenging contexts (Anselme, 2025).

Surprisingly, results from the second block of the PCA task suggested that the stimulating effect of uncertainty on ST/GT tendencies was significant during the first block only. A two-block analysis has already been carried out in the study of human sign-

tracking (Dinu et al., 2024; Garofalo & di Pellegrino, 2015), however, it is quite common to consider only the second block of conditioning trials for the learning to be in place and stable (Colaizzi et al., 2023; Garofalo & di Pellegrino, 2015). However, a similar pattern of transient modulation has been reported by Cho and Cho (2021), who found that uncertainty effects on cue-directed attention in the UMAC task also diminished after the initial block. A plausible explanation for this pattern is that participants' knowledge of what happens during the task is substantially different from Block 1 to Block 2. By the start of Block 2, they had already experienced the CS-US contingency once and may have learned that the US followed the CS approximately 50% of the time. This prior exposure likely reduced the novelty and unpredictability of the contingency, meaning that the sense of uncertainty was less salient in Block 2 than during the initial learning phase in Block 1. At least in humans, this suggests that uncertainty may exert a short-lived but potent influence on initial cue engagement, possibly through heightened orienting responses that taper as the task progresses and participants adapt to contingencies. These findings were not anticipated in the original design and hypotheses, and focusing on Block 1 departs from typical practice in human ST/GT research. Therefore, caution is warranted. Replications are clearly needed to support our interpretation.

Contrary to our expectations, alcohol administration did not increase ST/GT scores, suggesting that a moderate dose (0.5 g/kg) was perhaps not sufficient to modulate sign-tracking tendencies in our task or that its effects were more subtle or indirect. This finding contrasts with earlier rodent studies—for instance, Tomie, Cunha, and colleagues (1998) reported a significant increase in sign-tracking behavior in rats following ethanol administration. As outlined in the introduction, impulsivity and AB (both traits often linked to sign-tracking tendencies) are frequently shown in the literature to increase following alcohol administration, which further reinforced our expectation that alcohol would enhance sign-tracking. However, other studies have yielded opposite results. Versaggi et al. (2016) for instance, observed that ethanol administration reduced sign-tracking and increased goal-tracking behavior across several days, concluding that ethanol decreased the incentive salience attributed to the CS. Similarly, Fiorenza et al. (2018) found that while chronic intermittent ethanol (CIE) exposure and Pavlovian conditioning with alcohol rewards enhanced dopamine release, this effect was not accompanied by greater sign-tracking; instead, CIE shifted behavior from sign-tracking

toward goal-tracking. These inconsistencies highlight the complexity of alcohol's influence on cue-motivated behavior. Notably, the present study used a single acute ethanol dose, which may partly explain the divergent findings. From an attentional perspective based on Alcohol Myopia Theory, it has also been suggested that due to attentional capacity reduction, acute alcohol could decrease cue-related attention, which has been shown experimentally in a VMAC study (Watson, Pearson & Le Pelley, 2020). It is worth noting that the present study is among the very few to examine alcohol's influence on sign-tracking behavior in humans. Our findings suggest that the relationship between alcohol and sign-tracking may be more complex and context-dependent than previously assumed. Dose-dependent effects may also be a key factor: an experiment from Duckworth's thesis (2017) found that sign-tracking was increased following a low dose of alcohol (0.3 g/kg) but remained unaffected at a higher dose (0.6 g/kg), indicating that alcohol's influence on sign- versus goal-tracking may vary non-linearly with dosage. Our intermediate dosage (0.5g/kg) was possibly too elevated for optimal effects.

Regarding our second, exploratory hypothesis on reward omission, we observed a pattern that diverged from our initial predictions. Specifically, a significant interaction between Omission block and certainty revealed that sign-directed attention *increased* during extinction in the 100% (certainty) conditions (both Alcohol and Placebo). Rather than the anticipated attenuation of cue-directed attention under non-reinforcement in this group, reward omission was associated with a paradoxical increase in attention toward the sign when prior reward contingencies were fully predictable (Figure 24). Additionally, a significant reduction in goal dwell time was observed across all high-certainty (100%) conditions (Figure 25), which is consistent with a straightforward extinction-like decline in attention to the goal location once reward delivery ceased.

One plausible explanation for this unexpected pattern of results is related to the limited number of omission trials included in the present study ($n = 15$). In animal conditioning preparations, early extinction is often characterized by an initial transient increase in the vigor of conditioned responding (referred to as an *extinction burst*, Shahan, 2022) before a gradual decline occurs. Because the extinction phase in our study was intentionally brief to preserve participant engagement and avoid excessive task duration, it is possible that the increase in sign-directed attention we observed reflects this early, transient burst rather than a genuine failure of extinction learning. Similar

increases in responding have also been linked to greater behavioral variability during early extinction (Donoso et al., 2021).

From the perspective of reward prediction error (RPE) frameworks, early extinction represents a moment of unexpected ambiguity: the organism's prediction is violated, and this mismatch can redirect attention toward the broader environment, promoting exploratory behaviors that help reduce uncertainty (Beesley et al., 2015; J. Gottlieb et al., 2013; Rosas et al., 2006). A familiar example is a dog repeatedly retrieving a thrown object—attention remains tightly focused on the throw. However, when the owner pretends to throw the object and withholds it, the dog rapidly shifts to scanning and sniffing the surroundings. This attentional reorientation occurs precisely because the previously reliable cue no longer predicts its expected outcome. In the context of the present study, participants in the 100% group had experienced fully predictable CS-US pairings during acquisition. For them, the transition to omission introduced a novel source of ambiguity: the CS no longer guaranteed reward delivery. This shift may have encouraged exploratory behavior, such as increased attention to the alternative stimulus on the screen and shifting attention away from the goal, as participants attempted to update their beliefs about the task structure. In other words, participants may simply react to the unexpected change in the task by *"trying to figure out what is going on"*. By contrast, participants who had already encountered uncertain cue-reward contingencies during acquisition may have been less affected by this change, as ambiguity was already a familiar feature of their learning environment.

To further explore the factors contributing to reward omission-phase behavior, we conducted two multiple linear regression analyses: one predicting sign-oriented dwell time, and the other goal-oriented dwell time, during reward omission. In each model, we included initial ST/GT scores, reward uncertainty, alcohol administration, and their interactions as predictors. The results indicate that in the placebo groups (regardless of probability during the PCA task), individuals having higher initial ST/GT scores (indicative of sign-tracking behavior), were more focused on the Sign cue during the non-rewarded omission phase. This result is consistent with the literature on sign-tracking during traditional extinction (Ahrens et al., 2016). Additionally, the three-way interaction, indicated that participants most likely to persist in sign-oriented attention during reward omission were those who had not consumed alcohol and who exhibited higher initial

ST/GT scores. Interestingly, participants who had consumed alcohol also demonstrated greater persistence in sign-oriented attention when they combined strong sign-tracking tendencies with prior reward certainty (100%), highlighting a more conditional role of alcohol effects (Figure 26).

In the model predicting goal-oriented dwell time during reward omission, we observed a significant main effect of uncertainty (medium effect size), with participants in the 50% condition exhibiting greater goal-directed attention than those in the 100% condition, regardless of alcohol administration. Additionally, a significant interaction between alcohol administration and the ST/GT score (small effect size), revealed that the negative association between ST/GT score and goal-oriented attention was stronger in the placebo group than in the alcohol group (Figure 26, bottom panel). In other words, in the absence of alcohol, baseline ST/GT tendencies more strongly predicted resistance to disengaging from the goal location during reward omission: individuals with more goal-tracking-like behaviors (i.e., lower ST/GT scores during initial PCA task) were more likely to maintain attention to the reward location despite non-reinforcement. This pattern contrasts with findings from the animal literature, where goal-trackers typically show rapid reductions in goal-directed behavior during Pavlovian extinction (Ahrens et al., 2016). One possible explanation is that alcohol introduced additional variability or noise in attentional deployment, thereby attenuating the relationship between baseline tracking tendencies and extinction behavior.

It is noteworthy that we observed a significant positive correlation between initial sign- and goal-tracking tendencies and sign-oriented attentional behavior during reward omission ($\rho = 0.47$, $p < .001$). The regression analyses further indicated that this association was more pronounced in placebo conditions, whereas alcohol appeared to blunt the relationship between baseline ST vs GT-like behavior and reward omission-phase attention.

Regarding the exploratory findings of this study, several observations merit attention. First, although not statistically significant, we observed a positive correlation between the ST/GT score and alcohol consumption variables ([Appendix D](#), Table T) in the 100% placebo group—the condition that resembles the most the conditions tested in other works. Notably, the magnitude of these correlations was similar to those reported in our earlier study using the same task (Heck, Simon, et al., 2025). In contrast, results

concerning impulsivity dimensions were less consistent. Statistically significant positive correlations between ST/GT scores and impulsivity traits emerged only in groups that received alcohol. However, all of these correlations should be interpreted with caution due to the limited statistical power inherent in performing correlational analyses at the group level.

Although not directly related to the primary objectives of the present study, a noteworthy secondary finding emerged. In the alcohol group (but not the placebo group), AUDIT scores were significantly negatively correlated with subjective ratings of alcohol intoxication, as measured by the DEQ *"feel"* and *"high"* dimensions (see [Appendix D](#)), and positively correlated with the *"more"* dimension. This exact pattern was previously observed (Morean et al., 2013) during validation of the DEQ. Morean and collaborators proposed it may reflect tolerance (i.e., a reduced subjective response to alcohol associated with heavier use). This finding aligns with broader evidence suggesting that heavy drinkers exhibit blunted subjective responses to alcohol, consistent with a low-response phenotype (Schuckit et al., 2011). Furthermore, BrAC levels measured at the end of the experiment were positively correlated with DEQ *"feel"* and *"high"* ratings, with medium to large effect sizes, supporting the construct validity of these DEQ subscales as reliable subjective indices of alcohol intoxication.

Limitations and Perspectives

The main strength of this study lies in its contribution to the growing body of evidence demonstrating the stimulating effect of uncertainty on approach behavior toward reward-predictive stimuli. As outlined in the introduction, converging results in humans are beginning to mirror findings from decades of research in animal models (see Anselme et al., 2013; Crawford et al., 1985; Glueck et al., 2018; J. M. Pearce et al., 1985), reinforcing the translational relevance of this phenomenon.

In contrast, the effects of alcohol on sign-tracking tendency in this study were less conclusive. Future research should examine the impact of varying alcohol doses within this PCA paradigm, as dose-dependent effects have been observed both in humans (Duckworth, 2017) and animals (Tomie, Aguado, et al., 1998; Tomie, Cunha, et al. 1998) for sign-tracking behavior.

An important aspect to emphasize is that human PCA tasks inherently differ from rodent models in terms of the spatial and attentional demands of sign- and goal-tracking behavior. Because the CS and reward location were spatially proximate in our setup, and shifting gaze between them was uncostly, human participants may have adopted a more fluid strategy (moving their eyes up and down regularly) or an overlapping strategy (maintaining gaze in the middle of the screen). This may sharply contrast with rodent paradigms, where the physical separation of the lever CS and reward magazine imposes clear behavioral choices and hence exclusive approach patterns. Moreover, whereas human sign-tracking scores are typically derived from a relatively small number of CS-US pairings (e.g., two blocks of 20 trials), sign- and goal-tracking behaviors in animal studies are often established across multiple sessions, usually containing 30+ trials per training day. Additionally, our design did not allow for direct comparisons between individuals formally classified as STs versus GTs, since we did not assess baseline ST/GT behavior prior to experimental manipulation, which may have contributed to variability in the results. Thus, future research should address this limitation by conducting within-subject (repeated measures) designs with an initial task using more conventional parameters (e.g., CS-US contingencies around 80%, 30 trials) to enable a clearer phenotypic classification before examining how uncertainty and alcohol interact with these individual differences. Incorporating a reinstatement phase following extinction would also be valuable, as it could reveal whether sign- versus goal-tracking-prone individuals differ in reacquiring Pavlovian attentional responses to both sign and goal cues, and whether reinstatement is modulated by reward probability or alcohol administration.

As already mentioned, current knowledge of the factors that modulate human sign- and goal-tracking remains limited. Consequently, we cannot yet assert with confidence that simplified, computerized adaptations of PCA tasks fully capture the same underlying processes as observed in animal models. For example, our task does not allow us to conclude with certainty that incentive salience has been attributed to the CS, because our procedure did not include a control cue (not associated with reward delivery). Nevertheless, recent theoretical and empirical work has begun to establish explicit links between incentive salience attribution and human sign-tracking. In particular, VMAC paradigms suggest that reward-associated cues acquire motivational significance, increasing their attentional salience and influencing behavior accordingly (Le Pelley et al.,

2024). Complementing this, fMRI-based evidence from PIT tasks indicates differential incentive salience attribution in human sign- versus goal-trackers (Schad et al., 2020). Importantly, this remains the only study to date that has addressed the question directly, underscoring the need for further research. Future work should clarify the role of incentive salience attribution in human sign- and goal-tracking and develop robust, standardized methods for assessing it in tasks such as computerized PCA.

Additional limitations may also account for the inconclusive effects of alcohol, including individual differences in response to intoxication. Although we attempted to standardize intoxication levels across participants by adjusting doses according to body weight and requiring participants to fast for five hours before testing, there was still considerable variability in subjective and observable intoxication. Some participants exhibited only mild signs of intoxication, while others showed more pronounced effects. This variability is, however, common in alcohol research and is likely attributable to individual differences in alcohol metabolism (Gentry 2000). A possible improvement would be to calculate alcohol dosage based on body mass index rather than body weight alone, as this may better account for individual differences in alcohol distribution volume (Jones 2007).

Beyond its main hypotheses, the study also yielded theoretically important secondary findings concerning placebo effects in single-blind alcohol administration paradigms and subjective intoxication ratings. Specifically, while the experimental groups differed significantly in their ratings of *"feeling high"* and *"feeling alcohol effects"*, they did not differ in ratings of *"liking the effects"* or *"wanting more"*. Notably, participants in the placebo group scored significantly above zero on all subscales, indicating that even without consuming actual alcohol, the experience of drinking a non-alcoholic beverage presented as rum elicited appreciable subjective effects. These participants reported liking and wanting these effects to the same extent as those who consumed real alcohol. From an applied perspective, these findings support the idea that non-alcoholic beverages (or *"mocktails"*) may hold promise in reducing alcohol consumption while still providing positive experiential outcomes, with potential implications for harm-reduction strategies and the development of appealing alcohol-free alternatives. However, from an experimental perspective, the strength of the placebo effect observed in the mocktail condition may plausibly contribute to the absence of a detectable alcohol effect in the

present study. Specifically, the placebo group may have exhibited an alcohol-like conditioned response, thereby diminishing observable differences between conditions. However, our hypotheses pertained to the pharmacological effects of alcohol rather than expectancy-based mechanisms. Future research should address this limitation by explicitly separating these components—for example, by including a control group that knowingly consumes a non-alcoholic beverage—to better isolate pharmacological effects from expectancy and conditioning influences.

In summary, while the study has some methodological limitations, it provides valuable experimental insights into human ST/GT behavior and highlights, most notably, the role of uncertainty in modulating responses to reward-predictive cues. Still, given the novelty of this experimental investigation, caution is warranted, and further research is essential before drawing firm conclusions or generalizing beyond the present context.

Conclusion

This study provides novel insights into how environmental factors (such as reward uncertainty) and pharmacological influences (such as alcohol intoxication) shape reward cue-reactivity. These findings mark a step forward in the translational implementation of sign- and goal-tracking behaviors, a field that has long been established in animal research but remains in its early stages with respect to humans. By advancing our understanding of the mechanisms underlying these behaviors, this work contributes to the broader effort to uncover both individual and environmental vulnerability factors relevant to addiction and other cue-driven psychopathologies. In particular, it highlights how uncertainty can intensify attentional focus on reward-predictive cues—a process that, while adaptive in some contexts, may become maladaptive by promoting compulsive approach behavior and increasing susceptibility to addiction.

Declarations

Data Availability and Transparency

The experimental data are available at: <https://osf.io/9zfkb/overview>. The code for the experimental task is available upon request from the authors. This study's design and its analysis were not pre-registered. Data analysis code is not available.

Use of IA

AI (ChatGPT, OpenAI, 2024) was used exclusively to enhance the readability and stylistic clarity of the manuscript. No AI tools were employed in the generation of scientific ideas, data analyses, or interpretations. The authors take full responsibility for the content and accuracy of the information presented in this article.

The reference list of this article has been incorporated into the [general bibliography of this thesis](#).

Part III

Syntheses, Perspectives &
Conclusions

Chapter 8

Motivation, Attention, and Uncertainty

Insights from Animal and Human Research & Implications for Addiction

Michelle Heck

Etienne Quertemont

Patrick Anselme

The content of this chapter is based on the following [published paper](#):



Publication

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Abstract

Motivational and attentional processes jointly determine how environmental cues influence behavior. Reward-predictive cues can acquire incentive salience, automatically capturing attention and eliciting approach responses even in the absence of deliberate intention, a phenomenon central to both adaptive behavior and certain forms of psychopathology.

This review integrates animal and human evidence to examine how cue-triggered motivation and attention interact, and how these interactions are shaped by reward uncertainty, a dimension that has received limited interest in human research despite its robust effects in animals.

Across species, uncertain or variably reinforced cues reliably intensify motivated behaviors. In animals, they enhance sign-tracking and promote persistent cue-directed responding, while in humans, paradigms such as Uncertainty-Modulated Attentional Capture (UMAC) show that uncertain cues exert a greater pull on attention, even when this impairs performance. We argue that these effects reflect an evolutionarily conserved mechanism that biases organisms toward exploration and information-seeking under unpredictable conditions. However, the same mechanisms can become maladaptive in modern environments, such as gambling or drug use, where artificially amplified reward signals can mimic or exaggerate the motivational impact of uncertainty, leading to compulsive cue attraction.

By bridging motivational and attentional perspectives across animal and human research, this review offers a unified framework for understanding how reward cues gain motivational significance, how uncertainty modulates these processes, and why they may contribute to vulnerability in addiction-related behaviors.

Keywords: Incentive salience, Reward, Uncertainty, Attentional Capture, Motivation, Addiction

Introduction

Environmental cues exert a powerful influence on everyday behavior. In a supermarket, for example, consumers may attend to specific products simply because a red or yellow price tag signals a discount, even before consciously evaluating the actual price. Likewise, the sound of a smartphone notification often elicits an almost automatic urge to check the device, as this auditory cue has become associated with rewarding social or informational content. Our understanding of such cue-driven behaviors originates from Pavlov's classical conditioning experiments (Pavlov, 1927), which demonstrated that a previously neutral stimulus can acquire the status of a CS when repeatedly paired with a reinforcing US, famously illustrated by dogs salivating at the sound of a bell preceding food delivery. Pavlov interpreted this phenomenon as a change in what the dogs learned about the association between the two stimuli. However, subsequent decades of animal research have revealed that conditioning also involves a shift in the organism's motivational state regarding the initially neutral stimulus: the CS not only predicts the timing of US delivery but also becomes imbued with the motivational salience of the US (Berridge & Robinson, 1998; Bindra, 1978; Toates, 1986). This capacity for cue-triggered behavior is highly conserved across the animal kingdom, from unicellular organisms (Carrasco-Pujante et al., 2021) to "higher" vertebrates, including humans.

Under some conditions, cue-triggered responses can become excessively automatic, rigid, and misaligned with an individual's broader goals. These characteristics are particularly evident in addictive behaviors and have been extensively investigated in laboratory animals. In the context of drug addiction, *cue reactivity* plays a pivotal role in both the persistence of addictive behavior and the heightened risk of relapse among abstinent individuals (Everitt et al., 2001; T. E. Robinson & Berridge, 1993; Wiers & Stacy, 2006; Witteman et al., 2015). This incentive process is largely unconscious and cue-driven, as it requires neither deliberate choice nor cognitive inference (T. E. Robinson & Berridge, 2025). The capacity of reward-associated cues to capture attention and enhance incentive salience is not limited to drugs of abuse. Attentional bias (AB) toward reward-paired cues has been documented across various reward domains, including food (e.g., Deluchi et al.,

2017; Field et al., 2016; Yokum et al., 2011) and sexual stimuli (e.g., Mechelmans et al., 2014; Sklenarik et al., 2020).

Addictive-like effects are also observed in gambling and gambling-like contexts, which involve mere exposure to reward uncertainty, i.e. when predictive cues are followed by a reward or its omission in a random manner. For instance, rats exhibit stronger responses to a CS that inconsistently predicts food compared to a CS that consistently predicts food (Anselme et al., 2013; Glueck et al., 2018; M. J. F. Robinson et al., 2023), an effect documented across other species as well (Crawford et al., 1985; D. A. Gottlieb, 2004). Notably, reward uncertainty seems to induce long-lasting increases in cue responsiveness, persisting even after uncertainty diminishes or disappears (Crawford et al., 1985; M. J. F. Robinson et al., 2014). In humans, casinos exemplify gambling environments saturated with cues, such as flashing lights and celebratory sounds, that are repeatedly presented both prior to and during reward delivery (Griffiths, 1993; Noseworthy & Finlay, 2009; Parke & Griffiths, 2006). Over time, these cues can acquire excessive attractiveness and motivate individuals to continue gambling (Barrus & Winstanley, 2016; Brevers et al., 2014; Dixon et al., 2014).

This review proposes an integrative view of how motivation, attention, and uncertainty interact in a context of reward-predictive cues influencing motivated behavior in human and nonhuman animals. We examine how incentive motivation and attentional priority interact to shape cue-driven behavior, with a particular focus on the role of reward uncertainty, a dimension that has surprisingly been poorly investigated in the human literature despite its robust effects in animal research. In this article, we focus specifically on cue-related uncertainty in situations in which uncertainty is expected and stable over time, as is typical in most laboratory conditions. Situations in which uncertainty is unexpected, fluctuates over time (volatility) or is transient (such as during extinction or reversal learning) may involve overlapping processes but will not be discussed here (for details, see Soltani & Izquierdo, 2019). Risk, as a form of uncertainty typically distinguished from ambiguity, is also excluded. In the present review, we are interested in the incentive, often unconscious and automatic, effects that reward uncertainty exerts on behavior, even though uncertainty-sensitive neurons are also found in cortical regions traditionally associated with higher-order cognitive functions, such as the anterior cingulate cortex and the orbitofrontal cortex (e.g. M. P. Karlsson et al., 2012; Monosov, 2020; Romero-Sosa et

al., 2025). The incentive and addictive effects of reward uncertainty are likely to be more directly controlled by subcortical regions such as the ventral tegmental area and nucleus accumbens (Singer et al., 2020). By bringing together findings from animal models and human paradigms, we highlight how uncertainty can amplify the impact of reward-associated cues and fundamentally alter their processing. Table 16 summarizes converging findings from both animal and human studies on the effects of uncertainty, alongside the key theoretical explanations proposed in the literature and discussed throughout this paper. Finally, we consider the functional significance of these uncertainty-driven effects, emphasizing their adaptive role in exploration and information-seeking, as well as their potential to become maladaptive in modern contexts such as gambling and addiction.

Table 16. *Comparative Summary of Uncertainty-Driven Modulation of Cue-Guided Behavior in Rodents and Humans*

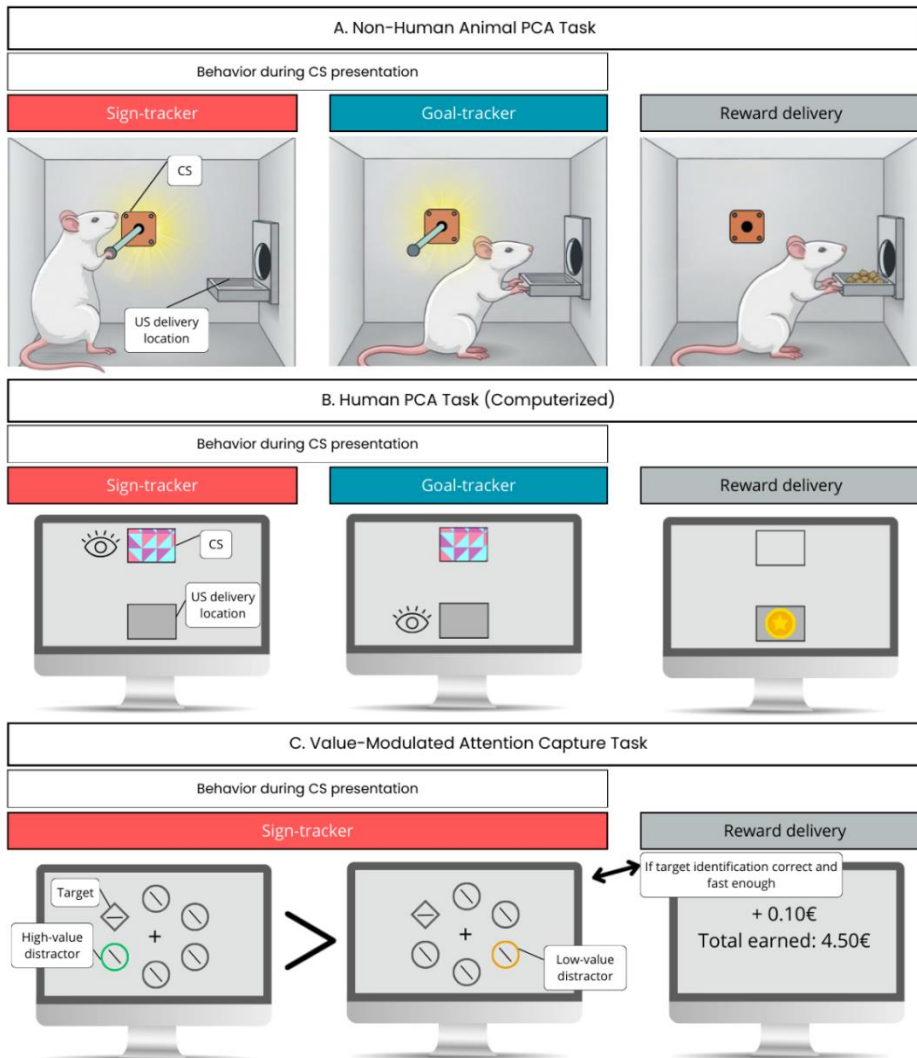
Context	Population	Effect	Proposed Explanations
Pavlovian Conditioned Approach Behavior	Non-Human Animals	↑ Sign- tracking & ↑ DA release in sign- trackers	• Reward uncertainty continuously signals that learning is incomplete, thereby maintaining elevated mesolimbic dopamine levels (Schultz et al., 1993). • Uncertainty-driven behavior mostly results from effort mobilization via the hypothalamo-pituitary-adrenal (HPA) axis and locus coeruleus to increase success rate (Anselme, 2025). • Uncertainty directly contributes to information- and novelty-seeking, meaning the strategy may disambiguate context and reduce uncertainty (Bromberg-Martín & Monosov, 2020; Monosov, 2024).
Early, Prolonged Uncertainty Exposure in Pavlovian Tasks	Non-Human Animals	↑ Sensitization process (related to IST)	• Early exposure to uncertainty might produce lasting behavioral sensitization, with effects resembling drugs of abuse and gambling-like tasks (Mascia et al., 2019; M. J. F. Robinson et al., 2015; Singer et al., 2012; Swintosky et al., 2021; Zack et al., 2014). • Addictive drugs may artificially trigger phasic dopamine surges mimicking motivational amplifications observed under unpredictable reward conditions.
UMAC	Humans	↑ Attentional capture by "high uncertainty" cues	• Cues with high uncertainty attract greater attention because their consequences potentially require increased monitoring (Uncertainty Principle; J. M. Pearce & Hall, 1980). • Parallel suggested between uncertainty-driven attentional capture and exploration (Cho & Cho, 2021; Chow et al., 2025; Ju & Cho, 2023; Le Pelley et al., 2019; Pearson et al., 2024). Uncertainty-related attentional capture may reflect a functional mechanism to update internal models of reward contingencies rather than maladaptive distraction.

