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The basolateral amygdala and lateral hypothalamus bias learning towards motivationally significant events

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Every day we are faced with a huge amount of new information. We can't learn about everything, we have to select what to learn about. We have many systems that contribute to learning in different ways, allowing us to select the most relevant information to learn about. This review will focus on one such system, comprising the basolateral amygdala and lateral hypothalamus, which we argue works to favor learning about information most relevant to current goals. Specifically, we will discuss work that has revealed the role of the basolateral amygdala in encoding the sensory-specific aspects of rewarding information. Then, we discuss new data implicating lateral hypothalamus in biasing learning towards reward-predictive cues, and away from information distal to rewards. Finally, we offer a framework of how these regions communicate to relay this information to the midbrain dopamine system, allowing them to bias ongoing learning towards the best predictors of motivationally relevant information.

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Introduction

Learning about predictors of motivationally significant outcomes, like food or pain, is essential for approaching rewards and avoiding punishments. Some of these predictors are proximal to outcomes, like the taste of ice cream from your neighborhood's ice-cream truck. Others are more distal from outcomes, like hearing the nostalgic tune of the ice-cream truck play throughout your neighborhood. We must balance learning about proximal and distal outcomes, and devote learning to predictors that best facilitate arrival at our eventual goal. Dysfunction in the balance between learning about proximal and distal predictors of outcomes plays an important role in psychological disorders like anxiety, addiction, and schizophrenia [1,2].

Two regions of the brain that are important for learning about motivationally significant outcomes are the lateral hypothalamus (LH) and the basolateral amygdala (BLA). Both structures encode information that is proximal to food (or pain, under some conditions [10••]), which facilitates the ability to respond appropriately to these predictors in the future [3–8,9••,10••]. Yet when it comes to learning about the distal predictors of food outcomes, the function of these regions diverges. Specifically, the BLA will only be involved in encoding information about distal predictors if these predictors have already been established as related to something motivationally significant [3,8,9]. For example, the BLA will encode the ice-cream truck tune, but only if you know the truck is likely to sell ice cream. On the other hand, the LH biases learning toward proximal predictors and actively opposes learning about distal predictors, even if those distal cues are related to something motivationally significant. Thus, in contrast to the BLA, the LH will always want to prevent you from encoding the sound of the ice-cream truck tune, even if you've bought ice cream from these trucks a hundred times before. Here, we review the function of these regions in the context of Pavlovian conditioning and discuss potential models of how these regions may interact to facilitate the balance of proximal and distal learning about motivationally significant outcomes.

Basolateral amygdala function

Much of the early research on the BLA has centered around the role of this region in fear. The BLA has been shown to be critical for both the acquisition and expression of conditioned fear in rodents, humans, and primates [11,12,13•]. In a simple fear conditioning task, where subjects are learning to associate a cue with something aversive like a mild foot shock, inhibiting BLA function reduces the subsequent ability of the shock-predictive cue to elicit fear [14–16,17•]. Similarly, leaving BLA function intact during learning, but disrupting its function in a subsequent test of fear to the shock-paired cue, also reduces fear [14–16,18]. These results demonstrate that the BLA is necessary for developing and storing fear memories that facilitate appropriate behavior in the presence of predictors of aversive outcomes.

While most of the work examining the role of the BLA in learning focuses on predictors of aversive outcomes, the BLA is also critical for learning about the predictors of rewards [3–7,19,20]. However, its contribution to reward learning is more nuanced, such that inhibiting BLA function does not abolish learning or responding to cues that predict rewarding outcomes, like it does during fear conditioning [19,20]. Instead, appetitive learning studies have revealed that the BLA is important for encoding the sensory-specific representation of the reward, demonstrated by using Pavlovian-to-instrumental Transfer (PIT) and devaluation studies [3–6]. For example, during PIT, subjects first learn that two cues (e.g. light or tone) lead to two different rewards (e.g. pellets or sucrose). Then, subjects learn to make two actions (e.g. lever press or chain pull) to receive the two outcomes. Finally, subjects are given a test where the cues are played and either action can be made (in the absence of reward). Encoding of the sensory-specific representation of these rewards is revealed when subjects make the action that leads to the reward congruent with that predicted by the current cue being played (e.g. sucrose action made during sucrose cue). However, lesions of the BLA impair the specific PIT effect, characterized by indistinguishable action selections in the presence of either cue, despite the ability of the cues to generally invigorate motivated responding remaining intact [6]. These findings demonstrate that the BLA is necessary for encoding the relationship between cues and a sensory-specific representation of rewards [4–6].

