Appetitive Behavior

Impact of Amygdala-Dependent Mechanisms of Emotional Learning

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ABSTRACT: In this chapter, we review data from studies involving appetitive conditioning using measures of pavlovian approach behavior and the effects of pavlovian conditioned stimuli on instrumental behavior, including the pavlovian-to-instrumental transfer effect and conditioned reinforcement. These studies consistently demonstrate double dissociations of function between the basolateral area and the central nucleus of the amygdala. Moreover, the data show marked parallels with data derived from aversive (fear) conditioning studies and are consistent with the idea that these subsystems of the amygdala mediate different kinds of associative representation formed during pavlovian conditioning. We hypothesize that the basolateral amygdala is required for a conditioned stimulus to gain access to the current affective value of its specific unconditioned stimulus, whereas the central nucleus mediates stimulus-response representations and conditioned motivational influences on behavior. Although these systems normally operate together, they can also modulate behavior in distinct ways. In many circumstances, then, emotional behavior can be seen as a coordinated combination of processing by these amygdaloid subnuclei, reflecting the superimposition of a phylogenetically recent basolateral amygdala subsystem that encodes and retrieves the affective value of environmental stimuli and thereby directs complex, adaptive behavioral responses onto a phylogenetically older central amygdala subsystem that enables cortical structures (including the basolateral amygdala) to recruit incentive motivational processes and thereby invigorate emotional responding.

KEYWORDS: pavlovian conditioning; conditioned motivation; emotional behavior; appetitive behavior; conditioned reinforcement; approach behavior; autoshaping; pavlovian-instrumental transfer; affect

INTRODUCTION

The amygdala has long been accepted to be involved in emotional processing and, especially, in pavlovian learning processes that impact upon appetitive and aversive

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behavior. As reviewed elsewhere in this volume, the amygdala is well positioned neuroanatomically to fulfill such functions. The lateral and basal amygdala receives sensory information and has been shown to act as a site of conditioned stimulus (CS)–unconditioned stimulus (US) association. This learned information can then be used by the basolateral amygdala (BLA) to control the activity of the central nucleus (CeN) which, via its distributed projections, can in turn control hypothalamic and brain-stem structures to orchestrate behavioral, autonomic, and neuroendocrine responses. There is abundant evidence that the amygdala does operate in this way in some situations.[1–9] We have also emphasized previously that the BLA does more than simply control the CeN, projecting as it does to structures including the ventral striatum and prefrontal cortex, thus enabling it to influence complex behavior.[10–12] Additionally, the CeN itself receives direct sensory input as well as projections from other cortical areas, such as the cingulate cortex,[13–16] and it may be capable of learning and/or subserving behavioral expression independently of the BLA.[10,17–20] In this review, we consider the types of learning that depend upon these amygdaloid nuclei and the nature of the representations these structures might subserve.

MULTIPLE REPRESENTATIONS ARE FORMED DURING PAVLOVIAN CONDITIONING

Representations formed during pavlovian conditioning allow novel stimuli, through associative pairing with primary rewards or goals, to control relevant innate, species-specific response mechanisms. They also enable animals to predict events occurring in their environment and thus adapt to different situations. Pavlovian conditioning is not a unitary process, and it is now clear that pairings between a CS and a US may cause the CS to enter into several associations[21–23] (FIG. 1) subserved in part by dissociable mechanisms within the amygdala.[10,11,24]

First, a CS may become directly associated with an unconditioned response (UR), a simple stimulus–response association that carries no information about the identity of the US (e.g., Ref. 25). However, a single US may elicit several types of response; for example, a US such as a puff of air delivered to the eye may elicit a specific motor act, such as blinking, and an ancillary enhancement of arousal or attention. Such US-elicited responses can be considered to fall into two classes: "preparatory" responses, which are not specific to the type of US involved (e.g., orienting to a stimulus or enhancing arousal), and "consummatory" responses, which are specific to the US (e.g., salivation to food or blinking to an air puff). As a US may elicit both a preparatory and a consummatory response, the CS may enter into simple stimulus–response associations with several kinds of response. The nature of the CS itself can therefore determine which response is evoked; for example, a well-localized light CS will elicit a conditioned approach response, whereas a poorly localized auditory tone CS will not.

