Disentangling pleasure from incentive salience and learning signals in brain reward circuitry

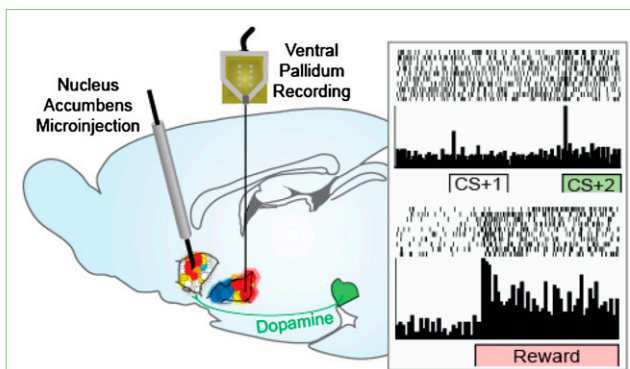Kyle S. Smith[1,2], Kent C. Berridge, and J. Wayne Aldridge
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AUTHOR SUMMARY

Reward can be separated into several components, which include sensory pleasure (liking), incentive motivation triggered by related cues (wanting), and predictive associations that allow cues to raise expectations of the pleasure to come (learning). Attraction to food in the refrigerator when hungry, for example, involves learned predictions of tasty treats, motivation to eat, and finally, pleasure enjoyed on eating. In the brain, signals for each of these components are funneled together through looping pathways connecting the nucleus accumbens with the ventral pallidum (VP), which form a circuit mediating motivation, behavior, and emotions (1). This circuit is crucial for healthy reward processing, and its dysfunction plays a special role in pathological drug addiction, eating disorders, and emotional disorders. However, it

Fig. P1. Rats learned a serial cue sequence that separated moments of maximal reward signals: Pavlovian prediction (maximal to the first CS+1), incentive salience (maximal to the second CS+2), and hedonic impact (maximal to the UCS reward). Neural firing was recorded for each stimulus in the VP, whereas opioid and dopamine were stimulated by drug microinjections in the nucleus accumbens to modulate enhancement of specific reward signals. Raster histogram representations of neuronal firing to stimuli across trials are shown on the right. In this example, a neuron recorded after opioid stimulation shows enhanced phasic activity to the incentive CS+2 and enhanced sustained activity to the hedonic UCS. In other tests, dopamine stimulation enhanced firing only to the CS+2.

is not known how the different reward components are kept separate within this circuit. If they are funneled together, how are they independently encoded as distinct signals? Here, we report that distinct signatures of neuronal firing in the VP track each reward component. We also report that selective enhancements of liking vs. wanting brought about by specific neurochemical activations in nucleus accumbens can be tracked independently from one another in downstream firing of VP neurons, all without distorting signals related to prediction of reward (Fig. P1).

We teased apart these different reward signals using a specially designed serial cue task, which included neurochemical manipulations of the nucleus accumbens to selectively boost one or another signal and electrophysiological recordings of neural firing in VP to track each signal. Rats learned to associate a fixed series of Pavlovian cues predicting a reward. An initial conditioned stimulus (CS) +1 (auditory tone; seconds 1–5) preceded a second CS+2 (different tone; seconds 10–15) and finally, a pleasant reward unconditioned stimulus (UCS; 10-s infusion of sucrose solution into the mouth by oral cannulae in seconds 13–23), all in a fixed timetable. This sequence allowed us to separate moments of maximum intensity for each reward component. The predictive contingency between CS+1, CS+2, and UCS in these time intervals meant that CS+1 presentation created a nearly 100% certainty (i.e., minimal entropy in an information theory context) that CS+2 and reward UCS would both follow (2–4). The CS+2 adds little or no additional predictive information value or reduction in uncertainty about UCS occurrence. However, despite being redundant as a predictor,

the CS+2 occurs closest in time to the actual reward and can carry high-incentive motivational value (5). The final event in the sequence, the UCS sucrose infusion (i.e., the reward), carried the strongest hedonic impact as a sweet taste (1). In separate trials randomly interleaved during the session, a distinct CS− tone was presented as a control stimulus. It predicted nothing and thus, carried little reward value of any kind.