Interestingly, this role of the BLA in learning about cues that predict either rewarding or aversive outcomes can extend to learning about information that is distal to these outcomes. However, this only occurs if the information being learned carries motivational significance at the time these relationships are encoded. For example, the BLA is not involved in sensory preconditioning [8,9,21,22]. In this procedure, two neutral cues are first paired together, where neither carry any motivational significance (e.g. A → B). The next day, cue B is paired with a motivationally significant outcome (e.g. B → shock), endowing this cue with motivational significance. After this training, when cue A is presented alone, rats will freeze because it leads to B, which they learned predicts shock. Inhibition of BLA function during initial A → B learning has no impact on the later ability of A to elicit freezing after B is paired with shock, demonstrating that the BLA is not involved in learning the initial A → B association [8,9]. However, the BLA can be recruited to learn about these same relationships if rats have previously experienced shock in the same context as where they will receive initial pairings of the neutral cues (A → B) [9], or if these A → B pairings are learned after B has been established as predictive of shock (termed 'second-order conditioning') [3,8]. Under these conditions, inactivating the BLA during A → B pairings reduces subsequent freezing to A [8]. This shows that the BLA can be engaged to learn about complex sensory-specific associations that are distal from outcomes, but only if that information is motivationally significant at the time of encoding.

The importance of the BLA in prioritizing encoding of information that is motivationally significant is also indexed by the pattern of cue-evoked firing seen in electrophysiological studies. In one study, rats were trained to discriminate responding to two different odors predictive of either a rewarding sucrose solution or an aversive quinine solution [23]. Neurons in the BLA were recorded in these rats during a reversal of these contingencies. This revealed that neuronal populations in the BLA switch their firing preference to follow their preferred outcome. That is, after a reversal, the same neuron that was once firing to an odor predictive of sucrose will now preferentially fire for that opposite odor that is now predictive of sucrose. Thus, these neurons change selectivity to follow the reward and not the odor. Similarly, in another study, BLA neurons increased firing rate with an unexpected change in reward magnitude or delay, exhibiting a short burst of increased activity whether these changes meant more or less reward, or delivered over a shorter or longer timescale [24]. This is reminiscent of an unsigned attentional signal [24], strengthening the idea that BLA is concerned with the specific outcomes predicted by environmental stimuli and their motivational significance [24,25]. Altogether, these studies provide evidence to support the BLA as an associative structure important for learning about motivationally significant events by encoding sensory-specific information about these events, including their current predictive status.

Lateral hypothalamus function

While the BLA has been known to be critical for associative learning for some time, it is only recently that the LH has been conclusively shown to be necessary for reinforcement learning [10••,26–28,29•,30,31]. Before this, the function of the LH was relatively restricted to promoting approach to food and its consumption (but see: Castro *et al.* [32]; Petrovich [33••]). For example, early studies demonstrated that lesions made in the LH would reduce spontaneous feeding behavior, suggesting the necessity for this region for food consumption and the prevention of starvation [34]. Similarly, electrical stimulation of the LH was shown to increase food intake in sated rats [34–36]. In fact, the LH itself supports intracranial self-stimulation (ICSS) [35–38]. Specifically, subjects will perform an action to receive electrical or optical stimulation of LH, argued to reflect a role for this region in processing primary rewards, like food [35–38]. Further, neural recordings in LH show that it responds to rewards, such as glucose and ICSS [39,40•,41]. Together, these findings have demonstrated the importance of the LH in processing primary rewards.

