Dynamic Computation of Incentive Salience: “Wanting” What Was Never “Liked”

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Pavlovian cues for rewards become endowed with incentive salience, guiding “wanting” to their learned reward. Usually, cues are “wanted” only if their rewards have ever been “liked,” but here we show that mesocorticolimbic systems can recompute “wanting” de novo by integrating novel physiological signals with a cue’s preexisting associations to an outcome that lacked hedonic value. That is, a cue’s incentive salience can be recomputed adaptively. We demonstrate that this recomputation is encoded in neural signals coursing through the ventral pallidum. Ventral pallidum neurons do not ordinarily fire vigorously to a cue that predicts the previously “disliked” taste of intense salt, although they do fire to a cue that predicts the taste of previously “liked” sucrose. Yet we show that neural firing rises dramatically to the salt cue immediately and selectively when that cue is encountered in a never-before-experienced state of physiological salt depletion. Crucially, robust neural firing to the salt cue occurred the first time it was encountered in the new depletion state (in cue-only extinction trials), even before its associated intense saltiness has ever been tasted as positively “liked” (salt taste had always been “disliked” before). The amplification of incentive salience did not require additional learning about the cue or the newly positive salt taste. Thus dynamic recomputation of cue-triggered “wanting” signals can occur in real time at the moment of cue re-encounter by combining previously learned Pavlovian associations with novel physiological information about a current state of specific appetite.

Introduction

When attributed with incentive salience, learned reward cues (Pavlovian conditioned stimuli; CSs) can trigger “wanting” for their reward (unconditioned stimulus; UCS) and become attractive “motivational magnets” (Toates, 1986; Robinson and Berridge, 1993; Dickinson and Balleine, 2002; Mahler and Berridge, 2009). Incentive salience at a given moment depends on current physiological state as well as on learned associative values of a cue. For example, a cue for ice cream may have greater motivational pull (“wanting”) when the perceiver is hungry or hot.

Natural appetites (e.g., thirst, hunger, salt appetite) and some drug states (e.g., intoxication priming, long-term sensitization) potentiate the intensity of cue-triggered “wanting” for relevant rewards (e.g., hunger potentiates food cues) (Toates, 1986; Berridge, 2001; Tindell et al., 2005; Mahler and Berridge, 2009). Interestingly, in some new physiological states, enhanced “wanting” may occur the first time a relevant CS is re-encountered even before the reward UCS itself is experienced in the new state (Toates, 1986; Robinson and Berridge, 2003; Ber-
Training and “CS Plus UCS” Trials

Sucrose

Salt

CS-

UCS

5 sec taste

no reward

Extinction - “CS Only” Trials

Sucrose

Salt

CS-

UCS

5 sec taste

no reward

Test Blocks: CS-, “CS Only”, “CS Plus UCS”

5 x CS-  Randomize: 10 x CS_sucrose and 10 x CS_salt  5 x CS-


d and the modulation of reward impact by physiological states (Tindell et al., 2004, 2005, 2006).

Our question here was the following: can dynamic recomputation of incentive salience be detected in ventral pallidal neural activity correlated to cue presentation? We show that it can.

Materials and Methods

To test whether signals for dynamically recomputed incentive salience are carried in VP circuits, we recorded VP neural responses and behavioral affective reactions to cues and tastes in rats that had learned Pavlovian associations between auditory predictive cues (Cs) and oral infusions of fluids containing either sucrose or intense NaCl (UCs). One auditory cue (CSsalt) predicted a taste infusion directly into the mouth of a “disliked” intense salt UCS (1.5 M NaCl: an aversive concentration three times higher than seawater or an order of magnitude above isotonic). Another auditory tone (CSsucrose) predicted infusion of a “liked” 0.5 M sucrose UCS. A third control tone (CS) predicted no UCS (Fig. 1). Recording took place on two separate days: once in normal physiological homeostasis, and 24 h later in a novel sodium-depleted state of salt appetite (induced overnight). Neuronal activity was recorded on one day in normal homeostasis and on another day after sodium depletion, using multiwire electrodes implanted into the posterior portion of the VP. The posterior VP was targeted because previous studies showed it contains a 1 mm “hedonic hotspot” where opioid stimulation causes increase in “wanting” and “liking” for food rewards, and where neuronal firing codes the motivational value of Cs that predict reward, as well as the hedonic impact of UCS taste rewards (Tindell et al., 2004, 2005, 2006; Smith and Berridge, 2005, 2007; Smith et al., 2007). Rats had never before experienced a salt appetite before the depletion test. To ensure that we were isolating the dynamic motivational value of the cues alone on a given test day (uncontaminated by any accompanying unconditioned reward), each recording session began with extinction trials (CSs presented with no reward UCs: “CS only” trials) (Fig. 1). No UCS stimulus fluid was delivered to the rat during extinction trials. Subsequently, a second series of trials with actual tastes (“CS plus UCS” trials) (Fig. 1) was presented on the same days to confirm the increase in palatability of NaCl taste by assessing behavioral affective orofacial reactions during VP recordings.

