CellPress

Trends in Cognitive Sciences

Review

Separating desire from prediction of outcome value

Kent C. Berridge[1,*]

Individuals typically want what they expect to like, often based on memories of previous positive experiences. However, in some situations desire can decouple completely from memories and from learned predictions of outcome value. The potential for desire to separate from prediction arises from independent operating rules that control motivational incentive salience. Incentive salience, or 'wanting', is a type of mesolimbic desire that evolved for adaptive goals, but can also generate maladaptive addictions. Two proof-of-principle examples are presented here to show how motivational 'wanting' can soar above memory-based predictions of outcome value: (i) 'wanting what is remembered to be disgusting', and (ii) 'wanting what is predicted to hurt'. Consequently, even outcomes remembered and predicted to be negatively aversive can become positively 'wanted'. Similarly, in human addictions, people may experience powerful cue-triggered cravings for outcomes that are not predicted to be enjoyable.

Creating objects of desire

Individuals usually want outcomes that they predict they will like. These **learned predictions** (see Glossary) are often based on affective memories of similar outcomes in the past (Box 1 and Figure 1) [1–6].

Some psychologists, neuroscientists, and philosophers view prediction and desire as identical. This view essentially reduces desire to nothing more than prediction of gain, and thus eliminates any need for additional motivation processes [6–9]. For example, as one prediction advocate expressed it: 'As always, PP (predictive processing) here replaces desires with predictions…' [7] (cf. [10–12]). Similarly, in computational reinforcement learning frameworks based on prediction errors, such as **temporal difference models**, cached predictions of outcome value may be posited to guide behavior toward rewards without positing any additional motivational processes [13–16].

Yet evidence indicates that motivational desire can detach from prediction [17–21]. In particular, **incentive salience**, or motivational **'wanting'**, has distinct operating rules of its own [20,22–26]. The rules arise from operations of brain mesocorticolimbic circuitry, which include dopamine projections from midbrain to nucleus accumbens, neostriatum, and other brain regions that interact with corticolimbic glutamate signals [27–35]. Incentive salience gives motivational urgency to many conscious desires but also can occur unconsciously [25,27,28,36]. 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 [21,25,27,28,36]. Cognitive wanting, as consciously experienced, may be mediated primarily by cortically weighted systems that depend less on subcortical mesolimbic dopamine signals [29–33] (Figure 1 and Box 1).

Highlights

Motivational desires usually match predictions of outcome gain. The match is so close that some define desire as nothing more than the prediction of gain.

Opposing evidence is presented here that desire is psychologically distinct from prediction and has different underlying neural mechanisms. Consequently, desire as incentive salience can separate completely from learned predictions, and can even create desires for outcomes that are remembered and predicted to be bad.

The operating rules of incentive salience that power such desires emerge from brain mesolimbic dopamine-related systems.

Two laboratory examples are described here to show how desire can separate from learned predictions of value: (i) 'wanting what is remembered to be disgusting', and (ii) 'wanting what is predicted to hurt'.

In people, similar separations of motivational desire from outcome prediction can occur in addiction and related clinical conditions.

[1]Department of Psychology, University of Michigan, Ann Arbor, MI 48109, USA

*Correspondence: berridge@umich.edu (K.C. Berridge).

Box 1. Reward: motivational 'wanting', predictive learning, and hedonic 'liking'

Reward contains the major dissociable psychological components of 'liking', 'wanting', and 'learning' [65] (Figure I). These components typically cohere together but can be separated by particular brain manipulations and by some human clinical conditions, including addiction and anhedonia [12,21,26,45,120].

Cognitive and associative learning allows predictions of outcome value. 'Liking' is the hedonic impact of pleasant rewards that is most familiar as conscious pleasure feelings. However, under some conditions 'liking' reactions also can occur unconsciously as objective 'liking' alone [27,36,66]. To acknowledge this dual conscious/unconscious status, quotation marks are put around the term 'liking' here. Similarly, 'wanting' refers to motivational incentive salience mediated especially by mesolimbic dopamine/glutamate systems. Incentive salience gives urgency to consciously felt desires, but in some conditions can also occur unconsciously as objective 'wanting' alone [27,36,66]. 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 [17,18,20,25,84].

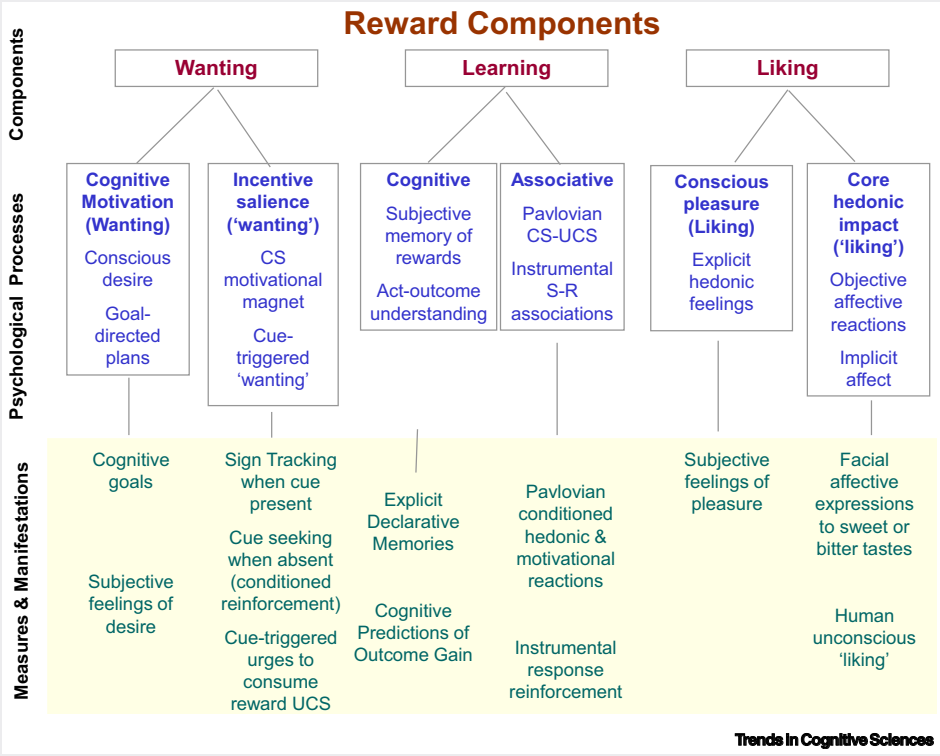

Figure I. Reward as a multicomponent process. Liking (hedonic impact of pleasure), wanting (motivational desire), and learning (memory and prediction) are three major component categories of reward (top row). Each category contains within it several subordinate psychological processes, some that are always subjectively conscious (explicit) whereas others are potentially unconscious (implicit) (middle section boxes). Typical measures or manifestations of various component processes are listed in the bottom colored section. Abbreviations: CS, conditioned stimulus; S-R, stimulus–response; UCS, unconditioned stimulus. Figure modified, with permission, from [65].

