

Research report

Basolateral amygdala lesions in the rat produce an abnormally persistent latent inhibition with weak preexposure but not with context shift

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Abstract

Latent inhibition (LI) refers to retarded conditioning to a stimulus as a consequence of its nonreinforced preexposure. We have recently reported that basolateral amygdala (BLA) lesions lead to an abnormally persistent LI under conditions that normally disrupt LI, namely, extended conditioning. This study tested whether BLA lesions would induce abnormally persistent LI under two additional conditions disrupting LI in controls, namely, context shift and weak preexposure. LI was measured in an active avoidance procedure. In the first experiment, rats received 100 nonreinforced preexposures and were conditioned either in the same or in a different context from that of the preexposure stage. In the second experiment, rats received 50 nonreinforced preexposures and were conditioned in the same context as that of preexposure. Sham-operated rats showed LI in the same but not in the different context condition or with low number of preexposures. BLA lesions produced abnormally persistent LI with low number of preexposures but not with context shift. It is suggested that the BLA is involved in LI modulation based on the impact of preexposure and conditioning but not on contextual information.

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1. Introduction

Latent inhibition (LI) is the retarded capacity of a stimulus that had been preexposed without consequences to subsequently acquire behavioral control through pairings with reinforcement, compared to the same stimulus that was not preexposed (for reviews see [10,27,45–47]). Investigations of the neural substrates of LI have shown that LI is disrupted by lesions of the shell subregion of the nucleus accumbens and the entorhinal cortex (e.g. [6,20,44,48]), suggesting that these regions play a role in regulating LI. Surprisingly, intact LI has been found following lesions to numerous brain

areas, including the nucleus accumbens or its core subregion [20,22,36,48,49], the hippocampus ([6,16,17,35,44]; but see [13]), the medial prefrontal cortex [19,23], and in some reports, the basolateral amygdala (BLA; [40,50]; but see [5]). While an absence of a behavioral change following damage to these regions would routinely be interpreted as indicating that they play no role in LI, the effects of some of these lesions had been shown to emerge following various environmental manipulations that *disrupted* LI in controls. Specifically, rats with lesions of the nucleus accumbens showed LI when conditioning was preceded by low number of preexposures [21], hippocampal lesions preserved LI in spite of context change between preexposure and conditioning [16,17], and lesions of the basolateral amygdala (BLA) and orbitofrontal cortex preserved LI in spite of increased number conditioning trials [40]. This novel phenomenon of abnormally persistent LI offers several advantages. First, it enables uncovering the otherwise masked involvement of certain brain regions in LI.

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Second, it enables reaching clearer conclusions regarding the non involvement of some brain areas, such as the medial prefrontal cortex, whose damage neither disrupts nor potentiates LI [19,23,40]. Finally, it may allow a refinement of the functions (e.g. contextual or reinforcement-related modulation) of the different brain regions in LI.

Our recent finding that BLA lesion induced abnormally persistent LI with strong conditioning [40] fits the evidence showing that lesions of the BLA impair animals' ability to alter behavior to stimuli when reinforcement contingencies or reward values are changed [1,14,26,37,41]. Testing the effects of BLA lesion on LI using additional manipulations that disrupt the phenomenon in control rats may help to refine the function of BLA in LI. This is of particular interest given that studies of the effects of BLA lesion on LI have yielded inconsistent results: while we have demonstrated BLA lesion-induced persistence of LI, Coutureau et al. [5] reported that excitotoxic BLA lesions disrupted LI. We, therefore, tested whether BLA lesion would counteract the disruptive effects of two additional manipulations, namely, context change between preexposure and conditioning or low number of preexposures. We used an electrolytic BLA lesion, because we found that such lesions produce the same effects on LI like excitotoxic but without impairing fear conditioning in the nonpreexposed group [40,50].

2. Materials and methods

2.1. Subjects

Male Wistar rats (Sackler Faculty of Medicine, Tel-Aviv University, Israel) approximately 4 months old and weighing 360–490 g, were housed four to a cage under reversed cycle lighting (lights on: 07:00–19:00) with ad lib access to food and water. All experimental protocols conformed to the guidelines of the Institutional Animal Care and Use Committee of Tel-Aviv University, Israel; and to the guidelines of the NIH (animal welfare assurance number A5010-01, expires on 11/30/06). All efforts were made to minimize the number of animals used and their suffering.

