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Research report

The effect of stress and reward on encoding future fear memories

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ABSTRACT

Prior experience changes the way we learn about our environment. Stress predisposes individuals to developing psychological disorders, just as positive experiences protect from this eventuality (Kirkpatrick & Heller, 2014; Koenigs & Grafman, 2009; Pechtel & Pizzagalli, 2011). Yet current models of how the brain processes information often do not consider a role for prior experience. The considerable literature that examines how stress impacts the brain is an exception to this. This research demonstrates that stress can bias the interpretation of ambiguous events towards being aversive in nature, owed to changes in amygdala physiology (Holmes et al., 2013; Perusini et al., 2016; Rau et al., 2005; Shors et al., 1992). This is thought to be an important model for how people develop anxiety disorders, like post-traumatic stress disorder (PTSD; Rau et al., 2005). However, more recent evidence suggests that experience with reward learning can also change the neural circuits that are involved in learning about fear (Sharpe et al., 2021). Specifically, the lateral hypothalamus, a region typically restricted to modulating feeding and reward behavior, can be recruited to encode fear memories after experience with reward learning. This review discusses the literature on how stress and reward change the way we acquire and encode memories for aversive events, offering a testable model of how these regions may interact to promote either adaptive or maladaptive fear memories.

1. Introduction

Throughout our lifetime we have many unique experiences that change the way we conceptualize our world. This is part of an adaptive strategy designed to promote survival. We need to encode information about the predictors of reward and danger to guide our future behavior. Remembering a particularly tasty taco truck will allow us to find it again in future, just as we need to remember to avoid food trucks that make us feel ill. These experiences do not just allow us to respond in a more efficient manner when encountering these scenarios again, they can also change the way our brains encode similar experiences in the future [11,19,44,98,104,110]. For example, having adverse experiences in early in life can increase the likelihood of developing an anxiety disorder, owed to a bias toward interpreting ambiguous events that occur in the future in a threatening manner ([49,61,62,67,87] – for review). Similarly, positive relationships help promote adaptive behaviors that allow individuals to cope well with ambiguous circumstance in the future [17]. Despite this, variability in demographics of research study participants- which relate to their prior experiences- is considered a confound in human research. In conducting experiments with human participants, we try to sample from homogenous groups and carefully control for varying factors when interpreting and analyzing data.

Indeed, one of the advantages of working with rodent models in research is the opportunity to use experimentally-naïve subjects. This provides the benefit of carefully controlled experiments by removing the variability in prior experience that complicates human research. However, a realistic model for how our brains process information requires an understanding of how these prior experiences influence learning. The few lines of research that have manipulated experience as an experimental variable in rodent studies have found dramatic effects on the way the brain processes information in the future [24,26,66,69,98,110,123]. This research has generally focused on how stressful events alter fear processing in the future and is consistent with the findings in humans literature that trauma predisposes individuals to developing psychological disorders [32,44,87,122]. For example, rodents exposed to an extremely stressful event will learn about a future aversive event so mild it would not support learning under normal conditions [98,99,115,116]. This is accompanied by significant changes in the neural circuits surrounding the amygdala, which houses fearful memories [88,89,95,107]. Consequently, it is generally thought that adverse experiences produce

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changes in fear circuitry that "primes" future processing of aversive events.

The finding that traumatic experiences can prime the processing of aversive events in future may be evidence of a more general model for how experience changes the way neural circuits encode learning. If this is the case, positive experiences should change the way we encode information too. Indeed, we have recently demonstrated that prior experience with reward learning recruits the lateral hypothalamus, which is restricted to encoding memories of rewarding events in experimentally-naïve rats, to learn about fearful events in the future [110]. These data suggest two things: 1) the phenomenon of priming neural circuits to learn in the future is not restricted to experience with stressful events, and 2) once a particular neural circuit (e.g. a reward circuit) is primed by a specific experience, it may contribute to learning about information that is outside their traditional specialization (e.g. fear learning). These data are important because rodent studies are usually conducted with experimentally-naïve rats, and as a result we may have drawn overly specific boundaries as to which neural circuits encode which types of memories. These data suggest we may need to reopen these neural boundaries.

The finding that prior experience can influence how and where fear memories are encoded also has implications for psychiatric disorders in humans. Could the balance of fearful and rewarding experiences in an individual's past influence how and where fearful events in the future are encoded, making them more or less likely to develop a disorder that is driven by aberrant fear processing? Here, we will review the literature that has examined a role for prior experience in changing how we encode memories for aversive events. We will focus on the basolateral amygdala (BLA) and lateral hypothalamus (LH) in the context of Pavlovian fear conditioning using rodents, where much of the research examining the impact of prior experience on fear conditioning lies [98,99]. In doing so, we hope to encourage new directions of research that employ prior experience as an experimental variable and provide some potential mechanisms that could account for the findings within this literature.