Animals. The University Committee on the Use and Care of Animals approved all experimental methods. Male Sprague Dawley rats (300–450 g; N = 18) were maintained on an ad libitum sodium-free diet (Purina) and distilled water. Rats also had ad libitum access to a separate drinking tube containing 0.5 M NaCl solution (except for the 24 h period when sodium depletion was being induced). Detailed surgical procedures have been described (Tindell et al., 2006). Briefly, animals were anesthetized with a ketamine/xylazine (100 mg/kg/10 mg/kg) for sterile, stereotaxic surgery. Bilateral intraluminal cannulae for taste infusions were implanted along with multiwire (50 μm tungsten) electrodes into the posterior ventral pallidum (range of recording sites: AP: −0.11 to −1.53; ML: 1.8–3.3; DV: 6.8–7.7). This anatomic region encompassed the hedonic hotspot of posterior VP identified by Smith and Berridge (Smith and Berridge, 2005, 2007; Tindell et al., 2006). Anchoring bone screws in the skull served as ground references. Animals were allowed 7 d to recover before training and testing began.

Pavlovian training. Training and testing was conducted in a 25 cm cylinder with a glass floor with a mirror underneath for video recording orofacial taste reactivity and other behavior. A laboratory computer program controlled cue (conditioned stimulus, “CS”) and reward (unconditioned stimulus, “UCS”) presentations. Rats received five training sessions in which they learned discriminative associations between three distinct auditory cues (Fig. 1). Two 5 s cues predicted oral infusions that began at their offset. A third cue (CS) predicted nothing. The sucrose or salt taste infusion (0.1 ml per infusion at 0.02 ml/s) lasted for 5 s. The “CS sucrose cue” predicted a concentrated NaCl infusion (1.5 M). A different “CS sucrose” predicted sucrose infusion (0.5 M concentration). For each rat, CS assignments were counterbalanced between a 400 Hz, 0.75 s cue and salt cue infusion/infusion presented randomly (Fig. 1) on a variable intertrial interval with a mean value of 1 min. Each session began and ended with presentation of five CS cues under the same intertrial interval schedule to bracket the block of 20 CSsalt and CSsucrose trials (Fig. 1). There was no gap between the CS+ and CS− blocks other than the 1 min intertrial interval. The bracket design presented CS+ blocks and CS− blocks in a balanced ABBA pattern (CS−, random CSsalt or CSsucrose) to rule out gradual drift in neural firing over the trial.

Testing and recording. Neuronal activity was recorded in two sessions spaced 24 h apart. On day 1, rats were in normal homeostasis; on day 2, rats were in sodium appetite. A syringe containing sucrose or NaCl solution was connected to the intraoral delivery tube so as to create a dead space (extending over ~2 cm of tubing) visible as an air bubble in front of an advancing UCS solution. This bubble, which could be seen clearly through the translucent delivery tube, marked the onset point of the advancing UCS solution. During extinction testing, the position of this bubble space was monitored carefully to be sure that no solution would enter the rat’s mouth until later trials when the pump was turned on. The bubble blocked fluid delivery until the beginning of the reinforced CS−UCS session when the syringe pump was activated to advance the solution. As in training, each test day began with five CS presentations (Fig. 1). Those were followed by the extinction block of CS+ alone trials (unaccompanied by UCS). A block of CS−UCS reinforced trials followed, followed by another block of CS− trials (so that CS− presentations bracketed all CS+ and UCS presentations, occurring both before and after them). A 10 min period was imposed between each block.
We emphasize that the CS+ extinction block was the most important test block for assessing dynamic recomputations: it contained 20 CS+ trials in random order (10 CSsalt and 10 CSsucrose), in which CS+s occurred alone without accompanying UCS taste infusions (“CS only” trials) (Fig. 1). Thus crucially, in extinction tests, rats did not taste any UCS. Instead, rats had only associative information based on previous CS–UCS experiences of CSsalt obtained from pairings on previous days. On those previous days animals were in normal physiological state and thus the association with NaCl tastes had been aversive (i.e., “disliked”). In the second phase of each test day, actual taste rewards followed the appropriate cues (“CS plus UCS”). CSsalt and CSsucrose trials were intermixed randomly in both phases (10 each) (Fig. 1, bottom).

