

Parallel Information Processing in the Dorsal Striatum: Relation to Hippocampal Function

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We investigated the effects of localized medial and lateral CPU lesions and fornix/fimbria lesions on responses to a local cue and to behavior based on cognitive–spatial information in the water maze. Rats were trained concurrently on the cue (visible platform) and spatial (submerged platform) components of the task, followed by a test in which responses to the two types of information were dissociated by a measure of competing response tendencies. Bilateral lesions of lateral CPU did not affect acquisition of either cue or spatial responding but produced a preference for the spatial response on the competition test. Bilateral lesions of the medial CPU retarded but did not prevent learning both components and produced a preference for the cue response on the competition test. The latter effect was accompanied by increased thigmotaxis (swimming in the periphery of the pool), primarily during the early acquisition trials, which was attributed to an impaired ability to respond to

learned spatial information. Fornix/fimbria lesions prevented spatial but not cue learning and produced a preference for the cue response on the competition test. Asymmetric lesions (unilateral hippocampus and contralateral medial CPU) produced mild retardation of acquisition of both the cue and spatial tasks and a preference for the cue response on the competition test. These findings dissociate the functions of the lateral and medial CPU and suggest that the hippocampus and medial CPU may be parts of a system that promotes responding based on learned cognitive–spatial information, particularly in competitive cue–place response situations.

Key words: dorsal striatum; medial CPU; lateral CPU; fornix/fimbria; hippocampal–striatal interactions; water maze; cue/place learning; competition test; asymmetric lesion; functional limbic circuit

Studies of mnemonic function in rats frequently employ spatial or “place” cues to test cognitive forms of learning (Tolman, 1948; O’Keefe and Nadel, 1978) and discrete cues to measure habit or stimulus–response (S–R) learning (Thorndike, 1911, 1933; Hull, 1943). Evidence suggests that different neural systems contribute to each form of learning (Milner et al., 1968; Hirsh, 1974; O’Keefe and Nadel, 1978). Lesions of the dorsal striatum (caudate putamen; CPU) and hippocampus or fornix/fimbria were previously shown to have opposite effects on behavior in cued and spatial versions of the radial maze task (Packard et al., 1989; McDonald and White, 1993). These findings are consistent with the hypothesis that a corticostriatal system mediates S–R habit formation, whereas a hippocampus-based system contributes to cognitive–spatial learning (Mishkin et al., 1984; Mishkin and Petri, 1984; Petri and Mishkin, 1994).

Anatomical studies have shown that the dorsal striatum is a heterogeneous structure, both in terms of its intrinsic compartmentalization of neurochemical constituents (Graybiel, 1990; Groves et al., 1995) and its regionally diverse connectivity with other cortical/subcortical structures (Alexander et al., 1986; Mc-

George and Faull, 1989; Groenewegen et al., 1990). Behavioral studies further suggest that the striatum is functionally differentiated (Winocur, 1974; Divac et al., 1978; Dunnett and Iversen, 1981, 1982a,b; Iversen, 1984; Viaud and White, 1989; Pisa and Cyr, 1990; Reading et al., 1991; Hauber and Schmidt, 1993, 1994; Fricker et al., 1996). Lesions of the lateral CPU disrupt sensorimotor function and S–R learning (Dunnett and Iversen, 1981, 1982a; White, 1989, 1997; Reading et al., 1991), whereas lesions of the medial CPU have been reported to produce impairments on cognitive–spatial tasks (Whishaw et al., 1987; Colombo et al., 1989; Devan et al., 1996; Furtado and Mazurek, 1996).

In the water maze, rats’ ability to learn the location of a hidden (submerged) platform, a cognitive–spatial task, is impaired by fornix/fimbria (Sutherland and Rodriguez, 1989; Devan et al., 1996) or hippocampal (Morris et al., 1982; Sutherland et al., 1983) lesions, whereas acquiring the response of swimming directly to a visible platform, an instance of S–R learning, is impaired by lateral CPU lesions (McDonald and White, 1994). Because lesions confined to the medial CPU impaired responses based on place cues (Devan et al., 1999), we compared the effects of separate medial and lateral CPU lesions with fornix/fimbria lesions on a combined cue–place learning task in the water maze (McDonald and White, 1994).

In the second experiment, we studied the relationship of the medial CPU to the hippocampus in the same water maze task using asymmetric lesions consisting of damage to the hippocampus on one side of the brain and damage to the medial CPU on the other side. This lesion preparation has been used to define routes of serial information processing between other brain structures (Mishkin, 1958, 1966; Horel and Keating, 1969, 1972; Olton, 1978; Gaffan and Harrison, 1987; Gaffan et al., 1988, 1989;

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Everitt et al., 1991; Sutherland and Hoising, 1993; Gaffan and Parker, 1996; Floresco et al., 1997; Han et al., 1997).

MATERIALS AND METHODS

Subjects. Ninety Long–Evans hooded rats weighing ~300–400 gm at the time of surgery were used. They were housed individually in hanging wire-mesh cages located in a temperature-controlled room on a constant 12 hr light/dark cycle. All behavioral testing was conducted during the light phase at approximately the same time each day. *Ad libitum* food (Purina lab chow) and tap water were available in the home cage throughout the experiments.

Experimental conditions. In experiment 1, rats were assigned to four bilateral lesion groups: lateral CPu ($n = 15$), medial CPu ($n = 11$), fornix/fimbria ($n = 10$), and a group of sham-operated controls ($n = 10$). In experiment 2, rats were assigned to two unilateral lesion groups: medial CPu ($n = 10$) or hippocampus ($n = 10$), or to the asymmetric lesion condition (unilateral hippocampus–contralateral medial CPu) ($n = 12$). There were also 12 sham-operated controls.