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. Two laboratory-induced examples of dissociated desire are described here that illustrate how the brain can produce intense desires for outcomes that

Glossary

Anhedonia: the inability to experience pleasure or 'liking' that is traditionally posited to accompany schizophrenia, major depressive disorder, and unmedicated Parkinson's disease.
Avolition: an alternative reinterpretation of anhedonia syndromes as, in some cases, a selective motivational loss of 'wanting' for life rewards, despite pleasure and liking capacity remaining intact. Also called anticipatory anhedonia, avolition is distinct from true or consummatory anhedonia.
Counterconditioning: a Pavlovian paradigm that can reverse from negative to positive the valence of response evoked by an originally mild aversive conditioned stimulus (CS), after the CS is associatively paired with a strongly rewarding unconditioned stimulus (UCS).
Hedonic alliesthesia: hedonic shift in the perceived pleasure of a stimulus ('liking') induced by a change in a relevant physiological or brain state.
Incentive alliesthesia: desire shift in incentive salience ('wanting') for a reward induced by a change in a relevant physiological or brain state.
Incentive salience: a motivational reward process, separate from hedonic pleasure, which transforms percepts into attractive, attention-grabbing objects of desire, mediated by mesolimbic dopamine systems.
Instrumental conditioned reinforcement: a paradigm that can assess 'wanting' for an absent reward cue. First, a CS is associatively paired with a reward UCS. Then the individual is allowed an opportunity to earn brief presentations of the CS (without the UCS) by learning a new instrumental response and performing that response.
Learned prediction: 'learned prediction of outcome value' is meant here to include all types of prediction: cognitive predictions based on describable declarative memories, associative predictions based on Pavlovian or instrumental associations that may sometimes be implicit, and even model-free predictions of value based on cached prediction errors (as posited by some computational models of reinforcement learning). All these predictions have been suggested by prediction/reinforcement advocates to guide choices and actions without a need for additional motivational desires.
Pavlovian instrumental transfer: a paradigm that can experimentally isolate

are remembered and predicted to be bad: (i) adaptive 'wanting what is known to disgust', and (ii) maladaptive 'wanting what is predicted to hurt' [17,18]. These laboratory examples show that the answer to the question 'is desire reducible to prediction of gain?' is a resounding 'no'. Instead, desire operates by rules of its own. This understanding provides insight into how addictions can give rise to intense desires that may seem irrational to observers. It also sets the stage to explore possibilities that milder dissociations of desire from prediction may occur in ordinary daily life, during transient states of appetites, stress, emotional excitement, or others that modulate the reactivity of mesolimbic systems.

Incentive salience features

Before introducing the examples, it may be helpful to describe major psychological rules that govern mesolimbic incentive salience. Psychological rules of incentive salience were first described in Pavlovian-guided incentive motivation theories beginning in the 1970s [22,23,25] which posited that learned reward cues [i.e., a Pavlovian conditioned stimulus (CS) associated with a rewarding

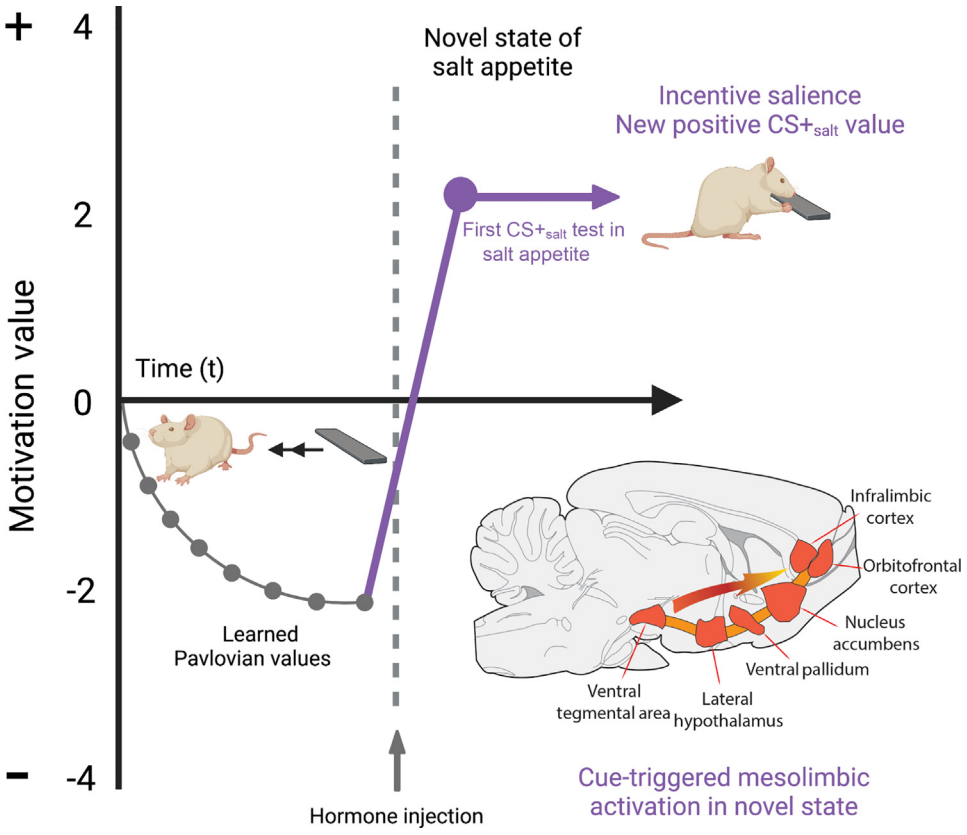

Figure 1. 'Wanting something that is known to be disgusting'. Instant reversal from learned repulsion to sudden desire elicited by a $CS+_{salt}$ cue was motivationally shifted by a new salt-appetite state [17] (Video S1 in the supplemental information online). Rats were ordinarily repulsed by presentations of the $CS+_{salt}$ lever in their normal state because they had learned the cue predicted a squirt of disgusting Dead Sea saltiness into the mouth as the UCS. Then one day they were given a hormonal treatment that produced a novel salt-appetite state the next day. When tested in the new appetite state, the $CS+_{salt}$ instantly elicited positive desire on its very first re-encounter – even though the salty UCS taste had never yet been retasted as being positively 'liked'. The rats now approached, jumped onto, and avidly nibbled the $CS+_{salt}$ lever in the novel state (i.e., sign tracking), exactly as they always did to the different $CS+_{sucrose}$ lever that predicted a pleasant sugar taste. Neurobiologically, the transformation was mediated by mesolimbic brain activations underlying incentive salience. Abbreviations: CS, conditioned stimulus; UCS, unconditioned stimulus. Figure modified, with permission, from [17]. Created with BioRender.com.

cue-triggered bursts of elevated 'wanting' which are magnified by mesolimbic dopamine stimulation. The procedure trains a Pavlovian CS association with a reward UCS (usually a food), and separately trains an instrumental response to earn a reward, and then occasionally presents the CS while individuals work for reward on the instrumental task (usually in extinction). The procedure helps to strip away stimulus–response habit explanations of increased responding because the CS has no association with the instrumental response (the CS was never previously paired with the response).

Sign tracking: the ability of reward cues to become attractive, riveting attention, and eliciting approach, even when doing so may result in the loss of an actual reward. Also called autoshaping.

Temporal difference models: computational models of reinforcement learning, based on model-free prediction errors. Originally devised in computer science as machine learning algorithms, they are also frequently applied to describe the firing of mesolimbic dopamine neurons that activate reward-predicting cues.

'Wanting': in quotation marks, 'wanting' refers to mesolimbic incentive salience that gives urgency to conscious desires, but also can occur unconsciously. By contrast, wanting without quotation marks refers to cognitive desires that are necessarily conscious, but may or may not involve incentive salience.

unconditioned stimulus (UCS)] did not simply predict the associated rewards but also took on some incentive motivational features related to those rewards. Relevant physiological states and brain states were further posited to modulate the motivational power of learned reward-related CS cues [17,20,23,25]. This theory has proved to be accurate in specifying rules of mesolimbic incentive salience, as later confirmed by affective neuroscience experiments [21,24–26].

Cues as motivational magnets

One motivational feature acquired by a reward CS cue attributed with incentive salience is that the learned cue itself becomes a target of 'wanting'. That is, the reward cue becomes an attractive motivational magnet able to rivet visual attention when encountered (i.e., the salience aspect of incentive salience [34,35,37–39]) and to elicit approach [40–45]. Cue-elicited approach is often measured as behavioral **sign tracking** in addiction neuroscience studies [40,44,46,47]. Sign-tracking attraction to reward cues can be boosted further by particular mesocorticolimbic stimulations [48–52]. Beyond eliciting approach, a sign-tracked cue may also elicit consummatory actions directed to the CS which ordinarily belong to the UCS reward. For example, a rat may eagerly nibble on an inedible metal cue for sucrose reward or a cue for cocaine reward [22,40,44,46,47], or a male quail may follow and attempt to copulate with a terrycloth object previously paired with a female quail [53].

Sign tracking also occurs in human children who are reported to approach and touch a CS cue associated with reward [54]. Similarly, adult human cocaine users may sometimes 'chase ghosts' – that is, compulsively scrabble for white specks of salt, sugar, or chalk on the grounds that they appear to be similar to cocaine, even when they know those specks contain no cocaine at all [55]. Ordinary human adults also show sign tracking more subtly as involuntary visual attention capture by reward-related cues in eye-tracking studies, even when the person deliberately tries to look for something else [34,38,39,56,57]. That is, incentive salience can make it difficult to not look at or approach reward cues.

