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Research report

Fimbria-fornix cut affects spontaneous activity, two-way avoidance and delayed non matching to sample, but not latent inhibition

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Abstract

Latent inhibition (LI) consists of a decrement in conditioning to a stimulus as a result of its prior nonreinforced preexposure. Based on evidence pointing to the involvement of the hippocampus and the nucleus accumbens (NAC) in LI disruption, it has been proposed that LI depends on the integrity of the subicular input to the NAC. Since fibers originating in the subiculum and destined for the NAC run through the fimbria-fornix, we assessed the effects of fimbria-fornix lesion, made using a knife cut, on LI. In addition, we assessed the effects of the fimbria-fornix cut in three tests known to be sensitive to lesions to the hippocampal region, namely, spontaneous activity, two-way active avoidance and delayed-non-matching-to-sample. In accord with previously documented effects of lesions to the hippocampus and related structures, the fimbria-fornix cut increased spontaneous activity (Experiment 1), facilitated the acquisition of two-way active avoidance (Experiment 3), and produced a delay-dependent deficit in the delayed-non-match-to-sample task (Experiment 4), demonstrating that it disrupted hippocampal functioning. In contrast, LI remained unaffected by the fimbria-fornix cut (Experiment 2), indicating that disruption of subicular input to the NAC is not responsible for the attenuation of LI following non-selective hippocampal lesions. The implications of these results for the neural circuitry of LI are discussed. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Fimbria-fornix; Latent inhibition; Activity; Two-way active avoidance; Delayed-Non-Match-to-Sample; Context; Lesion; Rat

1. Introduction

Recently, there has been increasing interest in the modeling of cognitive deficits in schizophrenia by paradigms that can be used in both humans and experimental animals. One such model is based on the paradigm of latent inhibition (LI) [28,35,39,62,65, 83,95,116,120], in which repeated nonreinforced preexposure to a stimulus retards subsequent associations with that stimulus [60,61,63].

LI is disrupted in rats and humans by the psychotomimetic dopamine releaser, amphetamine [37,54,55,95, 103,111–113,115], and in rats, this disruption is prevented by dopamine antagonists [109,119]. Neuroleptic treatment on its own potentiates LI in rats and humans [16,19,27,57,68,75,114,117,119,122]. The relevance of these findings to the behavioral impairments of schizophrenia has been demonstrated by findings that LI is disrupted in some subsets of schizophrenic patients, mainly in the acute stages of the disorder [5,6,20,36,38,106] but see [98], as well as in normal humans scoring high on questionnaires measuring schizotypy [7,18,59,64].

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Studies of the neural substrates of LI disruption in the rat have pointed to the involvement of the nucleus accumbens (NAC) [40,96,99,118,127] as well as the hippocampal formation and adjacent cortical areas [1,14,43,51,52,93,94,104,121,126], consistent with the central role attributed to medial temporal lobe and mesolimbic dopamine abnormality in schizophrenia (e.g., [10,11,13,15,17,50]). Since the hippocampal formation provides a major input to the NAC, which originates in the subiculum and runs through the fimbria-fornix [41,42,53,76,125,128], Weiner [116] proposed that LI depends on the subicular input to the NAC. According to this view, the abolition of LI by hippocampal lesions stems from the disruption of the subicular projection. In support of this suggestion, Honey and Good [47] found that excitotoxic lesion of the hippocampus, which did not damage the subiculum, preserved LI. These authors also concluded that the critical projections subserving LI are those from the subiculum via the fimbria-fornix to the NAC. The present study sought to test this possibility more directly by assessing the effects of a knife cut lesion of the fimbria-fornix on LI (Experiment 2). In addition to LI, we assessed the effects of the fimbria-fornix cut in three tests known to be sensitive to lesions to the hippocampus and related structures, namely, spontaneous activity (Experiment 1), two-way active avoidance (Experiment 3) and an operant delayed-non-match-to-sample (DNMS) task modeled after Dunnett [21] (Experiment 4) [4,21,24,34,45,48,49,79,80,86,87,98].

2. Materials and methods

2.1. Subjects

Forty eight male Wistar rats (Tel Aviv University Medical School, Israel) ≈ 4 months old, weighing 300–420 g, were housed four to a cage under reversed cycle lighting (lights on: 1900–0700). They were maintained on ad lib food and water except for 1 week prior to and throughout the LI and DNMS experiments (see below).

2.2. Surgery

Rats were anaesthetized by intraperitoneal injection of equithesine (3 ml/kg). They were placed in a stereotaxic headholder, and an incision was made in the scalp to expose the skull. Bregma and lambda were measured in order to align them in the same (head level) plane. A small square of bone was removed (about 3 mm wide and 5 mm long), beginning about 1 mm posterior to bregma, to expose the dura and sagittal sinus at the point where the knives were to be inserted. The transections were made using a pair of syringe needles (25-gauge) mounted in a brass jig that was fitted onto an electrode carrier. The needles were bent through 90 degrees close to the tip, to give a cutting blade length of 1.2 mm. The jig was designed so as to maintain the separation between the knife shafts at 2.4 mm, center to center, and to permit the knives to be rotated 180 degrees. Measurements for the stereotaxic coordinates were taken from the posterior limit of the blades.

