

# Amygdala Subsystems and Control of Feeding Behavior by Learned Cues

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**ABSTRACT:** A combination of behavioral studies and a neural systems analysis approach has proven fruitful in defining the role of the amygdala complex and associated circuits in fear conditioning. The evidence presented in this chapter suggests that this approach is also informative in the study of other adaptive functions that involve the amygdala. In this chapter we present a novel model to study learning in an appetitive context. Furthermore, we demonstrate that long-recognized connections between the amygdala and the hypothalamus play a crucial role in allowing learning to modulate feeding behavior. In the first part we describe a behavioral model for motivational learning. In this model a cue that acquires motivational properties through pairings with food delivery when an animal is hungry can override satiety and promote eating in sated rats. Next, we present evidence that a specific amygdala subsystem (basolateral area) is responsible for allowing such learned cues to control eating (override satiety and promote eating in sated rats). We also show that basolateral amygdala mediates these actions via connectivity with the lateral hypothalamus. Lastly, we present evidence that the amygdalohypothalamic system is specific for the control of eating by learned motivational cues, as it does not mediate another function that depends on intact basolateral amygdala, namely, the ability of a conditioned cue to support new learning based on its acquired value. Knowledge about neural systems through which food-associated cues specifically control feeding behavior provides a defined model for the study of learning. In addition, this model may be informative for understanding mechanisms of maladaptive aspects of learned control of eating that contribute to eating disorders and more moderate forms of overeating.

**KEYWORDS:** amygdala; hypothalamus; eating; feeding behavior; learning; goal-directed behavior; motivation

## INTRODUCTION

Amygdalar connectivity with the hypothalamus was first observed in normal material almost a century ago. Early on, this relation with the hypothalamus was a dominant theme in research on the amygdala complex. Referring to the functional anatomy of amygdalohypothalamic circuits, Kaada<sup>1</sup> surmised that “the amygdala

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adds plasticity to the basic inborn and more fixed reflex mechanisms.” Since then, the classic work of Krettek and Price in the 1970s, together with more recent analysis using the PHAL tract tracing technique, has provided detailed knowledge about the exact origin of different amygdalohypothalamic projections with respect to distinct amygdalar subsystems and specific target sites within the hypothalamus.<sup>2,3</sup> We now recognize that amygdalar nuclei provide a complex network of topographically organized direct and indirect projections to hypothalamic circuits. These regions of hypothalamus are implicated in a range of species typical functions involving defensive, ingestive, and reproductive behaviors. The fact that regions of the amygdala that figure in associative learning—the basolateral area/complex (BLA) and central nucleus (CEA)—are prominent components of amygdalohypothalamic circuits would allow for the adaptive influence of experience to gain control over these adaptive behavioral systems, as proposed by Kaada.

Despite the extensive base of knowledge on the anatomical organization of the BLA and CEA connections with the hypothalamus, little research has been conducted to functionally define these systems. Indeed, much more research has been focused on the functional neuroanatomy of CEA connectivity with brain stem<sup>4-7</sup> and BLA connectivity with ventral striatum and other areas of the forebrain.<sup>8,9</sup>

The current chapter focuses on the anatomical and functional relation between components of the amygdala complex that are involved in learning (i.e., BLA and CEA) and their connections with the hypothalamus in the domain of feeding behavior. It is well established that energy balance is not the sole factor determining food consumption.<sup>10-12</sup> The ability of “extrinsic” signals, including learned cues, to modify appetite and food intake has been subjected to rather extensive analysis of the neural systems and mechanisms involved. Notably, most attention in these investigations has focused on acquired aversions, in which food associated with malaise or illness is subsequently avoided.<sup>13,14</sup> Some other well-characterized effects of experience on the regulation of appetite and food consumption that occur in a variety of species, although less subject to neural analysis, have begun to show involvement of the amygdalar complex.<sup>15-18</sup>

Experience can be multifaceted in its relation to ingestive behavior, ranging from adaptation in an organism’s ingestion of particular food items, such as acquired taste aversions or taste preferences, to adaptations in how organisms use information to guide complex behavioral repertoires, such as foraging strategies. Notably, cues that predict food can acquire hedonic value,<sup>19</sup> an effect of experience that would assist in guiding animals to food sources in a naturalistic setting.