Animal Research

From Incentive Motivation to Addiction

Before examining how expected reward uncertainty alters behavior, we first provide a brief overview of incentive motivational processes (present section) and their interaction with attentional mechanisms (next section). Indeed, these two dimensions are consistently highlighted as key determinants of basic reactivity to this form of uncertainty in the animal literature (third sub-section, p. 278). In Pavlov's (1927) seminal experiments on CS-US associations in dogs, the animals were restrained during measurements because Pavlov's primary interest concerned physiological responses, such as salivation and gastric secretion, under tightly controlled conditions. Had the dogs been free to move, Pavlov might have observed some individuals approaching the ringing bell prior to food delivery. Decades later, such cue-triggered approach behavior was termed *sign-tracking* (Hearst & Jenkins, 1974) and is now understood to reflect not only associative learning but also incentive motivation, conceptualized through the notion of incentive salience or "*wanting*" (Berridge & Robinson, 1998). In other words, sign-trackers (STs) do not merely recognize the CS as a predictor of reward; they attribute to it a motivational value that makes the cue attractive and desirable in itself. The experimental paradigm that revealed sign-tracking, and remains widely used, is Pavlovian *autoshaping*. In this procedure, each trial consists of presenting a CS (typically a metal lever for rats) for a few seconds, followed immediately by the delivery of food pellets into a dish. Training sessions include multiple trials separated by inter-trial intervals during which no events occur. Importantly, no instrumental action is required for reward delivery. Apart from STs that approach and interact with (pressing, sniffing, nibbling, biting) the lever CS due to its acquired motivational properties (Flagel et al., 2007; T. E. Robinson & Flagel, 2009), other individuals, called goal-trackers (GTs), instead approach and inspect the food dish during CS presentation, anticipating reward delivery (Boakes, 1977). A third group exhibits an ambivalent profile, alternating between sign- and goal-tracking behaviors. Figure 27 (panel A) illustrates sign- and goal-tracking behaviors in a typical animal PCA task (*autoshaping*).

Figure 27. *Comprehensive Illustration of Sign- and Goal-Tracking Behaviors in Rodent and Human tasks.*



Note. The first panel illustrates characteristic sign- and goal-tracking behavior in a rodent PCA task. During CS presentation, ST animals orient toward the retractable lever and may approach, touch, or gnaw it. In contrast, GT animals orient toward the location of impending reward delivery (the food tray). The second panel illustrates analogous human ST and GT behaviors in a computerized PCA paradigm. While the CS (e.g., a fractal image displayed at the top of the screen) is presented, ST individuals show increased dwell time on the CS itself, whereas GT individuals allocate more gaze time toward the goal location where the reward will subsequently appear (e.g., a coin icon). The third panel illustrates

sign-tracking-like behavior in a VMAC task. Here, ST tendencies manifest as prolonged reaction times when the search display includes a high-value reward-predicting stimulus relative to a low-value CS. Although this task does not provide a direct behavioral analog of goal-tracking, sign-tracking is generally considered a continuum; thus, reduced sign-tracking-like effects may be interpreted as more GT-like behavior.

Interestingly, STs and GTs exhibit distinct neurobiological signatures in response to the CS, particularly regarding mesolimbic dopamine release from the ventral tegmental area to the nucleus accumbens (NAcc). Well-trained STs display a pronounced phasic dopamine surge at CS presentation, which drives approach toward the cue, whereas GTs show little or no dopamine release beyond baseline levels at this time (Flagel, Clark, et al., 2011). This dissociation is especially striking given that both phenotypes acquire the CS-US association with comparable efficiency (P. J. Meyer, Lovic, et al., 2012). These observations, among others, strongly support the incentive salience theory, which posits that dopamine confers motivational attractiveness to reward-predictive cues (e.g., J. J. Day et al., 2006; M. J. F. Robinson & Berridge, 2013; B. T. Saunders & Robinson, 2012). Experimental manipulations of dopamine release further demonstrate its role in “*wanting*”: altering dopamine release changes the propensity to approach a cue without affecting hedonic reactions to the reward (e.g., Flagel, Clark, et al., 2011; Peciña et al., 2003). Similarly, dopamine-deficient (DD) mice fail to attribute incentive salience to food-related stimuli. They do not initiate approach behavior and would starve even when surrounded by palatable food, due to a genetic inability to synthesize dopamine. Daily L-Dopa administration is required to restore feeding behavior (Palmiter, 2008). Remarkably, these deficits are not due to motor impairments: DD mice readily climb cage walls and traverse widely spaced metal grids without difficulty. Moreover, when food intake is assisted, they consume normal amounts and exhibit intact hedonic preferences, favoring sucrose over less palatable options (Cannon & Bseikri, 2004; Cannon & Palmiter, 2003).

An alternative interpretation of dopamine’s role in this context is that it encodes reward prediction error (RPE), a mechanism fundamental to associative learning (Schultz, 1998; Starkweather & Uchida, 2021). Under this account, phasic dopamine responses initially occur at reward (US) delivery and progressively shift to the CS as learning unfolds, such that dopamine responses to the CS reflect the predictive value of the cue (Schultz et

al., 1997; Tobler et al., 2006). Although this shift is robustly observed in STs, it is noticeably absent in GTs, which exhibit sustained dopamine responses to the US across training despite having learned the CS-US contingency (Flagel, Clark, et al., 2011). This pattern challenges a pure RPE-based interpretation, as both phenotypes should exhibit similar dopaminergic dynamics, if dopamine is limited to encode prediction error. Pharmacological and circuit-level manipulations further dissociate predictive learning from incentive salience. For example, systemic or local blockade of dopamine receptors, lesions of the NAcc, or temporally precise optogenetic inhibition of ventral tegmental dopamine neurons during CS presentation selectively disrupt the acquisition of sign-tracking while sparing goal-tracking behavior (J. J. Chow et al., 2016; Flagel, Clark, et al., 2011; Iglesias et al., 2023; B. T. Saunders & Robinson, 2012).

These findings align more closely with the incentive salience theory, according to which dopamine release reflects the attribution of motivational properties to the CS rather than its predictive value (T. E. Robinson & Flagel, 2009). Consistent with this view, an experimentally induced increase in dopamine can instantly transform a strongly aversive CS into an intensely “*wanted*” stimulus without requiring relearning (e.g., M. J. F. Robinson & Berridge, 2013; Tindell et al., 2009). Integrative models were proposed to reconcile incentive salience and RPE accounts, suggesting that dopaminergic RPE signals mediate incentive salience attribution, with individual differences reflecting the dominance of distinct learning systems (Dayan & Berridge, 2014; Flagel, Clark, et al., 2011; Huys et al., 2014; Schad et al., 2020). Within this framework, STs rely predominantly on dopamine-dependent, model-free learning processes, whereas GTs depend more on model-based learning centered on state prediction errors. Consistent with this interpretation, behavioral and computational studies show that sign-tracking is associated with stronger model-free reinforcement learning across both Pavlovian and instrumental domains (Moin Afshar et al., 2023). Furthermore, recent computational modeling suggests that, during the transfer phase of a Pavlovian-to-instrumental transfer (PIT) task, STs exhibit slower updating of Pavlovian cue values rather than an overweighting of Pavlovian values relative to instrumental action values (Degni et al., 2026). Collectively, these behavioral, neurobiological, and computational findings converge on the conclusion that dopamine-dependent model-free learning underlies incentive salience attribution, providing a coherent account of individual differences between STs and GTs.

The attribution of incentive salience to a cue does not require any conscious awareness; this process has been suggested to originate in deep brain structures, largely independent of cortical influences and phenomenal consciousness (Berridge, 2003; Winkielman & Berridge, 2003). Unlike desires, which can be pursued or inhibited based on circumstances due to their goal-directed and cognitive properties, incentive salience may drive the irrational pursuit of cues, even at the expense of physical and mental health. Consistent with this view, animal research has documented the role of incentive salience in addiction. For instance, numerous studies report that STs, that attribute high incentive salience to reward-predictive cues, are more vulnerable to drugs of abuse than GTs (Flagel et al., 2010; B. T. Saunders & Robinson, 2011; Tomie et al., 2008).

STs and GTs differ markedly in their sensitivity to key features of addiction. STs exhibit reduced behavioral flexibility and stronger cue-driven motivation compared to GTs. For example, they persist in approaching the CS even when the associated reward becomes less palatable (reward devaluation; Morrison et al., 2015) or when the reward is no longer delivered (extinction; Ahrens et al., 2016). In contrast, GTs adjust their behavior more readily to changing contingencies (Pellón et al., 2018; Strand et al., 2022). Persistence despite negative outcomes is a hallmark of addictive behavior. Accordingly, STs display a greater propensity to self-administer drugs and to prefer drugs over food rewards compared to GTs (Tunstall & Kearns, 2015; Versaggi et al., 2016). Furthermore, they are more prone to relapse when exposed to cues previously associated with drug consumption (B. T. Saunders et al., 2013; Versaggi et al., 2016; Yager et al., 2015). Beyond these behavioral outcomes, STs differ from GTs in what has been described as a *"constellation of cognitive-motivational characteristics"* that confers heightened vulnerability to continued drug use following initial exposure (Flagel et al., 2021; T. E. Robinson et al., 2018). Specifically, STs tend to be more impulsive (Lovic et al., 2011; Tomie, Aguado, et al., 1998) and to exhibit weaker top-down executive control (Enkel et al., 2019; Koshy Cherian et al., 2017; Paolone et al., 2013), traits that have been systematically associated with substance use and addiction in humans (Lejuez et al., 2010; Verdejo-Garcia & Albein-Urios, 2021). Once drug use becomes established, drugs of abuse exert their addictive potential primarily through the dopaminergic system. They act as powerful activators of mesolimbic dopamine pathways and, with repeated exposure, induce enduring neurochemical changes that sensitize dopamine neurons (T. E. Robinson

& Berridge, 1993, 2025). This process, known as incentive sensitization, represents a pathological overactivation of the “wanting” system. Unlike normal motivational states (e.g., hunger, sex, play), which are transient and regulated by homeostatic mechanisms, drug-induced sensitization is persistent and leads to exaggerated dopamine responses in mesocorticolimbic regions, particularly the NAcc. This enduring change explains why drug-associated cues remain highly motivational and can trigger craving and relapse long after withdrawal symptoms have subsided (Castner & Goldman-Rakic, 1999; Paulson & Robinson, 1995). Taken together, these findings suggest that sign-trackers are uniquely vulnerable to addiction due to their heightened tendency to attribute incentive salience to reward-predictive cues combined with a cognitive-motivational profile characterized by impulsivity and diminished executive control. This vulnerability increases the likelihood of drug initiation, facilitates the maintenance of drug use, and heightens the risk of cue-induced relapse. Moreover, with prolonged drug exposure, incentive sensitization processes further amplify cue reactivity (but importantly, not only in STs but also in GTs see Kawa et al., 2016).

Interaction Between Incentive Motivation and Attention: Dopamine–Acetylcholine Dynamics

Motivation and attention often operate in tandem. Greater motivation for a stimulus typically biases attention toward that stimulus. In Pavlovian *autoshaping*, STs approach the CS while GTs approach the food dish, suggesting that each phenotype allocates more attention to its preferred cue. But does this difference in preference translate into differences in attentional performance? A key neurochemical correlate of attentional performance is cortical acetylcholine, a neurotransmitter known to interact with dopaminergic mechanisms underlying incentive motivation (Sarter et al., 2006; Sarter & Bruno, 1999). Paolone et al. (2013) examined rats performing a sustained attention task and reported fluctuations between periods of good and poor performance, as well as automatic attraction to salient stimuli, in STs compared to GTs (but see Kindedji & Huppé-Gourgues, 2024; Thériault et al., 2025). The poorer performance of STs was attributed to lower extracellular levels of cortical acetylcholine, a finding consistent with evidence for reduced top-down (cortical, cognitive) control over behavior in these individuals relative to GTs (Flagel, Cameron, et al., 2011). Differences in acetylcholine levels emerged during

attentional tasks, although baseline levels were similar across these phenotypes (Sarter & Phillips, 2018). Experimental manipulations further support this interpretation: cholinergic agonists improve STs' performance, whereas antagonists can prevent the development of goal-tracking behavior (Koshy Cherian et al., 2017; Sarter & Phillips, 2018).

In summary, STs exhibit higher mesolimbic dopamine activity and lower cortical acetylcholine activity compared to GTs, indicating that these phenotypes differ neurobiologically in how they process the "meaning" of the CS. When a CS is detected, the weak top-down regulation of dopamine by cortical acetylcholine in STs likely promotes a bias toward stimulus-driven (bottom-up) attention, facilitating progressive CS attraction through incentive salience. For these individuals, the CS becomes a potent incentive stimulus. In contrast, CS detection in GTs increases acetylcholine without altering dopamine levels. This top-down cholinergic control inhibits dopamine neurons, supporting the formation of expectations and the expression of goal-directed behavior. Consequently, the CS functions as an informational signal predicting imminent reward rather than as an attractive object (Flagel, Cameron, et al., 2011; Pitchers, Phillips, et al., 2017). Interestingly, however, the stronger attentional control of GTs in Pavlovian tasks does not fully protect them from drug-related vulnerability. T. E. Robinson et al. (2014) reported that GTs are more sensitive to contextual cues than to localized discrete cues. Similarly, Pitchers, Phillips et al. (2017) found that discriminative stimuli, signaling drug availability without direct association with drug delivery, induce stronger relapse in GTs than in STs (see also Ndiaye et al., 2024). Finally, following intermittent access to cocaine self-administration, behavioral differences between sign- and goal-trackers largely disappear (Kawa et al., 2016).

The Stimulating Effects of Reward Uncertainty

The role of uncertainty in modulating cue-driven behavior is both striking and theoretically puzzling. While the incentive salience theory provides a robust account of how reward-predictive cues become attractive, it does not explicitly address why unpredictability should enhance this effect. Yet, uncertainty often emerges as a powerful modulator of conditioned approach behavior, enhancing the motivational value of cues

far beyond what their predictive value alone would suggest (e.g. Anselme et al., 2013; Glueck et al., 2018; Hellberg et al., 2019; Kaneko et al., 2025).

In most autoshaping studies, animals are trained under conditions of reward certainty, where each CS reliably predicts food delivery. However, when reward delivery becomes uncertain, for example with only half of the trials randomly rewarded, making each CS presentation only 50% predictive, a remarkable shift occurs. Animals exposed to this inconsistent CS-US association typically exhibit stronger and more persistent sign-tracking behavior than those trained with a fully predictive CS. This phenomenon, known as the partial reinforcement acquisition effect, is now well documented across species (e.g., Anselme et al., 2013; Crawford et al., 1985; D. A. Gottlieb, 2004; J. M. Pearce et al., 1985; M. J. F. Robinson et al., 2014).

This behavioral effect is robust, yet its theoretical basis remains poorly understood. It seems to contradict the incentive salience theory, which does not explicitly incorporate reward probability and would rather predict the opposite pattern, i.e. a decrease in sign-tracking when reward likelihood is lower. According to the incentive salience theory, the CS acquires motivational value proportional to the reward, which should diminish under uncertainty (Anselme, 2025; see Zhang et al., 2009, for a mathematical model of incentive salience). One might argue that uncertain rewards are inherently valued more than certain ones (Kahneman, 2011), but such claims extend beyond the original model and require additional mechanisms not specified in its original formulation (Anselme, 2025). Interestingly, GTs exhibit the reverse pattern: their tendency to approach the food dish decreases under uncertainty (D. A. Gottlieb, 2005; Harris & Carpenter, 2011; Navarro et al., 2024). Notably, this reduction in goal-tracking was observed in conditions where animals had limited opportunities to interact with the inconsistent CS, which was presented as a light or tone. When the CS is a lever, both manipulable and retractable, a substantial proportion of individuals shift toward a sign-tracking profile and increase their response rates to the cue under reward uncertainty compared to reward certainty (M. J. F. Robinson et al., 2015). Beyond probabilistic uncertainty, temporal uncertainty can also enhance sign-tracking behaviors. Studies manipulating the inter-trial interval (ITI) show that animals display stronger cue-directed behavior when the ITI varies unpredictably than when it is fixed (Kaneko et al., 2025). Also, a longer ITI introduces unpredictability in the expected timing of both the CS and the US, making it difficult for animals to anticipate

when reward-related events will occur (Gibbon et al., 1980; Lee et al., 2018; Mahmoudi et al., 2023).

In addition to increasing their response rates to the CS, STs exhibit greater dopamine release during uncertainty rather than certainty training (Hart et al., 2015). If dopamine is considered a marker of incentive motivation, this finding presents a conceptual puzzle: why should uncertainty act as an enhanced appetitive signal? Uncertainty reduces the predictive value of the CS, making it less attractive than a certain CS due to a lower transferability of the reward properties to the CS. Consistent with this, when animals are given a choice, they almost never prefer uncertain rewards over certain ones (de Jonge et al., 2008; Eisenreich et al., 2019; Gneezy et al., 2006; Kahneman, 2011). Therefore, uncertainty appears more aversive than appetitive, like a challenge to overcome rather than a reward cue to pursue (Anselme, 2025). This interpretation suggests that the dopaminergic surge observed under uncertainty may not reflect incentive salience. Instead, cue inconsistency could signal a difficulty that mobilizes effort-related systems, such as glucocorticoids via the hypothalamo-pituitary-adrenal (HPA) axis and noradrenaline via the locus coeruleus, two biological systems not directly involved in incentive salience attribution (Lopez et al., 2021; Varazzani et al., 2015). However, moderate glucocorticoid release is known to enhance dopamine activity (Lemos et al., 2012), making the observed dopamine increase partly an indirect effect of stress-related mechanisms. In this view, uncertainty-driven behavior may result from the combined influence of incentive salience and effort mobilization, rather than from cue attractiveness alone.

Taken together, these findings suggest that uncertainty-driven invigoration cannot be attributed to a single mechanism. Short-term effects likely arise from the combined influence of stress-related effort mobilization and heightened dopaminergic activity, whereas longer-term persistence may reflect gradual incentive sensitization. These processes also interact. When cues are unreliable, stress-related systems energize behavior and indirectly enhance dopamine release, such that repeated exposure to uncertainty progressively sensitizes dopaminergic pathways and sustains cue attraction over time. In pathological gamblers, this compensatory stress response appears to collapse (Biback & Zack, 2015), yet the dopaminergic sensitization produced by chronic

exposure to inconsistent cues persists (van Holst et al., 2018) rendering these cues particularly compelling and difficult to resist.

An alternative explanation for the link between reward uncertainty and dopamine release can be found in RPE theory (Schultz, 1998). We reported earlier that with repeated exposure to a CS-US association, the predictive value of the CS increases, and the dopamine signal gradually shifts from the US to the CS until the US response disappears, becoming indistinguishable from baseline activity (Mirenowicz & Schultz, 1994). However, dopamine continues to be released even after extensive training when the interval between CS and US is randomly variable, because the association is impossible to learn (Schultz et al., 1993). In other words, reward uncertainty continuously signals that learning is incomplete, thereby maintaining elevated mesolimbic dopamine levels. Preuschoff and Bossaerts (2007) suggested that dopamine release does not only serve learning but also the ability to choose a more rewarding option, compared to a poorer one, as well as to track prediction risk, i.e., the scaling of prediction errors by means of the covariance between predictions and prior prediction errors. The mathematics behind this view captures how reward uncertainty influences dopamine release, as well as some aspects of the decision to prefer more potent rewards, which may be relevant to addictive processes. However, interpreting dopamine release as a predictive signal has limitations: it does not explain the direction or intensity of behavior in the absence of a motivational component (Anselme, 2016), whether the task requires instrumental action or Pavlovian responses such as sign-tracking. Also, there are situations in which motivation can be detached from prediction, that is, where intense “wanting” occurs despite prediction of a bad outcome (Berridge, 2023). For example, salt-deprived rats become instantly attracted by a lever predictive of the delivery of salt water in their mouth, after learning the aversive effect of this event in the absence of salt deprivation (M. J. F. Robinson & Berridge, 2013). Similarly, rats develop strong “wanting” about a metal rod predictive of electric shock, if approaching the rod is associated with optogenetic stimulation of central amygdala (Warlow et al., 2020).

Nevertheless, the RPE framework enables a functional perspective suggesting that behavioral invigoration under unavoidable reward uncertainty may reflect adaptive exploration rather than an appetitive response or a simple learning deficit. Beyond its role as a teaching signal, RPE can redirect attention toward the broader context when

ambiguity arises (Rosas et al., 2006), a mechanism that facilitates uncertainty resolution in natural environments. In this perspective, uncertainty directly contributes to information- and novelty-seeking, in the sense that this behavioral strategy may disambiguate context and hence reduce uncertainty (Bromberg-Martin & Monosov, 2020; Monosov, 2024). Although originally proposed to account for extinction learning, where the CS becomes ambiguous early in extinction, this interpretation can be extended to autoshaping under uncertain reward conditions. RPE signals may trigger attentional shifts and exploratory behavior aimed at reducing uncertainty. For example, a dog that repeatedly retrieves a thrown object focuses exclusively on the task; but if the owner pretends to throw and hides the object instead, the dog quickly shifts to sniffing and searching the surroundings. This attentional reorientation and exploration occur because the previously rewarded CS (the throwing gesture) fails to predict the expected outcome. Similar patterns are observed in operant settings, where early extinction produces heightened behavioral vigor (Shahan, 2022) and increased behavioral variability (Donoso et al., 2021). A comparable process may underlie sign-tracking amplification when a cue fails to fully predict reward, an effect that likely reflects adaptive search behavior rather than a mere failure of learning or a purely appetitive reaction. This functional view of RPE is consistent with our suggestion that behavioral invigoration under reward uncertainty reflects an adaptive response to a challenge that occurs in the form of CS ambiguity (see also Anselme, 2025).

Dopamine release during uncertainty-related behaviors helps explain why gambling, and gambling-like situations in animals, can become addictive. Evidence shows that uncertainty amplifies or accelerates the sensitization process central to the incentive sensitization theory of addiction. For example, D. A. Gottlieb (2006) reported that pigeons trained under uncertain reward conditions pecked a cue far more than those trained with predictable rewards, and this heightened response persisted even when the cue was replaced by a novel stimulus. Similarly, M.J.F. Robinson et al. (2014) exposed rats to sequences of high, moderate, or low uncertainty in autoshaping tasks. Rats that started with high uncertainty continued to respond more vigorously to cues later, regardless of recent conditions. Converging findings across species suggest that early exposure to uncertainty can produce lasting behavioral sensitization, effects resembling those seen

with drugs of abuse and in gambling-like tasks (Mascia et al., 2019; M. J. F. Robinson et al., 2015; Singer et al., 2012; Swintosky et al., 2021; Zack et al., 2014).

Dopamine release under uncertainty might also offer clues about addiction. It is possible that addictive drugs, by artificially triggering phasic dopamine surges, mimic the motivational amplification observed under unpredictable reward conditions. If so, these drugs could accelerate incentive sensitization and create an exaggerated motivational state, somewhat analogous to the invigoration produced by uncertainty, but without the natural constraints that typically limit this effect in everyday environments. This interpretation closely follows Redish's (2004) computational account of addiction in which addictive drugs introduce a non-compensable dopaminergic prediction error that prevents the value function from converging. Because this error cannot be canceled through learning, the value of drug-associated states increases progressively, biasing action selection toward drug-seeking despite stable or even superior alternative rewards. Reward uncertainty may constitute a functional analogue of this process. When CS-US contingencies are probabilistic, the prediction error signal cannot be fully driven to zero, allowing dopaminergic responses to persist across trials and sustaining value updating. However, a motivational account is necessary to explain the behavioral effects of this process and, in an addictive context, how this process can persist and cause relapse, even after months or years of abstinence (T. E. Robinson & Berridge, 2025).

Recent developments in Redish's framework provide further support for the idea that uncertainty can produce addiction-like motivational amplification. While the original model (Redish, 2004) attributed addictive behavior to a non-compensable dopaminergic prediction error induced by drug pharmacology, later work by his group has generalized this mechanism to broader failures of internal model updating. Kalhan et al. (2021) show that dysfunctions in anterior cingulate cortex dopamine circuits lead to misaligned internal representations in which cues with high apparent salience—such as drug-predictive stimuli—are overweighted during learning, while other cues and negative feedback are underweighted. More recently, Kalhan et al. (2023) formalized these ideas in a computational salience weighting model, demonstrating that any condition producing elevated or volatile prediction errors (including environmental uncertainty) can produce asymmetric learning, reduced sensitivity to costs, steeper delay discounting, and persistent cue-driven behavior. This suggests that reward uncertainty, by maintaining

high prediction error signals, may drive the same kind of salience misattribution and value distortion attributed to addictive drugs in the initial Redish model. Interpretations in line with this account have been recently proposed by Zack et al. (2020), who suggest that gambling disorder might be a *"sensitization-like syndrome caused in part by chronic exposure to intermittent, unpredictable reward and mediated by sustained hyper-reactivity of brain dopamine pathways"* (p. 5). The same computational logic extends to modern digital environments. As recently noted (L. Clark & Zack, 2023; White et al., 2024), features such as infinite scrolling, unpredictable notifications, and swipe-to-refresh interfaces replicate variable-ratio reward schedules, maximizing anticipation and uncertainty. These design features might maintain elevated prediction errors, bias learning toward positive outcomes, and reduce the impact of negative feedback. Consistent with this view, design features of online applications that rely on variable reinforcement schedules have been suggested to promote dysregulated and addictive online behaviors (Flayelle et al., 2023).

Interim Conclusion on Animal Research

Evidence from animal studies demonstrates that reward-predictive cues can acquire strong motivational and attentional properties through Pavlovian learning, driving approach behavior even in the absence of instrumental contingencies. Critically, when reward delivery is uncertain, these cue-triggered responses are markedly amplified: sign-tracking intensifies, dopaminergic activity surges, and attention becomes disproportionately biased toward reward-associated cues. This pattern suggests that uncertainty acts as a powerful enhancer of persistent and sometimes maladaptive engagement with predictive stimuli. These processes operate largely automatically, independent of explicit expectations or goal-directed control. Addictive drugs might mimic these uncertainty-driven effects by artificially inducing phasic dopamine release, thereby accelerating incentive sensitization and promoting compulsive cue attraction. While this hypothesis remains to be fully demonstrated, it offers a compelling framework for understanding parallels between uncertainty and drug-induced motivational effects. Taken together, the evidence suggests that uncertainty functions as a potent modulator of cue-driven motivation, providing a mechanistic bridge between adaptive learning strategies and the compulsive behaviors characteristic of addiction.

