

Research report

Latent inhibition is disrupted by nucleus accumbens shell lesion but is abnormally persistent following entire nucleus accumbens lesion: The neural site controlling the expression and disruption of the stimulus preexposure effect

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Abstract

Latent inhibition (LI) is the proactive interference of repeated nonreinforced preexposure to a stimulus with subsequent performance on a learning task involving that stimulus. The present experiments investigated the role of the nucleus accumbens (NAC) in LI. LI was measured in a thirst motivated conditioned emotional response procedure with low or high number of conditioning trials, and in two-way active avoidance procedure with the stages of preexposure and conditioning taking place in the same or different contexts. Sham-lesioned rats showed LI with low but not high number of conditioning trials and if preexposure and conditioning took place in the same context but not if the context was changed between the stages. Lesion to the shell subregion of the NAC disrupted LI but LI was preserved in rats with a combined lesion to the NAC shell and core subregions. Moreover, rats with a combined shell-core lesion persisted in showing LI in spite of high number of conditioning trials and in spite of context change. These results show that the NAC is not essential for the *acquisition* of LI but rather plays a key role in regulating the *expression* of LI. Moreover, they suggest that the two subregions of the NAC contribute competitively and cooperatively to this process, selecting the response appropriate to the stimulus-no event or the stimulus-reinforcement association in conditioning.

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1. Introduction

Organisms that receive repeated nonreinforced preexposure to the conditioned stimulus (CS) are slower in generating a conditioned response to this stimulus when it is subsequently paired with reinforcement. This biasing effect of past experience on current performance, latent inhibition (LI), enables efficient allocation of attentional and learning resources by downgrading the behavioral control of stimuli that have no significant consequences, and can be demonstrated in a broad range of learning procedures and species, including humans. LI has played a central role in learning theory and research [9,38,40,58,68]. In the past two

decades, attention has focused on the neural substrates of LI [17,42,58,69,70].

The investigation of the neural substrates of LI has indicated that the nucleus accumbens (NAC) is a key region regulating LI. Disruption of LI by systemic amphetamine is prevented by intra-accumbal infusion of dopamine DA antagonist or by 6-hydroxydopamine (6-OHDA)-induced DA depletion from the NAC [29], and infusion of dopamine DA agonist into the NAC may under some conditions disrupt LI ([29,62]; but see [31]). The role of NAC DA has been supported by the demonstration that DA release in the NAC elicited by a conditioned stimulus was eliminated by nonreinforced preexposure of the stimulus prior to conditioning [78]. Consistent with the extensive evidence that the NAC contains two anatomically and functionally distinct subregions, shell and core (e.g., [10,19,20,

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25,30,41,47,48,79)) it has been shown that LI is disrupted by shell but not by core lesion [28,65,72,73]. Accordingly, reduction in the NAC DA release by stimulus preexposure was shown to be confined to the shell [26,27,44]. Given the above, it is puzzling that lesions to the entire NAC leave LI intact [32,72]. Moreover, NAC DA depletion or blockade led to the emergence of LI following low number of preexposures that did not produce LI in controls [29].

This inconsistency can be reconciled if it is assumed that LI is modulated by, but not dependent on, the NAC. One model that specified precisely such a role for the NAC in LI is the switching model of LI [69,70,71]. According to this model, LI involves the acquisition of two independent and conflicting associations in preexposure (CS-no event) and in conditioning (CS-reinforcement), which compete for behavioral expression during conditioning or during subsequent retention. The NAC determines whether in conditioning, the animal responds according to the CS-no event or to the CS-reinforcement contingency. Briefly, the NAC is activated when the previously nonreinforced stimulus is followed by reinforcement. Since such activation leads to excessive behavioral and cognitive switching [45,63,67], it promotes a switch of responding according to the CS-reinforcement association. The CS-no event association acquired in preexposure continues to control behavior in conditioning because the switching mechanism of the NAC is temporarily inhibited.

