# Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus

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**Fear-arousing stimuli elicit innate reactions and can reinforce acquisition of new responses. We tested whether mechanisms mediating these conditioned stimulus (CS) properties were isomorphic or dissociable within the amygdala. Rats trained on a fear-conditioning task (CS paired with footshock) were then trained on an escape-from-fear task (EFF) in which the CS reinforced a locomotor response terminating the CS. Lateral nucleus (LA) lesions blocked acquisition of both conditioned freezing responses and the CS's reinforcement of a new response in the EFF task. Central nucleus (CE) lesions blocked conditioned freezing but not the EFF, whereas basal nucleus (B) lesions blocked the EFF but not conditioned freezing. Thus, activation of the LA by a CS seems to trigger conditioned reactions via CE and conditioned aversion via B activation, reduction of which reinforces new actions .**



Stimuli in the presence of painful or threatening stimuli acquire aversive properties and, as a result, later elicit fear reactions. This form of learning is extensively studied using a Pavlovian fear-conditioning protocol. In a typical experiment, a tone (conditioned stimulus) is paired with an unconditioned stimulus (US), a footshock. Subsequently, the CS elicits unlearned species-typical defense reactions in the absence of the US[1,2]. Thus, fear conditioning does not create fear responses, but instead establishes the environmental conditions under which innate fear responses will be expressed.

Although innate fear reactions may be adaptive, ability to take novel actions in threatening situations may also be advantageous. In the present study we used a modified escape-from-fear[3] task to demonstrate mediation of these two kinds of responses by different neural pathways. The task involved two phases. In the first, fear reactions were conditioned to a CS by pairing it with shock. Subsequently, the animals were placed in a new chamber, where the CS was presented. They then learned that an arbitrary response, stepping into the adjoining identical chamber, terminated the CS. Termination of the CS reinforced the novel action, presumably because it decreased the conditioned fear elicited by the CS. The CS from the conditioned fear task thus functioned as a conditioned negative reinforcer in the EFF task[4].

The neural basis for the acquisition of Pavlovian fear conditioning is well studied[5–7], but the manner in which it fits into a broader network of mental and behavioral systems is poorly understood. Here we begin to integrate the anatomy of fear conditioning with other systems involved in more complex aspects of behavior.

Fear conditioning is believed to involve the relay of sensory information about the CS first to the lateral nucleus of the amygdala and from there to the central nucleus of the amygdala[5–7]. The conclusion that these circuits are involved in fear conditioning is based on anatomical tracing, lesion, pharmacological and unit-recording studies. Particularly relevant here, lesions of LA and CE interfere with the Pavlovian conditioning of fear reactions[8–13]. In contrast, several lines of investigation in which LA and basal nucleus of the amygdala were lesioned together suggest that the LA or B is involved in the ability of a CS to serve as a conditioned reinforcer[14,15], but it is not clear whether both are involved. Further, given that LA projects to CE directly and by way of B[16,17], it is important to determine whether the Pavlovian conditioning of fear reactions is mediated by the direct projection from LA to CE or by way of the projection from LA to B and from there to CE. Therefore, we examined the effects of lesions of LA, B or CE on the acquisition of both a Pavlovian and an instrumental conditioned response, with the stimulus that served as the CS in the Pavlovian task also serving as the conditioned reinforcer in the instrumental task.

## Results

### Histology

The LA was targeted in 20 rats. Fourteen rats were excluded because of either insufficient tissue damage to the LA or damage that grossly infringed on the B and/or CE. The final LA group consisted of six rats. These animals had lesions destroying most of the dorsal LA and approximately 75% of the ventral LA (**Fig. 1b** and **2a**). The lesions infringed slightly on the dorsal endopiriform nucleus laterally, but spared both B and CE. Fifteen animals received lesions of CE. Nine of these animals were excluded either because CE was spared or because lesions damaged LA and/or B. The remaining six animals included in the analysis had lesions destroying most of both the medial and lateral subnuclei of CE but sparing both LA and B (**Fig. 1c** and **2b**). Of the 16 rats that underwent B lesions, 8 were excluded from behavioral analyses because the lesions spared most of B or infringed on LA and/or CE. Acceptable lesions in eight animals damaged much of B and infringed on the ventral portion of LA as well as the accessory basal nucleus (**Fig. 1d** and **2c**). The damage to the accessory basal was not consistent and was not evident in all the animals included in this experimental group.