Human Research

Evidence for Incentive Motivation and Sign-Tracking Behaviors

Following the same logic as in the animal research section, we first review human research on motivation and attention (present and upcoming section) before discussing the relatively limited number of studies explicitly examining reward uncertainty in humans (third sub-section, p.290). Research on incentive motivation and sign-tracking has been extensively conducted in laboratory animals since the late twentieth century (Boakes, 1977; Hearst & Jenkins, 1974). However, systematic empirical investigations of these phenomena in humans have only begun to emerge more recently (Anselme & Robinson, 2020; Colaizzi et al., 2020; Heck, Durieux, et al., 2025). In a recent scoping review, we showed that the paradigms used to assess human sign-tracking are considerably more diverse than those employed in animal studies, and that no consensus yet exists regarding the most appropriate methods to identify individual differences in sign- and goal-tracking behaviors (Heck, Durieux, et al., 2025). Among the available procedures, Pavlovian Conditioned Approach (PCA) tasks remain the closest human analogue to the traditional autoshaping paradigm used in animals, and they have been instrumental in demonstrating the expression of incentive salience in humans. PCA tasks can be implemented in a physical format, allowing direct interaction with a predictive cue and a reward receptacle, as in animal research, or in a virtual, computerized format, where eye-movement measures are typically used to infer sign- versus goal-tracking tendencies. Across formats, PCA tasks rely on an initially neutral cue (CS) acquiring predictive value through its association with a reward (US). Whereas food rewards are universally used in animal autoshaping, human studies more commonly employ monetary incentives, often represented by images of coins or banknotes (Cherkasova et al., 2024; Duckworth et al., 2022; Garofalo & di Pellegrino, 2015; Schad et al., 2020; Schettino et al., 2024). Figure 27 (panel B) illustrates sign- and goal-tracking behaviors in a human PCA task.

Recent findings provide preliminary support for the existence of ST and GT phenotypes in humans, both in physical implementations of PCA tasks (Colaizzi et al., 2023; Cope et al., 2023) and in computerized versions (Garofalo & di Pellegrino, 2015; Heck, Simon, et al., 2025; Schad et al., 2020; Schettino et al., 2024). However, identifying

clear-cut phenotypes in humans is considerably more challenging than in animal models, often resulting in intermediate or ambiguous categories such as “*non-STs*” or “*non-GTs*” (e.g., Colaizzi et al., 2023; Heck, Simon, et al., 2025; Joyner, 2019). Several human PCA studies (e.g., Garofalo & di Pellegrino, 2015; Lehner, Balsters, Bürgler, et al., 2017; Schad et al., 2020) have incorporated a non-reinforced cue (CS-) in addition to the reinforced cue (CS+). The two cues are perceptually identical, making the CS- a useful control for determining whether preferential attention to the CS+ reflects genuine motivational attraction rather than a non-specific AB. Consistent with findings from animal autoshaping, robust evidence shows that some participants attend to the CS+ more than to the US location, supporting the involvement of incentive salience in these tasks. Paralleling animal studies, several human investigations have also reported associations between sign-tracking tendencies and measures of impulsivity (Colaizzi et al., 2023; Cope et al., 2023; Garofalo & di Pellegrino, 2015; Heck, Simon, et al., 2025). Nonetheless, substantial heterogeneity in experimental methods and analytic approaches, along with the presence of non-significant findings, often found in dissertations rather than published articles (Colom, 2023; Doran, 2016; Joyner, 2019), raises concerns about potential publication bias and limits the strength of current conclusions, although some interesting non-significant findings have also been published (Cherkasova et al., 2024; Dinu et al., 2024). More broadly, research using human PCA paradigms still lacks sufficient replication and validation, making it premature to assert that stable ST and GT phenotypes exist in humans (Heck, Durieux, et al., 2025). Addressing this issue, a recent study by Badioli et al. (2026) examined the test-retest reliability of an eye-gaze-based index over a four-month interval. Although the measure demonstrated good reliability for detecting sign-tracking, it showed poor consistency for identifying goal-tracking, yielding suboptimal overall reliability. These findings underscore the need for further methodological refinement and the development of more robust and standardized measures before stable phenotypic classifications can be confidently established in human populations.

Focus on Motivated Attention: Value-Modulated Attentional Capture Studies

Although incentive salience and sign-tracking behaviors have only been modestly explored in humans using PCA paradigms, a substantial literature has examined how reward history shapes attentional prioritization, leading to closely related conclusions. Attention can be defined as *“the cognitive mechanisms used to allocate mental resources to the processing of certain aspects of sensory inputs”* (Le Pelley et al., 2015, p. 4). But why do we preferentially attend to some stimuli rather than others? A widely accepted framework distinguishes three processes that bias attention toward particular stimuli (Theeuwes, 2019). The first is stimulus-driven bottom-up attention, whereby physically salient stimuli (e.g. those that are bright, large, or loud) automatically capture attention. The second is goal-directed top-down attention, which is strategically deployed toward stimuli relevant to an individual’s current objectives. The third is *“selection history”*, reflecting persistent attentional biases toward stimuli that have been associated with reward or other significant outcomes in the past, independent of physical salience or current goals. This last category is especially relevant for motivated attention: for instance, one may instantly notice a €2 coin on the ground not because it is perceptually striking, but because it is motivationally salient due to its learned value. Indeed, a considerable body of research shows that rewards can act as a potent source of incentive motivation for the control of attention (Chelazzi et al., 2013; Failing & Theeuwes, 2018), enhancing performance across a variety of tasks by increasing the priority of reward-associated stimuli.

The Value-Modulated Attentional Capture (VMAC) paradigm was specifically designed to examine how reward history shapes motivated attention. Whereas PCA paradigms focus on overt approach behavior, VMAC paradigms quantify the attentional consequences of incentive salience by measuring how strongly reward-predictive cues draw gaze or slow down task performance. VMAC refers to the robust finding that stimuli previously associated with higher rewards capture attention more effectively than those linked to lower rewards, even when such capture is detrimental to the task goal (Le Pelley et al., 2015, 2019). In the standard VMAC task, each trial begins with a central fixation cross, followed by a visual search display composed of six shapes, five circles and one

diamond, arranged symmetrically around the cross (Figure 27, panel C). The diamond target and four of the circles appear in gray, whereas the remaining circle act as a distractor and is colored according to the reward magnitude it predicts (e.g., green for a high-value cue worth 500 points, orange for a low-value cue worth 10 points). Participants are instructed to identify the orientation of a line segment within the diamond (vertical or horizontal). Points are awarded based on response speed and accuracy, and cumulative performance determines the final amount of money/points obtained. A commonly used variant replaces manual responses with eye-movements, requiring participants to locate the diamond as quickly as possible. Even though ignoring the distractors is the optimal strategy, participants reliably exhibit attentional capture by the high-value distractors. Eye-tracking studies show that gaze is disproportionately drawn toward these colored stimuli, while reaction-time data reveal slower detection of the target when high-value distractors are present (Le Pelley et al., 2015; Pearson et al., 2015). Such findings indicate that reward-associated cues acquire an elevated attentional priority, consistent with the idea that motivationally salient stimuli can exert automatic, bottom-up influence on attentional allocation, even when this conflicts with top-down goals.

The VMAC effect has been proposed as a potential human analogue of the sign-tracking behavior observed in animal autoshaping (Albertella, Watson, et al., 2019; Byrom & Murphy, 2018; Le Pelley et al., 2015, 2024; Wiers et al., 2021). This parallel is based on their shared behavioral bases: in both cases, a stimulus predictive of reward acquires incentive salience, thereby biasing attention and/or approach behavior toward it. In animal autoshaping, sign-tracking is expressed through overt approach and physical interaction with the reward-predictive cue (e.g., a lever). In contrast, in human VMAC paradigms, sign-tracking is inferred indirectly from attentional capture, manifested as slower identification of the target when a high-value distractor is present. Although the behavioral readouts differ (approach vs. attentional interference), the underlying mechanism is conceptually similar: reward-associated cues acquire motivational significance that competes with, and at times overrides, goal-directed control. Whether in autoshaping or VMAC tasks, attention and motivation are tightly intertwined. In both cases, cues endowed with incentive salience exert a disproportionate influence on behavior, revealing a common mechanism through which reward history shapes perceptual prioritization and action. Figure 27 provides a comprehensive visual overview

of sign-tracking and goal-tracking behaviors, as observed in PCA tasks in both nonhuman and human animals, as well as in VMAC tasks.

Yet, the VMAC paradigm does not fully reproduce the defining characteristics of animal autoshaping procedures (Anselme & Robinson, 2020; Colaizzi et al., 2020; Heck, Durieux, et al., 2025). Several key differences are notable. First, reward delivery in VMAC is not response-independent; participants must respond correctly and within a specific time window to obtain points. Second, the paradigm does not allow a direct comparison between cue-directed and reward-directed approach behaviors, a central feature of autoshaping used to distinguish sign- and goal-tracking profiles. Third, VMAC tasks typically include instrumental contingencies, such as reward omission following incorrect or delayed responses, that are absent from classical Pavlovian procedures in animals. Despite these structural differences, there is no evidence that VMAC fails to capture processes related to incentive salience. Rather, it measures these processes indirectly, through the degree of attentional interference produced by reward-associated distractors. Importantly, findings from VMAC studies converge remarkably well with decades of animal research, particularly in their consistent associations with addiction-related traits and behaviors (e.g. Albertella et al., 2017, 2021; Albertella, Watson, et al., 2019; C. Liu et al., 2021; Watson et al., 2024). Consequently, although VMAC may be less suited than PCA paradigms for identifying clear sign- and goal-tracking phenotypes in humans, it nevertheless provides a powerful tool for capturing differential cue attraction and AB for reward cues. Consistent with this, a recent study achieved the first successful back-translation of the VMAC paradigm to mice and rats (Bradfield et al., 2026), showing that reward-predictive distractors impair instrumental performance in rodents in a manner closely mirroring VMAC effects in humans. Notably, the VMAC effect persisted following outcome devaluation via conditioned taste aversion, indicating that the attentional disruption cannot be explained by simple sign-tracking alone or habitual responding, but instead points to a more compulsive process. However, these conclusions are based on relatively small samples, and while the approach is elegant and the findings promising, replication across laboratories and conditions will be essential to establish rodent VMAC as a robust back-translational model of cue-driven attentional capture.

VMAC effects were originally interpreted within the selection-history framework, according to which prior stimulus-reward contingencies leave a persistent trace that biases attention toward previously rewarded cues, even when such attentional capture is detrimental to current task performance (Le Pelley et al., 2015). At a functional level, it has been suggested that reward selection history changes a stimulus' representation, rendering it more salient to the visual system (Failing & Theeuwes, 2018; Theeuwes, 2019). As Failing and Theeuwes (2018) noted, this mechanism closely mirrors incentive salience: a previously neutral cue is reshaped at the neural level so that, through its link to a rewarding outcome, it becomes a powerful attractor of attention. Thus, a complementary interpretation views VMAC through a motivational lens, proposing that reward-associated cues attract attention because they elicit a conditioned "approach-like" response mediated by dopaminergic signaling. From this perspective, the learned association between a stimulus and its reward outcome enhances its incentive salience, thereby granting it attentional priority even when this conflicts with the individual's explicit goals. Supporting this view, converging neurobiological evidence shows that striatal dopaminergic mechanisms contribute directly to VMAC. Anderson et al. demonstrated that the striatum, a central structure of the basal ganglia involved in motivational processing, generates an attentional priority signal for reward-predictive stimuli (B. A. Anderson, Laurent, et al., 2014). Extending these findings, a subsequent PET study revealed that dopamine release in the dorsal striatum predicts the magnitude of VMAC, with higher dopaminergic activity corresponding to stronger attentional capture by high-value distractors (B. A. Anderson et al., 2016). These results are particularly noteworthy given the well-established role of dopamine in attributing incentive salience to reward cues (Berridge & Robinson, 1998) and in the broader neurobiology of addiction (T. E. Robinson & Berridge, 1993, 2025). Together, they suggest that the attentional biases observed in VMAC reflect the same dopaminergic processes that underlie cue-triggered motivation in animal models, reinforcing the translational link between motivational attention and addiction-related behaviors.

The role of dopamine in motivated attention has also been examined through direct comparisons of human sign-trackers and goal-trackers. In a study by Schad et al. (2020), sign-tracking was operationalized using a PIT task, in which a Pavlovian cue-reward association facilitates subsequent instrumental responding. Eye-tracking,

pupillometry, fMRI and computational modeling were used. The results indicated that human sign-tracking is primarily driven by model-free, dopamine-dependent processes that endow cues with motivational value and influence both attention and physiological markers such as gaze patterns and pupil dilation. In contrast, goal-tracking behavior appeared to rely more heavily on model-based computations supported by higher-order cognitive processes. This dissociation closely mirrors findings in animal research: STs exhibit heightened mesolimbic dopamine activity but reduced cortical acetylcholine modulation, resulting in poorer sustained attention and stronger cue attraction, whereas GTs show enhanced cholinergic regulation and more stable attentional performance (Flagel, Cameron, et al., 2011; Paolone et al., 2013; Sarter & Phillips, 2018). Consistent with this framework, Albertella et al. (2017) reported that VMAC was associated with illicit drug use only among individuals with low top-down control of selective attention, suggesting that weaker top-down regulation increases vulnerability to cue-driven, dopamine-mediated behavior. Together, these findings reinforce the view that human individual differences in motivated attention reflect underlying distinctions analogous to those observed in animal models.

In conclusion, most human PCA studies have focused primarily on the motivational and behavioral aspects of sign- and goal-tracking, while giving comparatively little attention to related processes such as attentional prioritization of reward-related cues or the influence of reward uncertainty on attentional and behavioral performance. Yet, as recently emphasized by Le Pelley et al. (2024), cues that acquire incentive salience are especially likely to capture attention, thereby increasing their impact on subsequent behavior. These authors further argue that a comprehensive understanding of motivated behavior requires acknowledging how selective attention shapes the encoding and evaluation of stimuli, processes that ultimately guide actions and decisions.

Effects of Uncertainty on Human Motivated Attention

Although the impact of uncertainty on attentional and motivational processes, especially on sign-tracking, has been well documented in nonhuman animals, systematic investigation of these mechanisms in humans is relatively recent. This emerging line of research has largely relied on VMAC-based procedures in which the reward associated with a distractor is made inconsistent, giving rise to what has been termed

Uncertainty-Modulated Attentional Capture (UMAC). The UMAC paradigm offers a controlled approach to examine how unpredictable reward outcomes alter the attentional priority of cues, thereby providing a human analogue to uncertainty-driven effects observed in animal conditioning studies.

The UMAC paradigm introduced by Le Pelley et al. (2019) closely mirrors the traditional VMAC design, with one critical modification: one distractor is associated with either a high reward (e.g., 500 points) or a low reward (e.g., 10 points) with equal probability (50/50) (called the *"non-predictive"* distractor by the authors, since the upcoming reward magnitude cannot be anticipated). This manipulation introduces explicit, high reward uncertainty (50%) while keeping physical stimulus properties constant, allowing researchers to isolate the effects of unpredictability on attentional capture.

A growing number of studies have now shown that inconsistent distractors, i.e. stimuli associated with unpredictable reward outcomes, capture attention more strongly than fully predictive distractors (Cho & Cho, 2021; J. Y. L. Chow et al., 2025; Ju & Cho, 2023; Le Pelley et al., 2019; Massa et al., 2024; Pearson et al., 2024). These findings align with the uncertainty principle proposed by Pearce and Hall (J. M. Pearce & Hall, 1980), which posits that cues with a high uncertainty attract attention more because their potential consequences require increased monitoring. They also parallel evidence from animal research showing that uncertain cues elicit heightened motivational and attentional engagement, reflected in enhanced sign-tracking (Anselme et al., 2013; Glueck et al., 2018; Kaneko et al., 2025). Classical learning theories have long debated whether attentional allocation is better explained by the uncertainty principle (J. M. Pearce & Hall, 1980) or by the predictiveness principle (suggesting, conversely, that more reliable cues attract greater attention, Mackintosh, 1975), for which evidence has accumulated (e.g., Degni et al., 2025; Trick et al., 2011). Although Le Pelley et al.'s (2016) review concluded that predictiveness effects were historically more robust in human studies, the authors noted that many earlier paradigms may not have been suited to adequately test the role of uncertainty. More recent work has renewed both theoretical and empirical support for uncertainty-driven attentional prioritization in humans (Beesley et al., 2015; Folk & Anderson, 2010; Frings et al., 2019; Morriss et al., 2024). Together, these findings indicate that, under appropriate task conditions, uncertainty can serve as a

powerful driver of attentional priority, mirroring mechanisms documented in nonhuman species and reinforcing the translational relevance of uncertainty-modulated motivated attention.

Additional evidence suggests that the influence of uncertainty on attention is both rapid and largely automatic. For instance, UMAC persists even when participants are explicitly informed that the inconsistent distractor is non-predictive, showing that the effect cannot be reduced to conscious expectations (J. Y. L. Chow et al., 2025). In line with this, Le Pelley et al. (2019) reported that attentional capture by inconsistent distractors is maximal on the first eye saccade, demonstrating an immediate, stimulus-driven bias (see also Ju & Cho, 2023). Cho and Cho (2021) further observed that this effect is transient under some conditions, emerging during the initial block of trials but diminishing thereafter.

These results suggest that UMAC may be short-lived depending on the experimental context. However, several studies have documented sustained uncertainty effects across multiple blocks (Le Pelley et al., 2019; Massa et al., 2024), indicating that the persistence of UMAC varies as a function of task parameters or of the strength of the learned reward associations. Animal research reveals a contrasting pattern. Once uncertainty invigorates sign-tracking, the effect tends to be robust and enduring across repeated trials and sessions (e.g., M. J. F. Robinson et al., 2014). These species differences are not necessarily incompatible. In humans, rapid habituation of the automatic orienting response may reflect a diminishing need to monitor an inconsistent cue. In contrast, in animals, the motivational arousal triggered by uncertainty remains elevated as long as unpredictability persists. This disparity may be especially evident in physical PCA procedures, such as autoshaping, where behavior provides a more direct expression of incentive motivation than eye-movement-based measures do. It may also reflect the fact that sign-tracking in animals is less constrained by top-down attentional control. Moreover, human studies indicate that multiple forms of uncertainty contribute to UMAC (Cho & Cho, 2021; Ju & Cho, 2023; Pearson et al., 2024), paralleling the effects of probabilistic and temporal uncertainty observed in rodent autoshaping paradigms (Anselme et al., 2013; Kaneko et al., 2025).

Taken together, these findings suggest that uncertainty modulates motivated attention through mechanisms that are broadly conserved across species. Preliminary

evidence also supports a translational account in which reward uncertainty drives dopamine release, an effect well established in animal studies but not yet directly examined in the context of UMAC. Although no human study has empirically tested the link between dopaminergic activity and UMAC, the animal literature showing that uncertainty enhances dopaminergic signaling (Fiorillo et al., 2003; Hart et al., 2015; Schultz, 1998) provides a strong rationale for anticipating a similar relationship in humans.

Interim Conclusion on Human Research

Human research converges with animal findings in showing that reward-associated cues exert a powerful influence on attention and motivation, often overriding goal-directed intentions. Under conditions of reward uncertainty, these effects are further amplified: cues associated with variable or unpredictable rewards attract disproportionate attention and elicit stronger approach-related tendencies. This uncertainty-modulated attentional capture reflects rapid and largely automatic processes, likely supported by dopaminergic mechanisms, that bias behavior toward reward-predictive stimuli regardless of explicit knowledge or conscious strategies. Such cue reactivity reveals an implicit motivational pull that persists even when individuals attempt to ignore or suppress it. Overall, the human literature suggests that uncertainty enhances both the attentional and motivational effects of reward cues, possibly reinforcing the translational link between uncertainty-driven cue engagement and the mechanisms underlying addictive behaviors.

The Adaptive Function of Cue-Triggered Behavior

The association between sign-tracking and vulnerability to addiction should not obscure the adaptive origins of cue-triggered behavior. In natural environments, predictive cues and rewards are rarely separable: the perceptual features of prey, food odors, or mate-related signals typically provide reliable, proximal access to biologically significant outcomes. In many contexts, particularly when rewards are distal or partially hidden, using the cue itself as a motivational signal is advantageous. This functional role helps explain why sign-tracking is evolutionarily conserved across diverse species. As

noted by Krause and Domjan (2017), Pavlovian conditioning evolved because biologically important events are systematically preceded by early, predictive cues embedded within natural environments. A parallel perspective was suggested in the human attentional selection literature, where the tendency for reward-related stimuli to capture attention has likewise been framed as an adaptive (evolutionary shaped) process (Della Libera & Chelazzi, 2006, 2009; Pitchford & Arnell, 2025).

Uncertainty often enhances the adaptive value of cue responding. Inconsistent or ambiguous cues draw attention (Esber & Haselgrove, 2011; J. M. Pearce & Hall, 1980) because they signal that a greater engagement in the task is required (but see Mackintosh, 1975; O'Reilly et al., 2013; Wittmann et al., 2016). Under such conditions, sign-tracking not only intensifies but also becomes more prevalent across individuals (M. J. F. Robinson et al., 2015). Amplification effects observed in animals, such as prolonged engagement with cues, greater response vigor, and increased behavioral variability (e.g., Blaisdell et al., 2016; Fuentes-Verdugo et al., 2020), can be understood functionally as strategies that increase reward discovery in sparse or unpredictable environments (Anselme & Güntürkün, 2018). Computational foraging simulations support this view. Organisms exposed to fewer, less predictable cues show greater exploratory variability and improved survival (Anselme et al., 2017, 2018).

In humans, parallels between UMAC and uncertainty-driven attentional exploration have been discussed (Cho & Cho, 2021; J. Y. L. Chow et al., 2025; Ju & Cho, 2023; Le Pelley et al., 2019; Pearson et al., 2024). These findings align with exploration-exploitation accounts of decision making, which posit that uncertainty promotes exploratory attention to reduce future uncertainty (Beesley et al., 2015; J. Gottlieb et al., 2013). From this perspective, uncertainty-related attentional capture reflects a functional mechanism designed to update internal models of reward contingencies rather than maladaptive distraction.

However, human studies have not yet demonstrated the full range of “amplification” effects observed in animals, such as increased cue-directed vigor or behavioral variability. These phenomena extend beyond attentional capture and require a motivational framework capable of explaining how uncertainty energizes behavior and why repeated exposure to inconsistent cues can foster addiction-like patterns, particularly in gambling contexts (Anselme, 2025; Anselme & Güntürkün, 2019). A comprehensive

theory should therefore integrate both the functional, evolutionarily conserved aspects of sign-tracking and its maladaptive potential in modern environments where reward cues are artificially intensified and uncertainty is systematically engineered.

General Discussion and Conclusions

Across this review, we examined how reward-predictive cues shape motivated behavior and attentional allocation in both humans and nonhuman animals, and how these processes are strongly modulated by reward uncertainty. Animal evidence shows that uncertain or partially reinforced cues elicit heightened sign-tracking behaviors, increased dopaminergic responses, and persistent approach tendencies (Anselme et al., 2013; Hellberg et al., 2019; Mascia et al., 2019; M. J. F. Robinson et al., 2014). Parallel findings in humans, particularly from UMAC paradigms, demonstrate that inconsistent reward cues attract greater attention than fully predictive ones, even when this impairs task performance (Cho & Cho, 2021; J. Y. L. Chow et al., 2025; Ju & Cho, 2023; Pearson et al., 2024). Together, these observations indicate that uncertainty amplifies cue-triggered motivation and attentional capture through rapid, automatic mechanisms operating largely outside conscious control.

The convergence of human and animal data suggests that sign-tracking under uncertainty and UMAC rely on shared mechanisms, likely involving dopaminergic systems that attribute incentive salience to ambiguous cues (Hart et al., 2015; Ju & Cho, 2023; Mascia et al., 2019; Massa et al., 2024; M. J. F. Robinson et al., 2015; M. J. F. Robinson & Anselme, 2019). Functionally, these mechanisms may reflect evolutionarily conserved strategies that promote exploration and information-seeking in unpredictable environments (Anselme, 2025; Bromberg-Martin & Monosov, 2020; Frings et al., 2019; Pearson et al., 2024). Heightened attention to uncertain cues is therefore not inherently maladaptive; rather, it can support the updating of internal models of reward contingencies.

A longstanding debate in associative learning concerns whether organisms allocate attention to cues because they reliably predict important outcomes or because they remain uncertain and therefore informative. According to the predictiveness principle (Mackintosh, 1975), attention is preferentially directed toward cues that most

accurately signal outcomes, facilitating exploitation of stable contingencies. Conversely, the uncertainty principle (J. M. Pearce & Hall, 1980) proposes that attention is allocated to ambiguous cues to promote exploratory learning.

Contemporary accounts converge on the idea that both mechanisms operate in parallel, with their influence varying according to task demands and learning history. Human studies support this dual-process view. For example, Easdale et al. (2018) showed that cues with high predictive validity receive greater attention, whereas unexpected uncertainty enhances associability and accelerates learning of new contingencies. This reciprocal relationship highlights how learned predictive value guides attention, while attention modulates the rate of associative learning.

However, greater attention to uncertain cues does not imply that all cue-triggered behaviors follow an uncertainty-driven pattern. Studies using PIT tasks point to a dissociation between attentional orienting and motivational influence. Trick et al. (2011) found that dwell time peaked for cues of intermediate predictiveness, whereas PIT effects increased with cue predictiveness. Therefore, uncertainty promotes attentional exploration, whereas motivational invigoration of instrumental responding follows a predictiveness gradient. Recent findings further support this distinction. Degni et al. (2025) demonstrated that weakening cue–outcome contingencies during Pavlovian training reduces the subsequent bias exerted by Pavlovian cues on instrumental decisions, suggesting that cue predictiveness, not uncertainty, drives maladaptive Pavlovian interference in value-based choice.

These observations carry important implications for addiction and gambling-related behaviors. From a Mackintosh perspective, drug-associated cues that consistently predict pharmacological reward acquire strong motivational control, consistent with cue-triggered craving and relapse. In contrast, the Pearce–Hall framework explains why uncertain or intermittently reinforced cues, common in gambling environments, remain highly attention-capturing despite limited predictive value. Addiction may reflect a pathological decoupling of these systems: uncertain cues dominate attentional orienting and learning, whereas highly predictive cues exert disproportionate motivational control over action. Addictive substances may further exacerbate this imbalance by generating persistent prediction-error-like signals (Redish, 2004), thereby maintaining both heightened cue salience and strong motivational impact.

From a neurobiological perspective, addictive drugs may artificially mimic and amplify the motivational effects normally produced by uncertainty. Pharmacologically induced dopaminergic surges can endow drug-associated cues with exaggerated incentive salience, bypassing natural constraints on uncertainty-driven learning. In this sense, addiction may hijack an evolutionarily adaptive system by generating an artificial form of uncertainty-like stimulation, rendering drug cues irresistibly attractive and persistently attention-capturing.

Despite these conceptual parallels, important translational challenges remain. Although the neural bases of uncertainty-driven cue attraction have been characterized in animals (Fiorillo et al., 2003; Hart et al., 2015), the relevant biological mechanisms in humans are only beginning to be investigated. Dopaminergic involvement has been demonstrated in VMAC (B. A. Anderson, et al., 2016; B. A. Anderson, Laurent, et al., 2014), but direct evidence linking dopamine release to UMAC is still lacking, and the role of stress-related systems such as the HPA axis has yet to be systematically assessed. Moreover, key behavioral amplifications observed in animals under uncertainty, such as heightened vigor, persistence, or increased variability, have not yet been systematically explored in humans.

Strengthening the translational bridge between species will require several methodological advances. Future research should (1) develop standardized paradigms for assessing cue-driven behaviors in humans, including analogues of sign-tracking; (2) systematically manipulate distinct dimensions of uncertainty (probability, magnitude, timing) to more closely match animal studies; and (3) investigate the neurobiological substrates of UMAC, with particular attention to dopaminergic and HPA-axis mechanisms. Additionally, identifying individual differences in susceptibility to uncertainty-modulated attention will be essential for determining who is most vulnerable to maladaptive cue reactivity.

Clarifying how uncertainty shapes motivated attention across species has significant implications for both basic neuroscience and psychopathology. Mechanisms that evolved to support adaptive exploration in uncertain environments can, in modern contexts such as gambling or drug use, be co-opted or exaggerated by artificial dopaminergic stimulation. A deeper understanding of these processes will refine theoretical models of incentive salience and attentional prioritization, while informing

prevention and intervention strategies targeting maladaptive cue reactivity, whether driven by uncertainty, by addictive substances, or by their interaction.