In terms of the switching model, the fact that rats with intact core (shell-lesioned) switch to respond according to the CS-reinforcement contingency (disrupted LI), whereas rats with intact shell (core-lesioned) continue to respond according to the CS-no event association (spared LI), suggests that in the intact brain: (a) the mechanism mediating switching to respond according to the CS-reinforcement contingency in the conditioning stage resides in the NAC core; and (b) the core-based switching mechanism can be inhibited by the shell [70–73]. This raises two major predictions: (1) While rats sustaining a shell lesion will not show LI, rats with a larger NAC lesion which includes a lesion to the core will show LI. (2) Rats with a combined shell-core lesion will persist in showing LI under conditions that disrupt the phenomenon in sham-lesioned rats.

The present experiments were designed to test these predictions. Because lesion-induced abnormally persistent LI can be only manifested under conditions that normally disrupt LI, we not only tested the effects of the NAC lesion under conditions yielding LI in sham operated controls, but also used two procedures which disrupted LI in sham rats, namely, an increase in the number of conditioning trials and a context change between preexposure and conditioning. Experiments 1 and 2 compared LI in rats with an electrolytic shell lesion and a combined shell-core electrolytic lesion using the conditions of restricted conditioning and same context that yielded LI in sham controls. Experiments 3 and 4 tested the effects of a combined shell-core electrolytic lesion on LI

using same or different context, and restricted or extended conditioning, respectively.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Sackler Faculty of Medicine, Tel-Aviv University, Israel) approximately 4 months old and weighing 360–480 g, housed four to a cage under reversed cycle lighting (lights on: 07:00–19:00 h) with ad lib access to food and water except for the duration of the CER experiments. 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 i.p. injection of avertin (0.01 ml/g). 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 same (level head) plane. A small square of bone was removed over the spots where the electrodes would later enter. Bilateral electrolytic shell and shell-core lesions were made using a 0.3 mm electrode, insulated except for the tip. A constant current DC source was used. Shell-lesioned rats were exposed to one anterior and one posterior lesion, bilaterally, using a 1 mA, 8 s current. Shell coordinates were: anterior –1.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 6.5 mm ventral to dura; posterior –1.1 mm anterior to bregma, 0.8 mm lateral to the midline, and 6.5 mm ventral to dura. Combined shell-core lesioned rats were exposed to an identical shell lesion, and in addition, to an anterior and posterior bilateral core lesion using a 1 mA, 15 s current. Core coordinates were: anterior –2.0 mm anterior to bregma, 1.8 mm lateral to the midline, and 6.5 mm ventral to dura; posterior –1.4 mm anterior to bregma, 1.8 mm lateral to the midline, and 6.8 mm ventral to dura [49]. Control (sham operated) rats underwent surgical procedure identical to that of shell- or combined-lesioned rats, but the electrodes were inserted 1 mm ventral to dura 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 and procedures

The effects of shell and combined shell-core lesions on LI were tested in two procedures, thirst motivated conditioned emotional response (CER) and two-way active avoidance. In each of these procedures, we used conditions that yielded or disrupted LI in sham controls. In the CER procedure, we manipulated the level of conditioning: 2 conditioning trials were used to yield LI, and 5 conditioning trials were used to disrupt LI. In the avoidance procedure we manipulated contextual conditions: preexposure and condition-

ing were conducted in the same context to yield LI, or in different contexts to disrupt LI.

2.3.1. LI in the CER procedure

2.3.1.1. Apparatus. Campden Instruments rodent test chambers with a retractable bottle, each enclosed in a ventilated sound-attenuating chest. When the bottle was not present, the hole was covered with a metal lid. The preexposed to-be-conditioned stimulus was a 10 s, 80 dB, 2.8 kHz tone produced by a Sonalert module. Shock was supplied through the floor by a Campden Instruments shock generator and shock scrambler set at 0.5 mA intensity and 1 s duration. Licks were detected by a Campden Instruments drinkometer. Equipment programming and data recording were computer controlled.