The knives were positioned so that they laid symmetrically on either side of the sinus, oriented parasagittally, at a location 1.2 mm posterior to bregma. A small slit was made in the dura, and the knives were lowered slowly into the brain. In rats allocated to the sham operated group the blades were lowered to a depth of 3 mm below dura and then removed. In rats allocated to the fimbria-fornix cut group the blades were lowered to two different dorso-ventral positions:

1. at a depth of 5.5 mm from dura, the blades were rotated inwards to align them in the coronal plane, moved up 2.5 mm, lowered again and rotated outwards to align them in the saggital plane. This procedure was repeated twice. Then the same steps were repeated, but the blades were rotated outwards.
2. At a depth of 3 mm from dura, the blades were rotated inwards to align them in the coronal plane, moved down 3 more mm, moved up again and rotated outwards to align them in the saggital plane. This procedure was repeated twice. Then the same steps were repeated, but the blades were rotated outwards, and then removed.

Sterispon was used to cover the hole in the bone, the scalp incisions were sutured by Michel clips, and Sulphonamide powder was sprinkled on the wound. Rats were allowed to recover for 4 weeks before the initiation of behavioral testing. Three rats (2 sham and 1 fimbria-fornix) did not survive surgery, leaving 23 fimbria-fornix-lesioned and 22 sham-operated rats.

2.3. Histology

After the completion of behavioral testing lesioned rats were anaesthetized with an overdose of Nembutal and perfused intracardially with physiological saline, followed by 10% formalin. Their brains were removed from the skulls and stored in 20% formalin-10% sucrose solution before being sectioned in the coronal plane at 40 microns thickness. Every section through the lesion was retained and mounted; sections were stained alternately with cresyl violet and with Gallyas silver stain [30] for histological examination. Verification of placements used the atlas of Paxinos and Watson [73].

2.4. Apparatus and procedure

2.4.1. Spontaneous activity

The apparatus consisted of eight plastic chambers that were located in a darkened and air-conditioned room. The internal dimensions of each chamber were $46 \times 57 \times 37$ cm, as measured from the raised grid floor. A Coulbourn Instruments infrared sensor unit (model E61-02) was installed in the center of the front wall 22 cm from the side walls, and 12 cm above the grid floor. The sensor was protected by a wire fence measuring $10 \times 13 \times 6$ cm to prevent animals' access. Blind areas of the sensor (the two corners of the triangles adjacent to the sensor, measuring $17 \times 17 \times 25$) were blocked by two 25×57 cm clear Perspex walls. The chambers were covered by 50×50 cm clear Perspex lids. The movements detected by the sensor were transmitted through a Coulbourn Instruments 8-channel infrared motion interface (model E61-08), to a Coulbourn Instruments infrared motion activity monitor controller/analyzer (model E61-01). Data recording was computer controlled.

Rats were individually placed in the activity chambers and allowed 60 min of free exploration. The duration of the movements performed by each rat was recorded in 6 min blocks.

2.4.2. Latent inhibition

The apparatus consisted of four Campden Instruments rodent test chambers (model 410), each set in a ventilated sound-attenuating Campden Instruments chest (model 412). A drinking bottle could be inserted into the chamber through a 0.5-cm diameter hole located at the center of the left wall 2.5 cm above the grid floor. When the bottle was not present, the hole was covered by a metal lid. Licks were detected by a Campden Instruments drinkometer circuit (model 453). The preexposed to-be-conditioned stimulus was a 5-s, 2.8 kHz, 80 dB 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 a shock scrambler (model 521/S) set at 0.5 mA, 1 s duration. Equipment programming and data recording were computer controlled.

Prior to the beginning of the LI experiment, rats were handled for about 2 min daily for 6 days. A 23-h water restriction schedule was initiated simultaneously with handling and continued throughout the behavioral testing. Water in the test apparatus was given in addition to the daily ration of 1 h given in the home cages.

LI was assessed in an off-baseline conditioned emotional response (CER) procedure consisting of the following stages:

2.4.2.1. Baseline. On each of 5 days, each rat was placed into the experimental chamber and allowed to drink for 15 min.

2.4.2.2. Preexposure. With the water bottle removed, each rat was placed into the experimental chamber. The preexposed rats received forty 5-s tone presentations with a variable inter-stimulus interval of 50 s. The nonpreexposed rats were confined to the chamber for an identical period of time without receiving the tones.

2.4.2.3. Conditioning. With the water bottle removed, each rat was given two tone-shock pairings 5 and 10 min after the start of the session. Tone parameters were identical to those used in preexposure. The 0.5 mA, 1 s shock immediately followed tone termination. After the second pairing, rats were left in the experimental chamber for an additional 5 min.