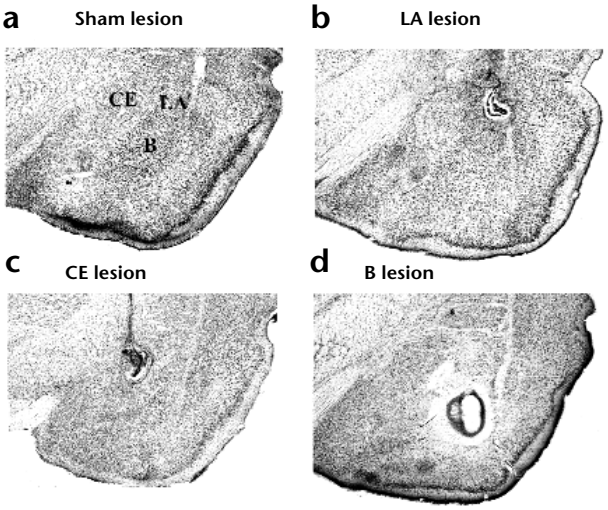


**Fig. 1.** Coronal unilateral images of representative lesions of amygdala subdivisions. (**a**) Sham; (**b**) lateral amygdala; (**c**) central amygdala; (**d**) basal amygdala.

### Behavioral results

Unlesioned animals receiving paired CS–US presentations froze significantly more than rats presented with unpaired stimuli ($F_{1,11} = 19.1$, $p < 0.05$; **Fig. 3a**). Behavior of the animals also differed with regard to the acquisition of the EFF (**Fig. 3b**). A one-way analysis of variance (ANOVA) comparing the number of escape responses over five trial blocks as a repeated measure with the CS–US relationship (paired versus unpaired) revealed a significant interaction between these two variables ($F_{3,33} = 3.2$, $p < 0.05$). There was no main effect, however, of either block of trials or CS–US relationship ($p > 0.05$). *Post-hoc* Newman-Keuls analyses with group and block as variables revealed that the escape scores for paired animals were significantly higher on block 4 than on block 1 ($p < 0.05$). Recipients of unpaired stimuli, however, demonstrated comparable escape responses on the first and last training blocks ($p > 0.05$). Thus, the acquisition of both the freezing and EFF were contingent on association of the CS with the US.

### Effects of amygdala lesions

Lesions of the LA and CE blocked the acquisition of Pavlovian fear conditioning, as measured by freezing to the CS (**Fig. 4a**). However, lesions confined to the B had no effect on freezing. An ANOVA comparing the freezing scores with groups revealed a significant effect of group ($F_{3,29} = 10.7$, $p < 0.05$). Newman-Keuls *post-hoc* tests indicated that the B and sham groups had comparable freezing scores ($p > 0.05$). Rats in groups CE and LA had similar scores ($p > 0.05$). Freezing scores in both the sham and B-lesioned groups were significantly different from scores in groups LA and CE ($p < 0.05$ for all). These results demonstrate that the LA and CE are necessary for the acquisition of freezing behavior, but the B is not.

The findings from the instrumental learning task (EFF) overlapped and diverged with those from the Pavlovian task. Lesions of the LA and B blocked acquisition of the EFF task (**Fig. 4b**), but lesions of the CE had no effect on this task. An ANOVA comparing the groups (sham, B, CE, LA) with the number of escape responses over 4 blocks of 5 trials revealed a significant interaction ($F_{9,87} = 4.3$, $p < 0.05$). Furthermore, there was a main effect of both group ($F_{3,29} = 5.6$, $p < 0.05$) and blocks ($F_{3,87} = 3.1$, $p < 0.05$). Newman-Keuls *post-hoc* analyses with group and block as variables revealed that all groups demonstrated comparable scores on block 1 ($p > 0.05$). Furthermore, only rats with either sham or CE lesions acquired the EFF task. Specifically, the scores for sham and CE rats from block 4 were significantly different from their respective scores on block 1 ($p < 0.05$). Conversely, rats with lesions of the B or LA did not differ between blocks 1 and 4 (or any of the other blocks; $p > 0.05$). These data demonstrate that the LA and B are necessary for the acquisition of the EFF task, but that the CE is not.

