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The Effects of Electrolytic Lesion to the Shell Subterritory of the Nucleus Accumbens on Delayed Non–Matching-To-Sample and Four-Arm Baited Eight-Arm Radial-Maze Tasks

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The effects of bilateral electrolytic lesions of the "shell" subterritory of the nucleus accumbens in the rat were examined on 2 tasks known to be sensitive to hippocampal damage. Experiment 1 tested the effects of shell lesion on delayed non–matching-to-sample (DNMS) task in a T-maze. The maze was rotated 180° after the end of acquisition. Experiment 2 used a 4-arm baited, 4-arm unbaited, 8-arm radial-maze task and its reversal. Shell lesion led to impaired acquisition of DNMS in a T-maze and of 4-arm baited, 4-arm unbaited, 8-arm radial maze tasks, suggestive of mnemonic deficits. Following analysis of animals' choice pattern in both tasks, the deficit was interpreted as being largely due to an extensive use of response strategy. The results suggest that the inappropriate use of response strategy by shell animals was a result of their inability to switch from initial response strategy to a later, more appropriate, memory-dependent strategy.

The nucleus accumbens (NAC) has been proposed to constitute a neural interface between the limbic and motor systems of the brain (Annett, McGregor, & Robbins, 1989; Cador, Robbins, & Everitt, 1989; Mogenson, Jones, & Yim, 1980; Mogenson & Yang, 1991; Reading & Dunnett, 1991; Seamans & Phillips, 1994; Taghzouti, Louilot, Herman, Le Moal, & Simon, 1985, Taghzouti, Simon, Louilot, Herman, & Le Moal, 1985; Van den Bos & Cools, 1989). Functions ascribed to the NAC include motor behavior, reward processes, and aspects of learning and memory (Kelley & Stinus, 1985; Mogenson & Nielsen, 1984a, 1984b; Robbins, Cador, Taylor, & Everitt, 1989; Seamans & Phillips, 1994; Whishaw & Kornelsen, 1993). In recent years, an increasing interest has been focused on the compartmentalization of NAC into a more caudomedially located "shell" and a more rostrolaterally located "core" (for an alternative way of compartmentalization, which includes the rostral pole, see Zahm & Brog, 1992). The shell and core subregions differ in many respects, including their pharmacological, morphological, immunohistochemical, and electrophysiological characteristics. Likewise, afferent projections to the NAC exhibit core–shell specificity. Thus, the shell receives inputs from both dorsal and ventral parts of the subiculum, the posterior part of the basolateral amygdala, and the infralimbic, ventral agranular insular and piriform cortices, whereas core receives inputs from the dorsal subiculum, the anterior part of the basolateral amygdala, and the prelimbic, anterior cingulate, and dorsal agranular insular cortices (Deutch & Cameron, 1992; Groenewegen, Vermeulen-Van Der Zee, te Kortschot, & Witter, 1987; Groenewegen, Berendse, Wolters, & Lohman, 1990; Kelley & Domesick, 1982; Voorn, Gerfen, & Groenewegen, 1989; Zaborsky et al., 1985; Zahm & Brog, 1992).

The behavioral functions of the two NAC subterritories have received increasing attention during the last two years (Besson & Louilot, 1995; Carlezon, Devine, & Wise, 1995; Hyytia & Koob, 1995; Maldonado-Irizarry & Kelley, 1994, 1995a, 1995b; Maldonado-Irizarry, Swanson, & Kelley, 1995; Pierce & Kalivas, 1995; Pontieri, Tanda, & Di Chiara, 1995; Prinssen, Balestra, Bemelmans, & Cools, 1994; Tai, Cassaday, Feldon, & Rawlins, 1995; Wan, Geyer, & Swerdlow, 1994; Weiner, Gal, Rawlins, & Feldon, 1996). The results of these studies showed that the two subterritories are involved in many functions ascribed to the NAC, such as locomotor activity, feeding behavior, and drug self-administration. In some studies both subterritories were found to play a similar, albeit quantitatively different, role (e.g., Maldonado-Irizarry & Kelley, 1995b; Maldonado-Irizarry et al., 1995; Pierce & Kalivas, 1995), whereas in others a clear differentiation was evident (e.g., Besson & Louilot, 1995; Carlezon et al., 1995; Maldonado-Irizarry & Kelley, 1995a). Recently, we have investigated the effects of electrolytic lesions to each of the two subterritories on the phenomenon of latent inhibition (retarded conditioning to a

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previously nonreinforced stimulus). Our results showed that lesion to the shell mimicked the effects of hippocampal lesion (Kaye & Pearce, 1987a, 1987b; Solomon, Lohr, & Moore, 1974) in that it disrupted latent inhibition, whereas core lesion had no such effect (Weiner et al., 1996; see also Tai et al., 1995). It has been often noted that NAC lesion-induced deficits are similar to those obtained following hippocampal lesions (Annett et al., 1989; Maldonado-Irizarry & Kelley, 1995; Reading & Dunnett, 1991; Schacter, Yang, Innis, & Mogenson, 1989; Seamans & Phillips, 1994; but see Sutherland & Rodriguez, 1989). Damage to either region produces deficits on tasks used to assess memory, such as Morris water-maze, radial-maze, and delayed non–matching-to-sample (DNMS) tasks, as well as behavioral inflexibility in response to environmental change, as reflected in slower reversal and extinction, and response perseveration (Annett et al., 1989; Gray & McNaughton, 1983; Jarrard, 1986; Reading & Dunnett, 1991; Seamans & Phillips, 1994; Sutherland & Rodriguez, 1989; Taghzouti, Louilot, et al., 1985; Taghzouti, Simon, et al., 1985).

