

## LESIONS TO THE BASOLATERAL AMYGDALA AND THE ORBITOFRONTAL CORTEX BUT NOT TO THE MEDIAL PREFRONTAL CORTEX PRODUCE AN ABNORMALLY PERSISTENT LATENT INHIBITION IN RATS

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**Abstract** —Repeated nonreinforced preexposure to a stimulus interferes with the establishment of conditioned responding to this stimulus when it is subsequently paired with reinforcement. This stimulus–preexposure effect is known as latent inhibition (LI). Rather remarkably, LI appears to be resistant to the effects of numerous lesions, including the prefrontal cortex (PFC) and the basolateral amygdala (BLA). However, intact behavioral expression of LI following damage to given brain regions does not preclude the possibility that such regions participate in the regulation of LI expression in the intact brain. The present study showed that lesions of the BLA and the orbitofrontal cortex (OFC) but not of the medial PFC (mPFC) led to an *abnormally persistent* LI which emerged under conditions that disrupted LI in control rats. LI was measured in a thirst motivated conditioned emotional response procedure by comparing suppression of drinking in response to a tone in rats which received 0 (non-preexposed) or 40 tone presentations (preexposed) followed by either two or five tone-shock pairings. Control rats showed LI with 40 preexposures and two conditioning trials, but raising the number of conditioning trials to five disrupted LI. OFC- and BLA-lesioned rats showed LI under the former condition but in addition persisted in exhibiting LI under the latter condition. Rats with lesion of the mPFC did not show persistent LI. Thus, although LI does not depend on the integrity of BLA and OFC (because it is present in BLA- and OFC-lesioned rats even under conditions disrupting the phenomenon in normal rats), these regions play an important role in the modulation of its expression, more specifically, in the control of the *non-expression* of LI when the impact of conditioning increases beyond a certain level. © 2004 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** latent inhibition, basolateral amygdala, medial prefrontal cortex, orbitofrontal cortex, rat, schizophrenia.

Latent inhibition (LI) refers to a retarded capacity of a stimulus that had been preexposed without consequences to subsequently acquire behavioral control through pairings with reinforcement, compared with the same stimulus that was not

preexposed (for reviews, see Gray et al., 1991; Moser et al., 2000; Weiner, 1990, 2003; Weiner and Feldon, 1997). Many theoretical accounts of LI share the view of LI as an acquisition deficit, namely, a failure to acquire the stimulus–reinforcement association as a consequence of the nonreinforced preexposure decreasing the associability of the conditioned stimulus (CS; Lubow et al., 1981; Mackintosh, 1975; Pearce and Hall, 1980; Schmajuk and Moore, 1988). However, others have argued that LI is an expression deficit whereby the stimulus–no event association acquired in preexposure competes for behavioral expression with the stimulus–reinforcement association acquired in conditioning (Bouton, 1993; Denniston et al., 2001; Grahame et al., 1994; Hall, 1991; Weiner, 1990).

Lesion studies have shown that LI is disrupted by lesions of the shell subregion of the nucleus accumbens (NAC) and the entorhinal cortex (eg, Coutureau et al., 1999; Jongen-Relo et al., 2002; Shohamy et al., 2000; Weiner et al., 1996a), suggesting that these regions play a role in regulating the expression of LI. Rather remarkably, intact LI has been found following lesions to the NAC or its core subregion (Jongen-Relo et al., 2002; Konstandi and Kafetzopoulos, 1993; Restivo et al., 2002; Weiner et al., 1996a, 1999), excitotoxic lesions or inactivation of the hippocampus (Coutureau et al., 1999; Holt and Maren, 1999; Honey and Good, 1993; Reilly et al., 1993; Shohamy et al., 2000; but see Han et al., 1995), lesions of the medial prefrontal cortex (mPFC), as well as smaller lesions confined to two of its subregions, the dorsal anterior cingulate area or the infralimbic cortex (Joel et al., 1997; Lacroix et al., 1998, 2000b), lesions to the agranular insular area (Lacroix et al., 2000b), and direct injections of DA agonists or antagonists into the mPFC (Broersen et al., 1996, 1999; Ellenbroek et al., 1996; Lacroix et al., 2000a). Lesions of the basolateral amygdala (BLA) were reported to spare LI in one study (Weiner et al., 1996b), but to disrupt LI in another study (Coutureau et al., 2001). While presence of LI following lesions to the above brain regions could be interpreted as indicating that these regions play no role in LI, intact behavioral expression of LI following damage to given brain regions does not preclude the possibility that such regions participate in the regulation of LI expression in the intact brain. We have recently pointed out that the assessment of LI following lesion manipulations under conditions that produce LI in control rats, may underestimate, or mask, the functional significance of a brain region in LI, because the effects of certain lesions on LI emerge

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**Abbreviations:** BLA, basolateral amygdala; CE, central nucleus; CER, conditioned emotional response; CS, conditioned stimulus; LI, latent inhibition; mPFC, medial prefrontal cortex; NAC, nucleus accumbens; NMDA, *N*-methyl-*D*-aspartate; NPE, nonpreexposed; OFC, orbitofrontal cortex; PBS, phosphate buffer saline; PE, preexposed; PFC, prefrontal cortex; QA, quinolinic acid.

under conditions that *disrupt* LI in controls. Thus, rats with lesions of the NAC as well as cell lesions or inactivation of the hippocampus, in addition to showing LI under conditions that yield LI in control rats, persist in exhibiting LI under conditions that disrupt the phenomenon in controls (low number of preexposures, high number of conditioning trials, or context change between preexposure and conditioning; Holt and Maren, 1999; Honey and Good, 1993; Joseph et al., 2000; Schiller et al., 2003). These findings suggest that perturbations of at least some brain regions whose damage spares LI under conditions producing LI in controls, impair rats' capacity to alter responding according to the changed reinforcement contingency in conditioning, so that lesioned rats persist in responding according to the stimulus–no event acquired in preexposure under conditions in which normal rats shift to respond according to the stimulus–reinforcement contingency prevailing in conditioning and thus cease to express LI (Weiner, 2003).