GABAergic neurons in the LH have become a heavily researched population in LH in recent years. This is partly owed to recent findings that stimulation of GABAergic neurons alone produces the effects on feeding found with LH stimulation prior [42–45]. Our lab recently investigated whether the GABAergic population might also contribute to learning about cues that predict food, over and above producing an innate drive to feed [26]. Specifically, we trained rats that a cue led to food, and optogenetically inhibited LH GABAergic neurons during the cue and not food delivery. This allowed us to isolate a role for LH in learning separate from food consumption. We found that rats showed a significant reduction in the appetitive response to approach the food port when LH GABA neuronal functioning was inhibited during cue presentation. This was despite intact food consumption when the food was delivered shortly after the cue. This demonstrated that all rats were capable of using other sensory predictors (e.g. the sight, smell, and sound of food), to go and retrieve the food, even if they were not using the food-predictive cue to do so. Importantly, this deficit was maintained when rats were presented with the food-paired cue after learning, when the LH GABAergic neurons were no longer inhibited. This confirmed an effect on learning and not a temporary effect on attention or motivation when the neurons were inhibited. Further, in a separate group of rats, inhibition of LH GABA neuronal activity during the cue, after learning had taken place, also reduced cue-evoked responding. These findings suggest that LH GABAergic neurons facilitate learning and responding towards food-predictive cues, revealing a new role for the LH in learning about predictors of motivationally significant outcomes beyond the innate motivation to approach and consume food.

More recently, we have implicated LH GABAergic neurons as playing a role in opposing learning about cues that are not directly relevant to predicting food [10••]. For example, when GABAergic neurons in LH were optogenetically inhibited during cue–cue learning (e.g. A → B) in a sensory preconditioning task, subjects showed elevated responding toward the preconditioned cue, A, after it's associate B was paired with food [10••]. This demonstrated that inhibition of LH GABA neuronal activity during A → B learning increased the association between the neutral cues, suggesting the general function of these neurons is to oppose learning of these associations. LH could oppose the initial A → B learning for two reasons: (1) because the cues did not hold any motivational significance at the time of learning, or (2) because the LH opposes any learning that is not directly relevant to predicting food during a session. To test this, another group of rats were trained first that B was a predictor of food, and then to associate A with B together, in a second-order conditioning design [10••]. Under these circumstances, inhibition of LH GABA neurons during the A → B pairings still enhanced subsequent appetitive responding towards A. This confirmed that LH GABAergic neurons oppose learning about cues that are distal to reward (e.g. those that do not predict rewards within a session), rather than simply those that do not possess any motivational significance at the time of learning (i.e. neutral cues). Taken together, these findings demonstrate that the LH is important for learning about cues that are proximal predictors of reward, while opposing learning for associations that are distal to rewards.

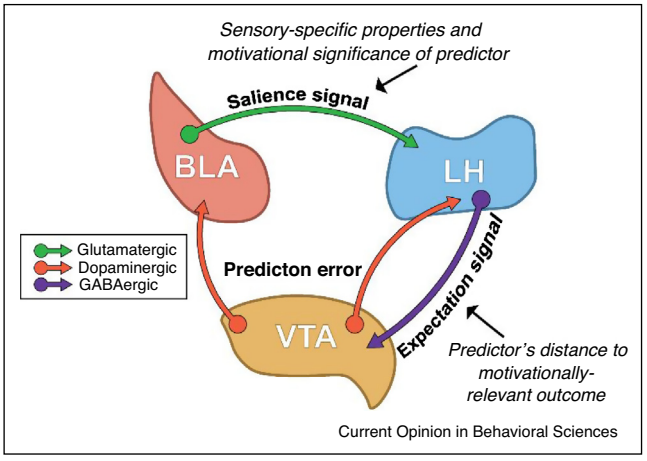
An interesting direction for future research would be to determine how this type of learning is encoded in the LH. For example, would the same neurons that facilitate feeding and ICSS also be those encoding relationships between cues and rewards (and their direct relevance for predicting reward), or would different neuronal populations encode distinct aspects of this process? While we know that LH GABAergic neurons are necessary for both feeding and cue-reward learning [10••,26,42–45], there are many different subtypes of GABAergic neurons in the LH [46]. Further, we also know that non-GABAergic LH neurons expressing orexin (ORX) play a role in reward learning [47], which is yet to be dissociated from the role that GABAergic neurons play in this process. Recent work has shown that it is likely that different aspects of learning could be encoded in different populations of neurons within the LH [43]. Specifically, Nieh *et al.* [43] showed that different neuronal populations (GABAergic or otherwise) in the LH exhibit distinct connections with the midbrain; one group of LH neurons appear to selectively project to the ventral tegmental area (VTA), while another receive inputs from the VTA. This suggests that these populations that have distinct connection profiles could be encoding different aspects of behavior. Given the development of modern-day neuroscience techniques, dissecting the exact cellular architecture and specific mechanisms within the LH itself to investigate these functions further is now certainly on the horizon.