2.2. Surgery

Rats were given an i.p. injection of diazepam (0.6 mg/kg) and 5 min later were anaesthetized with an i.p. injection of avertin (10 ml/kg). They were placed in a stereotaxic frame and an incision was made into the scalp to expose the skull. The vertical coordinates of bregma and lambda were measured in order to align them in the same (level head) plane. A small square of bone was removed over the spots where the electrodes would later enter. Bilateral electrolytic lesions were made by passing a 0.5 mA, 15 s current via a 0.3 mm electrode, insulated except for the tip. A constant current DC source was used. BLA lesion coordinates were: 2.8 mm posterior to bregma, 5 mm lateral to the midline, 8.5 mm ventral to the skull [31]. Sham-operated controls underwent the same surgical procedure, but the electrodes were inserted 6.5 mm ventral to the skull and no current was passed. At the end of surgery, the hole in the bone was covered by sterispon, and the scalp incisions were

sutured by Michel clips. Following surgery rats were returned to their home cages and allowed 14 days of recovery before the initiation of behavioral testing.

2.3. Behavioral apparatus

Campden Instruments shuttle boxes without a barrier between the two compartments, each enclosed in a ventilated sound-attenuating chest. The preexposed-to-be-conditioned stimulus was a 10 s flashing-light generated from two light sources each located at the center of two walls, flashing at a rate of 1.3 Hz. Shock was supplied to the grid floor by a Campden Instruments shock generator and shock scrambler set at 0.5 mA intensity and 1 s duration. Equipment programming and data recording were computer controlled. In Experiment 1, two sets of boxes were used, one as context A and the second as context B. Each set of boxes was housed in a different room in the laboratory. In addition, the two contexts differed in the following respects: one set of boxes (A) had an odor produced by the addition of a small amount of eucalyptus oil to the tray located below the grid floor, and the other set (B) had the odor produced by cinnamon oil. In the latter boxes, the door was covered with black and white checkered wallpaper and the grid floor was covered with a wooden board. In Experiment 2, only set A was used.

2.4. Procedure

The procedure consisted of two stages given 24 h apart. *Pre-exposure* The preexposed rats received 100 (Experiment 1) or 50 (Experiment 2) presentations of the flashing light with a fixed inter-trial-interval of 50 s, whereas the nonpreexposed rats were merely confined in the box for an identical period of time. *Conditioning* all rats received 100 avoidance trials presented on a variable interval of 50 s ranging from 1 to 100 s. Each avoidance trial began with the flashing light stimulus followed by a 1 s shock, the stimulus remaining on with the shock. A crossing response to the opposite compartment during stimulus presentation terminated the stimulus and prevented the delivery of the shock (avoidance response). A crossing response during shock terminated the stimulus and the shock (escape response). If the animal failed to cross during the entire stimulus-shock trial, the stimulus and the shock terminated after 11 s. The number of avoidance responses was recorded in 10 trial blocks. LI is defined as poorer avoidance of the preexposed compared to nonpreexposed rats. In Experiment 1, in the same context condition, preexposure and conditioning stages were conducted in context A, and in the different context condition, preexposure was conducted in context B and conditioning was conducted in context A. In Experiment 2, preexposure and conditioning were conducted in context A.

2.5. Histology

Within a week after the completion of behavioral testing, rats were anaesthetized with an overdose of sodium pentobarbital (60 mg/kg, i.p.) and perfused intracardially via the ascending aorta with a solution of 0.9% NaCl (saline) at room temperature for 5 min followed by 10% buffered formalin for 15 min (flow rate 35 ml/min). Their brains were then removed from their skulls and placed in 10% buffered formalin for at least 24 h. The brains were sectioned in the coronal plane using freezing microtome at 60 μ m thickness. Every

second section was mounted and stained with Cresyl violet for histological examination. Verification of the placement and the extent of the lesions used the atlas of Paxinos and Watson [31].