Declarations

Use of AI

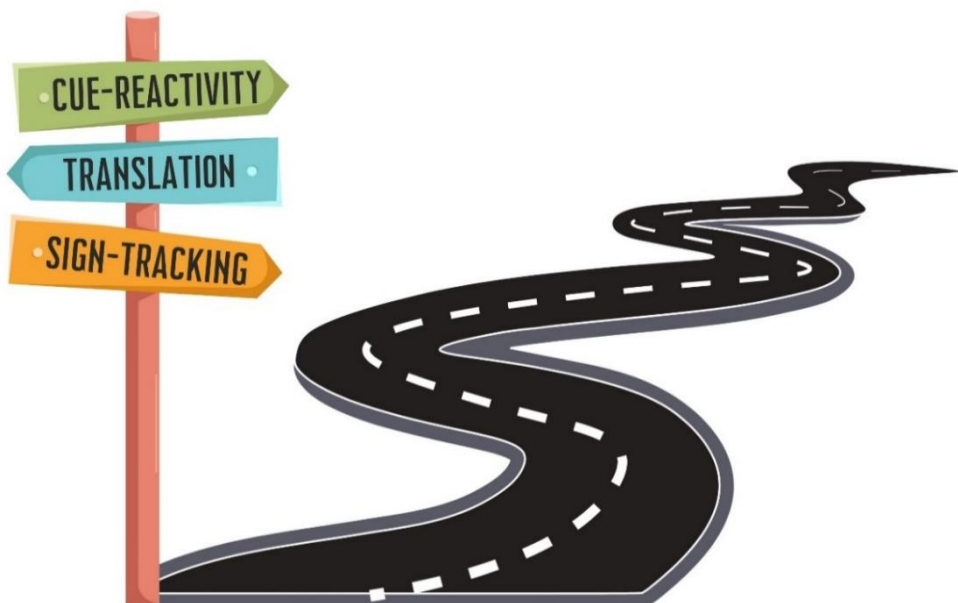
Portions of the manuscript were edited for clarity and flow using Microsoft 365 Copilot (Microsoft, Redmond, WA), a generative AI assistant based on a GPT-5 chat model (version 2.20260108.46.0). Copilot was used solely to improve language, grammar, and readability. Figure 27 (panel A) was developed using Canva's AI-based image tool (Canva AI, 2025). All scientific content, interpretations, and conclusions are the responsibility of the authors.

The reference list of this article has been incorporated into the [general bibliography of this thesis](#).

Chapter 9

From Findings to Future Directions

General Discussion, Perspectives
& Conclusions



To introduce the final part of this thesis, I would like to begin with an anecdote shared during a recent interview of the French comedian, actor, and producer Jérémy Ferrari (Clique TV, 2026). The following passage is translated from the original French interview. To provide some context, Ferrari has been sober for nearly ten years. During the interview, he was asked whether he still experiences moments of weakness (e.g., during difficult periods) that lead him to think about drinking again. Interestingly, his response suggested that cravings do not necessarily emerge during moments of distress. He explained:

"Strangely, it is not in difficult moments that I want to drink again. It happens in moments where you would not expect it at all. For example, sometimes I am in traffic on my scooter, I stop at a red light, and I see people drinking beers at a café. And suddenly there is an overwhelming urge [to drink]. [...] That is why this disease is terrible: it wakes up at moments when you do not expect it at all. This is also why so many people relapse. There was a testimony from a man during a meeting that really struck me. He explained that he had been abstinent for eight or nine years, he was stable, his life was going well [...], alcohol was not even a topic in his life anymore. Then one day, he left the subway, the weather was nice, he walked past a terrace, sat down, and ordered a beer. [...] He could not explain what happened or why he did it – he was not feeling bad and had not experienced any craving beforehand. His brain simply took over; his addiction took over and 'told' him to sit down and order a drink."

More than just anecdotal, these accounts vividly illustrate key mechanisms at the heart of contemporary addiction models, nicely reflecting some of the theoretical concepts discussed throughout this thesis. Most notably, they capture the phenomenon of *cue reactivity*, whereby seemingly benign environmental cues can evoke sudden, powerful motivational impulses toward substance use—often without conscious intention or awareness. This observation closely aligns with the incentive-sensitization framework proposed by Berridge and Robinson. Thus, although the present thesis is situated primarily within the domain of fundamental research, the processes examined (particularly cue reactivity and cue driven behavior) are nevertheless deeply grounded in real human experience. They are phenomena that shape the everyday lives of individuals living with addiction, underscoring the translational relevance and broader significance of this line of research.

Summary of Findings

The primary aim of this thesis was to investigate sign-tracking and goal-tracking behaviors in humans by developing and implementing a new computerized task designed to closely parallel the original animal paradigm. A second objective was to examine how these behaviors relate to theoretically relevant variables (related to alcohol use and personality traits). Although systematic investigation of this model in humans is a relatively recent endeavor (see Anselme & Robinson, 2020; Colaizzi, 2020; Heck, Durieux et al., 2025), its foundations (often discussed under the labels “*human autoshaping*” or “*superstitious behavior acquisition*”) date back to the end of the 20th century (V. J. Anderson et al., 1981; Pithers, 1985; G. A. Wagner & Morris, 1987; Wilcove & Miller, 1974).

As a preliminary step, we aimed to identify and map evidence on sign- and goal-tracking in humans, as well as to document the types of methods employed, by conducting a **scoping review** ([Chapter 4](#)). Broadly, this review (Heck, Durieux, et al., 2025) showed that the current human literature on sign- and goal-tracking is characterized by major heterogeneity, with no consensus on a “gold standard” for identifying those behaviors in humans. Although four broad categories of ST/GT assessments emerged (physical Pavlovian Conditioned Approach (PCA), virtual PCA, Value-Modulated Attentional Capture (VMAC), and alternative tasks), we argued that PCA-type tasks, in general, show the strongest resemblance to the animal paradigm and therefore warrant deeper investigation in future studies.

Importantly, inconsistencies extended beyond experimental procedures. Terminology (including the operational definition of sign-tracking), reward types (e.g., money, food, points), the approach used to categorize participants (STs vs. GTs vs. continuous scores), and analytic strategies also varied widely across studies. Overall, the review provided preliminary evidence for the existence of sign- and goal-tracking *behaviors* in humans (although most studies tend to conclude on the presence of distinct behavioral *phenotypes*; a point to which I will return later). However, associations with theoretically relevant constructs (e.g., substance use, impulsivity) were less consistent, underscoring the need for caution when making claims about clear ST and GT behavioral phenotypes in humans. Since the completion of this scoping review, several new studies

(including those in the present thesis) have been published and a brief update of the current experimental landscape will be presented later in this chapter.

The **very first experimental study** of this work ([Chapter 5](#)) implemented a new task to measure sign- and goal-tracking behavior, as simply as possible in humans based on classical animal task parameters (Heck, Simon, et al., 2025). The main objective was to test if there was a positive association between the tendency to sign-track, and alcohol consumption- and impulsivity-related variables; since the animal literature has long shown that STs are more vulnerable towards substance use (e.g., Flagel et al., 2008), as well as more impulsive (e.g., Lovic et al., 2011) than GTs. In line with theoretical predictions, this study's results suggested that those individuals that we identified as "STs" using our new task, also showed significantly higher levels of alcohol consumption severity (AUDIT-C, Figure 15). A trend for a positive association with one aspect of impulsivity (positive urgency) was also found ([Appendix B](#), Table N). Another noteworthy aspect of the results of this study was that the classification using a tertile split to create behavioral categories, and the one based on latent profile analysis (LPA) yielded highly similar results. Yet, the distribution of the ST/GT scores was highly left-skewed in this sample (i.e. toward goal tracking). As discussed earlier, several explanations may account for this pattern. One possibility concerns the novelty of the task, including the specific nature of its stimuli, which may not have been sufficiently salient or engaging to elicit robust visual interactions with the cue. Additional interpretations include potential variability in attentional capture mechanisms due to the task's relatively low cognitive demands, which may have shaped participants' response tendencies. A sampling bias favoring goal-tracking individuals cannot be ruled out either. Moreover, considering the relatively low response bias scores (RBS) observed even among participants classified as STs, one could argue that the sample as a whole exhibited only weak sign-tracking tendencies.

The second study ([Chapter 6](#)) aimed to test the relationship between sign-tracking and attentional bias (AB) for alcohol cues. It also aimed to further validate the new PCA task by replicating the differences between STs and GTs in alcohol consumption level. This study included two experiments.

In the first experiment, we sought to advance along the translational pathway by introducing a moving lever into the task (1). Unfortunately, this modification may have adversely affected participants' behavior, preventing us from replicating previous

findings. No relationship between sign-tracking and alcohol consumption emerged (in contrast to Study 1), nor did we observe any association with AB.

The second experiment (2) returned to our original task parameters, using abstract stimuli for conditioning. However, a new methodological complication emerged: participants were no longer offered entry into a prize draw as compensation⁴⁰. This change in reward structure may partly account for the reduced effect sizes observed in this study. First, regarding AB, no association was found with sign-tracking; an unexpected outcome given that sign-tracking and AB are theoretically expected to reflect closely related underlying processes (Anselme & Robinson, 2020). Consistent with previous results, the study revealed a small difference between STs and GTs in alcohol-consumption levels, although these effects were weaker than anticipated and should be interpreted cautiously due to the uneven group sizes. In the correlational analyses, no statistically significant associations were detected with additional alcohol-use or personality variables, although a modest trend with impulsivity appeared before correction for multiple comparisons.

Despite these challenges, several hypotheses emerged from this set of experiments. First, a manipulable lever may introduce unintended meaning for human participants. Although conceptually consistent with animal models, implementing such devices in human tasks may not be ideal, as individuals could infer operant contingencies or symbolic significance. Second, reward structure may play a more critical role than previously assumed. Offering participants the chance to enter a prize draw (a form of compensation or “reward”) versus providing no such incentive may significantly influence engagement and learning in tasks that rely on CS-US associations. These possibilities warrant direct investigation in future research. Additionally, incorporating a cognitive interviewing phase would likely have been beneficial. Such a step could have provided insight into participants’ expectations about the cues and how they perceived their reinforcing value⁴¹.

The third study of this thesis ([Chapter 7](#)) aimed to experimentally examine how acute alcohol intoxication and cue-reward uncertainty shape sign- and goal-tracking behavior in humans, using the same task as in the first experiment. Building on extensive

⁴⁰ due to a change in our faculty ethics committee's policy

⁴¹ You might wonder why this was not addressed in the third study; the reason is simply that the studies were launched in parallel due to timing constraints.

animal research showing that uncertain reward outcomes reliably increase sign-tracking tendencies, and that acute alcohol might potentiate cue attraction such as sign-tracking, the main objective was to determine whether these effects also appear in humans when measured with a computerized PCA task.

In line with theoretical predictions and the animal literature, this study found that cue-reward uncertainty significantly heightened attentional allocation to the reward-predictive cue, indicating an amplification of sign-tracking responses under uncertain conditions. Unexpectedly, however, acute alcohol intoxication (0.5 g/kg) did not produce reliable increases in sign-tracking, suggesting that alcohol may not modulate attentional components of cue-reactivity in the way observed in rodents. During the subsequent omission phase, mixed effects emerged: participants who had previously experienced certain reinforcement increased their attention toward the sign while reducing attention to the goal. This shift toward cue-directed attention aligns with what is described in the animal literature as an *extinction burst* (i.e. a transient increase in the vigor or frequency of conditioned responding during the early stages of extinction, Shahan, 2022). Interpreted through an adaptive lens, such a response may reflect individuals' attempts to cope with increased uncertainty by enhancing exploratory behavior and seeking additional information when established contingencies unexpectedly change.

These findings possibly provide a direct translational bridge between animal and human research, demonstrating that reward uncertainty can modulate the attentional components of sign-tracking behavior. The results reinforce the idea that uncertainty plays a central role in shaping how individuals orient their gaze toward reward-predictive cues, a mechanism that may be particularly relevant for understanding individual differences in vulnerability to addictive behaviors.

This interpretation is also highly consistent with a separate body of work using uncertainty-based variants of the VMAC task, in which uncertain reward cues reliably exert stronger attentional capture than certain ones (i.e. Uncertainty Modulated Attentional Capture, UMAC; J. Y. L. Chow et al., 2025; Ju & Cho, 2023; Le Pelley et al., 2019; Massa et al., 2024). Because these two lines of research (sign-tracking and attentional-capture effects under uncertainty) have historically developed within distinct scientific traditions, we wrote a **narrative synthesis** ([Chapter 8](#)) aimed at highlighting the key conceptual and empirical parallels between them. This integrative perspective emphasizes how uncertainty-driven motivation in animal models and uncertainty-driven attentional

processes in humans may reflect a shared underlying mechanism. Despite several methodological differences, VMAC (and by extension UMAC) remains conceptually close to sign-tracking and may tap into certain aspects of incentive salience. However, it likely captures these processes indirectly, through the attentional interference elicited by reward-associated distractors. At the same time, important translational gaps remain. While uncertainty-driven cue attraction is well characterized in animal models, its underlying neurobiological mechanisms in humans (e.g., the roles of dopamine and stress-related systems) are still poorly understood. Addressing these gaps will require more standardized human paradigms, finer manipulations of uncertainty, and greater attention to individual differences in vulnerability to uncertainty-linked cue reactivity.

Insights and Perspectives on Our Findings

ST/GT Profiles in Human Research

With the perspective gained throughout the development of this thesis, I wish to underscore an important conceptual point: most human studies have identified sign-tracking *behaviors*, but not necessarily ST/GT *phenotypes* per se. As discussed in Chapter 3, ST and GT phenotypes encompass more than differential responding to reward-predictive cues; they represent broader *cognitive-motivational profiles* (see Sarter & Phillips, 2018), which are thought to confer heightened vulnerability to addiction. To make valid claims about phenotypes, researchers should systematically relate observed sign- and goal-tracking behaviors to relevant traits (e.g., impulsivity, attentional control).

For the sake of simplicity, many studies, including ours, refer to ST and GT “*profiles*” or “*groups*”. However, these labels merely reflect categories derived within a specific experimental context, enabling comparisons along a continuum of sign- versus goal-tracking behavior. They should not be confused with the broader endophenotypic construct that characterizes the ST phenotype, which involves additional attentional and motivational traits (see Chapter 3).

Mixed Evidence for Human Sign- and Goal-Tracking

The mixed findings obtained in this thesis, across all experiments, make it difficult to draw firm conclusions as to whether our task reliably and unequivocally identified human sign- and goal-tracking (or the underlying phenotypes). Although the expected

association between alcohol consumption and sign-tracking behavior was identified in the first study (and to a smaller extent in the second study, Experiment 2), our sample was largely skewed toward goal-tracking. Theoretically, this pattern diverges from what is typically anticipated in the literature, i.e. approximately one third of each behavioral group (see P. J. Meyer et al., 2012). Nonetheless, heterogeneity among profiles is not rare in the literature: in rats, important genetic and phenotypic differences have been observed from different vendors (and even from different colonies of the same vendor, Fitzpatrick et al., 2013). In humans also, previous studies have reported markedly unbalanced distributions of sign- and goal-tracking phenotypes (some of which using data-driven classifications).

For example, Cope et al. (2023) observed an uneven distribution in a sample of emerging adults (based on an LPA classification) with almost no GTs (20% STs, 8% GTs, and 72% INTs). Similarly, in a sample of children aged 9-12, Colaizzi et al. (2023) identified a predominance of STs, effectively distinguishing between STs and non-STs due to the high positive RBS scores observed in most participants. Conversely, Thériault and colleagues, using a comparable data-driven approach in rodents, identified a majority of GTs (66% GTs, 15% INTs, and 19% STs). Enkel et al. (2019) further noted, in their discussion of aggregated data across many prior rat cohorts (total N = 193), a distribution of 35% GTs, 45% INTs, and 20% STs.

To obtain a clearer understanding of how these behavioral tendencies (and their underlying phenotypes) manifest in human populations, future research should adopt consistent and standardized tasks, task parameters, and classification systems. For example, it has been argued that data-based methods (e.g., clustering) yield more reliable ST/GT/INT categories than cut-off-based methods, as they better reflect the unique structure of the data (Godin & Huppé-Gourges, 2025). In their sample, early conditioning sessions (which span multiple days in animal studies, unlike in humans) produced predominantly negative PCA scores (indicative of goal tracking), while more positive scores emerged only across subsequent sessions. A similar pattern of initially negative PCA scores, shifting toward more positive values with continued training, was also observed in foundational studies such as in P. J. Meyer et al. (2012). In our own studies, we administered only a single PCA session for obvious feasibility reasons. Although conducting multiple conditioning sessions over several days in humans would

be challenging and time-consuming, such an approach could nonetheless yield valuable insights and enable more direct comparisons with findings from animal research.

Together, these results demonstrate that a wide range of phenotype distributions can be observed across studies, populations, and methodological frameworks. Consequently, we still lack a clear understanding of the true distribution of these phenotypes in humans, underscoring the need for standardized and comparable study designs.

The inconsistent findings in our second study raised questions about the robustness of our task to methodological adjustments, and its ability to reliably index true human sign- and goal-tracking behaviors. One may question whether the use of “false” rewards (point accumulation) was sufficiently incentive. Although prior studies have suggested that virtual point-based reward systems can elicit sign- versus goal-tracking-like behaviors (Albertella, Watson et al., 2019) comparable to monetary rewards (Watson, Pearson, Theeuwes, et al., 2020), these findings were based on VMAC tasks. VMAC differs substantially from our simplified PCA paradigm, in that such tasks are possibly more engaging and game-like, requiring participants to remain attentive on each trial (reward omission is possible if responses are slow or incorrect). By contrast, in our task, participants were relatively “passive,” only observing cues on a screen and pushing a button to collect virtual coins. These issues will be discussed further in the next section on validity.

However, results from the third experiment lend support to the validity of the paradigm, as they demonstrated theory-driven effects of reward uncertainty on cue-directed attention. Moreover, attention patterns during the omission phase aligned with participants’ earlier attentional behavior in the rewarded phase, suggesting that cue-focused attention may at least partially persist through omission. Additionally, during omission, participants who had previously experienced certain CS-US associations displayed increased cue-attention (i.e., sign-tracking), a pattern consistent with theoretical accounts of exploration and information-seeking. Taken together, these results suggest that despite limited robustness across methodological variations, our paradigm did capture relevant attentional processes associated with sign-tracking-like phenomena in humans.

Validity of Human ST/GT Paradigms

As noted in Chapter 2, face validity on its own is insufficient and should not be the sole validity criterion pursued. Yet, we tried to base our task design as much as possible on that from animal experiments. As highlighted in our scoping review (Chapter 4), the literature in the field of human sign-tracking is highly heterogeneous, with a wide range of tasks, reward types, and samples, underscoring the current lack of methodological standardization. Even if face validity alone does not guarantee the development of a reliable task, we argue that, in an emerging field, starting with a paradigm closely aligned with the original task represents a reasonable approach. Excessive departures from the original behavior may result in the task capturing constructs other than “pure” sign-tracking. In the scoping review, we have suggested basic features that should ideally be homologous in a human analogue of sign-tracking.

As an additional step, when evaluating whether a task translated from rodents to humans has sufficient validity, it is important to examine its *functional similarity*⁴². In this thesis, we assessed this across all three studies by testing associations with multiple variables linked to alcohol consumption (and related constructs such as AB), as well as personality traits like impulsivity (Studies 1 and 2), and reward uncertainty or acute alcohol administration (Study 3). While Studies 1 and 3 (Chapters 5 and 7) yielded significant associations with alcohol consumption levels, impulsivity, and reward uncertainty, Study 2 (Chapter 6) only partially (and weakly) replicated the findings from Study 1 and did not show any relationship between sign-tracking and AB. Consequently, rather than drawing firm conclusions, we can currently only suggest that our task may capture meaningful associations between these external variables and sign- and goal-tracking tendencies.

Validity questions can also be approached from another standpoint. As Prof. Xavier Noël pointed out during a conference last year (personal communication, 2025), researchers inevitably hold a “fantasy-driven” view of the validity of their experimental designs, since these designs will never fully capture the richness or complexity of individuals’ lived experiences. This consideration directly connects with the long-standing debate surrounding ecological validity⁴³ in experimental psychology.

⁴² i.e. “the extent to which there is overlap between variables that affect performance in the model and variables that affect the target phenomenon” (Boddez et al., 2023, p.12).

⁴³ A form of validity which concerns the extent to which research findings can be generalized to naturalistic contexts such as everyday clinical practice (Andrade, 2018).

From this perspective, a key question for future human sign-tracking research is whether the adoption of more ecologically valid paradigms would produce findings that are more robust or generalizable. As articulated by Schmuckler (2001), researchers aiming to enhance ecological validity should critically consider three core aspects when designing and interpreting their studies: (1) the nature of the stimuli, which should closely approximate those encountered in the participant's natural environment; (2) the characteristics of the experimental context, which should resemble real-world settings in which the target behaviors typically occur; and (3) the type of response elicited, which should draw upon participants' naturally available behavioral repertoires.

Taken together, these considerations raise important methodological questions about whether the simplified laboratory procedures commonly used in human sign-tracking tasks adequately capture the richness and complexity of real-world cue-reward interactions. Let's consider each point separately:

- 1) **Nature of the stimuli:** As a colleague once "kindly" remarked about my experiments, *"virtual coins displayed on a blue rectangle on a computer screen do not correspond to anything meaningful in people's real lives"* (personal communication, September 2025). Identifying stimuli that mirror the structure of rodent autoshaping procedures (where cues are cleanly separated in space and time from their associated rewards) is inherently challenging in human contexts. Many real-world predictive cues (e.g., a fridge when it comes to food or the sound of a coffee-machine) are encountered in close spatial and temporal proximity to the rewards themselves, thereby complicating the separation required for strict autoshaping analogues. Nevertheless, research on AB and approach bias (ApB) provides a promising proxy. A substantial body of evidence indicates that heavy drinkers tend to orient toward and approach alcohol-related cues, whether presented as images, videos, or objects embedded in virtual environments (e.g., Pennington et al., 2020; Rudaizky et al., 2026; Simon et al., 2020; Wiers et al., 2009, 2010).

This also connects to the debate on which types of rewards are most appropriate in human sign-tracking paradigms. Our scoping review (Chapter 4) revealed substantial variability across studies, including the use of food, water, money,

toys, or points. A common criticism of human paradigms is their reliance on secondary rather than primary reinforcers (Anselme & Robinson, 2020; Colaizzi et al., 2020). However, from an ecological perspective, rewards such as money (or symbolic incentives such as points or medals in gamified tasks), are arguably more representative of human lived experience than primary reinforcers like food or water.

- 2) **The experimental context:** The experimental context, particularly as a social situation in human research, presents inherent limitations, as discussed previously. To study human sign-tracking in a more ecologically valid manner, the implementation of measurements in participants' daily lives constitutes a promising avenue. One such approach was employed by Schettino et al. (2022), who used ecological momentary assessment over two days to capture participants' evaluations of ecologically relevant rewards (e.g., coffee) and their associated cues (e.g., the smell of coffee). However, to our knowledge, no subsequent studies have continued to investigate such approaches. I believe that future research on human sign-tracking might benefit from paradigms that more closely approximate real-world cue-reward dynamics.
- 3) **The type of response elicited:** With respect to response modalities, tasks based on eye-tracking rather than overt physical approach behaviors may offer greater ecological validity. In social contexts, it is often relatively unnatural for adult humans to physically touch objects encountered in their environment, whereas visual orienting responses are ubiquitous and spontaneous. Accordingly, studies on sign-tracking (or cue reactivity more broadly) that index visual attention or approach tendencies may better align with participants' natural behavioral repertoires and should therefore be prioritized in future research.

However, it is equally important to balance ambitions for ecological validity with a realistic assessment of what is practically achievable. I argue that it is probably neither possible nor necessary to develop a sign-tracking task that fully captures the complexity of everyday human experience (i.e. "*perfectly ecologically valid*"). Rodent autoshaping procedures are themselves artificial abstractions: in natural environments, rats do not encounter cleanly separated predictive cues and reward outcomes like in controlled laboratory conditioning protocols (Krause & Domjan, 2017). The very distinction between

a “*sign*” and a “*goal*” is a methodological construct rather than a naturally occurring dichotomy. This does not mean that simplified or “*artificial*” models lack value or should be abandoned. On the contrary, controlled laboratory tasks allow to isolate specific mechanisms and test how people respond to reward-related cues, potentially helping understand why some individuals may be more vulnerable to addictive behaviors. Even highly simplified sign-tracking paradigms therefore provide a useful and necessary window into processes that would be difficult (or impossible) to observe in fully naturalistic settings.

In sum, both approaches (well-controlled laboratory paradigms and more ecologically grounded real-life assessments) have merit and should continue to be developed in parallel. That said, from my current perspective, the constructs of AB and ApB appear particularly relevant to sign-tracking in animals. To examine this relationship more directly, future research could benefit from first identifying STs and GTs using a general appetitive AB task, rather than one involving substance-related cues. This would allow researchers to determine whether individuals with heightened cue responsivity (i.e., potential STs) can be detected independently of substance-specific attentional patterns—mirroring the fact that sign-tracking in rodents is initially characterized with food-based rewards. Potential directions for such research are outlined in an upcoming section (p.318).

Translating animal behavioral paradigms into human research remains a significant challenge, as extensively discussed in the literature (see Crombag et al., 2025, an update of Stephens et al., 2013). Beyond logistical, material, and financial constraints, numerous factors complicate the development of truly translational paradigms. Our attempt to adapt the ST/GT model illustrates these challenges, which span methodological, motivational, and ecological considerations inherent to human experimental settings.

Current Approaches and Emerging Directions in Human Sign- and Goal-Tracking

Learning From Model Diversity in Human Sign-Tracking Research

The fact that there are several different approaches in the current human literature on sign-tracking (e.g., PCA tasks, VMAC tasks, "*sign-tracking-like neural responses*") can be considered from a more optimistic point of view. Indeed, it has been argued that the availability of multiple ways to model the same phenomenon can ultimately lead to an integrated understanding that could not be achieved otherwise (Gerlee & Lundh, 2016b). To date, the literature has yielded several important insights:

1. Multiple markers appear to differentiate individuals who are more sensitive to reward-predictive cues. These include heightened neural reactivity to pleasant or motivationally salient stimuli (e.g., Versace et al., 2016; Webber et al., 2021) and increased dwell time on reward-predictive conditioned stimuli (e.g., Cope et al., 2023; Garofalo & di Pellegrino, 2015), among others.
2. These human profiles might be similar to (or, more optimistically, directly map onto) the ST phenotype described in animal research. This is supported by correlations with several co-occurring traits consistently documented as central in the animal literature
 - a. *Impulsivity* has been repeatedly linked to human sign-tracking or conceptually related behaviors (e.g., Cope et al., 2023; Garofalo & di Pellegrino, 2015; Schettino et al., 2022).
 - b. *Attentional control deficits* have also been associated in some studies with human analogues of sign- and goal-tracking (e.g., Colaizzi et al., 2023).
 - c. *Substance use and addiction-relevant variables* show similar patterns, with sign-tracking-like tendencies predicting higher vulnerability (e.g., Albertella et al., 2021; Albertella, Watson, et al., 2019; Watson et al., 2024).
 - d. *Neurofunctional differences* align with the animal literature, including greater involvement of subcortical reward systems in STs (e.g., Colaizzi et al., 2023; Duckworth et al., 2022; Schettino et al., 2024), as well as a

proposed double dissociation between model-free and model-based learning in STs versus GTs (Schad et al., 2020).