Importantly, sign tracking results from motivational incentive salience being attributed to the CS cue, rather than simply to the cue's prediction of subsequent reward UCS [58–60]. For example, sign-tracking behavior can persist even when doing so costs the loss of actual rewards [61–63]. Similarly, human nicotine smokers may find smoking sensory cues so attractive that they prefer to receive smoking sensations delivered without nicotine rather than receiving actual nicotine delivered without the sensory cues [64].

Seeking out absent cues

A second incentive salience feature is that reward cues may be 'wanted' and sought out even when they are absent [25,65]. In animal neuroscience studies, this is often studied as **instrumental conditioned reinforcement** in which an animal learns to work on a new response to obtain presentations of a CS that was previously learned to be associated with reward [18,67]. For example, rats that are maladaptively attracted to a shock rod, described in the following section, were also willing to learn a new nose-poke response to hear an auditory CS sound associated with electric shocks [18].

Cues evoke temptation

A third feature of incentive salience is the ability of CS cues to briefly boost 'wanting' to obtain and consume their associated UCS rewards [25,68]. For example, the smell of food may make you suddenly feel hungry when you have not eaten for a while, even if you were not hungry a moment earlier. In animal studies, cue-triggered 'wanting' to obtain UCS is often measured in a **Pavlovian**

instrumental transfer paradigm where brief presentations of Pavlovian CSs elicit temporary surges in instrumental effort to obtain the associated (or similar) UCS reward. The cue-triggered surge in motivation to pursue UCS can be further amplified by dopamine-stimulating or related microinjections in nucleus accumbens or related structures, or by prior drug-induced sensitization of mesolimbic systems [69,70]. Another manifestation of cue-triggered 'wanting' is the observation that providing reward-related cues to accompany earning an actual reward can amplify the motivation to pursue that reward: for example, the pursuit and consumption of cocaine or nicotine infusions in animals is markedly increased when drug cues are presented together with drug infusions, compared to pursuit levels when the same drug infusions are earned alone without cues [71–74] In short, CS cues amplify motivation to consume associated UCS rewards.

Cue-triggered 'wanting' is prominent in people with drug addiction, for whom drug cues can trigger transient peaks of craving, and sometimes induce addictive relapse despite a cognitive resolve to abstain [75–77]. Such cue-triggered cravings are not necessarily experienced as negatively valenced distress or absence (e.g., not as drug withdrawal feelings), but are instead often experienced as a positive incentive motivational urge to consume the associated reward [78].

Brain states modulate cue-triggered temptations

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 [20,23,25,79]. 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 [80–82].

State-induced changes in the intensity of cue-triggered 'wanting' can be called **incentive alliesthesia** [12,17,18,81,83,84] – 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 [85]. 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 incentive alliesthesia can also occur by itself due to changes in mesolimbic dopamine 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 UCS has been re-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.

Separating desire from learned prediction

We are now ready to see how motivational desires can dissociate from both past affective memories and future predictions of outcome value. In particular, the ability of changes in relevant brain states to modulate the intensity of cue-triggered 'wanting' sets the stage for related brain mechanisms under particular conditions to decouple 'wanting' completely from affective memories and learned predictions.

'Wanting what you know disgusts': transformation of learned repulsion into desire

Our first example to separate desire from learned prediction is 'wanting what disgusts'. A mouthful of a very salty taste, such as ocean seawater (i.e., 3% NaCl), can be disgusting. Saltier and even more disgusting is water from the Dead Sea, at a sodium chloride level threefold higher (i.e., 9% NaCl). An oral infusion of NaCl solution at Dead Sea concentration into the mouth of a rat typically elicits a strong 'disgust' reaction of gapes, headshakes, and forelimb flails [17,86]. Not surprisingly, a Pavlovian cue that reliably predicts the 0.9% NaCl UCS infusions quickly becomes repulsive and elicits retreat after a few pairings. For example, in a Pavlovian sign-tracking experiment, a Pavlovian $CS+_{salt}$ cue (a metal lever) popped out of a wall to predict an inescapable UCS squirt of Dead Sea saltiness into the mouth of a rat a few seconds later (delivered painlessly by a previously implanted oral cannula) [17]. Each rat quickly learned to shrink away from the $CS+_{salt}$ lever whenever it appeared, retreating to a far wall as if trying to escape from the Pavlovian cue and its predicted salty infusion [17]. By contrast, when a different $CS+_{sucrose}$ lever popped from another wall, predicting an oral squirt of pleasantly sweet sugar solution as the UCS, all rats quickly learned to sign-track, jumping onto and nibbling the metal $CS+_{sucrose}$ lever as soon as it appeared [17].

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 [87,88]. 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 UCS elicited positive facial 'liking' expressions similarly to sugar, rather than usual disgust gapes, via hedonic alliesthesia that transforms the salty UCS from disgusting to pleasant [17,86]. Crucially, on the test day, the rats re-encountered their Pavlovian $CS+_{salt}$ cue 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 UCS infusions on this day (i.e., what is traditionally called a 'CS extinction test').

The question was: would the rats initially retreat again from their $CS+_{salt}$ lever? Would they need to later 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 UCS, jumping onto and avidly nibbling the metal lever that had previously repulsed them, exactly as they always jumped onto the $CS+_{sucrose}$ lever (Figure 1 and Video S1 in the supplemental information online) [17]. 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 UCS as anything but 'disgusting', and had so far no positive memory of any pleasant saltiness outcome upon which to base a positive prediction [17].

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 ventral tegmentum (where mesolimbic dopamine neurons originate), nucleus accumbens (the target of ascending dopamine axons), and related limbic structures [17]. 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.

Psychologically, the transformation may also have arisen in part from the capacity of the brain to form parallel Pavlovian memories between a CS and (i) the affective value of its UCS outcome, and (ii) the sensory identity of its UCS outcome [19,89]. That is, the $CS+_{salt}$ cue triggered not only a negative affective memory of the previous Dead Sea 'disgust', but also a parallel sensory memory of the intense saltiness of the UCS. If the salty Dead Sea UCS had been retasted on the sodium appetite test day before cue encounters, hedonic alliesthesia could have switched the remembered affective value from 'disgusting' to 'liked' [17,68,86,87,90]. However, without any opportunity to retaste the salty Dead Sea NaCl solution before encountering the $CS+_{salt}$ lever in the extinction test, the rats' brains were able to draw only on their sensory saltiness memory. That sensory memory was apparently sufficient in the new state to recompute incentive salience on the fly. This instant recomputation of incentive salience for the $CS+_{salt}$ cue was able to overrule previous repulsion based on affective memories of disgust, and suddenly make the Pavlovian cue for saltiness become positively 'wanted' [17,19,91] (Box 2).

It is worth noting that such a prescient transformation of motivation cannot be explained by conventional concepts of context-dependent learning. A context-dependent learning explanation would suggest that the rats possessed two different affective memories of Dead Sea saltiness value: (i) a positive memory of 'liking' previously experienced in the context of any earlier salt-appetite state, and (ii) a negative memory of 'disgust' previously experienced in their normal physiological state. Having memories of two different values in two different contexts would allow the rats to draw on the proper contextual memory appropriate to the current context. Nevertheless, that explanation fails in this case because the rats lacked any positive contextual memory to draw on. They had never been in a sodium-deficiency state before the test day, had never yet tasted Dead Sea saltiness as positively 'liked', and thus had no positive memory of 'liking' associated with a sodium-deficient context.