Surgery. Each rat was handled for ~5 min/d for 3 d before surgery. All rats were given Xylazine analgesia (5 mg/kg, i.m.) and anesthetized with sodium pentobarbital (60 mg/kg, i.p.). Brain lesions were made using standard stereotaxic procedures. Flat skull stereotaxic coordinates were derived from the atlas of Paxinos and Watson (1986) using bregma of the skull surface as the reference point. The coordinates for dorsomedial CPu lesions were 0.7 mm anterior (A), 2.4 mm lateral (L), and 5.4 mm ventral (V). The coordinates for dorsolateral CPu lesions were 0.7 A, 3.4 L, and 5.4 V. Coordinates for fornix/fimbria lesions were 1.5 mm posterior (P), 0.8 and 2.2 L, and 4.5 V. The hippocampus was damaged using four separate lesions at the following coordinates: (1) 3.8 P, 2.0 L, 4.0 V; (2) 5.3 P, 3.5 L, 4.0 V; (3) 5.8 P, 5.0 L, 5.5 V; and (4) 5.8 P, 5.0 L, 7.5 V.

CPu and hippocampus lesions were made by passing 3 mA of direct anodal current for 15 sec through an insulated nichrome electrode exposed 0.8 mm at the tip. Fornix/fimbria lesions were made by radio frequency current (6 mA for 40 sec). The side of the unilateral lesions was counterbalanced within the appropriate groups. Sham animals received identical surgical treatment to the lesioned animals except that no electrode was lowered into the brain. Behavioral testing began 2 weeks after surgery.

Apparatus. A white swimming pool measuring 172 cm in diameter and 63 cm in height was used. The pool was elevated 20 cm above the floor in a room that contained many stationary cues, including wall posters, book shelves, and a computer rack. The pool was filled to a depth of 38 cm with 22°C water, made opaque by the addition of 100 ml white nontoxic tempera paint before daily swimming trials.

Two platforms were used. The visible platform, used on cued trials, was constructed of wood (top surface, 12 × 12 cm). Black and white terry cloth strips were permanently attached to the sides and top surface. The visible platform protruded 3 cm above the surface of the water when placed in the pool. The hidden platform, used on place trials, was constructed of Plexiglas with white terry cloth attached to the top surface (10 × 10 cm). The top of the hidden platform was submerged 1.5 cm below the surface of the water.

A video camera mounted above the pool was used to make recordings of swim trials. The recordings were used to measure escape latencies and peripheral pool time using a stop watch.

Procedure. The cue–place water maze task was adapted from McDonald and White (1994). On the first 2 d of the experiment, the rats were trained to swim to the visible platform located in the center of the northwest quadrant of the pool. Each daily training session consisted of four trials on which each rat was released once from each of the four start points. A trial began by placing a rat in the pool (facing the wall) at a randomly selected start position and ended when the rat climbed onto the visible platform, or after 30 sec had elapsed. If the rat had not escaped after 30 sec, it was gently guided to the platform by hand. Each rat was left on the platform for 5 sec and then returned to its home cage, located in an adjoining room. For each rat there was a delay of 10–15 min between successive trials within a daily session. During the delay, the remaining rats in the counterbalanced squad were run on the same trial. Thus, the intertrial interval varied slightly according to the rats' level of performance but was approximately equal for all rats within each training session.

On the day after the first 2 d of training with the visible platform (eight trials), each rat received a four-trial session in which the visible platform was replaced with the submerged platform at the same location. Identical training procedures were used during these hidden platform trials.

Subsequently, the 3 d sequence of two visible platform sessions followed by a hidden platform session was repeated two more times for a total of 36 trials (24 visible, 12 hidden) over a total of 9 d. Escape latency (time to reach the available platform) and peripheral pool time (time spent swimming within 20 cm of the edge of the pool) were measured on these acquisition trials.

On day 10, the competition test was given. The visible platform was moved to the center of the southeast quadrant (opposite to its location during the acquisition trials). Two trials were given from start positions equidistant to the center of the northwest and southeast quadrants. The video recordings were used to determine whether the rats swam within 5 cm of the perimeter of the former platform location in the northwest quadrant before escaping to the visible platform, now located in the southeast quadrant.

Histology. After behavioral testing, the rats were deeply anesthetized with an intraperitoneal injection of 1 ml of 30% chloral hydrate and perfused intracardially with 0.9% saline followed by 10% formol saline. The brains were removed from the skulls and stored in 10% formol saline for at least 1 week. Frozen coronal sections were cut at 30 μ m through the lesion area, and every fifth section was mounted on glass microscope slides. The mounted sections were stained with formol thionin (Donovick, 1974) and examined with a microscope.

Statistical analyses. Two-way mixed ANOVAs with lesion type as the between-groups factor and trial block as the repeated-measures factor (with conservative dfs) were computed for the escape latency and peripheral pool time (thigmotaxis) measures of acquisition performance. Separate analyses were conducted for trial blocks with the visible and hidden platform. Significant interactions were followed up by one-way ANOVAs of the group factor at each level of the repeated-measures factor. This procedure is considered to be a conservative way to test simple main effects involving overall sources with different error terms (Olson, 1988, p. 723). If a one-way ANOVA yielded significance then Scheffe's method was used to determine specific group differences. One-way ANOVA followed by Scheffe's *post hoc* test of lesion type were used to analyze latency and thigmotaxis scores on the competition test. In addition, likelihood ratio and Pearson's χ^2 analyses of lesion type were conducted for the response category measure.

RESULTS

Experiment 1: bilateral lesions of CPu subregions and fornix/fimbria

Histology

The minimal and maximal extent of damage to the structures lesioned in each group is shown in Figure 1. The dorsolateral CPu lesion primarily damaged the region of CPu underlying the corpus callosum and bordering the external capsule. At a posterior level, this lesion spared the more lateral portion of CPu adjacent to the external capsule. One animal in the dorsolateral CPu group sustained extensive damage to the medial CPu and lateral septum; data from this animal were not included in the final statistical analyses. The dorsomedial lesion was localized to the portion of CPu underlying the corpus callosum and bordering the lateral ventricles. This lesion did not produce any observable damage to the choroid plexus within the ventricles or to the lateral septum. The lesion also spared the nucleus accumbens anteriorly and ventromedial portions of CPu posteriorly.