3. However, not all findings align with theoretical predictions, and some studies have failed to identify significant associations. The presence of these null results is scientifically valuable. Examples include Dinu et al. (2024) and Cherkasova et al. (2024), who found no relationship between ADHD and sign-tracking and found goal-tracking to be linked to greater risk-promoting effects of cues, respectively. Additional null or inconsistent results have been documented in doctoral theses (such as the present thesis, Chapter 6 and Colom's 2023 thesis, Chapter 7, which did not identify robust ST/GT profiles using a computerized eye-tracking task).

In sum, although numerous approaches have been used to model human sign- and goal-tracking, these efforts have still offered meaningful theoretical progress. Indeed, the value of a model lies not only in its predictive value but also in the conceptual understanding it provides, especially when it helps guide the development of more refined models, and flaws of past models can inspire the development of more refined approaches (Gerlee and Lundth, 2016a). At the same time, given the abundance of existing modelling strategies, it remains essential to rigorously validate them if we aim to clarify how sign- and goal-tracking processes operate in humans. As recently stated by Krom and colleagues (2026) *"Given the possibility of even subtle procedural variations influencing phenotype identification, cross-validation of different paradigms used to measure ST/GT in humans is necessary to move the field forward"* (p.13). Accordingly, establishing robust and comparable validation across paradigms should be a priority for future research.

The Expanding Landscape of Sign-Tracking Research

As our scoping review included studies published up to January 2025, it is worth briefly considering more recent developments in the literature and their implications for sign-tracking research. These emerging findings also illustrate that the field remains highly active and evolving.

One area that has recently gained attention concerns the reliability of sign- and goal-tracking measures. Badioli et al. (2026) examined the test-retest reliability and longitudinal stability of the most commonly used gaze-based index over a four-month

period. Their findings indicated good stability for sign-tracking behavior, but limited consistency for goal-tracking. The authors suggest that this may reflect either a low prevalence of goal-tracking in the population or limitations in how it is captured by current indices. They consequently argue that methodological refinements, or the development of alternative measures, may be necessary to more reliably assess these behaviors in future research.

This concern aligns with recent arguments from the animal literature. Townsend & Smith (2025) highlighted important limitations of relying on automated readouts to characterize sign-tracking. Standard measures, such as lever deflections, may obscure the richness and variability of cue-directed behavior, as animals can continue to engage in actions such as sniffing or biting that are not captured by these indices. To address this, they advocate for combining traditional measures with more detailed, video-based behavioral analyses, allowing for a more comprehensive characterization of sign-tracking.

In relation to the type of rewards used in human sign-tracking research, several recent studies also merit attention. Papantoni et al. (2025) introduced a novel and translationally oriented paradigm combining elements of computerized PCA tasks with a physical reward delivery system. In their design, the CS was presented on a screen, while the US (M&M's) was delivered via a candy dispenser positioned next to the computer, with eye-tracking glasses used to assess sign- and goal-tracking behavior. Their results showed that sign-tracking was associated with a higher waist-to-hip ratio (though not with BMI), and with increased activation in visual, salience, subcortical, and mediofrontal brain networks when viewing a video containing palatable food stimuli. The authors conclude that this paradigm represents a successful translation of animal models to human research.

Sege et al. (2025) investigated *sign-tracking-like neural responses* in individuals with AUD, using a design similar to that of Versace et al. (2019). Participants viewed emotionally evocative, neutral, and reward-predictive cues (including alcohol-related images), with reward cues associated with candy (M&M's) delivery. The late positive potential (LPP) (as an index of stimulus salience), was used, and clustering methods identified subgroups. Two distinct patterns emerged: one group showed larger LPP responses to reward-predictive cues than to other appetitive stimuli, whereas the other showed the opposite pattern, replicating prior findings (Versace et al., 2016, 2023). Notably, both groups exhibited typical LPP enhancement to emotional stimuli but minimal

responses to alcohol cues, and no differences were observed in reward consumption, AUD symptoms, or drinking behavior. The authors interpret the roughly equal distribution of these profiles within a clinical sample as challenging the notion that sign-tracking constitutes a premorbid risk factor for addiction, as this would predict a higher prevalence of sign-trackers in such populations (Flagel et al., 2009).

Finally, a recent study in rodents demonstrated that sign-tracking to a lever CS can be leveraged to promote more adaptive, less impulsive decision-making (Mahmoudi & Madden, 2024). The authors aimed to develop a rapid and efficient method for reducing impulsive choice (operationalized as a preference for smaller-sooner (SSR) over larger-later rewards (LLR)), because existing procedures typically require extensive training in rodents (e.g., Rung et al., 2018). In their experiment, rats were assigned to either a Pavlovian (autoshaping procedure) or an unpaired group (lever CS and food delivery were unrelated but presented as often as in the Pavlovian group). During a subsequent impulsive-choice task, the lever previously used as the Pavlovian CS functioned as the choice lever for selecting the LLR. After a “LLR” choice, this lever remained present throughout the delay period (same for the SSR lever) until reward delivery. Results indicated that rats that had undergone Pavlovian training sign-tracked toward the lever CS and exhibited significantly fewer impulsive choices than rats in the unpaired condition. By showing that Pavlovian conditioning can quickly reduce impulsive choice in rodents, these findings demonstrate that sign-tracking can also be leveraged for adaptive ends rather than viewed solely as a rigid or maladaptive behavior. It will be important for future research to examine whether comparable Pavlovian-based strategies could also strengthen self-control or reduce impulsive decision-making in humans.

Recent Studies Are Challenging the Persistent/Rigid Aspect of Sign-Tracking

There is currently ongoing debate regarding the extent to which sign-tracking and VMAC reflect deliberative versus automatic processes, echoing the broader dual-process framework in psychology and neuroscience. A detailed treatment of this issue is beyond the scope of the present work, but it is important to note that automaticity itself is not a unitary concept. Rather, it encompasses a heterogeneous set of features—such as being unintentional, uncontrollable, goal-independent, stimulus-driven, unconscious, efficient, and fast (for an overview, see Moors & De Houwer, 2006). In line with this complexity,

several authors have argued against simplistic dual-process accounts⁴⁴ that overemphasize stimulus-driven mechanisms in explaining suboptimal behavior, instead highlighting the contribution of goal-directed processes (Moors et al., 2017). This discussion parallels longstanding debates in the addiction literature concerning which processes can meaningfully be considered automatic or compulsive, with both theoretical (Hogarth, 2018; Moors et al., 2017) and applied challenges (e.g., Bollens' findings on AB, Bollen et al., 2022; 2025) questioning strong automaticity claims.

Within this context, several rodent studies consistently characterized sign-tracking as rigid and largely insensitive to changes in outcome value, particularly in studies demonstrating resistance to taste-aversion devaluation conducted outside the training context (Keefer et al., 2020; Morrison et al., 2015; Nasser et al., 2015; Smedley & Smith, 2018). However, more recent evidence challenges this account. When devaluation occurs within the task environment, allowing the illness-reward association to generalize directly to the training context, rodent sign-tracking behavior shows clear sensitivity to outcome devaluation (Amaya et al., 2020; Derman et al., 2018; María-Ríos et al., 2023).

At the same time, in the absence of explicit outcome-value manipulations, sign-tracking remains notably persistent in animals. STs extinguish more slowly than GTs (Fitzpatrick et al., 2019), maintain responding despite degradation of instrumental contingencies (Ahrens et al., 2016), and display reduced susceptibility to Pavlovian blocking (Holland et al., 2014; María-Ríos et al., 2023). Moreover, sign-tracking persists under omission contingencies (Chang & Smith, 2016; Townsend et al., 2023; Townsend & Smith, 2025), with punished lever-directed responses failing to decline to zero. Together, these findings underscore the strong incentive salience attributed to reward-predictive cues, which can become partially dissociated from the reward itself (Berridge, 2004).

Comparable issues have been addressed more recently in the VMAC literature. VMAC is often described as automatic as it is seen as a parallel to sign-tracking behavior (B. A. Anderson, 2016; Le Pelley et al., 2015). Consistent with this view, Watson, Pearson, Most, et al. (2019) showed that once established, the VMAC effect persists even when reward-related stimuli no longer carry informational value. However, more recent work suggests a more nuanced picture, paralleling what has been found in animals. Garre-

⁴⁴ with single-process conceptualizations gaining traction (Kruglanski & Szumowska, 2020).

Frutos et al. (2025) demonstrated that verbal instructions and awareness of contingencies can significantly modulate attentional prioritization, indicating a role for higher-level, goal-directed influences. At the same time, earlier findings from the same group showed no reduction of the VMAC effect across blocks in an unrewarded phase (Garre-Frutos et al., 2024), suggesting resistance to Pavlovian extinction once learning has occurred.

Taken together, these findings point toward a hybrid account. As recently and nicely articulated by Garre-Frutos (2025), VMAC does not fit neatly within traditional dichotomies such as implicit versus explicit or automatic versus controlled. Instead, it reflects an interplay between associative learning, attentional dynamics, and motivational factors. By extension, a similar characterization may apply to sign-tracking, challenging the view that such learned ABs can be cleanly partitioned into binary categories (Garre-Frutos, 2025). This perspective also echoes recent arguments concerning habitual versus goal-directed behavior, which suggest that such distinctions are matters of degree rather than separate categories, with “habitual” behaviors being indeed goal-driven (Kruglanski & Szumowska, 2020). Clarifying the mechanisms governing the degree of automaticity in sign-tracking remains an important direction for future research, particularly given its implications for possible retraining and extinction-based applications.

Ongoing Translational Work

Ongoing translational work continues to advance the field and is producing promising insights. As described earlier, substantial parallels have emerged between reward-driven attentional processes in humans and animals (e.g. Liao et al., 2023; Ramamurthy et al., 2025), supporting the idea that value-guided attention may rely on evolutionary mechanisms that emerged early and have been conserved across species. A recent study by Bradfield and colleagues (2026) directly examined this cross-species correspondence by back-translating the VMAC task for rodents. Their findings demonstrated that reward-associated distractor cues disrupt instrumental behavior in mice and rats in a way that closely resembles human VMAC effects. Importantly, this attentional interference remained intact even after reducing the value of the reward through conditioned taste aversion, suggesting it may reflect a more compulsive or inflexible attentional process. However, because these conclusions come from relatively small samples, broader replication across labs and settings is needed before rodent VMAC can be considered a reliable back-translation model of cue-driven attentional

capture. Finally, as in human studies, it will also be essential to explore how reward omission and extinction procedures influence this AB.

Sign-Tracking and Beyond: Future Directions for Cue-Reactivity Research

Sign-Tracking and VMAC Research

Several findings from Martin Sarter's group suggest that bottom-up, stimulus-driven attention constitutes a core component of the psychological trait indexed by sign-tracking behavior (Koshy-Cherian et al., 2017; Sarter & Phillips, 2018). As mentioned earlier (Chapter 3), a substantial body of animal research has demonstrated robust differences between sign- and goal-tracking phenotypes with respect to bottom-up attentional control, executive processes, and behavioral flexibility (e.g., Koshy-Cherian et al., 2017; Kucinski et al., 2022; Sarter & Phillips, 2018; Paolone et al., 2013). These insights raise an important question for human research: when using attentional paradigms such as VMAC tasks, are we genuinely measuring an analogue of sign-tracking as a conditioned approach response toward a predictive cue, or are observed group differences better explained by broader trait-level differences (such as deficits in inhibitory control, altered attentional capacities, or reduced cholinergic transporter availability), that are known to distinguish STs from GTs?

Put differently, VMAC tasks may capture attentional control mechanisms that correlate with, but are not equivalent to, sign-tracking as traditionally defined. If this interpretation is correct, VMAC measures could serve as a valuable complement to a PCA task rather than as a standalone proxy for sign-tracking. Specifically, they could provide an index of attentional control processes that (based on theoretical accounts and extensive animal evidence) should be more efficient in goal-tracking individuals. This line of reasoning highlights an important gap: to advance the field, it will be crucial to evaluate both VMAC and PCA measures within the same participants.

From a future-research perspective, studies examining the convergent and discriminant validity of PCA-based sign-tracking indices and VMAC effects will be essential. Experiments assessing the degree to which these measures correlate would greatly clarify what each paradigm actually captures and whether they reflect a shared underlying trait. Ideally, such investigations would include longitudinal designs: for

example, administering both VMAC and PCA tasks at baseline (T0), applying clustering approaches such as latent profile analysis to identify participant subgroups, and testing whether these subgroups predict clinically relevant outcomes. This could include substance-use trajectories or addiction-related symptoms, as well as outcomes in other domains such as eating behavior or gambling. From a translational standpoint, parallel work in rodents will also be essential. With the recent development of rodent VMAC paradigm (Bradfield et al., 2026), such cross-species investigations are now entirely feasible.

Sign-Tracking and Attentional Bias Research

Clear conceptual parallels can be drawn between AB and sign-tracking, as both reflect heightened attentional or behavioral orienting toward reward-(predicting) cues, with both phenomena being associated to some extent with various addiction-related outcomes. Several authors have explicitly noted these similarities (e.g., Anselme & Robinson, 2020). Within the domain of eye-tracking-based AB measures, it has for instance been proposed that metrics such as the frequency of saccades into and out of alcohol-related images (e.g. Roy-Charland et al., 2017) may capture processes related to sign-tracking tendencies (Doñamayor et al., 2021).

A particularly relevant set of findings concerns the observation that heavy drinkers often display not only an AB toward alcohol stimuli but also toward other appetitive stimuli. This pattern has been interpreted as a form of “*spill-over*” or generalization from alcohol-related cues to reward cues more broadly (Bollen et al., 2020; Pennington et al., 2019). However, the causal direction may just as plausibly be reversed: individuals with a pre-existing bias toward reward-predictive cues (i.e., STs) may be at increased risk for heavy drinking and, subsequently, for developing alcohol-specific AB. Thus, as noted earlier, expanding research to examine reward-related AB more broadly may yield valuable insights and may, in some cases, offer more interpretable results than PCA-based sign-tracking paradigms alone. It is also essential for future work to directly test the relationship between sign-tracking and AB, given the strong theoretical links between them. Since STs attribute elevated incentive salience to reward-predictive cues, they should, by extension, allocate greater attention to substance-related cues (if they are consumers). If such a relationship is not observed (as in the present experiments, see Chapter 6) the heightened vulnerability of STs to addiction may be better explained by

co-occurring traits that comprise this endophenotype, rather than by amplified cue-attraction per se.

Encouraging evidence for the relevance of general reward-related AB comes from Van Hemel-Ruiter and colleagues (2013, 2015), who reported that enhanced attentional engagement with cues predicting potential reward or non-punishment correlated positively with adolescent substance use. These findings align with the notion that individuals exhibiting a heightened appetitive AB may be at elevated risk for developing heavier substance use patterns, suggesting a possible prognostic application of reward-related AB measures (that might be parallel to sign-tracking).

From an applied perspective, studying sign-tracking through the lens of AB research may also be promising. ApB and AB modification have been identified as effective adjunctive treatments for AUD (see Wiers et al., 2025 for a recent review, see Heitmann et al., 2018 for a systematic review). This raises the question of whether “sign-tracking retraining” (i.e. training individuals to be less captured by reward-associated cues) could similarly benefit individuals with a heightened tendency to attribute incentive salience to reward-predictive cues (STs). Additionally, integrating these concepts into psycho-educational interventions, as suggested in work on adolescents (Levitch et al., 2018), could help increase awareness of individual vulnerabilities associated with ST profiles.

Conclusion

This thesis investigated a novel human paradigm for assessing sign- and goal-tracking and yielded both promising findings and notable limitations. Although we cannot assert with certainty that the task captured sign-tracking in its strictest sense, the work nonetheless advances our understanding of cue-oriented behaviors in humans. For instance, individuals classified as STs in our task tended to report higher levels of alcohol consumption (although this effect was only weakly replicated), and our results suggest that the use of a movable lever may be suboptimal in computerized paradigms aiming to measure sign-tracking tendencies. Questions regarding the motivational sufficiency of hypothetical rewards were also raised and should be addressed in future designs. Consistent with extensive animal research, we further demonstrated that reward uncertainty enhances cue-directed attention in humans, providing additional evidence that such uncertainty-driven attentional amplification is a cross-species phenomenon that

can be adaptive in some contexts (e.g., survival-relevant learning) and maladaptive in others (e.g., gambling).

Beyond these specific outcomes, this thesis underscores the broader value of studying cue-reactivity (broadly defined) within translational frameworks that integrate human and animal research. Continued parallel investigation of these processes will be crucial for advancing addiction science, and several experimental pathways involving VMAC, PCA, and AB tasks have been outlined as promising avenues for future work.

Part IV

Lists, Appendices & References

List of General Abbreviations

For clarity, all non-standard acronyms and abbreviations were introduced and defined once at first mention in each chapter.

AB	Attentional Bias
ACE	Adverse Childhood Experiences
ADHD	Attention-Deficit/Hyperactivity Disorder
AI	Artificial Intelligence
AIC	Akaike Information Criterion
ANOVA	Analysis of Variance
APA	American Psychological Association
ApB	Approach Bias
ARRIVE	Animal Research Reporting of In Vivo Experiments
AUD	Alcohol Use Disorder
BAC	Blood Alcohol Concentration
BAS	Behavioral Approach System
BDMA	Brain Disease Model of Addiction
B-H	Benjamini-Hochberg
BIC	Bayesian Information Criterion
BrAC	Breath Alcohol Concentration
CAM	Cue-at-Manipulandum
CBT	Cognitive Behavioral Therapy
CFA	Confirmatory Factor Analysis
CIE	Chronic Intermittent Ethanol
CPP	Conditioned Place Preference
CR	Conditioned Response
CS	Conditioned Stimulus (or stimuli)
CS-	Non-Reinforced Cue
CS+	Reinforced Cue
DD	Dopamine Deficient
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
EPM	Elevated Plus Maze
fMRI	functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
ges	Generalized eta squared
GT	Goal-tracker

HOME CAGE	Home-cage Observation and Measurement for Experimental Control and Analysis in a Group-housed Environment
HPA	Hypothalamo-Pituitary-Adrenal axis
INT	Intermediate
IST	Incentive Sensitization Theory
ITI	Inter-Trial Interval
JARS	Journal Article Reporting Standards
JB	Joanna Briggs Institute
LLR	Larger-Later Rewards
LPA	Latent Profile Analysis
LPP	Late Positive Potential
NAcc	Nucleus Accumbens
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OCD	Obsessive Compulsive Disorder
OSF	Open Science Framework
PCA	Pavlovian Conditioned Approach
PD	Parkinson's Disease
PET	Positron Emission Tomography
PIT	Pavlovian-to-Instrumental Transfer
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
RBS	Response Bias Score
REML	Restricted Maximum Likelihood
ROI	Region of Interest
RPE	Reward Prediction Error
RSA	Research Society on Alcohol
SAT	Sustained Attention Task
S-R	Stimulus-Response
SSR	Smaller-Sooner Rewards
ST	Sign-tracker
ST/GT	Sign-tracker/Goal-tracker
STM	Sign-tracking Model

STRINGENCY	Acronym referring to ten recommendations for good practice guidelines for preclinical alcohol research (Meinhardt et al., 2025): S ystematic review prior to study plan, T ailored scientific data management, R egistration of study plan, I nception of study by calculated sample size, N etworks of centers for multi-site experiments, G eneralization of research data, E nunciation of data using ARRIVE, N ull-results should be published, C apturing DSM5/ICD11 criteria in animal models, M ethodology Y should be validated and under control
SUD	Substance Use Disorder
UMAC	Uncertainty Modulated Attentional Capture
US	Unconditioned Stimulus (or stimuli)
USV	Ultrasonic Vocalizations
VDAC	Value-Driven Attentional Capture
VMAC	Value-Modulated Attentional Capture
WFAIS	Wake Forest Alcohol Imagery Set
WHO	World Health Organization

List of Questionnaire-Related Abbreviations

ASQ	Alcohol Sensitivity Questionnaire
AUDIT	Alcohol Use Disorder Identification Test (-C = Consumption subscale)
BATCAP	Brief Assessment Tool for Compulsivity Associated Problems
BIS	Behavioral Inhibition System (RST-PQ subscale)
DASS-21	Depression Anxiety Stress Scale
DEQ	Drug Effects Questionnaire
GDP	Goal Drive Persistence (RST-PQ subscale)
KSS	Karolinska Sleepiness Scale
Lper (UPPS)	Lack of Perseverance (subscale of UPPS-P)
Lpre (UPPS)	Lack of Premeditation (subscale of UPPS-P)
PU (UPPS)	Positive Urgency (subscale of UPPS-P)
RI	Reward Interest (RST-PQ subscale)
RR	Reward Reactivity (RST-PQ subscale)
RST-PQ	Reinforcement Sensitivity Theory of Personality Questionnaire
SS	Sensation Seeking (subscale of UPPS-P)
TEPS	Temporal Experience of Pleasure Scale
UPPS-P	Short version of the Five Dimension UPPS-P Impulsive Behavior Scale
UR (UPPS)	Urgency (subscale of UPPS-P)

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Appendix A

Supplementary Information for Chapter 4

Scoping Review Search Strategies

Search run on April 26th, 2023.

Table A. *Detailed Search Strategies in Each Database*

Database	Terms	Records retrieved
MEDLINE	#1 ((sign OR goal) adj track*).ti.ab.kf.	634
(OVID)	#2 Reward/ #3 reward*.ti.ab.kf. #4 (attention* adj4 captur*).ti.ab.kf #5 autoshaping.ti.ab.kf. #6 (pavlovian adj2 instrumental adj2 trasnfer).ti.ab.kf. #7 (#2 OR #3) #8 (#4 AND #7) #9 (#1 OR #5 OR #6 OR #8) #10 Humans/ #11 human experimentation/ #12 exp Adult/ #13 Persons/ #14 Women/ #15 Men/ #16 Adolescent/ #17 exp Child/ #18 exp Infant/	

#19 (human* OR person* OR people OR adult* OR woman OR
women OR man OR men OR adolescen* OR teen* OR child*
OR infan* OR participant* OR "experimental subject*").ti.ab.kf
#20 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR
#17 OR #18 OR #19)
#21 (#9 AND #20)
#22 limit 9 to "humans only (removes records about animals)"
#23 (#21 OR #22)

PSYCINFO
(OVID)

#1 ((sign OR goal) adj track*).ti.ab.id.

598

#2 Rewards/

#3 Reward Learning/

#4 reward*.ti.ab.id.

#5 (attention* adj4 captur*).ti.ab.id.

#6 Autoshaping/

#7 autoshaping.ti.ab.id.

#8 (pavlovian adj2 instrumental adj2 transfer).ti.ab.id.

#9 (#2 OR #3 OR #4)

#10 (#9 AND #5)

#11 (#6 OR #7)

#12 (#1 OR #8 OR #10 OR #11)

#13 Human Males/

#14 Human Females/

#15 Experimental Subjects/

#16 (human* OR person* OR people OR adult* OR woman OR
women OR man OR men OR adolescen* OR teen* OR child*
OR infan* OR participant* OR "experimental subject*").ti.ab.id.

#17 (#13 OR #14 OR #15 OR #16)

#18 (#12 AND #17)

#19 limit #12 to humans

#20 (#18 OR #19)

EMBASE	#1 ((sign OR goal) NEXT/1 track*):ti.ab.kw #2 'reward'/de #3 reward*:ti.ab.kw #4 (attention* NEAR/4 captur*):ti.ab.kw #5 autoshaping:ti.ab.kw #6 (pavlovian NEAR/2 instrumental NEAR/2 transfer):ti.ab.kw #7 (#2 OR #3) #8 (#4 AND #7) #9 (#1 OR #5 OR #6 OR #8) #10 'human'/de #11 'human experiment'/de #12 'adult'/de #13 'child'/de #14 'adolescent'/de #15 'infant'/de #16 (human* OR person* OR people OR adult* OR woman OR women OR man OR men OR adolescen* OR teen* OR child* OR infan* OR participant* OR "experimental subject*"):ti.ab.kw #17 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) #18 (#9 AND #17) #19 (#9 AND [humans]/lim) #20 (#18 OR #19)	764
SCOPUS	#1 TITLE-ABS-KEY((sign OR goal) PRE/0 (track*)) #2 TITLE-ABS-KEY(reward AND (attention* W/4 captur*)) #3 TITLE-ABS-KEY(autoshaping) #4 TITLE-ABS-KEY(pavlovian W/2 instrumental W/2 transfer) #5 (#1 OR #2 OR #3 OR #4) #6 TITLE-ABS-KEY(human* OR person* OR people OR adult* OR man OR men OR woman OR women OR child* OR infan* OR teen* OR adolescen* OR participant* OR (experimental subject*)) #7 (#5 AND #6)	768

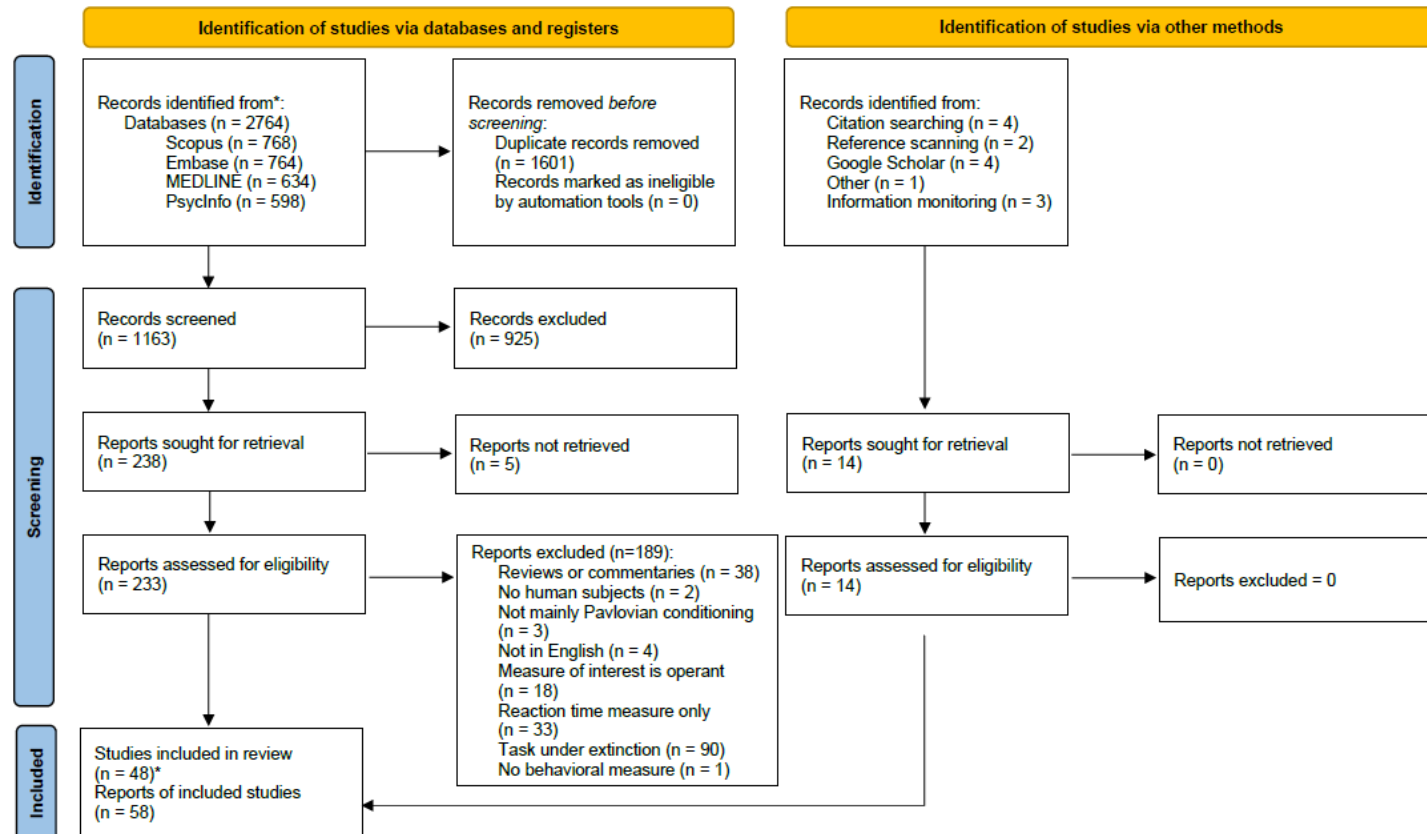
Extraction Instrument and Guidance Sheet

Table B. *Scoping Review Extraction Instrument*

Information to be extracted	Detail
Author(s), Year	-
Title	-
Type of literature	-
Aim/purpose	-
Online vs. physical	Did the study take place online or in-person?
Participants	N, gender, age
Measurement tool	How was sign- or goal-tracking (or "the tendency to attribute motivational/incentive value to reward stimuli", or "the vulnerability/susceptibility to the influence of Pavlovian cues") measured?
Reinforcer	What type of reward (if any) was delivered to the participant?
Explicit ST/GT	Is it explicitly and clearly mentioned that sign-tracking/goal-tracking behavior (or human analogue) is measured? Yes or No.
ST/GT categories	If ST and GT are measured, are people categorized according to their phenotype (ST, GT, maybe intermediates)? Yes or No.
Type of classification	If there are categories, how are they built or inferred? (Splitting in half, extreme values only, multivariate analysis, ... ?)
Percentage ST/GT	If there are categories, how many individuals are in each one?
Related variables	What related variables are of interest in the study and associated with ST/GT (or analogue) behavior?
Translational criteria	Which criteria for close translation of the animal paradigm were not met?
Results	What was the main result?