Box 2. Computational models of motivational reversal of the Dead Sea salt cue

The motivational transformation of a $CS+_{salt}$ cue from negatively repulsive to positively 'wanted' has been captured by computational models of incentive salience [122,123]. An initial computational model of the transformation was provided as $V(s_t) = r_t (r_t + log\ \kappa) + \gamma V(S_{t=1})$ [122]. In that model, $V(s_t)$ represents the incentive salience triggered by a learned $CS+_{salt}$ cue at re-encounter. The negative disgust value of the saltiness memory cache is expressed as r, but that value is modulated in the moment of re-encounter by the current physiological state, expressed as κ. In the normal physiological state, κ is <1, but the new salt-appetite state causes κ to rise above >1. This performs a logarithmic transformation ($log\ \kappa$) that reverses the negative r memory-based repulsion into a positive new $V(s_t)$ 'want' [122]. However, although this model mathematically describes the motivational valence reversal from negative to positive, it does not posit any psychological process to mediate the transformation (as its authors acknowledged). Instead, it simply imposes the logarithmic transformation as a computational act of force to produce the valence reversal. Such a 'model-free' model thus lacks explanatory usefulness for understanding the psychological mechanisms of reversal from repulsion to desire in real brains [19].

An improved computational model has been proposed, named a 'multi-attribute incentive salience' (MAIS) model [123]. The model draws more realistically upon the hypothesized role of a sensory saltiness memory that interacts with mesolimbic mechanisms to help to explain the incentive salience transformation. It characterizes the motivational transformation as $\check{r}(r,\kappa) = s \times exp(\kappa_{Na} r_{Na} + \kappa_h r_h)$ [123]. In it, the incentive salience of $CS+_{salt}$ is $\check{r}(r,\kappa)$, κ_{Na} represents the novel physiological appetite state, and r_{Na} is the sensory memory of Dead Sea saltiness UCS. By postulating the sensory saltiness memory r_{Na} to interact with the new appetite state κ_{Na} in recomputing incentive salience, this 'model-based' MAIS model can recompute a new positive desire as an act of incentive alliesthesia [19,89].

'Wanting what hurts': positive desire for a predicted negative outcome

Advocates of the 'desire equals prediction' view could still argue that incentive alliesthesia in the example described in the preceding text involved a new implicit prediction of positive outcome value, even though there was no positive affective memory on which to base that positive prediction. That is, the sensory salty memory alone may have been sufficient to generate a new value prediction in the sodium-depleted state, without ever needing to retaste actual Dead Sea saltiness as 'liked'.

However, our next example of 'wanting what hurts' has no such prediction-based escape route. Exactly the opposite: an accurate learned prediction of a negative affective outcome, namely an unpleasant electric shock, will actually contribute to forming a positive desire for its source, the shock rod [18,84]. This feature makes 'wanting what hurts' a particular challenge for prediction-based accounts of desire to explain.

'Wanting what hurts' has been induced in laboratory rats using a brain stimulation technique that recruits mesolimbic mechanisms of incentive salience: namely brief optogenetic excitations of neurons in the central nucleus of the amygdala (CeA) that are associatively paired with voluntary encounters of a 'shock rod' [18]. Why the amygdala? The amygdala is well known to help to assign motivational value to perceptions of learned stimuli related to rewards or threats [92–95]. That is, the amygdala helps to pick motivational targets, and it interacts with mesolimbic circuitry. The CeA in particular is a 'striatum-like' nucleus [96] which can generate an intense desire to obtain and consume food, drug, sex, etc. when neurobiologically stimulated [47,49,81,84,97,98]. Pairing brief amygdala CeA stimulations with shock-rod encounters in turn recruits activation of mesolimbic circuitry of incentive salience to specifically make the shock rod become maladaptively 'wanted' [18,84].

In more detail, the shock rod was a small metal rod wrapped with electrified wire that protruded from the wall [18]. Rats were never forced to touch the shock rod, but they could voluntarily touch it while exploring, and if so, would receive a mild electric shock sufficient to cause the rats to flinch away. Normal control rats (without amygdala stimulations) touched the electrified object once or twice (as humans may also do when bored [99]), 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 [100].

By contrast, the amygdala-stimulated rats, referred to as 'CeA ChR2' rats, had an optogenetic 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 gates 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 [18]. 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 hovering over the shock rod, continuously sniffed closely and repeatedly touched it again and again with paw, nose, mouth, or teeth (Figure 2 and Video S2 in the supplemental information online) [18]. 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, they also repeatedly climbed over a large protective barrier to reach and touch the shock rod again (Figure 2). 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 so as 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 (Figure 2 and Box 3).

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 [18]. 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 [18]. 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 [18].

The explanation of this maladaptive attraction may be that laser pairing 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 [18,84]. 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' [18,84]. Neurobiological evidence for this postulated mesolimbic recruitment was found as increased Fos activation in neurons in the ventral tegmentum, nucleus accumbens, and other mesolimbic structures in the brains of CeA ChR2 rats, when examined immediately after they were attracted to the shock rod [18]. The neurobiological activation of mesolimbic circuitry underlying maladaptive 'wanting' was essentially identical to mesolimbic activation during 'wanting' for conventional pleasant rewards [18,84] (Box 4).

Flipping the valence of motivational salience

In the same way as the motivational valence of $CS+_{salt}$ cue could flip between negative repulsion and positive 'wanting', it is also possible to flip the valence of motivation induced by CeA ChR2 pairings. In a Pavlovian fear conditioning situation, where a cue predicts an unavoidable and uncontrollable foot shock, combining CeA ChR2 laser stimulation with CS-UCS pairings in fear conditioning can paradoxically heighten fear-related defensive responses [18]. These negatively valenced responses included fearful freezing and avoidance behaviors, even in CeA ChR2 rats that were initially attracted to the shock rod paired with the laser. Increasing defensive reactions seems to rule out any possibility that CeA ChR2 laser pairing simply generates a rewarding experience. However, incentive salience and fearful salience both involve overlapping mesolimbic mechanisms of motivational salience [68,101]. Whatever the mechanism that switches the valence of motivational salience, the existence of such valence reversals indicates that CeA ChR2 stimulation does not simply enhance the perceived pleasantness of a laser-paired outcome. When CeA ChR2 pairing creates an addictive-like desire, it specifically amplifies motivational 'wanting' for the target – not hedonic 'liking'.

Human clinical implications

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 [21,106]. 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 distress feelings. 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.