2.4.2.4. Rebaseline. Each rat was given a drinking session identical to the baseline sessions.

2.4.2.5. Test. Each rat was placed into the chamber and allowed to drink from the bottle. When the rat completed 75 licks, the tone was presented, and lasted 5 min. The following times were recorded: Time to first lick, time to complete licks 1–50, time to complete licks 51–75 (pre-tone) and time to complete licks 76–100 (tone-on). The times to complete licks 76–100 were subjected to logarithmic transformation in order to allow analysis of variance.

The stages of preexposure, conditioning, rebaseline and test were given 24 h apart. Each rat was run throughout the experiment in the same chamber.

2.4.3. Two-way active avoidance

The apparatus consisted of four identical Campden Instruments shuttle boxes, measuring $48.5 \times 23 \times 20$ cm. The barrier between the two compartments of the box consisted of an aluminum wall with a central inverted U-shaped gate (12 cm high, 10 cm wide). Each box was set in a ventilated, sound-attenuating chest. The conditioned stimulus was a light flashing at a rate of 1.3 Hz for 10 s. Shock was supplied to the grid floor by a Campden Instruments scrambled shock generator (model 521C) set at 0.5 mA intensity. Equipment programming and data recording were computer controlled.

Prior to avoidance training, rats were given a 30-min session of exposure to the shuttle box during which the number of crossings between the two compartments was recorded in blocks of 5 min. On the next day, each rat was placed into the experimental chamber and received 100 avoidance trials, presented on a variable interval 60 s schedule ranging from 10 to 110 s. Each avoidance trial began with a 10-s flashing light followed by a 5-s shock, the flashing light remaining on with the shock. If the rat crossed the barrier to the opposite compartment during the flashing light, the stimulus was terminated and no shock was delivered (avoidance re-

sponse). A crossing response during shock terminated the flashing light and the shock. If the rat failed to cross during the entire light-shock trial, the light and the shock terminated after 15 s. The number of avoidance responses was recorded in ten trial blocks.

2.4.4. Delayed-non-match-to-sample

The apparatus consisted of eight Campden Instruments operant chambers, located four in a room, under on-line computer control. Each chamber was equipped with two retractable levers spaced 7.5 cm on either side of a central food tray that was accessed by a hinged Perspex panel lighted from behind. A houselight was located at the center of the chamber ceiling and a food dispenser delivered 45 mg P.U. Noyes precision Formula pellets.

One week before the beginning of behavioral testing rats were fed approximately 1.5 h daily until their body weights were reduced to 85%. This weight level was maintained throughout the experiment. Water was freely available. The DNMS task consisted of the following stages:

2.4.4.1. Adaptation to reward. During the 3 days preceding the beginning of lever press training, rats were adapted to the food pellets in their home cages.

2.4.4.2. Lever press training. On the first 2 days, rats were trained to collect food pellets from the food tray in the operant chamber. Each session lasted 10 min, and every 20 s a food pellet was delivered into the food tray, signaled by the panel light. Collection of the pellet extinguished the panel light, which was otherwise turned off after 10 s. The rats were then trained to lever-press on a continuous reinforcement schedule for five daily sessions. On days 1–3, each trial began with the insertion of both levers into the chamber which were retracted immediately after the rat made a response on one of them. Each response delivered a pellet, signaled by the panel light. Collection of the pellet started an inter-trial interval of 15 s and extinguished the panel light, which was otherwise turned off after 10 s. A trial was defined as a 'finished' trial if the rat pressed a lever and collected the food within 10 s. All other trials were recorded as 'unfinished'. Each session terminated after the rat completed 30 finished trials. On days 4–5, training continued as on days 1–3, but the levers were inserted one at a time, and remained until 15 finished trials were completed. This was done in order to prevent the establishment of side preference.

2.4.4.3. Delayed-non-match to sample training. Following lever press training rats were trained in the non-match to sample (NMS) procedure, consisting of 48 daily trials. Each trial included three components: sample response, delay interval, and choice response. At the start of each trial the houselight was turned on and 2 s later the sample lever was inserted. The side of the sample (left or right) was determined in a pseudo-random order. As soon as the rat made a lever press response, the lever was retracted, the food-tray light was turned on and a food pellet delivered, and the delay interval began. The food-tray light was turned off when the rat collected the food. The delay component was terminated by the rat's first nose poke at the food-tray door after the completion of the delay interval. In the choice component both levers were inserted into the chamber. A correct non-match response, i.e., to the lever not presented in the sample component, resulted in the levers being retracted, the houselight extinguished, a food pellet delivered, and the food-tray light switched on until a further nose poke was made, indicating that the pellet was collected. An incorrect response, i.e., to the lever presented in the sample component, resulted in the levers being retracted, the houselight switched off for 5 s (punishment), and no delivery of food. Following collection of the pellet on correct trials or punishment on incorrect trials, a 10-s inter-trial interval preceded the next trial. A trial was defined as a 'finished' trial if the rat made a choice response (correct or incorrect). All other trials were recorded as 'unfinished'. In the first stage of training rats were trained with no delay between the sample and choice components. Each rat was trained until it reached a criterion of at least 42 correct out of 48 finished trials on three consecutive days. Once all rats had reached criterion at the NMS stage, they were run for an additional 2 days, and on the subsequent day a variable delay interval schedule was introduced. On each trial the delay was chosen at random from a range of delays. The range of delays was increased over a period of days from a range of 0 and 4 s delays, via a range of 0, 4, 8 and 16 s delays, to a range of 0, 4, 16 and 32 s delays. Training with each delay range continued until all rats performed less than ten unfinished trials in a session and then the next delay range was introduced. The delays were introduced consecutively, with one exception. Due to constraints of the DNMS program, when the 32 s delay was introduced, the 8 s delay was removed. Training on the final range of delays (0, 4, 16, and 32 s) continued for 7 days.