There is extensive evidence that lesions of the prefrontal cortex (PFC) and the BLA impair animals' ability to alter behavior to stimuli when reinforcement contingencies or reward values are changed (Baxter et al., 2000; Gallagher et al., 1999; Hatfield et al., 1996; Málková et al., 1997; Rolls, 2000a,b; Schoenbaum et al., 2003). These findings raise the possibility that PFC and BLA lesions may produce an abnormally persistent LI, which would become evident under conditions that disrupt LI in controls. The present study tested this possibility. Because there is evidence that different prefrontal subregions in the rodent are involved in different types of behavioral flexibility (Birrell and Brown, 2000; Brown and Bowman, 2002; McAlonan and Brown, 2003), we tested the effects of lesions to two PFC subregions, the mPFC and the orbitofrontal cortex (OFC), which have been shown to mediate different forms of shift learning (Birrell and Brown, 2000; Dias et al., 1996, 1997; McAlonan and Brown, 2003).

LI was measured in a thirst motivated conditioned emotional response (CER) procedure by comparing suppression of drinking in response to a tone previously paired with a foot shock in rats that received nonreinforced exposure to the tone prior to conditioning and in rats for whom the tone was novel. Two parametric versions of the procedure were used, one that yields LI in normal rats (40 tone preexposures followed by two tone-shock pairings) and one which does not yield LI in normal rats (40 preexposures followed by five tone-shock pairings) and which has been shown by us in the past to allow the emergence of persistent LI following lesion and pharmacological manipulations (Gaisler-Salomon and Weiner, 2003; Schiller et al., 2003; Shadach et al., 1999, 2000; Weiner et al., 1997, 2003). Experiments 1 and 2 tested the effects of excitotoxic BLA and OFC lesions on LI, respectively. Because the effects of OFC lesions on LI have not been tested, and because studies with BLA lesions reported on both spared and disrupted LI, the effects of lesions to these regions were tested under parametric conditions that produce or disrupt LI in controls (low and high number of conditioning trials), in order to demonstrate spared and persistent LI, respectively. Since mPFC lesions were extensively re-

ported to spare LI under conditions allowing for LI in controls, experiment 3 tested the effects of excitotoxic mPFC lesion on LI only under conditions that disrupt LI in controls.

## EXPERIMENTAL PROCEDURES

### Subjects

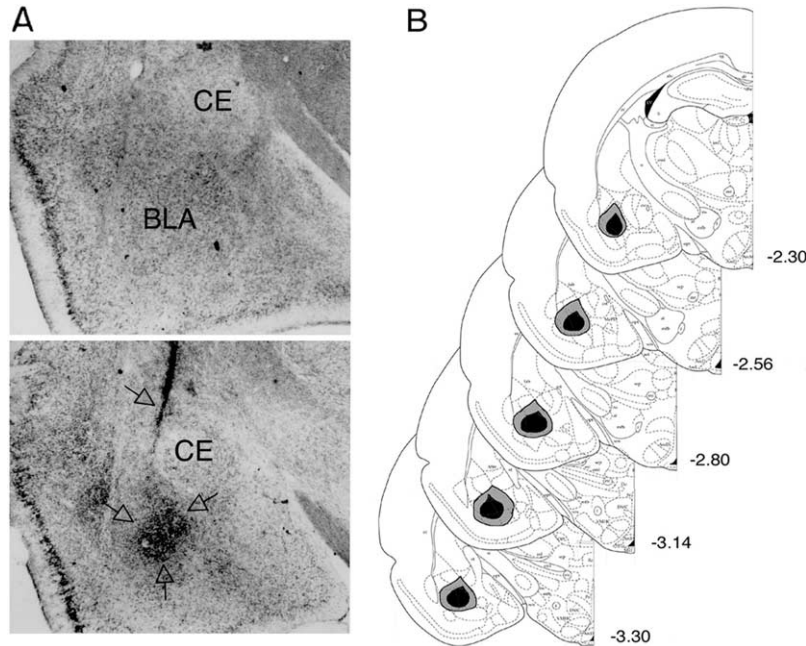
Male Wistar rats (Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel) approximately 4 months old and weighing 360–490 g, were housed four to a cage under reversed cycle lighting (lights on: 07:00–19:00 h) with *ad libitum* access to food and water except for the duration of the LI experiments (see below). 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.

### Surgery

Rats were given an i.p. injection of diazepam (0.6 mg/kg) and 5 min later were anesthetized 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 the same (level head) plane. A small square of bone was removed over the spot where the cannula would later enter. BLA lesions were made by bilateral infusions of 0.4  $\mu$ l quinolinic acid (QA; 0.12 M; Sigma Chemicals, Israel) dissolved in phosphate buffer saline (PBS; pH adjusted to 7.4 with 1 N NaOH), at the following coordinates: 2.8 mm posterior to bregma, 5.0 mm lateral to the midline, 8.6 mm ventral to the skull. OFC lesions were made by bilateral infusions of 0.3  $\mu$ l *N*-methyl-D-aspartate (NMDA; 0.12 M; Sigma Chemicals, Israel) dissolved in PBS, at the following coordinates: 3.2 mm anterior to bregma, 2.4 mm lateral to the midline, 5.5 mm ventral to the skull. mPFC lesions were made by bilateral infusions of 0.5  $\mu$ l QA dissolved in PBS, at the following coordinates: anterior, 3.7 mm anterior to bregma, 0.7 mm lateral to midline, 2.2 mm ventral to the skull; posterior, 2.7 mm anterior to bregma, 0.7 mm lateral to midline, 2.2 mm ventral to the skull. For BLA and OFC lesions, infusions were made through the tip of a Hamilton syringe (26 G cannula) using a manually driven pump (Kopf, microinjection unit, model 5000) mounted onto the stereotaxic frame. For mPFC lesions, infusions were made through a Hamilton syringe mounted onto electrically driven pump (model CMA/100) and connected to the injection cannula (31 G) with polyethylene tubing. All infusions were at a flow rate of 0.1  $\mu$ l/min. Following injections the cannulae were left at the injection site for a period of 5 min to allow complete diffusion of the neurotoxin. Sham-operated controls underwent the same surgical procedures, but received injections of a corresponding dose of PBS alone. Sterispon was used to cover the hole in the bone, 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.