2.3.1.2. Procedure. Ten days prior to the beginning of the LI procedure, rats were put on a 23 h water restriction schedule and handled for about 2 min daily for 5 days. On the next 5 days, rats were trained to drink in the experimental chamber for 5 days, 15 min/day. Water in the test apparatus was given in addition to the daily ration of 1 h given in the home cages. The LI procedure was conducted on days 11–14 and consisted of four stages given 24 h apart. **Preexposure:** With the bottle removed, the preexposed rats received 40 tone presentations with an inter-stimulus interval of 40 s. The nonpreexposed rats were confined to the chamber for an identical period of time without receiving the tone. **Conditioning:** With the bottle removed, each rat received 2 or 5 tone-shock pairings given 5 min apart. Shock immediately followed tone termination. **Retraining:** Rats were given a 15 min drinking session as in initial training. **Test:** Each rat was placed in the chamber and allowed to drink from the bottle. When the rat completed 75 licks the tone was presented for 5 min. Time to first lick, time to complete licks 1–50, time to complete licks 51–75 (before tone onset), and time to complete licks 76–100 (after tone onset) were recorded. Times to complete licks 76–100 were logarithmically transformed to allow analysis of variance. Longer log times indicate stronger suppression of drinking. LI consists of shorter log times to complete licks 76–100 of the preexposed as compared to nonpreexposed rats.

2.3.2. LI in the avoidance procedure

2.3.2.1. 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. 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.

2.3.2.2. Procedure. The procedure consisted of two stages given 24 h apart. **Preexposure:** The preexposed rats received 100 presen-

tations of the flashing light with a fixed inter-trial-interval of 50 s, whereas the nonpreexposed rats were confined in the box. **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 manifested as lower number of avoidance responses of the preexposed as compared to nonpreexposed rats. In the same context condition, the preexposure and conditioning stages were both conducted in context A. In the different context condition, preexposure was conducted in context B and conditioning was conducted in context A.

2.4. 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 [49].

2.5. Statistical analysis

In the CER procedure, times to complete licks 51–75 (prior to tone onset) and mean log times to complete licks 76–100 (after tone onset) were analyzed using a two-way (Experiment 1) or three-way (Experiment 3) ANOVA. In cases of significant interactions, Tukey's HSD post hoc comparisons were used to assess the difference between nonpreexposed and the preexposed groups within each condition.

In the avoidance procedure, mean number of avoidance responses was analyzed using a two-way (Experiment 2) or three-way (Experiment 4) ANOVA with a repeated measurements factor of 10 blocks. Significant interactions were followed by one-way ANOVAs with a repeated measurements factor of blocks comparing the nonpreexposed and preexposed groups within each condition.

3. Results

3.1. Histological assessment

Fig. 1 presents representative reconstructions of shell (A) and combined shell-core (B) electrolytic lesions in successive brain sections taken from the atlas of Paxinos and Watson [49].

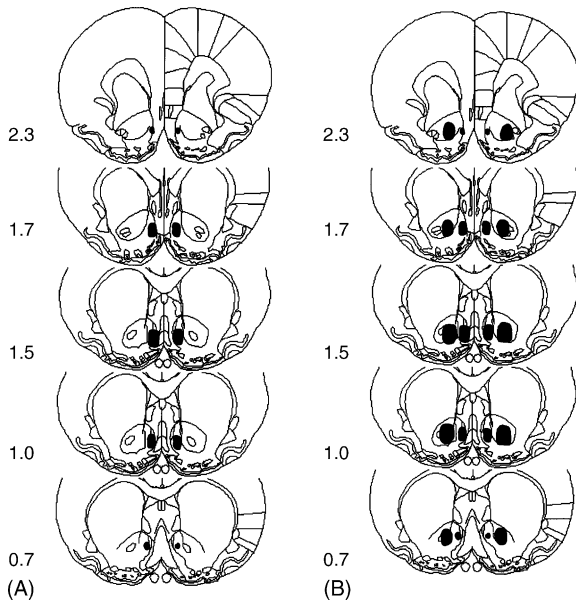


Fig. 1. Representative reconstructions of shell (A) and shell-core (B) lesions in successive brain sections taken from the stereotaxic atlas of Paxinos and Watson [49]. The black areas represent the maximal extent of neuronal damage in a single rat.

3.1.1. Shell lesion

The lesions obtained were oval in shape, the elongation being in the dorsoventral axis. The lesions extended from 0.7 to 2.0 mm anterior to bregma, with maximal damage at 1.2–1.8 mm anterior to bregma. In the mediolateral axis, the lesions extended, maximally, from 0.2 to 1.0 mm lateral to the midline. Enlarged lateral ventricles and reduction of anterior ventrolateral septum were detected in most of the rats. An additional damage to the islands of Calleja and the vertical limb of the diagonal band was detected in some rats.

