Dopamine, Addiction, and Reward

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Abstract

Addiction is a disease characterized by compulsive drug seeking and consumption observed in 20–30% of users. An addicted individual will favor drug reward over natural rewards, despite major negative consequences. All addictive drugs, despite their different molecular targets and the different interoceptive experience they induce, increase dopamine in the NAc, and it is this action that hijack the dopamine mesolimbic system (the "reward" system) producing intense motivations for the drug. Excessive dopamine signaling during drug use may induce long term epigenetic changes thereby altering patterns of gene expression, synaptic function, and circuit activity, leading over time to maladaptive behaviors in vulnerable individuals. These drug-induced neural adaptations or plasticity lead to excessive amplification specifically of psychological 'wanting' (incentive salience), especially triggered by cues, due to long-lasting changes, called "neural sensitization", in dopamine-related motivation systems of susceptible individuals. This sensitization may enhance the influence of drug-associated pavlovian-conditioned stimuli on drug seeking and relapse, Moreover, this excessive dopamine signaling and sensitization may facilitate the transition from voluntary, goal-directed, recreational drug-use to compulsive drug seeking habits, and on top of that, during time course of drug use, there is evidence for time-dependent impairments in the top-down prefrontal inhibitory control over this behavior. Taken together, these alterations in the brain circuits underlying motivational, cognitive, and motor processes, leading to compulsive drug seeking, can be regarded as the neural substrates of addiction. Understanding the neurobiological and neurochemical alterations underlying addiction would be of great importance for improving our ability to treat addiction – an incurable disease with substantial cost to the inflicted individuals and to society at large. Here we review the neurobiological and neurochemical alterations underlying this disease, particularly the role of dopamine and the dopaminergic reward system and offer a way to treat it accordingly.

Keywords: drug-addiction; dopamine; incentive salience; motivation; goal directed behavior; habits, compulsions

Contents

Introduction 4
The finding of dopaminergic reward system 4
The Reward System 5
The ventral tegmental area 5
Neurons of the VTA 5
VTA dopaminergic neurons connectivity 5
The nucleus accumbens 6
Structures and neurons 6
Connectivity 6
Other major structures of the mesolimbic dopamine system and their functions 6
The basolateral amygdala 7
The central nucleus of the amygdala 8
The ventromedial prefrontal cortex 8
The orbitofrontal cortex 8
The prelimbic prefrontal cortex 9
The mesolimbic reward system as part of the basal ganglia and summary 9
DA Function in Rewards 10
Drug-Addiction 13
The incentive sensitization theory of addiction 14
Concluding remarks 21
References 23
Box 1 49

Introduction

To survive animals must pursue things in their environment and engage in behaviors essential to their own and their species survival. In other words, animals must obtain natural rewards such as food and water, they must desire and seek them consistently, be responsive to them and to their predictors, and learn how to get them. Thus, organisms must imbue incentive salience to these rewards (i.e. learning to desire them, being motivated to seek them, and attributing attentional value to them thereby making the rewards attention grabbing), learn the environmental cues and contexts that predict these rewards and attribute incentive salience to them as well, learn the actions that led to the rewards by forming cognitive and motor associations (i.e. action-outcome and stimulus-response associations respectively) based on the environmental contingencies in which the rewards were obtained. These learning and motivational properties of rewards are critical for guiding behavior towards vital stimuli and thus are essential for the animal's survival. Because animals are usually separated from motivational natural rewards by long distance, obstacles, or response costs (i.e. time, cognitive resources, and effort), engaging in instrumental behavior often involves work. Animals must allocate considerable resources towards motivated seeking behavior, which can be characterized by substantial effort. Often the exertion of this effort must be sustained over long periods of time. Effort-related capabilities are highly adaptive, because in the natural environment survival can depend upon the extent to which an individual overcomes time- or work-related response costs. For these reasons, motivation has not only a directional component (i.e. driving behavior towards a reward or away from punishment), but also a behavioral activation component which is a fundamental aspect of motivation (Salamone et al., 2016, 2018; Salamone & Correa, 2002, 2012). Intuitively, there must be a system in the brain that achieves all that, shaping the animal's behavior to maximize rewards and minimize costs and punishments which are necessary for its own and for its species survival. It is precisely that system that is implicated in substance use disorder (SUD), and in fact being hijacked by drug of abuse.

The finding of dopaminergic reward system

Demonstration by Olds and Milner that rats would work for electrical stimulation in specific brain sites led to the idea that there is an anatomically identifiable reward circuit (Olds & Milner, 1954). Rats would learn to perform actions or move to places that are followed by electrical stimulation in their brain, will work hard to get it, and often choose these apparently rewarding stimuli over food and sex. They are highly motivated for such stimulations. Thus, this electrical stimulation must be "rewarding", it elicits a motivational state, a strong drive to perform an action that will deliver another stimulation and it triggers learning of those actions. "Rewarding" effects can be produced by electrical stimulation of sites at widespread areas of the brain. However, neural pathways associated with dopamine [DA] neurons are among the best targets for electrical self-stimulation (i.e. stimulations at sites causing release of DA from ventral tegmental area neurons especially in the nucleus accumbens). Pharmacological manipulation of those sites, in particular intracranial injections of drugs of abuse, supported the existence of such a circuit (Carlezon & Wise, 1996; Phillips & Fibiger, 1978). Although several brain areas are part of this circuit, self-stimulation, pharmacological, optogenetic, physiological, and behavioral studies showed that the nucleus accumbens [NAc] and the DA neurons of the ventral tegmental area [VTA] appear to be at the heart of this circuit (Di Chiara, 1998; Hikosaka et al., 2008; Kelley & Berridge, 2002; Koob & Bloom, 1988; McCullough & Salamone, 1992; Wise, 2004; Wise & Bozarth, 1987). The role of VTA dopaminergic projections, especially to the NAc, in reward was

established, and the reward system was "found" and identified – the mesolimbic dopaminergic reward system.

The midbrain (i.e. the VTA) DA neurons are activated by four kinds of external stimuli: rewarding stimuli, punishing stimuli, salient, and novel stimuli. When activated by unexpected rewards or punishers or by predicting cues, portions of the DA system discharge in bursts (Bromberg-Martin et al., 2010; Horvitz, 2000; Horvitz et al., 1997; Ljungberg et al., 1992; Schultz, 1998, 2006, 2007; Schultz et al., 1997) and correspondingly cause transient increase in DA in the NAc (Bassareo et al., 2002; Brown et al., 2011), or in simple words, "rewards" cause increases in DA release from VTA DA neurons terminals in the NAc. The NAc is a limbic associated structure and receives excitatory inputs from limbic cortices, and for this reason the term "mesolimbic system" was coined to refer to the "reward system". The NAc is part of the ventral striatal complex and serves as a hub where motivations derived from limbic regions interface with motor control circuitry to regulate appropriate goal-directed behavior (Alexander et al., 1991; Alexander & Crutcher, 1990; Groenewegen et al., 1996; Haber et al., 2000; Haber & Knutson, 2010; Mogenson et al., 1980; Wise, 2004; Zahm, 2006), or in other words, the NAc acts as a hub translating limbic motivations into actions (Haber & Knutson, 2010; Mogenson et al., 1980; Murray et al., 2015; Salamone & Correa, 2012; Sesack & Grace, 2010).

The Reward System

As mentioned, the two central brain regions of the mesolimbic dopamine system are the VTA in the midbrain, and NAc in the ventral striatum in the forebrain. Here, we briefly describe the different types of neurons in the VTA and NAc, their activity, and their connectivity with other brain areas, because we believe it will be necessary for understanding the later sections where we further describe the neural substrates of addiction.

The ventral tegmental area

Neurons of the VTA

Dopamine neurons make up about 60–65% of the cells in the VTA. Non-DA neurons in the ventral midbrain are primarily GABAergic and make up approximately 30–35% of the cells in the VTA (Nair-Roberts et al., 2008; Swanson, 2000). Dopamine neurons recorded in vivo are reported to display three main patterns of activity; an inactive, hyperpolarized state; a slow (2–10 Hz), irregular, single-spike or 'tonic' firing pattern; and a burst or 'phasic' mode (Grace & Bunney, 1983). Single-spike or 'tonic' firing is driven by an intrinsic pacemaker potential (Grace & Bunney, 1984b), similar to the way the heart's pacemaker maintains the organ's activity, and is believed to be related to motivational arousal, responsiveness to salient stimuli (Grace, 1991, 2016; Lodge & Grace, 2005; Schultz, 2007; Volkow et al., 2017; Wise, 2004; Wise & Jordan, 2021; Wise & Robble, 2020), and motivated performance (Cagniard et al., 2006; Niv et al., 2007; Peciña et al., 2003; Salamone & Correa, 2012; Yin et al., 2008; Yin, Zhuang, et al., 2006). Burst firing or 'phasic' activity is crucially dependent on afferent input and is believed to be the functionally relevant signal sent to postsynaptic sites to indicate reward and modulate goal-directed behavior (Berridge, 2007; Berridge & Robinson, 1998; Grace, 1991; Grace & Bunney, 1983, 1984a, 1984b; Schultz, 1998; Wise & Robble, 2020). A widespread interpretation of the burst firing or 'phasic' activity by researchers is that it encodes a "teaching signal" (Keiflin & Janak, 2015; Montague et al., 2004; Niv, 2009; Schultz, 1998, 2007; Schultz et al., 1997; Simon et al., 2008; Yagishita, 2023).