Second, the CS can evoke a representation of affect, such as fear or the expectation of reward (FIG. 2). This embodies the concept of an emotional "tone" that is tagged to a stimulus.[10,24] Affective states can be independent of the specific reinforcer and response, being pure "value" states, a concept widely used in theories of learning.[26–28]

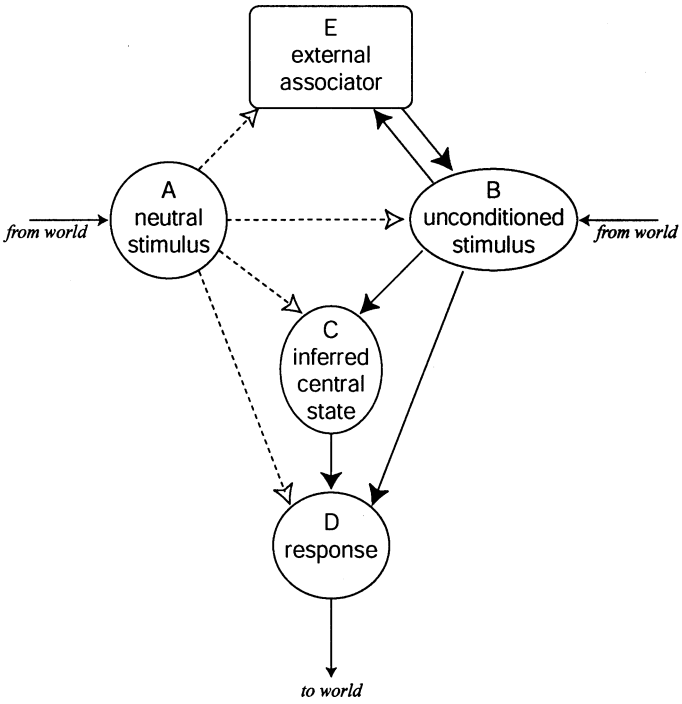

FIGURE 1. Pavlovian conditioning has the potential to create associations between a conditioned stimulus (CS) and representations of the unconditioned stimulus (US), central states such as fear, and unconditioned responses. Only a single response is shown; distinctions between different kinds of response are discussed in the text. Bidirectional communication also allows representations to be associated in "third-party" sites (E). Note that lesions of such a site might prevent conditioning without impairing any form of unconditioned response, as would selectively disconnecting the CS from a representation involved in responding. Reprinted from Ref. 10.

Third, the CS can become associated with the specific sensory properties of the US (e.g., visual appearance, sound, feel, and smell) and also "consummatory" qualities such as its taste and nutritive value. Evidence for US specificity of pavlovian associations comes from the effect of postconditioning changes in the value of the US. If a CS is paired with a desirable food and the food is subsequently devalued (by pairing it with LiCl injection to induce nausea), not only does the animal reject the food US, but also its reaction to the CS changes.[21,29] Therefore, the CS could not have been associated only with an abstract affective representation, as it was able to retrieve, by association, the new value of the US. As the LiCl–food pairing does not affect the reaction to a second CS predicting a different food, each CS must have been associated with some specific aspect of its US.

These representations that can be formed during pavlovian conditioning can greatly influence appetitive behavior, not only by bringing an animal into contact with goals, but also by influencing responses that are instrumental in obtaining them.

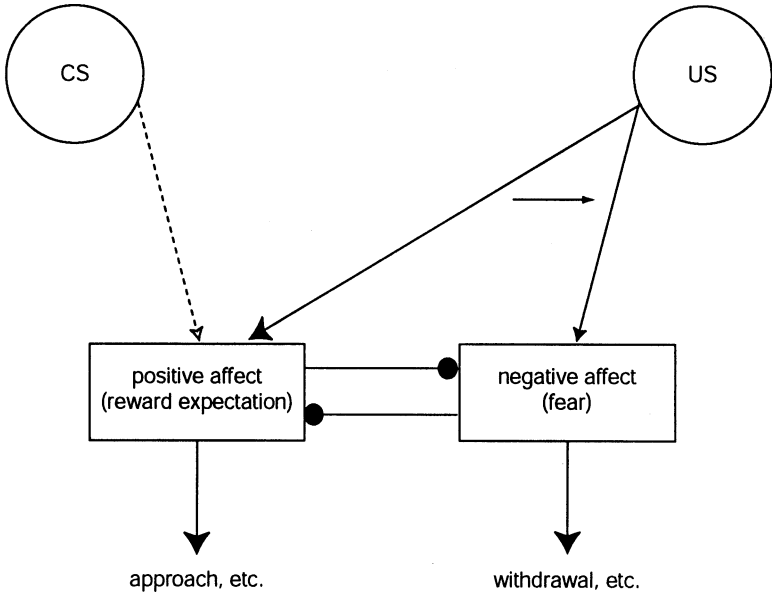

FIGURE 2. Conditioning to affective states leaves the response independent of the current value of the US. The CS associates with the affective state elicited by the US during conditioning, but if the US subsequently alters its value, the conditioned response (CR) will not alter. Reprinted from Ref. 10.