BLA-LH circuitry

In summary, the BLA and LH are critical for learning about proximal predictors of outcomes, but their function diverges when considering their contribution to the encoding of distal predictors. Specifically, BLA contributes to cue–cue associations (e.g. A → B), but only if one of these cues (or the context they're trained in) is already motivationally significant [3,8,9]. On the other hand, LH opposes cue–cue relationships, regardless of their motivational significance of prior experience, diverting learning away from cues that are distal to rewards [10••]. Given this, it becomes of interest to consider how these regions might functionally interact.

Anatomical studies for this circuitry suggest that it is likely the BLA relays information to the LH, as the BLA sends excitatory projections to the LH, and the LH is without reciprocal projections to the BLA [48]. Indeed, research investigating information flow from the

Figure 1



Schematic of a proposed BLA-LH framework.
Excitatory projections extending from the BLA provide a salience signal to the LH that contains sensory-specific information and expected outcomes that are motivationally significant. Upon receipt, the LH assesses whether this outcome is directly relevant to current motivational state and determines the predictor's proximity to the outcome. LH then relays this information as an expectation signal to the VTA, influencing resulting prediction errors relayed from this region throughout the brain to regulate ongoing learning.

BLA to the LH while rats respond to food-predictive cues supports an idea that BLA provides early information about the cue-predicted outcome to LH. For example, after learning a cue predicts food, LH-projecting BLA neurons show increased Fos expression in the presence of that cue (and not in response to other aspects of the experiment) [28]. Interestingly, BLA activity appears to increase earlier in learning than LH. Specifically, BLA activity, as measured by cFos, is evident after just one day of cue-reward training [49]. However, this is not seen in LH. Instead, LH populations appear to become recruited towards the later sessions of learning [50].

One interpretation of these data is that the recruitment of the LH for learning after initial sessions suggests LH may process cue information from the BLA to determine the relevance of its contingency to current motivational state (e.g. food to a hungry rat). That is, the LH is not involved in learning about the cue-food contingency *per se*, but rather, evaluates the relevance of this information to current goals, to influence the degree of resources that will be devoted to directing learning or responding to it. This is supported by electrophysiological recordings that show phasic firing of BLA neurons at the onset of an appetitive or aversive cue [51–53], whereas LH neural activity is long and sustained to reward-predicting cues [39,40•,41,54]. Collectively, this is consistent with a testable hypothesis that transients from the BLA may be acting as a salience signal, carrying information about the cue-predicted outcome, to alert the LH (and elsewhere) of what is about to happen. We would postulate that LH then ultimately assesses the direct relevance of these cues in predicting something the agent needs right now, to bias learning and responding towards those most proximal to motivationally significant outcomes (Figure 1).

After receiving information from BLA, LH GABA neurons can modulate ongoing learning and performance via dense projections to the VTA [26,43–45]. For example, we have found causal evidence that LH GABAergic neurons relay an expectation signal to VTA to modulate ongoing learning and prediction errors [26]. That is, when a reward-predictive cue is presented, LH GABA relays the expectation for reward to the VTA, preventing a prediction error from firing when the now expected reward is delivered. This type of mechanism does not appear to be supported by the circuitry between BLA and the VTA [55,56]. Specifically, BLA does not appear to have direct projections to VTA [55,56], consistent with an idea that BLA relays cue information to the LH, which then allows the LH to influence ongoing learning processes by virtue of signaling throughout the VTA (Figure 1). We would argue that this influence that LH has over VTA allows it to direct learning and responding towards proximal predictors, and away from distal predictors of rewards, providing a unique input to midbrain dopamine circuit, which data has shown is involved in increasingly complex and diverse forms of reinforcement learning [57,58,59•,60].

Conclusion

Here we have put forward a testable theory of how LH and BLA work together to regulate learning and behavior towards cues most relevant to predicting important outcomes. The brave new world of genetic neuroscience offers new methods to investigate the intricacies of this cognitive process that can be applied to study this circuit in the future [61–63]. For example, we can now target the specific glutamatergic projections from the BLA to the LH using optogenetics and inhibit these synapses with temporal precision during Pavlovian learning. Similarly, we could record the terminals that arise from the BLA in LH to examine their contribution to the learning process. This would allow us to unpack the specifics of how this system functions to influence learning and behavior.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Voon V, Retier A, Sebold M, Groman S: **Model-based control in dimensional psychiatry**. *Biol Psychiatry* 2017, **82**:391-400.