Salt depletion procedure. Sodium appetite was induced by a combined regimen of the diuretic furosemide (to promote sodium loss and stimulate angiotensin II production), the mineralocorticoid hormone deoxycorticosterone acetate (to mimic aldosterone elevation), and a sodium-free diet (to prevent sodium replacement). Rats received a subcutaneous injection of 7.5 mg/kg furosemide and 5 mg/kg deoxycorticosterone acetate immediately after testing on day 1 (Flynn et al., 2002), followed 2 h later by an additional injection of 7.5 mg/kg furosemide (Tamura and Norgren, 1997). NaCl was removed from the home cage after the first injection and not replaced for the next 24 h. Sodium–free chow (Purina) and distilled water were maintained. We previously found this regimen induces a robust salt appetite over 24 h that is sufficient to cause “disliked” 1.0 M NaCl taste NaCl taste to form an overall positive hedonic “liking” score and a negative aversive (“disliking”) score. Other behaviors, including orientation toward CS cues, typical occur in discrete events, including lateral tongue protrusions, paw licking, rhythmic mouth movements, and grooming (Grill et al., 1992). Behaviors that typically occur in discrete events, including lateral tongue protrusions, grooming movements (mouth, limbs) were counted each time they occurred. Behaviors that occur in continuous bouts (rhythmic tongue protrusions, paw licking, rhythmic mouth movements, grooming) were timed in seconds.

Hedonic/aversive reactions were summed into affective categories to form an overall positive hedonic “liking” score and a negative aversive “disliking” score. Other behaviors, including orientation toward CS cues (rearing, approach, head turns), grooming movements (mouth, limbs) were totaled separately. Mixed-design ANOVAs (day = between subject, taste = within subject) and Bonferroni-corrected post hoc tests were performed to evaluate effects of the cues (CSsalt, CSsucrose, CS+, UCS) on act. CSsucrose and CSsalt infusion period (or temporally matched period in extinction trials that had no infusion). Firing rate changes in each trial were normalized by dividing by baseline rate (average across trials of 5 s period before cue). A neuron was defined as responsive to a cue or taste if the firing rate across trials during the examined bin was significantly different (p < 0.05 in Bonferroni-corrected paired t tests) from the average firing rate during background (5 s before infusion).

To assess firing rate effects, we averaged the normalized firing rate for each responsive unit across trials (except when comparing trial effects explicitly), and compared response magnitudes across stimuli and test days using mixed-measures ANOVA (day/stimulus was treated as a between-subjects factor), test days was treated as a within-subject factor); post hoc comparisons were conducted by Bonferroni-corrected tests.

For population comparisons, numbers of neurons activated by the cues and/or tastes were tallied for a binomial analysis and compared across extinction versus normal trials and physiological conditions using ANOVAs.

Histology. After recordings were completed, rats were given an overdose of pentobarbital, and perfused transcardially with saline and formaldehyde. Brains were removed, sliced in 40 μm coronal sections, and stained with cresyl violet. Slices were examined under a microscope to verify electrode placement in VP, and electrode sites were mapped onto a computerized brain atlas (Paxinos and Watson, 2007).

Results

Neural coding in ventral pallidum

Most VP neurons responded phasically to auditory CS cues, rising within 100 ms of tone onset and decaying nearly back to baseline by 500 ms, although the physical tone continued another 4.5 s (Fig. 2). Even in extinction presentations of a CS by itself, 52% of neurons (66/128) were activated by a CS during the first
Phase of each test. Many neurons were responsive to more than one cue (41%) (Fig. 3). When cues were followed and reinforced with actual UCS tastes, in the second phase of each test day, the proportion of responsive neurons increased to 79% (97/123). VP responses to UCS tastes were slower and more prolonged than to CS tones, tending to last for much of the 5 s duration of the UCS. Responses to UCS tastes were slower and more prolonged than to CS tones, tending to last for much of the 5 s duration of the UCS.