Fornix/fimbria lesions included damage to the medial and lateral portions of the structure. Sparing of the lateral–ventral tips was observed in some cases. Occasional damage was observed in the triangular septal nucleus and dorsal hippocampus, along with minimal electrode tract damage to overlying cortex.

Cue–place acquisition

Figure 2 shows the escape latency data for each group. All groups learned to swim to the visible platform (*connected symbols*). However, rats with medial CPu lesions had longer latencies on the early trials. A two-way mixed ANOVA revealed a significant interaction between factors ($F_{(3,41)} = 2.89$; $p < 0.05$) as well as

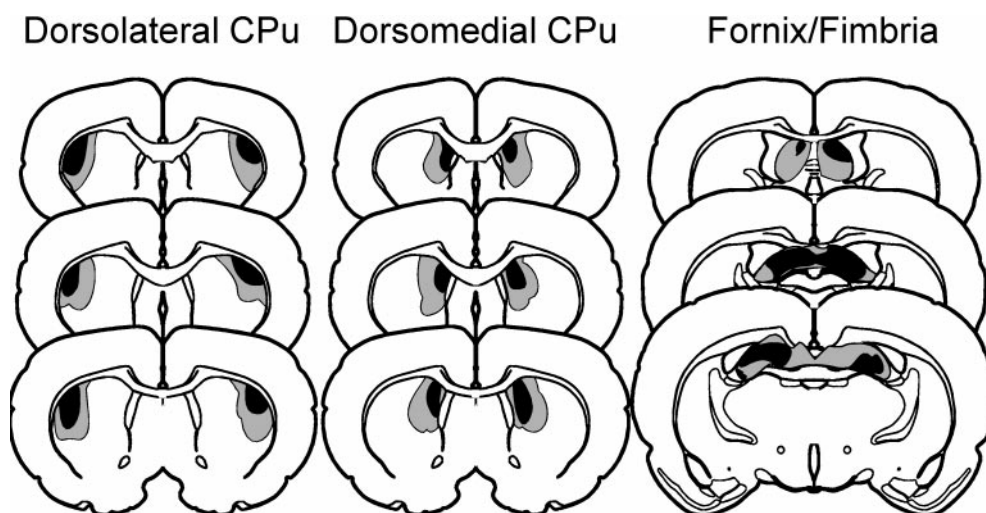


Figure 1. Minimum (dark hatching) and maximum (light hatching) extent of damage to the fornix/fimbria, lateral CPu, and medial CPu.

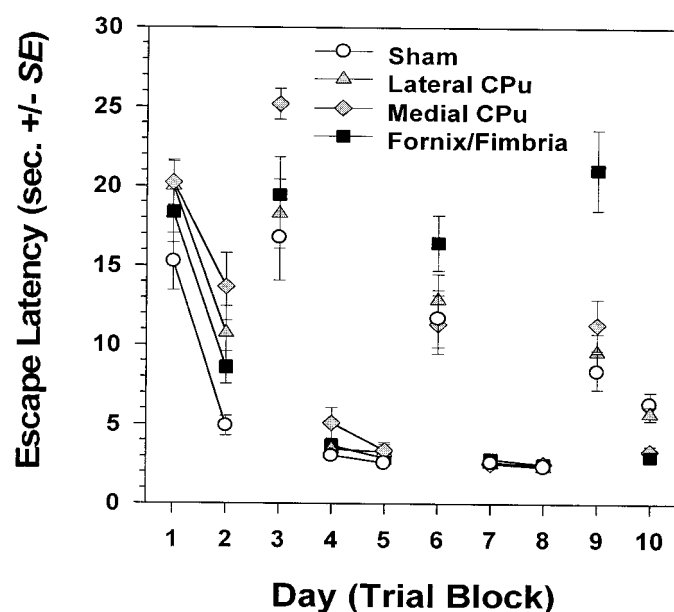


Figure 2. Mean escape latencies for each group in experiment 1. *Connected symbols* represent visible platform trial blocks (days 1–2, 4–5, and 7–8; four trials per block). *Disconnected symbols* represent hidden platform trial blocks (days 3, 6, and 9; four trials per block) and the competition test (day 10; two trials per block).

significant main effects of group ($F_{(3,41)} = 4.93$; $p < 0.01$) and trial block ($F_{(1,41)} = 202.51$; $p < 0.001$). *Post hoc* tests revealed a significant difference between the medial CPu and sham group on trial block 2 ($p < 0.01$). No other group differences were significant.

Mean escape latencies on the hidden platform trials are also shown in Figure 2 (days 3, 6, and 9). Rats with medial CPu lesions took longer than sham-lesioned rats to escape on the first hidden platform session. In contrast, rats with fornix/fimbria lesions took longer than shams to escape on the last hidden platform session. Analyses of the escape latency data for hidden platform trials showed a significant group by trial block interaction ($F_{(3,41)} = 3.30$; $p < 0.05$) as well as significant main effects of group ($F_{(3,41)} = 3.79$; $p < 0.01$) and trial block ($F_{(1,41)} = 27.09$; $p < 0.001$). *Post hoc* tests showed that the medial CPu group differed significantly from both the sham and lateral groups on trial block 3 (p values <

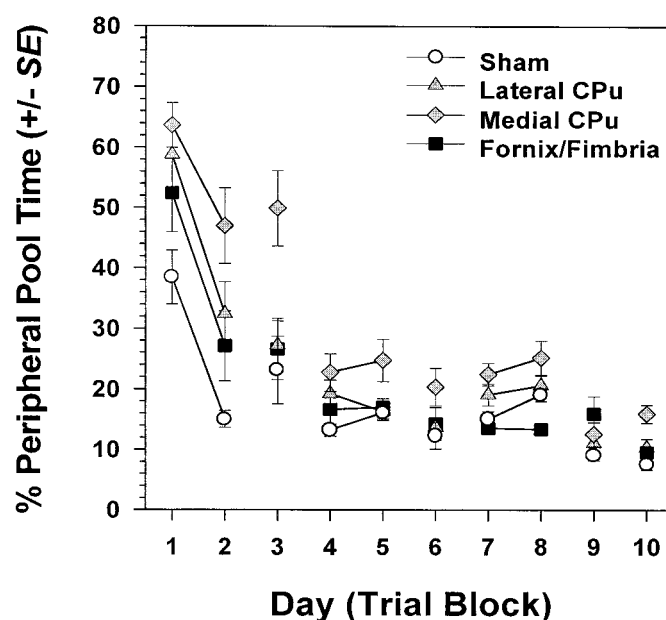


Figure 3. Mean percentage of swim time spent in the peripheral portion of the pool for each group in experiment 1. *Connected symbols* represent visible platform trial blocks (days 1–2, 4–5, and 7–8; four trials per block). *Disconnected symbols* represent hidden platform trial blocks (days 3, 6, and 9; four trials per block) and the competition test (day 10; two trials per block).