3.1.2. Combined shell-core lesion

The lesion covered most of the NAC extending from about 0.5 to 2.4 mm anterior to bregma, with maximal damage at 1.0–2.0 mm anterior to bregma. In the mediolateral axis, the lesions extended, maximally, from 0.2 to 2.4 mm lateral to the midline. Enlarged lateral ventricles, reduction of anterior ventrolateral septum, and anterior commissure damage were observed in most of the rats. An additional damage to the ventromedial caudate, the ventrolateral shell, or the olfactory bulb was detected in some rats.

3.2. Behavior

3.2.1. Experiment 1: the effects of shell and combined shell-core lesion on LI in the CER procedure with 2 conditioning trials

Fifty rats were randomly allocated to six experimental groups (n per group = 8–9) in a 2×3 factorial design with main factors of preexposure (preexposed, nonpreexposed) and lesion (sham, shell, shell-core).

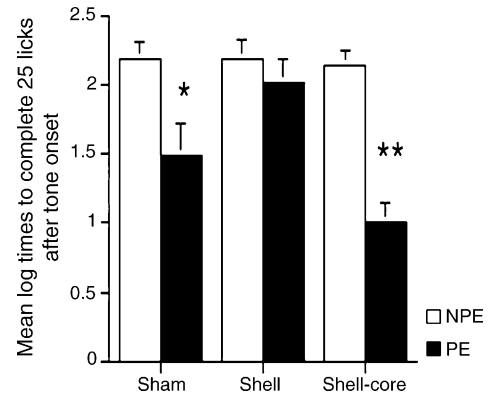


Fig. 2. Means and standard errors of the logarithmically transformed times (log times) to complete 25 licks after tone onset in the CER retention test stage of the preexposed (PE) and nonpreexposed (NPE) sham, shell and combined shell-core lesion rats conditioned with two tone-shock pairings. Asterisks indicate a significant difference (* $p < 0.05$, ** $p < 0.01$) between the PE and NPE groups.

The six experimental groups did not differ in their times to complete 25 licks before tone onset (all p 's > 0.1 ; overall mean A period = 6.27 s). Fig. 2 presents the mean log times to complete 25 licks after tone onset of the preexposed and nonpreexposed rats in the three operation conditions: sham, shell, and shell-core. As can be seen, LI was present in the sham-lesioned rats. Shell lesion abolished LI but LI was present in rats with shell-core lesion. A two-way ANOVA with main factors of preexposure and lesion yielded significant main effects of preexposure ($F_{(1,44)} = 30.29$, $p < 0.001$) and lesion ($F_{(2,44)} = 5.42$, $p < 0.01$), as well as a significant preexposure \times lesion interaction ($F_{(2,44)} = 5.74$, $p < 0.01$). Tukey's HSD post hoc comparisons yielded significant differences between the preexposed and nonpreexposed groups (indicating the presence of LI) in the sham and shell-core conditions ($p < 0.05$ and $p < 0.01$, respectively) but not in the shell condition.

3.2.2. Experiment 2: the effects of shell and combined shell-core lesion on LI in the avoidance procedure with same context

Forty-one rats were randomly allocated to six experimental groups (n per group = 6–8) in a 2×3 factorial design with main factors of preexposure (preexposed, nonpreexposed) and lesion (sham, shell, shell-core).

Fig. 3 presents the mean number of avoidance responses, divided into 10 blocks of 10 trials, of the preexposed and nonpreexposed rats in the three lesion conditions: sham (upper panel), shell (middle panel), and shell-core (lower panel). As can be seen, LI was evident in the sham condition from the 5th block onwards, and in the combined shell-core condition from the 3rd block onwards. In contrast, there was no LI in the shell-lesioned rats. A two-way ANOVA with main factors of preexposure and lesion, and a repeated measurements factor of blocks, yielded a significant preexposure \times lesion interaction of the linear trend ($F_{(2,35)} = 4.37$, $p < 0.05$), and a significant preexposure \times lesion \times blocks