The present study sought to investigate further the behavioral effects of shell lesion, and the extent to which these effects resemble those of hippocampal lesions. Experiment 1 tested the effects of shell lesion on a DNMS task in a T-maze. This task requires working memory for its solution (Honig, 1978, 1979; Olton, Becker, & Handelmann, 1979) because the animal must keep an ongoing record of the previously visited arm in the information (forced) run in order to choose the rewarded arm in the choice run. Hippocampal lesions are known to produce deficits in DNMS task in a T-maze (Aggleton, Keith, & Sahgal, 1991; Markowska, Olton, Murray, & Gaffan, 1989; Peinado-Manzano, 1990; Rothblat & Kromer, 1991; Thomas & Gash, 1988). In addition, several studies reported that lesioned rats adopted a side bias; that is, they chose the same arm over trials with no respect to the information run (Aggleton et al., 1991; Thomas & Gash, 1988). In the present experiment, the maze was rotated 180° after the end of acquisition, in order to test whether the side bias shown by rats reflects a response (egocentric) strategy (i.e., making the same turning response [left or right]), or a place (allocentric) strategy (i.e., going to the same location in the room). Response strategy is reflected in choosing the arm opposite to that preferred during training, whereas place strategy is reflected in choosing the arm in the same location in the room.

Experiment 2 tested the effects of shell lesion on a four-arm baited, four-arm unbaited, eight-arm radial-maze task. In this task the animal must learn the location of the arms that contain food (baited arms) and, in addition, must keep an ongoing record of which arms have been visited on any particular trial, so as to avoid reentering arms already visited. The former learning is considered to rely on reference memory (RM), and the latter on working memory (WM). Hippocampus-lesioned rats are impaired on this and similar tasks, but the precise nature of the deficit remains controversial. Some studies found deficits in the WM component of the task, that is, revisiting baited arms (Davis, Tribuna, Pulsinelli, & Bolpe, 1986; Jarrard, 1983; Jarrard & Elmes, 1982; Olton, Becker, & Handelmann, 1980), whereas others emphasized RM deficit, that is, visiting unbaited arms (Jarrard, 1983; Okaichi & Oshima, 1990). In order to provide a more stringent test of reference memory deficit, Experiment 2 followed the initial training by a reversal stage, in which the previously baited arms were unbaited, and the previously unbaited arms were baited. Because a rat with intact reference memory is expected to reduce its entries to unbaited arms to nearly none by the end of the initial training, the introduction of reversal trials should result in an increased number of entries to previously baited arms. In contrast, if a rat is not relying on reference memory, its performance should not be affected by the reversal.

General Method

Subjects

Fifty-four male Wistar rats (Tel Aviv University Medical School, Israel), approximately 5 months old, were housed one to a cage under reversed-cycle lighting. Twenty-four animals participated in Experiment 1, 30 animals in Experiment 2. Before the present experiments, animals participated in an experiment using conditioned emotional response procedure. One week before the beginning of each experiment, animals were fed approximately 12 g of laboratory pellets daily until their body weights were reduced to 85%. This weight level was maintained throughout the experiment. Animals were weighed twice during the first week of food deprivation and every week during the behavioral testing. Water was freely available.

Surgery

Rats were anesthetized with intraperitoneal injection of Equithesin (3.0 ml/kg). They were placed in a stereotaxic frame and an incision was made into the scalp to expose the skull. The vertical coordinates of bregma and lambda were measured in order to align them in same (level head) plane. A small square of bone was removed starting approximately at bregma and extending rostrally about 3 mm. Bilateral electrolytic lesions were made by passing a 1-mA, 7-s current through a 0.3-mm electrode, insulated except for the tip. A constant current DC source was used. Each animal was exposed to one anterior and one posterior lesion bilaterally with the following coordinates: anterior: 1.5 mm anterior to bregma, 0.8 mm lateral to the midline, and 6.5 mm ventral to dura; posterior: 1.0 mm anterior to bregma, 0.8 mm lateral to the midline, and 6.5 mm ventral to dura (Paxinos & Watson, 1986). Control (sham-operated) animals underwent the same surgical procedure, but the electrodes were inserted 1 mm ventral to dura and no current was passed. Sterispon was used to cover the hole in the bone, the scalp incisions were sutured by Michel clips, and Sulfonamide powder was sprinkled on the wound.

Histology

After the completion of behavioral testing, lesioned animals were anesthetized 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 embedded in gelatin and sectioned in the coronal plane at 80-μm thickness. Every second section was mounted and stained with thionin blue for

histological examination. For verification of placements, we used the atlas of Paxinos and Watson (1986).

Experiment 1

Method

Apparatus

The T-maze was built of unpainted wooden planks 9.5 cm wide, with an edge 1.5 cm high. The stem of the T was 81 cm long, and the cross piece was 136 cm long. A guillotine door was located 33 cm from the beginning of the stem. Food cups (2 cm diameter) were located at each end of the cross-piece. The maze stood on legs 30 cm high, and was placed on a table in a well-lit room. Four 45-mg food pellets (Campden Instruments, Noyes, England) were used as a reward.

Procedure

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

Pretraining. On each of 5 days, rats were placed in the T-maze for 10 min and allowed to explore it. During the first 3 days the guillotine door was raised and food pellets were scattered along the cross-piece. On the next 2 days, four food pellets were placed in each food cup, and the guillotine door was raised and lowered several times. The experimenter ensured that each rat consumed the food pellets.

Non–matching-to-sample acquisition. On Day 6 the behavioral testing began and lasted for 14 days. Each trial consisted of two runs through the maze. At the start of each trial, four food pellets were placed in each food cup, and a wooden block was placed in one arm, close to the choice point, blocking off access to that arm. On the forced run, the rat was placed at the starting point, the door was opened, and the rat was allowed to run to the goal arm and eat the food there. The rat was then picked up and returned to the starting point, and the wooden block was removed. The choice run followed with a minimal possible delay between the runs. The door was opened and the rat was allowed to choose between the two arms. Once it had entered an arm, the wooden block was placed behind the animal preventing it from retracing. If the arm not visited on the forced run was chosen, the rat was allowed to eat the food and then removed from the maze to a holding cage for the duration of the intertrial interval. If the other arm was chosen, the rat was confined to the arm for approximately 10 s and then removed from the maze to a holding cage for the duration of the intertrial interval. The intertrial interval was approximately 5 min. The arm that was blocked in the forced run was varied from trial to trial in a pseudorandom sequence so that each arm was blocked four times a day, with the provision that the same arm was not blocked on more than two consecutive trials. During the first 4 days of training, each rat was given four trials per day; thereafter the number of trials was increased to eight. The results of the first 4 days were combined to yield two scores of correct choices out of eight. Rats were trained until they reached a criterion of at least seven correct choices out of eight trials on two consecutive days. Once rats achieved criterion performance, delays were to be introduced between the sample and choice trials, but this part was not carried out, because lesioned animals failed to master the task at the no-delay condition (see below).