0.05), whereas the fornix/fimbria group differed significantly from the sham and lateral CPu groups on trial block 9 (p values < 0.01). Hence, lesions of the medial CPu retarded but did not prevent place learning, whereas lesions of the fornix/fimbria blocked place learning.

Figure 3 shows the mean percentage of time spent in the peripheral part of the pool (thigmotaxis) for each group. Rats with medial CPu lesions tended to be more thigmotactic than the other groups. A two-way mixed ANOVA on the visible platform means revealed a significant group by trial block interaction ($F_{(3,41)} = 2.79$; $p < 0.01$) as well as significant main effects of group ($F_{(3,41)} = 8.34$; $p < 0.001$) and trial block ($F_{(1,41)} = 92.61$; $p < 0.0001$). *Post hoc* tests showed significant differences between the medial CPu and all other groups (sham: blocks 1, 2 and 7, p values < 0.05; lateral CPu: block 5, $p < 0.05$; fornix/fimbria:

Table 1. Number of rats that swam to the former platform location (place responders) versus the new visible platform position (cue responders) on the competition test (day 10)

	Sham	Lateral CPu	Medial CPu	Fornix/Fimbria
Place responders	6	13	0	1
Cue responders	4	1	11	9

blocks 7 and 8, $p < 0.005$). Analyses of the hidden platform means revealed a significant group by trial block interaction ($F_{(3,41)} = 4.60$; $p > 0.05$) in addition to significant main effects of group ($F_{(3,41)} = 4.78$; $p < 0.01$) and trial block ($F_{(1,41)} = 52.70$; $p < 0.001$). *Post hoc* tests showed significant differences between the medial CPu and all other groups on trial block 3 (p values < 0.05) but no group differences on trial blocks 6 or 9 (p values > 0.10). Thus, the rats with medial CPu lesions showed a greater tendency than the rats in the other groups to swim in the peripheral part of the pool on the early trials.

Competition test

The mean escape latencies for each group on the competition test are shown in Figure 2 (day 10). Rats with fornix and medial CPu lesions escaped faster than controls and rats with lateral CPu lesions. A one-way ANOVA on the mean latencies averaged across the two competition test trials revealed a significant group effect ($F_{(3,41)} = 12.38$; $p < 0.001$). *Post hoc* tests showed that the fornix and medial CPu groups had significantly longer latencies than the sham and lateral CPu groups (p values < 0.01).

The mean percentage of time spent in the peripheral part of the pool on the competition test is shown in Figure 3 (day 10). Rats with medial CPu lesions were more thigmotactic than the other groups. A one-way ANOVA revealed a significant group effect ($F_{(3,41)} = 12.38$; $p < 0.001$). *Post hoc* tests showed that the medial CPu group differed significantly from the sham, lateral CPu, and fornix groups (p values < 0.05).

The rats' responses on the competition test were categorized as cue or place by examining the swim paths. If an animal swam from the start point to within 5 cm of the perimeter of the former platform location in the northwest quadrant before escaping to the visible platform in the southeast quadrant on either competition test trial, it was labeled a place responder. If an animal did not meet this criterion, it was labeled a cue responder. The number of place and cue responders in each group is shown in Table 1. Compared to controls, the lateral CPu group showed a significant place–response bias ($\chi^2 = 3.89$; $p < 0.05$), whereas both the fornix and medial CPu groups showed significant cue–response biases ($\chi^2 = 5.93$, $p < 0.05$; $\chi^2 = 9.24$, $p < 0.01$, respectively). Additional tests revealed that the lateral CPu group differed significantly from both the fornix ($\chi^2 = 16.47$; $p < 0.0001$) and medial CPu groups ($\chi^2 = 21.27$; $p < 0.0001$) but that the fornix and medial CPu groups did not differ significantly from each other ($\chi^2 = 1.15$; $p > 0.20$).

Figure 4 shows some representative swim paths of individual rats categorized as cue or place responders on the competition test. Escape latencies corresponding to each path are also shown. The differences in these latencies across response categories (cue or place) in the lesioned rats were minimal (Fig. 4: A vs B and C vs D) and not reliably predictable from response category (Fig. 4: E vs F). Hence, while latency provides an indication of the rats' progress in acquiring the tasks early in training, it does not