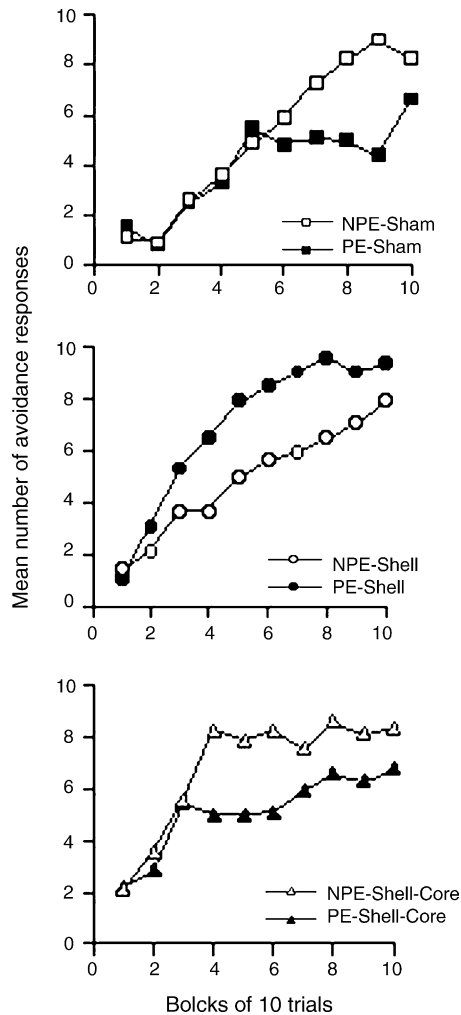


Fig. 3. Mean number of avoidance responses presented in 10 blocks of 10 trials of the preexposed (PE) and nonpreexposed (NPE) sham (upper panel), shell (middle panel), and combined shell-core (lower panel) lesioned rats preexposed and conditioned in the same context.

interaction ($F_{(18,315)} = 2.54, p < 0.001$). One-way ANOVAs with a repeated measurements factor of blocks comparing the number of avoidance responses of the preexposed and nonpreexposed groups within each lesion condition separately, yielded a significant preexposure \times blocks interaction in the sham condition ($F_{(9,117)} = 2.37, p < 0.05$), a preexposure \times blocks interaction that approached significance in the combined shell-core condition ($F_{(9,117)} = 1.83, p < 0.07$), and no significant outcomes in the shell condition.

3.2.3. Experiment 3: the effects of a combined shell-core lesion on LI in the CER procedure with 2 or 5 conditioning trials

Fifty-one rats were randomly allocated to eight experimental groups (n per group = 6–7) in a $2 \times 2 \times 2$ factorial design with main factors of preexposure (preexposed, nonpreexposed), lesion (sham, shell-core) and level of conditioning (2 pairings, 5 pairings).

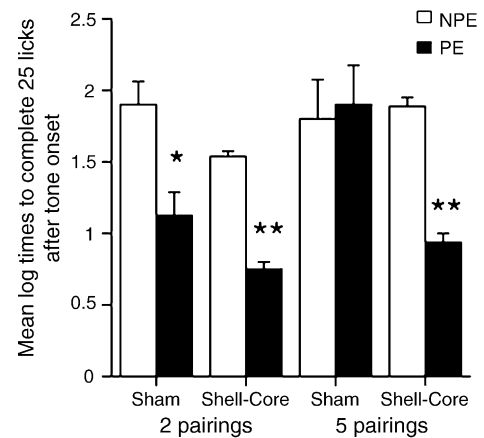


Fig. 4. Means and standard errors of the logarithmically transformed times (log times) to complete 25 licks after tone onset in the CER retention test stage of the preexposed (PE) and nonpreexposed (NPE), sham and combined shell-core lesioned rats conditioned with 2 or 5 tone-shock pairings. Asterisks indicate a significant difference ($*p < 0.05$, $**p < 0.01$) between the PE and NPE groups.

The eight groups did not differ in their times to complete 25 licks before tone onset (all p 's > 0.1 ; overall mean A period = 4.75 s). Fig. 4 presents the mean log times to complete 25 licks after tone onset of the preexposed and nonpreexposed groups in the sham-2 pairings, sham-5 pairings, shell-core-2 pairings and shell-core-5 pairings conditions. As can be seen, LI was present in sham and shell-core rats conditioned with 2 trials. With 5 conditioning trials, LI was disrupted in sham but not in shell-core rats. A three-way ANOVA with main factors of preexposure, lesion and level of conditioning yielded significant main effects of preexposure ($F_{(1,43)} = 25.52, p < 0.001$), lesion ($F_{(1,43)} = 6.14, p < 0.05$), and level of conditioning ($F_{(1,43)} = 11.16, p < 0.01$), as well as a significant preexposure \times lesion \times level of conditioning interaction ($F_{(1,43)} = 4.67, p < 0.05$). Tukey's HSD post hoc comparisons yielded significant differences between the preexposed and nonpreexposed groups (indicating presence of LI) in the sham-2 pairings, shell-core-2 pairings and shell-core-5 pairings conditions ($p < 0.05, p < 0.01$ and $p < 0.01$, respectively), but not in the sham-5 pairings condition.