PRISMA Chart of the Scoping Review

Figure A. *Prisma Chart*



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71.

* one study (thesis) was split into 3 sub studies due to drastically different methods used

Tables of the Scoping Review

As the tables exceeded the size limits of this format, they are available through the QR code provided below.



Appendix B

Supplementary Information for Chapter 5

Detailed Descriptions of Questionnaires

For conciseness, a more detailed description of the questionnaires used is provided here.

- *The Reinforcement Sensitivity Theory of Personality Questionnaire* (RST-PQ, Corr & Cooper, 2016), which assesses six dimensions related to the RST. In the present study, we only measured three dimensions (total number of items = 24): Reward interest (RI), Goal-drive persistence (GDP) and reward reactivity (RR). Given that our translated version of this questionnaire yielded mediocre model fit indices ($\chi^2/DF = 2.08$, SRMR = .13, RMSEA = 0.10, TLI = .93, CFI = .94), we did not include it in the main analyses (further details on CFA in hereafter, correlational analyses in Table M).
- *The Temporal Experience of Pleasure Scale* (TEPS, Gard et al., 2006), which measures individual trait dispositions in anticipatory and consummatory experiences of pleasure. Only the anticipatory scale, consisting of 10 items, was measured. Given that our translated version of this questionnaire yielded mediocre model fit indices ($\chi^2/DF = 2.73$, SRMR = .09, RMSEA = 0.13, TLI = .59, CFI = .68), we did not include it in the main analyses (further details on CFA in hereafter, correlational analyses in Table M).

Four visual analog scales ranging from 0 to 100 asked the participants about the level of attractiveness of the four visual stimuli used in the study (sign, goal and the two new items of the dot-probe task).

The last questionnaire was administered both in the pre- and post-experimental phases to identify changes in stimuli attractiveness. An attention check item was embedded in the questionnaires in order to identify and exclude careless responders

after collecting the data (Maniaci & Rogge, 2014). The item read: "Please select "completely agree" for this item", on a 6-level scale from "completely disagree" to "completely agree".

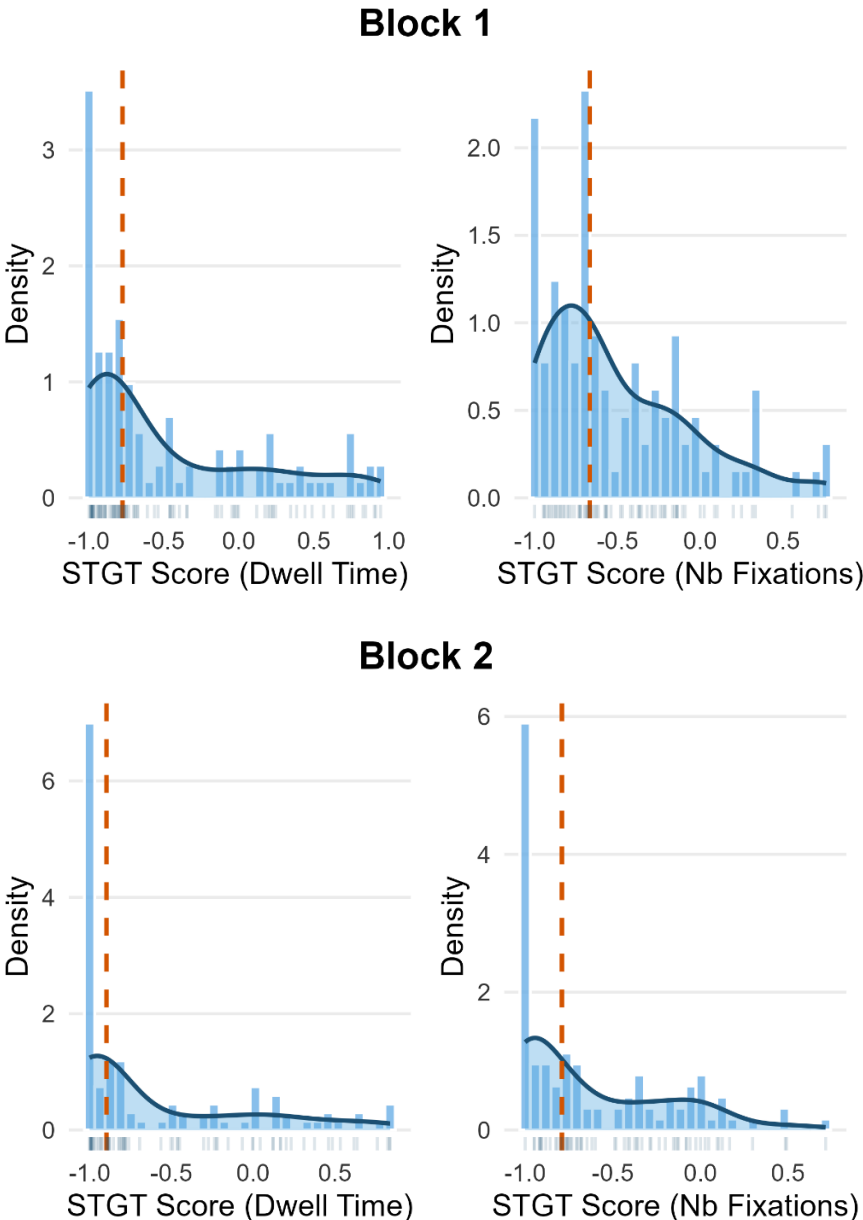
In the post-experimental phase, participants completed electronic versions of the following questionnaires:

- *The short Depression, Anxiety, Stress Scale* (DASS-21, Lovibond et al., 1995), which yields three subscale scores (21 items). A total score can be computed, representing general psychological distress.
- *The Alcohol Sensitivity Questionnaire* (ASQ, O'Neill et al., 2002), which assesses sensitivity to the acute effects of alcohol through 15 items. 9 items are associated with "lighter drinking" and 6 items are associated with "heavier drinking". High ASQ scores (indicating low sensitivity) have been associated with heavy alcohol use (Bartholow et al., 2003, 2007, 2010) and alcohol-related negative consequences (Bartholow et al., 2010; Fleming & Bartholow, 2014). Cronbach's alphas were .93 for the "heavy" and .77 for the "light" dimensions for the French translation of this questionnaire.
- *Questions about current alcohol consumption*. To gain insight into participants' recent drinking behavior, we included the following two questions into the protocol: "How many drinks have you had in the last 14 days?" and "On how many occasions have you drunk alcohol in the last 14 days?". A recent drinking index was computed by multiplying these two numbers. We also measured the following item: "How many times have you engaged in binge drinking in the past month? (Defined as consuming >5 drinks within 2 hours for men and >4 drinks within 2 hours for women.)"
- *The Brief Assessment Tool for Compulsivity Associated Problems* (BATCAP, Albertella, Le Pelley, et al., 2019), which assesses a range of compulsive symptom types. It covers alcohol use, gambling, binge eating and excessive Internet use (as well as contamination, checking, and ordering compulsions). In this study, we only used the addiction-related aspects. A "primary addiction score" is computed (score of the top-scoring domain across addictive behaviors. Cronbach's alpha was .84 for the French translation of this questionnaire.

- Two additional questionnaires were used, but not included in this report: The Edinburgh handedness inventory (Oldfield, 1971), which assesses handedness through 22 items. The 11-item version was used. The Karolinska Sleepiness Scale (KSS, Kaida et al., 2006), which measures the subjective level of fatigue at a particular time of day based on a nine-point Likert-type scale.

Distributions of ST/GT Scores (for Both Dwell Time and Number of Gazes), in the First and Second Block.

Figure B. *Distributions of ST/GT scores (Study 1)*



Note. The orange dashed line represents the median.

Analyses for Alcohol Consumption Level in the Three Groups for the 3 Other ST/GT Scores

Table C. *Kruskal-Wallis Test for Block 1 – Number of Gazes*

Variable Y	χ^2	df	p-value	Effect size (η^2)[H]	CI 95%
AUDIT-C	6.29	2	0.04	0.041	[-0.10 ; 0.09]

Table D. *P-values for Pairwise comparison* for Differences in Alcohol Consumption Level Between STs, GTs, and INTs Based on Number Based Index – Block 1*

	GT	INT
INT	0.06	-
ST	0.06	0.79

Table E. *Kruskal-Wallis Test for Block 1 – Total Dwell Time*

Variable Y	χ^2	df	p-value	Effect size (η^2) [H]	CI 95%
AUDIT-C	3.76	2	0.15	0.017	[-0.11 ; 0.05]

Table F. *P-values for Pairwise Comparison* for Differences in Alcohol Consumption Level Between STs, GTs, and INTs Based on Dwell Time Based Index – Block 1*

	GT	INT
INT	0.34	-
ST	0.18	0.34

*Wilcoxon rank test (with B-H correction)

Table G. *Kruskal-Wallis Test for Block 2 - Number of Gazes*

Variable Y	χ^2	df	p-value	Effect size (η^2) [H]	CI 95%
AUDIT-C	11.52	2	0.003*	0.092	[-0.06 ; 0.18]

Table H. *P-values for Pairwise Comparison* for Differences in Alcohol Consumption Level Between STs, GTs, and INTs Based on Number Based Index - Block 2*

	GT	INT
INT	0.058	-
ST	0.004*	0.115

*Wilcoxon rank test (with B-H correction)

Analyses Comparing Dot-Probe Sign- and Goal Trials in Comparison to New Stimuli

Table I. *Correlations Between the Dot-probe Index for Comparison With New Stimuli and the ST/GT score (PCA task)*

Attentional bias index	Spearman's Rho	Adjusted <i>p</i> -value	Raw <i>p</i> -value	CI lower (adjusted)	CI upper (adjusted)
Goal vs. New1	-0.01	0.94	0.94	-0.24	0.25
Goal vs. New2	-0.02	0.94	0.81	-0.27	0.22
Sign vs. New1	0.05	0.94	0.62	-0.20	0.29
Sign vs. New2	0.07	0.94	0.48	-0.18	0.31

Table J. *Kruskal-Wallis Tests* for Sign and Goal Bias Scores When Compared to New Stimuli 1 and 2.*

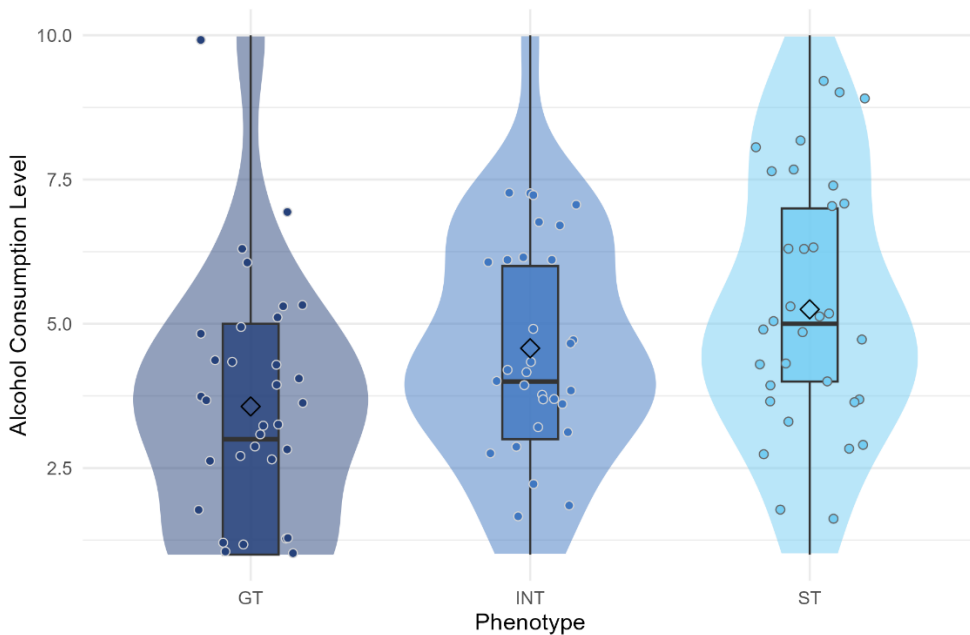
χ^2	df	<i>p</i> -value	Effect size (η^2) [H]	CI 95%
Goal vs. New1				
1.73	2	0.40	-0.001	[-0.11; 0.01]
Goal vs. New2				
0.36	2	0.83	-0.016	[-0.10; -0.01]
Sign vs. New1				
4.22	2	0.12	0.022	[-0.10; 0.06]
Sign vs. New2				
1.02	2	0.59	-0.009	[-0.10; -0.0004]

*with ST, GT and INT groups where those derived from LPA.

Hypothesis 1. Differentiating Human Sign- and Goal-Trackers – Results With Tertile Split Categorization

A Kruskal-Wallis rank-sum test was used to determine the impact of the ST/GT profile (based on a tertile split on the RBS) on general alcohol consumption level (AUDIT-C score). A significant effect of medium size ($\chi^2 = 10.70$, $p = 0.004$, $\eta^2(H) = 0.084$, 95% CI = [-0.07, 0.16]) was shown. The distribution of AUDIT-C in STs, INTs, and GTs is shown in Figure C. Post hoc pairwise Wilcoxon tests (corrected with a Benjamini-Hochberg correction for multiple comparisons) indicated that the ST and GT groups significantly differed from each other ($p = 0.006$), with STs showing higher alcohol consumption levels than GTs. The difference between GTs and INTs was also significant ($p = 0.04$), with INTs showing higher AUDIT-C scores than GTs. However, the difference between STs and INTs did not reach significance ($p = 0.22$).

Figure C. Alcohol Consumption Level in STs, GTs and INTs (Based on Tertile Split)



Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Gender Effects

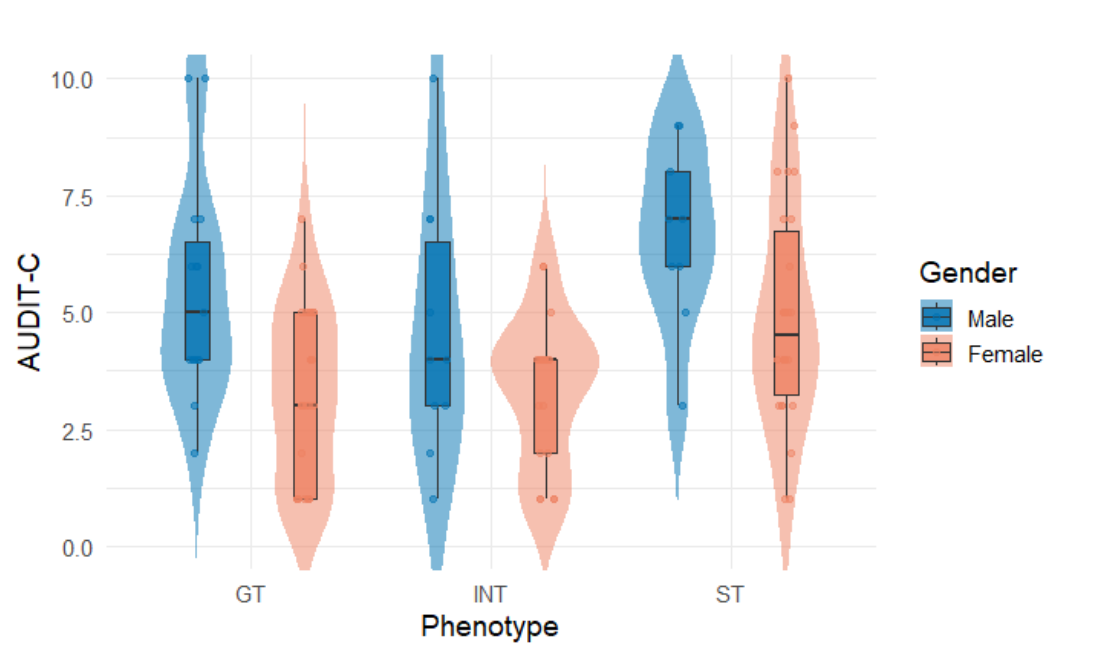
To examine potential gender differences in ST/GT scores, a Mann-Whitney U test was conducted comparing men and women. As the sample included only one non-binary participant, it was not feasible to include a third group in the analysis.

No statistically significant difference was shown, $W = 1079$, $p = .372$. The estimated effect size was very small ($r = 0.09$, 95% CI [0.004, 0.28]), which suggests no meaningful gender difference in ST/GT tendencies in our sample.

To examine whether AUDIT-C scores differed as a function of both gender and ST/GT group classification, we conducted a two-way ANOVA with gender and ST/GT group as independent variables, and AUDIT-C scores as the dependent variable. Assumptions of normality and homogeneity of variance were met for this analysis.

- The analysis revealed a significant main effect of gender, $F(1, 99) = 16.32$, $p < .001$, $\eta^2 = 0.13$, indicating that men reported significantly higher AUDIT-C scores than women. This replicates prior findings from the literature, where men consistently show a greater alcohol consumption and a higher AUD prevalence.
- A significant main effect of ST/GT group was also observed, $F(2, 99) = 6.76$, $p = 0.001$, $\eta^2 = 0.11$, supporting the main results of the manuscript: STs report higher AUDIT-C scores than GTs.
- There was no significant interaction between gender and ST/GT group, $F(2, 99) = 0.39$, $p = 0.67$, $\eta^2 = 0.006$, suggesting that the effects of gender and ST/GT phenotype on alcohol consumption level were independent in this sample (Figure D).

Figure D. AUDIT-C Scores by Gender and Sign-Tracking Phenotype



Note. Horizontal lines are the medians, the lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

Correlations Between the Dot-Probe Index and the ST/GT Score and Alcohol Variables

Table K. *Correlations Between the Dot-Probe Index and the ST/GT Score and Alcohol Variables*

Variable	Spearman's Rho	Adjusted P-value	Raw P-value	CI Lower (adjusted)	CI Upper (adjusted)
ASQ	0.14	0.71	0.15	-0.12	0.39
BATCAP (alcohol)	0.10	0.71	0.35	-0.17	0.35
Recent drinking index	0.05	0.71	0.59	-0.20	0.30
AUDIT-C	0.04	0.71	0.71	-0.22	0.29
ST/GT score	-0.05	0.71	0.59	-0.30	0.20

Note. The ST/GT score used here is the same as in the main analysis (based gaze duration during the second block). AUDIT-C = short version of the alcohol use disorder identification test. BATCAP-Alcohol is the total score for the "alcohol" subscale from the Brief Assessment Tool for Compulsivity Associated Problems. ASQ= alcohol sensitivity questionnaire. Only pairwise complete observations were included, since BATCAP and ASQ could present missing data (not due to actual missing data, but to participants not presenting the measured behavior).

Cronbach's Alpha and Learning Analysis

To test the internal consistency of the eye-gaze index derived from the PCA task, we computed Cronbach's Alpha for the 20 trials in each bloc for the following index (sign dwell time - goal dwell time)/ (sign dwell time + goal dwell time). Overall alpha for the first bloc was 0.95 (95% CI: 0.94-0.97) and for the second bloc, 0.97 (95% CI: 0.96-0.98).

To test if dwell time (towards the sign and the goal) significantly evolved throughout the two experimental blocks for the 3 behavioral profiles, we ran a linear mixed model with subjects nested within classes (LPA extracted) as the random factor.

Regarding dwell time toward the goal, all effects were highly significant ($p < 0.001$). When comparing classes, STs showed significantly shorter dwell times on the goal when compared to GTs ($t = -14.71$, $p < 0.001$). The same observation was true for INTs ($t = -4.43$, $p < 0.001$). All 3 profiles also differed when comparing the first and the second bloc, with INTs and STs gazing less at the goal in the second block, compared to GTs (INTs: $t = -3.68$, $p < 0.001$; STs: $t = -7.95$, $p < 0.001$).

Regarding gazes toward the sign, all effects were highly significant ($p < 0.001$), with STs scoring significantly above GTs ($t = 6.05$, $p < 0.001$). INTs also scored significantly higher than GTs ($p = 0.03$). STs also spent significantly more time gazing at the sign, when compared to GTs in the second block, compared to the first one ($t = 3.96$, $p < 0.001$). This effect was not significant when comparing INTs and GTs in the second Bloc ($t = -0.76$, $p = 0.44$).

Full Correlation Matrices

Table L. *Full Correlation Matrix for Table 4 (Alcohol Variables)*

Variable	ST/GT Score			
ASQ	$R_s = -0.03$ Adj. $p = 0.864$	ASQ		
BATCAP	$R_s = 0.10$ Adj. $p = 0.395$	$R_s = -0.004$ Adj. $p = 0.968$	BATCAP- Alcohol	
Recent Drinking Index	$R_s = 0.19$ Adj. $p = 0.061$	$R_s = 0.20$ Adj. $p = 0.059$	$R_s = 0.34^*$ Adj. $p = 0.002$	Recent Drinking Index
AUDIT-C	$R_s = 0.29^{**}$ Adj. $p = 0.006$	$R_s = 0.26^*$ Adj. $p = 0.014$	$R_s = 0.22^*$ Adj. $p = 0.045$	$R_s = 0.65^{***}$ Adj. $p < 0.001$

Note. ASQ = Alcohol sensitivity questionnaire, BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test (see 2.6. "Questionnaires"). The p-value differences between Table 4 and Table L reflect the scope of each analysis: Table 4 shows correlations only between ST/GT scores and alcohol variables, while Table L includes all correlations, including among alcohol variables. Thus, the number of comparisons (and the adjusted p-values) differs. $^* < 0.05$, $^{**} < 0.01$, $^{***} < 0.001$.

Table M. Full Correlation Matrix for Table 5 (Personality Variables, Except Impulsivity, including RST-PQ)

Variable	ST/GT Score					
TEPS	$R_s = 0.07$ $p = 0.520$	TEPS				
Psychological Distress	$R_s = 0.06$ $p = 0.591$	$R_s = 0.11$ $p = 0.341$	Psych. Distress			
RST-PQ-RR	$R_s = 0.09$ $p = 0.434$	$R_s = 0.58^*$ $p < 0.001$	$R_s = 0.12$ $p = 0.295$	RST-PQ- RR		
RST-PQ-Goal- per	$R_s = -0.01$ $p = 0.909$	$R_s = 0.22$ $p = 0.051$	$R_s = -0.07$ $p = 0.520$	$R_s = 0.38^*$ $p < 0.001$	RST-PQ- Goal-per	
RST-PQ-Goal- plan	$R_s = -0.17$ $p = 0.143$	$R_s = 0.19$ $p = 0.106$	$R_s = -0.04$ $p = 0.696$	$R_s = 0.18^*$ $p = 0.125$	$R_s = 0.52^*$ $p < 0.001$	RST-PQ- Goal-plan
RST-PQ- RI	$R_s = -0.13$ $p = 0.253$	$R_s = 0.17$ $p = 0.143$	$R_s = -0.14$ $p = 0.240$	$R_s = 0.37^*$ $p < 0.001$	$R_s = 0.30^*$ $p = 0.004$	$R_s = 0.32^*$ $p = 0.002$

Note. P-values are adjusted, $* < 0.05$. TEPS = temporal experience of pleasure scale, RST-PQ = The Reinforcement Sensitivity Theory of Personality Questionnaire, RR= reward reactivity, Goal-per= goal persistence, Goal-plan= goal planning, RI= reward interest

Table N. Full Correlation Matrix for Table 5 (Personality Variables, Impulsivity Dimensions)

Variable	ST/GT Score				
Urgency	$R_s = 0.18$ Adj. p = 0.101	Urgency			
Positive Urgency	$R_s = 0.25^*$ Adj. p = 0.023	$R_s = 0.45^{***}$ Adj. p < 0.001	Pos. Urgency		
Lack Premeditation	$R_s = 0.14$ Adj. p = 0.184	$R_s = 0.47^{***}$ Adj. p < 0.001	$R_s = 0.49^{***}$ Adj. p < 0.001	Lack Premed.	
Lack Perseverance	$R_s = 0.07$ Adj. p = 0.507	$R_s = 0.24^*$ Adj. p = 0.023	$R_s = 0.20$ Adj. p = 0.066	$R_s = 0.36^{***}$ Adj. p < 0.001	Lack Persev.
Sensation Seeking	$R_s = -0.001$ Adj. p = 0.990	$R_s = 0.14$ Adj. p = 0.185	$R_s = 0.20$ Adj. p = 0.073	$R_s = 0.16$ Adj. p = 0.149	$R_s = 0.08$ Adj. p = 0.438

Note. $^* < 0.05$, $^{***} < 0.001$.

Confirmatory Factor Analysis Results for Translated Questionnaires

TEPS

Confirmatory Factor Analysis (CFA) demonstrated poor model fit for the translated version of the questionnaire ($\chi^2/df = 2.73$, CFI = 0.68, TLI = 0.59, RMSEA = 0.13, SRMR = 0.09).

Examination of the factor loadings revealed that while some items, such as TEPS_9 (Std.all = 0.738) and TEPS_1 (Std.all = 0.672), showed strong associations with the latent variable, others, like TEPS_7 (Std.all = 0.281) and TEPS_4 (Std.all = 0.306), exhibited weaker relationships.

RST-PQ

Confirmatory Factor Analysis (CFA) using the Diagonally Weighted Least Squares (DWLS) estimator (to account for the ordinal nature of the 5-point Likert scale data) demonstrated modest to poor fit for the translated version of the RST-PQ ($\chi^2/df = 2.08$, CFI = 0.94, TLI = 0.93, RMSEA = 0.10, SRMR = 0.13).

