

# Instant Transformation of Learned Repulsion into Motivational “Wanting”

Mike J.F. Robinson<sup>1,\*</sup> and Kent C. Berridge<sup>1</sup>

<sup>1</sup>Biopsychology Department, 530 Church Street, East Hall, University of Michigan, Ann Arbor, MI 48109, USA

## Summary

**Background:** Learned cues for pleasant reward often elicit desire, which, in addicts, may become compulsive. According to the dominant view in addiction neuroscience and reinforcement modeling, such desires are the simple products of learning, coming from a past association with reward outcome.

**Results:** We demonstrate that cravings are more than merely the products of accumulated pleasure memories—even a repulsive learned cue for unpleasantness can become suddenly desired via the activation of mesocorticolimbic circuitry. Rats learned repulsion toward a Pavlovian cue (a briefly-inserted metal lever) that always predicted an unpleasant Dead Sea saltiness sensation. Yet, upon first reencounter in a novel sodium-depletion state to promote mesocorticolimbic reactivity (reflected by elevated Fos activation in ventral tegmentum, nucleus accumbens, ventral pallidum, and the orbitofrontal prefrontal cortex), the learned cue was instantly transformed into an attractive and powerful motivational magnet. Rats jumped and gnawed on the suddenly attractive Pavlovian lever cue, despite never having tasted intense saltiness as anything other than disgusting.

**Conclusions:** Instant desire transformation of a learned cue contradicts views that Pavlovian desires are essentially based on previously learned values (e.g., prediction error or temporal difference models). Instead desire is recomputed at reencounter by integrating Pavlovian information with the current brain/physiological state. This powerful brain transformation reverses strong learned revulsion into avid attraction. When applied to addiction, related mesocorticolimbic transformations (e.g., drugs or neural sensitization) of cues for already-pleasant drug experiences could create even more intense cravings. This cue/state transformation helps define what it means to say that addiction hijacks brain limbic circuits of natural reward.

## Introduction

Learned cues for reward (Pavlovian conditioned stimuli [CS]) often trigger pulses of intense motivation to consume their associated reward (unconditioned stimulus [UCS]). The smell of food may make one suddenly feel hungry when they weren't a minute before, and drug cues may trigger relapse in addicts trying to quit. Attribution of incentive salience to a Pavlovian reward cue can make the CS “wanted” or become a tempting and attractive “motivational magnet”; e.g., hard to ignore, eagerly approached, and sometimes “consumed” similar to a real reward [1–3]. Desires triggered by such Pavlovian cues seem almost entirely learned, but the purely learned

appearance may be largely an illusion, at least according to incentive salience theory, given that learned Pavlovian associations contribute only part of the input to the computations that make the CS “wanted” [4, 5] (Figure 1). The other “wanting” input comes from relevant states of brain mesocorticolimbic systems at the moment of cue reencounter. Brain state can be modulated by many physiological factors, such as natural appetite or satiety, stress, drugs, etc. A relevant change in brain state can powerfully transform the incentive salience elicited by a CS.

Perhaps the strongest proof of principle for incentive salience transformation would be to demonstrate that even a repulsive Pavlovian CS that was previously associated with unpleasantness can suddenly become a “wanted” motivational magnet if reencountered in an appropriate new state. Ideally, the transformation should come from a first reencounter in a completely novel brain/physiological state that was never experienced before in an individual's life. Novelty rules out any learning-based explanations for consequent changes in motivation—precluding the opportunity to learn about values in the new state.

Salt deficiency is a useful state because it is totally novel for most modern humans and laboratory rats (though it is frequently encountered by wild animals) [6]. In human history, the value deficiency given to salt is signified by the word “salary,” which derives from the Latin “sal” for salt, based on the *salarium* paid to Roman soldiers for its purchase [7]. In states of sodium deficiency, intense saltiness becomes pleasant and the associated cues become valuable [8–11]. However, it is unknown whether a CS for saltiness actually becomes transformed, as is suggested for “wanting” computations. If so, the CS could become instantly imbued with incentive salience on the first deficiency reencounter and, therefore, be instantly attractive and “wanted”—despite always being repulsive before and despite the salty UCS itself never having been tasted in the new deficiency state.

Saltiness at seawater concentration is generally unpleasant. Tastes saltier than seawater, such as the 3-fold saltier Dead Sea concentrations of sodium chloride (Dead Sea = 9%/1.5 M NaCl plus 20% other salts), are even more unpleasant. Can a cue for such intensely unpleasant saltiness ever become instantly desired? Here, we used a 9% Dead Sea concentration of NaCl as an unpleasant UCS (1.5 M/9% NaCl; reliably elicited disgust gapes from normal rats). In our novel autoshaping/sign-tracking paradigm, each salty UCS was infused as a pulse into a rat's mouth via implanted cannula (because rats usually will not voluntarily drink such high NaCl concentrations). The NaCl was always predicted by a distinctive Pavlovian CS+ (referred to as CS<sub>Salt</sub>; sudden appearance of a metal lever accompanied by an identifying sound, such as a tone). A second CS+ for sweetness (referred to as CS<sub>Sucrose</sub>) was the insertion of a different lever that emerged from the opposite wall, accompanied by a different sound (e.g., white noise), predicting the infusion of palatable sucrose UCS (0.5 M/17%; reliably elicited positive hedonic reactions of lateral tongue protrusions and paw licking). A third lever served as a control CS and predicted nothing. In order to ascertain whether incentive salience transformations occur for both sign-tracking and

\*Correspondence: [mikejfr@umich.edu](mailto:mikejfr@umich.edu)

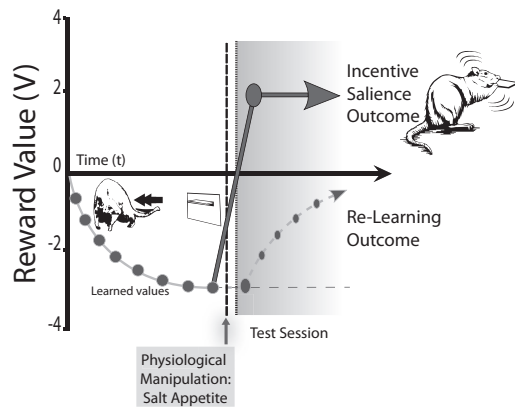


Figure 1. Theoretical Model of the Synergy between Learned Value and Mesocorticolimbic Activation