Table 1. The numbers of responsive neurons (numerator) relative to sample sizes (denominator) and the percentages they represented are reported for trials with cues alone (extinction CS-only trials) in the top part of the table and trials with both cues and tastes (paired CS+ with UCS trials) in the bottom half of table

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Homeostatic</th>
<th>Salt depleted</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS_sucrose</td>
<td>46/128</td>
<td>16/56 (29%)</td>
<td>30/72 (42%)</td>
</tr>
<tr>
<td>CS_salt</td>
<td>30/128</td>
<td>8/56 (14%)</td>
<td>22/72 (31%)</td>
</tr>
<tr>
<td>CS-</td>
<td>24/128</td>
<td>11/56 (21%)</td>
<td>13/72 (18%)</td>
</tr>
<tr>
<td>Paired CS+ with UCS trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS_sucrose</td>
<td>51/123</td>
<td>27/63 (43%)</td>
<td>24/60 (40%)</td>
</tr>
<tr>
<td>CS_salt</td>
<td>49/123</td>
<td>21/63 (33%)</td>
<td>28/60 (47%)</td>
</tr>
<tr>
<td>CS-</td>
<td>24/123</td>
<td>13/63 (21%)</td>
<td>11/60 (18%)</td>
</tr>
<tr>
<td>Sucrose taste</td>
<td>50/123</td>
<td>31/63 (49%)</td>
<td>19/60 (32%)</td>
</tr>
<tr>
<td>Salt taste</td>
<td>45/123</td>
<td>13/63 (21%)</td>
<td>32/60 (53%)</td>
</tr>
</tbody>
</table>

\*\(F(1,127) = 10.145, p < 0.001\) \(F(1,127) = 12.367, p < 0.001\).

Population coding

**Cue populations in extinction trials (“CS only”; no taste infusions)**

Even though no tastes were delivered in extinction trials (“CS only”), VP neurons responded discriminatively to CS cues (46% of units in homeostasis and 53% in salt-depleted conditions). The most dramatic evidence for dynamic recomputation of CS incentive salience came from firing rates of responsive VP neurons, confirming that a VP rate code sensitively represents the incentive salience of reward cues (overall main effect on model: \(F(4,127) = 4.848, p = 0.011\)).

Rate coding

The most dramatic evidence for dynamic recomputation of CS incentive salience came from firing rates of responsive VP neurons, confirming that a VP rate code sensitively represents the incentive salience of reward cues (overall main effect on model: \(F(4,127) = 4.848, p = 0.011\)).
Cue rate responses in extinction trials (“CS only”; no taste infusions)

On the first test day when rats were in normal homeostasis, sucrose cues (CSsucrose) evoked brief elevations of firing within 50–100 ms after onset of a CS+ tone (Fig. 2). Peak values were reached by 250 ms and rates declined toward baseline by 500 ms (Figs. 2, 4, 5). In some cells firing rates decreased with CSsucrose tone onset. On average though, the initial response was a marked increase that reached nearly 40% above background (post hoc *p* = 0.020, df = 25) (Fig. 4a,c). In contrast, the salt cue (CSsalt) evoked activity in only 23% of cells on day 1 normal homeostasis (Table 1). As with sucrose tones both excitation and inhibitions were observed; however with CSsalt responses, they essentially cancelled each other out so that on average there was no net change in firing rate compared with precue baseline (post hoc *p* = 0.812, df = 25) (Fig. 4a,c). Rates to the CS− also never significantly changed from baseline. Thus, on day 1 average firing rates to CSsalt and CS− were equally low (post hoc *p* = 0.367, df = 25). Firing rates to CSsucrose on the other hand, were higher than either CSsalt (post hoc *p* = 0.018, df = 25) or CS− (post hoc *p* = 0.020, df = 25).