2. Studying fear memories in the lab

Studying the neural circuits involved in fear conditioning is of particular interest to the field of behavioral neuroscience because it thought to provide a window into the way we learn and store memories of aversive events [124]. Given that aberrant processing of stimuli associated with fearful events is thought to underlie anxiety disorders, it is hoped that if we can understand how we encode such memories, we can understand what goes wrong when this process goes awry [19,28,44,62,67]. Indeed, anxiety disorders are typically characterized by an excessive fear response that impedes day to day life. Further, the prevalence of these disorders is increasing, suggesting an urgent need to understand the cause for these maladaptive fear responses [7,62].

In the lab, we typically model fear learning using Pavlovian conditioning. This is a process where a stimulus, like a light or tone, is paired with delivery of a mildly aversive event, like a brief, mild shock to a rat's foot or human's hand [28,38,102,103]. Following conditioning, participants will acquire a memory of this association. This in indexed by demonstration of a robust fearful response to the shock-predictive stimuli. This fearful response persists when the stimulus is presented in absence of the shock itself, long after the initial encounter of the stimulus-shock pairing [41]. This phenomenon is generally thought to parallel the process in our everyday lives, where we learn to fear stimuli that might lead to an aversive event in the future. For example, if you lived near a particularly aggressive dog as a child that was known to attack other dogs, or even required restraint around children, you might become conditioned to dislike or fear dogs for the rest of your life.

3. The basolateral amygdala (BLA)

The neural circuits involved in fear learning and anxious behaviors are complex and include many different neuronal populations and brain regions, which often interact in complex ways. However, for the purposes of this review, we will focus on the BLA, which is at the heart of nearly all models of Pavlovian fear learning. The BLA is thought to be the neural hub of Pavlovian fear associations as it is necessary for both the acquisition and storage of associations between stimuli and aversive outcomes ([27,35–37,68,70,72,75,77,79,80,84,86,92,106,118,120] - for review). In fact, one of the most robust reports in the behavioral neuroscience literature is that lesions or inactivation of the BLA will significantly attenuate Pavlovian fear conditioning in rodents [13,27,59,68,77,79,92]. Early works established the importance of the amygdala for learning about, and responding towards, aversive stimuli by demonstrating that amygdala lesions attenuate the physiological response (heart rate changes) to stressors as well as cues that predict those stressors [13,47,59]. These motivated further investigation into the role of the amygdala in fear processing, which established that pre-training electrolytic amygdala lesions in rodents resulted in little or no behavioral responding to a shock-paired stimulus [92]. Since then, this has also been demonstrated with excitotoxic BLA lesions, which offer more specificity than electrolytic lesions and result in a similar decrease in freezing response [27,68,77]. Importantly, this result is achieved regardless of whether the BLA is lesioned before or after the initial stimulus-shock pairing (i.e., an effect on acquisition or memory expression) and in response to auditory, visual, olfactory or even contextual cues [27,68,77]. Quite remarkably, deficits in freezing to a shock-paired stimulus resulting from lesions of the BLA can be found if the lesion or inactivation occurs up to 16 months after the initial stimulus-shock pairings [41,77]. Work with pharmacological or optical inhibition has confirmed the causal relationship between BLA activity and fear conditioning [45,84,118]. Pre-training infusions of muscimol, a GABA agonist, decreased fear responding to a shock-paired stimulus and associated contextual cues during subsequent testing, while pre-testing infusions of ammonium hydroxide also attenuated expression of fear to a shock-paired stimulus [45,84]. Further, optogenetic inhibition of BLA glutamatergic terminals in the entorhinal cortex during either acquisition or expression of contextual fear learning resulted in a decrease in freezing [118]. Together, these studies provide strong evidence for the fundamental role of the BLA as a likely site for acquisition and storage of aversive associative memories.