T-Maze Rotation

On Day 20, the maze was rotated 180°, and the animals were run for two additional days exactly as in acquisition.

Measures and Statistical Analyses

Two response measures were recorded throughout acquisition and rotation:

1. Number of correct choices: Logistic transformation of the number of correct choices per day was carried out on the raw data to allow analysis of variance (ANOVA; Mosteller & Tukey, 1977). The data were analyzed using ANOVA with a repeated measurements factor of days.
2. The arm chosen on each trial: The tendency to choose the left or the right arm was defined as a side bias if the same arm was chosen on seven or eight trials on the same day. The proportion of days on which side-bias criterion was reached was compared using *t* tests.

Twelve shell and 12 sham-operated animals participated in this experiment. Two sham-operated animals were excluded from the behavioral testing because they did not enter the goal arms or did not eat the food pellets during a period of 10 min. In addition, 2 sham-operated animals fell ill during the experiment.

Results

Anatomical

Figure 1 presents the shell lesion. Representative reconstruction of the shell lesions is presented in A, and a photomicrograph of a typical lesion in B. The lesions obtained were oval in shape, the elongation being in the dorsoventral axis. The typical lesion extended AP 0.7–1.7 mm, with maximal damage at 1.0–1.5 mm anterior to bregma. Restricted damage to the anterior ventrolateral septum was detected in most of the animals. In 3 animals the lesion extended AP 1.0–2.0 anterior to bregma. One animal was excluded because of damage to the ventral pallidum. Thus, the final analysis was performed on 11 shell- and 8 sham-operated animals.

Behavioral

There were no differences in body weight between shell- and sham-operated animals on the first day of food deprivation (mean weight of 353 g and 360 g, respectively), and both groups reached 85% of the initial body weight at the end of the first week.

Figure 2 presents the logistic transformation of the number of correct responses per day in shell- and sham-operated animals before and after T-maze rotation.

Initial Acquisition

As can be seen in Figure 2, left side, sham-operated animals improved their performance over trials, whereas shell-operated animals' performance remained at chance level. This was supported by a one-way ANOVA with a repeated measurements factor of days, which yielded a significant main effect of lesion, $F(1, 17) = 10.08$, $p < .01$,

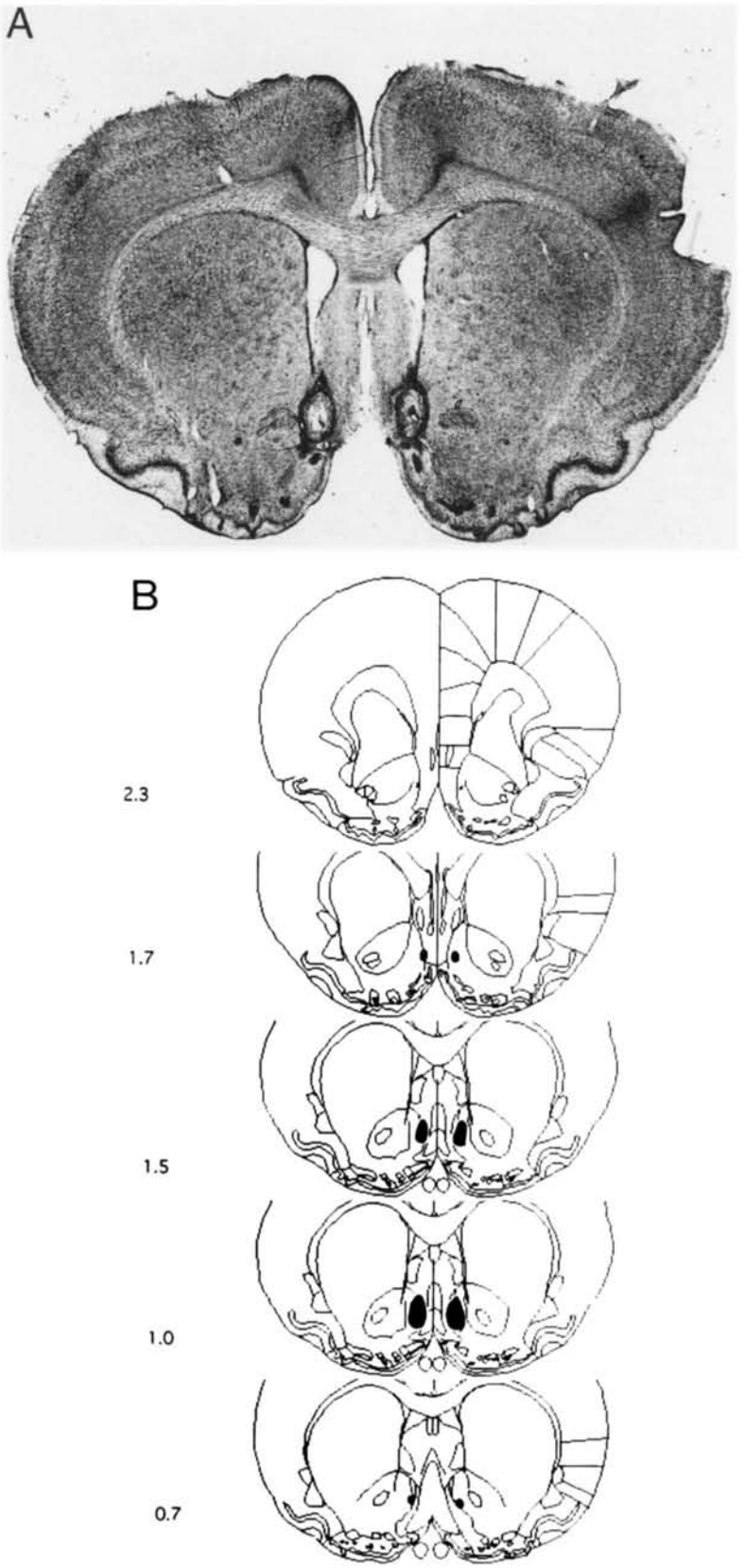

Figure 1. A: A photomicrograph of a typical shell lesion. B: Representative reconstructions of the shell lesions in successive brain sections, according to the atlas of Paxinos and Watson (1986). The blank areas represent regions of neuronal loss.