The diagram displays the impact of a sudden change in the internal/mesocorticolimbic state (novel salt appetite) on the value of a Pavlovian CS according to the predictions made by incentive salience or learning prediction theory [4]. Incentive salience theory predicts that a change in internal mesocorticolimbic state would be sufficient to drastically change the reward value of a CS from negative to positive without requiring new learning (presentation of the CS alone). In contrast, learning prediction theory suggests that the change in reward value would be progressive and would require successive experiences of the CS paired with the now-positive UCS.

goal-tracking phenotypes known for autoshaping, 75% of rats were prescreened in a standard autoshaping procedure (where a UCS sucrose pellet was delivered to a dish and its predictive CS was a fourth distinctive lever).

In their normal CS-UCS training state, all rats quickly learned to turn away and retreat from the CS<sub>Salt</sub> cue that predicted the disgustingly salty NaCl (Movie S1). Conversely, all rats rapidly learned to sign-track the CS<sub>Sucrose</sub> (i.e., they approached and nibbled the sucrose lever).

One night, after previous training with at least 50 discriminative CS-UCS pairings, rats were suddenly put into a novel state of salt appetite via injections (deoxycorticosterone and furosemide to mimic sodium deficiency brain signals normally triggered by angiotensin II and aldosterone), which produced avid salt appetite the next day for a crucial test [12–14]. The question was how would the rats respond toward the previously nasty lever/sound combination associated with CS<sub>Salt</sub> on the first reencounter when they had yet to retaste the NaCl UCS as pleasant in the new state?

## Results

### Sodium Depletion Converts CS<sub>Salt</sub> into an Instant Motivational Magnet

In a decisive behavioral test for instant motivational transformation of CS<sub>Salt</sub>, rats were presented first with the CS levers alone (in extinction, with no UCS infusion occurring) in the novel salt appetite state. The rats' behavior toward the very first presentation of the CS<sub>Salt</sub> lever in the new state was immediately transformed into an avid approach, accompanied by nibbles and sniffs ( $F_{[1,8]} = 29.350$ ,  $p = 0.001$ ; Figure 2; Movie S1). Rats immediately approached the CS<sub>Salt</sub> on the first appearance (Wilcoxon test,  $z = -2.079$ ,  $p = 0.038$ ), intensely grasped, sniffed, and nibbled the metal lever within a few seconds (Wilcoxon test,  $z = -2.666$ ,  $p = 0.008$ ), and depressed

the lever over 1,000% more than on any previous day (Wilcoxon test,  $z = -2.524$ ,  $p = 0.012$ ). The sudden transformation was specifically triggered by the insertion of the CS<sub>Salt</sub> lever for most rats, eliciting an immediate approach even when they had been distant moments before ( $t_{[11]} = 5.354$ ,  $p < 0.001$ ). One rat approached the location even before lever insertion (Movie S1; location and wall slot are also partial CS), though others waited until the first lever presentation, and all rats remained within 8 cm of the lever after the first appearance (in contrast to avoiding the lever on previous training days) (Wilcoxon test,  $z = -2.521$ ,  $p = 0.012$ ). The instant attraction occurred for essentially all rats, although none had yet tasted the NaCl UCS as positive in the new state, and all had previously avoided the location on all earlier days (during training, the CS<sub>Salt</sub> lever reliably evoked repulsion: turning away and sometimes keeping pressed against the opposite wall; Movie S1) ( $F_{[1,8]} = 58.542$ ,  $p < 0.0001$ ). Subsequent presentations of the CS<sub>Salt</sub> lever on the appetite day elicited the same “wanting” pattern, sometimes even more strongly.

Regarding autoshaping phenotypes, the instant transformation of the CS<sub>Salt</sub> lever into a motivationally attractive magnet occurred equally for all rats in the group, regardless of whether they had been previously ascertained to be sign- or goal-trackers when prescreened in a traditional autoshaping procedure (i.e., being presented with a sucrose pellet UCS that required voluntary approach and ingestion at a goal location different from the CS). Therefore, we conclude that instant CS transformation of incentive salience may occur in traditional goal-trackers, as well as in sign-trackers (at least when discriminative CS-UCS associations are formed in a pure Pavlovian procedure, such as ours where UCS solutions arrived automatically in the mouth without needing any instrumental action or active goal approach).

The CS<sub>Sucrose</sub> lever, by comparison, always evoked high levels of approach and consummatory nibbles and sniffs, regardless of normal training versus appetite test states (Wilcoxon test, appetitive:  $z = -1.599$ ,  $p = 0.110$ ; aversive:  $z = -0.690$ ,  $p = 0.490$ ; Figure 2; Movie S1). No increase in the approach to the CS<sub>Sucrose</sub> lever was induced by the new sodium-depletion state ( $F_{[1,10]} = 0.520$ ,  $p = 0.487$ ). A third CS<sub>Control</sub> lever that predicted nothing elicited nearly zero approaches on all days, with no enhancement by the new depletion state (Wilcoxon test,  $z = -1.116$ ,  $p = 0.265$ ). It remains possible that the motivational transformation of the CS<sub>Salt</sub> lever was aided by previous autoshaping to the CS<sub>Sucrose</sub> lever. For example, psychological attribution of incentive salience that allows a metal lever to be perceived as attractive may have been facilitated, opening the way for similar attributions to a new lever. However, the sudden transformation of the CS<sub>Salt</sub> lever was still quite specific. For example, no enhancement was transferred onto the third control lever that predicted nothing. Thus, there was clearly a special synergy between CS<sub>Salt</sub> and the sodium appetite state that controlled the direction of the motivational transformation and created a specific motivational magnet.

A conditioned alliesthesia reaction (state/learning generation of hedonic palatability) was also evoked by the CS<sub>Salt</sub> in over 80% of rats, reflected in the elicitation of positive hedonic or “liking” orofacial reactions near the end of CS<sub>Salt</sub> presentations in the novel state ( $t_{[11]} = 3.208$ ,  $p = 0.008$ ; Figure 3).