2.4.4.4. Match to sample training. After completion of DNMS training, rats were run for two additional days with no delay. On the third day match to sample (MS) training began. Training was identical to that of NMS, but the correct response consisted of pressing the lever that was presented in the sample stage. Each rat was trained until it reached a criterion of at least 42 correct out of 48 finished trials on three consecutive days. The two experimental rooms were counterbalanced between the groups.

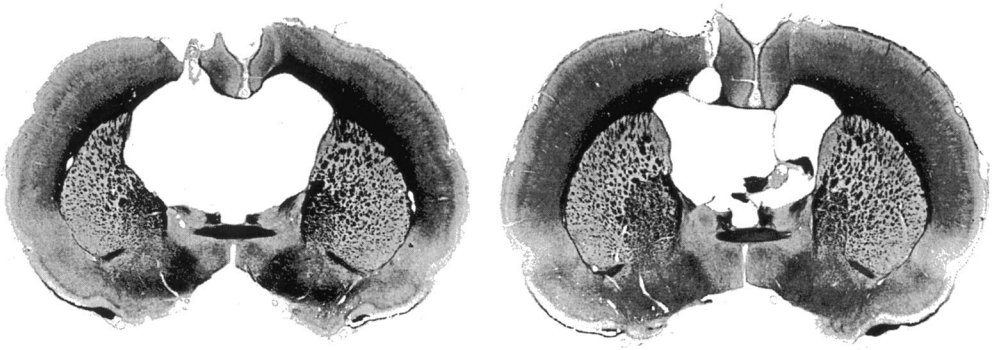

Fig. 1. Photomicrographs of Gallyas silver-stained coronal sections of brains bearing knife-cut induced lesions of the fimbria-fornix, at the level where the knives were inserted. Left side: a complete lesion; Right side: an incomplete lesion.

The percent of correct choices per daily session in the NMS and MS stages, and in each delay on each day during the DNMS stage was recorded. Arcsinus transformation of the square root of the percent of correct choices was carried out on the raw data to allow analysis of variance. The acquisition of the NMS and MS rules was assessed using two-way ANOVAs with main factors of room and lesion and a repeated measurements factor of 3 day blocks conducted on the transformed correct choices. Performance on the final range of delays was assessed using a two-way ANOVA with main factors of room and lesion and repeated measurements factors of delays and days.

2.5. Experimental design

2.5.1. Experiment 1: spontaneous activity

Forty five rats (23 fimbria-fornix-lesioned and 22 sham-operated) were tested in spontaneous activity. Data of three fimbria-fornix rats were discarded from statistical analysis after histological confirmation of the lesioned sites. Thus, the final analysis included 42 rats, 20 fimbria-fornix and 22 sham.

2.5.2. Experiment 2: latent inhibition

The 45 rats from Experiment 1 were tested 1 week after the completion of the spontaneous activity procedure. They were allocated to four experimental groups in a 2×2-factorial design with main factors of preexposure (0, 40) and operation (sham, lesion). Data of three fimbria-fornix rats were discarded from statistical analysis after histological examination. Thus, the final analysis included 42 rats, with the following number of rats in each condition: NPE-sham 11, PE-sham 11, NPE-fimbria-fornix 8, PE-fimbria-fornix 12.

2.5.3. Experiment 3: two-way active avoidance

Forty rats (20 fimbria-fornix and 20 sham) which participated in Experiments 1 and 2 were tested 2 weeks after the completion of the LI procedure. Data of two sham rats were lost due to apparatus failure and data of two fimbria-fornix rats were discarded from statistical analysis after histological examination. Thus, the final analysis included 36 rats, 18 fimbria-fornix and 18 sham.

2.5.4. Experiment 4: delayed-non-match-to-sample

Twenty eight rats (14 fimbria-fornix and 14 sham) were chosen randomly from the animals which participated in Experiments 1, 2 and 3, and tested ≈ 3 weeks after the completion of the avoidance procedure. One fimbria-fornix rat fell ill during training and the data of two fimbria-fornix rats were discarded from statistical analysis after histological examination. Thus, the final analysis included 25 rats, 11 fimbria-fornix and 14 sham.