The CSsucrose and CSsalt rate pattern changed with the induction of the novel sodium depletion state on the second test day. This change was highlighted by a dramatic and selective initial burst of activity to the CSsalt. The firing rates of this response to the salt cue on the salt appetite day almost doubled from the previous day in normal homeostasis (Fig. 4c) (post hoc on day *p* < 0.0001, df = 63). CSsalt elicited firing rose to 170% above baseline within 250 ms, and then fell to baseline levels after 500 ms after tone onset. This phasic response to salt cues resembled the CSsucrose peaks, which did not change with salt depletion. On day 2 firing rates to CSsalt did not differ from CSsucrose (post hoc *p* = 0.220, df = 63) (Fig. 4a–c). Activity evoked by the CS− control tone in sodium-depleted state was similar to normal homeostasis except for a slight but significant increase in rate during the first 500 ms (post hoc *p* < 0.05, df = 63) (Fig. 4d). This change may indicate some response generalization between the CS+ s and CS− tones.

The elevation in firing to CSsalt was evident even on the first “CS only” trials in extinction testing. For example, on the very first extinction trial after depletion, firing to the CSsalt was markedly enhanced (154%) above the level seen for the first presentation in homeostasis the day before (Fig. 5). Firing rate was higher on each of the 10 CSsalt trials in depletion state than in normal homeostasis, though there was a partial decline in normalized firing from trial 1 to trial 10 on both days (Fig. 5) (ANOVA across trial *F*(9,136) = 2.507, *p* = 0.011). The immediate and strong response to CSsalt in the first extinction trials demonstrates that the learned Pavlovian association between CSsalt and its UCS salt taste could be used to recompute a revised representation for this cue even before UCS salt had been tasted in the new appetite state.

The firing changes evoked by CS tones sometimes persisted at lower plateau levels for 4–5 s throughout the entire CS presentation after the initial phasic 0.5 s response peak, and those prolonged changes could occur as either excitatory plateaus or inhibitory troughs. For example, the CSsucrose elicited a prolonged excitatory plateau lasting ~5 s on both test days, at a level which was statistically elevated above baseline on the sodium-depleted day (*p* < 0.0001, df = 38) and marginally elevated on the normal homeostatic test day (*p* = 0.052, df = 25). In contrast, on the normal homeostatic test day the CSsalt elicited an opposite inhib-
there was a small initial decrease after CSSucrose offset, rates at the true prediction error in VP firing on extinction trials. Although mine neurons (Schultz, 2006). However, we did not observe a negative prediction error as has been reported for mesolimbic dopamine neurons (Schultz, 2006). During trials "CS plus UCS" with actual taste reward infusions. On normal day 1, VP neurons fire to CSSucrose and to sucrose taste UCS, but not significantly to Csaltsalt or salt taste. On sodium-depleted day 2, neurons fire to Csaltsalt as well as CSSucroseSucrose and fire even more vigorously to salt taste than to sucrose taste. The format follows Figure 4, with the brown line indicating the timing of actual taste infusions. *p < 0.05.

Figure 6. VP firing rate coding of CS and UCS during phase two on day 1 (normal homeostasis) and day 2 (sodium depletion) during trials “CS plus UCS” with actual taste reward infusions. On normal day 1, VP neurons fire to CSSucrose and to sucrose taste UCS, but not significantly to Csaltsalt or salt taste. On sodium-depleted day 2, neurons fire to Csaltsalt as well as CSSucroseSucrose and fire even more vigorously to salt taste than to sucrose taste. The format follows Figure 4, with the brown line indicating the timing of actual taste infusions. *p < 0.05.

Figure 7. Taste reactivity to UCS actual taste infusions. a, b, Sucrose taste elicited stronger positive hedonic reactions (a) on the normal homeostasis test of day 1, when NaCl taste instead elicited many negative aversive reactions (b). Conversely, after sodium depletion on day 2, NaCl elicits predominantly positive hedonic reactions, similar to the sucrose taste.

Rate changes to UCS omission
In extinction tests (“CS only”), the moment a taste UCS would have occurred during training represents a UCS omission at 5 s after CS+ onset, a situation that permits the possibility of a negative prediction error as has been reported for mesolimbic dopamine neurons (Schultz, 2006). However, we did not observe a true prediction error in VP firing on extinction trials. Although there was a small initial decrease after CSSucrose offset, rates at the moment of UCS omission did not differ from the precue baseline. After a CS+ that elicited a strong firing peak (CSSucroseSucrose on both days; Csaltsalt on depletion days), firing rates declined from their CS+ peak levels toward baseline at the moment of UCS omission (p < 0.005, df = 25 or 38), but never dipped below the precue baseline.