In summary, an intense and immediate transformation of CS incentive salience was induced by the first combination of the external Pavlovian lever and the internal depletion state. New “wanting” was specifically targeted to the CS<sub>Salt</sub> lever,

## Sodium Depletion instantly turns a Salt CS into a motivational magnet

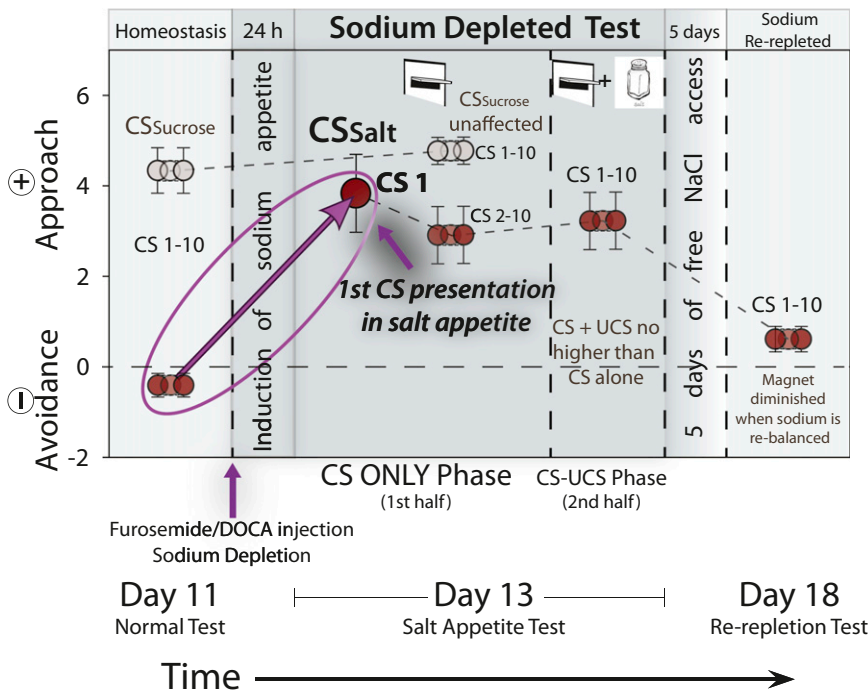


Figure 2. Instant Transformation of the CS<sub>Salt</sub> from Disgusting and Avoided into an Attractive Motivational Magnet

The overall intensity of motivated behaviors is shown on each trial (total number of appetitive-consummatory behaviors [e.g., approaching, sniffing, nibbling] minus aversive behaviors [avoidance]) per CS<sub>Salt</sub> presentation (red circles) or CS<sub>Sucrose</sub> presentation (gray circles). The effects of transition are shown across different internal physiological/mesocorticolimbic conditions (homeostasis [Day11], sodium depletion [Day13], sodium repletion [Day18]). On the very first presentation of the CS<sub>Salt</sub> in extinction (CS1–CS ONLY Phase), at a time when the triple seawater UCS has never been experienced as anything other than highly disgusting, CS<sub>Salt</sub> suddenly becomes a powerful motivational magnet. In contrast, motivated behaviors toward CS<sub>Sucrose</sub> remain unchanged. In a subsequent test (CS–UCS Phase), where each CS<sub>Salt</sub> presentation is followed by the triple seawater solution that has now become strongly “liked,” there is no further increase in the motivational value of the cue. After returning to normal physiological sodium levels (Sodium Rerepleted), the value of the CS<sub>Salt</sub> in extinction instantly decreases to levels similar to those prior to the induction of the novel salt appetite. Data are represented as mean ± SEM. See also [Movie S1](#).

and the cue transformation occurred in advance of any reevaluation experience with the UCS. Thus, clearly no relearning about the improved hedonic value of NaCl taste was required to make its CS suddenly “wanted.”

### Subsequent Hedonic Reactions to UCS Confirm Alliesthesia Flip

Later, on the same day of novel depletion state, we confirmed that palatability of the intensely salty UCS flipped to positively hedonic or “liked” (e.g., eliciting lateral tongue protrusions; [Figure 3](#)), in a round of reinforced CS–UCS trials subsequent to the extinction CS tests. Infusions of 1.5 M/9% NaCl solution into the rat’s mouth elicited mostly positive hedonic reactions, at levels 40-fold higher than on any previous day ( $t_{[11]} = 6.050$ ,  $p = 0.000$ ), and 6-fold higher than to the CS<sub>Salt</sub> alone in extinction on the same day. At the same time, aversive disgust reactions to NaCl were cut to less than half of previous levels ( $t_{[11]} = 5.358$ ,  $p = 0.0001$ ; [Figure 3](#)).

We independently confirmed the induction of salt appetite later that night by using a traditional test of voluntary intake beginning 24 hr after injections (3% NaCl solution; overnight access plus water and food). A 775% increase in the amount of voluntary NaCl consumed in the home cage was induced by the salt appetite treatment ( $t_{[11]} = 6.745$ ,  $p = 0.000$ ; 20.67 ml NaCl sodium deficient versus 2.67 ml NaCl normal state). NaCl intake gradually declined back to initial baseline levels over the next 2–5 days as bodily sodium homeostasis was restored.

Finally, another CS-only or extinction test, similar to the novel state test was performed after several days’ recovery of sodium homeostasis. Results confirmed that the motivation value of the CS<sub>Salt</sub> lever partly flipped back to negatively repulsive again when sodium homeostasis was regained (depleted to rerepleted: Wilcoxon test,  $z = -2.549$ ,  $p = 0.011$ ; [Figure 2](#)).