VTA dopaminergic neurons connectivity

Afferent connections to the VTA. Burst firing of DA neurons is dependent upon excitatory glutamatergic stimulation of NMDA receptors (Chergui et al., 1993; Floresco et al., 2003; Grace et al., 2007). Thus, glutamate-driven burst firing in the VTA occurs only in DA neurons that are already spontaneously active. Dopamine neurons that are inactive, presumably owing to GABA-mediated hyperpolarization, are unresponsive to activation of NMDA receptors. There are several potential sources for this glutamatergic input, including the prefrontal cortex [PFC], pedunculopontine tegmentum [PPTg] and lateral preoptic–rostral hypothalamic area. The PPTg is a glutamatergic–cholinergic region driven by limbic afferents, including the

PFC and extended amygdala, and activated by auditory, visual, and somatosensory stimuli. Moreover, the PPTg has been demonstrated to directly regulate burst firing of dopaminergic neurons in the VTA. Thus, activation of the PPTg triggers a transition to burst firing in DA neurons of the VTA. The PPTg is, therefore, positioned to serve as a site of convergence, whereby a variety of sensory inputs can modulate burst firing of DA neurons (Bromberg-Martin et al., 2010; Grace et al., 2007; Lodge & Grace, 2005).

The nucleus accumbens

Structures and neurons

The NAc is divided into two major territories: the core, and the shell (Haber et al., 2000; Haber & Knutson, 2010; Ito et al., 2004; Zahm & Brog, 1992). Whereas the core is striatal region, the shell is really a hybrid structure: part basal ganglia (striatal) and part limbic region (Heimer et al., 1991; Zahm & Brog, 1992). In addition to being a ventral extension of the striatum, with striatal cell types and input–output connections, the shell is also part of the extended amygdala complex and is set apart from the rest of the ventral striatum [VS] by a specific set of connections derived from the medial part of the central nucleus of the amygdala [CeA], periamygdaloid cortex, and the medial nucleus of the amygdala, and it sends projections to hypothalamic and brainstem structures important for visceral motor control and affect (Alheid & Heimer, 1988; Waraczynski, 2006). The NAc core and shell share striatal characteristics, in that approximately 90% of the cells are typical medium spiny projection neurons [MSNs] which are GABAergic projection neurons (Meredith, 1999). The remainder are local circuit interneurons, including cholinergic and parvalbumin cells (Kawaguchi et al., 1995). Within the striatum, including the NAc, about half of MSNs expresses D1 DA receptors selectively, and the other half selectively expresses D2 DA receptors, and only a few cells express both (Gerfen & Surmeier, 2011). D1-like DA receptors (D1 and D5) are coupled to stimulatory G-protein, whereas D2-like DA receptors (D2-D4) to inhibitory G-protein. D1 receptors have low affinity for DA and are thus infrequently occupied by DA molecules, while D2 receptors have high affinity for DA (Rice & Cragg, 2008; Richfield et al., 1989) and are usually occupied by DA molecules (Dreyer et al., 2010).

Connectivity

As mentioned above, the NAc receives inputs from multiple limbic associated areas that provide it with excitatory innervations, including the medial and lateral divisions of the PFC especially the ventromedial PFC [vmPFC] and medial orbitofrontal cortex [mOFC], the entorhinal cortex and ventral subiculum of the hippocampus [vSub], and the basolateral amygdala [BLA]. The NAc shell is innervated primarily by ventral portions of the prelimbic [PL] cortex, the infralimbic [IL], medial orbital, and ventral agranular insular cortices, whereas the core receives input mainly from dorsal parts of the PL and dorsal agranular insular areas as well as the mOFC. The vSub projects preferentially to the NAc shell, whereas the dorsal subiculum projects to more rostrolateral regions including the core. The BLA generates a complex rostral to core and caudal to shell topography that also varies according to patch–matrix compartments in the NAc (Averbeck et al., 2014; Berendse et al., 1992; Brog et al., 1993; Gabbott et al., 2005; Geisler & Zahm, 2005; Haber et al., 2000; Haber & Knutson, 2010; Heilbronner et al., 2016; Kelley et al., 1982; Kelley & Domesick, 1982; Reynolds & Zahm, 2005; Voorn et al., 2004; Zahm, 2006)

Other major structures of the mesolimbic dopamine system and their functions

As mentioned above, the connections that are at the heart of the "reward system" are VTA dopaminergic projections to and DA release in the VS (in which the NAc is a major structure). However, these two structures are by no means the only structures of this circuit, and thus we feel obliged to discuss on them as well. First, we will briefly review some of the functions of some structures in this circuit and then we will touch in more detail on other major structures and their functions. Finally, it's important to note here, as we will be further described later, that this so called "reward circuit" is actually a "motivational circuit", as it is involved in motivations, and by extent actions, triggered by cues (both external cues and internal

imagery), and as such it can be termed the mesolimbic DA system of incentive salience. The *Ventral Hippocampus* (vHipp) provides the motivational impact of spatial and contextual information to the NAc, influencing motivational arousal state, responsiveness, behavioral activation, and vigor (Everitt & Robbins, 2005, 2016; Goto & Grace, 2005; Grace, 2016; Grace et al., 2007; Lodge & Grace, 2005; Pascoli et al., 2014; Sesack & Grace, 2010; Wolf, 2016). The ventral pallidum [VP] is the target of both D1 – and D2- MSNs of the NAc (indirect pathway; Kupchik et al., 2015). The VP is a key structure in modulation of motivation and motivated behaviors, VTA DA activity and more (Creed et al., 2016; Grace et al., 2007; Lodge & Grace, 2005; Root et al., 2015; Soares-Cunha & Heinsbroek, 2023; Tindell et al., 2005). Activity in this region was also found to be associated with decision making (selection) and to encode reward prediction error (Ottenheimer, Bari, et al., 2020; Ottenheimer, Wang, et al., 2020; Root et al., 2015; Soares-Cunha & Heinsbroek, 2023). The lateral habenula (LHb) receives inputs from the VP and was found to encode aversive stimuli. Its' pattern of activity is opposite to that of the DA neurons: neurons in the LHb are inhibited by rewards or by the anticipation of rewards and are phasically activated by aversive outcomes or by the anticipation of them. LHb sends its glutamatergic excitatory projections to the GABAergic neurons in the rostromedial tegmental nucleus (RMTg), which in turn directly and strongly inhibits the dopaminergic neurons in the VTA. The LHb inhibition of DA neurons via the RMTg, is critical for the activity patterns of DA neurons and by extension to the functioning of the "reward" circuit (Bromberg-Martin et al., 2010; Hong et al., 2011; Hong & Hikosaka, 2008; Lüscher & Janak, 2021; Soares-Cunha & Heinsbroek, 2023).

The basolateral amygdala

A major function of the BLA can be considered as allowing a specific conditioned stimulus [CS]-unconditioned stimulus [US] association to influence instrumental behavior (Cardinal, Parkinson, Hall, et al., 2002). The BLA is responsible for assigning incentive salience to stimuli and responses, particularly when animals must discriminate multiple rewards (USs) with reference to their sensory-specific properties (Balleine et al., 2003; Balleine & Killcross, 2006; Corbit et al., 2013; Corbit & Balleine, 2005; Johnson et al., 2009). Importantly, the specific sensory features of the US (reward) are encoded in in this Pavlovian incentive learning such that the BLA transfers the motivational value of the specific outcome to discreet sensory cues (Balleine & Killcross, 2006; Corbit et al., 2013; Corbit & Balleine, 2005, 2011; Fernando et al., 2013; Fisher et al., 2020; Johnson et al., 2009; Mannella et al., 2016; Murray et al., 2015; Namburi et al., 2015; Ostlund & Balleine, 2008). As a consequence, the BLA is required for specific "conditioned approach" (Fernando et al., 2013; Ostlund & Balleine, 2008), specific "conditioned motivation" or Pavlovian to instrumental transfer (PIT, and please see box 1; Belin et al., 2009; Corbit & Balleine, 2005; Fernando et al., 2013), and for conditioned reinforcement, transferring incentive value to the CS (cue) such that it becomes an incentive stimulus or conditioned reinforcer on its own right, supporting responding for long periods of time (for example bridging delays between seeking responses and obtaining the primary reward), and the acquisition of a new instrumental response. Thus, because conditioned reinforcers become goals themselves, they motivate the maintenance of motivated instrumental behaviors to achieve longer-term rewards while these are absent (Belin et al., 2009; Burns et al., 1993; Cador et al., 1989; Everitt, 2014; Everitt et al., 1989; Everitt & Robbins, 2005, 2016; Lüscher et al., 2020; Murray et al., 2015). The BLA receives highly processed sensory input from higher order sensory association areas, gustatory/visceral inputs input from insula, and hypothalamic regulatory inputs about ingestive (i.e. satiety state), reproductive and agonistic behaviors (McDonald, 2020; Sah et al., 2003). The BLA projects to the dorsomedial striatum [DMS] and NAc thereby directly influencing the activity of NAc- and DMS- MSNs in response to Pavlovian incentive sensory cues. In addition, BLA projections to the NAc core is critical for the acquisition of habitual cue-controlled seeking behavior (behavior controlled by conditioned reinforcer) by the recruitment of more dorsal striatal regions via substantia nigra pars compacta [SNc] DA neurons (striato-

nigro-striatal circuits), ultimately recruiting the dorsolateral [DLS] habit system (Belin et al., 2009; Everitt & Robbins, 2016; Lüscher et al., 2020; Murray et al., 2015). The BLA projects to the PL, sending information about "reward" incentive value. This projection is critical for acquisition and performance of instrumental goal-directed behavior, as it was shown that PL-DMS long term potentiation [LTP] is dependent upon the BLA-PL projections (Fisher et al., 2020). The reciprocal connections between the BLA and OFC are crucial for updating the current value of goal representations in the OFC and thus critical for appropriate action-selection and goal-directed behavior (Keefer et al., 2021; Rudebeck & Rich, 2018).