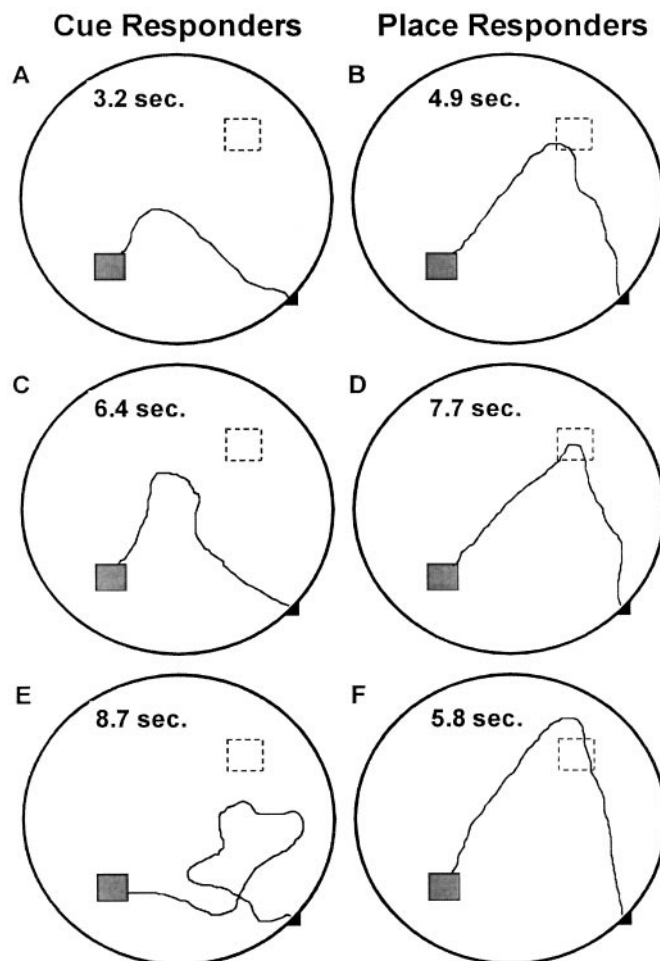


Figure 4. Representative swim paths of cue and place responders on the first trial of the competition test. The visible platform is in the *bottom left* quadrant, and the location of the platform during the preceding training trials is in the *top right* quadrant. Escape latencies for the trials illustrated are shown in each case. The rats with medial caudate putamen lesions (A, C) did not cross the former platform location, whereas the rats with lateral caudate putamen lesions (B, D) did. Differences between escape latencies (A, B and C, D) were small (1.7 and 1.3 sec, respectively). As illustrated in E and F, the escape latencies of control rats classified as cue responders were not necessarily shorter than those classified as place responders, even if the distance they had to swim was shorter.

accurately reveal which of the two response tendencies predominate in a given rat, as revealed by the competition test.

Summary and discussion

The results of this experiment reveal a dissociation between the effects of medial and lateral CPu lesions on the combined cue–place task in the water maze. Lateral CPu lesions did not affect acquisition rate but produced a significant place–response bias on the competition test. This finding is consistent with the results of a previous study (McDonald and White, 1994) and with the hypothesis that lesions of the lateral CPu impair learned responding to local cues (i.e., S–R learning).

As shown both in the present study and by McDonald and White (1994), the deficit in responding to the local cue revealed by the rats' responses on the competition test is not reflected in their latencies on the cued training trials. Moreover, the strength of the competition test finding may be influenced by the specific training parameters used. In a previous study (Devan et al., 1999),

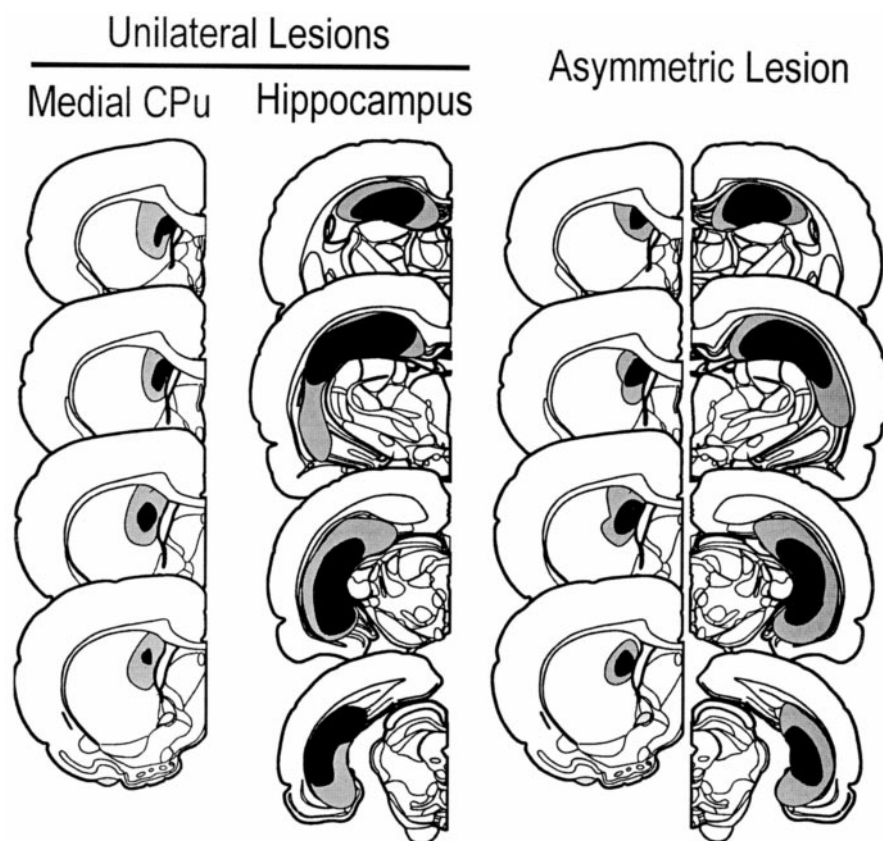


Figure 5. Minimum (dark hatching) and maximum (light hatching) extent of damage to the structures lesioned unilaterally in experiment 2. Although the reconstructions are illustrated within a single hemisphere, the side of lesion was counter-balanced within each group: unilateral-medial CPu, unilateral-hippocampus, and asymmetric (crossed-unilateral) lesion. Plates adapted from Swanson (1992).

rats with lateral CPu lesions exhibited a weaker place-response bias and a more subtle cue deficit than those in the present study. However, the rats in the previous study were fully trained on the place response before receiving any cue training whereas in the present study, and in the one by McDonald and White (1994), cue and place training were given concurrently. The 5 d delay imposed by intervening cue training in the Devan et al. (1999) study may have weakened spatial response tendencies resulting in more cue-directed responses on the competition test, thus masking the effect of lateral CPu lesions as presently and previously (McDonald and White, 1994) shown after contemporaneous experience with both types of training.

In contrast, lesions of the medial CPu increased escape latencies and thigmotaxis during acquisition and produced a cue-response bias on the competition test. The latter result is consistent with other reported cue enhancement effects (Mikulas, 1966; Winocur, 1980; Mitchell et al., 1985; Mitchell and Hall, 1988; Devan et al., 1996) after CPu lesions.