Firing rates in rewarded trials (“CS plus UCS”)
On CS−/UCS reinforced trials, the firing rates to salt UCS were enhanced by sodium depletion, as well as to Csaltsalt whereas firing to sucrose UCS infusions and to its CSSucrose remained equally high on both days.

The UCS tastes elicited firing rates proportional to their hedonic palatability in each physiological state. During normal homeostasis on the first test day, sucrose taste infusions elicited faster VP firing rates than NaCl taste infusions (Tindell et al., 2006) (post hoc on taste from above, p = 0.004, df = 25) (Fig. 6). Sucrose UCS elevations exceeded 50% above baseline within the first 1 s of oral infusion, and remained ~25% above baseline for most of the 5 s duration of sucrose infusion. Salt UCS infusion did not elicit significant changes from baseline in firing when rats were in a normal homeostatic state on the first day.

After sodium depletion on the second day, this UCS rate pattern reversed so that NaCl taste infusions actually elicited slightly higher firing rates than sucrose taste, similar to our previous report (Tindell et al., 2006) (day/taste interaction: F(2,127) = 18.946, p < 0.0001; post hoc p < 0.0001, df = 38) (Fig. 6). The reversal in UCS firing rates involved both a major increase to NaCl taste (post hoc p = 0.001, df = 63), and a minor decrease to sucrose taste (post hoc p < 0.0001, df = 63). During sodium depletion, salt taste elicited firing peaks of >60% above precue baseline within 2 s, and remained 20–40% above baseline level for most of the 5 s infusion (as well as above sucrose UCS levels) (Fig. 6). Thus sodium depletion specifically reorganized rate coding of UCSs in a manner that reflected the new relative hedonic values of sucrose and salt tastes, similar to population coding. Firing to CSs followed the pattern described above for extinction tests.

Baseline firing rates
Sodium depletion produced no changes in absolute baseline firing rates (measured in the absence of CS or UCS stimuli: 5 s periods before presentations of CS cues or UCS taste infusions (F(1,295) = 1.006, p = 0.317 for extinction phases; F(1,295) = 0.361, p = 0.548 for reinforced phases). Baselines within a trial similarly remained stable from before to after UCS taste infusions (CS only: F(2,297) = 0.047, p = 0.954; CS plus UCS: F(2,296) = 0.417, p = 0.660). In short, VP baselines were quite stable in this experiment, and none of the CS or UCS effects described above could be ascribed to changes in baseline firing.

Behavioral hedonic and aversive facial reactions to taste UCS
The relative hedonic impacts of taste UCS stimuli was confirmed by video analyses of affective orofacial behavioral reactions. Sucrose taste infusions always elicited a high number of positive hedonic affective reactions, during both homeostasis and depletion states (e.g., rhythmic or lateral tongue protrusions, paw licking). In contrast, NaCl infusions elicited mostly negative aversive reactions (e.g., gapes, headshakes, forelimb flails) on the first test day when rats were in normal homeostasis. After sodium depletion, however, the NaCl valence reversed to predominantly positive reactions (interactions: hedonic: F(3,90) = 3.459, p = 0.015, df = 2; aversive: F(2,30) = 39.982, p < 0.0001) (Fig. 7). On the salt appetite day, NaCl elicited as many positive hedonic reactions to NaCl taste to dramatically rise (p = 0.002, df = 31) (Fig. 7a), and the number of negative aversive reactions to fall to near zero (p < 0.0001, df = 30) (Fig. 7b). This pattern confirmed that intensely salty taste switched in palatability from relatively
“disliked” to “liked” as a consequence of the sodium-depleted physiological state, whereas sucrose remained constantly “liked.” Generally, affective reactions were not elicited in significant numbers by CS tones without UCS tastes.