Examination of the factor loadings revealed that most items exhibited strong standardized loadings (e.g., RR_4 = 0.813, RI_1 = 0.936, Goal_pers_2 = 0.910), indicating robust associations with their respective latent variables. However, some items, such as RR_6 (Std.all = 0.301), RI_5 (Std.all = 0.374), and Goal_pers_4 (Std.all = 0.457), showed weaker loadings, suggesting they may contribute less to measuring the underlying constructs. Significant covariances were observed among the latent variables (e.g., RR ~ RI = 0.408, RR ~ Goal = 0.489), highlighting their interrelated nature. These results suggest that while the translated questionnaire captures the intended constructs to some extent, further refinement is necessary to improve overall model fit and item performance.

Appendix C

Supplementary Information for Chapter 6

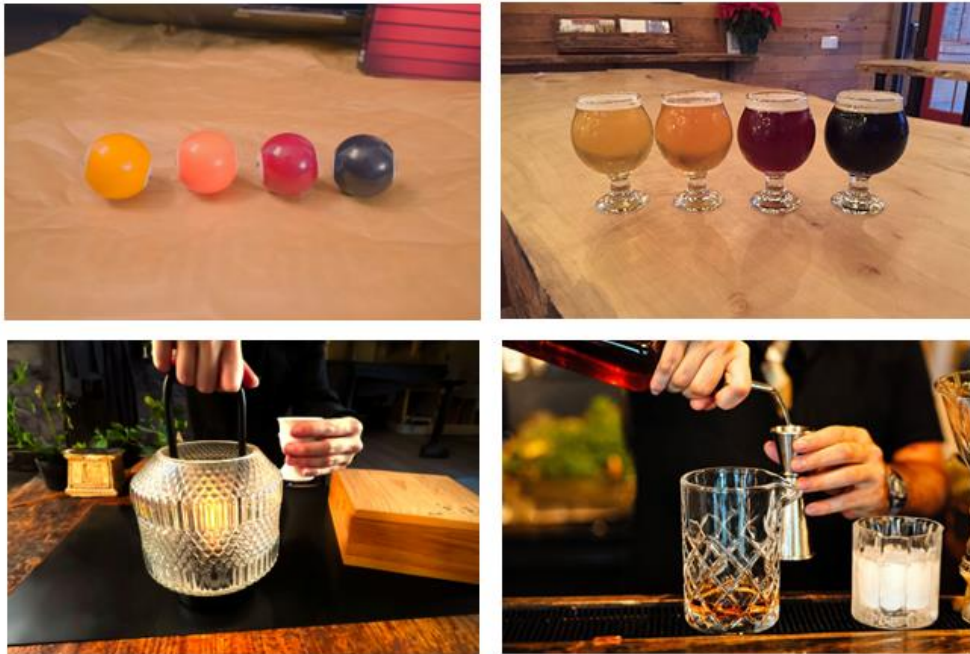
Additional Information on Stimuli Selection for Alcohol Attentional Bias Task (Pilot).

Table O. *Mean Alcohol-Relatedness Scores by Stimulus Category (Pilot Phase)*

Category	Mean score for Neutral Pictures (range)	Mean score for Alcohol Pictures (range)
Beer (N=13)	0.82 (0.23-3.85)	9.20 (8.31-9.46)
Champagne (N=13)	0.55 (0.23-1.31)	9.38 (9.31-9.46)
Cocktail (N=13)	0.81 (0.23-2.15)	9.05 (8.77-9.62)
Environment (N=13)	0.88 (0.23-2.62)	9.02 (8.23-9.62)
Liquor (N=13)	0.89 (0.31-1.85)	9.46 (9.15-9.85)
Wine (N=16)	0.92 (0.18-3.43)	8.51 (7.69-9.06)

Attentional Bias Task Illustration

Figure E. *Examples of Alcohol and Neutral Picture Pairs, for Beer and Liquor*



Gaze Evolution Analyses

Experiment 1

To examine whether dwell time (toward the sign and the goal) changed across trials and experimental blocks for the three behavioral profiles (extracted via LPA), we fitted a linear mixed-effects model including fixed effects of profile, trial number, block, and their interactions (profile $\times$ trial and profile $\times$ bloc). The model included a random intercept and a random slope of trial number for each participant to account for individual differences in overall dwell time and learning trajectories. To visualize how the profiles evolved in dwell time through the task, we plotted their dwell time on the first vs the last trial (Figures F and G).

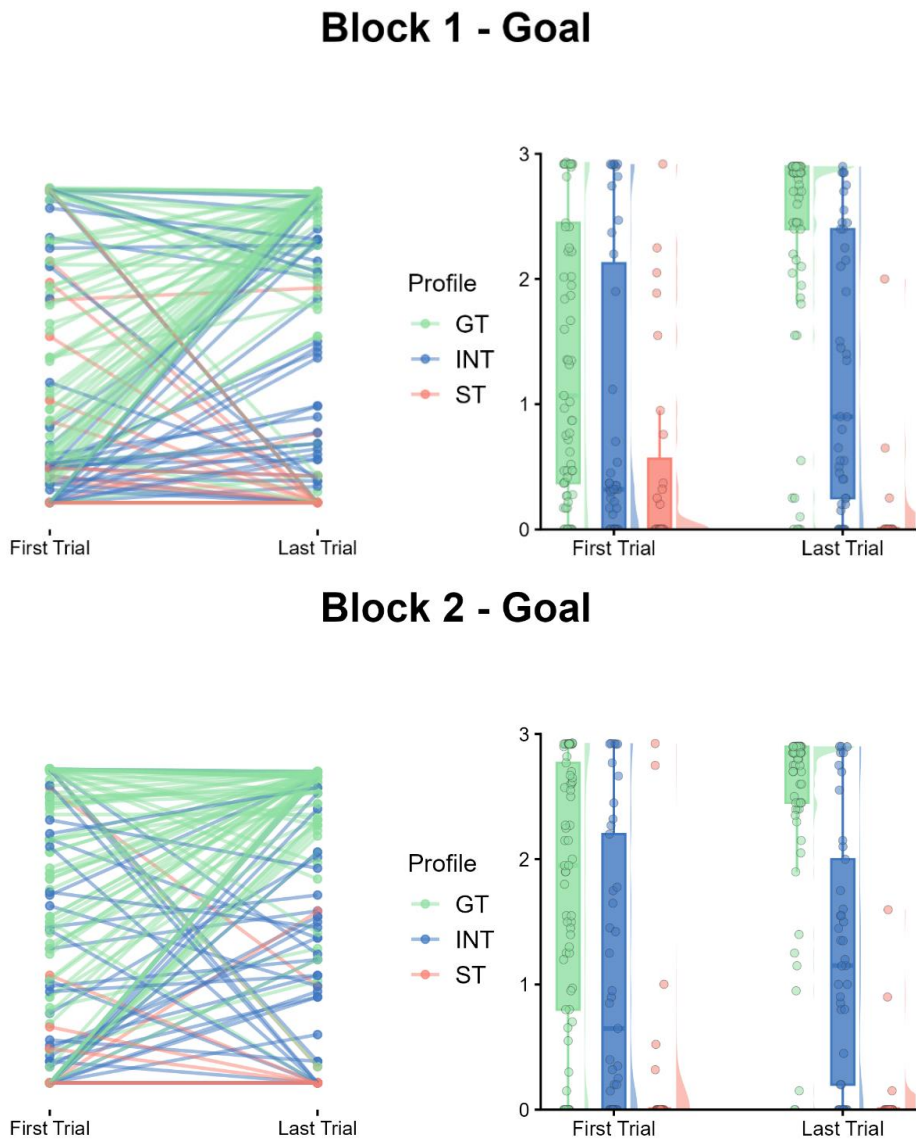
Regarding **dwell time toward the goal**, all main effects and interactions were highly significant (all $p < .001$). Examining the change from the first to the last trial in both blocks reveals clearly distinct trajectories for the three profiles (Figure F). GTs consistently exhibited the highest dwell times across the task. They showed a marked increase in goal-oriented dwell time over trials, whereas STs demonstrated a decrease in Block 1. In

both Blocks 1 and 2, all pairwise comparisons between profiles were significant (all $p < .0001$).

Regarding **dwell time toward the sign**, all effects were significant ($p < .05$). The change from the first to the last trial in each block again shows clearly distinct trajectories across profiles (Figure G). STs displayed the highest dwell times throughout the task, with an overall increase from the first to the last trial. GTs showed the opposite pattern in Block 1. In Block 2, INTs and GTs spent very little time looking at the sign on average, whereas STs maintained high levels of sign-oriented dwell time. All pairwise comparisons between profiles were significant in both blocks ($p < .05$), with the exception of the comparison between GTs and INTs in Block 2 ($p = .05$).

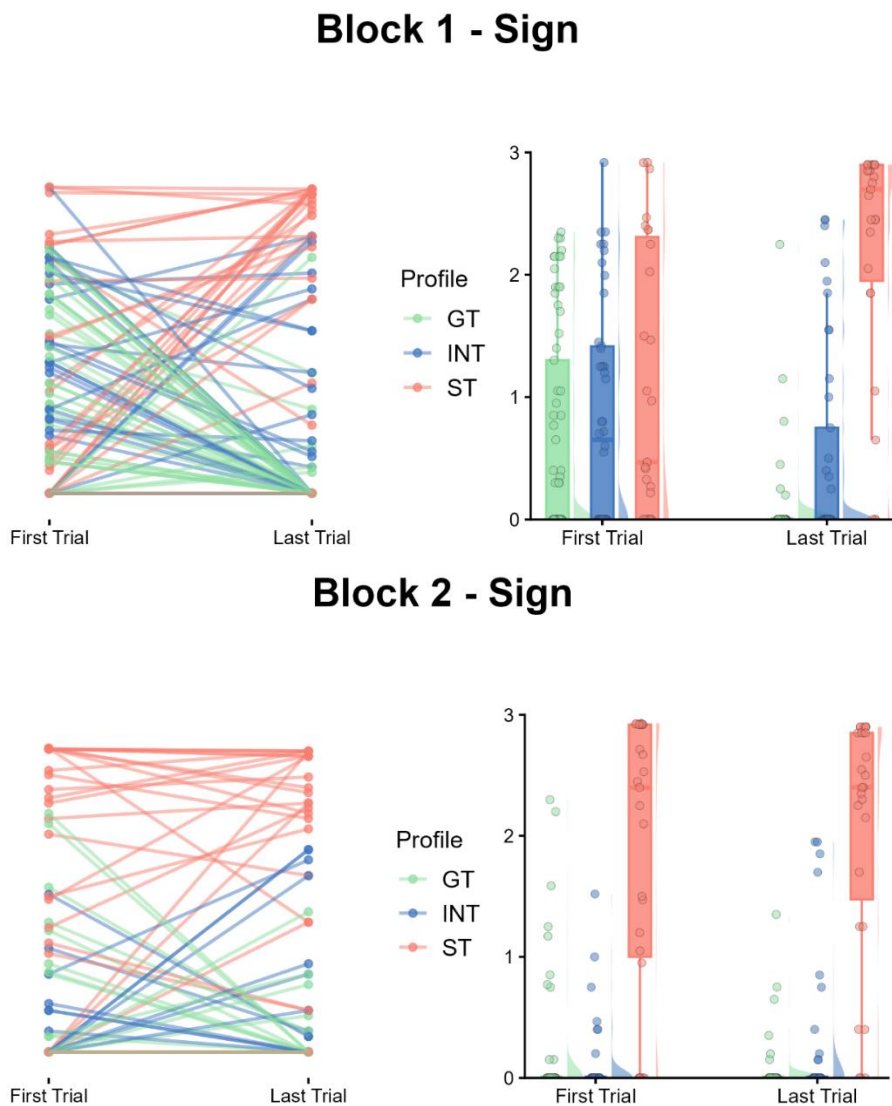
Comparing the trajectories across the main study and the parallel study using the lever reveals a notable difference: in the lever study, STs already show high sign-oriented dwell times from the very first trials in both blocks. This pattern suggests that their attention may not have been primarily driven by CS-US learning across trials, but instead by another factor (potentially the lever CS being too distracting).

Figure F. *Difference in Goal Dwell Time Between First and Last Trials, in Blocs 1 and 2 (Experiment 1)*



Note. In the left panels, each point represents an individual observation, and lines illustrate within-participant change from first to last trial. The right panel displays the distribution of performance scores for each profile at the First Trial and Last Trial. Boxplots represent the median and interquartile range, with whiskers indicating the full data range. Individual data points are overlaid to show variability within each profile.

Figure G. *Difference in Sign Dwell Time Between First and Last Trials, in Blocs 1 and 2 (Experiment 1)*



Note. In the left panels, each point represents an individual observation, and lines illustrate within-participant change from first to last trial. The right panel displays the distribution of performance scores for each profile at the First Trial and Last Trial. Boxplots represent the median and interquartile range, with whiskers indicating the full data range. Individual data points are overlaid to show variability within each profile.

Experiment 2

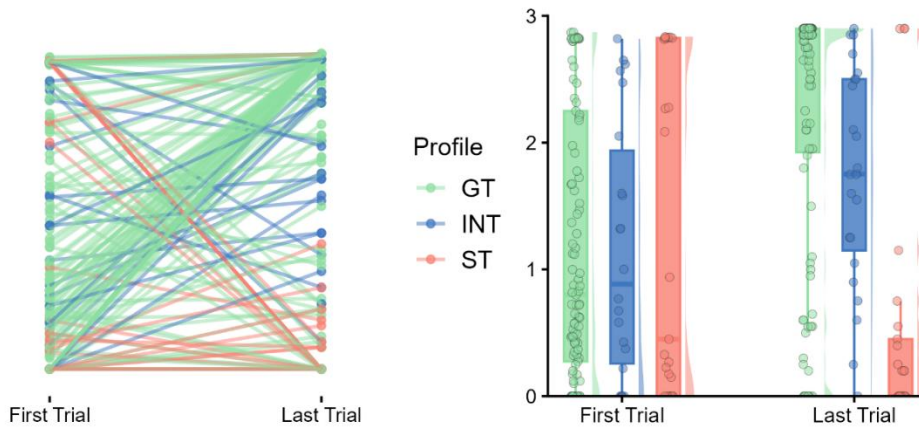
The same analyses as in experiment 1 were run on the present data.

Regarding **dwelt time toward the goal**, all main effects and interactions were highly significant (all $p < .001$), with the exception of the effect of *trial* ($p = .50$). Examining the change from the first to the last trial across both blocks reveals clearly distinct trajectories for the three profiles (Figure H). GTs displayed a clear increase in goal-oriented dwell time over trials, while (except some outliers) STs remained relatively low. In both Blocks 1 and 2, all pairwise comparisons between profiles were significant (all $p < .05$).

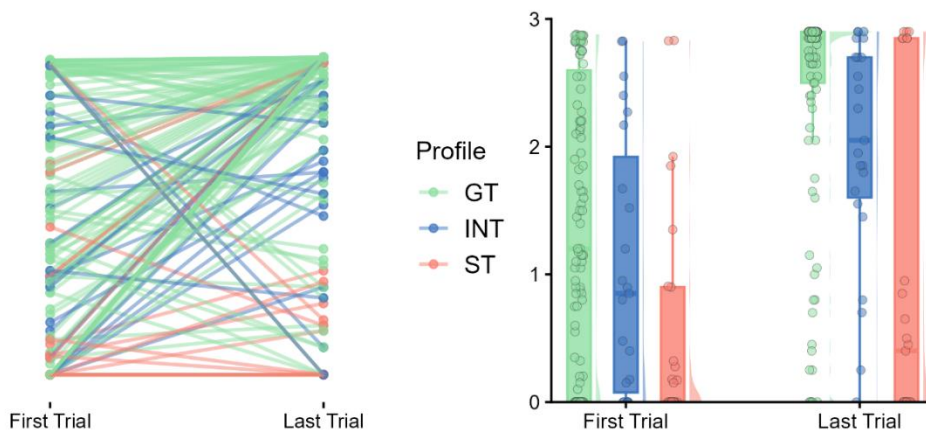
Regarding **dwelt time toward the sign**, all effects were highly significant (all $p < .001$), with the exception of the effect of *trial* ($p = .35$). Examining the change from the first to the last trial in both blocks shows that the three profiles follow clearly distinct trajectories (Figure I). STs exhibit the highest dwell times throughout the task, with an overall increase from the first to the last block, whereas INTs and GTs remain consistently low. In both Blocks 1 and 2, all pairwise comparisons between profiles were significant ($p < .0001$), except for the comparisons between GTs and INTs (Block 1: $p = .22$; Block 2: $p = .95$).

Figure H. *Difference in Goal Dwell Time Between First and Last Trials, in Blocs 1 and 2 (Experiment 2)*

Block 1 - Goal

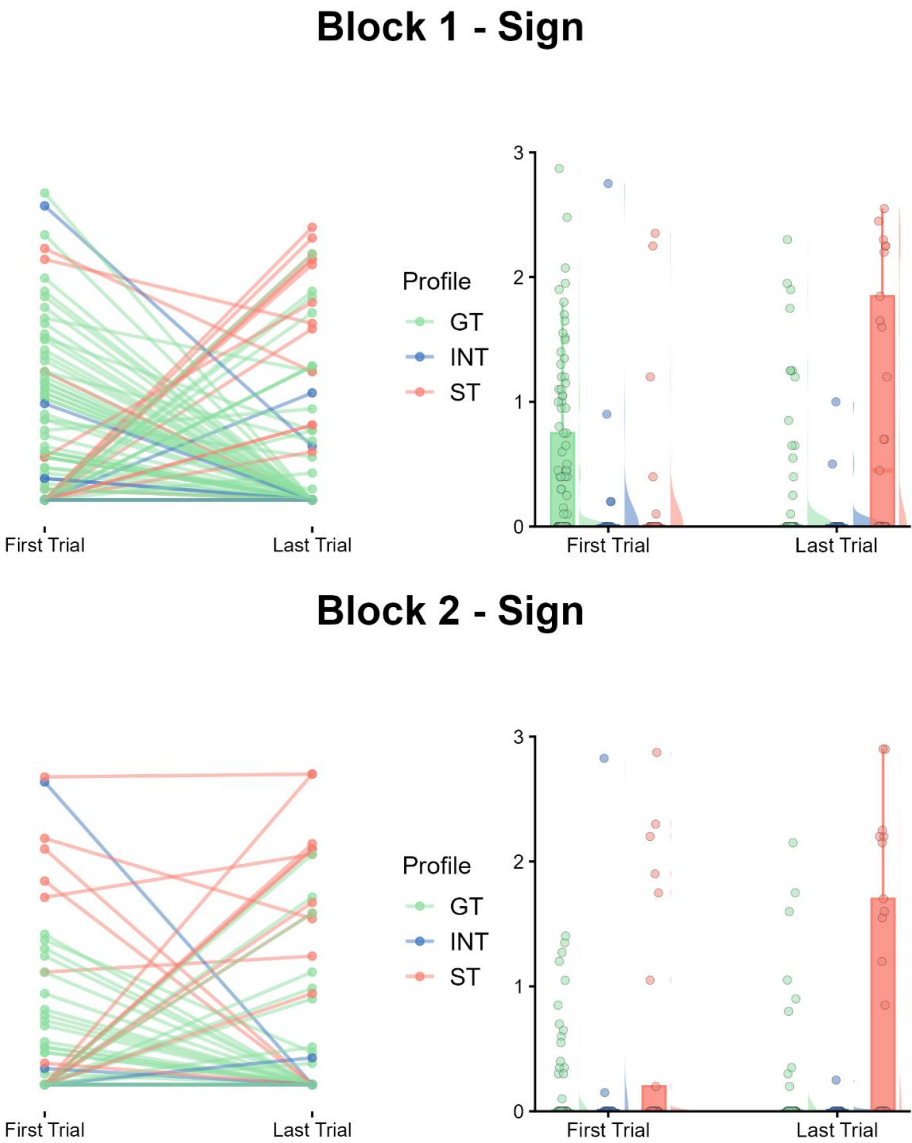


Block 2 - Goal



Note. In the left panels, each point represents an individual observation, and lines illustrate within-participant change from first to last trial. The right panel displays the distribution of performance scores for each profile at the First Trial and Last Trial. Boxplots represent the median and interquartile range, with whiskers indicating the full data range. Individual data points are overlaid to show variability within each profile.

Figure I. *Difference in Sign Dwell Time Between First and Last Trials, in Blocs 1 and 2 (Experiment 2)*



Note. In the left panels, each point represents an individual observation, and lines illustrate within-participant change from first to last trial. The right panel displays the distribution of performance scores for each profile at the First Trial and Last Trial. Boxplots represent the median and interquartile range, with whiskers indicating the full data range. Individual data points are overlaid to show variability within each profile.

Correlations Between AB Variables and Alcohol Consumption Variables in Experiment 1

Table P. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between Alcohol AB variables and Alcohol-Related Variables (Experiment 1)*

Total Alcohol Gaze (AB)					
Variable	Spearman Rho	Adjusted P-Value	Raw P-Value	CI Lower (Adjusted)	CI Upper (Adjusted)
AUDIT	0.05	0.579	0.580	-0.19	0.28
BATCAP (Alcohol)	0.05	0.579	0.578	-0.20	0.30
DrinkOccas	0.11	0.317	0.199	-0.13	0.34
AUDIT-C	0.19	0.112	0.026*	-0.05	0.41
Percent of First Alcohol Gazes					
AUDIT	-0.07	0.576	0.432	-0.30	0.17
BATCAP (Alcohol)	-0.19	0.112	0.042*	-0.42	0.06
DrinkOccas	-0.18	0.112	0.041*	-0.40	0.06
AUDIT-C	-0.14	0.224	0.112	-0.36	0.10

Note. As stated in the manuscript, N=131 for this analysis. BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test (see "Questionnaires"). * $p < 0.05$, *** $p < 0.001$

Correlations Between AB Variables and Alcohol Consumption Variables in Experiment 2

Table Q. Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between Alcohol AB variables and Alcohol-Related Variables (Experiment 2)

Total Alcohol Gaze (AB)					
Variable	Spearman Rho	Adjusted P-Value	Raw P-Value	CI Lower (Adjusted)	CI Upper (Adjusted)
AUDIT	0.25	0.02*	0.00**	0.02	0.46
BATCAP (Alcohol)	0.25	0.02*	0.01*	0.00	0.47
DrinkOccas	0.20	0.04*	0.02*	-0.04	0.41
AUDIT-C	0.21	0.03*	0.01*	-0.02	0.43
Percent of First Alcohol Gazes					
AUDIT	0.12	0.25	0.19	-0.12	0.34
BATCAP (Alcohol)	0.08	0.38	0.39	-0.17	0.32
DrinkOccas	0.10	0.28	0.25	-0.14	0.33
AUDIT-C	0.11	0.25	0.19	-0.12	0.34

Note. As stated in the manuscript, N=154 for this analysis. BATCAP (alcohol) = alcohol-related problems (assessed with the Brief Assessment Tool for Compulsivity Associated Problems), DrinkOccas = recent drinking index (number of alcoholic drinks consumed during the past two weeks x number of alcohol drinking occasions during the past two weeks), AUDIT-C = short version of the Alcohol Use Disorder Identification Test (see "Questionnaires"). *p<0.05

Appendix D

Supplementary Information for Chapter 7

Experimental Group Equivalence for Alcohol Consumption Variables

Table R. Means, Medians and Standard Deviations for Alcohol Consumption Variables in the Experimental Groups

	Group A-50			Group P-50			Group A-100			Group P-100		
	M	M _d	SD	M	M _d	SD	M	M _d	SD	M	M _d	SD
AUDIT-C	5.1	5	2.8	5.3	6	2.4	5.3	5	2.5	5	5	2.3
Drink Index	38.1	10	96.1	31.6	10	58.4	16.3	9	25	18.5	7	27.3

Note. M= Mean, Md= Median, SD= Standard Deviation; A= Alcohol, P= Placebo, AUDIT= Alcohol Use Disorder Identification Test (-C= Consumption version); Drink Index= number of alcohol drinking occasions during the last two weeks* number of drinks per occasion.

Kruskal Wallis tests confirmed that groups did not differ significantly for AUDIT-C scores ($\chi^2 = 0.40$, $p = 0.94$, $\eta^2(H) = -0.022$) nor for recent drinking index ($\chi^2 = 2.49$, $p = 0.47$, $\eta^2(H) = -0.004$).

Including Tertile Split ST/GT/INT Groups in the Analyses

In line with common practices in the sign-tracking/goal-tracking literature and to better capture potential interactions between ST/GT behavior and contextual manipulations, participants were also categorized into three discrete groups (sign-trackers (ST), goal-trackers (GT), and intermediates (INT)) based on a tertile split of their Block 1 ST/GT scores. We acknowledge that this classification is arbitrary, as participants did not all complete the same version of the ST/GT task: some were tested under alcohol intoxication and/or reward uncertainty, while others were not. Therefore, a given ST/GT score may not be strictly comparable across experimental conditions. Nonetheless, a high score across all groups should still reflect a greater tendency toward sign-tracking. Thus, this grouping offers a more intuitive framework for examining how ST tendency may interact with contextual factors during extinction. It's however important to keep in mind that these groupings rather reflect the upper and lower extremes of the ST/GT score spectrum during the main blocks of PCA task (and should not be interpreted as true phenotypes).

Learning Analysis

Trial-by-trial changes in attention allocated to the goal location were examined, using a linear mixed-effects model. The model included trial, "ST/GT/INT profile", and their interaction as fixed effects, with subject-specific random intercepts and slopes for trial to account for inter-individual variability in baseline attention and learning trajectories. Results revealed a significant main effect of trial on fixation duration toward the goal location, indicating an overall increase in attention to the goal across trials ($\chi^2(1) = 15.53$, $p < .001$). This pattern is consistent with progressive learning of the CS-US contingency at the group level, since dwell time was collected during the CS presentation. Importantly, while "ST/GT/INT profiles" differed in overall levels of goal-directed attention (which is to be expected) ($\chi^2(1) = 110.98$, $p < .001$), the absence of a significant profile $\times$ trial interaction ($\chi^2(1) = 0.19$, $p = 0.90$) suggests that the rate of change over trials did not differ between "profiles".

Reward Omission Phase

To explore this question, we conducted two separate three-way ANOVAs with "Profile", Uncertainty, and Alcohol Intoxication as between-subjects factors, assessing

whether attentional responses during extinction—specifically, dwell times on the Sign and Goal cues—varied as a function of “profile” and whether these effects were moderated by experimental manipulations. Table S shows the distribution of participants by “profile”, group and certainty.