## Discussion

LA is believed to be the sensory interface, the locus where CS information enters the amygdala[8,16–21]. Damage to LA should therefore disrupt amygdala-dependent responses elicited by sensory stimuli. Indeed, here and in other studies, damage to LA prevents conditioning of fear reactions to a CS, as well as expression of previously conditioned fear reactions[9,11]. We also found that lesions of LA disrupted the ability of the same CS to serve as a conditioned reinforcer of a novel instrumental response, a conditioned fear-motivated action. Furthermore, we have demonstrated that these two properties of a CS are differentially affected by lesions placed in different targets of LA within the amygdala. Specifically, lesions of the CE blocked the acquisition of the freezing response elicited by the CS in the Pavlovian task, but had no effect on the ability of the CS to reinforce acquisition of the instrumental response in the EFF task. Conversely, lesions of the B blocked reinforcing effects of the CS in the EFF task, but had no effect on acquisition of freezing to the CS in the Pavlovian task. Different outputs of LA thus seem to mediate the ability of the CS to elicit fear reactions and to reinforce novel actions.

The effects of CE lesions on the Pavlovian conditioned freezing response is consistent with previous reports that similar lesions block freezing as well as other conditioned fear responses, such as fear-potentiated startle, autonomic and endocrine changes and alterations in pain reactivity[9–13,22]. Thus, with regard to fear conditioning, the CE seems to be the motor output for the expression of various hardwired reactions elicited by the Pavlovian CS[5–7]. The failure of damage to B to affect conditioned freezing suggests that, although LA projects to CE directly and by way of B[16,17], the direct projection is sufficient to mediate Pavlovian fear conditioning.

**Table 1. Coordinates relative to the skull surface at bregma (mm) and current duration.**

| | Posterior | Medial/lateral | Ventral | Current duration (s) |
|---|---|---|---|---|
| **LA** | 2.3 | ±5.1 | 8 | 9 |
| | 3.2 | ±5.3 | 8.1 | 10 |
| | 4.0 | ±5.5 | 8.1 | 11 |
| **B** | 2.1 | ±4.9 | 9.1 | 12 |
| | 2.8 | ±4.9 | 9.3 | 15 |
| | 3.3 | ±5.3 | 9.2 | 15 |
| | 4.2 | ±5.3 | 9.3 | 15 |
| **CE** | 1.8 | ±4.4 | 8.4 | 12 |
| | 2.3 | ±4.4 | 8.4 | 12 |
| | 2.8 | ±4.4 | 8.4 | 12 |

