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Complementary Roles of the Orbital Prefrontal Cortex and the Perirhinal–Entorhinal Cortices in an Odor-Guided Delayed-Nonmatching-to-Sample Task

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Continuing efforts toward designing odor-guided tasks for rats that are similar in memory demands to tasks used typically with primates have resulted in the development of a continuous delayed-nonmatching-to-sample (cDNM) task that is guided by olfactory stimuli. The results indicate that normal subjects acquire the cDNM task rapidly and that subsequent performance deteriorates with increases in memory delay or interitem interference. Moreover, different aspects of cDNM performance were shown to be differentially sensitive to selective lesions of the orbitofrontal and parahippocampal areas. Orbitofrontal cortex lesions disproportionately impaired cDNM acquisition; delay performance was impaired only under conditions of elevated levels of interitem interference. Combined perirhinal and entorhinal cortical lesions had no effect on cDNM acquisition but impaired cDNM performance at longer delays across all levels of interference. Fornix lesions did not impair either acquisition of cDNM or subsequent performance across long delays and increased interference. This pattern of impaired and spared capacities is similar to that observed in monkeys after lesions of analogous areas and is consistent with the notion that the prefrontal cortical system contributes preferentially to learning general task "rules" such as the nonmatching rule that is inherent in cDNM, whereas the perirhinal and entorhinal cortical areas are involved in the intermediate-term maintenance of memories for specific information.

Recent advances in characterizing human memory processes indicate that the brain supports multiple memory systems. One account suggests that these systems can best be described as a "declarative" system, which subserves memory for facts and events, and a "procedural" system, which subserves the acquisition of skills and rules (Cohen, 1984; Cohen & Squire, 1980). Furthermore, a large body of converging evidence suggests that these distinct memory systems are mediated by different neural circuits (see Squire, 1987). In humans, damage to medial temporal lobe structures results in a severe memory impairment that is characterized by rapid forgetting of declarative information but leaves intact acquisition of a variety of perceptual, motor, and cognitive skills. A similar pattern of impaired and spared memory capacities is observed in both nonhuman primates and rodents after focal damage to structures within the medial temporal lobe system (for a review see Eichenbaum, Otto, & Cohen, 1992). Thus, considerable progress has been made toward understanding the psychological characteristics of the declarative and procedural memory systems and in delineating the neuroanatomical substrates that support these kinds of memory.

The nonhuman primate model of amnesia has been particularly valuable in demonstrating that medial temporal lobe structures are critical to declarative memory (Mishkin, 1978, 1982; for a recent review see Squire & Zola-Morgan, 1991). This progress has resulted in large part from assessments of monkeys' performance in an object recognition memory test—the delayed-nonmatching-to-sample (DNMS) task—in which the subject is initially rewarded for displacing a novel three-dimensional object and then, after a variable memory delay, is rewarded for selectively displacing another novel object that is presented along with the familiar object during a choice test (Gaffan, 1974; Mishkin & Delacour, 1975). Intact monkeys typically acquire this task in less than 200 trials and can perform well even with memory delays of several minutes. By contrast, monkeys with medial temporal lobe damage are severely impaired in acquiring this task when trained using the conventional 8–10-s memory delays; in subsequent testing with longer memory delays between sample and choice trials, monkeys with medial temporal lobe damage are severely and permanently impaired (Mishkin, 1978).

The DNMS paradigm has also been particularly useful in identifying the specific structures within the medial temporal lobe that are critical to declarative memory. It was originally concluded that recognition memory depended critically on the hippocampal formation (including the dentate gyrus, Ammon's horn, and the subicular complex; Scoville & Milner, 1957). However, in nearly all studies on monkeys, hippocampal lesions were accompanied by significant damage to surrounding parahippocampal areas (a term we will use to refer col-