The present observations are consistent with those of previous experiments in showing that thigmotaxis tends to occur during the early trials of escape training (Devan et al., 1996, 1999). Devan et al. (1996, 1999) suggested that this form of lesion-induced thigmotaxis may be caused by a transient deficit in initiating responses that move the animal away from the pool wall, toward a location defined by spatial cues. Such a difference could also be the source of the cue-response bias of these rats on the competition test. Hence, increased thigmotaxis and enhanced cue responding may both result from a common underlying cause, i.e., a weakened tendency to respond to spatial cues.

Lesions of the fornix/fimbria also produced a cue-response bias in the present study, as previously shown by McDonald and

White (1994). This bias is thought to be a reflection of the failure of rats with these lesions to acquire the cognitive-spatial information required to perform the place response (O'Keefe and Nadel, 1978).

Although lesions of both the medial CPu and fornix/fimbria decreased the rats' tendency to swim to the hidden platform location on the competition test, they may have done so for different reasons. This suggestion is partly based on differences in the effects of the two lesions on the acquisition trials. Fornix/fimbria lesions completely blocked place learning, whereas medial CPu lesions produced only transient increases in escape latencies, accompanied by thigmotaxis, on early cue and place acquisition trials. These findings are consistent with the hypothesis that the fornix/fimbria deficit is caused by impaired acquisition of cognitive-spatial information and that the medial CPu deficit may be caused by impaired acquisition of responses based on learned spatial information. The latter deficit is most clearly revealed in situations characterized by competing place- and cue-based response alternatives.

Experiment 2: unilateral and asymmetric lesions of medial CPu and hippocampus

Histology

The minimal and maximal extent of damage to the structure or structures lesioned in each group is shown in Figure 5. Unilateral lesions of the medial CPu were similar to the bilateral lesions in the previous experiment. Unilateral lesions of the hippocampus included extensive damage to the rostradorsal and posterior parts of the structure but typically spared the ventral part at the temporal pole. The dentate gyrus and CA subfields (Ammon's horn) were damaged at both dorsal and posterior sites. In addi-

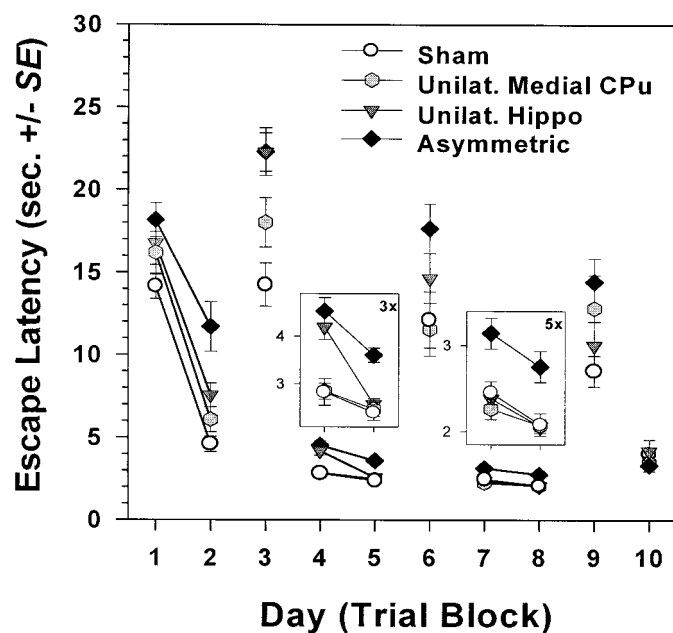


Figure 6. Mean escape latencies for each group in experiment 2. *Connected symbols* represent visible platform trial blocks (days 1–2, 4–5, and 7–8; four trials per block). *Disconnected symbols* represent hidden platform trial blocks (days 3, 6, and 9; four trials per block) and the competition test (day 10; two trials per block). *Inset graphs* illustrate significant group differences on visible trial blocks on an expanded ordinate: *inset 1* (blocks 4 and 5) is expanded 3 \times ; *inset 2* (blocks 7 and 8) is expanded 5 \times .

tion, the subiculum (including presubiculum and parasubiculum) was lesioned posteriorly with occasional damage extending more ventrally into the entorhinal cortex. As shown in Figure 5, lesions in the asymmetric group were similar to those in the corresponding unilateral lesion groups.

Cue-place acquisition

Figure 6 shows the mean escape latencies for each group. All groups learned to swim to the visible platform, however, escape latencies on these trials were slightly elevated in the asymmetric lesion group (Fig. 6, *insets*). A two-way mixed ANOVA revealed a significant group by trial block interaction ($F_{(3,40)} = 2.77$; $p < 0.05$), as well as significant main effects of group ($F_{(3,30)} = 12.94$; $p < 0.0001$) and trial block ($F_{(1,30)} = 247.67$; $p < 0.00001$). *Post hoc* tests revealed that the asymmetric lesion group differed from the sham (blocks 2, 4, 5, 7, and 8; p values < 0.05), unilateral-medial CPu (blocks 2, 5, 7, and 8; p values < 0.01), and unilateral-hippocampal (blocks 5, 7, and 8; p values < 0.01) groups. Because the mean differences were on the order of 1 sec or less on trials blocks 5, 7, and 8, the functional implications of these effects may be of minor importance.

The asymmetric lesion group also took longer than the shams to find the hidden platform (Fig. 6). A two-way mixed ANOVA revealed a significant effect of group ($F_{(3,40)} = 7.07$; $p < 0.001$) and trial block ($F_{(1,40)} = 30.99$; $p < 0.00001$) but no significant interaction between factors ($F_{(3,40)} = 1.76$; $p > 0.10$). *Post hoc* tests revealed that the asymmetric group differed from the sham group ($p < 0.001$) but not from the unilateral-hippocampal or unilateral-medial CPu groups (p values > 0.05).