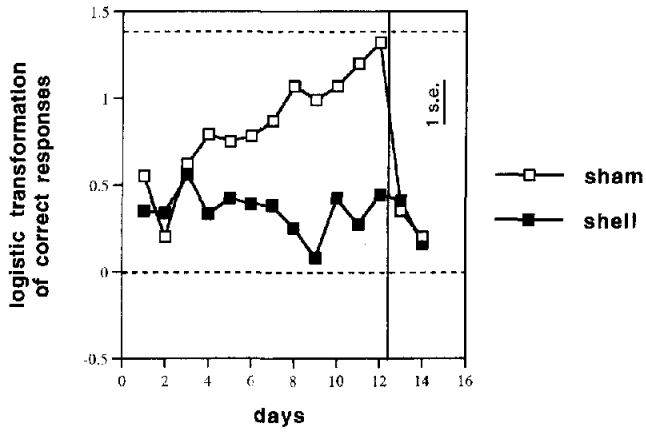

Figure 2. The logistic transformation of the number of correct responses per day in shell- and sham-operated animals before (left) and after (right) T-maze rotation. Dashed lines at the bottom and the top of the figure represent 50% and 100% correct choices, respectively. s.e. = standard error.

and a significant Lesion × Days interaction, $F(11, 187) = 3.85, p < .0001$.

It is noteworthy that while all sham-operated rats reached criterion (7 correct out of 8 trials on two consecutive days), 8 out of 11 shell-operated animals remained at chance level. Furthermore, 7 out of these animals exhibited a pronounced side bias; namely, they went to the same arm over trials and over days. This tendency was rarely seen in sham rats, and was restricted to the beginning of training. The stronger side bias exhibited by shell- compared with sham-operated rats, was supported by a t test performed on the mean percentage of days in which response bias criterion was reached; shell-operated: 30%, sham-operated : 4%, $t(17) = 2.51, p < .05$.

T-Maze Rotation

As can be seen in Figure 2, right side, sham-operated animals exhibited a marked drop in their performance following T-maze rotation, whereas there was no change in shell-operated animals' performance, which remained at chance level. A one-way ANOVA with a repeated-measurements factor of days, which compared animals' performance on the 2 days prior to rotation with their performance on the 2 days following rotation, revealed a significant lesion effect, $F(1, 17) = 7.19, p < .05$, and a significant Lesion × Rotation interaction, $F(1, 17) = 5.29, p < .05$.

Inspection of side bias revealed that the 8 shell-operated rats that exhibited side bias during training continued to do so after rotation. In addition, 3 of the sham-operated rats adopted side bias. The mean percentage of days on which side bias criterion was reached in the two groups were as follows: shell-operated: 41%, sham-operated: 25% (*ns*). Interestingly, the 3 sham-operated rats that showed side bias following reversal were the same rats that showed side bias during the first trials of acquisition, and their preferred side was identical to the preferred side during initial training; that is, they showed place preference. In contrast, of the 8 shell-operated rats that exhibited side bias, 7 showed response bias (i.e., turning to the left or to the right), and only 1 showed place bias (i.e., continued going to the same side of the room).

Experiment 2

Method

Apparatus

The radial eight-arm maze was constructed of unpainted wood. The octagonal center platform was 31 cm in diameter, and each arm, which radiated from a side of the octagon, was 76 cm long and 12 cm wide. A 1.5-cm high wooden rim extended the length of each arm. The maze was elevated 50 cm off the floor. Holes, 3 cm in diameter and 0.6 cm deep, drilled 1 cm from the end of each arm, served as food wells. A round opaque box, 26 cm high and 28 cm in diameter, was used to cover the animal at the start of each trial. The maze was situated in a well-lit room that contained several prominent extramaze cues, including a table, chairs, shelves, pictures, and an experimenter. These cues always remained in the same position with respect to the maze.

Procedure

Adaptation to reward. During 3 days preceding pretraining, rats were adapted to the food pellets in their home cages.

Pretraining. On each of 3 days, rats were trained to run on an elevated arm, using a T-maze located in a different room. Food pellets were placed in the wells at the end of both arms. Each rat was placed at the stem of the maze and given 10 min to run and collect the food reinforcement from both wells. The experimenter ensured that each rat consumed the food pellets.

Radial-arm maze training. During training, four arms were baited and four arms were unbaited. For each rat, the four baited arms were randomly chosen with the restriction that no more than two arms were adjacent. The location of the baited arms with respect to extramaze cues did not vary between trials. Each rat was given one trial a day for 6 days a week. On each trial, the food wells of the four baited arms were baited with four food pellets each. The rat was placed in the center of the maze and was covered with an opaque round box that was lifted after a few seconds. This was done in order to ensure a random initial orientation of the rat and to enable the experimenter to return to his seat. The rat remained on the maze until all four rewards had been consumed or until 10 min had elapsed. The order of arm choices was recorded. An entry was recorded only if the rat reached the last quarter of the arm. Training continued for 27 days.

Reversal. On Day 28 reversal training began and continued for 9 days. The procedure was identical to that of initial training, but for each rat the previously baited arms were now unbaited and the previously unbaited arms were now baited.