Importantly, the conclusion drawn from work with rodent models is supported by experiments with humans [18,22,39,64,65,71]. Brain activity in human subjects cannot be manipulated with the level of specificity used in rodents or primates. Instead, neural activity is often measured using functional magnetic resonance imaging (fMRI), which is generally considered a proxy for neural activity [23]. In addition, patients with bilateral amygdala damage can be tested on Pavlovian conditioning to investigate the impact of such damage on the acquisition and expression of fear-related memories [64]. Data collected using these approaches makes it clear that bilateral amygdala damage attenuates acquisition of conditioned fear responses in humans, without impacting the memory that participants have for the learning procedure itself ([64,133]). In addition, there are now many studies that have shown that the extent of conditioned fear developed to a stimulus paired with an aversive outcome, like an air puff or shock in the laboratory, correlates tightly with neural activity measured in the amygdala during the learning episode [22,39,71]. That is, the greater the activity seen in the amygdala during learning, as measured by fMRI, the greater the conditioned fear response in the subsequent test session. Additionally, fMRI scans of participants who have previous undergone fear conditioning with stimulus-shock pairings found a phasic increase in amygdala activity during the onset of the stimulus even when it no longer predicted a shock (i.e., extinction), possibly as a result of the amygdala's importance for updating the recently altered contingencies [65]. These

studies corroborate evidence from rodent research, suggesting that the amygdala is critical for the encoding of memories of aversive events in humans as well.

Prior experience with a stressful event appears to prime the amygdala to learn about stimuli that predict aversive outcomes in rats, which parallels the increased incidence of anxiety-based disorders after traumatic experiences in humans [87,98,99]. When rats are exposed to these stressful events, it results in exaggerated fear responses that are dependent on physiological changes in the amygdala [98,99]. Normally, a fear response is directly proportional to the intensity of the aversive stimulus, such as the number and duration of shocks [34]. However, when rodents are exposed to a significant stressor (4 or 15 shocks) they demonstrate a persistent and exaggerated freezing response to mildly aversive stimuli in the future [98,99]. Specifically, they will show fearful behavior after a single pairing of a stimulus and a shock, even when the shock is so mild that control animals do not learn about it [96]. This effect is known as stress enhanced fear learning (SEFL; [134]). This effect is robust; SEFL survives a change in context from the original stressor to the future aversive events, and is not restricted to stressors of the same modality. For example, prior experience with low intensity tail shocks or restraint stress can both facilitate learning about a stimulus that predicts a shock to the eyelid [115,116]. This demonstrates that prior experience with highly stressful events enhances future learning about aversive events.

Exposure to stressful events is correlated with physiological changes in the amygdala, in addition to wider circuits that influence amygdala activity, like prefrontal cortex [15,54,83,88,89,95,107,121]. For example, in-vivo electrophysiological recordings in rats that experienced chronic restraint stress revealed hyperexcitability in lateral amygdala pyramidal neurons [107]. Chronic restraint stress is also associated with changes in long-term potentiation and NMDA receptor expression in the lateral amygdala, linking stress exposure to increased plasticity and future fear learning [121]. Further, if rats receive a corticosterone blocker prior to a stressor, enhancement in learning about future aversive events is reduced [89]. This is correlated with decreased expression of excitatory (Glu1A AMPA) receptors in the BLA, which are implicated in fear learning [127]. This suggests that the impact of stress on future fear learning relies on corticosterone-dependent changes to receptors in the BLA that are important for acquisition of conditioned fear. Finally, Ponomarev et al. [95] identified clusters of genes from amygdala RNA that were over-represented in neurons or astrocytes (indicating importance for the structure or function of these cells) and assessed how expression of these genes changed after rats were exposed to stress. Expression of the genes enriched in neurons negatively correlated with future fear learning, while expression of genes enriched in astrocytes positively correlated with future fear learning. This suggests there is a coordinated response to stress in the transcriptome, which may underlie the changes in function seen at a cellular and behavioral level. Thus, the stress-induced behavioral changes modeled with procedures like SEFL are accompanied by electrophysiological, cellular and genetic changes in the amygdala of rodents [89,95,107]. Together, these help us to understand the mechanism by which prior stressful experiences change neural circuits and enhance the likelihood of pathological learning in the future.

The finding that changes in the amygdala can sensitize rodents to future fear learning bears resemblance to the human condition. Individuals that suffer from PTSD display overactive amygdala function, exaggerated fear responses, and difficulty regulating emotion and behavior [19,62,67]. Relative to healthy individuals, people with PTSD show enhanced amygdala activity during recall of personal trauma events [114], fear conditioning in the laboratory [16], and presentation of fearful faces or trauma-related words [4,29,97,100]. Indeed, patients with PTSD– ranging from combat-exposed veterans to adult survivors of childhood abuse – present with altered amygdala function [16,46]. Importantly, increases in amygdala activity are correlated with symptom severity as diagnosed with a comprehensive clinician-administered PTSD symptom scale (including invasive thoughts, exaggerated startle, and paranoia) in patients recalling memories of traumatic events, undergoing fear conditioning, or being presented with fearful faces [4,12,114]. These studies provide convincing evidence that traumatic events alter the amygdala and these stress-induced changes correlate with the exacerbation of PTSD.