CONTRIBUTIONS OF THE AMYGDALA TO ASSOCIATIVE INFLUENCES ON APPETITIVE BEHAVIOR

Amygdaloid Subnuclei Operate in Series, but Also in Parallel

Studies of conditioned fear provide perhaps the clearest evidence that the amygdala is involved in pavlovian conditioning of emotional responses. One measure frequently taken to indicate emotional states of fear in rats is freezing, a species-specific response to danger in which a rat remains motionless (another is fear-potentiated startle, discussed in this volume by Davis). Lesions of either the BLA or CeN impair aversive conditioning indexed by measures of freezing.[1,3] Although there is some controversy as to whether rats with BLA lesions can show freezing behavior at all, whether conditioned or unconditioned,[30] LeDoux[2] has shown that the sensory thalamus, sensory neocortex, and hippocampus convey increasingly complex information about environmental stimuli (CSs) to the BLA, where CS–US association takes place. Furthermore, lesions of these structures and lesions of targets of the CeN, such as the periaqueductal grey (PAG), lead to impairments in conditioned freezing.[1–4] A widely held hypothesis, therefore, is that the BLA (primarily the lateral nucleus) acts as the associative site for stimulus–outcome representations and the CeN provides the output pathway through which these associations gain access to appropriate responses, such as the conditioned freezing response. This is a *serial*

model of BLA/CeN function. Indeed, stronger forms of this hypothesis have been advocated: that fear conditioning does not survive without the BLA and that the CeN is not capable of supporting associative function without the BLA.[31]

However, not only can some forms of fear conditioning occur in animals in which the BLA has been lesioned, but also the involvement of the BLA and CeN in aversive and appetitive associative learning can be dissociated. Certain forms of fear conditioning may survive BLA lesions, that is, contextual fear conditioning (as assessed by an aversion to the environment in which the subjects experienced shock).[32] A double dissociation of the effects of BLA and CeN lesions was shown by Killcross *et al.*[17] Thus, although BLA lesions impaired instrumental avoidance, they did not affect simple pavlovian conditioned suppression in which an aversive CS suppresses appetitive responding (e.g., lick or lever-press suppression). By contrast, lesions of the CeN produced the opposite effect—persistently impaired conditioned suppression, yet preserved active avoidance. An analogous double dissociation using an appetitive version of the task has also been reported.[33] Similarly, Hitchcott and Phillips[19] demonstrated a double dissociation of the effects of the dopamine (DA) D2/D3 receptor agonist 7-OH-DPAT injected into the CeN and BLA, affecting pavlovian conditioned approach and instrumental responding for an appetitive conditioned reinforcer, respectively. Hatfield *et al.*[20] earlier showed a double dissociation, also within the domain of appetitive pavlovian conditioning, between second-order conditioning (requiring the BLA but not the CeN) and conditioned orienting (requiring the CeN but not the BLA).

These data therefore support what might be seen as a parallel processing view of amygdala function, in which representations stored in (or communicated through) the CeN and BLA can affect behavior through separate afferent and efferent pathways. It is important to appreciate that the CeN as well as the BLA receives sensory input from the thalamus[15,16] and cortex,[13] which could support association formation independent of the BLA (see also Ref. 34), and that the BLA and CeN have different and, in some sense, complementary efferent projections. From the vantage of these empirical and theoretical standpoints, further predictions can now be made about discrete amygdaloid functions, and previously published findings can be subjected to reinterpretation.[24]

The Basolateral Amygdala Is Required for a Pavlovian Conditioned Stimulus to Gain Access to the Current Motivational or Affective Value of the Specific Unconditioned Stimulus That It Predicts

Rats with BLA lesions are clearly able to acquire CRs.[17,18,20,32,33,35] However, these responses do not have the flexibility seen in intact animals, being insensitive to subsequent changes in the value of the US (reinforcer revaluation). Thus, rats with BLA lesions acquire normal conditioned responding to a CS paired with food (the CR being the approach to the location where food was delivered)[20] and also show normal acquisition of an aversion to that food when it is subsequently paired with LiCl.[20,35] However, BLA-lesioned rats fail to adjust their responding (orienting and food cup approach) to the CS spontaneously after the food is devalued.[20] Similar results have been observed in monkeys.[36] An effective explanation of these data is that the CRs learned by the BLA-lesioned rats were a result of direct associations between the CS and the response (pavlovian stimulus–response associations). BLA

lesions impaired the ability of rats to use the CS to access the value of a specific US and use that representation to alter their response (Holland[37] has called this "mediated performance," that is, the capacity to respond based on a CS-activated representation of the US).