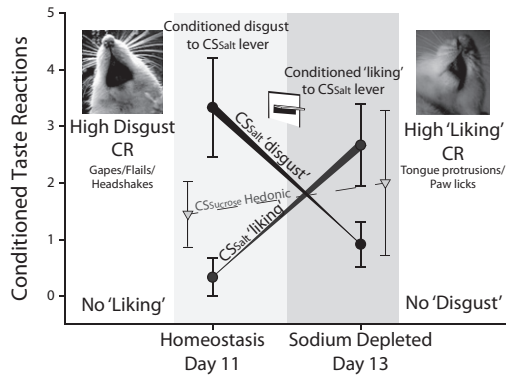
The flip back to repulsion occurred even though the rats had not retasted a 9%/1.5 M concentration of NaCl since their sodium-depletion test day. This flip back confirmed that the recomputation of CS<sub>Salt</sub> incentive salience was state-dependent. In other words, making the CS<sub>Salt</sub> positively “wanted” required the synergistic combined presence of both the external Pavlovian stimulus (CS<sub>Salt</sub>) and the internal physiological stimulus (depletion state).

### Mesocorticolimbic Fos Expression to Cue Plus Novel State

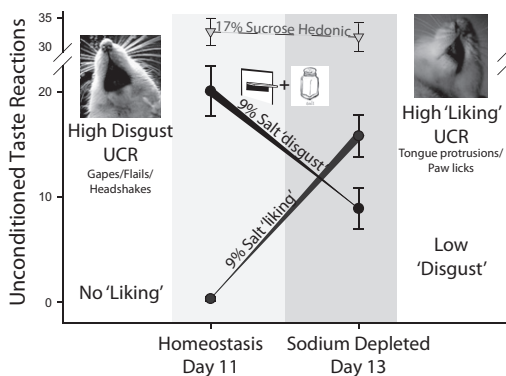
To identify brain systems recruited by the instant transformation of the CS<sub>Salt</sub> value, the expression of the Fos protein in the brain was assessed in separate rats under four conditions matched to the procedures above: (1) CS<sub>Salt</sub> presentations in extinction during a novel state of salt appetite, (2) novel salt appetite alone (no CS or UCS), (3) UCS retasting of NaCl during novel salt appetite, or (4) normal homeostatic physiological state (control baseline group).

Dramatic increases in neuronal Fos expression within mesocorticolimbic structures were recruited specifically by the synergistic combination of CS<sub>Salt</sub> and simultaneous salt appetite state ([Figure 4](#)). The highest increases in neuronal Fos to this combination (1700%) were seen in nucleus accumbens, especially in the rostral half of the medial shell component (compared to the normal control baseline levels) ( $t_{[5]} = 5.163$ ,  $p = 0.004$ ; [Figure 4](#)). The rostral half of the medial shell is the same region that contains a “hedonic hotspot” capable of neurochemically magnifying the hedonic impact of pleasant taste [15–17]. Intense increases in Fos were also observed throughout most of the core of nucleus accumbens ( $t_{[5]} = 2.880$ ,  $p = 0.035$ ). Less intense tripling of Fos was seen in the caudal half of the medial shell ( $t_{[10]} = 2.365$ ,  $p = 0.039$ ). Outside the nucleus accumbens, 3-fold or greater increases in Fos were observed in the limbic regions of the prefrontal cortex,

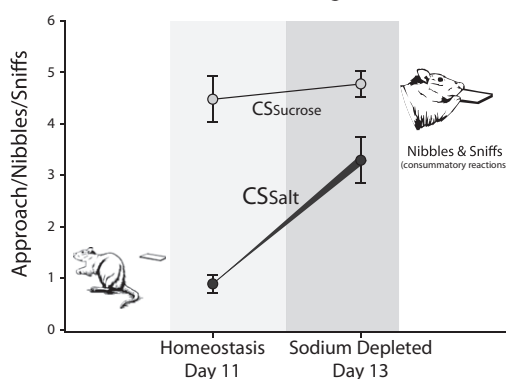
**A** Anticipatory ‘liking’ to CS<sub>salt</sub> (conditioned alliesthesia)



**B** Dead Sea NaCl (9%) UCS becomes ‘liked’ in depleted state



**C** CS<sub>salt</sub> lever becomes ‘edible’ target of nibbles and sniffs



**Figure 3.** CS<sub>salt</sub> in a Novel Salt Appetite Produces Conditioned Hedonic Taste Reactivity and Becomes a Nibbled and Sniffed Motivational Magnet (A) Conditioned taste reactivity to CS<sub>salt</sub> showing hedonic (tongue protrusions, paw licking [CS<sub>salt</sub> ‘liking’]) and aversive (gapes [CS<sub>salt</sub> ‘disgust’]) reactions to the presentation of the CS<sub>salt</sub> cue in extinction (no UCS salt solution) in the normal homeostatic physiological state and in the novel sodium appetite. Grey triangles represent hedonic responses to CS<sub>sucrose</sub>. (B) Unconditioned taste reactivity to a 9% Dead Sea Salt UCS infusions showing hedonic (tongue protrusions, paw licking [9% Salt ‘liking’]) and aversive (gapes [9% Salt ‘disgust’]) reactions in subsequent CS-UCS-reinforced trials in the normal homeostatic physiological state and in the novel sodium appetite. Grey triangles represent hedonic “liking” responses to 17% Sucrose UCS. (C) Appetitive (sniffs, nibbles) reactions toward CS<sub>salt</sub> and CS<sub>sucrose</sub> in extinction (no UCS) in the normal homeostatic physiological state and in the novel sodium appetite. Data are represented as mean ± SEM.

especially in the orbitofrontal (>333%;  $t_{[5]} = 1.930$ ,  $p = 0.111$ ) and infralimbic regions (homologous to the deeply ventral anterior cingulate cortex in humans; > 550%;  $t_{[5]} = 3.318$ ,  $p = 0.021$ ). Subcortically, a > 600% elevation was also observed in the rostral half of ventral pallidum ( $t_{[5]} = 4.501$ ,  $p = 0.006$ ), and > 450% elevation was observed in the midbrain ventral tegmentum area that contains dopamine neurons ( $t_{[5]} = 2.981$ ,  $p = 0.033$ ; **Figure 4**).

Sodium-depletion state alone (without the external Pavlovian CS<sub>salt</sub>) produced intermediate increases in Fos expression, lower than those mentioned above, and in fewer structures. We observed a > 500% increase in the nucleus accumbens core ( $t_{[10]} = 2.657$ ,  $p = 0.025$ ), a > 250% increase in the infralimbic region of prefrontal cortex ( $t_{[10]} = 3.175$ ,  $p = 0.010$ ), and a > 300% increase in the lateral hypothalamus (sodium depletion:  $t_{[10]} = 1.512$ ,  $p = 0.162$ ) during the salt appetite state alone (no Pavlovian CS<sub>salt</sub>).