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lectively to the perirhinal, parahippocampal, and entorhinal cortices). It has recently been shown that selective removal of some or all of these cortical areas results in a greater deficit in DNMS than does hippocampal damage that spares most of the surrounding cortex (Murray, 1991; Murray & Mishkin, 1986; Zola-Morgan, Squire, & Amaral, 1989a). Furthermore, fornix lesions, which disconnect the hippocampus from subcortical structures but spare the parahippocampal areas and connections with the neocortex, result in only a modest and transient impairment in DNMS (Bachevalier, Parkinson, & Mishkin, 1985; Gaffan, Gaffan, & Harrison, 1984; Zola-Morgan, Squire, & Amaral, 1989b) but severely impair spatial learning and memory (Gaffan & Harrison, 1984, 1988, 1989; Mahut, 1972; Murray, Davidson, Gaffan, Olton, & Suomi, 1989). Experimental data from recent studies on rats are consistent with this view and further call into question the role of the hippocampus in recognition memory. Selective hippocampal ablation, fornix transection, or damage to parahippocampal areas results in severe impairment in many spatial learning and memory tasks (see Jarrard, 1986; O'Keefe & Nadel, 1978), including some that involve nonmatching over delays (Aggleton, Hunt, & Rawlins, 1986; Olton, Becker, & Handlemann, 1979; Thomas, 1978), certain types of discrimination, and a variety of complex learning tasks (see Eichenbaum et al., 1988, 1992). However, lesions that are limited to the hippocampus do not impair performance in object-cued DNMS tasks in rats (Aggleton et al., 1986; Mumby, Wood, & Pinel, 1992; Rothblat & Kromer, 1991). Thus, in both monkeys and rats, the data suggest that, although some aspects of complex learning require the hippocampus and its connections through the fornix, storage of memories for specific items across delays in DNMS tasks depends disproportionately on the integrity of parahippocampal areas.

Relatively less experimental attention has been devoted to identifying the brain structures that mediate acquisition of the procedural aspects of DNMS performance. However, the results of a few studies suggest that the acquisition of the cognitive skills or rules involved in DNMS may be mediated in part by specific areas within the prefrontal cortex. For example, although lesions of the ventromedial prefrontal area (including the orbital prefrontal and anterior cingulate cortices) impair reacquisition of preoperatively trained DNMS and significantly accelerate forgetting (Bachevalier & Mishkin, 1986; Kowalska, Bachevalier, & Mishkin, in press), lesions of the inferior convexity of the prefrontal cortex or, to a lesser extent, the dorsolateral prefrontal cortex impair reacquisition but have no effect on subsequent delay performance. These data have led some investigators to suggest that components of the prefrontal cortex are critical to "rule learning" (Goldman, Rosvold, Vest, & Galkin, 1971; Kowalska et al., in press) as reflected in a deficit in postoperative reacquisition of the task with no subsequent deficit in performance across even long delays.

The effects of focal damage to components of the parahippocampal and prefrontal areas in monkeys suggest collectively that discrete areas within these systems play critical and complementary roles in DNMS performance. Specifically, the parahippocampal areas appear to be selectively involved in the maintenance of memory for specific objects, whereas some areas of the prefrontal cortex may participate selectively in learning the rules of the DNMS task. One goal of the present study was to test this hypothesis. More specifically we also sought to determine whether this account of multiple memory systems and their neuroanatomical substrates can be extended to rodents.

In our view, further exploration of the neural substrates of multiple memory systems might be facilitated by the development of tasks for use with rats that are conceptually analogous in memory demands to those used so successfully with primates. Such an approach would permit a comparative analysis of the respective roles of various brain systems in the acquisition and storage of different types of information and would provide a suitable and productive avenue for studies at the cellular and molecular levels of analysis. We (Eichenbaum, Otto, Wible, & Piper, 1991; Otto & Eichenbaum, 1992b, 1992c) and others (Lynch, 1986; Staubli, Fraser, Faraday, & Lynch, 1987) have suggested that the rodent olfactory system provides a fruitful domain in which to investigate the neurobiology of memory. Briefly, rats exhibit a remarkable facility for a variety of complex forms of odor-guided learning (reviewed in Otto & Eichenbaum, 1992b). Furthermore, odor-guided learning is sensitive to lesions of the hippocampal (Eichenbaum, Fagan, & Cohen, 1986; Eichenbaum, Fagan, Mathews, & Cohen, 1988), parahippocampal (Otto, Schottler, Staubli, Eichenbaum, & Lynch, 1991; Staubli, Ivy, & Lynch, 1984), and prefrontal cortical (Eichenbaum, Clegg, & Feeley, 1983) systems. With these advantages in mind, we have developed an odor-guided continuous delayed-nonmatching-to-sample (cDNM) task that is conceptually analogous to the visually guided DNMS task that is typically used with primates and to other DNMS tasks that have been developed for rodents (Dunnett & Martel, 1990; Mumby, Pinel, & Wood, 1990; Pontecorvo, 1983; Rothblat & Hayes, 1987; Wallace, Steinert, Scobie, & Spear, 1980). In this article, we present parametric data that assess both the rate of acquisition of odor-guided cDNM and the effects of increasing levels of memory delay and interference on subsequent performance in a group of intact subjects (Experiment 1). We also compared the effects of damage to the orbitofrontal cortex, the perirhinal and entorhinal cortices, or the fornix on cDNM performance (Experiment 2).