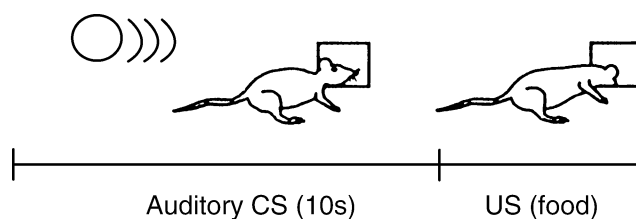
In a laboratory setting, rats normally acquire preference for simple, visual cues that were previously paired with food compared to cues that were not paired with food. Rats with amygdala lesions are impaired in the conditioned cue preference task.<sup>15</sup> Interestingly, this phenomenon may have a direct parallel in humans with amygdala damage. In a recent study, subjects developed a preference for (monochrome abstract) patterns that had been paired most often with food relative to preference ratings of patterns that had been paired less often with the same food items.<sup>16</sup> It is interesting that more favorable judgments made in the preference tests were typically attributed to intrinsic features of the stimulus (e.g., complexity of the pattern), rather than to an awareness of the relation with food reward, suggesting that cues acquired hedonic value as a consequence of implicit learning apart from explicit knowledge of the contingencies in that promoted favorable preference ratings.

Notably, patients with damage to the amygdala failed to develop this conditioned preference.<sup>16</sup>

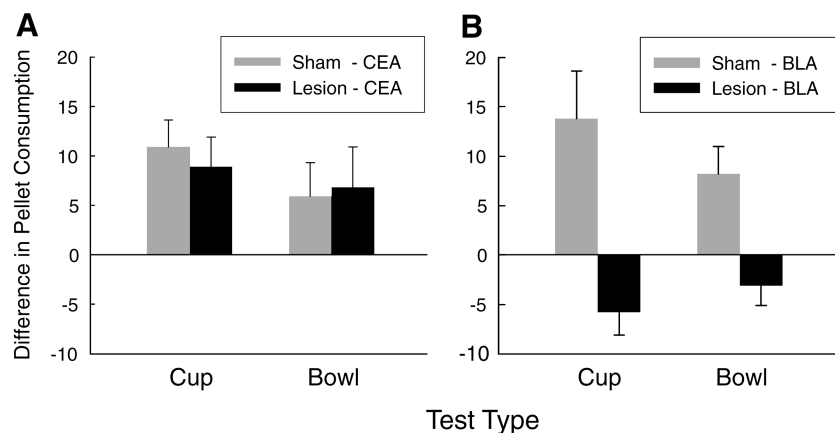
In addition to hedonic properties that may serve to support acquired preferences, cues associated with hunger can also acquire incentive value to guide goal-directed behavior. The sections that follow will deal with a behavioral paradigm for such learned effects on feeding behavior. A description of the behavioral phenomenon of conditioned potentiation of feeding will be followed by sections on the role of amygdala subsystems and neural circuits in this function. That research has revealed a functional role for a specific amygdalohypothalamic system.

### CONDITIONED POTENTIATED FEEDING: A PARADIGM FOR MOTIVATIONAL LEARNING

Conditioned potentiation of feeding is a behavioral paradigm first introduced by Weingarten<sup>20</sup> in 1983 that provides a model to study learning in an appetitive context. In this paradigm, a cue that acquires motivational properties through pairings with food delivery when an animal is hungry can override satiety and promote eating in sated rats. Thus, in an initial phase of the paradigm, a conditioned stimulus (CS) is paired with food delivery at a food cup. Hungry rats learn to approach the food cup during the CS in this conditioning phase (as shown in FIG. 1). In a second test phase, CS-driven food consumption is evident in sated rats, whereas rats consume little food that is made freely available in the test apparatus without CS presentations. This CS-potentiated feeding is based on an associative process rather than on some nonspecific activation by a sensory stimulus, because only the cue paired with food, but not an unpaired cue, increases eating.<sup>17,18</sup> Furthermore, potentiation occurs regardless of whether the food is presented in the same location as that used during pavlovian conditioning (i.e., food cup) or in a different location (FIG. 2), demonstrating that animals do not increase eating simply because of CS-induced conditioned responses (CR), which bring the rats to the food cup.<sup>17</sup> Indeed, in a subsequent section of this presentation, it will become apparent that the brain systems that mediate the two aspects of CS-induced behaviors, approach to the food cup



**FIGURE 1.** Conditioned responses elicited in a simple pavlovian appetitive procedure in which delivery of a food unconditioned stimulus (US) is preceded by a 10-second conditioned stimulus (CS). During the CS, the rats learn to approach the food cup where food is delivered.