The central nucleus of the amygdala

The CeA responses to salient events (Steinberg et al., 2020) and encodes the general incentive salience of reward and transfer it to the environmental predictive cue. This Pavlovian cue, now imbued with incentive salience, is able grab attention, attract, invigorate behaviors, and generate motivations (Balleine & Killcross, 2006; Berridge, 2018, 2023; Bromberg-Martin et al., 2010; Burton & Balleine, 2022; Corbit & Balleine, 2005; El-Amamy & Holland, 2007; Hogarth et al., 2013; M. J. F. Robinson et al., 2014; Warlow & Berridge, 2021). It receives input from brainstem, including DA from the VTA (Beier et al., 2015; Warlow & Berridge, 2021), from the BLA and the cortex via intercalated cell masses (Ehrlich et al., 2009; Janak & Tye, 2015; Marowsky et al., 2005), thalamus and insula (Berridge, 2018; Sah et al., 2003; Warlow & Berridge, 2021). It projects to the VTA, SNc, brainstem, thalamus, and hypothalamus (Beier et al., 2015; Berridge, 2018; El-Amamy & Holland, 2007; Sah et al., 2003; Steinberg et al., 2020; Warlow & Berridge, 2021; Watabe-Uchida et al., 2012). The acquisition of conditioned orientations to cues is dependent on the CeA projections to SNc (it projects especially to SNc GABAergic interneurons and thus disinhibit the DA neurons) that activate DA neurons that project to DLS (El-Amamy & Holland, 2007; Steinberg et al., 2020). Further, by these projections the CeA is also responsible for the maintenance of cue-controlled habitual behaviors (i.e. conditioned reinforcement; Everitt & Robbins, 2016; Fernando et al., 2013; Lüscher et al., 2020; Murray et al., 2015). The CeA (as well as the VTA and the NAc) is required for general PIT - the excitation and invigoration of behaviors in response to reward related cues, or in other words, the spikes of motivations and urges triggered by these cues (Belin et al., 2009; Corbit & Balleine, 2005, 2011; Hogarth et al., 2013; Holland & Gallagher, 2003; Mahler & Berridge, 2012). However, these motivational spikes aren't necessarily specific to the reward that these cues are associated with. The CeA (as well as the VTA and the NAc) is required for general conditioned approach (Belin et al., 2009; Cardinal, Parkinson, Lachenal, et al., 2002; DiFeliceantonio & Berridge, 2012; Fernando et al., 2013; Parkinson, Robbins, et al., 2000; Warlow & Berridge, 2021).

The ventromedial prefrontal cortex

The vmPFC sends projections to the NAc and encodes the subjective values of various types of rewards (note that the vmPFC includes parts of the mOFC, but also a distinct vmPFC region). The vmPFC has been shown to integrate different facets of rewards such as the magnitude, probability, and delay and encode the subjective value in a general way termed *"common currency"*. It is involved with representation of different goals in terms of their subjective values, and thus is crucial for decision making. Importantly, the vmPFC is equally important for encoding the experienced reward value. Thus, vmPFC may integrate value across different stimulus dimensions and different stimuli, update these values based on experience and current state, and thereby is critical for decision making between possible choices. (Balleine & O'Doherty, 2010; Chib et al., 2009; D'Argembeau, 2013; Everitt & Robbins, 2016; Haber & Knutson, 2010; Levy & Glimcher, 2012; O'Doherty et al., 2017; Sescousse et al., 2013).

The orbitofrontal cortex

The OFC sends Projections to the NAc and the DMS. The OFC can be thought of as a "cognitive map" of the environment (states) in terms of current goals. The OFC is involved in signaling the current "location" of the animal in an abstract task space, especially when that state is not immediately observable (i.e., when task states must be inferred or maintained).

Mapping task-space states allows choosing the best path for current goals (Groman et al., 2019; Rudebeck & Rich, 2018; Schoenbaum et al., 2016; Stalnaker et al., 2015; Wilson et al., 2014). The OFC is involved in updating values of rewards as a result of new information (posited to occur by the reciprocal connections with the BLA), and by integrating different independent stimulus-outcome [S-O] associations the OFC is capable of inferring novel values for situations never before being experienced, and as such it is critical for driving appropriate goal directed instrumental behavior based on the inferred consequences, and for controlling Pavlovian driven motivations and influences over behavior. Thus, by inferring new value the OFC is required for flexible behavior when new information has arrived. Neuroimaging studies have revealed evidence that outcome identity is represented in the OFC in response to stimuli predictive of those outcomes (Balleine et al., 2011; Howard et al., 2015; Stalnaker et al., 2015). This representation may be a mechanism through which the expected value of a particular stimulus or state could be computed. Although this possibility is still a matter of debate, the bulk of the evidence suggests that the OFC seems to be less involved in encoding information about actions than it is in encoding information about stimuli and outcomes (for a review, see Rangel & Hare, 2010). Ultimately, the OFC's role in state encoding and in outcome associations may service computations associated with the expected value based on stimulus–stimulus associations. The OFC is necessary for the representations of possible future outcomes, and thus it's vital for decision making processes and comparison between different options. It Projects to both the NAc core and DMS promoting goal directed (Hoover & Vertes, 2011).

The prelimbic prefrontal cortex

In mammalian species, the capacity for goal-directed action relies on a process of cognitive-emotional integration, which melds the causal and incentive learning processes that link action-goal associations with the current motivational value of the goal. Goal-directed behavior depends on tew explicit conscious components; a knowledge of causal action-outcome [A-O] association (i.e. prior knowledge that action A leads to outcome O); and on the motivational value of that outcome (i.e., outcome O is currently wanted and desired; Balleine et al., 2011; Balleine & Dickinson, 1998). The PL, part of the vmPFC, is critical for the acquisition (Baker & Ragozzino, 2014; Balleine & Dickinson, 1998), but not the expression (Ostlund & Balleine, 2005), of goal directed behavior as it encodes the A-O causal association (Balleine & Dickinson, 1998; Corbit et al., 2013; Corbit & Balleine, 2003; Fisher et al., 2020). Both the PL and the BLA project to the NAc and the DMS. Whereas the PL sends cognitive information about the A-O causal relationship, the incentive value signal is provided by the BLA (Balleine et al., 2003; Balleine & Killcross, 2006; Corbit et al., 2013; Corbit & Balleine, 2005, 2011; Fernando et al., 2013; Parkes & Balleine, 2013; Wassum et al., 2009). The BLA and the DMS are necessary for both the acquisition and expression of goal-directed behaviors (Corbit et al., 2013; Corbit & Balleine, 2003; Fisher et al., 2020; Yin et al., 2005). Plasticity between PL and D1-MSNs in the DMS is required for goal-directed instrumental behavior (Corbit et al., 2013; Corbit & Balleine, 2003; Fisher et al., 2020) and this potentiation is dependent on BLA inputs to the PL, on DA acting on DMS D1-MSNs, and on NMDA receptors (Fisher et al., 2020).

The mesolimbic reward system as part of the basal ganglia and summary

As we have just seen, the limbic critical areas, the striatum, the pallidum, and the thalamus are connected in the mesolimbic reward circuitry, under the modulatory input of midbrain DA. Indeed, the mesolimbic reward system is embedded in the basal ganglia (Haber & Knutson, 2010; Sesack & Grace, 2010), specifically the limbic cortico-striato-thalamo-cortical loops (i.e., the basal ganglia reentrant loops responsible for selecting goals and motivations). The vmPFC, Hippocampus and BLA send projections encoding all possible rewards to the NAc (main structure in the VS). The most active neuronal representation of a goal-value wins the competition, and the goal is chosen (Fisher et al., 2017; Redgrave et al., 1999, 2008, 2010). By the integration between different functional basal ganglia parallel reentrant loops, the NAc can influence cognitive and

motor loops, thus acting as a hub where motivations derived from limbic regions interface with motor control circuitry to regulate appropriate goal-directed behavior (Alexander et al., 1991; Alexander & Crutcher, 1990; Groenewegen et al., 1996; Haber et al., 2000; Haber & Knutson, 2010; Mogenson et al., 1980; Wise, 2004; Zahm, 2006), or in other words, the NAc acts as a hub translating limbic motivations into actions (Haber & Knutson, 2010; Mogenson et al., 1980; Murray et al., 2015; Salamone & Correa, 2012; Sesack & Grace, 2010). DA transients, by their modulating function, potentiate the neuronal representation of the most salient goals which leads to inhibition of less salience goals, and as such amplify the signal to noise output, attributes incentive salience to cues, contexts and actions that predict the availability of a reward thereby generating motivations and activating behaviors to achieve these potentiated selected goals (Berridge, 2007; Cannon & Palmiter, 2003; Fadok et al., 2009; Fisher et al., 2017; Palmiter, 2008; Redgrave et al., 1999, 2010). According to the position that DA may act as a teaching signal (reward prediction error), reinforcement of the action or state that preceded the reward is mediated by phasic DA- and NMDA-dependent LTP or long term depression [LTD] of specific inputs - the neural representation of the recently active motor program input to the BG (striatum) - whereby biasing selection of that motor program (Bromberg-Martin et al., 2010; Fisher et al., 2017; Haber & Knutson, 2010; Redgrave et al., 1999, 2010; Schultz, 1998, 2006, 2007). Mesolimbic DA is thus essential for imbuing incentive salience to novel rewards and later to cues and contexts that predict them, and consequently generating desires upon encountering these cues and activating behaviors to obtain their related rewards (Berridge, 2007; Berridge & Robinson, 2016; Salamone et al., 2018; Salamone & Correa, 2012). Thus, we can say that DA released in the NAc is reinforcing; attributes incentive value to stimuli that predict the reward so that we would repeat the behavior of seeking it upon encounters with it related cues (by the urges elicited by the cues which would motivate appetitive behavior).