2. Takahashi YK, Stalnaker TA, Marrero-Garcia Y, Rada RM, Schoenbaum G: **Expectancy-related changes in dopaminergic**

error signals are impaired by cocaine self-administration. *Neuron* 2019, **101**:294-306.e3.

3. Hatfield T, Han J, Conley M, Gallagher M, Holland P: **Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects**. *J Neurosci* 1996, **16**:5256-5265.

4. Blundell P, Hall G, Killcross S: **Lesions of the basolateral amygdala disrupt selective aspects of reinforcer representation in rats**. *J Neurosci* 2001, **21**:9018-9026.

5. Holland PC, Gallagher M: **Double dissociation of the effects of lesions of basolateral and central amygdala on conditioned stimulus-potentiated feeding and Pavlovian-instrumental transfer**. *Eur J Neurosci* 2003, **17**:1680-1694.

6. Corbit LH, Balleine BW: **Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of Pavlovian-instrumental transfer**. *J Neurosci* 2005, **25**:962-970.

7. Servonnet A, Hernandez G, El Hage C, Rompré P, Samaha A: **Optogenetic activation of the basolateral amygdala promotes both appetitive conditioning and the instrumental pursuit of reward cues**. *J Neurosci* 2020, **40**:1732-1743.

8. Parkes SL, Westbrook RF: **The basolateral amygdala is critical for the acquisition and extinction of associations between a neutral stimulus and a learned danger signal but not between two neutral stimuli**. *J Neurosci* 2010, **30**:12608-12618.

9. •• Holmes NM, Raipuria M, Qureshi OA, Killcross S, Westbrook F: **Danger changes the way the mammalian brain stores information about innocuous events: a study of sensory preconditioning in rats**. *eNeuro* 2018, **5** ENEURO.0381-17.2017

Expanding on their prior work, the authors blocked activity in either the perirhinal cortex (PRh) or the basolateral amygdala (BLA) during sensory preconditioning in a context that was deemed 'safe' or 'dangerous'. They found that the BLA encodes relationships between sensory stimuli (cue–cue associations), but only if this was experienced in a dangerous context. This reinforced the importance of this region in selectively learning about motivationally relevant information.

10. •• Sharpe MJ, Batchelor HM, Mueller LE, Gardner MPH, Schoenbaum G: **Past experience shapes the neural circuits recruited for future learning**. *Nat Neurosci* 2021, **24**:391-400

In this manuscript, the authors found that inhibition of LH GABA neurons opposed the development of cue–cue associations, which stands in contrast to the necessity of this neuronal population for associating cues and rewards together. The authors found this was this case whether both cues were neutral at the time of learning (i.e. during sensory preconditioning) or if one of these cues has been established as motivationally significant (i.e. second-order conditioning). This demonstrates that LH GABA neurons bias learning towards proximal predictors of outcomes, and away from distal predictors of outcomes, and distinguishes LH function from that of the BLA.

11. Fanselow MS, LeDoux JE: **Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala**. *Neuron* 1999, **23**:229-232.

12. Ressler RL, Maren S: **Synaptic encoding of fear memories in the amygdala**. *Curr Opin Neurobiol* 2019, **54**:54-59.

13. • Sun Y, Gooch H, Sah P: **Fear conditioning and the basolateral amygdala**. *F1000Res* 2020, **9** F1000 Faculty Rev-53

The authors describe the microcircuitry within the basolateral amygdala (BLA) that mediates the acquisition and expression of Pavlovian conditioned responding of fear. Specifically, this review describes recent findings for long-term potentiation of glutamatergic synapses carrying cue-related information in the BLA during acquisition of fear conditioning. Further, the authors discuss the crucial role of the diverse subtypes of GABAergic interneurons in cooperate to modulate the expression of conditioned fear.

14. Helmstetter FJ, Bellgowan PS: **Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats**. *Behav Neurosci* 1994, **108**:1005-1009.

15. Cousens G, Otto T: **Both pre- and post-training excitotoxic lesions of the basolateral amygdala abolish the expression of olfactory and contextual fear conditioning**. *Behav Neurosci* 1998, **112**:1092-1103.