**FIGURE 2.** Mean difference between consumption during the test with CS+ and the test with CS- presentations. At each panel, results are shown for tests in which food was placed in the food cup (“Cup”) used in pavlovian conditioning and for tests in which food was placed in a bowl (“Bowl”) on the side of the chamber opposite from the food cup used in training. **(A)** Food pellets consumed by sham rats and rats with CEA lesions during the food consumption tests. **(B)** Food pellets consumed by sham rats and rats with BLA lesions during the food consumption tests. Error bars indicate SEM. (Adapted from Holland *et al.*<sup>17</sup>)

and potentiated food consumption, are also distinct. Thus, CS-induced food consumption in sated rats appears to reflect acquired motivational properties of the CS that are separate from the food cup approach aspects of CS-driven behavior.

The exact psychological process underlying the phenomenon of potentiated eating is not well defined. Acquired motivational properties that promote food consumption could reflect activation of a “hunger-like” state. Alternatively, conditioning could modulate an animals’ acquired food preference. In other words, it is not clear at this time whether greater food consumption in sated rats is related to CS-evoked “wanting” or “liking” of the food in consumption tests.<sup>21</sup> Clearly, future research is needed to address this issue.

### CONDITIONED POTENTIATION OF FEEDING AND AMYGDALA SUBSYSTEMS

Both the BLA and CEA have been shown to be involved in associative functions.<sup>4–8,22–25</sup> The CEA role in associative learning is well established in a variety of aversive learning paradigms, as is the role of its brain-stem efferents in mediating the effects of learning on relevant behavioral systems. However, much less is known about the functional role of its well-known projections to the hypothalamus (but see Ref. 26 for indirect evidence on amygdalohypothalamic involvement in conditioned fear).

The projections from the CEA to the hypothalamus were among the first amygdalar connections observed. The preferential CEA innervation of the LHA,

rather than the medial hypothalamus, has been known for over two decades, even though the exact detailed topography of the terminal field within the LHA with respect to its origin within subdivisions of the CEA was only revealed recently.<sup>3</sup> One region of the LHA (perifornical area) innervated by the medial part of the CEA has been linked to ingestive behavior.<sup>27,28</sup> However, the functional role of this CEA-LHA pathway in feeding has not been examined, although there is indirect evidence for its role in drinking behavior.<sup>28</sup> In addition, the CEA could influence feeding mechanisms via other routes, via direct inputs to the brain stem<sup>29-31</sup> or indirect input to the periventricular hypothalamic nucleus.<sup>32,33</sup> Although anatomical evidence indicates that multiple routes permit CEA access to feeding circuitry, a role of the CEA in regulating feeding behavior by learned cues is less clear. (Evidence for a CEA role in conditioned taste aversion is still controversial.)

The BLA, similar to the CEA, has been implicated in learning and is now known to send a substantial output to the LHA. Although earlier studies characterized direct efferents from the BLA to the LHA as sparse,<sup>2,34</sup> recent analysis provides evidence for a much more substantial projection.<sup>3</sup> In addition, the BLA can reach the LHA by indirect pathways via relays in the ventromedial hypothalamus, the bed nuclei of the stria terminalis, substantia innominata, ventral striatum, prefrontal cortical areas, or hippocampal formation.<sup>2,3,34-36</sup>

Guided by anatomical evidence for CEA and BLA access to feeding circuitry in the hypothalamus, we examined their possible role in the control of food consumption by learned cues in the potentiated feeding paradigm. Separate groups of rats with bilateral excitotoxic lesions of either the BLA or CEA, along with appropriate sham-lesioned controls, were first trained in a pavlovian auditory discrimination task, with one auditory stimulus paired with food delivery (CS+) and another cue that was not paired with food delivery (CS-). All groups acquired comparable conditioned responses to CS+, but not to CS-, when they were trained in a hungry state. After that, training rats were sated and then tested for food consumption in the presence of CS+ or CS- on 2 separate days. Control rats and CEA-lesioned rats ate more food during presentations of the conditioned stimulus previously paired with food (CS+) than during presentations of the unpaired cue (CS-), as shown in FIGURE 2A. The potentiation of feeding by the CS+ was evident both when the food was available in the usual food cup and when it was presented in a bowl on the opposite side of the test chamber (that never previously contained the food). In contrast with the performance of rats in those groups, rats with neurotoxic lesions of the BLA exhibited no evidence of conditioned potentiation of eating, as shown in FIGURE 2B.