Measures and Statistical Analyses

Two performance measures were calculated from the order of arm choices. The first was the number of errors for each rat, classified into reference-memory errors (RMEs), working-memory errors (WMEs), and reference-working-memory errors (R-WMEs; see Okaichi & Oshima, 1990). RME consists of the first entry into an unbaited arm; WME consists of entry into arms that had been previously baited, but which had already been visited on that trial; and R-WME consists of reentry into already visited unbaited arms.

Statistical analysis of the errors was carried out using one-way ANOVA with a repeated measurements factor of 3-day blocks, for each error type. The second performance measure was turning responses, defined in terms of the angle between successively chosen arms (0°, 45°, 90°, 135°, or 180°). Since rats in both groups rarely chose the same arm on two consecutive choices, the 0° turning response was dropped from the analysis. The remaining four turning responses were counted in each block of nine trials. Same angle turning responses were combined irrespective of their direction (clockwise or counterclockwise). Response-strategy criterion was defined as a choice of the same angle on more than 44% of all turning responses within a 9-day block. This definition was derived from the following calculations: A rat that chooses randomly its entries has a 2/7 chance of making each of the 45°, 90°, and 135° turning responses, and 1/7 chance of making the 180° turning response. Since none of the rats showed preference for the 180° turning response, 2/7 was taken as the expected proportion for each angle. Within a 9-day block the minimum number of turning responses is 27. This number is obtained when a rat performs errorlessly; that is, it makes exactly four entries in a trial (i.e., three turning responses). Using the normal approximation to the binomial distribution, with $p = 2/7$ and $n = 27$ (this sample size gives the maximal standard error), choosing the same angle 44% or more of all turning responses within a 9-day block is significantly above chance level ($p < .05$). Statistical analysis of turning responses was carried out using the normal approximation of the two-sample proportion test comparing the proportions of rats that reached response strategy criterion in each group.

Fifteen shell- and 15 sham-operated animals began the experiment. Three shell- and 5 sham-operated rats were excluded from the experiment during training because they did not enter any arm for 10 min for at least 5 days. Thus, the final analyses were performed on the data of 12 shell- and 10 sham-operated animals.

Results

Anatomical results were the same as in Experiment 1. Body weight was also the same as in Experiment 1 (mean weight of shell- and sham-operated animals on the first day of food deprivation was 356 g and 350 g, respectively).

Radial-Arm Maze Training

Figure 3, left side, depicts the number of RMEs, in 3-day blocks, of shell- and sham-operated animals. As can be seen, although the performance of both groups improved with training, shell-operated animals exhibited a higher number of errors throughout. These observations were supported by a one-way ANOVA with a main factor of lesion and a repeated measurements factor of blocks carried out on the number of RMEs, which yielded a significant lesion effect, $F(1, 19) = 19.17, p < .001$, and a significant linear trend of the block factor, $F(1, 19) = 46.98\ p < .0001$; the linear trend of Lesion × Blocks interaction was not significant.

Figure 4, left side, depicts the number of WMEs, in 3-day blocks, of the shell- and sham-operated animals. As can be seen, the number of errors in the two groups was similar at the beginning and at the end of training, but sham-operated animals improved at a faster rate. This was supported by a one-way ANOVA with a main factor of lesion and a repeated measurements factor of blocks performed on the number of WMEs, which yielded a significant main effect of lesion,

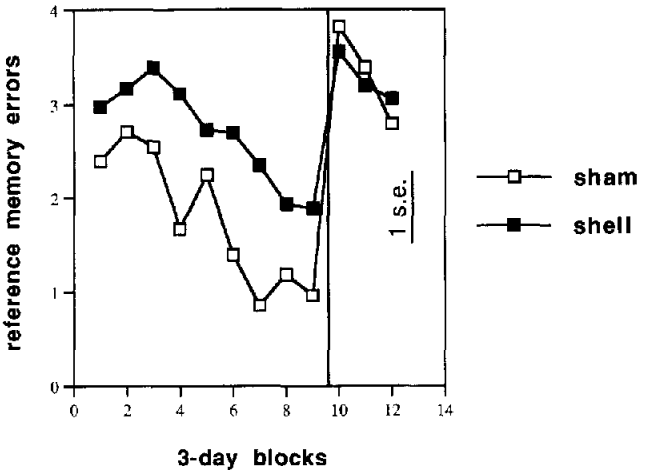

Figure 3. The number of reference-memory errors, in 3-day blocks, of shell- and sham-operated animals in the radial-arm maze, during the initial training (left) and following reversal (right). s.e. = standard error.

$F(1, 19) = 6.10, p < .05$, and a significant quadratic trend of the Lesion × Blocks interaction, $F(1, 19) = 4.84, p < .05$. The number of errors made by shell- and sham-operated animals in each block was compared with t tests, which revealed that shell-operated animals had higher number of WMEs in Blocks 3, 4, and 6 (all $ps < .05$).

Figure 5, left side, presents the number of R-WMEs of the shell- and sham-operated animals in 3-day blocks. As can be seen, shell-operated animals made more R-WMEs than sham-operated animals, and this difference was more pronounced at the initial stages of training. These observations were supported by a one-way ANOVA with a main factor of lesion and a repeated measurements factor of blocks performed on the number of R-WMEs, which yielded a significant main effect of lesion, $F(1, 19) = 12.03, p < .01$, and a significant linear trend of the Lesion × Blocks

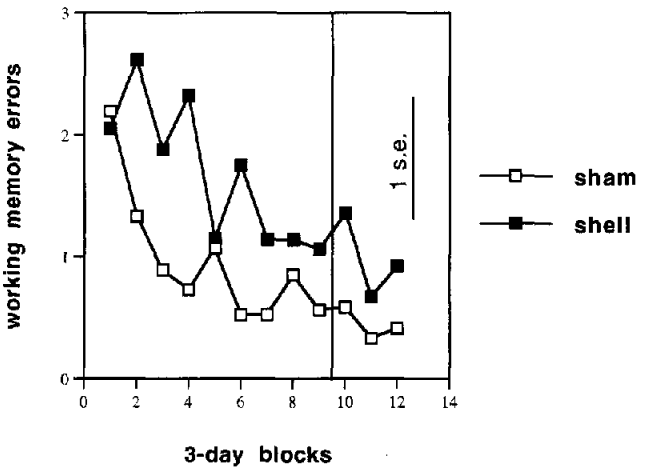

Figure 4. The number of working-memory errors, in 3-day blocks, of shell- and sham-operated animals in the radial-arm maze, during the initial training (left) and following reversal (right). s.e. = standard error.