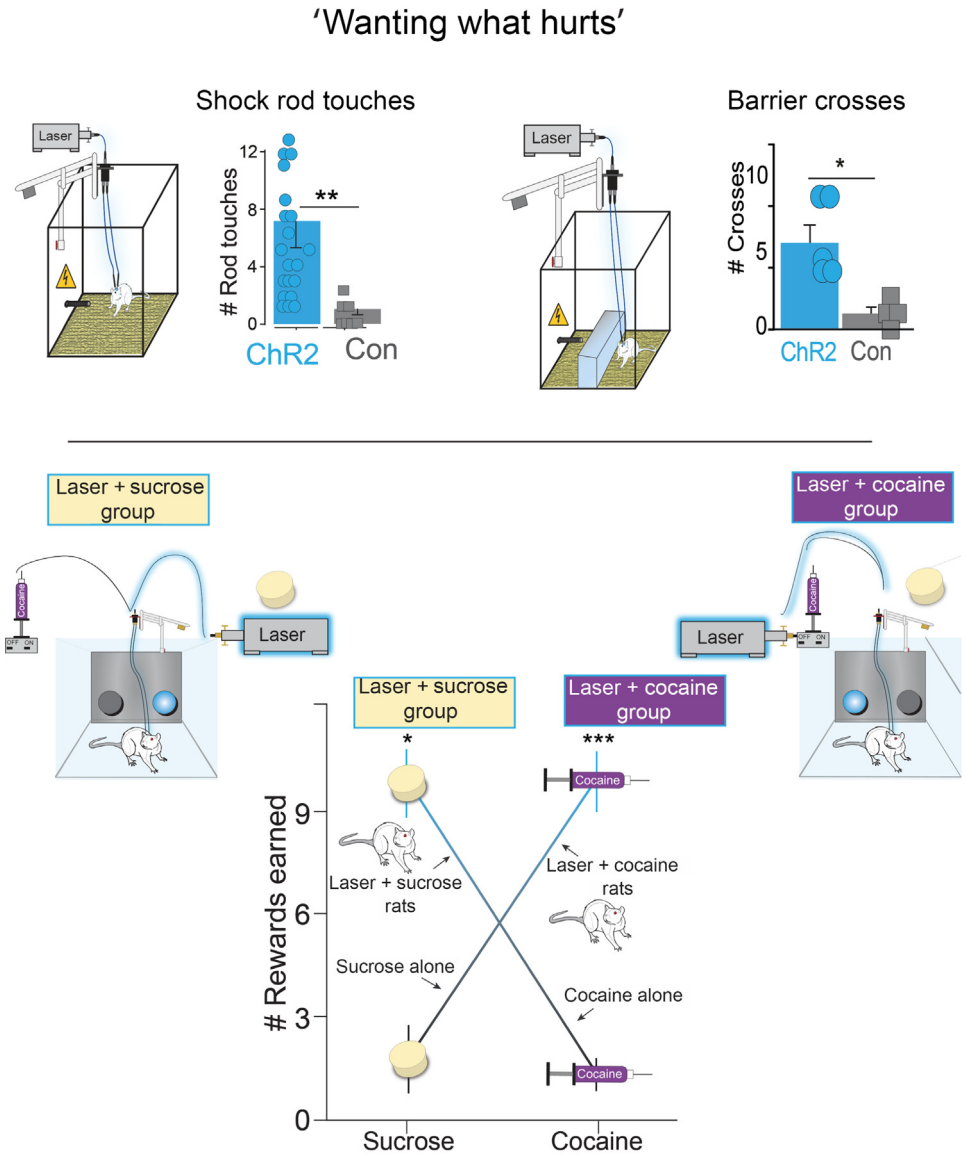

Figure 2. 'Wanting what hurts' and modeling addictions. (Top left) 'CeA ChR2' rats expressing channelrhodopsin (ChR2) in the central nucleus of amygdala (CeA) voluntarily approach and repeatedly touch the laser-paired shock rod, despite receiving multiple electric shocks on paws, nose, or mouth [18]. Abbreviation: Con, control rats. (Top right) CeA ChR2 rats repeatedly climbed over a safety barrier to reach and touch the rod, again receiving shocks each time they crossed. (Bottom) CeA ChR2 rats could freely choose between earning sucrose pellets or intravenous cocaine infusions (Box 4). CeA ChR2 rats whose CeA laser was paired with earning sucrose, but not with earning cocaine, became 'sucrose addicts' that pursued only sucrose and ignored cocaine. Conversely, other CeA ChR2 rats, whose laser was paired with cocaine but not with sucrose, became 'cocaine addicts' that pursued only cocaine and ignored sucrose. Modified, with permission, from [18].

Of course, no addicted human has ever received optogenetic brain stimulations. Nevertheless, vulnerable human individuals might encounter smaller endogenous excitations in amygdala and related mesolimbic circuitry that are triggered by encounters with addictive targets. Gradually

Box 3. Can counterconditioning explain shock-rod attraction?

Some readers may wonder whether a phenomenon known as **counterconditioning**, as originally described by Pavlov [124], might explain shock-rod attraction. The short answer is 'no'. In Pavlov's description, counterconditioning reverses the valence of the conditioned response elicited by a CS and occurs when a moderately aversive CS stimulus (e.g., mild electric shock) reliably predicts a strongly positive reward UCS (e.g., food when hungry). For example, Pavlov described a hungry dog who learned that a mild electric shock CS to its paw predicted a tasty food reward as UCS [124]. Initially, the CS shock evoked paw withdrawal, but after several counterconditioning CS pairings with food UCS, the dog began to salivate when the CS shock occurred, 'turning its head to where it usually received the food and smacking its lips' ([124], pp. 29–30, translated). Therefore, a shock rod as the CS could conceivably also become attractive via counterconditioning if the shock rod was reliably paired with a highly rewarding UCS. Other counterconditioning studies have suggested that an appetitive conditioned response to CS simply becomes appended in addition to the originally aversive response, rather than replacing it [125]. However, even Pavlov emphasized that a highly rewarding UCS was absolutely required for counterconditioning. As Pavlov wrote, counterconditioning 'can be brought about only when' the aversive response to a noxious CS 'is physiologically weaker and biologically of less importance' than the unconditioned appetitive response to the reward UCS ([124], p. 30). In the shock-rod situation, there was no food, sugar, cocaine, or other pleasant UCS stimulus. The only potential reward available was the CeA ChR2 laser itself. The question therefore becomes – was the CeA laser a powerful reward UCS that was sufficiently rewarding to support counterconditioning? The evidence indicates that answer is also 'no'. For example, in addition to relatively ignoring their dummy rod as described in the text (which did deliver CeA ChR2 laser but not shocks), most CeA ChR2 rats did not robustly self-stimulate CeA laser by itself even when they could earn laser without shock simply by touching an innocuous lever or poking their nose into a hole, or even only by staying in one particular chamber of a multi-chamber box [18,47,97]. Some CeA ChR2 rats failed to self-stimulate the laser at all in these easy tasks, even though the same CeA ChR2 rats were still highly attracted to their laser-paired shock rod [18]. Finally, CeA ChR2 laser oppositely increased negatively valenced defensive conditioned reactions in an uncontrollable Pavlovian fear conditioning situation. Thus, the evidence indicates that any rewarding qualities of CeA ChR2 laser by itself were insufficient to explain shock-rod attraction, and that Pavlovian counterconditioning is not the mechanism underlying maladaptive 'wanting what hurts'.

accruing in individuals who are vulnerable to mesolimbic sensitization [21,102–106], 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 relative neural sledgehammer of 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.

Similar sensitization of excessive incentive salience may also explain the development of behavioral addictions in vulnerable Parkinson's patients induced by dopamine 'direct agonist' medications that directly stimulate D2/D3 dopamine receptors [107]. These medication-induced behavioral addictions can include compulsive gambling, shopping, sex or pornography use, binge eating, etc. Neuroimaging evidence indicates that medicated Parkinson's patients who develop these addictive behaviors show hyper-reactivity in striatal dopamine release compared to other Parkinson's patients who take the same medications but remain free of compulsions [107]. In other words, their vulnerability to mesolimbic sensitization of dopamine-related systems appears to mediate the development of medication-induced compulsions [107].

Excessive incentive salience, detached from outcome value prediction, may also apply to some cases of spontaneous behavioral addictions, even in people who have never taken addictive drugs or medications. Several fMRI studies report a sensitization-like brain signature of mesolimbic hyper-reactivity to addiction-related cues in some individuals treated for gambling compulsions, binge eating compulsions, sexual compulsions, etc. [108–119].

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

Box 4. Mimicking addiction? CeA ChR2 pairing focuses 'wanting' on sugar or cocaine

'Wanting what hurts' is the strongest proof-of-principle demonstration so far that motivational 'wanting' can become completely independent of the predicted and experienced outcome 'liking', as postulated by the incentive-sensitization theory of addiction [21,106]. The shock rod gave no pleasure at all, but only a painful shock. In this sense, 'wanting what hurts' is a prototype of addictive motivation because the excessive and narrowly focused incentive salience upon a target is not justified by predictions, memories, or experiences of outcome 'liking' [21,106]. Of course, real addictions are usually focused on initially pleasant targets, not painful ones. What happens if CeA ChR2 pairing is applied to a conventionally pleasant target such as intravenous cocaine or sugar?

The result is an intense and narrowly focused, addictive-like desire for the laser-paired reward which far exceeds the normal motivational strength of that reward [18,47,97]. For example, other CeA ChR2 rats were offered a choice between earning either pleasant sucrose pellets by poking their nose into one wall porthole, or earning intravenous cocaine infusions (delivered painlessly via implanted intravenous canula) by poking into a different porthole [18]. Both portholes were freely available, allowing the rats to mix or match cocaine and sugar as they chose [18]. For some CeA ChR2 rats, CeA laser stimulation was selectively paired with earning sugar pellets, but not with cocaine. For different CeA ChR2 rats, their CeA laser was selectively paired with earning cocaine, but not with sugar. Normal control rats, with similar laser pairings but optically inactive control virus that lacked ChR2 in CeA, chose both sugar and cocaine at relatively moderate and equal levels [18]. After all, why not take both sugar and cocaine when both are easily available? By contrast, for CeA ChR2 rats, 'wanting' became intensified and narrowed onto only one target in an addictive-like fashion that was induced by laser pairings. For example, the CeA ChR2 rats whose laser was selectively paired with sucrose quickly became 'sugar addicts': they intensely pursued and consumed only sugar while ignoring the opportunity to earn cocaine [18] (see Figure 2 in main text). These 'sugar addicts' also demonstrated intensified desire to earn sugar rewards in an 'effort breakpoint' task that imposed increasingly strenuous effort demands as the session continued, working far harder for their laser-paired sugar than ordinarily seen for sugar rewards.