3. Results

3.1. Anatomical

Fig. 1 shows representative histology in Gallyas silver-stained coronal sections of knife-cut induced lesions of the fimbria-fornix, at the level where the knives were inserted (left side: a complete lesion; right side: an incomplete lesion). In most lesioned brains, the lesion to the fimbria-fornix complex was complete; however, in some cases, there were sections in which the medial and most ventrolateral parts of the fimbria-fornix were spared. The most extensive damage to the fimbria-fornix was seen at the level where the knives were inserted into the brain, just posterior to the most caudal level of the anterior commissure. At this level some damage to the triangular septal nucleus could also be observed. In addition, damage to the bed nucleus of the stria terminalis just dorsal to the anterior commissure was also common. Caudal to the bed nucleus of the stria terminalis, dorsal parts of the thalamus including midline, mediodorsal, intralaminar, and anteroventral thalamic nuclei were frequently damaged. Fiber damage additional to that of the fimbria-fornix included the

corpus callosum and the dorsal hippocampal commissure just ventral to the corpus callosum. The cingulum was typically damaged at the insertion tracks of the knives. Three animals had the medial part of the fimbria-fornix intact and were excluded from the final analyses.

3.2. Behavioral

3.2.1. Experiment 1: spontaneous activity

Fig. 2 presents the mean duration of movements in the fimbria-fornix and sham groups. As can be seen, activity level declined in both groups as the session progressed, but the fimbria-fornix animals were more active than shams throughout the session. One-way ANOVA with a repeated measurements factor of 6 min blocks yielded significant effects of blocks $F(9,360) = 60.34$, $P < 0.0001$ and of the linear, quadratic and cubic trends of this factor (all Ps < 0.0001), as well as a significant main effect of lesion $F(1,40) = 53.52$, $P < 0.0001$.

3.2.2. Experiment 2: latent inhibition

2×2 ANOVAs conducted on the times to complete licks 1–50 and 51–75 in the absence of the stimulus, yielded no significant results. The mean log times to complete licks 76–100 in the presence of the tone in the preexposed and nonpreexposed fimbria-fornix and sham rats are shown in Fig. 3. As can be seen, LI, i.e., shorter time to complete licks 76–100 in the preexposed as compared to the nonpreexposed rats, was evident in both conditions. This was supported by a 2×2-ANOVA with main factors of preexposure and lesion, which yielded only a significant main effect of preexposure $F(1,38) = 13.50$, $P < 0.001$.

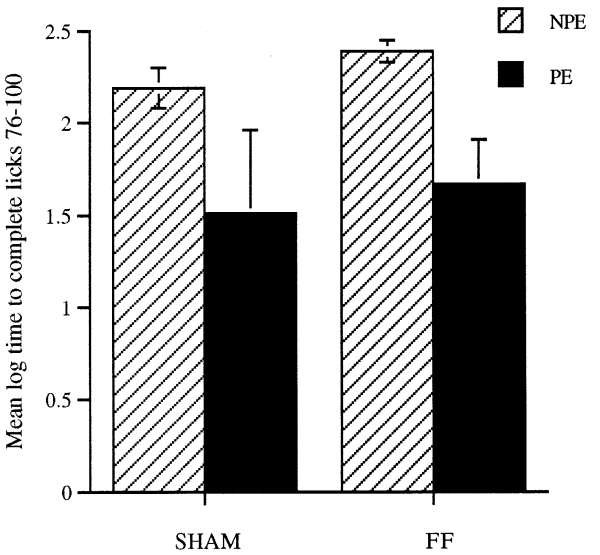

Fig. 3. Means and standard errors of log time to complete licks 76-100 in the presence of the tone in the fimbria-fornix (FF) and sham-operated preexposed (PE) and nonpreexposed (NPE) groups.

3.2.3. Experiment 3: two-way active avoidance

There was no difference between the two groups in the number of crossings during the 30 min session of exposure to the shuttle box. One-way ANOVA with a main factor of lesion and a repeated measurements factor of 5 min blocks yielded only a significant effect of blocks $F(11,374) = 32.67$, $P < 0.0001$.