3. Results

3.1. Histological assessment

A reconstruction of the maximal (gray) and minimal (black) extents of the BLA lesions is presented in Fig. 1. In most rats, the lesion extended from 2.3 to 3.3 mm anterior to bregma. In the mediolateral axis, the lesion extended from 4.2 to 5.6 mm lateral to the midline. The horizontal location of the lesion was typically at about the level of the bottom of the external capsule.

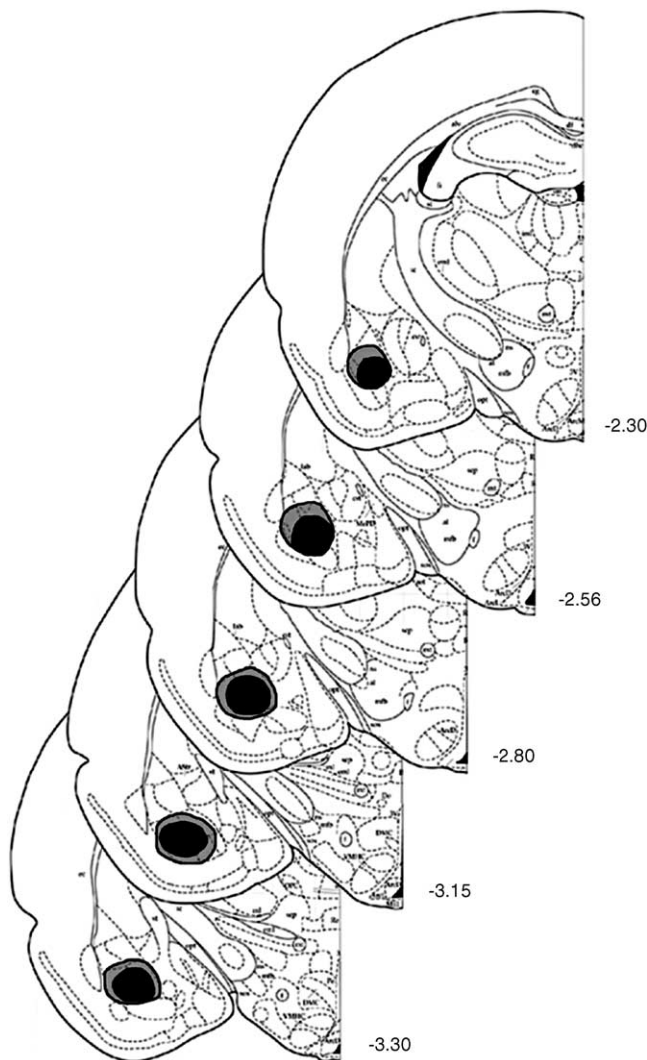


Fig. 1. Reconstruction of the minimal (black) and maximal (gray) extents of the BLA lesions. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson [31].

3.2. Behavior

3.2.1. Experiment 1—the effects of BLA lesion on LI with same or different context in preexposure and conditioning

20 sham and 20 BLA-lesioned rats were randomly assigned to eight experimental groups (n per group = 5) in a $2 \times 2 \times 2$ factorial design with main factors of preexposure (0, 100), lesion (sham, BLA) and context (same, different).

Fig. 2A presents the mean number of avoidance responses, divided into 10 blocks of 10 trials each, of the preexposed and nonpreexposed sham- and BLA-lesioned rats preexposed and conditioned in the same or in different contexts. As can be seen, LI, i.e. poorer avoidance performance of the preexposed as compared to the nonpreexposed rats, was present in sham and BLA rats that were preexposed and conditioned in the same context, but not in sham and BLA rats preexposed and conditioned in different contexts. This was supported by ANOVA with main factors of preexposure, lesion and context, and a repeated measurements factor of ten 10-trials blocks, which yielded a significant main effect of blocks ($F_{(9,288)} = 40.57, p < 0.0001$) and significant preexposure \times context \times blocks interaction ($F_{(9,288)} = 2.58, p < 0.01$). Fig. 2B presents this interaction, i.e. the mean number of avoidance responses, divided into 10 blocks of 10 trials each, of rats preexposed and conditioned in the same or in different contexts. As can be seen, there was LI in the same but not in the different context condition. LSD post-hoc comparisons comparing the nonpreexposed and preexposed rats in each block, confirmed the existence of LI in the same context condition on blocks 2–7 and 10 (all p 's < 0.05) but not in the different context condition throughout the 10 blocks.