**Controls for motor confound: absence of movement coding by VP neurons**

To ascertain whether VP firing reflected changes in stimulus processing or motor reactions, we assessed neuronal activation during movements identified by video. VP neuronal activity was not strongly associated to any spontaneous movements such as head turns, forelimb movements or mouth or tongue movements, confirming that VP firing does not primarily code movements per se (Tindell et al., 2004, 2006). For example, only 2% of VP units that responded to CS cues were activated during spontaneous head turn movements scored outside of a CS. Even during cues or UCS stimuli, VP firing typically occurred 500 ms or more before any elicited movement, which may be too early for a movement-coding signal. Further, neural responses to CS stimuli were equally strong regardless of whether any observable movements occurred or not. Thus we conclude that the intensity of VP firing to stimuli did not tend to reflect movement parameters, but rather most likely reflected the motivational value features of CS tones and UCS tastes as described above.

**“Wanting” versus “liking” for CS**

We observed no elicitation of hedonic “liking” reactions when CSs tones were presented alone. Still, we leave open the question of whether the increase in CS “wanting” was matched by any increase in CS “liking” or hedonic impact (Fudim, 1978; Toates, 1986; Berridge and Schulkin, 1989). Lack of orofacial “liking” reactions helped prevent motor confounds in interpreting VP firing, and so was useful here for isolating cue-triggered “wanting” signals. However, pure auditory tones are not the best CSs for evoking conditioned hedonic reactions, and it remains possible that future studies using CSs with oral or gustatory components might yet reveal CS “liking” in the future (Delamater et al., 1986; Holland et al., 2008).

**Discussion**

Our results demonstrate that neural signals within ventral pallidum (VP) circuits encode incentive salience for a reward-predicting cue (CS), by patterns of neural firing in the reward-related anatomical hotspot of posterior VP (Smith et al., 2009). They also demonstrate that representations of incentive salience can be dynamically recomputed at the moment of cue re-encounter if the incentive value of the cue is physiologically altered. Here, we provoked recomputation that inverted the incentive value of a specific cue (CS\text{salt}). CS\text{salt} normally predicted the taste of aversive salt solution (UCS); however, by inducing sodium depletion, a physiological appetite and satiety, the CS\text{salt} was revalued by some physiologically relevant properties of its UCS, the CS would can often interact with relevant physiological states as its UCS would. As a consequence, a CS can be revalued by some physiological states, such as specific appetites, even when the state is completely novel and the UCS is absent (Krieckhaus and Wolf, 1968; Fudim, 1978; Toates, 1986; Berridge, 2001).

Applied to neuronal signals, a novel state may transform cue-evoked neural representations of saltiness and endow the cue signal with a motivation value appropriate to what its UCS would carry at the moment. This can directly revalue a relevant CS—even before the UCS is re-encountered in the new state—making the cue a more potent attractor that is able to pull behavior and guide approach, or to trigger increased “wanting” of its UCS goal. Such preemptive neural coding could therefore adaptively contribute to smart and rapid guidance of behavior toward appropriate rewards in appetite states.

**Computational models of learning and motivation**

In more formal computational terms, an implication of our results is that the incentive salience of a Pavlovian cue may equal its previously learned value if and only if relevant physiological states are the same during learning as in subsequent tests. This conclusion is different from perspectives that equate incentive value to cached accumulations of previous learned values, such as the popular temporal difference model of reward learning (prediction error model):

\[
V(s_1) = \left( \sum_{i=0}^{\infty} \gamma r_{t+1} \right) = r_i + \gamma(r_{t+1}) + \gamma^2(r_{t+2}) + \cdots.
\]

If motivation simply always equaled the accumulated cache of prior rewards, then the incentive salience value of a cue would simply sum all previously learned values (\(r_i\)) (McClure et al., 2003; Daw et al., 2005; Redish et al., 2008). But Pavlovian motivation is not so stable (Niv et al., 2006; Niv, 2007). In particular, the dynamic reversal of CS incentive salience shown here requires something more. To accomplish that reversal, Zhang et al. (2009) recently proposed a model that more accurately recomputes in-
Incentive salience at the moment of cue re-encounter. That dynamic model explicitly incorporates a physiological factor ($\kappa$) reflecting current hypothalamic and mesocorticolimbic states: Thus, a current physiological state can interact with previous associations of a CS with relevant reward ($r_e$) to transform its cue-triggered incentive value ($V$). The interaction can be encapsulated roughly as $(r_e, \kappa)$. The $\kappa$ factor allows the incentive salience of an associated CS to be adjusted as physiological states emerge or disappear (e.g., hungers, satiety, drug intoxication, mesolimbic sensitization, etc.). Here, the specific reversal of “wanting” triggered by the salt cue from negative to positive could be expressed via an additive interaction for $(r_e, \kappa)$, according to the model of Zhang et al. (2009):