The hypothesis that BLA-lesioned animals cannot use a CS to gain access to the current value of their specific US has great explanatory power. In second-order conditioning, a stimulus, CS_1, is paired with a US, and a second stimulus, CS_2, is then paired with CS_1. A second-order CS becomes associated with the affective value that is called up by the first-order CS rather than its sensory properties.[22,38] Similarly, conditioned reinforcement depends on the affective or motivational value gained or accessed by the CS. BLA-lesioned rats cannot acquire second-order conditioning,[20] cannot acquire responding under second-order instrumental schedules,[39,40] and cannot use a first-order CS as a conditioned reinforcer.[41,42] Thus, the responses that still occur to the first-order CS in BLA-lesioned animals do not support second-order conditioning. However, the deficit in BLA-lesioned animals is not restricted to second-order conditioning, as BLA lesions also impair reward devaluation effects after first-order conditioning, another task that requires the subject to retrieve the affective value of the US using the CS, as just discussed.[20] The integrity of the BLA is also essential for the specific modulation of instrumental choice behavior by a CS, which requires that the subject use the motivational value of a particular US.[17,33] These studies further demonstrate that BLA lesions affect both appetitive and aversive conditioning.[10]

Associations between a CS and the affective value of a US may also account for responses such as conditioned freezing, which cannot readily be accounted for in terms of a CS–UR association. Thus, (1) freezing is likely not a UR;[38,82] the immediate UR to shock is agitation, jumping, vocalization, and escape, not freezing.[43-46] At the time of conditioning, therefore, there is no freezing response occurring to which a CS–UR association can be formed.[46] (2) After the initial locomotor response to the shock, a freezing response may subsequently be generated (so-called postshock freezing), which is probably the expression of a conditioned association formed between the shock and the experimental context.[45,46] (3) Freezing is a US-specific conditioned response (an adaptive response to environmental danger); hence, while freezing occurs to a CS for shock, it does not occur to a CS for the omission of expected food, even though both signal aversive events. Lesions of the BLA may therefore impair the acquisition of conditioned freezing, because they subserve the formation of a stimulus–outcome association between the CS and a neural representation of the affective properties of the particular US, that is, fear. [48]

SUMMARY: FUNCTIONS OF THE BASOLATERAL AMYGDALA

The hypothesis arising from these data is that the BLA is necessary for a CS to retrieve the value of its specific US; once retrieved, this value may be used to control multiple responses via different output systems—freezing via the CeN; instrumental choice behavior and responding with conditioned reinforcement via the striatum and/or prefrontal cortex. But several important questions remain concerning BLA function.

1. It is not known whether BLA-lesioned animals lack affective states entirely or are merely unable to call them up via a CS. As amygdala lesions do not affect food preferences other than to reduce food neophobia (e.g., Refs. 49 and 50), the latter appears more likely. The BLA may therefore maintain a representation of the affective or reinforcing properties of conditioned cues through direct connections with representations of the specific values of primary reinforcers, maintained elsewhere. Hence, BLA-lesioned rats cannot use a CS to retrieve the current motivational value of the specific US (e.g., Ref. 20).

2. It remains unclear whether the BLA is also involved in representing specific sensory information about USs, required for stimulus–stimulus (S–S) associations (see also Ref. 10). According to this view, BLA-lesioned animals make unconditioned responses and learn simple CS–UR associations, including "emotional" responses, but the CS conveys no information about the identity of the US. However, rats can learn stimulus discrimination tasks in the absence of the BLA,[51–53] and this provides a reason to question *a priori* whether the BLA is required for S–S associations. Moreover, BLA lesions do not impair sensory preconditioning,[54] which depends instead on sensory areas such as the perirhinal cortex.[55] We have proposed that the US-specific representation involving the BLA is purely affective;[24] according to this view, BLA-lesioned animals can learn CS–UR associations that are incapable of affecting instrumental choice behavior and can learn CS–US (sensory) associations, but cannot learn CS–US (affective) associations, and the sensory representation they can activate is without affective valence. See also Ref. 37 for a discussion of this possible dissociation.