Fig. 4 presents the mean number of avoidance responses in ten trial blocks of the fimbria-fornix and sham rats. As can be seen, both groups improved with training but the fimbria-fornix rats showed superior avoidance performance throughout. One-way ANOVA with a main factor of lesion and a repeated measure-

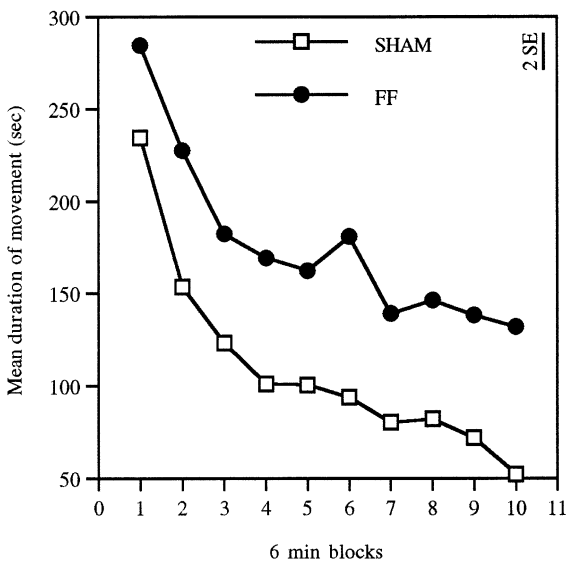

Fig. 2. Mean duration of movement performed by the fimbria-fornix (FF) and sham-operated rats, presented in 6 min blocks.

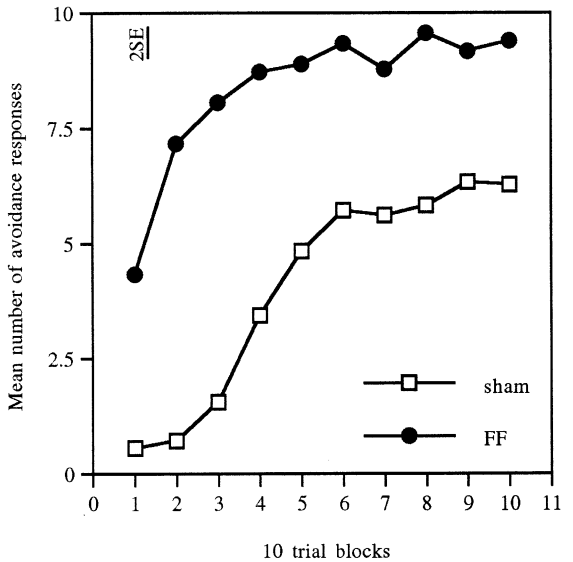

Fig. 4. Mean number of avoidance responses in 10 trial blocks of the fimbria-fornix (FF) and sham-operated rats.

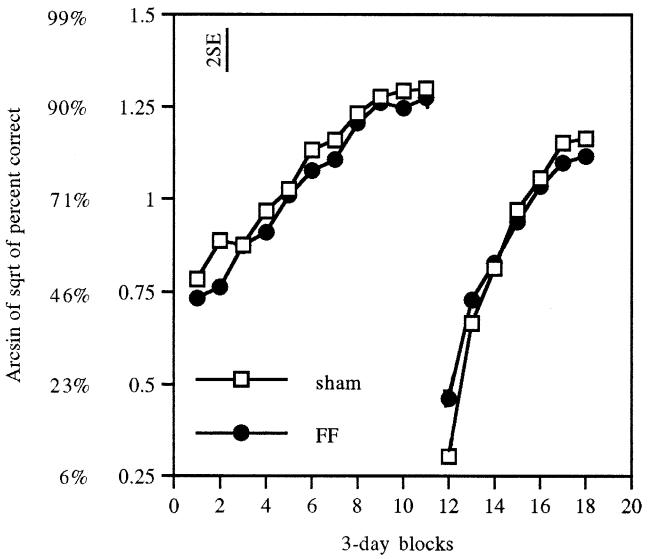

Fig. 5. The transformed percent correct choices, in three day blocks, of the fimbria-fornix (FF) and sham-operated groups during the acquisition of the NMS (left side) and MS (right side) rules. The corresponding percent correct choices are presented to the left of the transformation.

ments factor of ten trial blocks yielded a significant effect of blocks $F(9,306) = 45.88$, $P < 0.0001$, a significant main effect of lesion $F(1,34) = 56.15$, $P < 0.0001$, and a significant block × lesion interaction $F(9,306) = 5.93$, $P < 0.0001$.

3.2.4. Experiment 4: delayed-non-match-to-sample

There was no main effect of room nor significant interactions of this factor with any of the other factors. Consequently, the data from the two rooms were combined for statistical analyses.

Fig. 5 (left side) presents the transformed percent correct choices, in 3 day blocks, of the fimbria-fornix and sham groups during the acquisition of the NMS rule. As can be seen, both groups improved similarly with training and reached criterion level of performance by the end of training. This was supported by one-way ANOVA which yielded only significant effects of blocks $F(10,230) = 69.83$, $P < 0.0001$, and of the linear and qubic trends of this factor $F(1,23) = 352.53$, $P < 0.0001$ and $F(1,23) = 6.41$, $P < 0.05$, respectively.