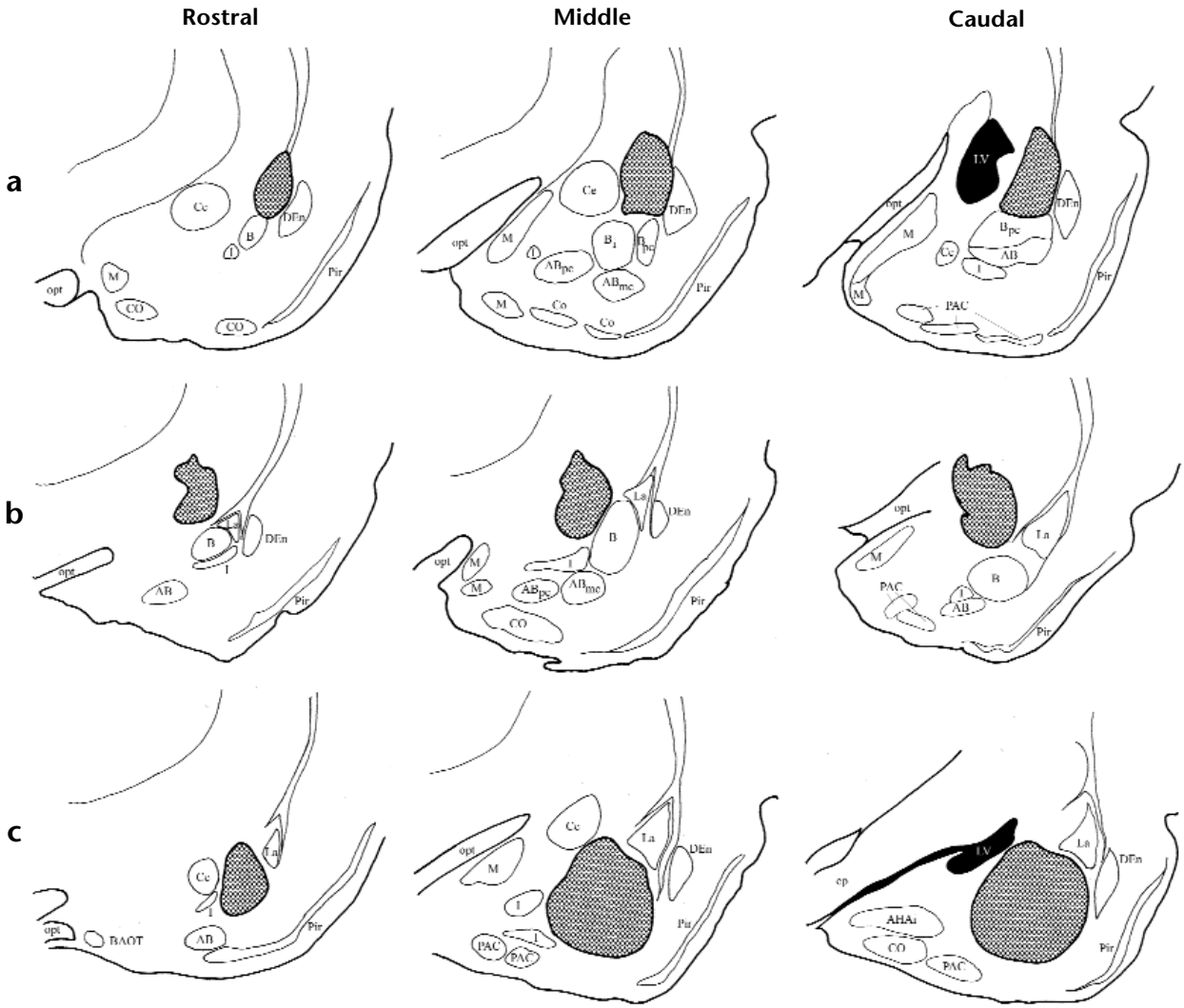


**Fig. 2.** Camera lucida drawings of the extent of (**a**) lateral (**b**) central and (**c**) basal amygdala lesions over three rostrocaudal planes. The stippled area represents the area of neuronal loss. LA, lateral nucleus; B, basal nucleus; Bi, intermediate division; $B_{pc}$, parvicellular division; AB, accessory basal nucleus; $AB_{mc}$, magnocellular division; $AB_{pc}$, parvicellular division; BAOT, bed nucleus of the accessory olfactory tract; CO, cortical nucleus; M, medial nucleus; PAC, periamygdaloid cortex; Ce, central nucleus; AHA, amygdalohippocampal area; $AHA_l$, lateral division; I, intercalated nuclei; Pir, piriform cortex; DEn, dorsal endopiriform nucleus; opt, optic tract; cp, cerebral peduncle.

The ability of a CS paired with a US to reinforce acquisition of a new task defines the CS as a conditioned reinforcer[23]. Lesions of B blocked the conditioned reinforcing properties of an aversively conditioned CS. Past studies using appetitive USs found that combined lesions of B and LA interfere with the ability of an appetitively conditioned CS to support acquisition of a new task[14]. Furthermore, combined lesions of LA and B block the acquisition of appetitive second-order conditioning[24]. Although B is required for the establishment of the new response by the conditioned reinforcer, B is not necessarily the locus of motor control nor the locus of plasticity underlying the association of the stimulus and response. B is instead more likely the source of the conditioned reinforcement. By way of anatomical interactions between the B and striatal response control circuits, conditioned reinforcement established in the amygdala may reinforce novel motor responses[14,25]. Taken together, the various results suggest some overlap in the mechanisms that enable a CS to reinforce new learning after being conditioned with either an appetitive or an aversive US. In addition, the lack of effect of damage to the CE on acquisition of conditioned reinforcement shows that CE, required for the expression of Pavlovian fear conditioning, does not mediate all of the effects of the fear-conditioned CS.