Adding the UCS of NaCl retasting and ingestion to the appetite state actually produced a suppressive trend toward reducing Fos expression in the lateral hypothalamus (>35% suppression of depletion alone;  $t_{[15]} = 0.877$ ,  $p = 0.394$ ), similar to the pattern reported by Liedtke et al., 2011 [12], and in the orbitofrontal cortex (>60% suppression;  $t_{[15]} = 1.769$ ,  $p = 0.097$ ). Conversely, after retasting the NaCl UCS in the deficient state, moderate increases were seen in the nucleus accumbens: in the rostral medial shell (>550%;  $t_{[17]} = 2.375$ ,  $p = 0.043$ ), in the caudal medial shell (>325%;  $t_{[18]} = 2.365$ ,  $p = 0.039$ ) and core (>525%;  $t_{[17]} = 2.657$ ,  $p = 0.025$ ), in both rostral and caudal ventral pallidum (rostral: > 262%;  $t_{[9]} = 2.197$ ,  $p = 0.058$ ; caudal: > 318%;  $t_{[11]} = 2.216$ ,  $p = 0.050$ ); and in the infralimbic region of the medial prefrontal cortex (>195%;  $t_{[18]} = 1.909$ ,  $p = 0.089$ ; see **Figure 4**).

**Discussion**

The instant transformation of incentive salience for the CS<sub>salt</sub> highlights the critical role played by moment-to-moment internal states in generating motivation for Pavlovian cues (**Figure 1**). The transformation occurred on the very first re-encounter with the metal lever cue for saltiness, despite its previous association with purely disgusting experiences. It occurred even though rats had never tasted the intense Dead Sea saltiness UCS itself as positively “liked” and without requiring any new relearning of CS-UCS values in the new state. Mesocorticolimbic brain circuitry recruited at the same moment by the synergistic reencounter provides a potential neurobiological mechanism to explain the psychological transformation of motivation.

We note that our motivation transformation comes in contrast with previous reports that rats have failed to cognitively infer a higher value for salt or to instrumentally pursue actions that would obtain NaCl when tested in the novel salt appetite state—failures that correspond to model-based reinforcement computations when models lack any experience-gained knowledge about the new salt value [18, 19]. Such failures to transform occur especially when decisions are guided primarily by memories of previous act-outcome reward values [18, 19]—in accordance with the logical assumption that past displeasure predicts future low value. Such value-based reinforcement computation and decisions are switched only by allowing the retasting of NaCl in the appetite state to gain knowledge about the new positive value [19, 20].

We suggest that a crucial feature of the instant desire transformation demonstrated here, which did not require



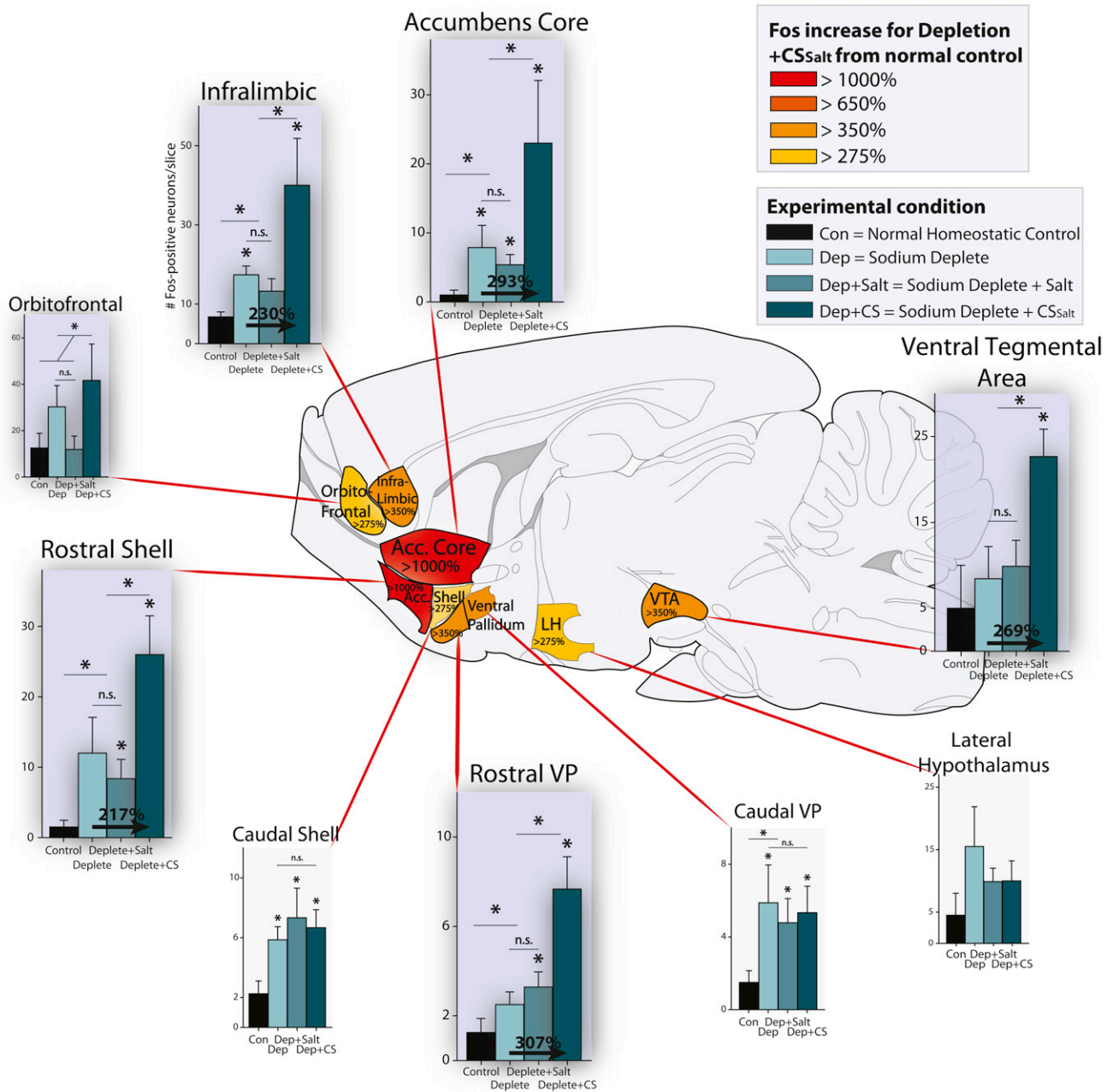


Figure 4. Presentation of CS<sub>Salt</sub> in a Novel Salt Appetite Increases Mesocorticolimbic Fos Activation