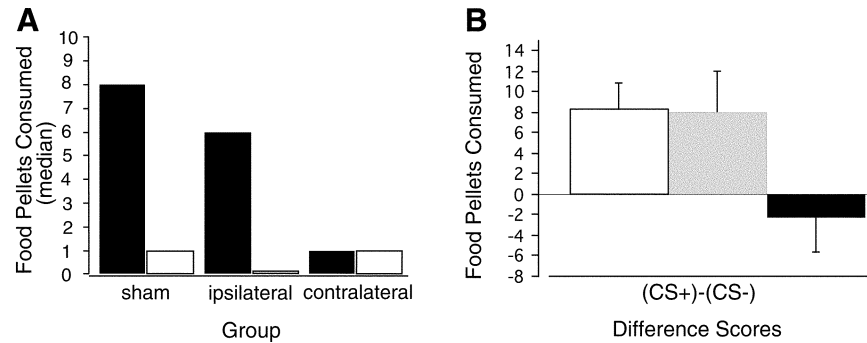
Some features of these results indicate that this paradigm provides a setting that is highly amenable to a neural systems analysis. From a behavioral perspective, the results show that conditioned potentiation of feeding can be abolished without any notable change in unconditioned ingestive behavior or generalized performance disruption in the learning paradigm. Notably, the BLA lesions that abolished CS-induced consumption of food did not interfere with acquisition of food cup CRs driven by the CS during initial conditioning.<sup>17,37-39</sup> Indeed, rats with BLA lesions actually approached the food cup in the consumption tests as readily as did control rats.<sup>17</sup> The BLA lesion also had no effect on baseline eating (as seen in a pre-test interval prior to CS presentation), showing that the effect of BLA lesions was specific to CS+ motivational properties and not a result of simple placement in the context with food. Thus, the BLA lesioned rats were only impaired in acquiring or expressing the

learned motivational properties of the CS manifested through modulation of food consumption.

In addition to the specificity of the behavioral result, the differing effects of BLA and CEA lesions in the paradigm are informative for a neural systems analysis. The fact that conditioned potentiation of feeding critically depends on the BLA but appears to occur independent of the CEA suggests that the prominent projection from BLA to CEA does not appear to be engaged in conditioned potentiation of feeding, in contrast to other forms of associative learning, such as fear conditioning.<sup>7</sup> The absence of any effect of CEA damage also implies that modulation of hypothalamic feeding systems through either direct or indirect pathways from the CEA are not critically involved. The potential regulation of feeding by BLA, independent of CEA, is interesting to consider in light of other information on amygdalohypothalamic circuits. For example, anatomical evidence suggests that the most prominent direct projections from the BLA and CEA reach topographically distinct regions of the LHA. The BLA projection, mainly originating in the posterior basolateral nucleus, most densely innervates a specific ventromedial region at tuberal levels of the LHA, whereas the primary input from the CEA innervates the dorsolateral (in part, corresponds to the “perifornical area”<sup>27</sup>) and caudolateral regions of the LHA. Although those targets of CEA also receive light inputs from the BLA, the ventromedial region innervated heavily by BLA appears to lack CEA innervation.<sup>3</sup> Although a functional understanding of these regions of LHA does not yet exist, it is likely that different parts of the LHA participate in different functions (e.g., ingestive behavior, motivation, and autonomic responses). In addition to a relatively distinct topography in direct projections to the hypothalamus, information from the BLA can reach the LHA by different indirect pathways (see above), whereas the CEA has much more restricted access by indirect routes (via the bed nuclei of the stria terminalis and substantia innominata<sup>40</sup>). Finally, a recent anatomical tracing study with pseudorabies virus showed connections to neuropeptide-Y- and leptin-receptor-expressing components of feeding systems in the hypothalamus originating in the BLA but not in the CEA.<sup>41</sup> Our behavioral results, together with such connective evidence, support the hypothesis that the BLA and CEA have distinct functional roles in the effects of learning on feeding behavior.