DA Function in Rewards

We briefly mentioned the role of mesolimbic DA in incentive salience and reinforcement, but we ought to further expand on it to have a better understanding of the neurobiological and neurochemical mechanisms underlying addiction and translate it into a possible treatment. Indeed, DA is famously associated with reward. But, first, we must begin with a clear definition of the vague construct of reward, what exactly is a reward? Reward can be parsed into three components: the *motivational* ('wanting'), *learning*, and *hedonic* ('liking') properties of reward (Berridge & Robinson, 1998, 2003, 2016). Reward is something we enjoy and reinforcing, and as such is central for driving incentive motivations, grabbing our attention, eliciting responses to stimuli, activating behaviors, and learning of both stimuli and actions that predict it (i.e. cognitive and associative learning). These components are essential for driving motivated goal-directed behavior. With repetition of voluntary motivated goal-directed behaviors, learned sensorimotor associations will be strengthened, habits consolidated, and the control over behavior will shift to the habit system albeit under prefrontal control (Balleine et al., 2007; Balleine & O'Doherty, 2010; Dickinson, 1985; Everitt & Robbins, 2005, 2016; Fisher et al., 2020; Lipton et al., 2019; Yin et al., 2008). Indeed, DA is essential for two of the properties mentioned, i.e., motivation and learning (Hyman et al., 2006; T. E. Robinson & Berridge, 1993; Schultz et al., 1997; Wise, 2004). Interestingly, however, DA is neither necessary nor sufficient for the third property of reward, that is, the experience of "hedonia" or "pleasure" induced by a reward, or put in other way, DA has no role in 'liking' a reward. Pleasure or hedonia, however, is related to activity in specific hedonic "hotspots" and neurotransmitters such as endorphins and endocannabinoids (Baldo & Berridge, 2022; Berridge, 2007, 2018, 2019; Berridge & Kringelbach, 2015; Berridge & Robinson, 1998, 2003, 2016; Cannon & Palmiter, 2003; Hamid et al., 2015; Pardo et al., 2015; T. E. Robinson & Berridge, 1993; Salamone et al., 1991; Salamone & Correa, 2002). The dopaminergic reward system is essential, however, in binding 'wanting' (motivation) to the innate hedonic

properties of a reward (goal) and later to neutral predictive cues. Thus, this dopaminergic system plays a critical role in the generation of motivations and invigoration of actions in response to reward-related cues and by extent to the regulation of behavior (Berridge & Robinson, 1998, 2003, 2016). With that in mind, these two components typically cohere together so we usually want what we like, or what we have learned to be pleasurable, however, in some physiological or pathalogical situations, or by particular brain manipulations, wanting and liking (and by extent wanting and learning) can be detached so that the animal would increase the 'wanting' for something while the 'liking' for it show no change or is even reduced, or want something it have never learned to like, but rather have always been disgusted by it (Berridge, 2012; Berridge & Robinson, 2016; Olney et al., 2018; M. J. F. Robinson & Berridge, 2013; Warlow et al., 2020; Warlow & Berridge, 2021) Further, Warlow et al., (2020) demonstrated that rats can intensely and narrowly "want what hurts" by optogenetic stimulation of the CeA while the animal approach and touch a shock rod that delivers a painful shock.

DA's function is a controversial debate. Probably DA has more than one function. First, as already mentioned, DA neurons show tonic activity (basal firing rate) and phasic activity (burst firing). A widely held position among researchers is that VTA DA neurons' phasic activity may encode *reward prediction error* [RPE], a discrepancy between the actual and predicted reward, and as such are used as a teaching signal. If indeed DA phasic signal encodes RPE, then it provides a link to precisely the same type of teaching signal used in prominent learning theories originating in computer sciences, especially, the *temporal difference reinforcement learning* (TDRL; Montague et al., 1996; Schultz et al., 1997).

Other researchers however, interpret phasic DA in the NAc as incentive motivational signal, important for the initiation and performance and of appetitive behavior, signaling the willingness to engage in effortful behaviors to achieve goals, the value of a goal in terms of work, and the probability to decide to initiate an action (Berke, 2018; Berridge, 2007; Cagniard et al., 2006; Caul & Brindle, 2001; Correa et al., 2002; Cousins et al., 1996; De Jong et al., 2015; Hamid et al., 2015; McCullough & Salamone, 1992; Nunes et al., 2013; Pardo et al., 2012, 2015; Peciña et al., 2003; Peciña & Berridge, 2013; Salamone, 2010; Salamone, 1988, 1992; Salamone et al., 1991, 1994, 2007, 2015, 2016; Salamone & Correa, 2002, 2012; Yin, Zhuang, et al., 2006; Yohn et al., 2015). Mesolimbic DA (i.e. DA released in the NAc) has also been shown not to be required for performance of simple actions that are immediately followed by reward, such as pressing a lever once to obtain food (Ishiwari et al., 2004). Rather, loss of mesolimbic DA reduces the incentive motivation generated by rewards, and especially by their related cues, to work, in the sense of investing time and effort in activities that are not inherently rewarding or interesting but may eventually lead to rewards (Hamid et al., 2015; Salamone & Correa, 2002, 2012; Yin et al., 2008). Conversely, increasing DA with drugs such as amphetamines increases motivation to engage in prolonged work, in both normal subjects and those with attention-deficit hyperactivity disorder (Rapoport et al., 1980; Wardle et al., 2011). It may be best considered as signaling the overall motivational excitement associated with reward expectation (Cagniard et al., 2006; Hamid et al., 2015; Niv et al., 2005, 2007; Peciña et al., 2003; Wise & Jordan, 2021). Moreover, it was shown that as animal approaches a reward, DA released in the NAc exhibits ramps. One opinion among researcher holds that it may represent a RPE signal, as the derivative of the value function might have this kind of "ramping" shape (i.e., RPE is proportional to the first derivative of the value function; Gershman, 2014; Starkweather & Uchida, 2021), whereas a second opinion views the ramping DA as representing the value function itself, as it has the shape of the value function, and thus dopamine ramps have been interpreted as tracking value, goal proximity, or motivation (Berke, 2018; Hamid et al., 2015; Howe et al., 2013). The latter view holds that DA in the NAc signals the motivational value, the amount of resources we are willing to allocate for that reward, or in other words, the value in terms of work and effort – how much we are willing to work for it or how much

we want it (Berke, 2018; Berridge, 2007, 2012, 2023; Hamid et al., 2015; Peciña & Berridge, 2013; Salamone et al., 2016, 2018; Salamone & Correa, 2012).

Although the striatum is known to be involved in mediating the A-O associations that underlie goal directed behavior, this effect is more generally attributed to neostriatal mechanisms, specifically, the DMS (or caudate in humans; Balleine et al., 2007; Balleine & O'Doherty, 2010; Belin et al., 2009; Belin & Everitt, 2008; Corbit et al., 2013; Everitt & Robbins, 2005, 2016; Fisher et al., 2020; Hogarth et al., 2013; Lipton et al., 2019; Palmiter, 2008; S. Robinson et al., 2007; Sotak et al., 2005; Yin et al., 2008; Yin & Knowlton, 2006), rather than NAc (i.e. VS; Palmiter, 2008; S. Robinson et al., 2007; Sotak et al., 2005; Yin et al., 2008). However, NAc DA is critical to many features of behavioural activation and invigoration of instrumental responding (e.g., increased response rate, and increased responding on high ratio schedules), and particularly it plays a vital role in the interaction between incentive Pavlovian stimuli and instrumental behaviors, or in other words, the influence of Pavlovian CS on instrumental behavior, either measured by Pavlovian approach (Cardinal, Parkinson, Lachenal, et al., 2002; Di Ciano et al., 2001; Flagel et al., 2009, 2011; Parkinson et al., 1999; Parkinson, Willoughby, et al., 2000), PIT (Corbit & Balleine, 2011; Hogarth et al., 2013; Peciña et al., 2003; Peciña & Berridge, 2013; Wyvell & Berridge, 2001; Yin et al., 2008), or conditioned reinforcement paradigms (Cador et al., 1989; Cardinal, Parkinson, Hall, et al., 2002; Di Ciano & Everitt, 2001, 2004; Everitt et al., 1989; Ito et al., 2004; Parkinson et al., 1999; Robbins, 1977; Robbins et al., 1989; Taylor & Robbins, 1984). However, there also are many fundamental features of motivation that are left intact following NAc DA depletions. Indeed, behavioural responses most sensitive to disruption in NAc DA transmission tend to be vigorous activities which are elicited and maintained by conditioned stimuli (either measured by Pavlovian approach, PIT, or conditioned reinforcement paradigms). Thus, the mesolimbic DA system is involved in functions related to the 'anticipation-invigoration' mechanism proposed by Cofer & Appley (1964) in their work on incentive motivation. In a sense, the integrity of mesolimbic DA transmission enables organisms to transcend the psychological distance that separates them from motivationally relevant stimuli.