### Apparatus and procedures

Rats were tested in Campden Instruments rodent test chambers (model 410) with a retractable bottle, each enclosed in a ventilated sound-attenuating chest. When the bottle was not present, a metal lid covered the hole. Licks were detected by a Campden Instruments drinkometer (model 453). The PE to-be-CS was a 10 s, 80 dB, 2.8 kHz tone produced by a Sonalert module (model SC 628). Shock was supplied through the floor by a Campden Instruments shock generator (model 521/C) and shock scrambler (model 521/S) set at 0.5 mA intensity and 1 s duration. Equipment programming and data recording were computer controlled.



**Fig. 1.** Photomicrographs and a reconstruction of the region of damage in BLA-lesioned rats. (A) Photomicrographs of coronal sections taken through the amygdala in a representative sham (top) and BLA-lesioned (bottom) rat. Accumulation of glia cells was evident in the BLA while the central nucleus (CE) remained intact. Arrows denote lesion borders and injection cannula track. (B) Schematic representations of the minimal (black) and maximal (gray) extent of the BLA lesions. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson (1998).

Prior to the beginning of each experiment, rats were handled for about 2 min daily for 5 days. A 23 h water restriction schedule was initiated simultaneously with handling and continued throughout the LI experiment. On the next 5 days, rats were trained to drink in the experimental chamber for 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 (PE) rats received 40 tone presentations with an inter-stimulus interval of 40 s. The nonpreexposed (NPE) rats were confined to the chamber for an identical period of time without receiving the tone. *Conditioning*: With the bottle removed, each rat received two or five tone-shock pairings given 5 min apart. Shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. After the last pairing, rats were left in the experimental chamber for an additional 5 min. *Retraining*: Rats were given a 15 min drinking session as in initial training. Data of rats that failed to complete 600 licks were dropped from the analysis. *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. The following times were recorded: 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). Times to complete licks 76–100 were logarithmically transformed to allow parametric analysis of variance. Longer log times indicate stronger suppression of drinking. LI is defined as significantly shorter log times to complete licks 76–100 of the PE as compared with NPE rats.

### Histology

After the completion of behavioral testing, rats were anesthetized with an overdose of pentobarbital (60 mg/ml) and perfused intracardially with physiological saline, followed by 10% formalin. Their brains were removed from the skulls and stored in 10% formalin for at least 24 h before being sectioned in the

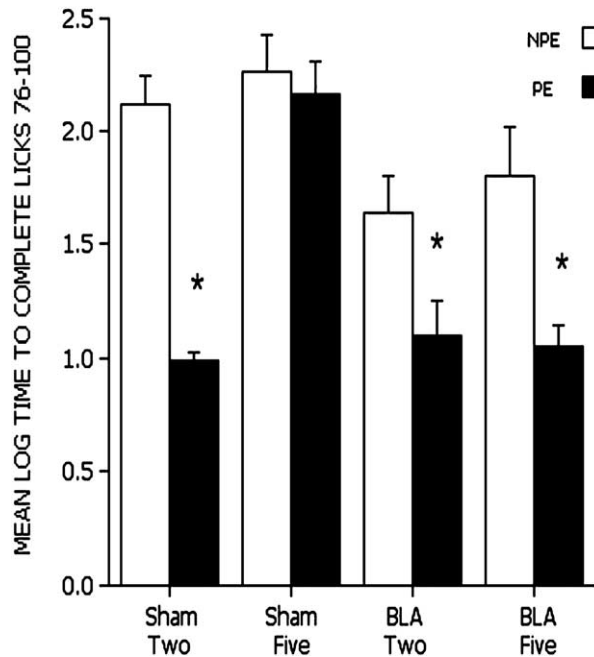
coronal plane at 50  $\mu$ m thickness. Every second section was mounted and stained with Cresyl Violet for histological examination. Verification of placements used the atlas of Paxinos and Watson (1998).

### Experiment 1: the effects of BLA lesions on LI with restricted or extended conditioning

Forty-eight rats were randomly allocated to eight experimental groups in a  $2 \times 2 \times 2$  factorial design with main factors of preexposure (NPE, PE) lesion (sham, BLA) and conditioning (two pairings, five pairings). Data of one BLA rat were discarded from statistical analysis after histological confirmation of the lesioned sites. Thus, the final analysis included 47 rats (24 sham, 23 BLA; per group  $n=5-6$ ).

### Histological results

Fig. 1A presents photomicrographs of coronal sections taken from a representative sham (top) and BLA lesioned (bottom) rat. Fig. 1B presents schematic representations of the minimal (black) and maximal (gray) extent of the BLA lesions. Histological analysis of the sections in QA-injected rats confirmed the presence of a bilateral lesion, characterized by gliosis and cell poor areas. The lesions extended rostrocaudally approximately from 2.3 to 3.3 mm caudal to bregma, and mediolaterally maximally from 4.2 to 5.6 mm lateral to the midline. Occasionally, the affected area extended to the ventral aspect of the lateral nucleus of the amygdala, the adjacent endopiriform nucleus, and to the overlying caudate-putamen along with the injection cannula track. Data of one BLA rat for which there was no discernable damage to the BLA in one hemisphere were excluded from statistical analysis. There was no discernable damage in any of the sham-lesioned rats. The only visible damage was the cannulae tracks toward the target areas.