Fos activation in the mesocorticolimbic circuit after either (1) presentation of the CS<sub>Salt</sub> cue in a novel salt appetite in extinction (Sodium Deplete + CS<sub>Salt</sub>), (2) retasting of NaCl UCS during a novel salt appetite (Sodium Deplete + Salt), (3) the novel salt appetite alone (no CS or UCS) (Sodium Deplete), or (4) the normal homeostatic physiological state (control baseline group) (Control). Colors represent the percentage increase in Fos activation in the Sodium Deplete + CS<sub>Salt</sub> condition for each brain region in comparison to the control baseline group. Arrows inside each bar graph represent the percent increase in Fos activation from the Sodium Deplete to the Sodium Deplete + CS<sub>Salt</sub> condition. Data are represented as mean ± SEM.

relearning, is the presence of a distinctive Pavlovian cue (CS<sub>Salt</sub>) that can be transformed in incentive salience by mesocorticolimbic systems to serve as a motivational magnet. Our demonstration is similar to reports that sodium depletion can directly increase rats' pressing on a lever distinctively paired with NaCl (which combines Pavlovian and instrumental associations to the lever) [10], increase their consumption of an almond or banana solution previously paired with NaCl (flavor as Pavlovian CS) [8], or favor their immediate return to a place or environment previously associated with

a NaCl UCS (location and/or context as Pavlovian CS) [9, 21]. Still, it was never clear whether those CS actually became positively "wanted" incentives with instant motivational magnetic properties or whether they simply signaled a possible route to alleviate distress. Until now, it was also not clear whether an instant transformation is powerful enough to reverse intense learned repulsion (such as to a CS for Dead Sea concentrations of 9% NaCl) into instant strong desire. Our results show that both do happen: a CS instantly gains positive incentive salience, and the transformation is

powerful enough to reverse cue value from strongly negative to strongly positive.

### Biological Mechanisms Underlying Transformation of CS “Wanting”

Natural physiological transformations of incentive salience are evolutionarily adaptive in the wild. For example, after previously chewing NaCl-containing rocks in a volcanic cave (UCS), Kenyan elephants are reported to follow the wafting odor of smoke (Pavlovian CS) from the erupting volcano back to the same mountain to find salt again [22]. Natural sodium deficiency produces elevations in blood-borne aldosterone and angiotensin II [6]. In the brain, aldosterone stimulates hormone receptors of neurons in extended amygdala structures, such as the amygdala central nucleus and the bed nucleus of the stria terminalis, and in the hindbrain nucleus of the solitary tract [6, 23, 24]. Angiotensin II stimulates thirst-related receptors of neurons in the subfornical organ and in ventral forebrain [12, 25]. The generation of appetite motivation requires mesocorticolimbic participation, such as the elevation of dopamine (reduced dopamine transporter binding) and opioid (enkephalin messenger RNA) signals in nucleus accumbens and striatum, and enhanced neuronal reactivity to relevant cues in ventral pallidum [13, 26]. Much of this brain-reward circuitry was also recruited in this study by the CS<sub>Salt</sub> reencounter in the novel salt appetite state, reflected by increases up to 10-fold in Fos expression in nucleus accumbens, ventral pallidum, ventral tegmentum, and the limbic prefrontal cortex.

### Psychological Processes Mediating Transformation

Psychologically, the transformation of incentive salience afresh on CS<sub>Salt</sub> reencounter requires model-based information, but involving a Pavlovian sensory memory of saltiness that is quite distinct from model-based information about prior values (the only value memory here was previous unpleasantness) [27, 28]. This sensory model makes the incentive salience transformation quite different from most model-based reinforcement computations that require the model to hold experience-gained information about positive reward value in some previously experienced state [29]. Here, only the sensory association between CS<sub>Salt</sub> and UCS gustatory saltiness could be used to freshly generate incentive salience upon cue reencounter.

The generation of CS value was based on the new positive value that UCS saltiness sensation would have in the appetite state, even though the actual NaCl had not yet been retasted as positive. This transformation of a sensory memory into a positive value was probably also responsible for the conditioned alliesthesia or positive taste-“liking” hedonic orofacial reactions that were elicited by CS<sub>Salt</sub> in the new appetite state before NaCl was ever encountered in the new state [14, 30, 31].

Computationally, this synergistic transformation of CS<sub>Salt</sub> motivational value can be described by the incentive salience model of Zhang et al., 2009 [4]. In that computational model, the incentive salience of CS<sub>Salt</sub> is called  $\tilde{V}(s_t)$  (S denotes the Pavlovian CS stimulus; the moment of cue reencounter is denoted as  $t$ , for time).  $\tilde{V}(s_t)$  is computed as:  $\tilde{V}(s_t) = \tilde{r}(r_t + \log \kappa) + \gamma V(s_{t+1})$ . The current mesocorticolimbic brain state reflecting sodium appetite state is represented in the model by a gain-control factor kappa ( $\kappa$ ), which transforms the current incentive salience from previously learned values. The previously learned Pavlovian association ( $r_t$ ) is derived from a temporal difference model, where  $\gamma$  is a discounting parameter for events more distant in future.