Finally, we can't end this section without briefly mentioning DA's role in the DLS. DA in the DLS (or putamen in humans) is necessary for the formation of habitual behavior. DA in the DLS is required for both the formation and expression of stimulus-response [S-R] associations underlying habits (Balleine et al., 2007; Balleine & O'Doherty, 2010; Belin & Everitt, 2008; Everitt, 2014; Everitt & Robbins, 2005, 2016; Faure et al., 2005; Gremel & Costa, 2013; Hogarth et al., 2013; Lingawi & Balleine, 2012; Lipton et al., 2019; Murray et al., 2015; Redgrave et al., 2010; Yin et al., 2004, 2005, 2008; Yin, Knowlton, et al., 2006; Yin & Knowlton, 2006). In addition, DA in the DLS is necessary for both primary and conditioned orientation (El-Amamy & Holland, 2007; Lee et al., 2005, 2006). The dopaminergic neurons of the SNc encode salience independent of valence. GABAergic neurons in the CeA response to both positive and negative salient stimuli (rewards and aversive stimuli) and by projections from CeA to the SNc, the message of saliency is sent to the dopaminergic neurons (it disinhibits DA neurons by inhibiting SNc GABAergic interneurons). Thus, by way of the amygdala, DLS-projecting DA neurons in the SNc response phasically to salient events, leading to attentional and eye orientation towards these events. Later, after learning has occurred, cues that predict these events are imbued with incentive salience themselves and dopaminergic response develops to the cues as well, leading to conditioned orientation towards cues (El-Amamy & Holland, 2007; Steinberg et al., 2020). Further, as mentioned in the previous section (subsection "the central nucleus of the amygdala"), it was demonstrated that by this pathway (i.e., CeA-SNc-DLS) the CeA, DA-dependently, is involved in maintaining cue-controlled habitual seeking (Murray et al., 2015).

Now, that we have a better understanding of the brain structures involved in goal selection and motivations, in mediating incentive Pavlovian processes and influences on instrumental behaviors, and the brain

structures involved in the mediating the associations underlying goal-directed behavior and habitual behavior, as well as the role of DA in these structures and processes, we are ready to address the topic of drug addiction, with the purpose of translating this knowledge into suggestions of possible treatment as to the so far incurable disease of addiction.

Drug-Addiction

Despite having different molecular structures, acting on different target proteins, having different physiological and behavioral effects and producing different subjective experiences, all addictive drugs increase DA in the NAc (Di Chiara, 1998; Hyman, 2005; Hyman et al., 2006; Koob & Bloom, 1988; Lüscher, 2016; Lüscher & Malenka, 2012; Wise, 2004; Wise & Bozarth, 1987; Wise & Jordan, 2021; Wise & Robble, 2020). As already discussed, the DA mesolimbic system is necessary for our survival as it is the site where motivations are translated to actions or the site responsible for incentive salience – being attentionally captured and motivated by cues which trigger intense 'wanting' or urges for the reward, driving us to seek and work for it. Thus, all drugs of abuse "hijack" the DA mesolimbic system of incentive salience – the so called "reward" system (Hyman, 2005; Lüscher & Malenka, 2011; Warlow et al., 2021). Addiction, like any other psychiatric disorder, is behaviorally defined (i.e. by behavioral symptoms; American Psychiatric Association, 2013). Addiction is defined as persistent compulsive drug seeking and drug taking despite negative consequences (Everitt & Robbins, 2016; Lüscher et al., 2020; Lüscher & Janak, 2021; Lüscher & Malenka, 2011; Nestler & Lüscher, 2019). The addict is often driven by a strong urge to take the drug, which is called drug craving. Addiction is a chronic relapsing disorder (Koob & Volkow, 2010). This means that individuals remain addicted for long periods of time and that drug-free periods (remissions) are often followed by relapses in which drug use recurs despite negative consequences (Berridge & Robinson, 2016; Bobadilla et al., 2017; Everitt & Robbins, 2016; Koob & Volkow, 2010).

Risk factors for transition to addiction. Clinical studies have estimated that only 10%–20% of people who recreationally use psychostimulants or opiates will eventually become addicts, with other drugs showing lower transition rates (Egervari et al., 2018; Vsevolozhskaya & Anthony, 2017). Clearly, an important question is what factors contribute to the risk for transition to addiction?

Genetics. Evidence for heritability of addiction is based on observations in twins. The monozygotic to dizygotic twin concordance ratios for drug addictions are approximately 2:1. Moreover, when quantified using h^2, heritabilities average 50% for all classes of abused substances studied to date (Bevilacqua & Goldman, 2009; Ducci & Goldman, 2012; Goldman et al., 2006). The underlying genetic mechanisms of addiction are highly complex. It is likely that sequence variations at many hundreds of genetic loci comprise the 50% heritability of addictions, with each individual locus contributing a minute fraction to individual differences in addiction vulnerability (Nestler & Lüscher, 2019).

Environmental/Psychosocial factors. Several environmental factors have been associated with addiction vulnerability in humans, including early life trauma, disrupted family structure, and peer pressure, among many others. Furthermore, the occurrence of stressful life events and an inability to cope with stress are important contributors to the risk of addiction. Additional risk factors: Starting at younger age, less education, nonwhite ethnicity, lack of employment, conduct problems during childhood and having substance-using friends(Chartier et al., 2010; Swendsen et al., 2009; Swendsen & Le Moal, 2011). Finally, having a mental disorder is linked with addiction. Drug-abusers and alcoholics are often diagnosed with anxiety, mood, or personality disorders in addition to their drug problem (Verheul & Van Den Brink, 2000).

Now, after providing a brief overview of drug addiction, its definition and associated risk factors, we can now address it in more detail. There are many neurobiological or psychological theories attempting to explain this complex condition, most prominent of those are the opponent process, learning, and incentive

sensitization theories of addiction. Here, for reasons concerning a lack of space, we will focus our attention on the incentive sensitization theory of addiction, as it is, for our humble opinion, a more accurate and consistent description of addiction, and due to the fact that its findings refuted the underlying hypothesis of the opponent-process theory, and also supported the motivational view of the role of DA and weakened the alternative 'teaching signal'/learning view of DA (whereby weakening the learning theory of addiction as well). This is not to say that we will completely neglect the other two major theories, on the contrary, we will pay the respect they deserve by incorporating and applying their principles and insights in our suggestion of a possible treatment program.

The incentive sensitization theory of addiction

As mentioned in the previous section, a reward contains the major dissociable psychological components of 'liking', 'wanting', and 'learning' (Berridge & Robinson, 2003). These components typically cohere together but can be separated by particular brain manipulations and by some human clinical conditions, including addiction and anhedonia (Berridge & Robinson, 2016; Grace, 2016; Grace et al., 2007; Moran et al., 2022; Olney et al., 2018; Salamone et al., 1994, 2015, 2016, 2018; J. D. Salamone & Correa, 2012). While 'liking' refers to the pleasure derived from rewards, 'wanting' refers to incentive salience, a specific motivation process underlying the desire to obtain and seek out those rewards. This "motivational desire" given to a reward can be conferred to learned cues and objects associated with that reward (Bindra, 1978), transforming them also into "wanted" incentives. Reward-related cues have the powerful ability to trigger bursts of motivation and reward seeking, mediated by mesolimbic circuitry involving DA and other neurotransmitters in NAc (Corbit et al., 2007; Holmes et al., 2010; Murschall & Hauber, 2006; Peciña & Berridge, 2013; Wyvell & Berridge, 2001). For example, the alluring smell of freshly baked bread can elicit consumption even in the absence of any need. However, in cases of pathological motivation, such as addiction, cues can become powerful enough to trigger intense cravings for rewards that may not even be consciously wanted or may have adverse consequences. Even an addict who has been able to abstain for many years, encountering a drug-related cue such as a physical location where purchases of an illicit drug had occurred or drug paraphernalia, may cause intense cravings that become hard to ignore, possibly resulting in relapse.

By being paired with a particular reward and its outcome, cues become imbued with incentive salience, making them attractive targets of attention (i.e., the salience aspect of incentive salience) and desire (Hickey & Peelen, 2015). These incentive cues attract approach behavior and invigorate actions. Experimentally, the attribution of incentive salience to cues can be measured using a variety of tests. Pavlovian sign-tracking or autoshaping assesses how attractive the cue has become by examining whether an animal, when encountering the cue, approach it as a conditioned response (Pavlovian approach). Beyond eliciting conditioned approach, a sign-tracked cue may also elicit sniffing, nibbling, or even biting directed to the inedible CS such as a protruding metal lever, because it has been previously paired with a reward (DiFeliceantonio & Berridge, 2012; Mahler & Berridge, 2012). Whether the cue has become a valued and desired object on its own is sometimes measured in animals by using the conditioned reinforcement test (Burns et al., 1993; Everitt et al., 1989; Everitt & Robbins, 2016; Taylor & Robbins, 1984), asking whether the animal will work or learn new instrumental behavior to gain the cue. Similarly, the ability of the reward-paired cue to trigger bursts of more intense motivation to seek the reward itself can be established using PIT, a measure of cue-triggered bursts of increased 'wanting' to obtain the unconditioned reward (Ostlund et al., 2014; Peciña & Berridge, 2013). For example, PIT studies in animal models have demonstrated that the mere presence of cues associated with various drugs of abuse (i.e., ethanol or cocaine) can drive intense bursts of seeking behaviors for those particular drugs through a Pavlovian motivational process such as incentive salience (Corbit & Janak, 2007; LeBlanc et al., 2012). A final signature feature of incentive salience, and perhaps the most important for understanding how desire can separate from prediction, is that the strength of cue-triggered

'wanting' motivation is not a stable learned response. Instead, cue-triggered 'wanting' is dynamically modulated in amplitude and valence by changes in relevant brain and physiological states such as hunger, satiety, drug intoxication, and stress (Berridge, 2012, 2018; Burton & Balleine, 2022; Gallistel, 1978; Toates, 1986). Physiological/brain states change over minutes, hours, and days, and the temptation power of relevant reward cues may change in parallel. For example, food cues are far more tempting when you have not eaten for several hours than immediately after a meal. Drug cues can become even more tempting after a single 'hit' of the drug, and thus precipitate a binge of further consumption. Stress may make a variety of reward cues become more tempting, and so on (Baumgartner et al., 2021, 2022; Koob, 2021; K. S. Smith et al., 2011). State-induced changes in the intensity of cue-triggered 'wanting' can be called *incentive alliesthesia* (Baumgartner et al., 2021; M. J. F. Robinson & Berridge, 2013; K. S. Smith et al., 2011; Warlow et al., 2020; Warlow & Berridge, 2021) – the motivational equivalent of *hedonic alliesthesia*. Hedonic alliesthesia refers to changes in 'liking' or the hedonic pleasure of a sensation caused by changes in a relevant physiological state (Cabanac, 1971). For example, a hot bath feels good when you are cold, but a cool pool feels pleasant when you are hot. Food tastes better when hungry than full, etc. Incentive alliesthesia correspondingly refers to changes in the temptation power of cue-triggered 'wanting' for a reward. Incentive alliesthesia usually accompanies hedonic alliesthesia, but it can also occur by itself due to changes in mesolimbic DA states, neural mesolimbic sensitization, etc. As we will see next, incentive alliesthesia can occur directly the first time a cue is encountered in a new physiological state, even before the hedonic alliesthesia of its US has been experienced in the new state. Thus, it will be shown that 'wanting' is not necessarily tied to affective memories of previous 'liking' for the outcome and to predicted value of the outcome.