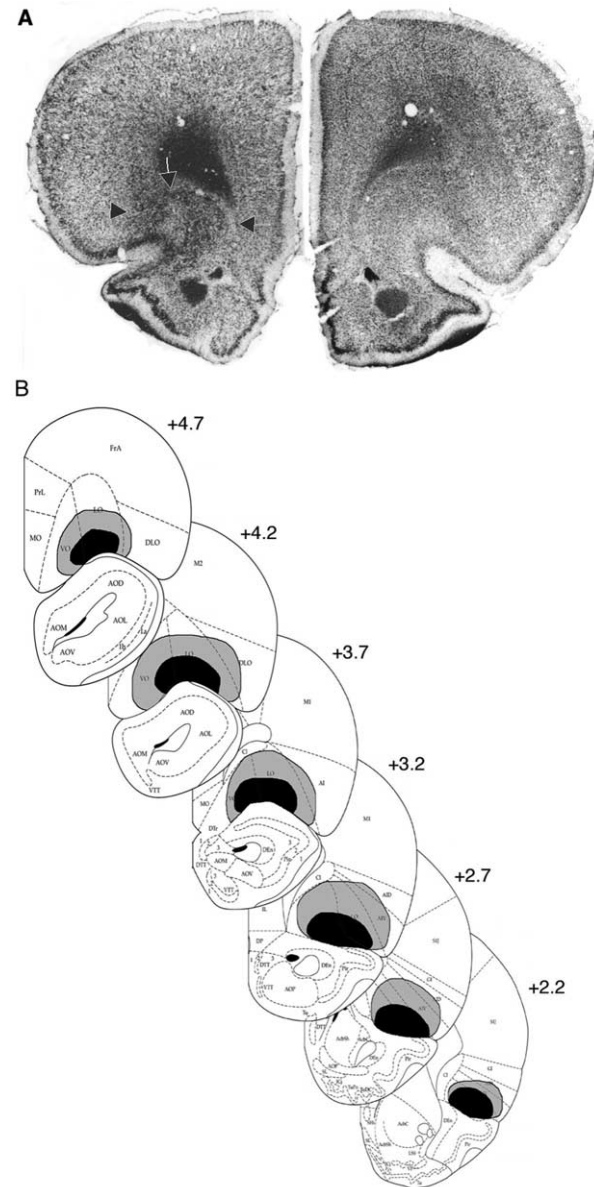
**Fig. 2.** Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the PE and NPE sham- or BLA-lesioned rats conditioned with two or five tone-shock pairings. Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI.

### Behavioral results

The eight experimental groups did not differ in their times to complete licks 51–75 before tone onset (all  $P$ 's > 0.1; overall mean A period = 8.13 s). Fig. 2 presents the mean log times to complete licks 76–100 (after tone onset) of the PE and NPE groups in the sham two pairings, sham five pairings, BLA two pairings and BLA five pairings conditions. As can be seen, LI was present in the sham and BLA rats conditioned with two trials. With five conditioning trials, LI was disrupted in sham rats but was present in BLA rats. This was supported by a two-way ANOVA with main factors of preexposure, lesion and conditioning, which yielded significant main effects of preexposure  $F(1,39)=38.62$ ,  $P<0.0001$ , lesion  $F(1,39)=23.01$ ,  $P<0.0001$ , and conditioning  $F(1,39)=12.31$ ,  $P<0.01$ , as well as significant lesion  $\times$  conditioning,  $F(1,39)=8.86$ ,  $P<0.01$ , and preexposure  $\times$  lesion  $\times$  conditioning,  $F(1,39)=9.33$ ,  $P<0.01$ , interactions. Post hoc two-tailed  $t$ -tests based on the error term of the ANOVA comparing the difference between PE and NPE groups within each condition, confirmed the presence of LI in the sham two pairings, BLA two pairings and BLA five pairings conditions,  $t(39)=5.63$ ,  $P<0.01$ ,  $t(39)=2.69$ ,  $P<0.05$ , and  $t(39)=3.57$ ,  $P<0.01$ , respectively, but not in the sham five pairings condition,  $t(39)=0.51$ , NS.

### Experiment 2: the effects of OFC lesions on LI with restricted or extended conditioning

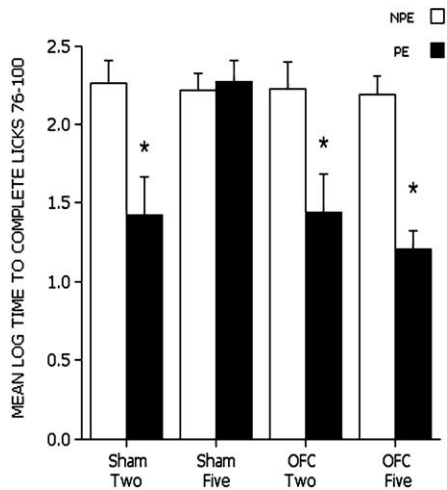
Forty-eight rats were randomly allocated to eight experimental groups in a  $2 \times 2 \times 2$  factorial design with main factors of preexposure (NPE, PE) lesion (sham, OFC) and conditioning (two pairings, five pairings). The data of one sham rat were excluded from the analysis because of failure to drink in the retraining stage. The data of one OFC rat were discarded from statistical analysis after histological confirmation of the lesioned sites. Thus, the final analysis included 46 rats (23 sham, 23 OFC; per group  $n=5-6$ ).



**Fig. 3.** Photomicrographs and a reconstruction of the region of damage in OFC-lesioned rats. (A) Photomicrographs of coronal sections taken through the OFC in a representative sham- (right) and OFC-lesioned (left) rat. Arrows denote lesion borders. (B) Schematic representations of the minimal (black) and maximal (gray) extent of the OFC lesions. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson (1998).