Incentive salience [ $\tilde{V}(s_t)$ ] (on the left side of equation) is generated dynamically at the moment of cue reencounter by logarithmically combining the previously established ( $r_t$ ) memory and the current  $\kappa$  state factor. If the current state remained similar to the training state, then  $\kappa = 1$ , which preserves the learned value of CS<sub>Salt</sub> as negative. But in the new salt appetite state, the kappa factor grows:  $\kappa \gg 1$ . Consequently, in the first CS<sub>Salt</sub> reencounter in the novel  $\kappa$  state, the incentive salience is logarithmically transformed to a positive value of  $\tilde{V}(s_t)$  (Figure 1). In that novel state, the previously repulsive and disgust-associated CS<sub>Salt</sub> is suddenly attractive, approached, and sniffed and nibbled as a “wanted” salty Pavlovian incentive.

### Relevance to Addiction

A dominant view in addiction neuroscience and reinforcement learning models of the past decade has been that the motivating value of a learned cue comes solely from its past association with rewarding outcomes [29, 32–34]. For example, Wise, 2012, nicely expressed that view:

It is only after the sight of food or a response lever has been associated with the reinforcing effects of that food or an addictive drug that the food or lever becomes an incentive motivational stimulus that can itself stimulate craving and elicit approach. The argument here is that it is yesterday’s reinforcing effects of a particular food or drug that establishes today’s cravings for that food or drug (p. 5) [33].

More computationally, Schultz, 2012, concurred by saying, “In learning situations governed only by experienced rewards, consecutive unrewarded trials lead to progressively decreasing reward prediction” (p. 4) [34].

In contrast, the argument here is that cravings today (for a salty cue) can far exceed the level of reinforcing effects on all yesterday’s previous cravings (salty disgust). Our results show that consecutive unrewarding trials (or even punishing trials) with a CS can still lead to that cue the triggering of intensely high levels of “wanting” in a new states, no matter how low (or even negative) the Pavlovian prediction of the previously learned value. Instant transformation in the motivational value of a learned Pavlovian cue is powerful and real, even if transformation contradicts views of reinforcement based on experientially learned values, which are the centerpiece of addiction-learning neuroscience approaches today [29, 32–34].

We suggest that the lesson to be drawn for addiction is: if brain mesocorticolimbic activation can transform learned negative revulsion into strong positive “wanting,” triggered by a cue for disgusting saltiness, how much more intense could mesocorticolimbic-amplified “wanting” become when triggered by cues for drugs, food, sex, gambling, and related already-pleasant experiences? As posited by the incentive sensitization hypothesis of addiction, such mesocorticolimbic amplifications of incentive salience create compulsively intense levels of motivation in drug addiction [2]. Drugs could even become “wanted” under conditions where their experience is known to be unpleasant, (similar to the salty cue). Incentive salience transformation as seen here helps define what it means to say that addiction hijacks brain limbic circuits of natural reward [2, 3, 35, 36].

### Experimental Procedures

The University Committee on Use and Care of Animals of the University of Michigan approved all experimental methods performed in this research.

These studies were conducted with female Sprague-Dawley rats (250–325 g; behavior,  $n = 12$ ; immunoreactivity,  $n = 21$ ). To permit oral solution infusions, rats were anesthetized and implanted with oral cannula following the methods described in detail elsewhere [37]. Pavlovian conditioning was carried out in standard Med Associates operant chambers, as described in detail elsewhere [3]. Most rats (75%) were initially prescreened on a standard autoshaping task that uses voluntary intake of a sucrose pellet UCS to determine whether they were goal-trackers or sign-trackers [3]. Prescreening did not alter subsequent behavior to CS<sub>Sucrose</sub> or CS<sub>Salt</sub> in the oral-delivery autoshaping tests, so results from all rats were combined ( $F_{[1,10]} = 1.826$ ,  $p = 0.206$  for CS-UCS reinforced baseline homeostasis test). Behavioral procedures consisted of blocked training of CS-UCS presentations, where CS<sub>Salt</sub> and CS<sub>Sucrose</sub> levers were diagonally located on opposite walls of the chamber and respectively predicted infusions of hypertonic NaCl (1.5 M; 9% NaCl) or sucrose (0.5 M; 17.1%) solution as UCS. Test days (baseline homeostasis, sodium depleted, sodium repleted) consisted of CS+ only extinction tests and CS-UCS reinforced tests. All behaviors during tests, including UCS elicited taste reactivity behaviors were video recorded and subsequently scored in slow motion in a manner previously described [3, 37]. Salt appetite was induced within 24 hr by injection of the diuretic furosemide (7.5 mg/kg; sc; Hospira) and deoxycorticosterone (DOCA, 1 mg/kg in propylene glycol, sc; Sigma Aldrich) [11]. Fos immunofluorescence was assessed in separate animals under four separate conditions ([1] CS<sub>Salt</sub> + novel salt appetite, [2] UCS retasting of 0.5 M/3% NaCl + novel salt appetite, [3] novel salt appetite alone, [4] normal homeostatic physiological state) following procedures described elsewhere [38, 39]. For more details, please refer to the [Supplemental Experimental Procedures](#).

#### Supplemental Information

Supplemental Information contains Supplemental Experimental Procedures and one movie and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2013.01.016>.

#### Acknowledgments

The authors would like to thank Aaron Garcia, Ryan Selleck, and Stephen Burwell for their technical assistance. This work was supported by National Institutes of Health grants DA015188-01-A1 and MH63649 to K.C.B.