The ability of reward-related cues to invigorate 'wanting' is dependent on two major components, the cue's predictive value and incentive value. The predictive value of a cue is essentially pure learning: how well it predicts the presence of reward (S-O contingency) and the value of that reward. In computational reinforcement learning frameworks based on prediction errors, such as TDRL models, stored predictions of outcome value may be posited to guide behavior toward rewards without the need for any additional motivational processes (Schultz, 1998, 2016; Schultz et al., 1997). Yet prediction by itself does not necessarily imbue the cue with incentive value (Anselme & Robinson, 2013; Berridge, 2012; T. E. Robinson & Flagel, 2009). There is evidence indicating that motivational desire can detach from prediction (Berridge, 2012; Berridge & Robinson, 2016; Dayan & Berridge, 2014; M. J. F. Robinson & Berridge, 2013; Warlow et al., 2020). In particular, incentive salience, or motivational 'wanting', has distinct operating rules of its own (Berridge, 2007, 2012, 2018; Bindra, 1978; Olney et al., 2018; Toates, 1986). The rules arise from operations of brain mesocorticolimbic circuitry, which include DA projections from midbrain to NAc, neostriatum, and other brain regions that interact with corticolimbic glutamate signals. Incentive salience gives motivational urgency to many conscious cognitive desires but also can occur unconsciously (Berridge, 2018; Berridge & Winkielman, 2003; Childress et al., 2008; Winkielman et al., 2005). The dual consciousness status of incentive salience is acknowledged here by referring to it as 'wanting' in quotation marks to distinguish incentive salience from the necessarily conscious cognitive desires usually meant by the unmodified word wanting (Berridge, 2018; Berridge & Robinson, 2016; Berridge & Winkielman, 2003; Winkielman et al., 2005). Cognitive wanting, as consciously experienced, may be mediated primarily by cortically weighted systems that depend less on subcortical mesolimbic DA signals (Touroutoglou et al., 2020; F. Wang et al., 2020; Watson et al., 2018).

Although 'wanting' is usually guided by the affective memories that underlie prediction, other inputs to 'wanting' allow desire to detach from prediction. In particular, the ability of physiological/neural state signals to modify 'wanting' without changing the predicted outcome sets the stage for mesolimbic rules of incentive salience to detach motivational 'wanting'

from learned prediction of outcome value in particular situations (Berridge, 2012, 2018, 2023; M. J. F. Robinson & Berridge, 2013; Warlow et al., 2020; Warlow & Berridge, 2021). Recent findings have revealed how mesolimbic incentive salience rules can, in specific conditions, cause desire to separate from memories of past outcome value, prediction of future value, and actual experienced outcome value. Separation of desire from prediction can be adaptive in some situations but maladaptive in others. Here, we describe two laboratory-induced examples of dissociated desire, that illustrate how the brain can produce intense desires for outcomes that are remembered and predicted to be bad: (i) adaptive "wanting what is known to disgust" (M. J. F. Robinson & Berridge, 2013), and (ii) maladaptive "wanting what is predicted to hurt" (Warlow et al., 2020). This understanding provides insight into how addictions can give rise to intense desires that may seem irrational to observers.

In one study the researchers trained mice that a particular metal lever is predictive of very salty water (Dead Sea saltiness) that will be inescapably and unavoidably injected to their mouth 5 seconds later, and another metal lever is predictive of a sweet sugar solution that will be injected to their mouth 5 seconds later. After learning these pavlovian cues, these cues were imbued with motivational salience, and any time the lever predictive of the salty water (a Pavlovian CS^{+salt} cue) popped out of a wall, predictive of an US squirt of Dead Sea saltiness into the mouth of a rat a few seconds later, the rats quickly learned to shrink away from the CS^{+salt} lever, retreating to a far wall as if trying to escape from the Pavlovian cue and its predicted salty infusion. By contrast, when the other and different $CS^{+sucrose}$ lever popped from another wall, predictive of an oral squirt of pleasantly sweet sugar solution as the US, all rats quickly learned to sign-track, jumping onto and nibbling the metal CS+sucrose lever as soon as it appeared (M. J. F. Robinson & Berridge, 2013).

However, on a particular test day, the rats suddenly found themselves for the first time in their lives in a new state of physiological sodium deficiency which produces a psychological salt appetite. The rats had received an injection of drugs the day before that mimic the natural brain hormonal signals of salt appetite – a combined rise in blood levels of angiotensin II and aldosterone which together activate brain circuitry to produce a salt appetite (Schulkin, 1991; C. M. Smith & Lawrence, 2018). Modern laboratory rats, like most modern humans, have never experienced a salt appetite because their food, like ours, contains more than enough salt. A physiological salt appetite was therefore as novel to those rats as it would be to most readers. During their new salt-appetite state, even the Dead Sea saltiness US elicited positive facial 'liking' expressions similarly to sugar, rather than usual disgust gapes, via hedonic alliesthesia that transforms the salty US from disgusting to pleasant (M. J. F. Robinson & Berridge, 2013; Tindell et al., 2006). Crucially, on the test day, the rats re-encountered their Pavlovian CS^{+salt} cue before ever experiencing the Dead Sea saltiness in their new physiological state, or put in other way, before ever experiencing new positive hedonic value of Dead Sea saltiness as 'liked' (that would come later in the day). They had only their past memories of Dead Sea disgust to guide their learned prediction of outcome value of the CS^{+salt} cue. Further, to ensure that the rats relied solely on their past memories of saltiness, the CS^{+salt} lever and the $CS^{+sucrose}$ lever were each presented without any accompanying salt or sugar US infusions on this day (i.e., what is traditionally called a 'CS extinction test').

The important question was whether the rats would initially retreat again from their CS^{+salt} lever, and subsequently need to relearn a new positive value, by retasting Dead Sea saltiness as newly 'liked' in their salt-appetite state. The answer was 'no'. Instead, the sodium-deficient rats immediately ran to their CS^{+salt} lever as soon as it appeared, before ever retasting the salty US, jumping onto and avidly nibbling the metal lever that had previously repulsed them, exactly as they always jumped onto the $CS^{+sucrose}$ lever. The previously learned negative value of the salt cue was instantly discarded. The CS^{+salt} cue instead now elicited positive desire in their novel sodium-deficient state, although they had never yet tasted its Dead Sea saltiness US as anything but 'disgusting', and had so far, no positive memory of any pleasant saltiness outcome

upon which to base a positive prediction (M. J. F. Robinson & Berridge, 2013).

How was this sudden reversal of motivational valence possible? Brain analyses conducted immediately after the rats were attracted to their CS^{+salt} cue revealed that their attraction was mediated neurobiologically by cue-triggered activation of mesolimbic incentive salience circuitry, measured as increased Fos expression in neurons of VTA (where mesolimbic DA neurons originate), NAc (the target of ascending DA axons), and related limbic structures (M. J. F. Robinson & Berridge, 2013). This mesolimbic activation caused psychological attribution of positive incentive salience to the CS^{+salt} lever on its first re-encounter in the new salt-appetite state. In this example of incentive alliesthesia, positive 'wanting' soared above any existing negative memories of past outcome value, and therefore also above any learned predictions of future value based on affective memory.

In a second study, (Warlow et al., 2020) demonstrated that it is possible to "want what hurts". In this study, a shock rod, a small metal rod wrapped with electrified wire, protruded from the wall. Rats are curious and explorative animals, and as such, if placed in a chamber would voluntarily touch the shock rod, and if so, would receive a mild electric shock sufficient to cause the rats to flinch away. Normal control rats touched the electrified object once or twice but then retreated as far as possible from the shock rod, and often began to emit fearful anti-predator reactions called "defensive burying" toward it (Treit et al., 1981).