3. The importance of the contribution of the BLA to pavlovian conditioning may change with training. Thus, it has been shown that postlesion overtraining can mitigate the deficits in conditioned freezing to contextual cues after BLA lesions[56–58] (see also Refs. 17, 59, 60, and 61). We have speculated that this might reflect changes in the psychological basis of conditioned responding that normally occur with prolonged training and perhaps that the contribution of conditioned affect (and hence the BLA) is most important early in training (see Ref. 21, p61, [62]). However, it was recently shown[108,109] that conditioned value survives if it is acquired before BLA lesions are made; BLA lesions instead appear to prevent rats from learning or altering (but not maintaining) the value of a CS.

4. The contribution of the BLA to instrumental conditioning requires further investigation. While BLA-lesioned rats are impaired at instrumental responding for a pavlovian CS, serving as a conditioned reinforcer,[41,42] they are not impaired in the general form of pavlovian–instrumental transfer (PIT), in which noncontingent presentations of an appetitive pavlovian CS will enhance instrumental responding.[63–65] However, they may disrupt the *specificity* with which pavlovian CSs influence instrumental responding (i.e., the ability of a CS associated with food to enhance responding on a lever that previously earned food more than on a lever that previously earned another reinforcer, such as water).[64] These data are compatible with the view that BLA-lesioned rats can learn simple pavlovian conditioned responses but not retrieve the value of specific USs. However, it is not known whether BLA lesions disrupt core aspects of instrumental conditioning, such as action–outcome contingency perception and the attribution of instrumental incentive value (but see Ref. 107). Although BLA-lesioned rats can acquire simple instrumental responses (e.g., Refs. 51 and 65), it is likely that the BLA does play some role in governing the incentive value

of the goals of behavior. Thus, although amygdala lesions do not impair preferences between foods,[49,50] they do affect monkeys' sensitivity to changes in the values of specific foods.[36] Furthermore, a disconnection of the amygdala and orbitofrontal cortex (unilateral lesions of each structure on opposite sides of the brain) impairs the ability of rhesus monkeys to adjust their choice behavior in response to reinforcer devaluation,[66] suggesting a serial interaction between these structures in mediating the impact of affective information on response selection.

5. Finally, the BLA has a prominent role in the emotional modulation of memory storage, being part of the mechanism by which emotionally arousing situations improve memory[67,68] (see also McGaugh, this volume). For example, the BLA is the critical site for the memory-enhancing effects of systemic adrenaline and glucocorticoids and for some of the amnesic effects of the benzodiazepines.[67] Many of these studies have used tasks such as passive and active avoidance and spatial memory, which may require contributions from several of the pavlovian and instrumental representations described above. It will be of interest, therefore, to establish whether the role of the BLA in memory consolidation can be tied to a particular type of psychological representation, such as the acquisition, but not the maintenance, of the value of CSs,[36] or whether this "modulatory" function of the BLA is independent of the information that it retrieves in pavlovian conditioning tasks.

THE CENTRAL NUCLEUS OF THE AMYGDALA CONTROLS BRAIN-STEM AROUSAL AND RESPONSE SYSTEMS AND SUBSERVES SOME FORMS OF STIMULUS–RESPONSE PAVLOVIAN CONDITIONING

The CeN projects to the hypothalamus, midbrain, and brain-stem neuroendocrine, autonomic and skeletomotor control centers[34] involved in aversive conditioned responding,[4] including the PAG (which mediates the freezing response), the caudal pontine reticular nucleus (PnC, which mediates potentiation of the startle reflex), the lateral hypothalamus (which mediates sympathetic activation), and the medial hypothalamus (which mediates activation of the pituitary–adrenal axis). The CeN also projects to reticular formation nuclei that provide the chemically defined, diffuse projection systems to the forebrain, such as the dopaminergic (DAergic) ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), the noradrenergic locus ceruleus, the serotonergic raphé nuclei, and basal forebrain cholinergic nuclei. Several conditioned responses have been shown to depend on the CeN and its projection to this array of nuclei.[10,24] In order to consider the functions of the CeN, it may be helpful to appreciate the similarities and differences between the effects on behavior of manipulating the CeN and the BLA (TABLE 1).

A number of pavlovian conditioning tasks require the BLA but not the CeN (TABLE 1). Thus, while producing deficits in a number of tests of pavlovian conditioning, lesions of the CeN (unlike those of the BLA) do not impair second-order conditioning[20] or responding for conditioned reinforcement.[69] Hatfield *et al.*[20] and Gallagher *et al.*[70] also showed that CeN-lesioned rats can acquire some first-order appetitive conditioned responses (such as conditioned behaviors directed at a food source). Those first-order conditioned responses (CRs) that they do acquire are sen-

sitive to reinforcer devaluation,[20] implying that a CS can still gain access to information about the identity and current value of its associated US in CeN-lesioned rats.