Although intra-amygdala pathways have been anatomically mapped in great detail[16,17,26], the paucity of studies explicitly examining contributions of component nuclei within the amygdala to fear conditioning prevents us from elaborating further on the intra-amygdala circuitry over which information is relayed. Most studies focus on lesions of LA, B or CE, so the effects of lesions of other areas of the amygdala are generally not known. However, preliminary studies aimed at addressing this question suggest that, whereas damage to LA and CE disrupt freezing, damage to other areas (medial, cortical, B and accessory amygdala nuclei) have no effect on auditory fear conditioning as measured by freezing (P. Majidishad, D. G. Pelli, & J. E. L., personal communication). The contribution of these and other amygdala areas to contextual fear conditioning and to conditioned reinforcement is not yet known.

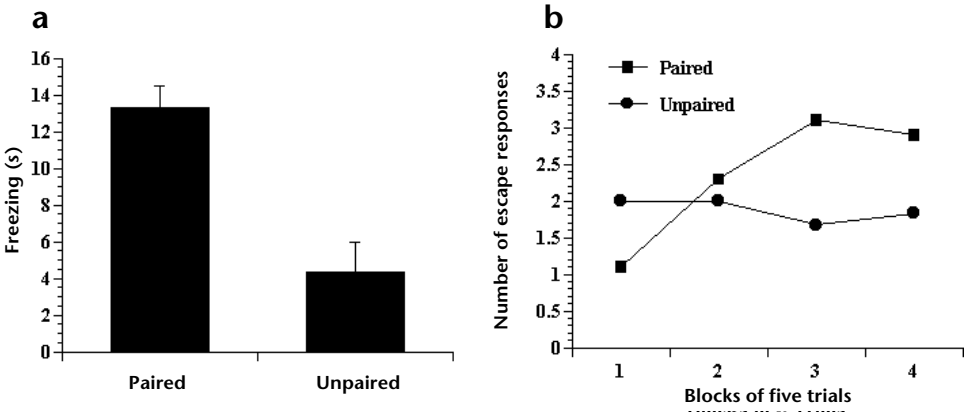


**Fig. 3.** Behavioral results from animals that received paired versus unpaired CS and US presentations. (**a**) Acquisition of freezing. (**b**) Escape-from-fear protocol. Bars represent s.e.

The behavioral effects of B and CE lesions are not due to general sensory, motor or learning impairments. Thus, as animals with lesions of the B showed normal freezing behavior in the presence of the CS, they were competent to perceive the CS, form an association and perform a conditioned response. By the same logic, the ability of rats with lesions of the CE to acquire the EFF task demonstrates that they could perceive the CS, form an association and perform an appropriate motor response.

To damage LA, B and CE, we used electrolytic lesions, which affect both cells in the region and fibers of passage. As a result, it is difficult to conclude whether the effect was due to damage to the cells within the lesion or to fibers of cells in other parts of the brain; we chose this method because it was the only one practical for inducing damage confined to the LA or B, with little or no involvement of the other. However, the dissociation we observed between effects of electrolytic lesions of LA and B, combined with studies using fiber-sparing excitotoxic lesions covering both the LA and B[11,15,27], allow us to conclude that cells in LA mediate the acquisition of conditioned fear reactions to the CS, and cells in B the acquisition of the conditioned reinforcing properties of the CS. That is, given that excitotoxic lesions of LA together with B prevent the acquisition of both conditioned fear and conditioned reinforcement, the dissociation produced by electrolytic lesions of the individual nuclei shows the necessity of cells within these structures.

An alternative interpretation of our findings is that the acquisition of the EFF task depends on the absence of freezing. That is, rats cannot perform the active response as long as they are freezing, so elimination of freezing by damaging some area (like CE) allows the rat to step into the other chamber. If freezing were simply competing with stepping into the adjacent chamber, then all groups with minimal freezing should have demonstrated high escape responses on the very first block. This was not observed. Animals with lesions of the CE or LA both had reduced freezing responses to the CS in the conditioned fear task. At the same time, in the EFF task, escape scores of both the LA- and CE-lesioned groups to the CS on block 1 were comparable to those of rats with B lesions (which had normal freezing scores) and also to those of the sham control group that received paired training. This demonstrates that the acquisition of the active response (stepping into the alternate environment) was not the default behavior of the rats in this situation and was instead gradually acquired over the training session.