3.2.2. Experiment 2—the effects of BLA lesion on LI following low number of preexposures

24 sham and 24 BLA-lesioned rats were randomly assigned to four experimental groups (n per group = 12) in a 2×2 factorial design with main factors of preexposure (0, 50) and lesion (sham, BLA).

Fig. 3 presents the mean number of avoidance responses, divided into 10 blocks of 10 trials each, of the preexposed and nonpreexposed sham- and BLA-lesioned rats. As can be seen, LI, i.e. poorer avoidance performance of the preexposed as compared to the nonpreexposed rats, was evident in the BLA-lesioned group but not in the sham group. This was supported by ANOVA with main factors of preexposure and lesion, and a repeated measurements factor of ten 10-trials blocks, which yielded a significant main effect of blocks ($F_{(9,396)} = 52.91, p < 0.0001$), as well as significant preexposure \times blocks ($F_{(9,396)} = 4.52, p < 0.0001$), lesion \times blocks ($F_{(9,396)} = 2.67, p < 0.01$), and preexposure \times lesion \times blocks ($F_{(9,396)} = 2.27, p < .05$), interactions. LSD post-hoc comparisons comparing the nonpreexposed and preexposed rats in each block confirmed the existence of LI in the BLA lesion condition in blocks 3–10 (all p 's $< .01$) but not in the sham condition throughout the 10 blocks.