4. The lateral hypothalamus (LH)

The lateral hypothalamus is a brain region typically thought of as a critical mediator of motivation, reward processing, and feeding [6,48,78,85,119]. Much of the evidence for its role in motivation and reward comes from studies demonstrating that rodents are willing to work to receive LH stimulation [6,48,78]. Rats with electrodes implanted in LH will press a lever to receive stimulation, an effect that increases when the rats are food deprived [78]. This rewarding effect is specific to the lateral region of the hypothalamus and does not occur when the medial hypothalamus is stimulated [48]. More recent evidence shows that intracranial self-stimulation is also supported by optogenetic stimulation of the GABAergic neuronal population in LH [6,85], which suggests GABA neurons contribute to the rewarding effects of LH stimulation. Indeed, optogenetic stimulation of the glutamatergic neurons in LH does not support self-stimulation, and instead produces behavioral aversion [85]. Thus, the LH appears to be involved in reward processing, which is likely mediated in part by the function of GABAergic neurons in this region.

The research showing that stimulation of LH can support intracranial self-stimulation was paralleled by investigation into its role in regulating feeding [3,6,48,78,105,132,136]. Early work demonstrated that rats with bilateral lesions to LH cease to feed entirely until they starve [3]. Further, the same electrical stimulation of LH that rats will press a lever to receive, will also induce voracious feeding behavior if food is available [25,78]. This consummatory behavior occurs even in the absence of food deprivation and continues only for the duration of the stimulation [78]. Jennings et al. [55] also demonstrated that specific optogenetic or chemogenetic activation of LH GABAergic neurons in mice leads to increased consummatory behaviors. Here, rats demonstrated time-locked increases in food consumption and time spent in the food-associated context when LH GABA neurons were activated. Additionally, optogenetic inhibition of LH GABA neurons has the opposite effect on these behaviors, suggesting they can bidirectionally modulate consummatory and appetitive behaviors [55]. Similarly to the effects of LH in supporting intracranial self-stimuluation, the effect of LH stimulation on feedin is specific to manipulation of the GABAergic population in LH – optogenetic stimulation of LH glutamatergic neurons does not produce increases in feeding, nor does electrical stimulation of the medial hypothalamus [48,78,85,105,132]. Interestingly, stimulation of LH GABA neurons also increase appetitive behaviors and interactions with a social stimulus or novel object [85]. Combined with the data showing rodents will work for LH stimulation, this firmly places LH as a critical node in driving motivated behavior to seek food and other rewards.

Despite the wealth of data on the role of LH stimulation-induced food consumption, there has been relatively less work examining the specific role of this nucleus supporting appetitive or aversive associative learning. That is, LH is typically thought to mediate processing of reward or producing a tendency to approach reward, but it is not generally conceptualized as a region that facilitates the development of learned associations [3,6,48,78,85,105]; Stanley et al., 1993; [119,132]. There are, however, a few earlier studies that indicated it could also be involved in learning about reward-directed behaviors [25,82]. For example, Mendelson and Chorover [82] found that electrical stimulation of the LH facilitated learning that one end of a T-maze task was food-baited and the other was not. Similarly, continuous electrical stimulation of LH helped rats to learn which of two available levers predicted food [25]. Perhaps the best evidence from the early literature

is that electrical stimulation of LH will not enhance feeding unless the food has been experienced before [132]. That is, given an entirely novel food, stimulation of LH will not impact food consumption. However, once the rat experiences a specific food, LH stimulation promotes its consumption. Despite this older work suggesting that the LH might be involved in the more cognitive aspects of eating, a potential role for the LH in learning has not received the attention it deserves.