It has been suggested that avoidance responses, such as running away in an active-avoidance protocol, are actually Pavlovian in nature and not instrumental[2], and that the particular response of an animal in a given task depends on the situation[28]. Thus, it is possible that the EFF task measured a hard-wired reactive response (running) that is only expressed when an exit is available. This is unlikely for a number of reasons. First, running is thought to be an unconditioned reaction to shock, and no shock was delivered in the EFF protocol[29]. Second, even when animals approach an exit, presentation of a previously fear-conditioned stimulus elicits freezing and not running away[30]. Third, if performance in the EFF task reflected Pavlovian rather than instrumental conditioning, then CS presentation should have elicited maximal escape responses on the first block of trials. Instead, they showed a gradual acquisition curve over trials, typical of what is observed in instrumental training. Thus, the EFF is unlikely to be sampling a Pavlovian response.

Our distinction between the B mediating active responses and the CE mediating reactive responses is similar to distinctions made by others[15], though important differences also exist. These researchers found that combined damage of LA and B interferes with the ability of an aversive CS to reinforce a new response, whereas lesions of CE, but not combined LA/B lesion, interfere with the conditioned reactive responses, and suggested that the amygdala has two learning systems, the LA/B (for conditioned reinforcement) and the CE (for conditioned reactions)[15]. However, as noted above, our finding that lesions restricted to the LA block Pavlovian conditioned reactions replicates several past studies[8,11]. At present, the reason for the discrepant findings is not apparent, although a number of possibilities have been proposed[31,32]. The most parsimonious explanation of the various results is that the LA is required for the Pavlovian conditioning of the CS–US association, and that projections of LA

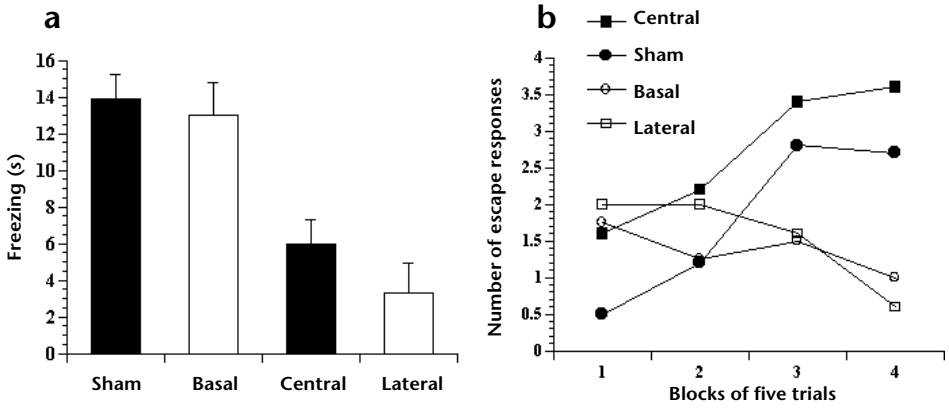


**Fig. 4.** The effects of various amygdala lesions on the acquisition of freezing (**a**) and the escape-from fear task (**b**). Group names refer to the specific subdivision destroyed. Bars represent s.e.