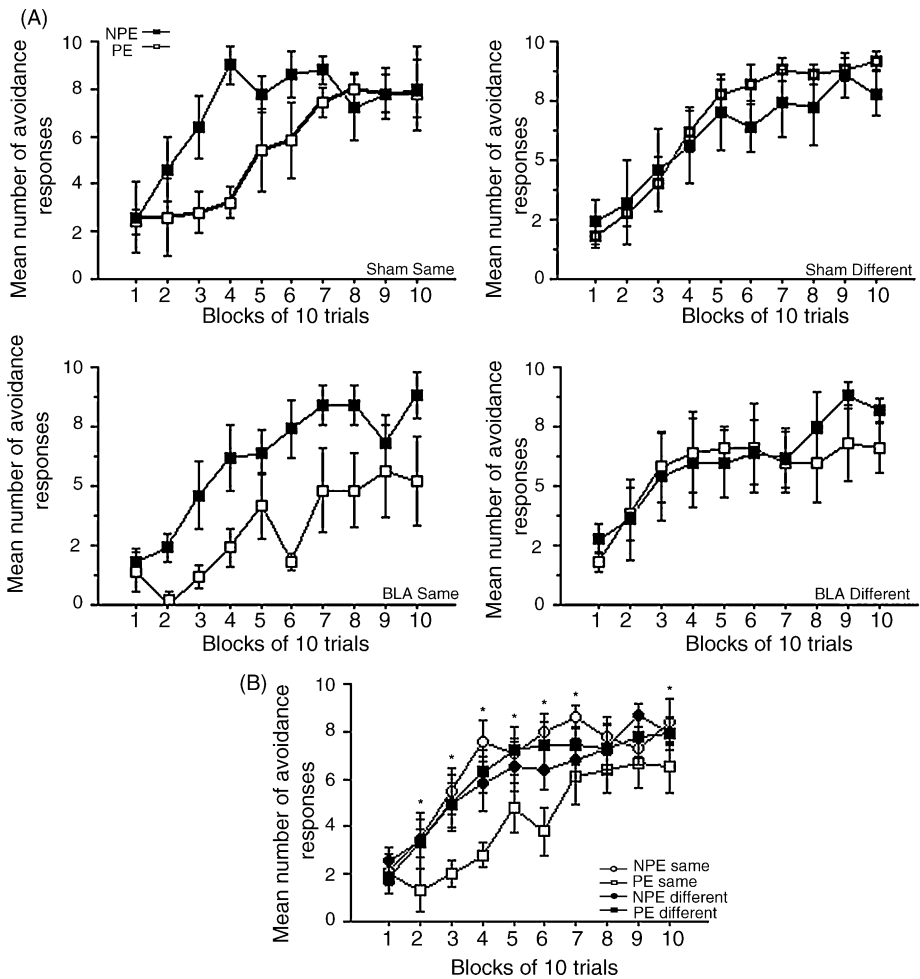


Fig. 2. (A) Means and standard errors of the number of avoidance responses of the preexposed (PE) and nonpreexposed (NPE) sham-lesioned rats preexposed and conditioned in the same (top left) or different (top right) contexts, as well as BLA-lesioned rats preexposed and conditioned in the same (bottom left) or different (bottom right) contexts. (B) Means and standard errors of the number of avoidance responses of the PE and NPE groups in the same and different context conditions. Asterisks indicate a significant difference between the PE and NPE groups.

4. Discussion

BLA-lesioned non-preexposed rats were able to acquire avoidance responding like their sham controls. This is consistent with some reports [18,30], although studies testing the effects of BLA lesions on avoidance have yielded various results, including less efficient acquisition of avoidance [4,51], as well as facilitated avoidance [12].

As expected, the manipulations of context shift and weak preexposure disrupted LI in sham lesioned rats [3,11,16,17,32,38,43]. Thus, in Experiment 1, rats that received 100 nonreinforced light preexposures showed LI, i.e. poorer avoidance than the nonpreexposed rats, if preexposure and conditioning took place in the same context, but if the context was changed between preexposure and conditioning, LI was lost, i.e. preexposed rats showed levels of avoidance equivalent to nonpreexposed rats. In Experiment 2 rats preexposed and conditioned in the same context but given 50 nonreinforced preexposures did not display LI.

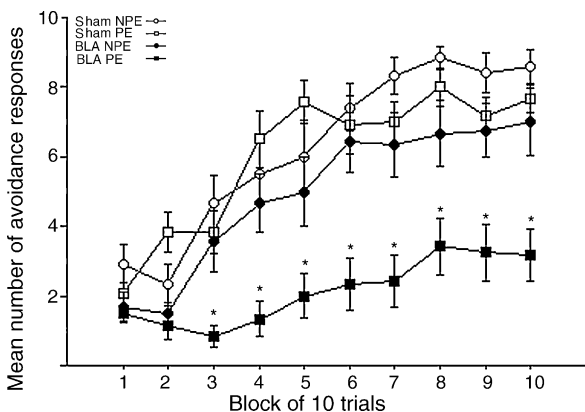


Fig. 3. Means and standard errors of the number of avoidance responses of the preexposed (PE) and the nonpreexposed (NPE) groups in sham and BLA lesioned rats. Asterisks indicate significant difference between the PE and NPE groups in each block.

Rats with BLA lesions showed LI under conditions that yielded LI in sham controls, namely, high number of preexposures in the context of conditioning. Moreover, reduction of the number of preexposures to 50 failed to disrupt LI in BLA-lesioned rats, suggesting that the lesion impaired rats' capacity to adjust their responding according to the altered outcome associated with the CS in conditioning. Damage to BLA is known to produce impairments in experimental tasks in which reinforcement contingencies or reward values are changed [1,14,26,37,41]. For example, animals with BLA lesions acquire discrimination normally but are impaired on reversal of discrimination [41]. Similarly, in reinforcement devaluation tasks, BLA animals acquire normally associations between stimuli and reinforcement, but fail to modify their response to the stimulus when the incentive value of the reinforcement is reduced [1,14,26]. Such findings have been taken to suggest that the BLA enables stimuli to access the current motivational/affective value of the associated outcome for guiding conditioned responding [1,2,7,9,14,15,34,37,41,42]. Presence of LI with weak preexposure is consistent with the above findings and notions in demonstrating that preexposed BLA-lesioned rats failed to form/encode the association between the preexposed stimulus and a representation of the outcome value in conditioning, thus promoting the expression of the effects of weak preexposure. Under conditions of strong preexposure, which overcome the effects of conditioning in sham rats, the effects of impaired BLA-dependent learning system cannot be seen. BLA lesion-induced LI with weak preexposure found here supplements our recent demonstration that this lesion produced LI under conditions of strong conditioning (high number of conditioning trials) which disrupted LI in sham lesioned rats. While strong conditioning overwhelmed the effects of preexposure in sham rats, it failed to do so in BLA-lesioned rats, consistent with a failure to form/encode stimulus-outcome associations in these rats [40].