### Histological results

Fig. 3A presents photomicrographs of coronal sections taken from a representative sham- (right) and OFC-lesioned (left) rat. Fig. 3B presents schematic representations of the minimal (black) and maximal (gray) extent of the OFC lesions. Histological analysis of the sections in NMDA-injected rats confirmed the presence of a bilateral lesion. Gliosis and cell poor areas were typically found in the ventral and lateral orbital cortex and occasionally extended to the dorsolateral orbital and agranular insular cortex. The lesions extended rostrocaudally approximately from 4.7 to 2.7 mm rostral to bregma, and mediolaterally maximally from 0.6 to 3.4 mm



**Fig. 4.** Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the PE and NPE sham- or OFC-lesioned rats conditioned with two or five tone-shock pairings. Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI.

lateral to the midline. Data of one OFC rat for which there was no discernable damage to the OFC in one hemisphere were excluded from statistical analysis. There was no discernable damage in any of the sham-lesioned rats. The only visible damage was the cannulae tracks toward the target areas.

### Behavioral results

The eight experimental groups did not differ in their times to complete licks 51–75 before tone onset (all  $P$ 's > 0.1; overall mean A period = 8.16 s). Fig. 4 presents the mean log times to complete licks 76–100 (after tone onset) of the PE and NPE groups in the sham two pairings, sham five pairings, OFC two pairings and OFC five pairings conditions. As can be seen, LI was present in the sham and OFC rats conditioned with two trials. With five conditioning trials, LI was disrupted in sham rats but was present in OFC rats. This was supported by a two-way ANOVA with main factors of preexposure, lesion and conditioning, which yielded significant main effects of preexposure  $F(1,38)=28.24$ ,  $P<0.0001$ , and lesion  $F(1,38)=5.25$ ,  $P<0.05$ , as well as significant preexposure  $\times$  lesion,  $F(1,38)=4.24$ ,  $P<0.05$ , lesion  $\times$  conditioning,  $F(1,38)=4.89$ ,  $P<0.05$ , and preexposure  $\times$  lesion  $\times$  conditioning,  $F(1,38)=5.12$ ,  $P<0.05$ , interactions. Post hoc two-tailed  $t$ -tests based on the error term of the ANOVA comparing the difference between PE and NPE groups within each condition, confirmed the presence of LI in the sham two pairings, OFC two pairings and OFC five pairings conditions,  $t(38)=3.40$ ,  $P<0.01$ ,  $t(38)=3.36$ ,  $P<0.01$ , and  $t(38)=4.19$ ,  $P<0.01$ , respectively, but not in the sham five pairings condition,  $t(38)=0.24$ , NS.

### Experiment 3: the effects of mPFC lesions on LI with extended conditioning

Because mPFC lesion was extensively shown to spare LI under conditions in which controls exhibit LI (e.g. Joel et al., 1997; Lacroix et al., 1998; 2000b), the effects of the lesion were tested only under conditions that disrupt LI in controls. Forty-eight rats were randomly allocated to six experimental groups in a  $2 \times 3$  factorial design with main factors of preexposure (NPE, PE) and condition of lesion and number of conditioning trials (sham two pairings, sham five pairings, mPFC five pairings). Data of four

mPFC rats were discarded from statistical analysis after histological confirmation of the lesioned sites. Thus, the final analysis included 44 rats (24 sham, 20 mPFC; per group: sham  $n=6$ , mPFC  $n=10$ ).

### Histological results

Fig. 5A presents photomicrographs of coronal sections taken from a representative sham (right) and mPFC-lesioned (left) rat. Fig. 5B presents schematic representations of the minimal (black) and maximal (gray) extent of the mPFC lesions. Histological analysis of the sections in QA-injected rats confirmed the presence of a bilateral lesion. Gliosis and cell poor areas were typically found in the dorsal mPFC, including the cingulate cortex and the dorsal part of the prelimbic cortex as well as the most medial aspect of the secondary motor cortex (medial agranular cortex). The lesions extended rostrocaudally approximately from 4.7 to 2.2 mm rostral to bregma, and mediolaterally maximally 1.0 mm lateral to the midline. Data of four rats for which there was no discernable damage to the mPFC in one hemisphere were excluded from statistical analysis. There was no discernable damage in any of the sham-lesioned rats. The only visible damage was the cannulae tracks toward the target areas.

### Behavioral results

The six experimental groups did not differ in their times to complete licks 51–75 before tone onset (all  $P$ 's > 0.1; overall mean A period = 8.34 s). Fig. 6 presents the mean log times to complete licks 76–100 (after tone onset) of the PE and NPE groups in the sham two pairings, sham five pairings and mPFC five pairings conditions. As can be seen, LI was present in the sham rats conditioned with two trials but not in sham- and mPFC-lesioned rats conditioned with five trials. This was supported by a two-way ANOVA with main factors of preexposure and condition, which yielded a significant preexposure  $\times$  condition interaction,  $F(1,38)=3.65$ ,  $P<0.05$ . Post hoc two-tailed  $t$ -tests based on the error term of the ANOVA comparing the difference between PE and NPE groups within each condition, confirmed the presence of LI in the sham two pairings condition  $t(38)=2.87$ ,  $P<0.01$ , but not in the sham five pairings and mPFC five pairings conditions,  $t(38)=0.16$ , NS, and  $t(38)=0.48$ , NS, respectively.