#### CONDITIONED POTENTIATED FEEDING AND THE BLA-LHA CIRCUIT

To test whether the BLA's connections with the LHA are necessary for allowing a learned cue to override satiety and promote eating, we examined conditioned potentiation of feeding in rats with a preparation that disconnects the two structures. We placed unilateral, neurotoxic lesions of BLA and LHA on opposite sides of the brain (contralateral group). Because BLA outputs are predominantly ipsilateral, this preparation disconnected the BLA and LHA in both hemispheres without disturbing other functional circuits involving each of these structures. A control group of rats had an equivalent amount of damage with unilateral lesions of BLA and LHA placed on the same side of the brain, sparing the BLA-LHA system in one hemisphere (ipsilateral group). Rats with contralaterally placed sham lesions of BLA and LHA were included to control for any effects due to surgical procedures alone.

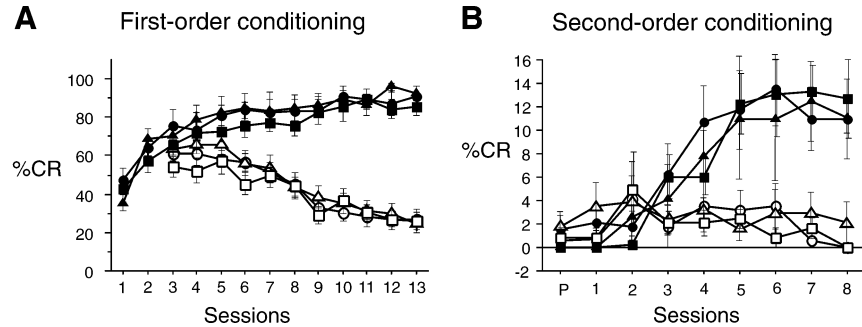


**FIGURE 3.** Food consumption tests. **(A)** Food consumption of sham, ipsilateral, and contralateral rats during the potentiated eating tests. *Black bars* show food consumption during tests with CS+, and *white bars* show consumption during tests with CS-. Amount of food consumed in the two tests differed for sham and ipsilateral groups (Wilcoxon signed rank,  $P = 0.006$  for sham, and  $P = 0.003$  for ipsilateral group), but not for the contralateral group ( $P = 0.3452$ ). **(B)** Mean difference between consumption during the tests with CS+ and during the tests with CS- presentations. Consumption of sham, ipsilateral, and contralateral rats is shown with *white*, *grey*, and *black bars*, respectively. Analysis of difference scores revealed a significant difference among the groups ( $H(2) = 13.968$ ,  $P = 0.0009$ ), and subsequent independent Mann-Whitney U tests showed that the sham and ipsilateral groups each differed significantly from the contralateral group ( $U = 39.0$ ,  $P = 0.004$ ;  $U = 14.5$ ,  $P = 0.0004$ , respectively), while the ipsilateral and contralateral groups did not differ from one another ( $U = 90.0$ ,  $P = 0.9999$ ). The error bars indicate the s.e.m.'s. (Adopted from Petrovich *et al.*<sup>18</sup>).

As with bilateral BLA lesions, the disconnection of the BLA-LHA system did not affect auditory pavlovian discrimination learning (food cup CRs during conditioning). All groups of rats (contralateral, ipsilateral, and sham) acquired discrimination rapidly between one auditory stimulus paired with food delivery (CS+) and another one unpaired with food delivery (CS-) (FIG. 4A). After training, which was conducted in a food-restricted state, rats were allowed food *ad libitum* for 1 week. Consumption tests for potentiated feeding were then performed in the sated condition on 2 consecutive days, when food was available in the test apparatus in the presence of either the CS+ or the CS-. As expected, rats in the sham control group as well as rats in the ipsilateral lesion group ate significantly more food in the presence of CS+ compared to CS-. By contrast, rats with contralateral lesions ate the same small amount of food in both tests (FIG. 3).