3.2.4. Experiment 4: the effects of a combined shell-core lesion on LI in the avoidance procedure with context shift

Fifty-three rats were randomly allocated to eight experimental groups (n per group = 6–7) in a $2 \times 2 \times 2$ factorial design with main factors of preexposure (preexposed, nonpreexposed), lesion (sham, shell-core) and context (same, different). Fig. 5 presents the mean number of avoidance responses, divided into 10 blocks of 10 trials each, of the preexposed and nonpreexposed sham (upper panel) and shell-core (lower panel) lesioned rats preexposed and conditioned in the same or in different contexts. As can be seen, LI was evident in the sham-same context condition from the 1st block onwards, and was absent in the sham-different context condition from the 2nd block onwards. In

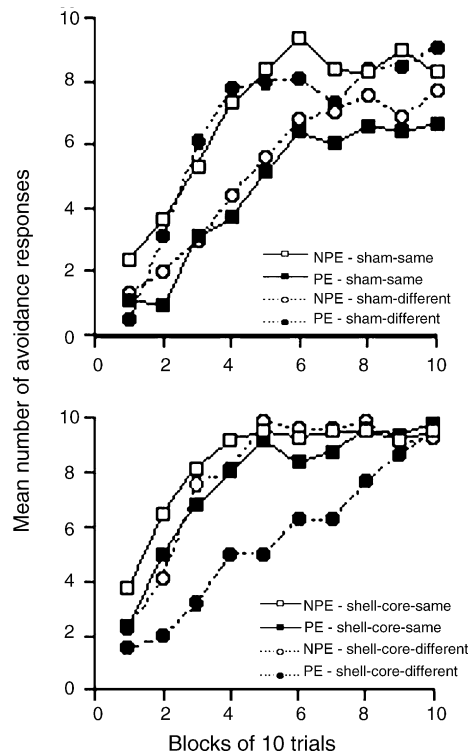


Fig. 5. Mean number of avoidance responses, presented in 10 blocks of 10 trials, of the preexposed (PE) and nonpreexposed (NPE), sham (upper panel) and combined shell-core (lower panel) lesioned rats, preexposed and conditioned in the same or different contexts.

contrast, shell-core lesioned rats showed LI in both the same and different contexts. A three-way ANOVA with main factors of preexposure, context and lesion and a repeated measurements factor of 10 blocks, yielded significant main effects of preexposure ($F_{(1,45)} = 5.85, p < 0.05$) and lesion ($F_{(1,45)} = 12.75, p < 0.0001$), as well as significant preexposure \times context \times lesion ($F_{(1,45)} = 11.22, p < 0.01$) and preexposure \times context \times lesion \times blocks ($F_{(9,405)} = 2.11, p < 0.05$) interactions. One-way ANOVAs with a repeated measurements factor of 10 blocks comparing the number of avoidance responses of the preexposed and nonpreexposed animals within each context by lesion condition separately, yielded a significant main effect of preexposure in sham-same context ($F_{(1,12)} = 5.48, p < 0.05$) and in shell-core-different context ($F_{(1,11)} = 17.40, p < 0.01$) conditions, and a main effect of preexposure that approached significance ($F_{(1,9)} = 4.03, p < 0.08$) in the shell-core-same context condition.