Experiment 1: Parametric Evaluation of the Performance of Normal Rats in the cDNM Task

Among the notable characteristics of DNMS performance in intact primates are rapid acquisition of the task and delay-dependent forgetting of specific to-be-remembered objects. There is also evidence suggesting that the performance of intact monkeys is sensitive to interference that is imposed by reducing the number of items from which samples are chosen (Jitsumori, Wright, & Cook, 1988; Mishkin & Delacour, 1975). Although rats acquire novel odor discriminations exceedingly rapidly (Eichenbaum et al., 1986; Otto et al., 1991; Slotnick & Katz, 1974) and are capable of learning a variety of complex odor-guided tasks including the "oddity" principle (Langworthy & Jennings, 1972) and transitive inference (Wible, Eichenbaum, & Otto, 1990), their ability to learn an odor-guided

analogue of the visually guided DNMS task used with primates has not been demonstrated. Thus, the purpose of Experiment 1 was, first, to determine how rapidly rats are capable of learning the odor-guided cDNM task and, second, to examine the effects of increasing both the memory delay and the level of interitem interference on the performance of a group of intact subjects.

Method

Subjects

Six male Long-Evans rats, which weighed an average of 250 g at the beginning of testing, served as subjects. They were maintained on a 12:12-hr light–dark cycle in an environmentally controlled room. All behavioral training was conducted during the light cycle. Food was continuously available, but water access was restricted to a 20-min period at the end of each day after training.

Apparatus

All behavioral training took place in a 30 × 30 × 30 cm Plexiglas chamber that was surrounded by a sound-attenuating wooden enclosure. A conical sniff port was centered on one wall of the chamber 5 cm above the floor. A circular well-shaped water port (1 cm in diameter) was located immediately above the sniff port. Responses to the sniff and water ports were monitored by separate infrared photoelectric cells. Two 24-V flashlight bulbs ("houselights") were mounted above the sniff and water ports at a height of 13 cm above the floor. Individual odors were delivered as required by a 16-channel flow-dilution olfactometer. Clean air flowed continuously at a rate of 0.5 L/min; odorized airstreams (0.5 L/min) were added to the clean airstreams when appropriate to produce a final flow rate of 1.0 L/min. Odorized and clean airstreams were presented to a solenoid valve that was mounted just outside the behavioral chamber; during the intertrial interval (hereafter referred to as the "delay"), the airstreams were diverted by this valve to a vacuum dump that flowed at twice the final odor flow rate. Odors were presented to the subject when appropriate by deactivating the vacuum solenoid, which thereby allowed the odorized airstream to enter the behavioral chamber through the sniff port. Lingering odors were exhausted from the behavioral chamber by means of a fan that was mounted on the outside of the wooden enclosure and attached to a length of 3-in. (7.62-cm) flexible hose, which in turn was attached to the top of the inner Plexiglas chamber. All procedural events were controlled, and all behavioral responses were recorded, by a microcomputer with custom-designed interfaces.

Procedure

Training and testing for the cDNM task was conducted in three phases, each of which is detailed.

Shaping. Water-deprived rats were shaped to place their nose into the sniff port and to retrieve water reinforcers at the water port during two 60-trial sessions. On each trial, a 500-ms nose poke into the sniff port resulted in the presentation of a single odor that was chosen on a pseudorandom basis from among a set of 16; subsequent water port responses terminated odor presentation and were reinforced with 0.05 ml water. During these shaping sessions, the odor that was presented on each trial was always different from the odor that was presented on the immediately preceding trial. A 3-s delay was imposed between trials; the houselights were extinguished during the delay and were subsequently reilluminated to signal the availability of another trial. Nose pokes into the sniff port during the last 2 s of the delay extended the delay by an additional 2 s.