$$V(s_t) = \bar{r}(r_e + \log \kappa) + \gamma V(s_{t+1}).$$

Cue-triggered “wanting” is thus transformed in valence and intensity by a relevant state factor. “Wanting” is also focused in an appropriate direction (e.g., toward salt), because the $\kappa$ factor is specific to its own particular CS and UCS reward combinations. Thus, a specific appetite for salt need not alter incentive computations for sucrose CSs, nor a caloric hunger state alter the value of salt CSs. Similarly, drug addicts may excessively “want” drugs most of all, whereas binge eaters particularly “want” food.

We note that other reward-related learning processes (e.g., cognitive expectations and act–outcome representations or simpler associative S–R habits) also operate alongside Pavlovian-guided incentive salience, using different rules and different brain systems. Some, such as cached habits or cognitive-based instrumental learning, may require actual retasting of a revalued UCS to change (Dickinson and Dawson, 1987; Berridge, 2001; Dayan and Balleine, 2002; Dickinson and Balleine, 2002a). In contrast, the CS incentive salience dynamically changed here in advance of UCS retasting.

Mesocorticolimbic circuitry

Signals in the VP reflect circuits from other mesocorticolimbic components, including orbitofrontal and insular cortex, ventral tegmentum, and nucleus accumbens (Groenewegen et al., 1993; Kalivas and Volkow, 2005; Zahm, 2006). Salt appetite signals, such as angiotensin II and aldosterone, activate the subfornical organ, extended amygdala, and brainstem sites to recruit limbic circuits of motivation (Johnson et al., 1999; Krause and Sakai, 2007). Recruitment includes enhancement of dopamine and opioid neurotransmission in the nucleus accumbens shell and in neostriatum (e.g., reduced dopamine transporter binding and increased enkephalin mRNA expression), which might help modulate “wanting” and “liking” encoded in the firing of VP neurons (Lucas et al., 2003).

VP in natural reward and addiction

A powerful way for drugs of abuse and addiction to usurp brain circuitry of natural rewards would be to hijack VP-related circuits that evolved to dynamically modulate the motivation value of natural incentives. Although salt appetite is relatively unique as a natural appetites (e.g., food hunger, water thirst) and also addiction-related states (e.g., mesolimbic sensitization; drug intoxication) (Berridge, 2001; Robinson and Berridge, 2003; Tindell et al., 2005; Zhang et al., 2009).

The incentive-sensitization theory of drug addiction posits that drug sensitization usurps mesocorticolimbic circuits to dynamically amplify the attribute of incentive salience to drug cues, producing excessive cue-triggered “wanting” to take drugs, just as biological sodium hunger here amplified the value of a salt cue (Robinson and Berridge, 2003; Tindell et al., 2005). In support of this convergence, we note that we previously reported drug sensitization to produce an incentive salience enhancement for a reward cue that was similar to the salt cue enhancement shown here, as a dynamic integration of $(r_e, \kappa)$ (Tindell et al., 2005). It also seems interesting that repeated sodium depletions may produce cross-sensitization to psychostimulant drugs (Bernstein, 2003; Clark and Bernstein, 2006). Thus natural salt appetite and drug sensitization and addiction may share underlying mesolimbic mechanisms. However, we also note a difference in that natural salt appetite enhances hedonic impact (“liking”) as well as incentive salience (“wanting”) for a relevant reward, whereas drug sensitization may enhance only “wanting” for targeted rewards (Robinson and Berridge, 2003; Tindell et al., 2005). Either may be sufficient to pull animals in a state of sodium deficiency toward a salt lick or pull addicts reluctantly toward drug-related cues and their addictive targets.

In conclusion, VP signals encode the current incentive salience of appropriate reward cues, in ways that can dynamically reverse a CS cue from “unwanted” to “wanted.” Firing patterns of VP-related circuits may in this way adaptively modulate motivation to guide behavior toward relevant goals. As a downside, this may also create vulnerabilities to addiction to drugs that usurp the VP-related capacity for dynamic revaluation to cause excessive “wanting” for particular rewards.

References