4. Discussion

Sham-lesioned rats that received 40 tone preexposures in the CER procedure showed LI if they were subsequently conditioned with two tone-shock pairings, but not if the same number of preexposures was followed by five tone-shock pairings [15,57]. Consistent with the well documented context-specificity of LI [39], sham-lesioned rats showed LI

in the avoidance procedure if preexposure and conditioning took place in the same context, but not if the two stages took place in different contexts. In line with previous studies using electrolytic or excitotoxic lesions [28,65,72,73], lesion to the shell subterritory of the NAC abolished LI in both the CER and the avoidance procedures. As predicted, the LI effect was preserved in rats that sustained a larger NAC lesion that included a lesion to the core in addition to the same shell lesion, replicating previous results with entire NAC lesions [72]. Furthermore, rats with a combined shell-core lesion persisted in exhibiting LI under the two conditions which disrupted the phenomenon in sham controls, namely, extended conditioning in the CER procedure and different context in the avoidance procedure. Importantly, neither shell nor entire NAC lesion affected fear conditioning or avoidance performance in the nonpreexposed rats. Thus, both shell lesion-induced loss of LI and NAC lesion-induced persistence of LI were due to the lesions' action on the preexposed groups, where the CS signals conflicting associations.

The finding that shell and combined shell-core lesion produced distinct effects on LI demonstrates that both NAC subregions play a role in LI. This conclusion is consistent with data showing that LI was associated with DA responses in both the dorsomedial shell and the core, and that these DA LI-related responses were distinct in the two NAC subregions [26]. At the same time, however, our results showed that LI does not depend on the integrity of the NAC, because it was present in NAC-lesioned rats even under conditions disrupting the phenomenon in normal rats. This indicates that the NAC is not involved in the associative processes underlying the acquisition of LI (acquisition of the CS-no event and CS-reinforcement associations) but rather modulates the expression of LI. Moreover, an analysis of the effects produced by shell and NAC lesions allows several speculations on the contribution of the two NAC subregions to such modulation.

Disruption of LI in shell-lesioned rats indicates that this subregion mediates the behavioral expression of the CS-no event association. Although LI disruption in shell-lesioned rats could reflect impaired acquisition of the CS-no event association, this was ruled out by the finding that LI was reinstated by an addition of core lesion to the shell lesion. Thus, shell-lesioned rats were able to acquire the CS-no event association but this association could not be expressed in behavior. Instead, shell-lesioned rats switched to respond according to the CS-reinforcement association. This suggests that shell lesion disrupted a mechanism that normally inhibits switching to respond according to the CS-reinforcement association. The fact that such switching was prevented in rats sustaining a combined shell-core lesion suggests that lesion to the core disrupted a mechanism that mediated switching in shell-lesioned rats. This received strong support by the findings that rats with a combined shell-core lesion persisted in responding according to the CS-no event association under the two conditions in which sham rats switched to respond according to the CS-reinforcement association. We have recently shown that rats sustaining a selective excitotoxic core lesion also

exhibited persistent LI under the two conditions tested here, further supporting the notion that an intact core contains the mechanism controlling the behavioral expression of the CS-reinforcement association [unpublished observations]. The latter result taken together with the present results further indicates that shell lesion is able to cause switching to respond according to the CS-reinforcement contingency (disrupt LI) only if the core is intact: if the core is lesioned, LI is present whether the shell is lesioned (entire NAC lesion) or intact (core lesion alone). This implies that normally the shell can inhibit core-mediated responding to the CS, and that this is the mechanism by which the shell enables the expression of the CS-no event association in behavior.

Much data suggests that the shell is involved in the attribution of motivational valence to stimuli or in mediating/potentiating responding in the presence of motivationally significant stimuli, whereas the core mediates the behavioral expression of motivated or conditioning-dependent behaviors [5,10,25,30,48]. The present results are consistent with this gross functional distinction, but they suggest that the shell may also mediate the motivational *insignificance* of stimuli, and *inhibit* responding to such stimuli.

We suggest that the two subregions act in tandem to produce the response appropriate to the CS-no event or the CS-reinforcement association depending on the degree of mismatch between the conditions of preexposure and conditioning. Under conditions of low mismatch between the conditions of preexposure and conditioning (here, same context, weak conditioning), shell inhibits the switching mechanism of the core, so that the CS-no event association gains control over behavior. Under conditions of high mismatch between the conditions of preexposure and conditioning (here, different context and strong conditioning), shell's inhibition is removed, allowing the expression of the CS-reinforcement association.