Training to criterion. The procedure during these initial training sessions differed from shaping sessions only in the sequence of odors presented, the consequent reward contingencies, and the length of the delay. During training, unlike during shaping, on half of the trials the odor that was presented was different from the odor that was presented on the preceding trial; on the other half of the trials the odor was the same as that presented on the preceding trial. Responses to the water port during training were reinforced only if the odor on the current trial was different from the odor that was presented on the preceding trial. Thus, the rat was required to remember across the delay the odor that was presented on the immediately previous trial and to respond by breaking the photobeam at the water port only if the current odor was a "nonmatch." Water port responses on "match" trials were not reinforced and resulted in the immediate offset of the houselights. If no water port response was made within 5 s of odor onset, the odor and the houselights were turned off simultaneously, and the delay began. Correct responses ("go" responses on nonmatch trials; "no-go" responses on match trials) were followed by a 3-s delay; errors of commission (go responses on match trials) and errors of omission (no-go responses on nonmatch trials) were followed by a 7-s delay. One 100-trial session was run daily for 6 days each week.

A correction procedure for errors of commission was used in the early stage of training. Correction trials were identical in all respects to the match trial on which the error was made. If the rat again made an error, then a second correction trial was presented; the quasi-random odor sequence ensued after the second correction trial regardless of the subject's response. This correction procedure was discontinued when the rat reached a performance criterion of 18 correct responses in 20 consecutive trials; correction trials were not included in the calculation of trials to criterion. After attainment of the criterion, subjects were trained in several additional 100-trial sessions using a 3-s delay after every trial regardless of the response until performance exceeded 85% correct on each of two consecutive sessions.

Testing with increased memory delay and interitem interference. After acquisition of the cDNM task using 3-s delays and a large odor set (16 odors), two manipulations were introduced to examine performance under greater memory demands and at greater levels of interitem interference. To assess the persistence of odor memory, the delay was lengthened to either 30 or 60 s. To examine the effect of increased interitem interference, the size of the set of odors from which individual stimuli were chosen for each trial was reduced from 16 to 8, 4, or 2 odors. In this phase of training, sessions were reduced to 50 trials; a particular combination of delay length and interference was used throughout each session. The specific combination of delay and interference parameters for a given session was chosen on a pseudorandom basis, with the provision that consecutive sessions could not have the same delay. One session was run at each of the 12 combinations of delay and interference; the percentage of correct responses for the entire session was used to evaluate performance at that combination of delay and interference parameters. After sessions in which performance fell below 70%, a session with the original parameters of 16 odors and a 3-s delay was given to reestablish baseline performance.

Results

On average, the 6 subjects reached a criterion of 18 correct responses in 20 consecutive trials in 347 trials (SE = 66.1) and consistently performed at better than 80% correct after the third session (see Figure 1).

The average percentage of correct responses for sessions composed of the various combinations of memory delay and interitem interference appears in Figure 2. A two-way analysis of variance with repeated measures revealed a significant effect of delay, $F(2, 10) = 28.01$, $p < .001$, and level of

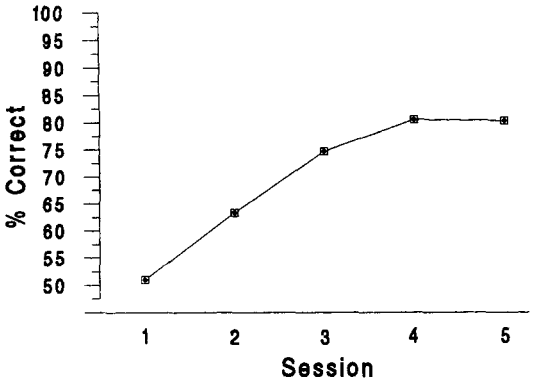

Figure 1. Average percentage of correct responses across the first five continuous delayed-nonmatching-to-sample acquisition sessions for the group of 6 unoperated rats in Experiment 1.

interference, $F(3, 15) = 12.67$, $p < .001$. The interaction between delay and interference did not reach statistical significance, $F(6, 30) = 1.66$, *ns*. Thus, performance accuracy declined as either the memory delay or the level of interference increased.