A related study showed that CeA ChR2 rats will continue to seek laser-paired sugar despite incurring an electric footshock as an adverse consequence [126]. The other group of CeA ChR2 rats, whose laser was selectively paired with cocaine, instead became 'cocaine addicts': these rats intensely pursued only cocaine while ignoring sugar in the choice situation, and escalated effort far above ordinary cocaine-motivated levels in their effort breakpoint task [18]. Once again, the CeA laser by itself held relatively little incentive value for either group of CeA ChR2 rats: some even failed to self-stimulate laser at all despite having intensely and single-mindedly pursued their laser-paired sugar or laser-paired cocaine option [18,47,97]. Thus, similarly to the shock-rod situation, CeA ChR2 pairings recruited mesolimbic circuitry to synergistically focus intense incentive salience only on the laser-paired target, making that target intensely and narrowly more 'wanted' in an addiction-like fashion [18,47,97,126].

Does CeA ChR2 pairing make its target more motivationally 'wanted' by making that target more hedonically 'liked'? The evidence suggests that the answer is 'no'. For example, CeA ChR2 rats that are made to excessively 'want' sugar reward by laser pairings, fail to show any laser-induced enhancement of orofacial 'liking' expressions to the sweet taste when they actually receive sucrose [97].

Outstanding questions

Can lesser separations of desire from prediction be identified in daily human life that are induced during occurrences of stress, appetite states, fatigue, intoxication, etc.?

What neural mechanisms underlie the reversal of motivational valence, such as transformation of a noxious shock rod into an object of desire? The phenomenon indicates an overlap between limbic activations triggered by conventional rewards and those triggered by a CeA ChR2 laser-paired shock-rod encounter. However, the crucial neural and psychological overlap that is necessary to convert fear into desire remains unknown.

Are upward dissociations of excessive desire from prediction in addiction and laboratory examples matched by downward dissociations of impaired desire in other conditions? For example, although anhedonia (loss of pleasure) has traditionally been viewed as a feature of schizophrenia, major depression, and Parkinson's disease, many such cases recently have been suggested to instead be avolition, involving selective loss of motivational value while pleasure capacity remains intact. In such cases, life rewards may become no longer desired, even if still experienced as hedonically pleasant, thus raising the question of whether memories and predictions of value might also remain intact.

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

Prediction and desire do usually cohere in daily life, but desire cannot be reduced to prediction of gain. Desire has its own distinct neural mechanisms of incentive salience that operate according to particular psychological rules. These rules allow desire to decouple from prediction in some situations. In the laboratory and in the clinical situations discussed here, desire can maladaptively soar above outcome predictions, and above the hedonic outcome experience when received. Conversely, it would be of interest to know whether an opposite dissociation might apply to traditional **anhedonia** syndromes (i.e., pleasure incapacity) in cases of schizophrenia, depression, and Parkinson's disease that have been recently reinterpreted as **avolition** syndromes (i.e., selective loss of desire, but intact pleasure capacity) [12,26,45,120,121] (see also Outstanding questions). More generally, even when prediction and desire go together in ordinary life, the potential independence of 'wanting' mechanisms may be never lost, merely hidden. A slight neural or psychological push induced by a fluctuating internal state might be all that is necessary to momentarily separate desire from prediction again.

Acknowledgments

The research described here was supported by grants from the National Institutes of Health (MH063649 and DA015188).

Declaration of interests

The author declares no conflicts of interest.

Supplemental information

Supplemental information associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tics.2023.07.007.

References

1. Braver, T.S. *et al.* (2014) Mechanisms of motivation–cognition interaction: challenges and opportunities. *Cogn. Affect. Behav. Neurosci.* 14, 443–472
2. Dickinson, A. and Balleine, B. (2010) Hedonics: the cognitive–motivational interface. In *Pleasures of the Brain* (Kringelbach, M.L. and Berridge, K.C., eds), pp. 74–84, Oxford University Press
3. Smith, R. *et al.* (2019) Neurocomputational mechanisms underlying emotional awareness: insights afforded by deep active inference and their potential clinical relevance. *Neurosci. Biobehav. Rev.* 107, 473–491
4. Tschantz, A. *et al.* (2022) Simulating homeostatic, allostatic and goal-directed forms of interoceptive control using active inference. *Biol. Psychol.* 169, 108266
5. Barrett, L.F. and Quigley, K.S. (2021) Interoception: the secret ingredient. *Cerebrum* 2021 cer-06-21
6. Seth, A.K. and Critchley, H.D. (2013) Extending predictive processing to the body: emotion as interoceptive inference. *Behav. Brain Sci.* 36, 227–228
7. Clark, A. (2019) Beyond desire? Agency, choice, and the predictive mind. *Austral. J. Philos.* 98, 1–15
8. Friston, K. and Kiebel, S. (2009) Predictive coding under the free-energy principle. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 364, 1211–1221
9. Hutchinson, J.B. and Barrett, L.F. (2019) The power of predictions: an emerging paradigm for psychological research. *Curr. Dir. Psychol. Sci.* 28, 280–291
10. Klein, C. (2018) What do predictive coders want? *Synthese* 195, 2541–2557
11. Holton, R. (2016) Think ahead: arguing that all of our core mental states are predictions. *Times Lit. Suppl.* 7 October
12. Romer Thomsen, K. *et al.* (2015) Reconceptualizing anhedonia: novel perspectives on balancing the pleasure networks in the human brain. *Front. Behav. Neurosci.* 9, 49
13. Schultz, W. (2016) Dopamine reward prediction-error signalling: a two-component response. *Nat. Rev. Neurosci.* 17, 183–195
14. Schultz, W. *et al.* (1997) A neural substrate of prediction and reward. *Science* 275, 1593–1599
15. Montague, P.R. *et al.* (2004) Computational roles for dopamine in behavioural control. *Nature* 431, 760–767
16. Niv, Y. and Schoenbaum, G. (2008) Dialogues on prediction errors. *Trends Cogn. Sci.* 12, 265–272
17. Robinson, M.J. and Berridge, K.C. (2013) Instant transformation of learned repulsion into motivational 'wanting'. *Curr. Biol.* 23, 282–289
18. Warlow, S.M. *et al.* (2020) The central amygdala recruits mesocorticolimbic circuitry for pursuit of reward or pain. *Nat. Commun.* 11, 2716
19. Dayan, P. and Berridge, K.C. (2014) Model-based and model-free Pavlovian reward learning: revaluation, revision, and revelation. *Cogn. Affect. Behav. Neurosci.* 14, 473–492
20. Berridge, K.C. (2012) From prediction error to incentive salience: mesolimbic computation of reward motivation. *Eur. J. Neurosci.* 35, 1124–1143
21. Berridge, K.C. and Robinson, T.E. (2016) Liking, wanting, and the incentive-sensitization theory of addiction. *Am. Psychol.* 71, 670–679
22. Bindra, D. (1978) How adaptive behavior is produced: a perceptual-motivation alternative to response reinforcement. *Behav. Brain Sci.* 1, 41–91
23. Toates, F. (1986) *Motivational Systems*, Cambridge University Press
24. Berridge, K.C. (2001) Reward learning: reinforcement, incentives, and expectations. In *The Psychology of Learning and Motivation* (Medin, D.L., ed.), pp. 223–278, Academic Press
25. Berridge, K.C. (2018) Evolving concepts of emotion and motivation. *Front. Psychol.* 9, 1647
26. Olney, J.J. *et al.* (2018) Current perspectives on incentive salience and applications to clinical disorders. *Curr. Opin. Behav. Sci.* 22, 59–69
27. Winkielman, P. *et al.* (2005) Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. *Personal. Soc. Psychol. Bull.* 31, 121–135
28. Berridge, K.C. and Winkielman, P. (2003) What is an unconscious emotion? (The case for unconscious 'liking'). *Cogn. Emot.* 17, 181–211
29. Fisher, S.D. *et al.* (2020) Amygdala-cortical control of striatal plasticity drives the acquisition of goal-directed action. *Curr. Biol.* 30, 4541–4546
30. Watson, P. *et al.* (2018) Conflicted between goal-directed and habitual control, an fMRI investigation. *eNeuro* 5 ENEURO.0240-18.2018
31. Touroutoglou, A. *et al.* (2020) The tenacious brain: how the anterior mid-cingulate contributes to achieving goals. *Cortex* 123, 12–29
32. Wang, F. *et al.* (2020) Interactions between human orbitofrontal cortex and hippocampus support model-based inference. *PLoS Biol.* 18, e3000578
33. Dickinson, A. *et al.* (2000) Dissociation of Pavlovian and instrumental incentive learning under dopamine antagonists. *Behav. Neurosci.* 114, 468–483
34. Bollen, Z. *et al.* (2020) Craving is everything: an eye-tracking exploration of attentional bias in binge drinking. *J. Psychopharmacol.* 34, 646–647
35. Doolan, K.J. *et al.* (2015) Attentional bias to food-related visual cues: is there a role in obesity? *Proc. Nutr. Soc.* 74, 37–45
36. Winkielman, P. and Gogolushko, Y. (2018) Influence of suboptimally and optimally presented affective pictures and words on consumption-related behavior. *Front. Psychol.* 8, 2261
37. Hickey, C. and Peelen, M.V. (2017) Reward selectively modulates the lingering neural representation of recently attended objects in natural scenes. *J. Neurosci.* 37, 7297–7304
38. Barbaro, L. *et al.* (2017) Valence, not utility, underlies reward-driven prioritization in human vision. *J. Neurosci.* 37, 10438–10450
39. Hickey, C. and Peelen, M.V. (2015) Neural mechanisms of incentive salience in naturalistic human vision. *Neuron* 85, 512–518
40. Tomie, A. (1996) Locating reward cue at response manipulandum (CAM) induces symptoms of drug abuse. *Neurosci. Biobehav. Rev.* 20, 31
41. Flagel, S.B. *et al.* (2021) Comment on Pohorala *et al.*: sign-tracking as a predictor of addiction vulnerability. *Psychopharmacology* 238, 2661–2664