Table S. *Distribution of Participants by Profile, Group, and Certainty Condition*

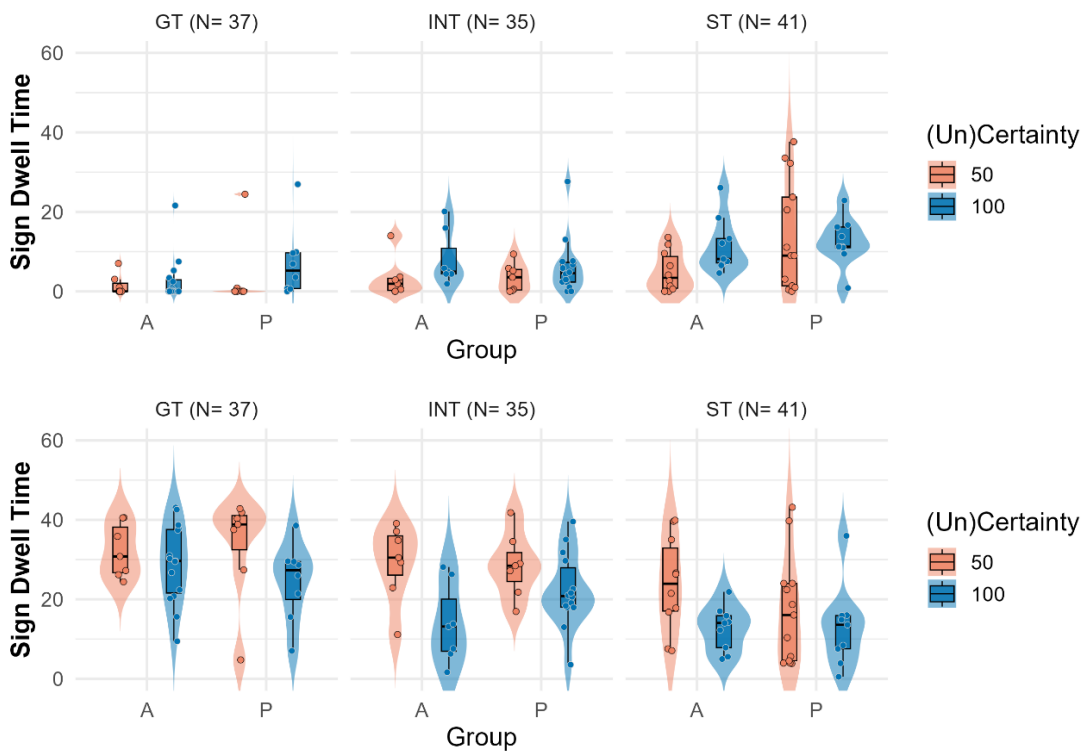
Group	Profile	Alcohol (n)	Placebo (n)	Total (n)
50% (Uncertain)	Sign-trackers (ST)	10	13	23
	Intermediates (INT)	7	7	14
	Goal-trackers (GT)	7	7	14
	Subtotal	24	27	51
100% (Certain)	Sign-trackers (ST)	9	9	18
	Intermediates (INT)	7	14	21
	Goal-trackers (GT)	15	8	23
	Subtotal	31	31	62

Note. The analyses conducted on the extinction block included a total of $N = 113$ participants (compared to $N = 118$ in the primary analyses), due to the application of additional data quality criteria specific to the extinction phase (see Methods section for details).

A three-way ANOVA was conducted to examine the effects of Group (Alcohol vs. Placebo), Certainty (50% vs. 100%), “ST/GT Profile”, and their interactions on **Sign Dwell Time during Extinction**. The analysis revealed a significant main effect of “Profile”, $F_{(2, 101)} = 15.96$, $p < 0.001$, partial $\eta^2 = 0.24$, indicating coherent Sign-oriented attention during Extinction across “ST/GT groups”. There was also a significant main effect of Group, $F_{(1, 101)} = 5.21$, $p = 0.025$, partial $\eta^2 = 0.03$, with participants in the Alcohol group showing lower Sign Dwell Times compared to those in the Placebo group. The effect of Certainty was not statistically significant, $F_{(1, 101)} = 3.22$, $p = 0.076$, partial $\eta^2 = 0.07$, and no significant two-way or three-way interactions were observed (all $ps > 0.16$). Figure J (upper panel) shows Sign Dwell Times during extinction according to Certainty, Alcohol Group, and ST/GT Phenotype.

The same three-way ANOVA conducted on **Goal Dwell Time during Extinction** revealed a significant main effect of Certainty, $F_{(1, 101)} = 7.68, p = 0.006$, partial $\eta^2 = 0.12$, indicating that participants exposed to 50% uncertainty looked longer at the goal than those of the 100% certainty group. A significant main effect of “ST/GT profile” also emerged, $F_{(2, 101)} = 15.00, p < 0.001$, partial $\eta^2 = 0.23$, suggesting eye-gaze behavior lingering through extinction. However, no significant main effect of Group ($p = 0.32$) nor any interaction reached significance (*all ps* > 0.23). Figure J (lower panel) shows Goal Dwell Times during extinction according to Certainty, Alcohol Group, and “ST/GT Profile”.

Figure J. Sign and Goal Dwell Times during Extinction as a Function of Certainty, Group, and “ST/GT Profile”



Note. Violin plots show data distribution, boxplots indicate medians and interquartile ranges, and individual dots represent participants. In printed version, light grey = 50%, dark grey = 100%. Panels correspond to Sign-tracker (ST), intermediate (INT), and Goal-tracker (GT) “profiles” respectively. A= Alcohol Group, P= Placebo Group.

Additional Exploratory Correlational Analyses – ST/GT

Additional exploratory correlational analyses revealed divergent patterns across experimental groups (Table T). In the Alcohol-100% Certainty Group, negative (although non-significant) correlations were observed between alcohol consumption levels and ST/GT scores, suggesting that, under alcohol intoxication and in a fully predictable task environment, individuals with higher alcohol use tended to exhibit more goal-tracking tendencies (contrary to what was expected based on prior findings). In contrast, in the Placebo-100% Certainty Group (arguably the condition most comparable to our previous study using the same task) a positive correlation was observed between ST/GT scores and AUDIT-C scores (as well as the other consumption-related variables). Although these associations did not reach significance, their direction and magnitude are consistent with those previously reported ($r = .29$), lending partial support to the robustness of this relationship in the absence of alcohol and under stable task contingencies.

Table T. *Correlation Coefficients, P-values and Confidence Intervals for Spearman Correlations Between the ST/GT Score and Alcohol-Related Variables*

Alcohol Group - 100% (N=31)				
Variable	Spearman's Rho	P-Value	CI Lower	CI Upper
AUDIT-C	-0.25	0.17	-0.55	0.11
AUDIT	-0.25	0.17	-0.55	0.11
BATCAP (Alcohol)	-0.09	0.64	-0.44	0.29
Drink Index	-0.31	0.08	-0.60	0.04
N° Binges	-0.25	0.17	-0.55	0.11
Imp - Urgency	0.32	0.07	-0.03	0.60
Imp- Positive Urgency	0.50	0.00*	0.18	0.72
Imp - SS	0.27	0.14	-0.09	0.56
Imp - Lack Pers	-0.04	0.81	-0.04	0.31
Imp - Lack Prem	0.42	0.02*	0.09	0.67
Placebo Group - 100% (N=31)				
AUDIT-C	0.21	0.23	-0.14	0.51
AUDIT	0.11	0.53	-0.24	0.43
BATCAP (Alcohol)	0.19	0.30	-0.18	0.51
Drink Index	0.33	0.06	-0.01	0.60
N° Binges	0.20	0.26	-0.15	0.50
Imp - Urgency	-0.11	0.52	-0.44	0.23
Imp- Positive Urgency	-0.06	0.75	-0.39	0.29
Imp - SS	-0.06	0.75	-0.39	0.29
Imp - Lack Pers	-0.24	0.17	-0.54	0.10
Imp - Lack Prem	0.04	0.82	-0.30	0.37

Alcohol Group - 50% (N=24)				
Variable	Spearman's Rho	P-Value	CI Lower	CI Upper
AUDIT-C	-0.05	0.81	-0.44	0.35
AUDIT	-0.03	0.90	-0.42	0.37
BATCAP (Alcohol)	0.12	0.58	-0.50	0.30
Drink Index	-0.03	0.89	-0.42	0.37
N° Binges	0.07	0.73	-0.33	0.45
Imp - Urgency	-0.11	0.59	-0.49	0.29
Imp- Positive Urgency	0.12	0.57	-0.29	0.49
Imp - SS	0.42	0.04	0.03	0.70
Imp - Lack Pers	-0.01	0.95	-0.41	0.38
Imp - Lack Prem	-0.12	0.56	-0.49	0.29
Placebo Group - 50% (N=27)				
AUDIT-C	0.19	0.35	-0.21	0.53
AUDIT	-0.08	0.69	-0.45	0.31
BATCAP (Alcohol)	0.26	0.18	-0.13	0.58
Drink Index	0.23	0.25	-0.17	0.56
N° Binges	-0.07	0.73	-0.44	0.32
Imp - Urgency	0.02	0.91	-0.36	0.40
Imp- Positive Urgency	0.00	0.98	-0.38	0.38
Imp - SS	-0.24	0.23	-0.57	0.16
Imp - Lack Pers	0.20	0.32	-0.20	0.54
Imp - Lack Prem	0.02	0.94	-0.37	0.39

Note. CI= Confidence Interval; AUDIT= Alcohol Use Disorder Identification Test (-C= Consumption version); BATCAP= Brief Assessment Tool for Compulsivity Associated Problems; Drink Index= number of alcohol drinking occasion during the last two weeks* number of drinks per occasion; N° Binges= number of binge drinking episodes during the past month; Imp= Impulsivity; SS= sensation seeking; Lack Pers= Lack of perseverance; Lack Prem= Lack of premeditation.

Additional Exploratory Correlational Analyses – Alcohol Variables

In both the Alcohol and Placebo groups, self-reported drinking indices (Drink Index and BATCAP Alcohol) were strongly associated with both AUDIT-C and AUDIT scores ($r_s > .50$). Tables U and V show correlations between alcohol-related variables in the Alcohol and Placebo Group, respectively. In the Alcohol Group, both DEQ Feel and DEQ High scores were significantly negatively correlated with AUDIT and AUDIT-C scores. This pattern suggests that heavier drinkers reported feeling less intoxicated after consuming alcohol, possibly reflecting tolerance effects. In contrast, these associations were absent or non-significant in the Placebo group, where subjective ratings were generally unrelated to drinking severity, as would be expected in the absence of alcohol. Breath Alcohol Concentration (BrAC) measures in the Alcohol group showed modest but significant associations with subjective intoxication. For instance, BrAC at the end of the session was positively correlated with DEQ Feel ($r_s = .49$, $p < .01$) and DEQ High ($r_s = .38$, $p < .01$), supporting the validity of these subjective ratings.

Table U. Correlation Matrix for Alcohol-Related Variables in the Alcohol Group (N=57)

AUDIT-C		AUDIT		DEQ Feel		DEQ High		DEQ Like		DEQ more		BATCAP		Drink Index		BrAC	
AUDIT	$R_s = 0.87^*$ $p < 0.01$	AUDIT		DEQ Feel		DEQ High		DEQ Like		DEQ more		BATCAP		Drink Index		BrAC	
DEQ Feel	$R_s = -0.38^*$ $p < 0.01$	$R_s = -0.41^*$ $p < 0.01$															
DEQ High	$R_s = -0.35^*$ $p = 0.01$	$R_s = -0.34^*$ $p = 0.01$	$R_s = 0.79^*$ $p < 0.01$														
DEQ Like	$R_s = 0.26$ $p = 0.05$	$R_s = 0.10$ $p = 0.48$	$R_s = 0.01$ $p = 0.93$	$R_s = -0.04$ $p = 0.75$													
DEQ More	$R_s = 0.24$ $p = 0.07$	$R_s = 0.27^*$ $p = 0.04$	$R_s = -0.21$ $p = 0.12$	$R_s = -0.31^*$ $p = 0.02$	$R_s = 0.47^*$ $p < 0.01$												
BATCAP	$R_s = 0.44^*$ $p < 0.01$	$R_s = 0.50^*$ $p < 0.01$	$R_s = -0.09$ $p = 0.51$	$R_s = 0.00$ $p = 0.99$	$R_s = 0.22$ $p = 0.12$	$R_s = 0.34^*$ $p = 0.01$											
Alcohol																	
Drink Index	$R_s = 0.79^*$ $p < 0.01$	$R_s = 0.72^*$ $p < 0.01$	$R_s = -0.36^*$ $p = 0.01$	$R_s = -0.36^*$ $p = 0.01$	$R_s = 0.21$ $p = 0.12$	$R_s = 0.25$ $p = 0.06$	$R_s = 0.45^*$ $p < 0.01$										
BrAC	$R_s = 0.12$ $p = 0.38$	$R_s = 0.12$ $p = 0.38$	$R_s = 0.33^*$ $p = 0.01$	$R_s = 0.25$ $p = 0.06$	$R_s = 0.01$ $p = 0.95$	$R_s = -0.14$ $p = 0.29$	$R_s = -0.01$ $p = 0.92$	$R_s = 0.23$ $p = 0.09$									
before PCA																	
BrAC end	$R_s = 0.09$ $p = 0.79$	$R_s = 0.02$ $p = 0.86$	$R_s = 0.49^*$ $p < 0.01$	$R_s = 0.38^*$ $p < 0.01$	$R_s = 0.01$ $p = 0.95$	$R_s = -0.08$ $p = 0.53$	$R_s = 0.07$ $p = 0.63$	$R_s = 0.16$ $p = 0.22$	$R_s =$ 0.44^* $p < 0.01$								

Note. AUDIT= Alcohol Use Disorder Identification Test (-C= Consumption version); DEQ= Drug Effect Questionnaire; BATCAP= Brief Assessment Tool for Compulsivity Associated Problems; Drink Index= number of alcohol drinking occasions during the last two weeks* number of drinks per occasion; BrAC= Breath Alcohol Concentration

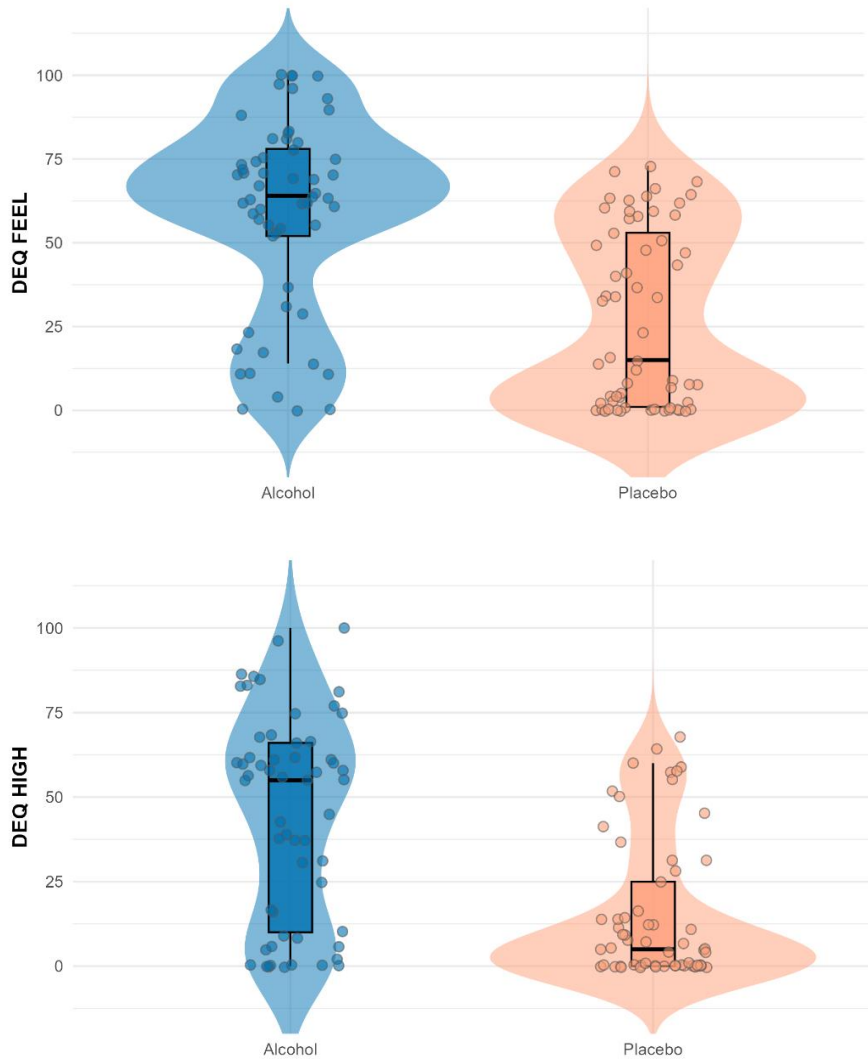
Table V. Correlation Matrix for Alcohol-Related Variables in the Placebo Group (N=61)

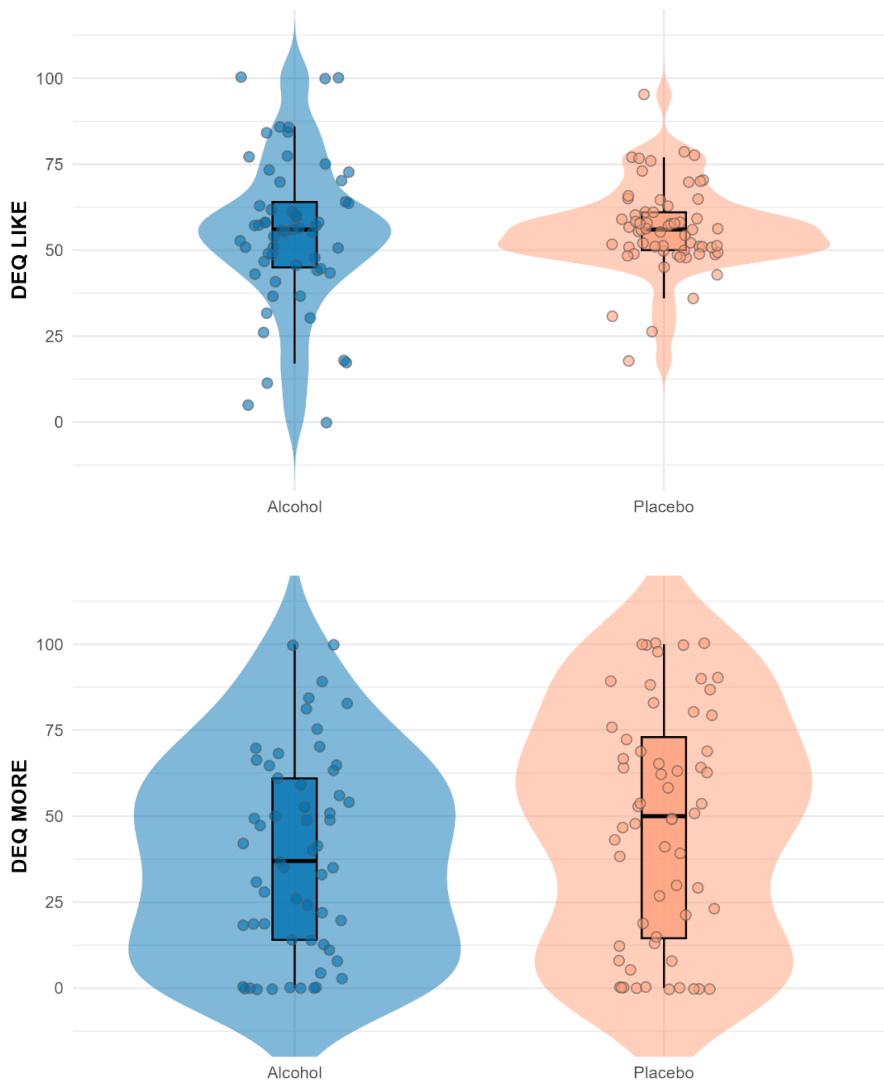
AUDIT-C							
AUDIT	$R_s = 0.84^*$ $p < 0.01$	AUDIT					
DEQ Feel	$R_s = -0.14$ $p = 0.28$	$R_s = 0.03$ $p = 0.79$	DEQ Feel				
DEQ High	$R_s = 0.06$ $p = 0.63$	$R_s = 0.12$ $p = 0.34$	$R_s = 0.59^*$ $p < 0.01$	DEQ High			
DEQ Like	$R_s = 0.12$ $p = 0.35$	$R_s = 0.09$ $p = 0.49$	$R_s = 0.33^*$ $p = 0.01$	$R_s = 0.20$ $p = 0.12$	DEQ Like		
DEQ More	$R_s = 0.21$ $p = 0.10$	$R_s = 0.11$ $p = 0.42$	$R_s = 0.03$ $p = 0.83$	$R_s = 0.20$ $p = 0.13$	$R_s = 0.37^*$ $p < 0.01$	DEQ more	
BATCAP Alcohol	$R_s = 0.53^*$ $p < 0.01$	$R_s = 0.63^*$ $p < 0.01$	$R_s = 0.01$ $p = 0.92$	$R_s = 0.05$ $p = 0.72$	$R_s = 0.18$ $p = 0.18$	$R_s = 0.27^*$ $p = 0.04$	BATCAP Alcohol
Drink Index	$R_s = 0.72^*$ $p < 0.01$	$R_s = 0.66^*$ $p < 0.01$	$R_s = -0.27^*$ $p = 0.04$	$R_s = -0.11$ $p = 0.42$	$R_s = 0.09$ $p = 0.51$	$R_s = 0.09$ $p = 0.50$	$R_s = 0.54^*$ $p < 0.01$

Note. AUDIT= Alcohol Use Disorder Identification Test (-C= Consumption version); DEQ= Drug Effect Questionnaire; BATCAP= Brief Assessment Tool for Compulsivity Associated Problems; Drink Index= number of alcohol drinking occasions during the last two weeks* number of drinks per occasion

Graphical Representation of DEQ Scores

Figure K. *Distribution of DEQ scores for Each Subscale in the Experimental Groups*



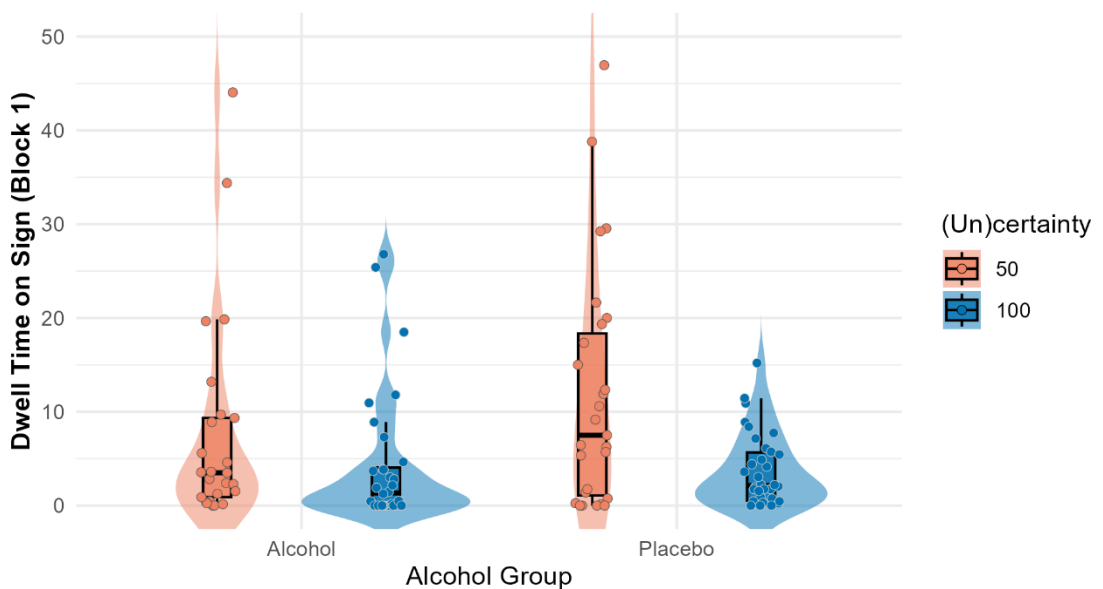


Note. Horizontal lines are the medians of DEQ (Drug Effect Questionnaire) items. The lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group.

ANOVA Results for Sign Dwell Time

A two-way ANOVA was conducted to examine the effects of Group (Alcohol vs. Placebo) and Reward Uncertainty (50% vs. 100%) on the total Dwell Time on the Sign (first block, Figure L.). The analysis revealed a statistically significant main effect of Uncertainty ($F_{(1, 114)} = 9.18$, $p = 0.003$, partial $\eta^2 = 0.07$), indicating that reward uncertainty significantly increased participants' attention to the CS. The main effect of Group was not significant ($F_{(1, 114)} = 2.29$, $p = 0.13$, partial $\eta^2 = 0.02$). The Group $\times$ Certainty interaction was also not statistically significant ($F_{(1, 114)} = 0.03$, $p = 0.87$, partial $\eta^2 < 0.001$).

Figure L. Dwell Time on the Sign in Each Group (block 1)



Note. Horizontal lines are the medians of Dwell Time on the sign (Block 1). The lower and upper limits of the boxes are lower and upper quartiles, the ends of the whiskers represent the lower and upper extremes. The lines around the boxes represent the distribution of the data in each group. The non-transformed variable is shown in this graph for representational purpose.

Complete Figures for Omission phase

Figure M. Sign-Directed Dwell Time Across Blocks and Omission by (Un)Certainty and Alcohol Group

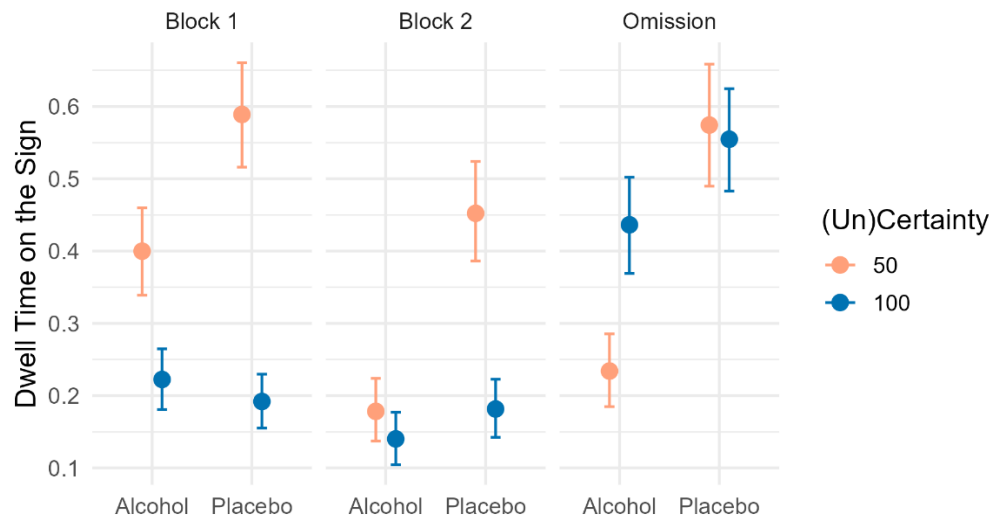
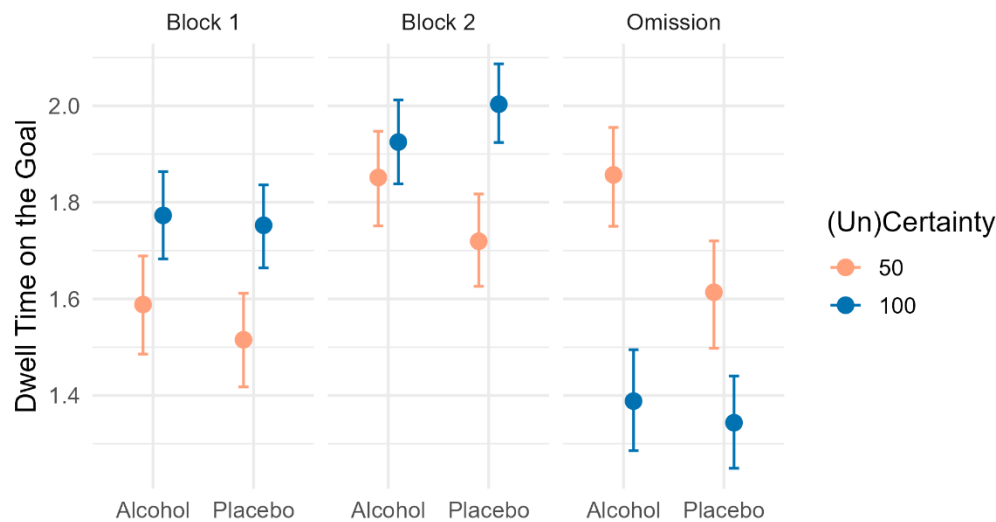


Figure N. Goal-Directed Dwell Time Across Blocks and Omission by (Un)Certainty and Alcohol Group



Note. Points represent the means, and vertical error bars indicate the 95% bootstrap-based confidence intervals.

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