Discussion

The results of this first experiment indicate clearly that rats rapidly acquire an odor-guided cDNM task that is analogous in memory and performance demands to the visually guided DNMS task that is used frequently with monkeys. Moreover, rats' performance in this task is sensitive to manipulations that increase memory demands and interference. Because successful performance in cDNM requires the subject to remember across the imposed delay the odor that was presented on the immediately preceding trial, the pattern of performance of normal subjects as a function of increasing delay reflects, in our view, the time-dependent decay of odor memory. On the other hand, the performance decrement associated with decreasing the size of the odor set from which individual samples are chosen is likely due to increasing levels of interitem interference because, as the odor set size decreases, individual odors are presented more often on both match and nonmatch trials.

In an attempt to evaluate how well rats perform on this version of delayed nonmatching, we compared both acquisition rate and delay performance in cDNM to previous reports on other delayed nonmatching tasks that used rats or monkeys. Rats have been trained to perform a number of such tasks, including cDNM tasks that use tones, lights, or both as memory cues and DNMS tasks that use either trial-repetitive spatial cues or trial-unique visual–tactile cues. These tasks often differ both in the procedures used and in the data analyzed and reported, thereby precluding meaningful statistical comparisons among them; a general comparison will nevertheless be made in an attempt to support our conclusion that, in the odor-guided cDNM task, rats exhibit both rapid acquisition of the rules governing performance and persistent memory for specific stimuli. In tasks that use the same spatial or nonspatial cues repetitively on each trial, acquisition rates in relation to those in odor-guided cDNM are quite slow: Subjects typically require many hundreds to thousands of trials before they perform consistently well (Dunnett & Martel, 1990; Knoth & Mair, 1991; Pontecorvo, 1983; Raffaele & Olton, 1988; Sakurai, 1987; Wallace et al., 1980). In light of the present data, it is likely that this slow acquisition is due to a high degree of interitem interference. Also, in those tasks for which decay curves are reported, memory performance falls to chance relatively rapidly, often within less than 10 s (Knoth & Mair, 1991; Wallace et al., 1980), although intact retention across 10-s delays has been reported (Pontecorvo, 1983). The only exception to this pattern of results for tasks with trial-repeated stimuli occurs when spatial cues are used in a Y-maze apparatus (Olton et al., 1979) rather than in an operant apparatus. In nonspatial DNMS tasks that use trial-unique cues, acquisition rates are at least as fast as in odor-guided cDNM: Rats typically require under 300 trials to perform well (Aggleton et al., 1986; Mumby et al., 1992; Rothblat & Hayes, 1987). Furthermore, memory in these tasks is considerably more persistent than in tasks in which cues are trial-repetitive. In tasks for which nonspatial cues are trial-unique, memory decay rates in rats are comparable to or slightly slower than those observed in the present cDNM task, in which cues were repeated only occasionally.

A comparison of the present results with the performance of monkeys in the conventional DNMS task revealed that subjects in this first experiment required approximately twice as many trials to acquire the task (cf. Mishkin & Delacour, 1975). Furthermore, the decay curves for the present task are somewhat steeper than those obtained in tests of monkey DNMS performance; accuracy at 1-min delays was approximately 75% for rats compared with 90% for monkeys. These quantitative distinctions in performance may reflect inherent differences between species in acquisition rate and memory persistence, differences that are associated with the stimulus materials used in the respective tasks, or differences in procedures that are used in cDNM and DNMS. With regard to task procedures, there are several differences in training protocol that could have contributed to the observed discrepancies in the performance of rats and monkeys. First, in the

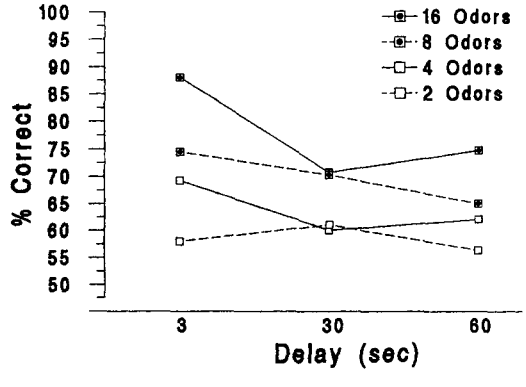

Figure 2. Average percentage of correct responses across various combinations of memory delay and interitem interference for the group of 6 unoperated rats in Experiment 1.