42. Flagel, S.B. and Robinson, T.E. (2017) Neurobiological basis of individual variation in stimulus–reward learning. *Curr. Opin. Behav. Sci.* 13, 178–185
43. Saunders, B.T. *et al.* (2018) Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. *Nat. Neurosci.* 21, 1072–1083
44. Uslaner, J. *et al.* (2006) The attribution of incentive salience to a stimulus that signals an intravenous injection of cocaine. *Behav. Brain Res.* 169, 320–324
45. Moran, E.K. *et al.* (2022) Anhedonia in schizophrenia. *Curr. Top. Behav. Neurosci.* 58, 129–145
46. Hearst, E. and Jenkins, H. (1974) *Sign-Tracking: The Stimulus–Reinforcer Relation and Directed Action*, Psychonomic Society
47. Warlow, S.M. *et al.* (2017) Optogenetic central amygdala stimulation intensifies and narrows motivation for cocaine. *J. Neurosci.* 37, 8330–8348
48. DiFeliceantonio, A.G. and Berridge, K.C. (2016) Dorsolateral neostriatum contribution to incentive salience: opioid or dopamine stimulation makes one reward cue more motivationally attractive than another. *Eur. J. Neurosci.* 43, 1203–1218
49. Mahler, S.V. and Berridge, K.C. (2012) What and when to 'want'? Amygdala-based focusing of incentive salience upon sugar and sex. *Psychopharmacology* 221, 407–426
50. Difeliceantonio, A.G. and Berridge, K.C. (2012) Which cue to 'want'? Opioid stimulation of central amygdala makes goal-trackers show stronger goal-tracking, just as sign-trackers show stronger sign-tracking. *Behav. Brain Res.* 230, 399–408
51. Mahler, S.V. and Berridge, K.C. (2009) Which cue to 'want?' Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue. *J. Neurosci.* 29, 6500–6513
52. Haight, J.L. *et al.* (2015) Lesions of the paraventricular nucleus of the thalamus differentially affect sign- and goal-tracking conditioned responses. *Eur. J. Neurosci.* 42, 2478–2488
53. Cetinkaya, H. and Domjan, M. (2006) Sexual fetishism in a quail (*Coturnix japonica*) model system: test of reproductive success. *J. Comp. Psychol.* 120, 427–432
54. Colaizzi, J.M. *et al.* (2020) Mapping sign-tracking and goal-tracking onto human behaviors. *Neurosci. Biobehav. Rev.* 111, 84–94
55. Rosse, R.B. *et al.* (1993) Transient compulsive foraging behavior associated with crack cocaine use. *Am. J. Psychiatry* 150, 155–156
56. Castellanos, E.H. *et al.* (2009) Obese adults have visual attention bias for food cue images: evidence for altered reward system function. *Int. J. Obes.* 33, 1063–1073
57. Hickey, C. *et al.* (2010) Incentive salience in human visual attention. *J. Vis.* 10, 31
58. Flagel, S.B. *et al.* (2011) A selective role for dopamine in stimulus-reward learning. *Nature* 469, 53–57
59. Saunders, B.T. and Robinson, T.E. (2012) The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. *Eur. J. Neurosci.* 36, 2521–2532
60. Robinson, T.E. and Flagel, S.B. (2009) Dissociating the predictive and incentive motivational properties of reward-related cues through the study of individual differences. *Biol. Psychiatry* 65, 869–873
61. Chang, S.E. and Smith, K.S. (2016) An omission procedure reorganizes the microstructure of sign-tracking while preserving incentive salience. *Learn. Mem.* 23, 151–155
62. Kawa, A.B. *et al.* (2016) Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. *Psychopharmacology* 233, 3587–3602
63. Williams, D.R. and Williams, H. (1969) Auto-maintenance in the pigeon: sustained pecking despite contingent non-reinforcement. *J. Exp. Anal. Behav.* 12, 511–520
64. Rose, J.E. *et al.* (2010) Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. *Psychopharmacology* 210, 1–12
65. Berridge, K.C. and Robinson, T.E. (2003) Parsing reward. *Trends Neurosci.* 26, 507–513
66. Winkielman, P. and Berridge, K.C. (2004) Unconscious emotion. *Curr. Dir. Psychol.* 13, 120–123
67. Meyer, P.J. *et al.* (2012) Quantifying individual variation in the propensity to attribute incentive salience to reward cues. *PLoS One* 7, e38987
68. Berridge, K.C. and Kringelbach, M.L. (2015) Pleasure systems in the brain. *Neuron* 86, 646–664
69. Pecina, S. *et al.* (2006) Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress? *BMC Biol.* 4, 8
70. Wyvell, C.L. and Berridge, K.C. (2001) Incentive-sensitization by previous amphetamine exposure: Increased cue-triggered 'wanting' for sucrose reward. *J. Neurosci.* 21, 7831–7840
71. Arroyo, M. *et al.* (1998) Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: effects of conditioned cues and continuous access to cocaine. *Psychopharmacology* 140, 331–344
72. Caggiula, A.R. *et al.* (2001) Cue dependency of nicotine self-administration and smoking. *Pharmacol. Biochem. Behav.* 70, 515–530
73. Schenk, S. and Partridge, B. (2001) Influence of a conditioned light stimulus on cocaine self-administration in rats. *Psychopharmacology* 154, 390–396
74. Di Ciano, P. and Everitt, B.J. (2004) Conditioned reinforcing properties of stimuli paired with self-administered cocaine, heroin or sucrose: implications for the persistence of addictive behaviour. *Neuropharmacology* 47, 202–213
75. Bechara, A. *et al.* (2019) A neurobehavioral approach to addiction: implications for the opioid epidemic and the psychology of addiction. *Psychol. Sci. Public Interest* 20, 96–127
76. Tiffany, S.T. and Wray, J.M. (2012) The clinical significance of drug craving. *Ann. N. Y. Acad. Sci.* 1248, 1–17
77. Vafaie, N. and Kober, H. (2022) Association of drug cues and craving with drug use and relapse: a systematic review and meta-analysis. *JAMA Psychiatr.* 79, 641–650
78. Childress, A.R. *et al.* (1988) Classically conditioned responses in opioid and cocaine dependence: a role in relapse? *NIDA Res. Monogr.* 84, 25–43
79. Gallistel, C.R. (1978) Irrelevance of past pleasure. *Behav. Brain Sci.* 1, 59–60
80. Baumgartner, H.M. *et al.* (2022) Corticotropin releasing factor (CRF) systems: Promoting cocaine pursuit without distress via incentive motivation. *PLoS One* 17, e0267345
81. Baumgartner, H.M. *et al.* (2021) Activating corticotropin-releasing factor systems in the nucleus accumbens, amygdala, and bed nucleus of stria terminalis: incentive motivation or aversive motivation? *Biol. Psychiatry* 89, 1162–1175
82. Koob, G.F. (2021) Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. *Pharmacol. Rev.* 73, 163–201
83. Smith, K.S. *et al.* (2011) Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proc. Natl. Acad. Sci. U. S. A.* 108, E255–E264
84. Warlow, S.M. and Berridge, K.C. (2021) Incentive motivation: 'wanting' roles of central amygdala circuitry. *Behav. Brain Res.* 411, 113376
85. Cabanac, M. (1971) Physiological role of pleasure. *Science* 173, 1103–1107
86. Tindell, A.J. *et al.* (2006) Ventral pallidum firing codes hedonic reward: when a bad taste turns good. *J. Neurophysiol.* 96, 2399–2409
87. Smith, C.M. and Lawrence, A.J. (2018) Salt appetite, and the influence of opioids. *Neurochem. Res.* 43, 3–9
88. Schulkin, J. (1991) *Sodium Hunger: The Search for Salty Taste*, Cambridge University Press
89. Konorski, J. (1967) *Integrative Activity of the Brain: An Interdisciplinary Approach*, University of Chicago Press
90. Fortin, S.M. and Roitman, M.F. (2017) Physiological state tunes mesolimbic signaling: Lessons from sodium appetite and inspiration from Randall R. Sakai. *Physiol. Behav.* 178, 21–27
91. Huebner, B. and Schulkin, J. (2022) *Biological Cognition: Elements in Philosophy of Mind*, Cambridge University Press
92. Tye, K.M. (2018) Neural circuit motifs in valence processing. *Neuron* 100, 436–452