Several specific pavlovian conditioned responses require the CeN, but also the BLA (TABLE 1). While CeN lesions abolish conditioned freezing, fear-potentiated startle, and conditioned bradycardia,[4,6,8,9,34,71–74] these behaviors are also sensitive to BLA lesions (as discussed above and see Ref. 75) and appear to depend on the CeN simply because the BLA gains access to various brain-stem motor nuclei (PAG, PnC, and dorsal motor nucleus of the vagus) via the CeN, part of its role in a serial circuit (see Refs. 2 and 34). One prediction arising from this view is that temporary inactivation of the CeN during fear conditioning should not prevent a subsequent conditioned freezing response.

However, some CeN-dependent conditioned responses, such as the conditioned suppression described above,[17] require the CeN but not the BLA (TABLE 1). Although it is possible to induce cessation of licking behavior by presenting a CS paired with a strong electric shock, such a CS will also induce conditioned freezing.[5,76] This freezing is incompatible with licking behavior, and the resultant conditioned suppression, attributable to freezing, is impaired by BLA lesions.[5,32]

TABLE 1. Summary of some of the behavioral effects sensitive to lesions of the central nucleus (CeN) and/or basolateral amygdala (BLA) and the likely underlying associative representations

Behavior	Association type	Sensitive to lesions of: CeN	BLA
1. *Appetitive conditioning*			
Conditioned approach (autoshaping)	CS→UR	+	–
Conditioned orienting	CS→UR	+	–
Pavlovian–instrumental transfer (PIT)	CS→UR (affective/motivational UR)	+	–
Conditioned reinforcement	CS→US affect/value	–	+
Second-order conditioning	CS→US affect/value	–	+
Second-order instrumental responding	CS→US affect/value	–	+
Reinforcer revaluation	CS→US affect/value	–	+
2. *Aversive conditioning*			
Conditioned suppression (–ve PIT)	CS→UR (affective/motivational UR)	+	–
Conditioned freezing	CS→US affect/value	+	+
Fear-potentiated startle	CS→US affect/value	+	+
Conditioned punishment (–ve conditioned reinforcement)	CS→US affect/value	–	+

Note: Conditioned suppression can also be affected by inactivation of the BLA, under conditions of high shock intensity and after few CS–US pairings. The precise explanation in terms of associative representations underlying conditioned suppression requires further investigation. CS, conditioned stimulus; US, unconditioned stimulus; UR, unconditioned response; CeN, central nucleus of the amygdala; BLA, basolateral area of amygdala.

However, if mild shock is used, conditioned suppression of ongoing instrumental responding is induced in the absence of freezing,[17] in which case the conditioned suppression represents aversive pavlovian–instrumental transfer (PIT) and is persistently impaired by CeN lesions, but survives BLA lesions.[17]

Finally, some appetitive CRs also require the CeN but not the BLA (TABLE 1). For example, in rats, an orienting response (OR) can be conditioned to a CS for food; conditioned ORs depend on the CeN, but not the BLA,[20,70] and the critical circuit appears to involve projections from the CeN via the dopaminergic substantia nigra pars compacta (SNc) to the dorsolateral striatum.[77] Despite the lack of the conditioned response, the corresponding unconditioned response remains unimpaired in CeN-lesioned rats.[70]

Conditioned locomotor approach is another appetitive CR that depends on the CeN but not the BLA. In autoshaping,[78] a visual stimulus (CS+) is presented on a computer screen and followed by the delivery of food in a different spatial location; a second stimulus (CS–) is also presented, but never followed by food.[79] Although food delivery is not contingent on any behavioral response, animals develop a CR of selectively approaching the CS predictive of food, before returning to retrieve the primary reward. Autoshaping has been shown to be a pavlovian CR.[38,79–82] Lesions of the CeN greatly impair acquisition of autoshaping, whereas BLA lesions do not.[18] As acquisition of the autoshaping CR also requires the nucleus accumbens core[83] and its dopaminergic innervation,[84,85] and as the CeN does not project directly to the nucleus accumbens[14,86–89] but does project to the source of its DAergic innervation in the VTA,[90,p35, 91–94] we have hypothesized that this CR depends on the regulation by the CeN of the dopaminergic projection from the VTA to the nucleus accumbens core.[10,11,95] Indeed, recent data have shown that increased extracellular levels of dopamine in the nucleus accumbens in response to food presentation depend on the functioning of the CeN, and not the BLA,[96] thereby providing strong evidence in favor of this hypothesis. Further evidence that the CeN is important in conditioned approach comes from the observation that posttraining intra-CeN injection of a dopamine receptor agonist enhanced the conditioned approach behavior, whereas intra-BLA injections did not.[19]