16. Maren S: **Neurotoxic basolateral amygdala lesions impair learning and memory but not the performance of conditional fear in rats**. *J Neurosci* 1999, **19**:8696-8703.

17. • Sengupta A, Yau JOY, Jean-Richard-Dit-Bressel P, Liu Y, Millan EZ, Power JM, McNally GP: **Basolateral amygdala neurons maintain aversive emotional salience**. *J Neurosci* 2018, **38**:3001-3012

The authors found that optogenetic inhibition of BLA neurons during Pavlovian fear conditioning reduced learning about shock-paired stimuli in a manner that reflected a reduction in the salience attributed to the shock-paired stimulus. This was also demonstrated by recording of calcium transients in BLA, which showed phasic excitation of BLA neurons at the onset of shock delivery, early in fear conditioning. This work supports the view that BLA neurons encode a salience signal to alert other areas of the brain about the motivational significance of the upcoming event predicted by available stimuli.

18. Gale GD, Anagnostaras SG, Godsil BP, Mitchell S, Nozawa T, Sage JR, Wiltgen B, Fanselow MS: **Role of the basolateral amygdala in the storage of fear memories across the adult lifetime of rats**. *J Neurosci* 2004, **24**:3810-3815.

19. Wassum KM, Izquierdo A: **The basolateral amygdala in reward learning and addiction**. *Neurosci Biobehav Rev* 2015, **57**:271-283.

20. Malvaez M, Shieh C, Murphy MD, Greenfield VY, Wassum KM: **Distinct cortical-amygdala projections drive reward value encoding and retrieval**. *Nat Neurosci* 2019, **22**:762-769.

21. Blundell P, Hall G, Killcross S: **Preserved sensitivity to outcome value after lesions of the basolateral amygdala**. *J Neurosci* 2003, **23**:7702-7709.

22. Dwyer DM, Killcross S: **Lesions of the basolateral amygdala disrupt conditioning based on the retrieved representations of motivationally significant events**. *J Neurosci* 2006, **26**:8305-8309.

23. Schoenbaum G, Chiba AA, Gallagher M: **Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning**. *J Neurosci* 1999, **19**:1876-1884.

24. Esber GR, Roesch MR, Bali S, Trageser J, Bissonette GB, Puche AC, Holland PC, Schoenbaum G: **Attention-related Pearce-Kay-Hall signals in basolateral amygdala require the midbrain dopaminergic system**. *Biol Psychiatry* 2012, **72**:1012-1019.

25. Nasser HM, Calu DJ, Schoenbaum G, Sharpe MJ: **The dopamine prediction error: contributions to associative models of reward**. *Front Psychol* 2017, **8**:244.

26. Sharpe MJ, Marchant NJ, Whitaker LR, Richie CT, Zhang YJ, Campbell EJ, Koivula PP, Necarsulmer JC, Meijas-Aponte C, Morales M *et al.*: **Lateral hypothalamic GABAergic neurons encode reward predictions that are relayed to the ventral tegmental area to regulate learning**. *Curr Biol* 2017, **27**:2089-2100.

27. Petrovich GD, Setlow B, Holland PC, Gallagher M: **Amygdalo-hypothalamic circuit allows learned cues to override satiety and promote eating**. *J Neurosci* 2002, **22**:8748-8753.

28. Petrovich GD, Holland PC, Gallagher M: **Amygdalar and prefrontal pathways to the lateral hypothalamus are activated by a learned cue that stimulates eating**. *J Neurosci* 2005, **25**:8295-8302.

29. • Cole S, Keefer SE, Anderson LC, Petrovich GD: **Medial prefrontal cortex neural plasticity, orexin receptor 1 signaling, and connectivity with the lateral hypothalamus are necessary in cue-potentiated feeding**. *J Neurosci* 2020, **40**:1744-1755

The authors investigated the role of the lateral hypothalamus (LH) and medial prefrontal cortex (mPFC) in mediating the cue potentiated feeding effect. This is an effect whereby a food-predictive cue can increase feeding in sated animals. The authors found that disconnection of mPFC and LH prevented cue-potentiated feeding. Further, inactivating LH orexin signaling to mPFC also reduced the cue-potentiated feeding effect. This suggested that LH relays information about food-paired cues to mPFC to modulate appropriate responding behavior, arguing against a role for LH as a passive switch to produce feeding behaviors.