Part of the reason for the relative lack of focus on LH in learning, over and above a role in processing reward or reward approach, is because it is inherently difficult to manipulate LH function in ways that can impact learning about food while leaving food consumption itself intact. Indeed, while there were suggestions that the function of LH in reward processing could reflect learning [10,90,91], it was not possible to dissociate a role for learning over and above the consumption or approach response. There are two studies that have been an exception to this. Firstly, Keefer et al. [60] used an elegant design to implicate orexin/hypocretin within the LH in Pavlovian conditioning with food rewards. Specifically, they trained rats to associate a stimulus with food. During this learning, the rats received a systemic injection containing either an orexin antagonist or vehicle. Rats that received the orexin antagonist demonstrated decreased food seeking behavior and increased latency to approach the food cup relative to vehicle rats. Importantly, the differences between the groups only became evident during the second session of training. That is, the rats' food consumption and behavior directed towards the food port was normal during the initial session, suggesting that this is a learning deficit rather than a non-specific behavioral change. A second study was conducted by Sharpe et al. [112], and used the temporal specificity of optogenetics to inhibit neuronal firing in LH GABAergic neurons during only the conditioned stimulus (and not food presentation) as rats were learning an association between the and food. Here, optogenetic inhibition of LH GABAergic neurons significantly reduced rats' food-port approach during the stimulus, indicating an inability to use the stimulus to predict food delivery. Importantly, all rats consumed the food from the port shortly after termination of the food-predictive stimulus, demonstrating that all rats experienced the food and stimulus in close succession. Further, this reduction in responding to the food-predictive cue was maintained in an unrewarded test without inhibition of LH GABAergic neuronal function, which implicates this neuronal population as involved in memory of the stimulus-food association and not temporary changes in motivation or attention. Sharpe et al. [112] also trained rats on a stimulus-food association (without any inhibition of LH) and then inhibited LH GABAergic neurons during presentation of the stimulus alone. Again, this resulted in a reduction in food port approach during the food-predictive stimulus. This indicates that LH GABAergic neurons are also important for the expression of learnt food associations. Together, this establishes that LH, and GABAergic and orexin-releasing neurons in particular, as important in both the learning and expression of memories about food-predictive cues.

Given the role of the LH in learning about predictors of reward, it becomes of interest to investigate whether the LH could also be involved in learning about the predictors of aversive events. To test this, Sharpe et al. [110] presented rats with stimulus-shock pairings, and examined the effect of inhibiting LH GABAergic neurons during the stimulus and not the shock (mimicking parameters used in their reward procedures with LH manipulation; [112]). In experimentally-naïve rats, LH GABAergic neurons were not necessary for associating the stimulus and shock. That is, all rats learned about the shock-predictive stimulus, regardless of whether LH GABAergic neurons were optogenetically inhibited or not. However, in rats that had previously experienced reward learning, LH GABAergic neurons suddenly became important for learning about the shock-predictive stimulus. This was characterized by an almost complete block of learning about the shock-predictive stimulus, indexed by a lack of freezing to the stimulus during learning. These same rats also subsequently showed attenuated freezing to the shock-predictive stimulus in an extinction test when LH GABAergic neurons were no longer inhibited, confirming an effect on memory formation. Importantly, a number of control experiments verified that this was not due to generalization between the appetitive and aversive memories, extra handling, food restriction, or context exposure that was experienced during reward learning. These data suggest that reward learning primes the LH, and specifically GABAergic neurons, to encode memories of aversive events. This bears similarity to how stressful events prime the amygdala to learn about aversive events in the future, and expands this phenomenon in two important ways. First, experience with rewards can also prime neural circuits for future learning and this effect is not restricted to stressful events. Second, if a neuronal population is primed by a particular experience (e.g. reward learning), it can be recruited to encode information it would not usually encode (e.g. fear learning). Together, these results demonstrate that prior experience shapes the neural circuits that are involved in future learning and calls into question the strict neural boundaries we have drawn as to what regions contribute to particular learning phenomena.

The involvement of LH in appetitive and aversive learning procedures raises the question of whether it supports associative learning about sensory stimuli in the absence of food or shock. To investigate this, Sharpe et al. [110] trained rats on second-order conditioning. Rats first learned to associate a stimulus and food reward (e.g., B→ food). Next, rats learned to associate a second stimulus with the original reward-predictive stimulus (i.e., A→B). Following training, A will usually motivate appetitive behavior due to its pairing with food-predictive B (i.e., the second-order conditioning effect). Surprisingly, inhibition of LH GABAergic neurons during the A→B pairings led to an *increase* in appetitive responding to A, relative to control animals. That is, the A→B association was facilitated by inhibition of LH GABAergic neurons. This indicates that LH GABAergic neurons oppose learning about relationships between stimuli that are not paired with a motivationally significant outcome. As a result, inhibiting LH GABAergic neurons removed the inhibitory influence and ultimately enhanced learning. To confirm that this effect was not contingent on the prior experience with reward that occurs in second-order conditioning, new rats received inhibition of LH GABAergic neurons during sensory preconditioning. Here, rats are trained that A leads to B, prior to either stimulus being paired with food (i.e., A→B). Then, B is paired with food. Sensory preconditioning is indicated when rats are presented with A show that they anticipate the arrival of food via the inference that A is likely to lead to food because it's associate B is food predictive (A→B→food). Sharpe et al. [110] found that inhibition of LH GABAergic neurons will still enhance the A→ B association under these conditions. Thus, the enhanced relationships between sensory stimuli seen after inhibition of LH GABAergic neurons establish a role for the LH in opposing learning about stimuli that are not motivationally significant. Taken together, these data demonstrate that LH bias learning towards stimuli that predict motivationally-relevant outcomes (like food or pain), and away from information that does not predict anything that is currently relevant to the animal.