cDNM task, each cue acts both as a sample and as a test stimulus; in the DNMS task, these functions are dissociated as a result of the discrete-trials procedure that is used. Second, in the present task, individual cues recur occasionally within a session, whereas in the conventional DNMS task, stimuli are trial-unique and thus are associated with less interitem interference. Third, acquisition sessions in the cDNM task consisted of 100 trials/day, whereas acquisition sessions in DNMS typically involve only 20 trials/day. Any one or all of these differences might result in cDNM exceeding DNMS in difficulty and thereby may have led to the observed differences in acquisition and delay performance. Indeed, in Experiment 2, a simple reduction in the number of trials that were administered in each training session increased the cDNM acquisition rate of rats to a level comparable to that for DNMS acquisition in primates. Nevertheless, despite these quantitative differences in learning and forgetting rates of intact subjects, the patterns of performance by rats in odor-guided cDNM parallel those of monkeys in the object-cued, visually guided DNMS task.

Experiment 2: Effects of Lesions to the Orbital Prefrontal Cortex, the Perirhinal and Entorhinal Cortices, or the Fornix on cDNM Performance

As discussed in the introduction, the results of a number of studies suggest that the prefrontal cortical and parahippocampal areas play complementary roles in DNMS performance in monkeys: Lesions of certain prefrontal cortical areas selectively impair acquisition of the task, whereas lesions of the parahippocampal areas produce a profound, rapid forgetting of trial-specific information. One goal of this second experiment was to determine whether the prefrontal cortical and parahippocampal areas play parallel roles in cDNM performance in rats. A second goal of this experiment was to compare the behavioral effects of lesions to these cortical areas with those of damage to the fornix. If the role of these structures in memory processes is similar across species, then fornix lesions should produce only mild and transient effects on cDNM performance, whereas lesions of the parahippocampal areas should result in rapid forgetting of odor-item information.

There is good reason to expect functional dissociations between regions of the rodent prefrontal cortex and for these functions to correspond to those observed in primates. The rodent prefrontal cortex is composed of functionally distinct medial and orbital subdivisions (see Kolb, 1990). Selective damage to the medial subdivision selectively impairs spatial learning and memory in rats (Becker, Walker, & Olton, 1980; Kesner & Holbrook, 1987; Kolb, Sutherland, & Whishaw, 1983). In monkeys, lesions of the dorsolateral (Goldman-Rakic, 1990; Rosenkilde, 1979) or anterior cingulate (Mishkin & Bachevalier, 1986) cortex, both of which have thalamic connections similar to those of the rodent medial prefrontal area, also produce selective deficits in spatial learning and memory. By contrast, lesions of the orbital subdivision, which is homologous with the inferior convexity and orbital prefrontal areas in primates (Price et al., 1991), selectively and severely impair olfactory discrimination learning (Eichenbaum et al., 1983). In primates, lesions of specific sites in the inferior convexity and orbital prefrontal cortex impair acquisition of a variety of tasks that are cued by specific sensory cues including olfactory (Tanabe, Yarita, Iino, Ooshima, & Takagi, 1975) and visually cued tasks (for a review see Rosenkilde, 1979), including the DNMS task (Bachevalier & Mishkin, 1986; Kowalska et al., in press). Combining these anatomical and behavioral observations, we postulated that the orbital subdivision of the prefrontal cortex might be specifically involved in learning the procedural aspects of the cDNM task. Because the memory delay and interference levels during initial training on the cDNM task were minimal (see the *Apparatus and Training Procedure* section), we took acquisition rate in this phase of training to reflect primarily the ability to learn the rules governing cDNM performance and not the ability to maintain memories for specific odor cues. Thus, we predicted that animals with selective orbitofrontal damage would be significantly retarded in the initial acquisition of the task but would perform normally in subsequent performance tests that challenge retention capacity.