After animals learned the sequence, they were tested after microinjections in the hedonic hotspot site of the medial shell of nucleus accumbens with an opioid drug to stimulate μ-receptors ([D-Ala2, N-MePhe4, Gly-ol]-enkephalin; DAMGO) located pre- and postsynaptically to neurons. This stimulation is known to increase both hedonic liking and motivational wanting for sucrose reward (1). In contrast, increasing synaptic dopamine levels by amphetamine microinjections only enhances wanting and has no impact or even diminishes liking. Vehicle injections served as controls. We found that, under control (vehicle) conditions, neural firing in the VP was greatest to the first CS+1 cue, with maximal predictive value. This finding indicates that VP activity normally represents prediction signals most strongly. The greatest firing occurred consistently as a rapid, phasic burst that peaked in response to CS+1, a pattern that is consistent with the prediction coding scheme proposed for dopamine neurons in normal physiological states (3, 4).

After dopaminergic or opioid stimulation of the accumbens, pallidal firing changed dramatically with a new pattern of enhanced responses to the CS+2 (specifically, the incentive cue that marks maximal wanting). Firing to the CS+1 or the control CS− was unchanged with drug treatment. These changes were evident even on the first cue presentations before the animals

had the opportunity to experience the actual reward and form new CS–UCS associations, indicating the changes were not a result of learning. Although CS+2 responses were enhanced, activation to CS+1 persisted normally, indicating that the drug-evoked shift in motivation did not distort the accuracy of neural representations for learned predictions or expectations about future reward. Behavioral confirmation of enhanced motivation for reward was seen later in increased consumption of M&M candies in a voluntary intake test at the conclusion of neural recordings.

During delivery of the actual sucrose reward into the mouth, rats emitted hedonic orofacial reactions of lip licking that are indicative of taste liking, and pallidal neurons simultaneously increased firing to the sucrose taste as a liking representation (1). Only microinjection of the opioid-stimulating drug enhanced these reactions and enhanced firing of VP neurons to the taste. In stark contrast, the dopamine-stimulating drug failed to enhance either hedonic behavioral reactions or neuronal firing to the taste of sucrose. Thus, in all, accumbens opioid stimulation increased both liking and wanting signals represented in VP firing and reflected in behavioral measures, whereas dopamine stimulation increased only wanting signals and behaviors. Neither neurochemical modulation altered Pavlovian predictive signals, leaving reward predictions stable and unchanged.

Finally, we focused on how patterns of neuronal activity could distinguish hedonic vs. motivational signals even when both were enhanced together after opioid stimulation. We found that these signals were still tracked separately in the VP in part by a segregation of different groups of neurons that encoded each signal (i.e., responding to the CS+2 but not to the UCS or vice versa) and also, by distinct patterns of fast and phasic vs. slow and sustained firing for wanting vs. liking in these neurons as well as in other neurons that encoded both signals jointly.

In summary, these experiments identify distinct neural representations of liking, wanting, and predicting for the same reward, even when multiple reward signals are funneled together into the same nucleus accumbens–VP path or onto the same neurons in VP. An implication for behavior is that one reward component, say motivation, can be enhanced selectively by recruitment of the particular neuronal activity signatures identified here. This result might be adaptive, for example, in guiding behavior to food in a natural appetite state without the need for new learning or tasting of the food first. However, a related implication is that pathological states can potentially usurp the same amplification of one particular reward component. For example, in drug addiction, as posited by the incentive–sensitization theory, excessive motivation to take more drugs can result from hijacking and elevating the specific channel for wanting alone, even if liking were suppressed by tolerance or if predictions about the drug's value remained normal. Another implication for addiction is an explanation of why drug-related cues can often trigger relapse and consumption and why their ability to do so fluctuates. We suggest that the motivation power of cues is amplified by states of mesolimbic reactivity that magnify incentive salience as observed here. Fluctuations in the ensuing state of those mesolimbic systems, such as those states caused by drug intoxication or stress, will produce fluctuations in the reactivity of the circuit to cue encounters and thus, different intensities of wanting for the related drug reward (similar to fluctuations induced by microinjections here). Likewise, the UCS proximity of peak incentive salience signals may reflect why it is easier to resist cues that are temporally distant from rewards (e.g., seeing a crack house; comparable with encountering CS+1) than to resist other cues that are temporally closer to reward (e.g., seeing crack in one's own hand; comparable with CS+2).

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