5. The BLA and LH: mediating a balance in encoding of adaptive fear memories?

Traditionally, a line is drawn between the BLA fear circuit on the one hand, and the LH reward circuit on the other. However, the discovery that LH can be recruited to learn about aversive events under particular circumstances challenges this conception. Further, we have known for a long time that the BLA is also involved in the encoding of appetitive memories and has a well-established role in motivation and reward learning [33,14,20,40,109,125,135] for review, see: [5,51,128]. As such, this work forces a more fluid model of how information is encoded within the brain. It is interesting to think about how prior experience influences involvement of these respective circuits in learning about aversive events. How might the BLA and LH form an integrative fear circuit? And what consequences could this have for the future processing of aversive events? That is, could a shift in the balance of where the fear

memory is encoded reduce the likelihood of developing pathological fear in the future?

Prior work examining the role for BLA and LH in appetitive behaviors could provide some useful information as to how these regions might interact during fear conditioning. Such research has demonstrated that the BLA projects both direct and indirectly (through the nucleus accumbens) to LH [63,90,91,101]. There is strong evidence the projections from BLA to LH are active during appetitive learning tasks [90,91]. For example, the BLA-LH circuit has been implicated in the cue-potentiated feeding phenomenon, which is characterized by increased in feeding behavior in sated rats when a food-predictive stimulus is presented. Specifically, when the connections between BLA and LH are severed with a neurotoxic lesion, this cue-potentiated feeding effect is abolished [91]. Further, activity in BLA to LH projections increases to a food-paired stimulus [90]. That is, expression of mRNA markers (Arc and H1A) that appear following neuronal activation increase in BLA→LH circuitry following presentations of the food-predictive stimulus. This indicates that projections from the BLA transmit information relevant to stimulus-food relationships to LH, which allow these food-predictive stimuli to regulate learned appetitive behavior.

Research illustrating the excitatory role the BLA plays in relaying information to LH during appetitive learning suggests that a similar mechanism could be engaged during aversive learning after subjects have had experience with reward learning. However, it is unlikely that BLA is acting to simply increase LH-dependent behavior. This is because we now know that the LH is itself important for *learning* associations between stimuli and food or shock. That is, optogenetic inactivation of LH GABAergic neurons during presentation of a stimulus *prior* to immediate delivery of food or shock reduces responding to the predictive stimulus, and this reduction in responding is maintained in a test session when LH GABAergic neurons are no longer inhibited [110,112]. This demonstrates that LH inactivation reduces *acquisition* of these associative memories, rather than just generally reducing appetitive responding. Further, optogenetic inhibition of LH GABAergic neurons while rats are associating two sensory stimuli produces the opposite effect.