The CeN also is important for pavlovian conditioned motivational influences on instrumental action. Pavlovian–instrumental transfer is abolished by lesions of the CeN, but not the BLA.[17,33,65] Moreover, lesions of the CeN, but not the BLA, impair the ability of intra-nucleus accumbens infusions of amphetamine to enhance responding for conditioned reinforcement,[41,69] again indicating that the CeN influences dopaminergic mechanisms within the nucleus accumbens, possibly via projections to the VTA, to provide a conditioned motivational influence on behavior.

Additionally, Gallagher, Holland, and co-workers have shown that the CeN is involved in the control of attentional aspects of stimulus processing through its projections to the reticular formation. The CeN plays a role in stimulus detection in a test of visuospatial attention[97] and also appears to regulate the associability of stimuli under some circumstances.[98–100] Specifically, the ability to upregulate associability depends on the integrity of the CeN,[101,102] together with its projections to cholinergic neurons in the nucleus basalis magnocellularis (NBM),[103] and possibly from there to the posterior parietal cortex.[104]

There is no direct evidence to suggest that the CeN is itself a site of association, even though it receives neuronal afferents appropriate to support them; it might re-

ceive an already associated input. However, it is clear that animals lacking a BLA can form some kinds of association, the expression of which is sensitive to CeN, but not BLA, lesions.[17,18,63,65,98] One possibility is that the CeN does form simple CS–UR (sensorimotor) associations, which do not depend on a specific US[105]: these "pavlovian habits," as they might be called, are independent of the identity and current motivational value of the US and are also unable to support second-order conditioning. We have suggested[10] that the responses subserved by CeN-dependent associations especially include the modulation of reflexes organized within the brain stem, including some that might conventionally be regarded as "affective," including conditioned suppression, conditioned orienting, and pavlovian–instrumental transfer. These are all disrupted by CeN, but not BLA, lesions. Conditioned suppression may influence instrumental behavior nonspecifically (i.e., influence the ongoing level of all instrumental responses), but is insufficient to modulate instrumental behaviors differentially (i.e., affect choice).[17] Finally, just as the BLA has a role in memory modulation,[67] the CeN is also able to modulate the associability of representations stored elsewhere in the brain.[98–100]

Representations encoded by amygdalar nuclei may therefore be categorized using a well-defined psychological dichotomy if it is considered that the CeN encodes or expresses pavlovian stimulus–response (CS–UR) associations, whereas the BLA encodes or retrieves the affective value of the predicted US. However, not all stimulus–response associations depend on the CeN. For example, nictitating membrane/eyeblink conditioning depends instead on the cerebellum, even though the eyeblink clearly is part of the UR to eyeshock; the underlying circuit has been extensively mapped and appears to involve CS–UR associations. Eyeblink conditioning can occur in the absence of the amygdala, even though simultaneously conditioned changes in heart rate are amygdala dependent (see, e.g., Ref. 106). One suggestion is that the CeN subserves pavlovian CS–UR associations when the response is controlled by a hypothalamic or brain-stem nucleus governed by the CeN; such responses include autonomic changes, motivational arousal, and attentional enhancement.

SUMMARY

It appears likely that the BLA enables the CS to retrieve the affective or motivational value of its particular US, a form of pavlovian stimulus–outcome association (FIG. 3). This information can be used to control the CeN and thereby its hypothalamic, midbrain, and brain-stem targets, giving rise to "affective" responses such as freezing and modulation of arousal and attention. The BLA can also use this information to modulate instrumental actions, presumably via its projections to the ventral striatum and/or prefrontal cortex.[24] In addition to its role as a recipient of information from the BLA, the CeN also receives parallel input from cortical and subcortical structures; it receives or may encode direct stimulus–response (S–R) pavlovian associations, thereby influencing specific conditioned responses organized in the hypothalamus, midbrain, and brain stem as well as modulating arousal and attention through the diffuse projection systems of the reticular formation. The differentiated outputs of the CeN and BLA are therefore both able to affect emotional expression of the same response, the BLA via retrieval of the specific affective value of the CS (e.g., conditioned reinforcement) and the CeN via a more general