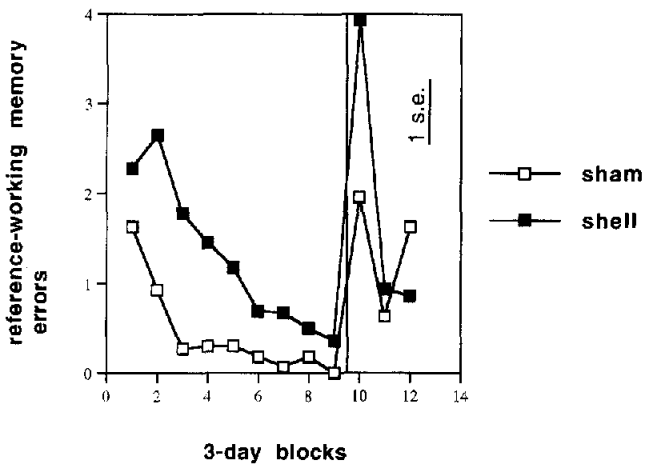

Figure 5. The number of reference-working memory errors, in 3-day blocks, of shell- and sham-operated animals in the radial-arm maze, during the initial training (left) and following reversal (right). s.e. = standard error.

interaction, $F(1, 19) = 7.61$, $p < .05$. The performance of shell- and sham-operated animals in each block was compared with t tests, which showed that shell-operated animals had higher number of R-WMEs in Blocks 2, 3, and 4 (all $ps < .05$).

Shell-operated animals were using response strategy significantly more than sham-operated animals in the first block of 9 days (10 out of 12 shell- and 4 out of 9 sham-operates; $z = 1.87$, $p < .05$), and in the second block (9 out of 12 shell- and 3 out of 9 sham-operates) ($z = 1.91$, $p < .05$). The same trend was preserved in the last block (6 out of 12 shell-, 2 out of 9 sham-operates), but the difference between the groups was not statistically significant.

Reversal

The number of the RMEs, WMEs, and R-WMEs of the shell- and sham-operated groups following reversal is depicted on the right side of Figures 3, 4, and 5, respectively. As can be seen, both groups showed substantial increase in the number of RM and R-WM but not WM errors following reversal. This was supported by two-way ANOVAs comparing the last three trials prior to reversal with the first three trials after the reversal for each type of error, which yielded significant main effect of reversal for RMEs and R-WMEs, $F(1, 19) = 51.94$, $p < .0001$, $F(1, 19) = 32.30$, $p < .0001$, respectively. However, Lesion × Reversal interactions were not significant, indicating that the effect of reversal was similar for both groups.

Comparisons of RMEs and R-WMEs of the two groups in the 9 days following reversal (see Figures 3, 4, and 5) revealed that rats in both groups reduced the number of errors and reached a similar level of performance by the end of reversal training. This was supported by one-way ANOVAs with repeated measurements factor of 3-day blocks, carried out on the number of each error type, which yielded no significant lesion effects, significant linear trends (all $ps < .0001$), and no Lesion × Linear Trend interactions. Regarding WMEs, there were no significant differences between the two groups, nor did the groups improve significantly on this measure during reversal training.

There was no difference between the two groups in the use of response strategy in the nine reversal trials: 8 out of 12 shell-operates and 5 out of 9 sham-operates used this strategy (*ns*).

General Discussion

Electrolytic lesion of the shell subterritory of the NAC led to impaired acquisition of DNMS in a T-maze and of four-arm baited, four-arm unbaited, eight-arm radial-maze tasks. The lesion did not result in gross motor or motivational impairments. Although manipulations of the shell have been shown to result in alterations in feeding response and weight (Maldonado-Irizarry & Kelley, 1995a, 1995b), in the present study there were no differences in body weight between the shell- and sham-operated animals, and the rats did not seem to have altered their feeding behavior. In addition, Weiner et al. (1996) have found that shell lesion did not result in changes in spontaneous activity.

Impaired performance obtained in the T-maze and radial-maze tasks is consistent with previous demonstrations of deficits in similar tasks following NAC lesions involving both subregions (Reading & Dunnett, 1991; Seamans & Phillips, 1994). Since similar impairments are typically obtained with lesions to the hippocampus (Davis et al., 1986; Jarrard, 1983; Jarrard & Elmes, 1982; Markowska et al., 1989; Nagahara & McGaugh, 1992; Okaichi & Oshima, 1990; Olton et al., 1980; Peinado-Manzano, 1990; Rawlins & Olton, 1982; Shaw & Aggleton, 1993; Sutherland & McDonald, 1990; Thomas & Gash, 1988), the present results seem to support the notion of concordance between NAC and hippocampal lesions and suggest that impairments in these tasks may stem from disrupted connections between the hippocampus and the NAC shell. However, the nature of the impairment seen in shell-lesioned animals is not easily interpretable as reflecting mnemonic deficits.

In the T-maze, our intention was to test lesioned animals' performance as a function of delay; however, shell-operated animals showed profound deficit in performance already at the no-delay condition, remaining at chance level throughout training. Since criterion performance at a no-delay condition is also considered to require WM (Honig, 1978, 1979; Olton et al., 1979), one could interpret our results as showing that shell lesion leads to WM deficit. However, a stricter interpretation of selective WM impairment which can be separated from confounding lesion-induced alterations in learning capacity, motivational state, sensitivity or attention to relevant stimuli, etc., requires a demonstration of delay-dependent disruption of performance (Dunnett, Evenden, & Iversen, 1988; Thomas & Gash, 1988). Therefore, although the impairment exhibited by shell-operated animals could be a result of a WM deficit, the absence of a condition in which they were not impaired prevents firm conclusions regarding the nature of their deficit.