The deficit in rats with BLA-LHA disconnection shared other features with prior findings on BLA lesions alone. Thus, we did not find any difference in food consumption among the groups during a pre-testing interval in the absence of either the CS+ or the CS- (baseline condition). Moreover, animals in all groups gained the same amount of body weight when food was available *ad libitum* during the week prior to tests for potentiated feeding.

Our results demonstrated that BLA and LHA are critical components of a system through which learned cues override satiety and increase eating. It is not certain, however, that direct projections from the BLA to the LHA are used for this function.



**FIGURE 4.** (A) First-order conditioning. Acquisition of discrimination between an auditory conditioned stimulus (CS) that predicted food delivery (CS+) and another auditory stimulus that was not paired with food (CS-) during the initial phase of training in rats with contralateral (■), ipsilateral (▲), or sham (●) lesions of the BLA and LHA. Conditioned responses to the CS+ are represented by *filled symbols* and conditioned responses to the CS- are represented by *open symbols*. Conditioned responses (CRs) are expressed as the mean percentage time  $\pm$  SEM expressing food cup behavior. CRs directed to the food cup during the occurrence of CS+ were significantly elevated compared to CRs during CS- for all groups (Wilcoxon signed rank,  $p = 0.0022$  sham;  $p = 0.0077$  ipsilateral;  $p = 0.0033$  contralateral group). No significant effects were evident in a Kruskal-Wallis analysis comparing the CRs to CS+ ( $H(2) = 2.567$ ,  $P = 0.2770$ ) or CRs to CS- ( $H(2) = 0.622$ ,  $P = 0.7328$ ), among groups with different lesion treatments (sham, ipsilateral, or contralateral). (B) Second-order conditioning. Acquisition of second-order CRs (food cup behavior) to the light CS2 during the second phase of training in rats with contralateral (■), ipsilateral (▲), or sham (●) lesions of the BLA and LHA. Rats that received paired CS2-CS+ presentations are represented by *filled symbols*, and rats that received unpaired presentations of CS2 and CS+ are represented by *open symbols*. Session P refers to the pretest of the light at the beginning of training. The difference in conditioned responses to the light between groups given paired, compared to groups given unpaired, presentations of CS2 and CS+ was statistically significant (sham,  $U = 3.500$ ,  $P = 0.0046$ ; ipsilateral,  $U = 2.500$ ,  $P = 0.0298$ ; and contralateral,  $U = 0.500$ ,  $P = 0.0043$ ). The lesion treatments (sham, ipsilateral, or contralateral) did not produce a significant difference in conditioned responses in either the paired ( $H(2) = 0.088$ ,  $P = 0.9570$ ) or unpaired ( $H(2) = 1.029$ ,  $P = 0.5979$ ) conditions. Error bars indicate SEM. (Adapted from Petrovich *et al.*<sup>18</sup>)

Indeed, the BLA could influence the LHA via a number of indirect pathways (see above). A major projection from the BLA to the nucleus accumbens (ACB) is of particular interest in the context of feeding. Specifically, an area of the ACB that innervates the LHA<sup>42</sup> and has been implicated in feeding behavior<sup>43</sup> receives BLA input. In addition, the BLA-ACB system is perhaps more generally important for functions that depend on the value of cues acquired in associative learning. Like conditioned potentiation of eating, those other functions appear to be independent of the amygdala CEA (see below). With that background in mind, we examined rats with BLA-LHA disconnection in one of those settings.



### BLA-LHA SYSTEM AND SECOND-ORDER CONDITIONING

Previous research has demonstrated that the BLA is crucial in tasks that employ a first-order CS to support new learning. Deficits in rats with BLA lesions occur in both second-order conditioning, to be described more fully,<sup>37</sup> and in instrumental conditioning in which rats learn to make a response with the CS+ as reinforcer<sup>9</sup> (also see Ref. 44 for the role of BLA NMDA receptors in second-order fear conditioning). Notably, neurotoxic lesions of the CEA have no effect on acquisition of second-order conditioning<sup>37</sup> or secondary reinforcement in instrumental learning when food reinforcers are used,<sup>45</sup> but removal of BLA input to ACB does produce impairment similar to bilateral BLA damage.<sup>46</sup>

To assess the role of the BLA-LHA system, which may include an indirect pathway via ACB, in second-order conditioning, we returned the rats used in the potentiated feeding tests to a food-restricted regimen and paired a new stimulus (a light, referred to as CS2) with the original auditory first-order stimulus (CS+) in further training sessions. Control groups received unpaired presentations of CS2 and CS+. The lesion treatments (sham, ipsilateral, or contralateral) did not produce a difference in second-order learning. All groups trained with paired presentations acquired comparable conditioned responses to the light CS2, as shown in FIGURE 4B.