Fig. 6 presents the transformed percent correct choices of the fimbria-fornix and sham groups during the 7 days of training with the final set of delays (0, 4, 16 and 32 s). As can be seen, the performance of both groups deteriorated as a function of delay, and was at chance level with the 32 s delay; however, the delay effect was stronger for the fimbria-fornix group, particularly at the 4 s delay. These observations were supported by one-way ANOVA, which revealed significant effects of delay $F(3,69) = 141.10$, $P < 0.0001$ and of the linear and quadratic trends of this factor $F(1,23) = 338.23$, $P < 0.0001$ and $F(1,23) = 27.97$, $P < 0.0001$, respectively, as well as a nearly significant delay × lesion interaction $F(3,69) = 2.66$, $P = 0.055$, and a significant linear trend of this interaction $F(1,23) = 5.04$, $P < 0.05$.

Fig. 5 (right side) presents the transformed percent correct choices, in 3 day blocks, of the fimbria-fornix and sham groups during the acquisition of the MS rule following reversal. As can be seen, fimbria-fornix rats made less errors than shams in the first block of training, but as training progressed the two groups reached similar levels of performance. This was supported by one-way ANOVA which revealed significant effects of blocks $F(6,138) = 151.87$, $P < 0.0001$, and of the linear, quadratic and qubic trends of this factor (all Ps < 0.05), as well as a significant blocks × lesion interaction $F(6,138) = 2.95$, $P < 0.01$ and a significant linear trend of this interaction $F(1,23) = 5.41$, $P < 0.05$.

4. Discussion

Fimbria-fornix cut increased spontaneous activity, facilitated the acquisition of two-way active avoidance, and produced a delay-dependent deficit in the DNMS task. These results are in accord with previous studies of lesions to the hippocampus and related structures

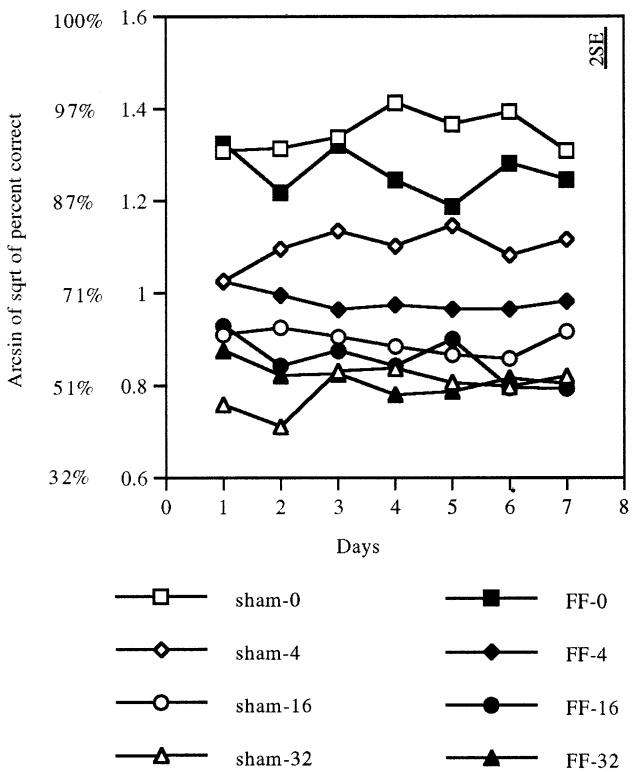

Fig. 6. The transformed percent correct choices of the fimbria-fornix (FF) and sham-operated groups during the 7 days of training with the final set of delays (0, 4, 16 and 32 s). The corresponding percent correct choices are presented to the left of the transformation.

which found increased spontaneous activity [24,44,45, 79,80,86,87,102], but see [107,108], facilitated acquisition of two-way active avoidance [34,48,49], and a delay-dependent deficit in DNMS tasks [2–4,21,22, 25,67,70,74,80,84,91,97,102,123,124]. The hippocampal-like effects exerted by the fimbria-fornix cut in these three tests indicate that the cut disrupted hippocampal function.

Enhanced spontaneous activity following hippocampal lesions has been typically attributed to retarded habituation to the context [24,45,79,80]. Impaired context learning has been also suggested to underlie facilitated acquisition of two-way avoidance following hippocampal lesions [33,72]. Since in two-way avoidance, an animal receives shock in both compartments of the shuttle box, it can only avoid shock by approaching cues that had been previously associated with shock. Impaired contextual learning would therefore be expected to reduce the impact of such cues, thereby facilitating avoidance acquisition [33,72]. Delay-dependent deficits in DNMS tasks are considered to reflect impaired working memory, i.e., the capacity to hold information temporarily 'on line' until a behavior is produced (although the contribution of non-mnemonic factors to such deficit is not always easily ruled out; see [21,44,77,102,110]). Thus, the fimbria-fornix cut appears to have disrupted two main behavioral functions attributed to the hippocampus, namely, context learning and working memory.

In addition, the fimbria-fornix cut facilitated reversal from the NMS to the MS rule. While lesions to the hippocampus or related structures typically retard reversal learning [8,26,46,66,70,71,85,92], but see [22], there is an important distinction between these tasks and the present one. Whereas most tasks use reversal of a specific solution (e.g., reversing the correct and incorrect stimuli in discrimination learning tasks), the present task used reversal of a general rule (i.e., from the NMS to the MS rule). Reversal deficits exhibited by hippocampal animals seem to be particularly evident in the former type of tasks, whereas the ability to acquire and shift general rules remains relatively intact (e.g., [8,22,23,26,66,101], but see [85]). The normal acquisition of the NMS rule by the fimbria-fornix rats found in the present study is consistent with this pattern.