93. Kyriazi, P. *et al.* (2018) Multi-dimensional coding by basolateral amygdala neurons. *Neuron* 99, 1315–1328
94. LeDoux, J.E. (2020) Thoughtful feelings. *Curr. Biol.* 30, R619–R623
95. Adolphs, R. *et al.* (2019) What is an emotion? *Curr. Biol.* 29, R1060–R1064
96. Swanson, L.W. (2005) Anatomy of the soul as reflected in the cerebral hemispheres: neural circuits underlying voluntary control of basic motivated behaviors. *J. Comp. Neurol.* 493, 122–131
97. Robinson, M.J. *et al.* (2014) Optogenetic excitation of central amygdala amplifies and narrows incentive motivation to pursue one reward above another. *J. Neurosci.* 34, 16567–16580
98. Gosnell, B.A. (1988) Involvement of mu opioid receptors in the amygdala in the control of feeding. *Neuropharmacology* 27, 319–326
99. Wilson, T.D. *et al.* (2014) Just think: the challenges of the disengaged mind. *Science* 345, 75–77
100. Treit, D. *et al.* (1981) Conditioned defensive burying: a new paradigm for the study of anxiolytic agents. *Pharmacol. Biochem. Behav.* 15, 619–626
101. Berridge, K.C. (2019) Affective valence in the brain: modules or modes? *Nat. Rev. Neurosci.* 20, 225–234
102. MacNiven, K.H. *et al.* (2018) Association of neural responses to drug cues with subsequent relapse to stimulant use. *JAMA Netw. Open* 1, e186466
103. Reinhard, I. *et al.* (2015) A comparison of region-of-interest measures for extracting whole brain data using survival analysis in alcoholism as an example. *J. Neurosci. Methods* 242, 58–64
104. Prisciandaro, J.J. *et al.* (2014) The relationship between years of cocaine use and brain activation to cocaine and response inhibition cues. *Addiction* 109, 2062–2070
105. Samaha, A.-N. *et al.* (2021) Dopamine 'ups and downs' in addiction revisited. *Trends Neurosci.* 44, 516–526
106. Robinson, T.E. and Berridge, K.C. (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* 18, 247–291
107. O'Sullivan, S.S. *et al.* (2011) Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain* 134, 969–978
108. Devoto, F. *et al.* (2018) Hungry brains: a meta-analytical review of brain activation imaging studies on food perception and appetite in obese individuals. *Neurosci. Biobehav. Rev.* 94, 271–285
109. Singer, B.F. *et al.* (2020) An overview of commonalities in the mechanisms underlying gambling and substance use disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 101, 109944
110. Limbrick-Oldfield, E.H. *et al.* (2017) Neural substrates of cue reactivity and craving in gambling disorder. *Transl. Psychiatry* 7, e992
111. Rømer Thomsen, K. *et al.* (2014) Applying incentive sensitization models to behavioral addiction. *Neurosci. Biobehav. Rev.* 45, 343–349
112. Zilberman, N. *et al.* (2018) Evidence for a differential visual M300 brain response in gamblers. *Clin. Neurophysiol.* 129, 2228–2238
113. Schettino, M. *et al.* (2022) From skinner box to daily life: sign-tracker phenotype co-segregates with impulsivity, compulsivity, and addiction tendencies in humans. *Cogn. Affect. Behav. Neurosci.* 22, 1358–1369
114. Toates, F. (2022) A motivation model of sex addiction – relevance to the controversy over the concept. *Neurosci. Biobehav. Rev.* 142, 104872
115. Golec, K. *et al.* (2021) Aberrant orbitofrontal cortex reactivity to erotic cues in compulsive sexual behavior disorder. *J. Behav. Addict.* 10, 646–656
116. Gola, M. *et al.* (2017) Can pornography be addictive? An fMRI study of men seeking treatment for problematic pornography use. *Neuropsychopharmacology* 42, 2021–2031
117. Boswell, R.G. *et al.* (2020) The neurobiology of binge-eating disorder compared with obesity: implications for differential therapeutics. *Clin. Ther.* 43, 50–69
118. Yokum, S. *et al.* (2014) Individual differences in striatum activity to food commercials predict weight gain in adolescents. *Obesity (Silver Spring)* 22, 2544–2551
119. Stice, E. and Yokum, S. (2021) Neural vulnerability factors that predict future weight gain. *Curr. Obes. Rep.* 10, 435–443
120. Treadway, M.T. and Zald, D.H. (2013) Parsing anhedonia: translational models of reward-processing deficits in psychopathology. *Curr. Dir. Psychol. Sci.* 22, 244–249
121. Sienkiewicz-Jarosz, H. *et al.* (2013) Sweet liking in patients with Parkinson's disease. *J. Neurol. Sci.* 329, 17–22
122. Zhang, J. *et al.* (2009) A neural computational model of incentive salience. *PLoS Comput. Biol.* 5, e1000437
123. Smith, B.J. and Read, S.J. (2022) Modeling incentive salience in Pavlovian learning more parsimoniously using a multiple attribute model. *Cogn. Affect. Behav. Neurosci.* 22, 244–257
124. Pavlov, I.P. (1927) *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*, Oxford University Press
125. Lovibond, P.F. and Dickinson, A. (1982) Counterconditioning of appetitive and defensive CRs in rabbits. *Q. J. Exp. Psychol. B.* 34, 115–126
126. Tom, R.L. *et al.* (2018) Optogenetic activation of the central amygdala generates addiction-like preference for reward. *Eur. J. Neurosci.* 50, 2086–2100