By contrast, the amygdala-stimulated rats, referred to as "CeA ChR2" rats, had a virus containing a channelrhodopsin [ChR2] gene previously microinjected into their CeA, and it caused excitatory ChR2 photoreceptor molecules to sprout on CeA neurons. When laser light was shone onto those neurons – delivered via an optic fiber implanted in the CeA – their ChR2 photoreceptors opened ion channels to cause the neurons to fire action potentials. The CeA laser was turned on whenever a rat approached within 2 cm of the shock rod to touch it and turned off again as soon as the rat retreated >2 cm further away. Thus, brief laser CeA ChR2 stimulations were associatively paired with shock-rod encounters. The behavioral consequence was that CeA ChR2 rats quickly returned to the shock rod after their first encounter with shock and eagerly hovered over it, continuously sniffed closely, and repeatedly touched it with paw, nose, mouth, or teeth. CeA ChR2 rats often touched the shock rod 10 or more times and so received ten or more shocks in a daily 20 min session. Further indicating that this reflected a positive appetitive motivation, when a large vertical "protective" barrier was placed in the chamber between the shock rod and the rats, so that they couldn't directly see it and needed to work and exert effort to reach it, they repeatedly climbed over a large protective barrier to reach and touch the shock rod again. Finally, in a separate instrumental conditioned reinforcement test (without shock rod or laser), CeA ChR2 rats were willing to learn a new nose-poke response to hear brief presentations of a shock-associated CS sound that had been previously paired with shock-rod touches, seeking the shock-related CS sound as if it were a reward cue. The electric shocks appeared to remain painful, in the sense that CeA ChR2 rats still typically flinched to each shock, and momentarily jerked back their paw or head before returning. Further, once attraction had been induced by laser pairings over several days, on one subsequent test day the laser was kept off. On this day, the CeA ChR2 rats reverted within moments to negative avoidance and defensive burying. That is, the rats appeared to have learned during previous encounters that the shock rod delivered a noxious outcome and were ready to quickly become defensive in the absence of laser stimulation. Paradoxically, however, the shock from the shock rod also appeared to contribute to their maladaptive incentive attraction. For example, an unelectrified 'dummy rod' that never shocked, but similarly delivered laser, did not become as attractive to CeA ChR2 rats as the shock rod, meaning that it wasn't the laser stimulation of the CeA that elicited the incentive attraction to the rod, but the electric shock combined with the CeA stimulation (Warlow et al., 2020).

The possible explanation of this maladaptive attraction may be that laser stimulation of the CeA paired with shock-rod encounters synergistically transformed

the perception and evaluation by CeA ChR2 rats of the shock rod and associated cues into incentive objects of desire. This was neurobiologically mediated by recruiting the activation of mesolimbic circuitry underlying incentive salience attribution to make the shock rod and its cues become maladaptively 'wanted' (Warlow et al., 2020; Warlow & Berridge, 2021). Neurobiological evidence for this postulated mesolimbic recruitment was found as increased Fos activation in neurons in the VTA, NAc, and other mesolimbic structures in the brains of CeA ChR2 rats, when examined immediately after they were attracted to the shock rod (Warlow et al., 2020). The neurobiological activation of mesolimbic circuitry underlying maladaptive 'wanting' was essentially identical to mesolimbic activation during 'wanting' for conventional pleasant rewards (Warlow et al., 2020; Warlow & Berridge, 2021).

The CeA's ability to recruit incentive salience circuitry is so powerful that it can even create maladaptive addictive-like 'wanting' for a painful shock-rod and its cues, and narrowly focus the motivation on that specific target in the absence of any 'liking' and in absence of any pre-existing habits, in contrast to some contemporary learning models that posit those features to be required for addictive compulsions (Belin et al., 2009; Belin & Everitt, 2008; Everitt & Robbins, 2005, 2016; Hogarth et al., 2013; Lesscher & Vanderschuren, 2012; Lipton et al., 2019; Lüscher et al., 2020; Murray et al., 2012, 2015). Do maladaptive attractions described here have potential clinical implications? Important features of addictive motivation include maladaptive motivated pursuit that becomes focused narrowly on the addictive target, escalation of consumption, and persistence despite adverse consequences. Narrowly focused pursuit and escalated consumption were seen here and in previous effort-breakpoint studies. These results demonstrated that single-minded CeA ChR2 pursuit can be generated and focused narrowly on an incentive target of experimenter's choice, arbitrarily creating even maladaptive attraction to a painful shock rod. Eventually treatments that target such brain circuitry may aid in preventing drug relapse, or escalation of drug intake.

While mesocorticolimbic brain structures evolved to generate 'wanting' for natural rewards crucial to survival, they are especially heavily activated by modern drugs of abuse, hyperpalatable foods, and rewarded behaviors such as gambling. Activation of 'wanting' circuitry by these rewarding stimuli or incentive cues related to them, involves surges of DA release. Over time, drugs can induce particular neural changes that cause sensitization in mesolimbic circuitry, which once formed may be extremely long lasting (Evans et al., 2006; Paulson et al., 1991; T. E. Robinson & Becker, 1986). Sensitization causes mesocorticolimbic activation to become increasingly sensitive to those particular rewards and their related cues, such that higher levels of DA are released, and greater neural responses are evoked in target structures when cues are encountered. In sensitized individuals, presentation of the reward or reward-related cue causes an enhanced release of DA among mesocorticolimbic brain structures responsible for generating reward 'wanting'. The incentive sensitization theory of addiction posits that vulnerable individuals who are susceptible to mesolimbic sensitization may develop urges to take drugs that are sufficiently intense to be arguably compulsive (Berridge & Robinson, 2016; T. E. Robinson & Berridge, 1993). This is especially true in a subset of individuals partaking in particular binge/purge patterns of drug use or behaviors, such as episodic/binge gambling (Cowlishaw et al., 2018), who may be particularly vulnerable to sensitization due to their genes, steroid hormones, previous stress experiences, etc. (Kawa et al., 2016; Piazza et al., 1989; Rougé-Pont et al., 1993).

That intense motivational 'wanting' is not accompanied by enhanced 'liking' for drug pleasure and sensitized 'wanting' can persist in the absence of any aversive withdrawal or other feelings of distress. On the contrary, liking for the drug can even be reduced due to tolerance mechanisms (homeostatic adaptations to the DA bombardment induced by drugs, which include for example D2 DA receptors down regulation), while 'wanting' for the drug, and the incentive salience of the drug-related cues, is sensitized and enhanced. This is possible because tolerance and sensitization are

mediated by two distinct and parallel intracellular signaling mechanisms (Berridge & Robinson, 2016). Moreover, during prolonged abstinence from drug use, after the adaptive cellular changes of tolerance and withdrawal are long gone along with its accompanied withdrawal symptoms, which together form the basis of the "anhedonia"/"opponent processes"/"reward deficiency" theories of addiction, the mesolimbic DA system continues to be further sensitized, a phenomena called "incubation of craving", in which after abstinence from drug use there is an increase in craving and urges for drug demonstrated by enhanced drug seeking behavior after prolonged withdrawal (Grimm et al., 2001; Wolf, 2016). These withdrawal-reward deficiency-related theories cannot explain this phenomenon, as the cellular adaptations underlying these theories are mostly temporary and soon after abstinence they are normalized and there is a return to healthy homeostasis. Incentive sensitization results in excessive cue triggered bursts of 'wanting' that can consequently soar above the remembered, predicted, and experienced hedonic 'liking' value of the same outcome. Further, the magnitude of incentive salience evoked by a cue can be augmented even further by current states of intoxication, stress, or excitement (Anselme & Robinson, 2013; Berridge, 2012; M. J. F. Robinson & Berridge, 2013; Sinha, 2013). Thus, being primed with drug consumption, stress, or emotional excitement states, and then encountering incentive cues, can cause intense cravings for and heightened motivation to seek out that particular drug. For many individuals with addiction, this desire is overwhelming and intense enough to cause relapse.

Similar sensitization of excessive incentive salience may also explain the development of behavioral addictions in vulnerable Parkinson's patients induced by DA receptor "direct agonist" medications that directly stimulate D2/D3 DA receptors. These medication-induced behavioral addictions can include compulsive gambling, shopping, sex or pornography use, binge eating, among others. Neuroimaging evidence indicates that medicated Parkinson's patients who develop these addictive behaviors show hyperreactivity in striatal DA release compared to other Parkinson's patients who take the same medications but remain free of compulsions. In other words, their vulnerability to mesolimbic sensitization of DA-related systems appears to mediate the development of medication-induced compulsions. This pattern demonstrates intense and individually diverse 'wants' arising from DA-stimulating medications, and is also provide a further contradiction of the notion that DA-suppression causes addictions (i.e., because Parkinson's patients are in DA suppression states prior to medication or if taken off medication, but no longer have compulsive motivations at those times). It provides further support for the sensitization idea that DA overstimulation is the more likely the criminal behind addictive compulsions (i.e., while taking high doses of medications that stimulate DA receptors). Finally, such patients with intense motivations have virtually never been reported to experience intense pleasure from their medications or compulsions, any more than individuals with spontaneous behavioral addictions or some drug addicts. In short, evidence continues to build that DA hyperreactivity produces intense reward 'wanting' but not 'liking' and can cause addictions. (O'Sullivan et al., 2011; Pettorruso et al., 2016).

As we mentioned, sensitized mesolimbic system becomes hyperreactive to the drug and to drug related cues (including internal imagery cues) and contexts that have been paired with drug-taking. For example, a heightened brain response in limbic circuitry is triggered by reward-related cues after sensitization (Tindell et al., 2005) and drug paraphernalia in human addicts (Cox et al., 2009; Kühn & Gallinat, 2011; Leyton & Vezina, 2013; Vezina & Leyton, 2009). Furthermore, cue reactivity in mesolimbic VS correlates with years of cocaine use such that the more years of use, the greater the brain activation (Prisciandaro et al., 2014). Additionally, time-dependent increases in cue-induced craving have been observed in methamphetamine addicts (G. Wang et al., 2013) as well as in alcoholics (P. Li et al., 2015), and these time-dependent increases in cue-induced craving (also referred to as incubation) are dependent on mesolimbic structures such as the CeA (X. Li et al., 2014; Lu et al., 2005, 2007) and NAc (Xi et al., 2013).