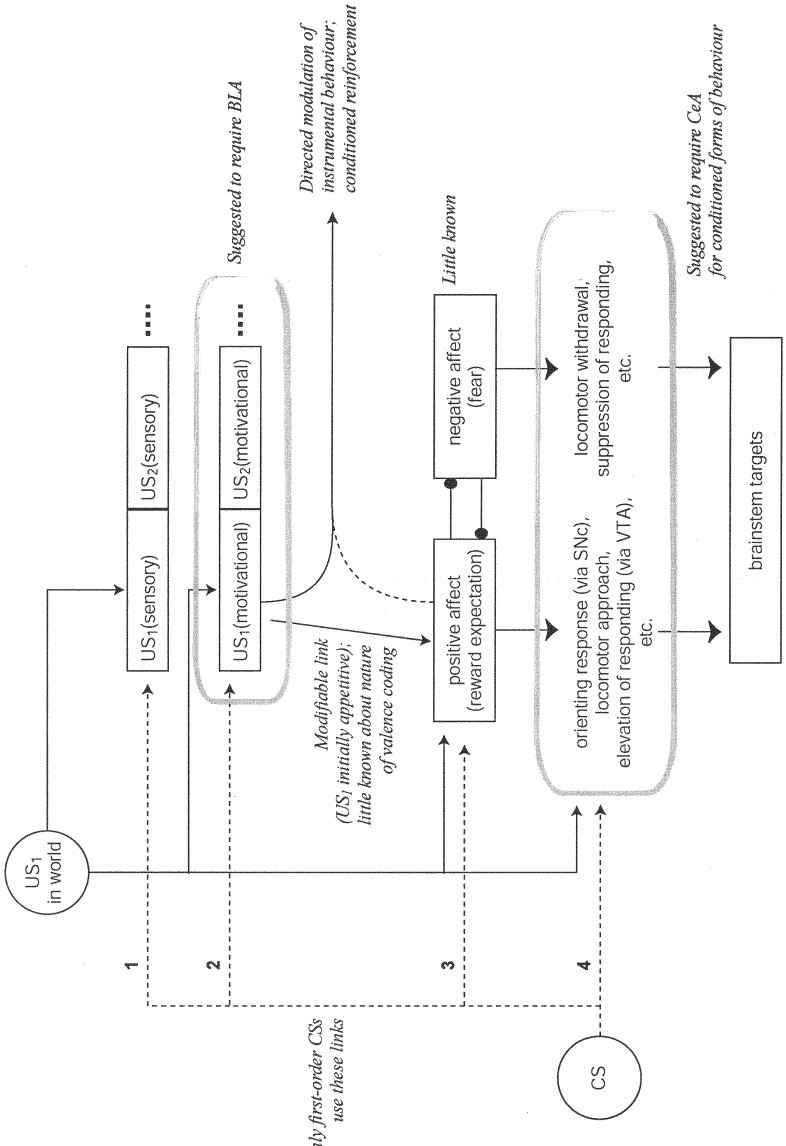

FIGURE 3. *See following page for legend.*

incentive motivational process through its communication with the DAergic VTA. Thus, emotional behavior in many circumstances can be seen as a coordinated combination of processing by these amygdaloid subnuclei, reflecting the superimposition of a phylogenetically recent BLA subsystem that encodes and retrieves the affective value of environmental stimuli to direct complex, adaptive behavioral responses onto a phylogenetically older CeN system that enables cortical structures (including the BLA) to recruit incentive motivational systems (such as the mesolimbic DA pathway) and thereby invigorate emotional responding.

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FIGURE 3. Schematic of representations that may be involved in pavlovian conditioning, emphasizing the hypothesized role of amygdaloid subregions. The bilateral amygdala (BLA) is required for a conditioned stimulus (CS) to gain access to the current value of its specific unconditioned stimulus (US). In the figure, the CS has been associated with US_1, initially appetitive, while an unrelated US_2 maintains a separate value (connections not shown for clarity). As discussed in the text, the precise nature of the information encoded in the BLA is uncertain; here, it is illustrated as binding US-specific sensory information to an affective value. The BLA may use this information to control central nucleus (CeN) function, but also to modulate specific instrumental (choice) behavior, as in conditioned reinforcement tasks; the nucleus accumbens is a key target of this information. By contrast, the CeN is required for CS–UR learning, particularly when the response involves modulation of hypothalamic and brain-stem functions. Reprinted from Ref. 10.

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