30. Bracey EF, Burdakov D: **Fast sensory representations in the lateral hypothalamus and their roles in brain function**. *Physiol Behav* 2020, **222**:112952.

31. Burkadov D, Peleg-Raibstein D: **The hypothalamus as a primary coordinator of memory updating**. *Physiol Behav* 2020, **223**:112988.

32. Castro DC, Cole SL, Berridge KC: **Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry**. *Front Syst Neurosci* 2015, **9**:90.

33. •• Petrovich GD: **Lateral hypothalamus as a motivation-cognition interface in the control of feeding behavior**. *Front Syst Neurosci* 2018, **12**:14

In this review, the author highlights recent findings that demonstrate that the lateral hypothalamus (LH) is a critical structure in regulating feeding, motivation, and cue-reward learning. The author discusses the heterogeneity of neuronal populations within the LH and how these distinct populations modulate different motivational and cognitive processes. The review reinforces the idea that recent studies demonstrate that the LH contributes in important ways to associative learning, beyond its canonical function for metabolic regulation.

34. Anand BK, Brobeck JR: **Localization of a "feeding center" in the hypothalamus of the rat**. *Proc Soc Exp Biol Med* 1951, **77**:323-324.

35. Hoebel BG, Teitelbaum P: **Hypothalamic control of feeding and self-stimulation**. *Science* 1962, **135**:375-377.

36. Margules DL, Olds J: **Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats**. *Science* 1962, **135**:374-375.

37. Wise RA: **Lateral hypothalamic electrical stimulation: does it make animals 'hungry'?** *Brain Res* 1974, **67**:187-209.

38. Urstadt KR, Berridge KC: **Optogenetic mapping of feeding and self-stimulation within the lateral hypothalamus of the rat**. *PLoS One* 2020, **15**:e0224301.

39. Ono T, Nakamura K, Nishijo H, Fukuda M: **Hypothalamic neuron involvement in integration of reward, aversion, and cue signals**. *J Neurophysiol* 1986, **56**:63-79.

40. • Otis JM, Zhu M, Namboodiri VMK, Cook CA, Kosyk O, Matan AM, Ying R, Hashikawa Y, Hashikawa K, Trujillo-Pisanty I *et al.*: **Paraventricular thalamus projection neurons integrate cortical and hypothalamic signals for cue-reward processing**. *Neuron* 2019, **103**:423-431.e4

In this study, the authors use *in-vivo* two-photon calcium imaging of terminals from the lateral hypothalamus (LH) to many regions of the brain during cue-reward learning. Here, the authors show that LH axons, which are primarily GABAergic, exhibit long and sustained excitatory responses to a reward-predictive cue. This is different from responses seen in the basolateral amygdala, which show a short burst of excitatory activity at cue onset.

41. Noritake A, Nakamura K: **Encoding prediction signals during appetitive and aversive Pavlovian conditioning in the primate lateral hypothalamus**. *J Neurophysiol* 2019, **121**:396-417.

42. Jennings JH, Ung RL, Resendez SL, Stamatakis AM, Taylor JG, Huang J, Veleta K, Kantak PA, Aita M, Shilling-Scrivo K *et al.*: **Visualizing hypothalamic network dynamics for appetitive and consummatory behaviors**. *Cell* 2015, **160**:516-527.

43. Nieh EH, Matthews GA, Allsop SA, Presbrey KN, Leppla CA, Wichmann R, Neve R, Wildes CP, Tye KM: **Decoding neural circuits that control compulsive sucrose-seeking**. *Cell* 2015, **160**:528-541.

44. Barbano MF, Wang H, Morales M, Wise RA: **Feeding and reward are differentially induced by activating GABAergic lateral hypothalamic projections to VTA**. *J Neurosci* 2016, **36**:2975-2985.

45. Nieh EH, Vander Weele CM, Matthews GA, Presbrey KN, Wichmann R, Leppla CA, Izadmehr EM, Tye KM: **Inhibitory input from the lateral hypothalamus to the ventral tegmental area disinhibits dopamine neurons and promotes behavioral activation**. *Neuron* 2016, **90**:1286-1298.