## DISCUSSION

### The effects of BLA and OFC lesions on LI

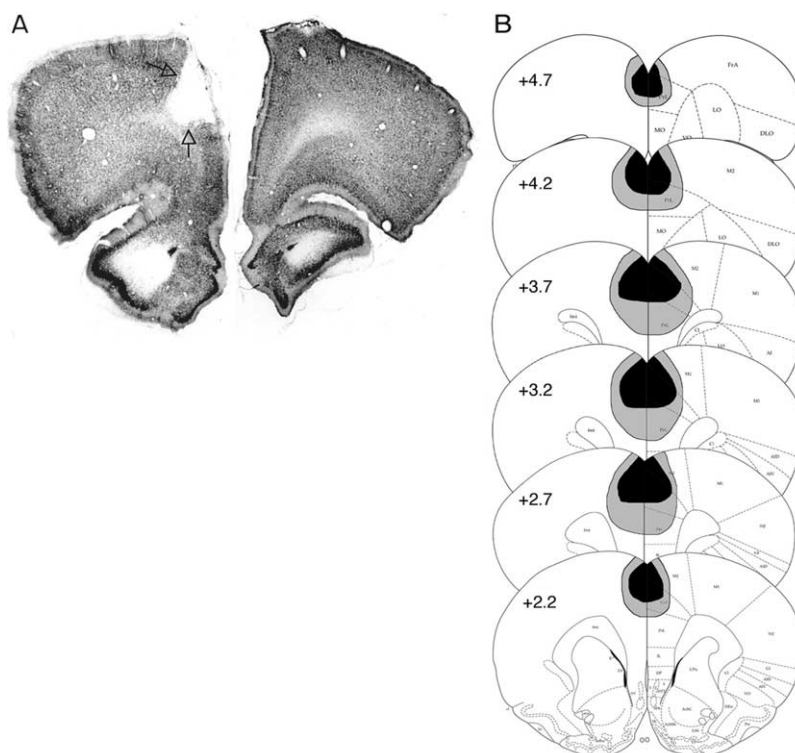
As shown by us previously in intact rats in the CER procedure used here (Gaisler-Salomon and Weiner, 2003; Schiller et al., 2003; Shadach et al., 1999, 2000; Weiner et al., 1997, 2003), sham-lesioned rats preexposed to 40 tones and subsequently conditioned with two tone-shock pairings, showed lower suppression than their NPE counterparts, i.e. there was LI, but when the same number of nonreinforced preexposures was followed by five tone-shock pairings, PE sham rats showed suppression levels similar to those of their NPE counterparts, i.e. LI was lost. Rats with BLA and OFC lesions showed LI under conditions that yielded LI in sham controls. In contrast to sham rats, however, BLA- and OFC-lesioned PE rats conditioned with five trials continued to exhibit lower level of suppression than their NPE counterparts, i.e. persisted in exhibiting LI despite the repeated pairings of the stimulus with reinforcement. Thus, whereas PE sham rats conditioned with five trials switched to respond according to the stimulus–reinforcement contingency prevailing in conditioning, PE BLA- and OFC-lesioned rats were apparently

unable to adjust their responding to the changed stimulus–reinforcement contingency.

Damage to BLA and OFC is known to produce impairments in experimental tasks in which reinforcement contingencies or reward values are changed (Baxter et al., 2000; Gallagher et al., 1999; Hatfield et al., 1996; Málková et al., 1997; Rolls, 2000a,b; Schoenbaum et al., 2003). For example, animals with BLA and OFC lesions acquire discrimination normally but are impaired on reversal of discrimination (Dias et al., 1997; Meunier et al., 1997; Rolls et al., 1994; Schoenbaum et al., 2002, 2003). Similarly, in reinforcement devaluation tasks, BLA and OFC 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 (Baxter et al., 2000; Gallagher et al., 1999; Hatfield et al., 1996; Málková et al., 1997). Such findings have been taken to suggest that BLA and OFC form a functional system which enables stimuli to access current affective value of the associated outcome for flexible adjustment of conditioned responding (Baxter et al., 2000; Cardinal et al., 2002; Everitt and Robbins, 1992; Hatfield et al., 1996; Holland and Gallagher, 1999; Gallagher and Schoenbaum, 1999; Gallagher et al., 1999; Pickens et al., 2003; Rolls 1996, 1999, 2000a,b; Schoenbaum and Setlow, 2001; Schoenbaum et al., 2002, 2003; Setlow et al., 2002).

Our data are consistent with the above findings and notions in demonstrating that BLA- and OFC-lesioned rats

failed to reverse their CS–no event association when the predictive value of the CS was altered. It should be noted in this context that presence of LI with strong conditioning indicates that the lesion did not impair the capacity to acquire the CS–no event contingency (in the lesioned PE groups) or the capacity to acquire the CS–reinforcement contingency (in the lesioned NPE groups). Rather, the lesions specifically impaired rats' capacity to switch their responding from the CS–no event association to the CS–reinforcement association. Notably, although BLA lesion attenuated conditioning in the NPE group compared with sham NPE, in line with the well-documented deleterious effects of BLA lesions on the acquisition of motivational significance of stimuli, and in particular, on aversive conditioning (e.g. Cousins and Otto, 1998; Sananes and Davis, 1992; Schoenbaum et al., 2003; Selden et al., 1991; Setlow et al., 2002; Weiner et al., 1996b), conditioning was further attenuated in BLA-lesioned rats following preexposure, allowing for the emergence of LI. These results suggest that the effects of BLA lesion were more pronounced when reinforcement contingencies signaled by the stimulus were altered than when the stimulus signaled one contingency (reinforcement). Such a differential effect was clearly evident in the OFC-lesioned rats, because this lesion led to the emergence of LI exclusively via reducing conditioning in the PE group while having no effect on conditioning in the NPE group.



**Fig. 5.** Photomicrographs and a representative reconstruction of the region of damage in mPFC-lesioned rats. (A) Photomicrographs of coronal sections taken through the mPFC in a representative sham- (right) and mPFC-lesioned (left) rat. Arrows denote lesion borders. (B) Schematic representations of the minimal (black) and maximal (gray) extent of the mPFC lesions. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson (1998).

Finally, the fact that LI persists in BLA- and OFC-lesioned rats even after strong conditioning, implies that LI does not depend on the integrity of BLA and OFC. To the contrary, in lesioned rats, LI becomes a more robust phenomenon whereby the effects of stimulus preexposure continue to be manifested also when the impact of conditioning increases to a level disrupting LI in normal rats. It follows from this that in the intact brain BLA and OFC are not necessary for the expression of LI, but rather for the *prevention* of its expression (i.e. disruption of LI) when the impact of conditioning increases.