Received: November 28, 2012

Revised: January 8, 2013

Accepted: January 8, 2013

Published: January 31, 2013

#### References

- Toates, F. (1986). *Motivational Systems* (New York: Cambridge University Press).
- 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.
- 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.
- Zhang, J., Berridge, K.C., Tindell, A.J., Smith, K.S., and Aldridge, J.W. (2009). A neural computational model of incentive salience. *PLoS Comput. Biol.* 5, e1000437.
- Berridge, K.C. (2012). From prediction error to incentive salience: mesolimbic computation of reward motivation. *Eur. J. Neurosci.* 35, 1124–1143.
- Krause, E.G., and Sakai, R.R. (2007). Richter and sodium appetite: from adrenalectomy to molecular biology. *Appetite* 49, 353–367.
- Pliny the Elder (77 AD). *Natural History*. H. Rackham and W. H. S. Jones, eds. (Cambridge, Massachusetts: Harvard University Press).
- Fudim, O.K. (1978). Sensory preconditioning of flavors with a formalin-produced sodium need. *J. Exp. Psychol. Anim. Behav. Process.* 4, 276–285.
- Kriackhaus, E.E. (1970). “Innate recognition” aids rats in sodium regulation. *J. Comp. Physiol. Psychol.* 73, 117–122.
- Kriackhaus, E.E., and Wolf, G. (1968). Acquisition of sodium by rats: interaction of innate mechanisms and latent learning. *J. Comp. Physiol. Psychol.* 65, 197–201.
- Tindell, A.J., Smith, K.S., Peciña, S., Berridge, K.C., and Aldridge, J.W. (2006). Ventral pallidum firing codes hedonic reward: when a bad taste turns good. *J. Neurophysiol.* 96, 2399–2409.
- Liedtke, W.B., McKinley, M.J., Walker, L.L., Zhang, H., Pfenning, A.R., Drago, J., Hochendoner, S.J., Hilton, D.L., Lawrence, A.J., and Denton, D.A. (2011). Relation of addiction genes to hypothalamic gene changes subserving genesis and gratification of a classic instinct, sodium appetite. *Proc. Natl. Acad. Sci. USA* 108, 12509–12514.
- Lucas, L.R., Grillo, C.A., and McEwen, B.S. (2003). Involvement of mesolimbic structures in short-term sodium depletion: in situ hybridization and ligand-binding analyses. *Neuroendocrinology* 77, 406–415.
- Tindell, A.J., Smith, K.S., Berridge, K.C., and Aldridge, J.W. (2009). Dynamic computation of incentive salience: “wanting” what was never “liked”. *J. Neurosci.* 29, 12220–12228.
- Peciña, S., and Berridge, K.C. (2005). Hedonic hot spot in nucleus accumbens shell: where do  $\mu$ -opioids cause increased hedonic impact of sweetness? *J. Neurosci.* 25, 11777–11786.
- Smith, K.S., Berridge, K.C., and Aldridge, J.W. (2011). Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proc. Natl. Acad. Sci. USA* 108, E255–E264.
- Thompson, R.H., and Swanson, L.W. (2010). Hypothesis-driven structural connectivity analysis supports network over hierarchical model of brain architecture. *Proc. Natl. Acad. Sci. USA* 107, 15235–15239.
- Daw, N.D., Niv, Y., and Dayan, P. (2005). Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. *Nat. Neurosci.* 8, 1704–1711.
- Dickinson, A. (1986). Re-examination of the role of the instrumental contingency in the sodium-appetite irrelevant incentive effect. *Q. J. Exp. Psychol. B* 38, 161–172.
- Dickinson, A., and Balleine, B. (2010). Hedonics cognitive motivation interface. In *Pleasures of the Brain* (United States: Oxford University Press), pp. 74–84.
- Stouffer, E.M., and White, N.M. (2005). A latent cue preference based on sodium depletion in rats. *Learn. Mem.* 12, 549–552.
- Denton, D. (1982). *The hunger for salt: An anthropological, physiological, and medical analysis* (Berlin, New York: Springer-Verlag).
- Alheid, G.F., Shammah-Lagnado, S.J., and Beltramino, C.A. (1999). The interstitial nucleus of the posterior limb of the anterior commissure: a novel layer of the central division of extended amygdala. *Ann. N Y Acad. Sci.* 877, 645–654.
- Geerling, J.C., and Loewy, A.D. (2008). Central regulation of sodium appetite. *Exp. Physiol.* 93, 177–209.
- Floharty, S.J., and Epstein, A.N. (1983). Sodium appetite elicited by intracerebroventricular infusion of angiotensin II in the rat: II. Synergistic interaction with systemic mineralocorticoids. *Behav. Neurosci.* 97, 746–758.
- Lucas, L.R., Grillo, C.A., and McEwen, B.S. (2007). Salt appetite in sodium-depleted or sodium-replete conditions: possible role of opioid receptors. *Neuroendocrinology* 85, 139–147.
- Holland, P.C. (1990). Event representation in Pavlovian conditioning: image and action. *Cognition* 37, 105–131.
- Konorski, J. (1967). *Integrative activity of the brain: An interdisciplinary approach* (Chicago: University of Chicago Press).
- Schultz, W., Dayan, P., and Montague, P.R. (1997). A neural substrate of prediction and reward. *Science* 275, 1593–1599.
- Berridge, K.C., and Schulkin, J. (1989). Palatability shift of a salt-associated incentive during sodium depletion. *Q. J. Exp. Psychol. B* 41, 121–138.
- Delamater, A.R., LoLordo, V.M., and Berridge, K.C. (1986). Control of fluid palatability by exteroceptive Pavlovian signals. *J. Exp. Psychol. Anim. Behav. Process.* 12, 143–152.
- Redish, A.D. (2004). Addiction as a computational process gone awry. *Science* 306, 1944–1947.
- Wise, R.A. (2012). Dual Roles of Dopamine in Food and Drug Seeking: The Drive-Reward Paradox. *Biol. Psychiatry*. Published online October 5, 2012.
- Schultz, W. (2012). Updating dopamine reward signals. *Curr. Opin. Neurobiol.* Published online December 22, 2012.
- Vezina, P., and Leyton, M. (2009). Conditioned cues and the expression of stimulant sensitization in animals and humans. *Neuropharmacology* 56(Suppl 1), 160–168.
- Volkow, N.D., Wang, G.-J., Telang, F., Fowler, J.S., Logan, J., Childress, A.R., Jayne, M., Ma, Y., and Wong, C. (2006). Cocaine cues and

dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J. Neurosci.* 26, 6583–6588.

37. Mahler, S.V., Smith, K.S., and Berridge, K.C. (2007). Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances ‘liking’ of a sweet reward. *Neuropsychopharmacology* 32, 2267–2278.
38. Paxinos, G., and Watson, C. (2007). *The Rat Brain in Stereotaxic Coordinates*, Sixth Edition (London: Elsevier).
39. Faure, A., Reynolds, S.M., Richard, J.M., and Berridge, K.C. (2008). Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. *J. Neurosci.* 28, 7184–7192.