46. Bonnavion P, Mickelsen LE, Fujita A, de Lecea L, Jackson AC: **Hubs and spokes of the lateral hypothalamus: cell types, circuits and behaviour**. *J Physiol* 2016, **594**:6443-6462.

47. Aston-Jones G, Smith RJ, Moorman DE, Richardson KA: **Role of lateral hypothalamic orexin neurons in reward processing and addiction**. *Neuropharmacology* 2009, **56(Suppl. 1)**:112-121.

48. Reppucci CJ, Petrovich GD: **Organization of connections between the amygdala, medial prefrontal cortex, and lateral hypothalamus: a single and double retrograde tracing study in rats**. *Brain Struct Funct* 2016, **221**:2937-2962.

49. Cole S, Powell DJ, Petrovich GD: **Differential recruitment of distinct amygdalar nuclei across appetitive associative learning**. *Learn Mem* 2013, **20**:295-299.

50. Cole S, Hobin MP, Petrovich GD: **Appetitive associative learning recruits a distinct network with cortical, striatal, and hypothalamic regions**. *Neuroscience* 2015, **286**:187-202.

51. Johansen JP, Tarpley JW, LeDoux JE, Blair HT: **Neural substrates for expectation-modulated fear learning in the amygdala and periaqueductal gray**. *Nat Neurosci* 2010, **13**:979-986.

52. Morrison SE, Saez A, Lau B, Salzman CD: **Different time courses for learning-related changes in amygdala and orbitofrontal cortex**. *Neuron* 2011, **71**:1127-1140.

53. Grewe BF, Gründemann J, Kitch LJ, Lecoq JA, Parker JG, Marshall JD, Larkin MC, Jercog PE, Grenier F, Li JZ *et al.*: **Neural ensemble dynamics underlying a long-term associative memory**. *Nature* 2017, **543**:670-675.

54. Li JX, Yoshida T, Monk KJ, Katz DB: **Lateral hypothalamus contains two types of palatability related taste responses with distinct dynamics**. *J Neurosci* 2013, **33**:9462-9473.

55. Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N: **Whole-brain mapping of direct inputs to midbrain dopamine neurons**. *Neuron* 2012, **74**:858-873.

56. Breton JM, Charbit AR, Snyder BJ, Fong PTK, Dias EV, Himmels P, Lock H, Margolis EB: **Relative contributions and mapping of ventral tegmental area dopamine and GABA neurons by projection target in the rat**. *J Comp Neurol* 2019, **527**:916-941.

57. Sharpe MJ, Chang CY, Liu MA, Batchelor HM, Mueller LE, Jones JL, Niv Y, Schoenbaum G: **Dopamine transients are sufficient and necessary for acquisition of model-based associations**. *Nat Neurosci* 2017, **20**:735-742.

58. Gardner MPH, Schoenbaum G, Gershman SJ: **Rethinking dopamine as generalized prediction error**. *Proc R Soc B Biol Sci* 2018, **285** 20181545.

59. • Engelhard B, Finkelstein J, Cox J, Fleming W, Jang HJ, Ornelas S, Koay SA, Thiberge SY, Daw ND, Tank DW, Witten IB: **Specialized coding of sensory, motor and cognitive variables in VTA dopamine neurons**. *Nature* 2019, **570**:509-513

The authors use two-photon calcium imaging to record VTA dopaminergic neuronal activity mice navigate through a virtual T-maze. The authors found that VTA dopamine neurons encode a vast array of variables during the task, including spatial positioning, food-predictive cues, and reward history. This demonstrates the diversity of function in VTA dopamine neurons beyond the value hypothesis of dopamine, consistent with other recent findings.

60. Keiflin R, Pribut HJ, Shah NB, Janak PH: **Ventral tegmental dopamine neurons participate in reward identity predictions**. *Curr Biol* 2019, **29**:93-103.e3.

61. Roth BL: **DREADDs for neuroscientists**. *Neuron* 2016, **89**:683-694.

62. Liu J, Bello NT, Pang ZP: **Presynpatic regulation of leptin in a defined lateral hypothalamus-ventral tegmental area neurocircuitry depends on energy state**. *J Neurosci* 2017, **37**:11854-11866.

63. Cosme CV, Palissery GK, Lerner TN: **A dLight-ful new view of neuromodulation**. *Trends Neurosci* 2018, **41**:566-568.