In contrast to the clear behavioral effects of the fimbria-fornix cut in the above tasks, the cut had no effect on LI, i.e., stimulus preexposed fimbria-fornix rats, like sham rats, exhibited lower suppression of drinking than their nonpreexposed counterparts. This contrasts with the bulk of extant results on the effects of conventional lesions to the hippocampus and related structures, which have been found to abolish LI [1,14,43,51,52,93,94,100,104,121,126]. It should be pointed out that several studies using conventional hippocampal lesion found preserved [29] or even facilitated [81,82] LI. These results, however, were obtained using conditioned taste aversion paradigm which differs from other classical conditioning paradigms. The present results suggest that disruption of hippocampal efferents and afferents traversing the fimbria-fornix are not responsible for the attenuation of LI following non-selective hippocampal lesions. In particular, given the evidence pointing to the involvement of the hippocampal region and the NAC in LI disruption (see Introduction), it has been suggested that the critical projections subserving LI are those from the subiculum through the fimbria-fornix to NAC. Intact LI following the fimbria-fornix cut is inconsistent with this suggestion. However, there remains a possibility that subicular output could reach the NAC via a disynaptic pathway, from the subiculum to the entorhinal cortex and from the latter to the NAC [56,107,125]. Recent studies have shown that LI is disrupted by exitotoxic lesions of the entorhinal cortex and ventral subiculum [126], as well as by lesions of the shell but not core subterritory of the NAC [99,118], suggesting that LI depends on inputs to the NAC shell from the entorhinal cortex and/or ventral subiculum. Since a large portion of entorhinal projections to the NAC do not traverse the fimbria-fornix [105] the present results suggest that the critical pathway underlying LI disruption may be that from the entorhinal cortex to the NAC shell. Whether subicular output to the entorhinal cortex plays a role in LI, remains an open question. Interestingly, two recent neural network models of LI have also suggested that the entorhinal cortex is the critical hippocampal substructure for LI [32,69,89].

In this context, the possibility that fimbria-fornix cut disrupts context learning may have interesting implications for the functional role of the entorhinal and hippocampal inputs to the NAC in LI. During recent years, theoretical accounts of LI have stressed its context dependency, namely, dependence on the similarity of context between preexposure and conditioning (e.g., [12,32,63,65,90]). Thus, it is assumed that during preexposure, there is learning about the stimulus (accounting for stimulus specificity of LI) as well as about the context (accounting for context specificity of LI), and both types of learning are considered to be subserved by the hippocampal region [31,32,47,88]. Honey and Good [47] have provided evidence for the involvement of the hippocampus proper in the context- but not stimulus-dependence of LI: they showed that excitotoxic lesion limited to the major cellular components of the hippocampus (CA1-CA4) and dentate gyrus spared LI, while at the same time eliminating its normal context dependence. Thus, whereas in normal animals, LI is disrupted by context change between preexposure and conditioning, in lesioned animals LI was resistant to such context-change. Recently we have obtained similar results with electrolytic NAC lesion, that is, this

lesion spared LI but eliminated its context dependence (unpublished observations). This leads us to speculate that information about the context in LI encoded by the hippocampus is transmitted to the NAC via the fimbria-fornix, whereas the information about the stimulus reaches the NAC (shell) via a different pathway. Given the evidence that LI is dependent on the entorhinal cortex and the NAC shell, the pathway likely to carry stimulus information in LI is that from the entorhinal cortex to the NAC shell. This possibility is consistent with a recent finding that lesion to the fimbria-fornix but not the entorhinal cortex, disrupted contextual conditioning [78]. It follows from the above that spared LI following fimbria-fornix lesion should be context-independent, i.e., resistant to context shift, similarly to spared LI following axon sparing lesion to the hippocampus.

The above suggestion may be of interest given the fact that disrupted LI is considered to provide an animal model of schizophrenia. There is increasing evidence that pathology in temporolimbic structures is an essential feature of schizophrenia (e.g., [5,9–11,13,15,17,58]), and this pathology has been suggested to underlie LI disruption observed in schizophrenic patients [35,116]. However, the fact that LI is apparently disrupted following damage to some limbic structures (excitotoxic lesion of entorhinal cortex), but not to others (excitotoxic lesion of the hippocampus, fimbria-fornix damage), suggests that the relationship between limbic pathology and LI disruption is not simple, and that such pathology may result in disrupted or in potentiated (context-independent) LI. This may explain the inconsistent findings which have emerged with regard to LI (disruption versus lack of thereof) in different studies testing this phenomenon in schizophrenic patients [6,20,36,38,98,106].

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