In the training stage of the radial-maze task, shell rats made more RM, R-WM, and WM errors. However, in-

creased number of WMEs and R-WMEs was evident only in the rate at which rats improved their performance, with shell rats improving at a slower rate; there was no difference between shell- and sham-operated groups at the beginning and at the end of training in both types of errors. Similarly, the two groups did not differ in their WME and R-WME pattern following reversal. Therefore, it is impossible to determine whether the observed difference in WME was a result of a primary WM deficit or of some other underlying difference between the two groups. In contrast, shell-operated animals made more RMEs throughout training (although they improved with training), suggesting the existence of an RM deficit. However, in the reversal stage, shell-operated animals made the same number of RMEs and R-WMEs (i.e., entering and reentering the previously baited arms) as sham-operated animals. As noted in the introduction, an animal with an impaired RM should be less affected by reversal (i.e., should not make more RMEs than prior to reversal). Thus, although shell-operated animals' error pattern in the initial training could reflect an RM deficit, their error pattern in the reversal trials refutes such an interpretation.

In sum, although shell-operated animals performed worse than sham-operated animals in both DNMS and the radial-maze tasks, the pattern of their errors suggests that these animals do not have a RM deficit and does not permit firm conclusions regarding a possible WM deficit.

While in both tasks optimal performance must rely on memory, imperfect performance could result from either a memory impairment or from the use of an inappropriate, nonmnemonic, strategy. Indeed, the analysis of the animals' response pattern in the two tasks indicates that shell-operated animals showed a marked tendency to use nonmnemonic strategies. Thus, in the T-maze many shell-operated animals exhibited a pronounced side bias, namely, entering the same arm over trials and over days. This nonmnemonic strategy ensures that the animal earns reinforcement on 50% of the trials in each day. Other response patterns may lead to 50% reinforced trials on the average over days, but not in each day. Side bias was rarely seen in sham-operated rats and was restricted to the beginning of training. On the rare occasions that side bias was observed in controls, it could be dissociated from shell-operated animals' side bias, because the former used place strategy, whereas the latter used response strategy. Also in the radial maze, shell-operated animals exhibited a greater tendency to use response strategy (i.e., repeating the same turning response over trials and over days), compared with sham-operated animals. This nonmnemonic strategy increases the reinforcement per arm-entry ratio because it reduces the animal's chance to reenter previously visited arms. The use of this strategy can explain the error pattern exhibited by shell-operated animals during training, namely, slower rate of improvement in WMEs and R-WMEs, as well as persistent RMEs. Moreover, such an animal would be expected to have the knowledge of the location of the baited arms, consistent with the error pattern in reversal trials.

In light of the above, it appears that the impairment of shell-operated animals consisted of replacement of memory-dependent strategy by response strategy. However, it is not clear whether mnemonic strategies were overwhelmed by a lesion-enhanced prepotency of response strategy, or whether the memory functions were impaired by the lesion, and the animals regressed to a simpler response strategy. The available data indicate that response strategy was not a result of a primary RM deficit, but no comparable conclusion can be made with regard to WM, because the possibility of a primary WM deficit cannot be ruled out. After the completion of our study, we learned about results obtained in shell-lesioned animals trained in a DNMS task in a T-maze, which support the suggestion that their primary deficit consists of an inappropriate use of response strategy. In this study, the initial side bias exhibited by shell-lesioned animals was corrected by the experimenter, and consequently, these animals were able to master the task even when delays were introduced (Purves, 1994).

The present results and their interpretation are consistent with reports on the effects of NAC lesions not restricted to its subterritories. Thus, Reading and Dunnett (1991) found that excitotoxic lesions of the NAC caused a delay dependent performance deficit on a delayed matching-to-position task, which could be interpreted as a mnemonic deficit, but a more detailed analysis of the results led them to conclude that the deficit reflected a side-dependent response bias and a failure to inhibit behavior. Reading and Dunnett suggested that the NAC lesion disinhibited an underlying strategical tendency to choose a particular side. Similarly, Seamans and Phillips (1994) found that lidocaine-induced lesion of NAC produced a deficit in a four-arm baited, four-arm unbaited task suggestive of WM impairment, but such an impairment could not be substantiated. NAC lesions seem to have no pronounced effect on RM (Seamans & Phillips, 1994; Sutherland & Rodriguez, 1989). The effects of restricted shell or core lesions on tasks of this kind have not been tested. Recently, Maldonado-Irizarry and Kelley (1995b) tested the effects of injection of excitatory amino acid blockers into the NAC shell or core on spatial learning using a free-choice spatial-discrimination task in a hole-board apparatus. Both shell and core injections disrupted acquisition and retention of the task, but the results suggested that the core is more involved than the shell in spatial learning. These authors raised the possibility that the deficit found in shell rats was a result of diffusion of the NMDA antagonist into the core. Our results indicate that shell manipulations do produce impaired performance in spatial tasks, although the nature of the deficit in the two studies cannot be compared because of differences in the tasks, the types of measurements, and the physiological manipulations.

Regarding the behavioral similarity between hippocampal and shell lesions, the analysis of the impairment obtained here calls for a cautious conclusion. Most studies that tested hippocampal animals in DNMS in a T-maze task included only one delay, similar to the experiment used here (Peinado-Manzano, 1990; Rawlins & Olton, 1982; Shaw & Aggleton, 1993; Thomas & Gash, 1988). As pointed out by Thomas and Gash (1988), such results can not be easily interpreted in terms of memory deficit. Interestingly, these authors also found pronounced side bias in rats with hippocampal

lesions. However, some studies with hippocampus-lesioned rats used several delays and did demonstrate a delay-dependent deficit (Markowska et al., 1989; Nagahara & McGaugh, 1992; Sutherland & McDonald, 1990), pointing to a selective WM deficit.