With respect to the hippocampal system and adjacent cortical areas, a severe and lasting impairment in monkeys' DNMS performance is produced by lesions of what we have called the parahippocampal area (the perirhinal, entorhinal, and parahippocampal cortices) but not by lesions of the fornix. One objective of this second experiment was to examine the effects of removal of the homologous areas in rats. Although there is general agreement on the homology between rat and monkey entorhinal cortex (e.g., Witter, 1989), the precise homologies of the perirhinal and parahippocampal cortices are as yet unclear. In rats, it has been suggested that the perirhinal area is composed of three adjacent subdivisions that are differentiated by the sources of their neocortical input: rostral perirhinal, caudal perirhinal, and postrhinal cortices; but whether there exists a rodent homologue of primate parahippocampal cortex is unclear (Deacon, Eichenbaum, Rosenberg, & Eckmann, 1983). It was our intent to include all three of these subdivisions in our experimental lesions; we therefore will use the term "perirhinal cortex" to refer collectively to all three subdivisions. Furthermore, because the primary olfactory cortex projects directly to the entorhinal cortex, we used combined lesions of the perirhinal and entorhinal cortices. The effects of these lesions on cDNM performance were compared with those after complete fornix transection.

Method

Subjects

Twenty-nine male Long-Evans rats, which weighed an average of 250 g at the beginning of testing, served as subjects. They were maintained on a 12:12-hr light–dark cycle in an environmentally controlled animal vivarium. All surgical and behavioral procedures were conducted during the light cycle. Both food and water were continuously available before surgery and during the postsurgical recovery period; access to water during the period of behavioral training was limited to a 15-min period after completion of each daily training session.