Figure 7 shows the mean percentage of time spent in the peripheral part of the pool for each group. Rats with asymmetric lesions were more thigmotactic than controls. A two-way

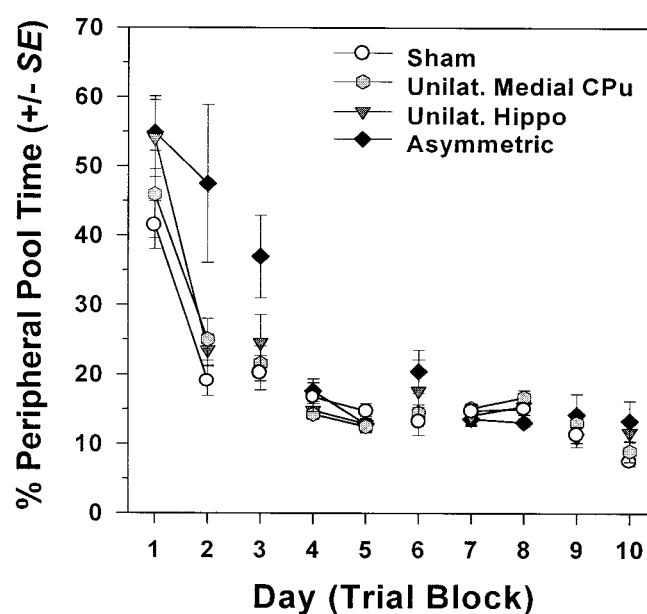


Figure 7. Mean percentage of swim time spent in the peripheral portion of the pool for each group in experiment 2. *Connected symbols* represent visible platform trial blocks (days 1–2, 4–5, and 7–8; four trials per block). *Disconnected symbols* represent hidden platform trial blocks (days 3, 6 and 9; four trials per block) and the competition test (day 10; two trials per block).

ANOVA on the data for the visible platform sessions revealed a nonsignificant effect of group ($F_{(3,40)} = 1.66$; $p > 0.10$), a significant effect of trial block ($F_{(1,40)} = 116.74$; $p < 0.00001$), and a significant group by trial block interaction ($F_{(3,40)} = 2.33$; $p < 0.05$). *Post hoc* tests showed that the asymmetric group differed significantly from the sham group on trial block 2 ($p < 0.05$). Analyses of hidden platform sessions showed a significant effect of trial block ($F_{(1,40)} = 33.28$; $p < 0.00001$) but no effect of group or interaction between factors (F values < 2.8 ; p values > 0.05).

Competition test

The mean escape latencies for each group on the competition test are shown in Figure 6 (day 10), whereas the mean percentages of peripheral pool time are shown in Figure 7 (day 10). One-way ANOVAs computed for each measure failed to reveal any significant group differences (escape latency, $F_{(3,40)} = 0.94$, $p > 0.40$; peripheral pool time, $F_{(3,40)} = 2.14$, $p > 0.10$).

The number of place and cue responders in each group, defined using the same criteria as in experiment 1, is shown in Table 2. The asymmetric lesion group showed a significant cue-response bias in comparison to controls ($\chi^2 = 4.44$; $p < 0.05$). In contrast, the unilateral-medial CPu and unilateral-hippocampal groups did not differ from the sham or asymmetric lesion groups (p values > 0.09).

Summary and discussion

In this experiment, asymmetric lesions of the hippocampus and medial CPu impaired escape learning on both visible and hidden platform trials, increased thigmotaxis (peripheral pool time) on early trials, and produced a significant cue-response bias on the competition test. Unilateral lesions of the hippocampus or medial CPu had none of these effects. Hence, these findings show a synergistic effect when the two forms of unilateral damage were combined to produce asymmetric lesions.

Table 2. Number of rats that swam to the former platform location (place responders) versus the new visible platform position (cue responders) on the competition test (day 10)

	Sham	Unilateral medial CPu	Unilateral hippocampus	Asymmetric med. CPu/Hippocampus
Place responders	7	5	4	2
Cue responders	5	5	6	10

On the early acquisition trials, the effects of asymmetric lesions were similar to (but not the same as) those of bilateral medial CPu lesions in experiment 1; both lesion groups exhibited increased escape latencies and increased thigmotaxis, especially on the early trials. As already suggested, this pattern of effects may be caused by an impaired ability to learn to initiate the appropriate response of swimming to the platform location on the basis of cognitive–spatial information.

On the later acquisition trials, the increased latencies of the asymmetric lesion group resembled those of the fornix/fimbria group in experiment 1, although the deficit was not as severe in the asymmetric as in the fornix/fimbria group (Figs. 2 and 5, compare block 9). Thus, whereas bilateral fornix/fimbria lesions appeared to prevent learning the location of the hidden platform almost completely, the asymmetric lesion produced only a partial deficit of this type. This is consistent with the hypothesis that medial CPu lesions do not impair acquisition of the spatial information required to locate the hidden platform.

On the competition test, the asymmetric lesioned rats exhibited a clear cue–response bias, resembling both the medial CPu and fornix/fimbria groups in experiment 1. Based on the hypothesized effects of the two lesions, this bias may have been caused by disruption of the flow of information between the two structures that is required to initiate a learned response to spatial-cognitive information in the presence of a competing local cue, the visible platform.

DISCUSSION

The results of experiment 1 suggest that the medial and lateral subregions of the CPu are functionally heterogeneous and may interact competitively at a behavioral level when inconsistent response alternatives are available. The findings also indicate that under similar behavioral conditions the hippocampal system may interact competitively with the lateral CPu and cooperatively with the medial CPu. In experiment 2, the effects of the asymmetric lesions suggest that this cooperative interaction may be based on serial information processing within a functional neural circuit that includes (but is not limited to) both hippocampus and medial CPu.