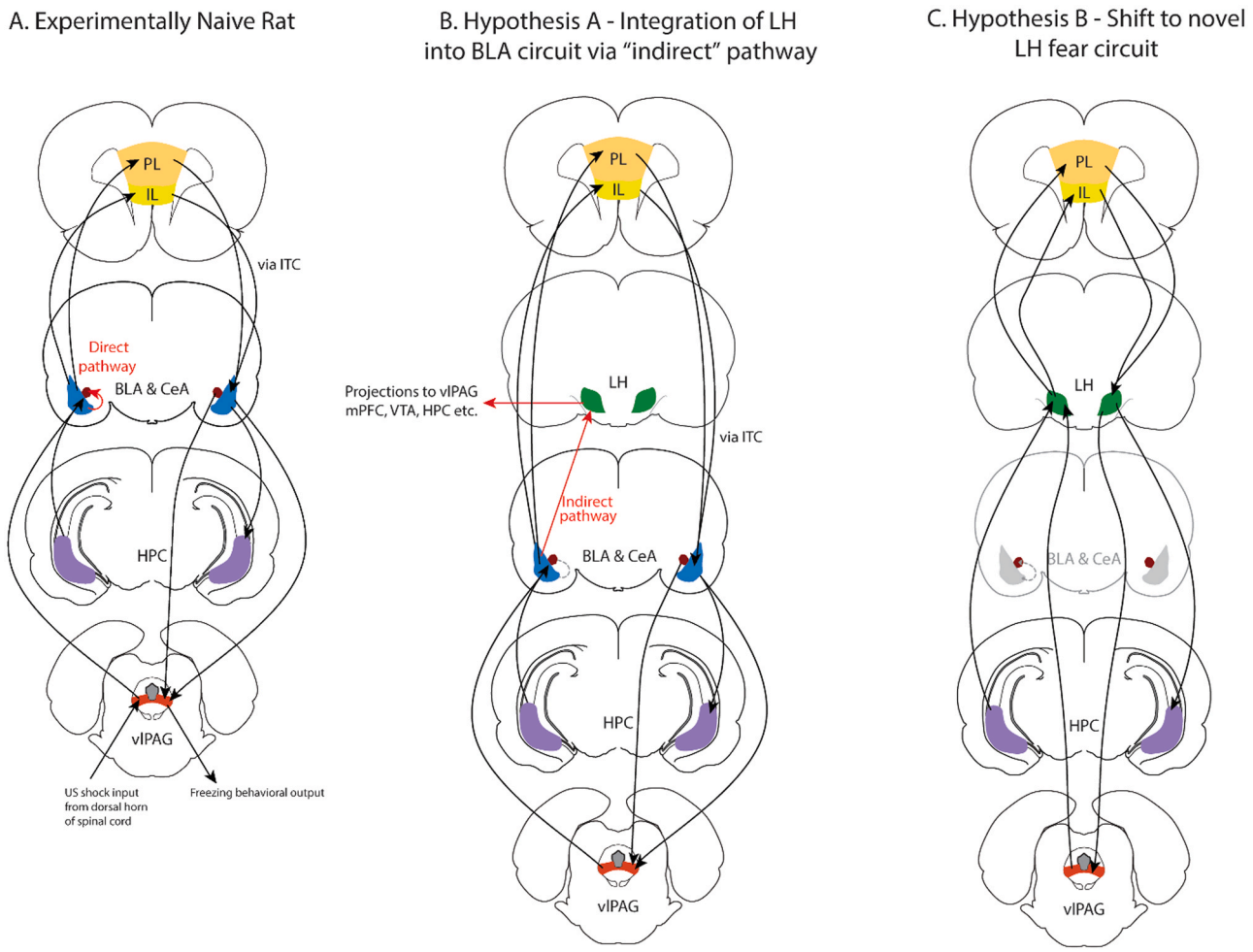

Fig. 1. Possible ways that the lateral hypothalamus might be integrated into the Pavlovian fear circuit after experience with reward learning. The fear circuit is complex, where many different neural regions, populations, and projections contribute to the encoding of fear memories [2,30,42,52,74,76,81,108,111,113,117,126,131]. A) The amygdala is generally conceptualized as the center of these models, implicated in the acquisition and storage of the fear memory. In experimentally-naïve subjects, the ventrolateral periaqueductal grey (vlPAG) sends the aversive prediction error to facilitate the linking together of information that forms the fear memories [57,81]. The prelimbic (PL) and infralimbic (IL) cortices have reciprocal projections with BLA, where these connections are thought to facilitate the development of the context specificity of fear memories following extinction, contributed to also by the hippocampus (HPC[76,81,93]). B) After reward learning, it is possible that the lateral hypothalamus (LH) becomes integrated into the traditional amygdala fear circuit, where LH would receive information from BLA about upcoming predictions, which may help LH to bias learning and ongoing behavior towards or away from fear-related stimuli, depending on current circumstance. C) It is also possible that the recruitment of LH for the encoding of the fear memory constitutes a shift away from the amygdala circuit and towards a novel LH fear circuit. Given the LH has many comparable connections with the neural regions critical to Pavlovian fear learning in the amygdala fear circuit, there is physiologically plausibility to the existence of such a circuit [8,43,50,56,101,129].

Specifically, optogenetic inhibition of LH GABAergic neurons enhances stimulus-stimulus associations. This suggests LH biases learning towards motivationally significant events, and actively opposes those that are irrelevant to current biological needs. This does not happen in the BLA. While inhibition of BLA neurons attenuates learning about motivationally-significant information [31,49], inhibition of BLA has no effect on learning associations between sensory stimuli if both stimuli are neutral at the time of learning [27,49,128]. This work suggests that BLA likely relays information to influence learning occurring in LH, but that the LH appears to be adding something unique to this process, which allows LH to arbitrate between different types of learning.