Thus, in contrast with potentiated eating, in which a CS augments food consumption, disruption of the BLA-LHA system did not interfere with a CS's ability to reinforce new learning, indicating some independence of potentiated feeding from other behavioral functions that depend on BLA-ACB projections. It has yet to be determined, however, whether indirect projections from BLA via ACB still contribute to potentiated eating, that is, whether disconnection of BLA and ACB entirely spares conditioned potentiation of feeding.

### CONCLUDING REMARKS

In the current presentation we described recent findings from a neural systems analysis of a behavioral model for motivational learning. That work has defined a specific subsystem of the amygdala (BLA) and its connectivity with the lateral hypothalamus. This model may be viewed within a broader scheme that allows experience to gain control over species typical behaviors that are important for survival. Perhaps the best studied of these involving the amygdala complex is fear conditioning, whereby animals display a repertoire of adaptive behavioral and physiological responses in the presence of cues that signal danger. In the current case, cues that signal the availability of food promote eating, a potentially adaptive function under naturalistic conditions in which animals can be challenged by scarcity of nutrients. As with fears and phobias, learning in the domain of appetitive behavior can also become maladaptive. Specifically, learned cues that promote eating in food-sated subjects are of special relevance to conditions that may induce overeating. Studies in both laboratory animals and humans show that external cues previously associated with food (learned cues) exert powerful control over food consumption in a variety of settings. Learned cues that can override regulatory signals linked to energy balance<sup>20</sup> can lead to overeating.<sup>10,11,47</sup> According to that view, conditioned potentiation of feeding not only allows for a neural analysis of motiva-

tional learning, but also may be relevant to maladaptive consequences of learning in the control of eating.

In addition to its projections to the LHA, the BLA can reach defensive and reproductive hypothalamic systems.<sup>3</sup> Those connections may mediate adaptive effects of learning on other functions that are basic to survival, such as aggression and mating. These collective amygdalohypothalamic systems, along with the amygdala projections to the brain stem, allow access to a remarkably wide repertoire of behavioral functions. Indeed, it is tempting to speculate that the role of the amygdala complex may extend beyond the independent regulation of such behaviors, but it may also provide a more integrative and coordinating function, possibly resolving competition among behavioral systems. For example, an animal that has been fasting will be highly motivated to eat in the presence of food. In that hungry state, the occurrence of a cue signaling imminent danger would provide an adaptive function by activating defense responses (such as freezing). At the same time, inhibition of behavioral systems that promote feeding could provide a further benefit. In such circumstances, amygdalohypothalamic circuits (whether originating in BLA, CEA, or both) may contribute to resolving competition among motivational systems. Support for that general concept exists. For example, lesions of the periaqueductal grey abolish freezing in the presence of an aversively conditioned CS, but do not abolish suppression of appetitive behavior when that same aversive CS is presented to hungry rats bar-pressing for food.<sup>48</sup> Thus, suppression of appetitive behavior in the presence of a fear-inducing CS is not merely due to activating a behavioral response, that is, freezing, which is incompatible with food consumption. Deficits in conditioned suppression of appetitive behavior as well as deficits in conditioned freezing behavior are reported after amygdala damage. Clearly many avenues exist for further informative research.

In closing, research in recent years has led to a new understanding of the behavioral contribution of the amygdala complex. This work has led to a definition of subsystems within the amygdala and connectivity with other brain circuits. Such neural systems analysis has revealed the functional importance of well-defined circuits involving the amygdala and brain-stem systems in the control of both behavioral and autonomic outputs during fear conditioning. Additionally, studies of amygdalostriatal and amygdaloprefrontal systems have been highly informative.<sup>8,9,25,49</sup> Further research on the long-recognized connections between the amygdala and hypothalamus is certain to add to an essential understanding of the complex adaptive functions of the mammalian brain.

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