Previous experiments using different versions of the radial arm maze task (Packard et al., 1989; McDonald and White, 1993, 1995) showed that large lesions of the dorsal striatum (including parts of both medial and lateral subregions) produced different behavioral effects from lesions of the fornix/fimbria or hippocampus. It was suggested that the two structures may mediate different kinds of mnemonic functions that may compete for behavioral expression in certain situations. A similar conclusion was suggested by the results of a study of place versus response learning on a cross maze task (Packard and McGaugh, 1996) involving temporary inactivation of lateral CPu or hippocampus. The present findings are consistent with this interpretation, but they suggest that it may apply only to the lateral CPu. In contrast,

the medial CPu subregion of the dorsal striatum may interact cooperatively with the hippocampal system, mediating the behavioral expression of certain hippocampus-dependent mnemonic functions.

Lesions of the medial CPu have been reported to produce impairments in acquisition and retention of both place and cue tasks in the water maze (Whishaw et al., 1987; Devan et al., 1996). The latter findings cannot be attributed to a selective deficit in cognitive–spatial learning because, as in the present study, cue navigation was also compromised to some extent, and thigmotaxis was present. The fact that impairments of both place and cue acquisition after medial CPu lesions are accompanied by transient increases in thigmotaxis (as also reported by Devan et al., 1996, 1999) suggests that the behavioral impairment may be related to a deficiency in learned response initiation, such as that previously shown to occur on simple reaction time tasks after medial but not lateral CPu lesions (Brown and Robbins, 1989; Hauber and Schmidt, 1994). Moreover, as shown in the acquisition trials of the present experiment, rats with medial CPu lesions can acquire information about spatial/place cues and express such information when it provides the only possible solution to a task. This spared function may be mediated by allocortical and/or neocortical output to the pyramidal motor system. As shown in the competition test, however, when an alternative solution involving local cues is available, rats with medial CPu damage tend to respond to those cues rather than to the cognitive–spatial information they have acquired (see also, Whishaw et al., 1987).

Differences in the anatomical connections of the lateral and medial CPu are consistent with the proposed functional dissociation between these two parts of the dorsal striatum. The lateral CPu receives descending projections primarily from sensorimotor neocortex (McGeorge and Faull, 1989) and ascending dopaminergic input from the substantia nigra pars compacta (Heimer et al., 1995). These patterns of connectivity combined with the results of several studies involving lesions and post-training manipulation of memory consolidation functions (Packard and White, 1991; White and Viaud, 1991; McDonald and White, 1994; Packard and McGaugh, 1996) suggest that this striatal subregion may specialize in S–R habit formation (for review, see White, 1989, 1997).

In contrast, the patterns of connectivity and the present lesion findings suggest that the medial CPu may contribute to the control of behavior by the cognitive–spatial functions of other structures afferent to it. The medial CPu receives input from several mesocortical and allocortical areas (see introductory remarks), including the hippocampal formation. In the present study, asymmetric lesions of the hippocampus and medial CPu produced effects similar to bilateral but not unilateral lesions of these structures. Because the asymmetric lesions did not affect direct interhemispheric connections through the commissures, it is likely that the lesion effects resulted specifically from the

disconnection of ipsilateral connections, that is, efferent hippocampal projections to medial CPu on the hippocampus lesion side, and both hippocampal afferents and medial CPu efferents on the medial CPu lesion side.

There are at least four possible functional links between the hippocampal formation and the dorsomedial striatum. First, although direct projections from the CA1 subfield of the hippocampus and subiculum project primarily to the ventral striatum via the fornix/fimbria (Heimer and Wilson, 1975; Groenewegen et al., 1987; Brog et al., 1993), Groenewegen et al. (1987) have shown that subicular afferents also reach the most medial, ventral, rostral and caudal parts of the CPu. Second, the perirhinal cortex projects to the dorsal hippocampal CA1 field (Liu and Bilkey, 1996), to the entorhinal cortex (Amaral and Witter, 1995), and to the nucleus accumbens/medial CPu (McGeorge and Faull, 1989; Vaudano et al., 1990; Burwell et al., 1995), and hippocampal output from the entorhinal cortex reaches the nucleus accumbens and medial CPu (Krayniak et al., 1981; Sørensen and Witter, 1983; Swanson and Köhler, 1986). Third, hippocampal output may influence striatal function through connections with the posterior cingulate cortex, which projects strongly to the medial CPu (Domesick, 1969; McGeorge and Faull, 1989). Finally, the hippocampal formation projects to sectors of the medial prefrontal cortex (Swanson, 1981; Swanson and Köhler, 1986; Jay et al., 1989; Sesack et al., 1989; Jay and Witter, 1992; Condé et al., 1995), which in turn project to the ventral and dorsomedial striatum (Gerfen, 1984; McGeorge and Faull, 1989; Groenewegen et al., 1990).

The possibility that spatial information may be conveyed to the medial CPu via one or more of these indirect routes is supported by reports that bilateral lesions of the entorhinal/perirhinal cortex (Schenk and Morris, 1985; Nagahara et al., 1995), perforant path (Skelton and McNamara, 1992), posterior cingulate cortex (Sutherland et al., 1988; Sutherland and Hoising, 1993), and medial prefrontal cortex (Sutherland et al., 1982; Kolb et al., 1994) all impair the ability to learn the location of a hidden platform in the water maze. Furthermore, Floresco et al. (1997) found that temporary asymmetric lesions of the ventral hippocampus and prefrontal cortex selectively disrupted performance of a delayed win-shift task involving spatial cues, but had no effect on a random foraging task. Temporary disconnection of the ventral hippocampus and nucleus accumbens had an opposite pattern of effects. Thus, different limbic circuits may mediate different kinds of functional interactions between the hippocampal formation and the striatum.

In conclusion, the present results provide empirical evidence for a dissociation between medial and lateral subregions of the CPu and for different behavioral interactions between these CPu subregions and the hippocampal system. These interactions can be competitive or cooperative, depending on: (1) at a behavioral level, the type or types of information available in a particular learning task and (2) at a neural level, the subregion of dorsal striatum that is engaged by this information. The findings also suggest that the medial and lateral regions of the CPu can function in parallel and with some degree of independence, based on their functionally segregated corticostriatal connections. The lateral CPu may contribute to S–R-based behavior and the medial CPu, as part of a system that includes the fornix/fimbria and hippocampus, may contribute to behavior based on cognitive–spatial forms of information processing.

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