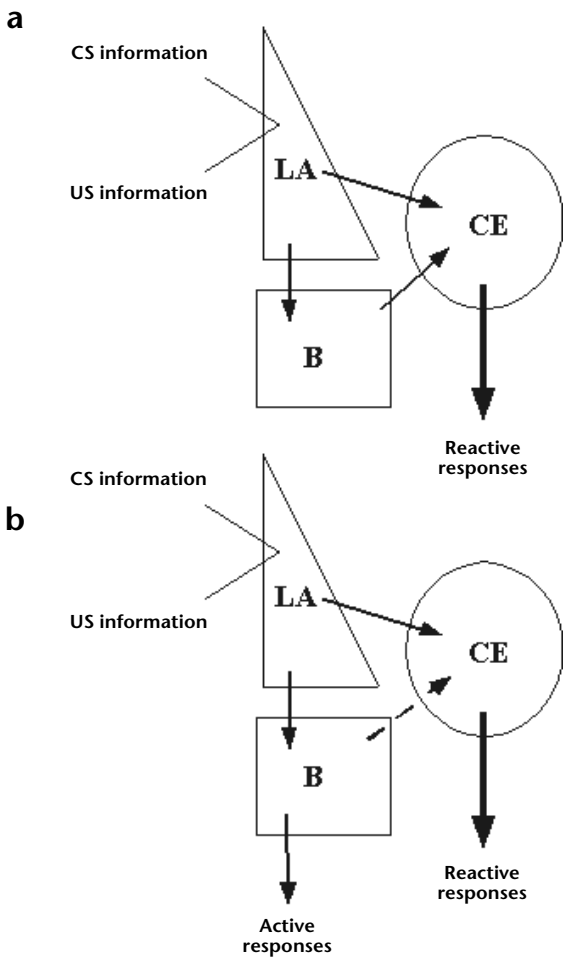


**Fig. 5.** Models of fear conditioning. (**a**) The traditional model of information flow within the amygdala mediating Pavlovian fear conditioning. CS and US information converge in the lateral nucleus (LA). Information is then relayed to the central nucleus (CE) either directly or via the basal nucleus (B). The CE mediates motor output of the various conditioned fear responses. (**b**) The new model of how fear is organized in the amygdala. CS and US convergence still occurs in the LA. The direct pathway from the LA to the CE is sufficient to mediate reflexive or 'reactive' responses, whereas the indirect pathway is not necessary. The broken arrow from the B to the CE indicates that sufficiency of the indirect pathway to mediate these behaviors has not been established. In addition, there is a second, qualitatively different output of the amygdala: projections from the LA to the B mediate the ability of a CS to reinforce the acquisition of new or 'active' responses.

to CE mediate conditioned reactions whereas projections to B mediate conditioned reinforcement of action. Regardless of the differences, the two studies are concordant in suggesting different outputs of the amygdala mediate conditioned reinforcement and conditioned reflexive responses.

Our findings also address in two ways the controversy over whether the amygdala is actually required for fear conditioning or whether it simply modulates the formation of a memory in some other area[33,34]. First, given that damage to LA disrupts both the Pavlovian and instrumental leaning tasks and that damage to B and CE disrupt only one task, LA is probably the key site of learning that supports the expression of fear responses (through the CE) and conditioned aversion (through the B), the reduction of which reinforces a new response. Second, the LA/B, but not the CE, mediates the ability of emotional events to modulate the consolidation of memory[35]. This is in contrast to traditional models of fear conditioning which posit the CE as the motor output for fear conditioning. Although these two phenomena may be mediated by distinct processes, our finding that the B can act as an independent output of the fear system somewhat reconciles these two positions. It is possible that the conditioned aversive properties mediated by the B contribute to memory consolidation. For this to be the case, however, memory consolidation would have to be a conditioned rather than an unconditioned phenomenon.

In real time, the reactive and active systems are probably engaged over different temporal scales. The reactive responses are automatic, instantaneous responses to danger. In contrast, to perform an action, it is necessary to call upon previously learned actions, to learn the action at the time through trial and error or to devise a plan of action on the spot. By studying how different actions develop in response to a single eliciting stimulus, we will be able to further explore aspects of these cognitive–emotional interactions in the brain.

In conclusion, the findings of the present study demonstrate that the neural pathways and mechanisms mediating the ability of a CS to elicit reactive responses and to reinforce new responses can be dissociated (**Fig. 5**). We suggest that the CE is part of a reactive response output system that responds to stimuli that predict danger by eliciting hard-wired defense responses, whereas the B is part of an active fear output system through which new responses are acquired to minimize exposure to a noxious stimulus, as proposed by two-process theory[4,36–38]. Furthermore, these two systems are outputs of a common learning system involving the LA and its afferent input from sensory systems processing the CS.