### Comparison to previous results with BLA perturbations

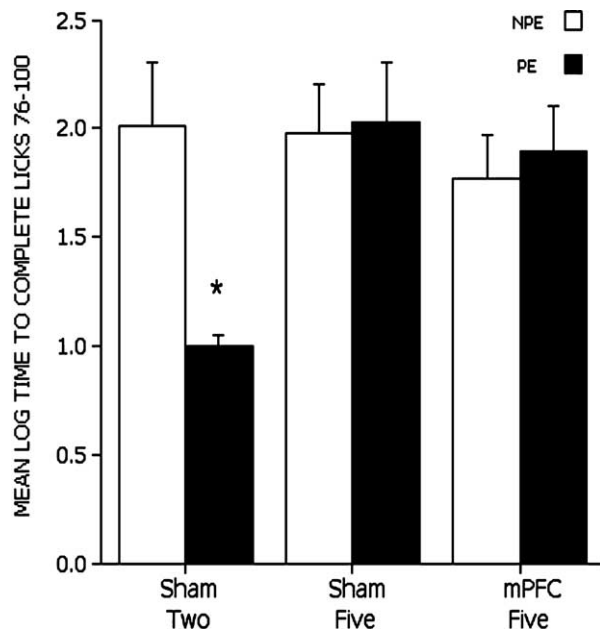
To the best of our knowledge, this is the first demonstration of the involvement of the OFC in LI. To date, only one study tested the effects of excitotoxic lesions to the agranular insular area, which corresponds to part of the primate OFC (Krettek and Price, 1977; Kolb, 1990; Uylings and van Eden, 1990), and reported spared LI (Lacroix et al., 2000b).

The present results with BLA lesion confirm our previous finding of spared LI following electrolytic BLA lesion (Weiner et al., 1996b), but conflict with those of Coutureau et al. (2001) and Schauz and Koch (2000). Schauz and Koch (2000) showed that the infusion of the competitive NMDA antagonist AP-5 into BLA before preexposure only, disrupted LI. While this result supports the contention that LI persistence following BLA lesion is not due to lesion effects at preexposure, it raises the question as to how an interference with BLA processing can lead to disrupted LI when occurring in preexposure

yet lead to persistent LI when occurring in both the preexposure and conditioning stages. We have suggested that this inconsistency can be reconciled if it is assumed that BLA manipulations in preexposure do not prevent the acquisition of the stimulus–no event association but rather decrease its strength. While this would be expected to disrupt LI if BLA lesion is confined to preexposure, because in such a case, the impact of conditioning remains unchanged, when BLA lesion is present in both stages, decreased functional impact of preexposure is presumed to be followed by a decreased impact of conditioning, and under such conditions, LI can emerge (Weiner, 2003). This suggestion implies that the effects of BLA perturbations on LI should be modifiable by changes in the parameters of the LI procedure.

Disruption of LI has been also obtained by Coutureau et al. (2001) following cell lesion of BLA. One reason for the discrepancy between our results and those of Coutureau et al. (2001) could stem from the different USs used, appetitive versus aversive, suggesting that the role of the BLA in the control of LI depends on the nature of the US. This possibility seems unlikely because there is no evidence that the effects of lesions or pharmacological manipulations on LI depend on the nature of the US used. For example, disruption of LI by amphetamine and its potentiation by dopaminergic blockers, have been shown in procedures using aversive and appetitive reinforcers (e.g. Killcross et al., 1994a,b; Weiner et al., 1988, 1997), and in motivationally neutral procedures used in humans (e.g. Gray et al., 1992; McCartan et al., 2001; Williams et al., 1997). Lesion and microdialysis studies have likewise yielded the same results irrespective of the procedure used for LI measurement or the nature of reinforcement (Holt and Maren, 1999; Honey and Good, 1993; Jeanblanc et al., 2002; Murphy et al., 2000; Oswald et al., 2002; Shohamy et al., 2000; Yee et al., 1995). However, it remains to be determined whether BLA lesion would produce persistent LI with appetitive reinforcement.

Another reason could be the difference in the size of the lesions, because our lesions were sub-maximal compared with that used by Coutureau et al. (2001). While smaller lesion size could explain findings of spared LI following the lesion, because the spared anterior region of BLA may have been sufficient to maintain a full LI effect, it cannot explain the finding that LI does not remain similar to that in sham rats, but becomes abnormally resistant to disruption. However, size of lesion could be a critical factor when considering the possibility that BLA lesion may exert competing effects in preexposure and in conditioning. Thus, it is possible that with a highly extensive lesion of BLA like that used by Coutureau et al. (2001), the effects of lesion at preexposure override its effects in conditioning. A similar phenomenon, albeit in an opposite direction, is seen with lesions to the NAC: while a lesion to the shell subregion disrupts LI, a larger NAC lesion produces persistent LI (Weiner, 2003). 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



**Fig. 6.** Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the PE and NPE sham-lesioned rats conditioned with two or five tone-shock pairings and mPFC-lesioned rats conditioned with five pairings. Asterisk indicates a significant difference between the PE and NPE groups, namely, presence of LI.

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.