In support of incentive sensitization theory, mesolimbic hyperreactivity to drugs of abuse has been well documented. For example, repeated amphetamine administration in both humans and rodents causes sensitization to reward cues in limbic areas such as the amygdala, VP, and NAc (O'Daly et al., 2014; Tindell et al., 2005; Wyvell & Berridge, 2001), and this sensitization involves an increase in DA release (Evans et al., 2006; Kalivas & Duffy, 1990; Saal et al., 2003; Thomas et al., 2008). Similarly, repeated cocaine administration induces long-lasting sensitization of the mesolimbic DA system (Bocklisch et al., 2013; Calipari et al., 2013, 2016; Creed et al., 2016; Pascoli et al., 2012, 2014; Terrier et al., 2016;for comprehensive reviews of the synaptic plasticity underlying this mesolimbic sensitization see Dong & Nestler, 2014; Lüscher, 2016; Lüscher et al., 2020; Lüscher & Janak, 2021; Nestler & Lüscher, 2019; Wolf, 2016; Zinsmaier et al., 2022). Animal studies have also shown elevated DA levels (Carlson & Drew Stevens, 2006; McBride, 2002), increased DA receptor expression and sensitivity (Tournier et al., 2016), and enhanced synaptic strength (Saal et al., 2003; Stuber et al., 2008) in reward-related brain regions following repeated exposure to such drugs as alcohol, marijuana, or nicotine. These changes and increased DA release causes heightened responses and attribution of incentive salience to reward cues (Ostlund et al., 2014; Tindell et al., 2005). Animal models have further demonstrated that this drug-induced sensitization chronically heightens DA release, increases susceptibility to drug cues, and causes increases in 'wanting' (Peciña et al., 2003; Peciña & Berridge, 2013; Wyvell & Berridge, 2000, 2001). Further, this increased 'wanting' has been shown to produce a narrow focus onto one particular reward, even when equivalent alternatives are available (DiFeliceantonio & Berridge, 2012; Mahler & Berridge, 2012; M. J. F. Robinson et al., 2014; Warlow et al., 2017). In line with the narrowing of cue salience, human studies have shown the heightened response to drug cues and heightened DA release to be directly related to reports of drug 'wanting' (Boileau et al., 2016; Evans et al., 2006). Individuals with a history of extensive alcohol, marijuana, and/or nicotine use also exhibit heightened activity in various reward-related regions in response to drug or drug-related cues, whereas casual users or nonusers do not exhibit hyperreactivity to such stimuli (Charboneau et al., 2013; Claus et al., 2011; Cousijn et al., 2013; Filbey et al., 2009; Ihssen et al., 2011; Kühn & Gallinat, 2011; Metrik et al., 2016; Myrick et al., 2003; Tapert et al., 2003). Furthermore, activity in these regions has been shown to be directly correlated with self-reported craving (Charboneau et al., 2013; Myrick et al., 2003; Tapert et al., 2003), and duration of dependence (Claus et al., 2011; Filbey et al., 2009). Taken together, these findings demonstrate that abuse of such substances is characterized by hyperreactive limbic-related brain structures. This heightened activity is not observed in casual users and/or nonusers and often corresponds with the severity of abuse. Thus, incentive sensitization likely can be attributed to neurobiological changes in the mesolimbic DA pathway that leaves the individual primed to respond to drugs and drug-related cues.

As a concluding remark, sensitizing these findings with the findings of the CeA ChR2 rats study previously mentioned, perhaps vulnerable human individuals might encounter endogenous excitations in amygdala and related mesolimbic circuitry that are triggered by encounters with addictive targets. Gradually accruing in individuals who are vulnerable to mesolimbic sensitization (Berridge & Robinson, 2016; MacNiven et al., 2018; Prisciandaro et al., 2014; Reinhard et al., 2015; T. E. Robinson & Berridge, 1993; Samaha et al., 2021), such endogenous excitations might conceivably create an amplification and narrowed focusing of 'wanting' in addicted humans over months to years, similarly to that which the paired laser stimulations creates in CeA ChR2 rats over minutes to hours. Sensitized addicted persons can thus experience strong urges to relapse due to excessive incentive salience, even after abstaining from drugs for months or years, even if free from distress, even if they know that relapse will carry adverse consequences, and even if they no longer expect to like the drug very much.

Thus, intense, and narrowly focused 'wanting', exceeding the predicted and experienced hedonic value of target outcomes, may involve a shared

mesolimbic sensitization mechanism that gives compulsive motivational strength to both drug addictions and behavioral addictions. Excessive and focused incentive salience can create addictive 'wants' that appear to be irrational, even to the addicted persons themselves, in the sense that the predicted outcome value gives insufficient reason to justify their intense desire. However, incentive salience mechanisms operate by rules rather than by reason, making even irrational desires possible.

Concluding remarks

Despite major advances in understanding the neuropsychological and molecular mechanisms involved in drug addiction, few if any new medications have been introduced clinically that might prevent relapse and prolong periods of abstinence (Everitt & Robbins, 2016). There may be, however, another approach to addiction treatment which also involve taking advantage of our advanced knowledge of the disease but channel it in another direction; developing effective psychological treatment programs that specifically address the main impairments and major hardships associated with addiction. The main interest of such a program in preventing relapse should be by diminishing the impact of drug associated CSs on craving and drug seeking, or in other words, reducing the incentive salience of both external and internal cues. Furthermore, as we know that drug addiction is associated with impulsivity and impairments in executive functions (Ersche et al., 2010, 2013; Ersche, Jones, et al., 2012; Ersche, Turton, et al., 2012; Everitt & Robbins, 2016; Robbins et al., 2012), such program must focus on enhancing inhibitory control skills and reducing impulsivity, providing the patient with strengthen top-down control over his incentive habits. To do so, the program must be all-encompassing engulfing all aspects of the patient's life, providing opportunity to make new friends, hopes, goals, and gradually facilitating the incorporation of the addicted individual's life as part of a community, by the establishment of new social networks, learning professional skills, and finding a job. When the severely addicted individual is isolated from his old environment, where external cues are abundant and internal cues are frequently triggered, and simultaneously and gradually becomes an integral part of new environment, with new desires, life goals, dreams and hopes, equipped with improved cognitive and mental skills of planning, impulse inhibition, and decision making, the likelihood of relapse will be greatly diminished. Of course, in the context of richer social life within the community, and going through these processes with similar patients, the program must include close psychological therapy, combining behavioral, cognitive, and existential methods, as to change "bad habits" by extinguishing learned behaviors and habits and learning new adaptive ones, treat cognitive and emotional deficits, and generate new goals and motivations by pouring meaning into the patients' lives. There is numerous evidence in support of such social, cognitive, and emotional treatment, since comorbidity with other psychological disorders associated with emptiness, and impulsiveness, is very high (Leichsenring et al., 2023; Verheul & van den Brink, 2000). Exercise (Robison et al., 2018) and a healthy diet are of great importance (Blanco-Gandía et al., 2021), neurologically, psychologically, cognitively, and most importantly behaviorally, since pathalogical motivations (Berridge, 2007, 2012, 2018, 2022; Berridge & Robinson, 2016; Olney et al., 2018; T. E. Robinson & Berridge, 1993; Warlow et al., 2021; Warlow & Berridge, 2021; Wyvell & Berridge, 2000), lifestyle, and habits are at the core of this disease (Belin et al., 2009; Belin & Everitt, 2008; Everitt, 2014; Everitt & Robbins, 2005, 2016; Hogarth et al., 2013), therefore incorporating healthy lifestyle to such program can facilitate its efficiency. Considering the costs and complexity of such a comprehensive project, one might think that this proposal is illusional as it would be too expensive and complex to develop. However, appraising the annual costs of addiction to society, the complexity and costs involved in institutional structures responsible for the enforcement drug-related laws (e.g. police departments devoted to catching addicts), and the potential of turning the addicted individuals into productive and beneficial citizens, the society might in large benefit from such expanses.

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Box 1

Autoshaping. Behavioral procedure used to study conditioned approach. Animals are trained to associate a readily localizable CS (e.g. a light-lever combination) with the presentation of an appetitive reinforcer through pavlovian conditioning. During training, the CS comes to elicit approach responses that may be directed towards the CS itself (termed sign-tracking) or towards the location in which the reinforcer is delivered (termed goal-tracking). Often a control CS, not associated with a reinforcer, is included in the procedure, and animals are considered to have acquired the association when they approach more during presentation of the reinforcer-associated CS than during the control CS.

Conditioned/Pavlovian approach. The psychological process by which a CS acquires reinforcing properties that promote approach towards it; often the CS will also elicit responses that are appropriate to the reinforcer (e.g. a rat will lick a CS associated with a liquid reinforcer).

Pavlovian to instrumental transfer (PIT). The behavioral procedure with which appetitive the effects of a Pavlovian CS on the levels of instrumental responding can be assessed, or in other words, the incentive motivational properties of the CS such as invigorating and activating behaviors can be measured. Animals are trained separately on an instrumental association (during instrumental training phase) and a pavlovian association (during the Pavlovian training phase) for the same reinforcer. As such, no direct S-R association has never been formed as the CS has never been presented in the instrumental training phase. At the test phase, the CS is presented for the first time during the animal's performance of instrumental behavior for the reward. Increases in instrumental responses made in the presence of the pavlovian CS can be taken as a direct measure of conditioned motivational properties of the CS. The increases in instrumental responses may be for the reward itself (specific transfer) or for other rewards (general transfer). In short, transfer of learning whereby conditioned stimuli associated with a reward can increase a separately trained instrumental response.

Conditioned reinforcement. Refers to the process of transferring incentive value to the CS (cue) such that it becomes an incentive stimulus or conditioned reinforcer on its own right, supporting responding for long periods of time during which the animal is motivated to respond to obtain the CS despite the reward being absent. Thus, because conditioned reinforcers become goals themselves, they motivate the maintenance of motivated instrumental behaviors to achieve longer-term rewards while these are absent (for example, bridging delays between seeking responses and obtaining the primary reward). Furthermore, because conditioned reinforcers become goals themselves, they support the acquisition of a new instrumental response for the CS (which is acting as a conditioned reinforcer).