## Methods

**Surgery.** Sprague-Dawley rats weighing 300–350 g were injected with 0.15 mg per kg atropine intraperitoneally (ip), anesthetized with Nembutal (i.p., 45 mg per kg) and placed in a stereotaxic frame. Electrolytic lesions were made by passing positive current (0.5 mA) at each site through a monopolar electrode insulated with epoxy to within 200 μm of the tip. Coordinates for the various lesion sites and current times are given in Table 1. Sham animals received the identical treatment with the following two exceptions. First, the electrodes were placed 0.5–1 mm dorsal to the target structure. Second, no current was passed through the electrode. After surgery, animals were allowed to recover undisturbed for one week before commencement of behavioral procedures.

**Apparatus.** The apparatus consisted of three distinct chambers differing in their dimensions, odor, lighting and location. Fear conditioning occurred in a standard fear-conditioning chamber (Chamber A, Model E10-10, Coulbourn Instruments, Lehigh Valley, Pennsylvania). Tests for freezing were performed in a distinct room using standard operant boxes, housed in sound attenuated shells (Chamber B, ENV-001, Med Associates, Georgia, Vermont).

The avoidance chamber used for the modified EFF task consisted of a rectangular Plexiglas box containing two identical compartments separated by a sliding guillotine door that was manually controlled by the experimenter. Both compartments had black Plexiglas floors. The avoidance chamber itself was situated on the floor of the same room in which fear conditioning took place. The drop pan beneath the chamber contained animal bedding. The sole source of illumination was a red light bulb centered over the top of the apparatus. The avoidance chamber was made completely of Plexiglas backed by black construction paper. The neutral retaining box was of the same type as the animal's home cage and was lined with animal bedding.

**Behavioral procedures.** All animals were habituated to all three chambers in a counterbalanced manner for 15 min over three consecutive days.

**Phase 1: fear conditioning.** Either paired or unpaired fear-conditioning trials were administered to animals on days 1 and 2. Paired fear-conditioning consisted of 5 presentations a day for 2 consecutive days of a 10-kHz, 75-dB tone for 20 s that coterminated with a 0.5-s, 0.5-mA scrambled footshock (Chamber A). The mean intertrial interval was 120 s with a range from 90 s to180 s. Unpaired procedures entailed the same number of CS and US presentations as the paired groups; however, the two never occurred within 60 s of one another.

**Phase 2: test.** On day 3, individual rats were placed in chamber B and allowed to explore for 2 min. At this time, the CS was presented for 20 s, and the amount of time spent freezing was recorded. Freezing was defined as immobility with the exception of respiratory-related movement.

**Phase 3.** In each trial, the animal was placed in the compartment of the avoidance chamber designated as the start side and allowed to explore. After 10 s, the experimenter opened the door, and the 10-s pre-CS period began, followed by a 30-s presentation of the CS. If the animal stepped into the alternate environment, the CS was immediately terminated, and the rat was allowed to spend 1.5 min in the safe side before being moved to a neutral holding cage for the intertrial interval (1.5 min). If an animal failed to make a response before CS termination, then it was immediately moved to the holding cage for the inertrial interval[3]. The animals were given a total of 20 training trials over 2 days.

**Experimental groups.** Two groups of rats did not receive any surgery. These animals were run to verify that the acquisition of both the EFF task and freezing were contingent on an associative as opposed to non-associative relationship between the CS and US. The paired group ($n = 7$) received paired fear conditioning, and the second group, Unpaired ($n = 6$), received unpaired fear conditioning. Both groups then received phase 2 and 3 as above.

All surgical groups received paired presentations of the CS and US during fear conditioning and then received EFF training. The group sizes, after discarding animals with unacceptable lesions, were sham ($n = 10$), B ($n = 8$), CE ($n = 6$) and LA ($n = 6$).

**Histology.** Upon completion of the behavioral studies, sham and lesioned animals were given an overdose of Nembutal (45 mg per kg), and were perfused with physiological saline followed by 10% buffered formalin. The brains were stored in 30% sucrose/formalin solution and sectioned on a cryostat at 60 µm. Every other section was collected on a subbed slide and stained with cresyl violet. Sections were examined and images digitally captured under bright-field microscopy using Stereo Investigator (v.3.16, MicrobrightField).



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