The finding that NAC-lesioned rats failed to switch behavior under conditions in which sham-lesioned rats did so, is consistent with other demonstrations of loss of flexible responding in core-lesioned rats [3,25]. In addition, the fact that NAC lesion eliminated the influence of strong conditioning and context change on performance indicates that normally, NAC-mediated responding to the CS is modulated by motivational and contextual information. The NAC has been often suggested to play a key role in modulating responding to stimuli to reflect the value of their associated outcomes [2,47,59,60], and NAC lesions impair performance in a variety of tasks in which reinforcement contingencies or reward values are altered, such as extinction and reversal learning [1,5,13,53,64]. Although there has been less focus on the involvement of the NAC in modulating behavior based on contextual information, electrophysiological and behavioral studies indicate that this region processes information about context [21,33,34,55,66,75]. Our results support the role of NAC in context-dependent modulation of behavior.

It is generally accepted that the NAC is involved in modulating the expression of motivated behavior, but the asso-

ciative, motivational and contextual knowledge underlying this operation is derived from regions afferent to the NAC [2,11,14,16,30,47,54,56]. Consistent with this notion, the effects of lesions found here are paralleled by effects of lesions to three of the major sources of input to the NAC: excitotoxic lesion as well as functional blockade by TTX of the entorhinal cortex, like shell lesion, disrupt LI [6–8,27,61,76,77], suggesting that normally this region conveys the “CS-no event” information; excitotoxic lesion as well as muscimol inactivation of the hippocampus, like NAC lesion, spare LI [6,22,23,61] and eliminate the influence of context change on LI [22,23], consistent with the role of this region in contextual processing [12,52]; and lesion to the basolateral amygdala spares LI and eliminates the effects of strong conditioning [57,74], consistent with its role in reinforcement and motivational processes [56,60]. These data are in line with evidence that the NAC integrates associative, motivational and contextual information from various input regions to influence response selection, i.e., choosing or switching between competing behaviors. The convergence of glutamate-coded inputs from limbic regions processing affective and contextual information and their modulation by dopamine at the NAC level have often been suggested to play a key role in the ability to switch between behavioral repertoires in response to changing environmental contingencies [14,16,24,30,47,48,50]. A role of NAC DA-mediated switching in LI is supported by findings that LI disruption requires phasic DA release within the NAC, whereas LI expression is associated with a reduction of NAC DA release in the shell or with DA blockade/depletion within the NAC [26,29,44]. Given that afferent activity from the basolateral amygdala and the hippocampus can increase DA release in the NAC [14,36,37,43,51], whereas functional BLA inactivation prevents an increase in core DA release [35], it may be suggested that information on the impact of reinforcement and context relayed from these regions to the core, would act simultaneously to direct switching in the NAC core and to facilitate such a switch by increasing DA release in this region. The latter can be counteracted by the switch-inhibiting information of CS-no event channeled from the entorhinal cortex via the shell to the core. One pathway via which information from the shell can reach the core is the shell's inhibitory projections to the regions of ventral tegmental area, which innervate the core and the latter's DA projections to the core [20,46,79]. It is suggested that via these projections, the shell can attenuate DA input to the core, thus preventing the switch to the CS-reinforcement association and allowing the expression of the CS-no event association.

In sum, our results show that the NAC is not essential for the *acquisition* of LI, because LI is present in NAC-lesioned rats even under conditions disrupting the phenomenon in normal rats, but rather plays a key role in modulating the *expression* of LI. Moreover, they suggest that the two subregions of the NAC contribute competitively and cooperatively to this process, selecting the response appropriate to the CS-no event or the CS-reinforcement association in conditioning,

depending on situational conditions. Apparently, the main role of the NAC is to restrict the expression of LI to certain conditions, and thus to ensure that LI is flexible and responsive to environmental demands. It is important to emphasize that in the absence of modulatory mechanisms responsible for restricting the expression of LI to specific conditions, the effects of inconsequential stimulus preexposure would have been extremely robust and maladaptive, generalizing across contexts and counteracting the expression of subsequent conditioning to the stimulus. Because LI is believed to reflect psychological processes that are impaired in schizophrenia [70], and schizophrenia patients can exhibit disrupted or excessively strong LI [4,18], the identification of brain regions whose damage leads to disrupted versus persistent LI in the rat may provide valuable cues on dysfunctional brain circuits in schizophrenia.

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