While the present results confirm our previous findings of intact and potentiated LI following both excitotoxic and electrolytic BLA lesions in a conditioned emotional response procedure [40,50], they conflict with those of Coutureau et al. [5] and Schauz and Koch [39]. They found disrupted LI following excitotoxic BLA lesion. Coutureau et al. [5] suggested that one reason for the discrepancy could be the use of aversive versus appetitive unconditioned stimulus (US). This possibility is unlikely because there is no evidence that the effects of various lesions or pharmacological manipulations on LI depend on the nature of the US used. Moreover, in the present study, non-preexposed BLA-lesioned rats performed equally to non-preexposed controls, indicating that BLA lesions did not affect aversive conditioning. Nevertheless, it remains to be determined whether BLA lesion would produce persistent LI with appetitive reinforcement. Differences in the size of the lesions could be another reason (for an elaborated discussion of the inconsistency between our and Coutureau et al.'s results, see [40]). Schauz and Koch [39] showed that LI was disrupted by infusion of the competitive NMDA

antagonist AP-5 into BLA before preexposure only, raising the question as to how an interference with BLA processing can lead to disrupted LI when occurring in preexposure yet spare LI when occurring in both the preexposure and conditioning stages. This inconsistency could be reconciled by assuming that BLA manipulation in preexposure did not prevent the acquisition of the CS-no outcome association but rather decreased its strength, making the situation functionally equivalent to low number of preexposures as used here. While this by itself would be expected to disrupt LI, presence of BLA perturbation also in conditioning would impair rats' capacity to encode the association between the CS and the outcome value in conditioning, and under such conditions, LI could emerge, as found here. Taken together, the extant data on the effects of BLA perturbations on LI suggest that the role of this region in LI may be complex, and that the elucidation of LI alterations resulting from impaired BLA functioning would be best addressed by using reversible manipulations confined to either preexposure or conditioning while manipulating the balance between the impact of preexposure and conditioning.

No LI was seen in BLA-lesioned rats with context shift: these rats, like sham controls, did not show LI under this condition, suggesting that BLA lesion does not impair the processing of contextual information in LI. Although BLA has been shown to play a central role in contextual conditioning [8,28,33], this applies to situations in which the context serves as the CS. In LI to discrete stimuli, context plays a very different role, namely, that of an "occasion setter" that modulates the expression of the CS-no consequence association, and this function of the context is apparently mediated by the hippocampus [16,24,25,29]. Indeed, hippocampal cell lesion or inactivation have been shown to produce persistent LI with context shift [16,17], pointing to a dissociation between hippocampal and BLA roles in LI. Importantly, the fact that BLA lesion did not prevent LI disruption by context shift indicates that this lesion does not produce a general impairment in animals' capacity to alter responding, but rather impairs the processing of a specific type of information. We have recently suggested that the hippocampus provides information on context, whereas BLA provides information regarding the current motivational/affective value of the CS, which determine whether LI is present or disrupted [46].

In sum, while previous LI studies focused on disrupted LI, the present study joins a growing body of evidence introducing the phenomenon of abnormally persistent LI. It is becoming evident that the expression of LI does not depend on the integrity of several brain areas, namely, the orbitofrontal cortex, the nucleus accumbens, the hippocampus and the BLA, because damage to these areas spares LI under conditions allowing for it in controls. Instead, these regions play a role in the *non-expression* of LI when the impact of conditioning is increased, the impact of preexposure is reduced, or the context changes between preexposure and conditioning. The fact that BLA lesions produced abnormally persistent LI with strong conditioning and weak preexposure

but not with context shift, while the hippocampus was shown to potentiate LI with context shift, implies that the ability of each of the above areas to restrict the expression of LI is specific to certain conditions. Thus, BLA might be involved in LI modulation based on the impact of preexposure and conditioning, while the hippocampus is involved in contextual modulation of LI. Without the intact and integrated activity of these areas the LI phenomenon would become rigid and insensitive to the ever-changing situational demands.

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