### **mPFC–OFC dissociation in LI**

In contrast to OFC lesion, mPFC lesion did not produce persistent LI. This outcome is at first sight perplexing given the numerous demonstrations that animals with mPFC lesions, including dorsal mPFC, have difficulty in altering their behavior when reinforcement contingencies change, typically persisting in responding according to previous contingency (e.g. Aggleton et al., 1995; de Bruin et al., 1994; Dias and Aggleton, 2000; Dias et al., 1997; Joel et al., 1997; Kolb, 1984; Morgan and LeDoux, 1995; Ragozzino et al., 1999a,b). However, it has been shown that the mPFC and the OFC may subserve different types of behavioral flexibility (Birrell and Brown, 2000; Dias et al., 1996, 1997; McAlonan and Brown, 2003). For example, OFC but not mPFC lesions impair behavioral flexibility at the level of stimulus–reinforcement associations, as exemplified in disrupted reversal learning, whereas mPFC but not OFC lesions impair behavioral flexibility at the level of attentional selection (Dias et al., 1996, 1997), as exemplified in disrupted extradimensional shift (requiring the animal to shift attentional set from one dimension to another). Our results provide additional evidence for a functional differentiation between the mPFC and the OFC, whereby the OFC but not mPFC plays a role in the prevention of LI expression in response to altered reinforcement contingencies. It has been suggested that the OFC may subserve switching of stimulus–reinforcement associations while mPFC may be involved in switching of general rules, strategies or attentional sets (Birrell and Brown, 2000; Brown and Bowman, 2002; Dias et al., 1996, 1997; McAlonan and Brown, 2003; Kesner, 2000), or, in terms suggested by Wise et al. (1996), lower order and higher order rules, respectively. Because prevention of LI expression (LI disruption) requires switching between stimulus–outcomes associations involving the same stimulus, this process would be expected to be sensitive to OFC but not to mPFC damage.

To date, various mPFC perturbations, including electrolytic and excitotoxic lesions, and direct injections of DA agonists or antagonists into the mPFC, were consistently reported to spare LI under conditions yielding LI in controls (Broersen et al., 1996, 1999; Ellenbroek et al., 1996; Joel et al., 1997; Lacroix et al., 1998, 2000a,b). Here we showed that rats with mPFC lesion, like controls, fail to exhibit LI with increased number of conditioning trials. Taken together, the findings that mPFC lesions do not disrupt LI nor induce abnormally persistent LI, strongly suggest that the mPFC is not involved in LI.

### **Persistent LI and schizophrenia**

The interest in the neural substrates of LI has been spawned by the proposition that this phenomenon reflects the operation of a cognitive process that may be impaired in schizophrenia, namely, the ability to ignore inconsequential stimuli. This proposition was supported over years

by demonstrations of disrupted LI in rats and normal humans treated with the psychosis inducing dopamine releaser amphetamine, in high schizotypal humans, and in schizophrenia patients in the acute stage of the disorder, raising the proposition that disrupted LI may model positive symptoms of schizophrenia (for reviews, see Gray et al., 1991; Moser et al., 2000; Weiner, 1990, 2003; Weiner and Feldon, 1997). At the same time, however, the fact that LI is intact in chronic schizophrenia patients and in some studies also in acute patients has been taken to weaken the strength of the LI model. The present demonstration of abnormally persistent LI following BLA and OFC lesions, together with our recent demonstration of the same phenomenon following pharmacological blockade of NMDA receptors (Gaisler-Salomon and Weiner, 2003), indicates that abnormality of LI is not exclusively manifested as a loss of this phenomenon but also as its abnormal persistence. We (Weiner and Feldon, 1997; Weiner, 2003) have suggested that abnormally persistent LI in the rat may be particularly relevant to negative symptoms of schizophrenia which are characterized by behavioral inflexibility (e.g. Anscombe, 1987; Carlsson et al., 1999; Moghaddam et al., 1997; Morice, 1990; Pantelis et al., 1999; Weiner and Joel, 2002). The implication of this to clinical research of LI is that schizophrenia patients suffering from negative symptoms should show persistent or enhanced rather than disrupted LI. Although persistent LI is a new notion, recently this abnormality has been demonstrated in schizophrenia patients, and, most importantly, has been shown to positively correlate with the level of negative symptoms (Cohen et al., 2003; Rasclé et al., 2001). These findings support the possibility that persistent LI in the rat may provide a model of negative symptoms. Moreover, the present results suggest that enhanced LI seen in patients with negative symptoms might be related to amygdalar and/or orbitofrontal dysfunction, consistent with the notions that pathology of the OFC (Baaré et al., 1999; Gur et al., 2000; Sanfilippo et al., 2000) and the amygdala (Anderson et al., 2002; Haber and Fudge, 1997) may play a role in negative symptoms. Given that schizophrenia patients can exhibit disrupted, spared or persistent LI whereby the status of LI is associated with different stages (acute vs. chronic) or symptoms (positive vs. negative), the identification of brain regions whose damage leads to disrupted versus persistent LI in the rat may provide valuable cues on dysfunctional brain circuits involved in positive and negative symptoms of schizophrenia.

## **CONCLUSIONS**

The present findings with BLA and OFC lesions indicate that the null effect on a given behavioral phenomenon following specific brain lesions cannot be readily concluded as evidence of the brain regions involved being normally indifferent to its behavioral expression. Thus, although LI does not depend on the integrity of BLA and OFC, because it is present in BLA- and OFC-lesioned rats even under conditions disrupting the phenomenon in normal rats, these regions play a role in the modulation of its

expression, more specifically, in the control of the *non-expression* of LI when the impact of reinforcement in conditioning is increased beyond a certain level. As noted in the introduction, other findings show that intact hippocampus is not necessary for LI expression but rather for preventing its expression when the context of conditioning differs from that of preexposure (Holt and Maren, 1999; Honey and Good, 1993). It remains to be determined whether BLA and OFC are involved in contextual modulation of LI and whether conversely, the hippocampus is involved in LI modulation based on the impact of conditioning. It is important to emphasize that in the absence of modulatory mechanisms responsible for restricting the expression of LI to specific conditions, the LI phenomenon becomes inflexible and unresponsive to situational demands, akin to other perseverative phenomena associated with negative symptoms of schizophrenia (Weiner, 2003). An elucidation of brain regions whose damage leads to perseverative LI might therefore promote the understanding of brain mechanisms that go awry in this disorder.

*Acknowledgments*—This research was partly supported by the Wolf Foundation Award to D.S.

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