In regard to the four-arm baited, eight-arm radial maze, some studies with hippocampus-lesioned rats have found deficits in the WM component of the task (Davis et al., 1986; Jarrard & Elmes, 1982; Olton et al., 1980), whereas others emphasized an RM deficit (Jarrard, 1983; Okaichi & Oshima, 1990). Our results indicate that shell lesion produces impairment in the RM component of the task during acquisition, but our reversal results demonstrate that the error pattern in the training stage is not a result of an RM deficit. Interestingly, Schacter et al. (1989) found that pharmacological interruption of the hippocampal input to the medial NAC produced an increase in the number of RMEs, similar to the error pattern exhibited by shell-operated rats in the training stage of the present experiment. However, since Schacter et al.'s (1989) study did not include a reversal stage, it is not possible to compare our results further.

In sum, although shell lesion-induced deficits resemble those of hippocampal lesion, it appears that the latter reflects primary memory deficits, whereas the former is at least partly a result of an inappropriate use of response strategy. In addition, Moser, Moser, and Andersen (1993) found that performance in the water maze was disrupted more severely following lesions of the dorsal hippocampus than following lesions of the ventral hippocampus, which provides one of the major sources of input to the shell (Groenewegen et al., 1987; Zahm & Brog, 1992). Since lesioning of the shell is expected to resemble the effects of lesions to its afferent structures, the apparent incompatibility between Moser et al.'s (1993) and our results is surprising. Two explanations are possible. Since Moser et al. found that extensive ventral hippocampal lesions did produce deficits in spatial learning, it is possible that shell lesion mimics the effects of a nearly total ventral hippocampal lesion. This is a reasonable assumption because partial lesions to ventral hippocampus may leave enough undamaged tissue in this structure to compensate for the lesion-induced deficit, whereas a lesion to the output station (i.e., the NAC shell) may prevent any such compensation. Alternatively, it is possible that the effects of shell lesion observed here are not solely attributable to disruption of flow of information from the hippocampus. An additional major input to the shell arises from the medial prefrontal cortex (mPFC; Berendse, Galis-de Graaf, & Groenewegen, 1992; Groenewegen et al., 1990; Zahm & Brog, 1992), which also plays a critical role in spatial behavior (Becker, Olton, Anderson, & Breitinger, 1981; Kolb, 1990; Kolb, Nonneman, & Singh, 1974; Kolb, Pitman, Sutherland, & Whishaw, 1982; Poucet & Herrmann, 1990; Winocur & Moscovitch, 1990). In addition, one of the major outputs of the shell is directed to the mPFC, via the ventral pallidum and the mediodorsal thalamic nucleus (MD; Berendse et al., 1992; Groenewegen et al., 1990; Zahm & Brog, 1992). Lesion of the shell can be therefore expected to disrupt the normal functioning of this circuit. Interestingly, MD lesions also result in deficits very similar to those obtained here (Kolb et al., 1982; Stokes & Best, 1988).

An intriguing question is why an animal that apparently has the required abilities for the use of the optimal strategy (i.e., mnemonic) uses a different, less effective, strategy. It is well documented that the NAC plays a major role in behavioral switching, namely, altering behavior in response to changed environmental demands (Annett et al., 1989; Reading & Dunnett, 1991; Taghzouti, Louilot, et al., 1985; Taghzouti, Simon, et al., 1985), and it has been suggested that rats with NAC lesions are deficient in switching between different behavioral strategies. The present results suggest that a similar deficiency is produced by a lesion to the shell subterritory. Indeed, it will be recalled that response strategy was seen in sham-operated animals at the beginning of training but was subsequently replaced by a more appropriate, memory-dependent strategy. Thus, it is possible that the inappropriate use of response strategy by shell-operated animals was a result of their inability to switch from the initial response strategy to a later, more appropriate, memory-dependent strategy. Robbins and Everitt (1982) originally proposed that the hippocampus relays, via the subiculum, a switching signal to the NAC (see also Burns, Annett, Kelley, Everitt, & Robbins, 1996). We recently proposed, on the basis of differential effects of shell and core lesions on latent inhibition, that the switching mechanism of the NAC resides in the core subterritory, and that the switching signal is not relayed directly to the core from the ventral subiculum and/or entorhinal cortex, but indirectly via their projections to the shell, so that shell output can in turn modulate the switching mechanism of the core (Weiner et al., in press).

Given that the mPFC is also known to play a central role in animals' ability to change behavioral strategies in response to changing environmental contingencies (Becker et al., 1981; Devenport, Hale, & Stidham, 1988; Kolb, 1990; Kolb et al., 1974; Winocur & Moscovitch, 1990), switching-relevant information to the shell is most probably provided also by the mPFC. Indeed, the intrinsic neurons of the shell region form a convergent link between three brain systems implicated in behavioral switching, namely, the descending cortical inputs from mPFC and hippocampus, and the ascending mesolimbic dopaminergic system (Burns et al., 1996; Deutch & Cameron, 1992; Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991; Sesack & Pickel, 1990, 1992; Zahm & Brog, 1992; Weiner et al., 1996), and may thus be in a unique position to comodulate these inputs to produce optimal behavioral switching geared to task demands. It would be of interest to distinguish between the switching signals relayed from the subiculum and mPFC; it is possible that the switching signal from the subiculum primarily relays the excitatory or inhibitory effects of novelty (Burns et al., 1996), whereas the switching signal from the mPFC relays the effects of affective and motivational aspects of the learning situation (given that the major input to the shell arrives from the infralimbic cortex). In the present context, it is of interest that the core has been suggested to mediate motor learning, that is, "the incorporation of corticolimbic information into a learned locomotor response" (Maldonado-

Irizarry & Kelley, 1995b, p. 536; 1994; 1995a). It is thus possible that the core mediates initially the response strategy exhibited by animals, but as they come to rely increasingly on spatial cues based on information received from the environment, a switching signal from the shell enables a transition to a different learned locomotor response, which is memory dependent.

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