There are many ways that the BLA and LH may interact to influence learning (Fig. 1). For example, the LH might become integrated into the existing fear circuit comprising amygdala (Fig. 1B), or a novel LH fear circuit could "take over" fear learning, reducing the role of BLA (Fig. 1C). We would advocate for a model that envisions prior experience with reward learning extending the fear circuit surrounding the BLA to include an "indirect" pathway that implicates the projections from BLA to LH (Fig. 1B; [63,90,91,101]). Specifically, we would argue that after reward learning, this indirect pathway becomes primed to receive and evaluate information from BLA about shock-predictive cues. For example, when a shock-predictive cue is presented, LH receives information from the BLA about the upcoming predicted shock, and arbitrates between whether it should devote more learning or responding towards the shock-predictive stimulus, at the expense of pursuing or learning about other goals (e.g. foraging for food). That is, the LH could become integrated into the fear circuit in a manner that allows it to establish a balance between learning about shock-predictive stimuli, relative to learning about other stimuli, in light of which stimuli are most relevant to individual's current motivational goals. To this end, we might envision recruitment of this indirect pathway with LH as protective against pathological fear, which evaluates whether to learn or respond to fearful cues on the basis of other priorities that may be apparent in the environment.

Further research is needed to determine the specifics of the relationship with BLA and LH and how these regions may work together to achieve a balance of encoding information about aversive and appetitive stimuli. Currently, our best evidence for how stressful experiences might translate into physiological changes that alter learning circuits comes from physiological investigation of BLA [88,89,95,107]. Moving forward, it is essential to determine how rewarding and stressful experiences might differentially affect these properties in both LH and BLA. For example, in an environment where danger is pervasive, such as active combat, it is reasonable to expect that the neural circuits would adapt to prioritizing learning about fear cues. This might be biologically characterized by an upregulation of the "direct" BLA fear circuit, where involvement of LH is limited (Fig. 1A). In this case, the associative information received in the BLA would activate projections to the central nucleus (CeA), which communicate with other hypothalamic areas and the brainstem to trigger the behavioral fear response [76,94]. In contrast, an individual that has had many positive experiences in life may be more likely to recruit the indirect BLA-LH circuit to encode future aversive memories, where GABAergic neurons in LH would ensure that learning and behavioral resources are only devoted towards cues that warrant those resources in the current circumstances. Here, BLA projections to LH become involved in encoding memories of aversive events and LH projections could influence the degree to which BLA promotes pathological fear [101,130]. This would create a distinction where healthy individuals utilize the indirect circuit to prioritize learning about aversive events when it is motivationally necessary to focus on fear, but do not develop tendencies towards fear learning in situations where it is not adaptive. Future work is needed to test these speculative hypotheses and might also explore the wider nature of this potential indirect fear circuit, to investigate how it could influence fear learning and responding.

In summary, nearly all neurobiological research with experimental rodents comes from subjects that only have experience with either fear learning or reward learning. However, as we have discussed in this review, prior aversive or appetitive experience can profoundly change the way BLA and LH are recruited to encode fear memories in the future [107,110,112,122,123,24,26,32,44,66,69,87–89,95,98]. Given humans have many and varied experiences across their lifespan, it becomes imperative that we investigate how fear memories are encoded after varied experiences. While there is a large literature that has investigated how stress primes the amygdala to learn about aversive events in future, the research discussed here suggests we need to consider how positive experiences could influence encoding of future fearful events. Further, an important and fruitful direction for research would be to understand how the wider circuits involved in fear learning might be changed with prior experience, and how the LH is recruited into this wider circuit. For example, recent work has shown that the prefrontal cortex regulates sensitivity to punishment in the context of reward learning, and this regulation changes with stressful experience [53]. It could be that the recruitment of LH to learn about fear is influenced by mechanisms that drive a shift in the fear circuit. Finally, it may be the case that positive experiences protect against pathological fear, just as stressful experiences predispose individuals to developing pathological fear. This is good news. If we can establish the protective nature of reward learning and recruitment of the LH in encoding of fear memories, we could try to recruit these circuits in humans that are at risk of experiencing trauma, to reduce the likelihood of developing pathological fear.

Competing Interests

MSF is a board member of Neurovation, Inc. The other authors declare no competing interests.

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