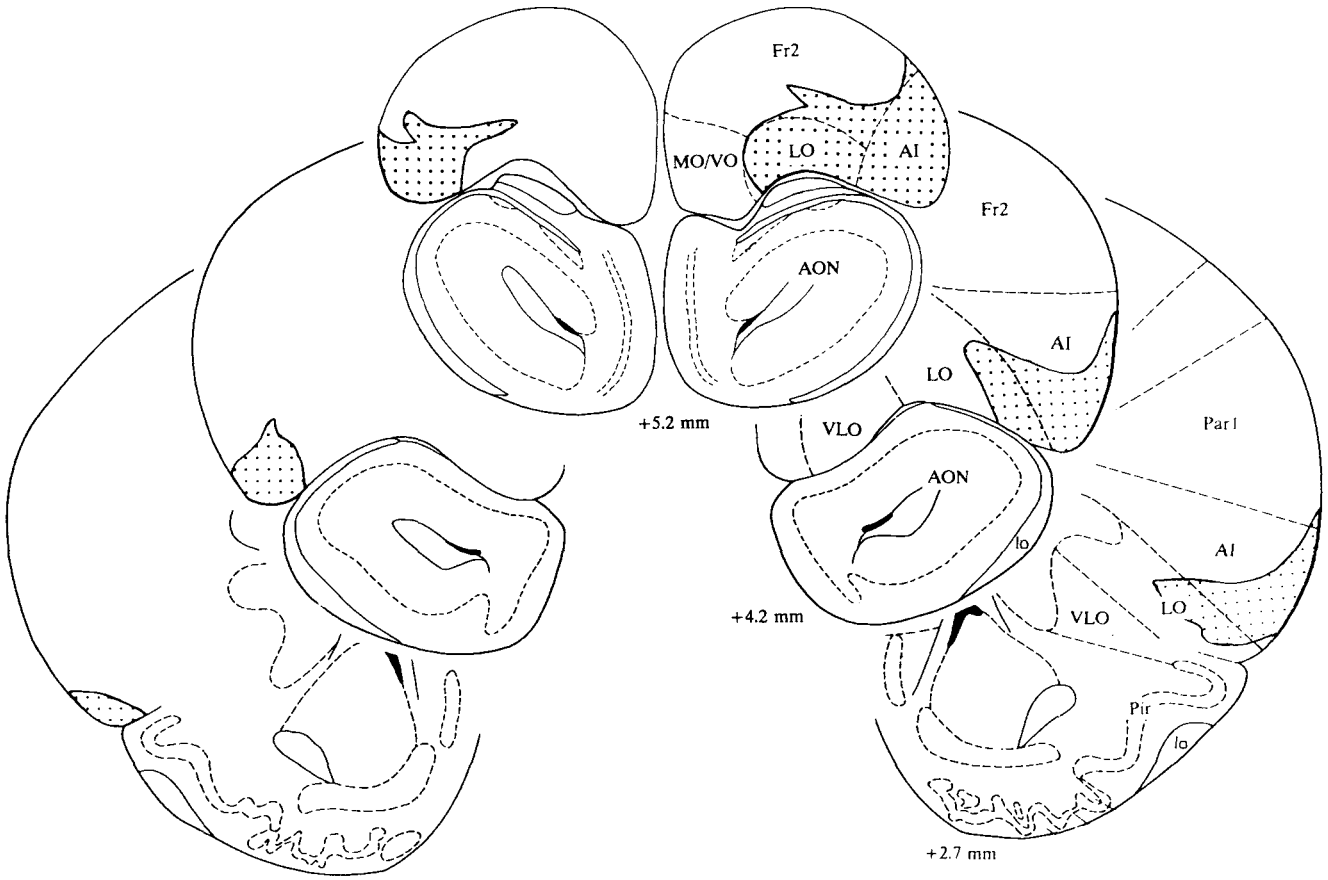

Figure 3. Representative lesion of the orbital prefrontal cortex. (AI = agranular insular cortex; AON = anterior olfactory nucleus; Fr2 = frontal cortex, area 2; LO = lateral orbital cortex; lo = lateral olfactory tract; MO/VO = medial–ventral orbital cortex; Parl = parietal cortex, area 1; Pir = piriform cortex; VLO = ventrolateral orbital cortex. Numbers at the lower left of each section represent distance of representative sections from bregma. Adapted from *The Rat Brain in Stereotaxic Coordinates* [2nd ed., Plates 4, 6, and 9] by G. Paxinos and C. Watson, 1986, San Diego, CA: Academic Press. Copyright 1986 by Academic Press. Adapted by permission.)

Surgical and Histological Procedures

General. All subjects were anesthetized with a mixture of ketamine (50 mg/kg ip) and xylazine (10 mg/kg ip) and prepared with focal lesions to the perirhinal and entorhinal cortices, the fornix, or the orbital prefrontal cortex (see specific subsections). After surgery, the wound was sutured and treated with a topical antibiotic ointment (Furazone) to control infection. A 10–12-day postoperative recovery period preceded all behavioral testing. After the completion of all behavioral training, subjects were deeply anesthetized with sodium pentobarbital (100 mg/kg) and perfused intracardially with 0.9% buffered saline, which was followed by 10% buffered formol–saline. The brain was excised and stored in 10% formalin for 8 hr and then placed in 30% sucrose for 12 hr, after which it was either sectioned immediately or frozen and maintained at −70 °C for later sectioning. All brains were sectioned at a thickness of 30 μm and stained (see specific subsections for details) for subsequent examination.

Orbital prefrontal cortex. Subjects (OFs, $n = 5$) were anesthetized and positioned in a custom-designed head holder that permitted full, bilateral access to the lateral–temporal surface of the skull. The temporal muscle was retracted from the portion of skull overlying the ventrolateral aspect of the frontal cortex, and the underlying cortex was exposed using a dental drill and fine-tipped rongeurs. Subpial aspiration of the orbital prefrontal cortex just dorsal to the rhinal sulcus was performed under visual guidance using a curved and blunted 20-gauge hypodermic needle. Three other rats (OF-shams) were prepared similarly, but no cortex was removed. Gelfoam that had been soaked in physiological saline was then placed over the skull hole, the temporal muscle was replaced, and the wound was sutured and treated as described earlier. After training, the brain was sectioned in the coronal plane, and every fifth section through the frontal cortex was stained with cresyl violet.

A reconstruction of a representative lesion of orbital prefrontal cortex is illustrated in Figure 3; these lesion sites coincide well with the areas of the prefrontal cortex that receive both direct and indirect (via the mediodorsal thalamus; Krettek & Price, 1977) olfactory projections. Although anterior aspects of the lateral orbitofrontal cortex were completely removed in all subjects, the lesions were in general smaller than intended in posterior aspects. The anterior portion of the agranular insular cortex was also damaged in all subjects. A small, unilateral aspiration of the dorsolateral-most portion of the anterior olfactory nucleus was observed in 1 subject. Although this rat was significantly impaired in cDNM acquisition, as were all OF subjects, it

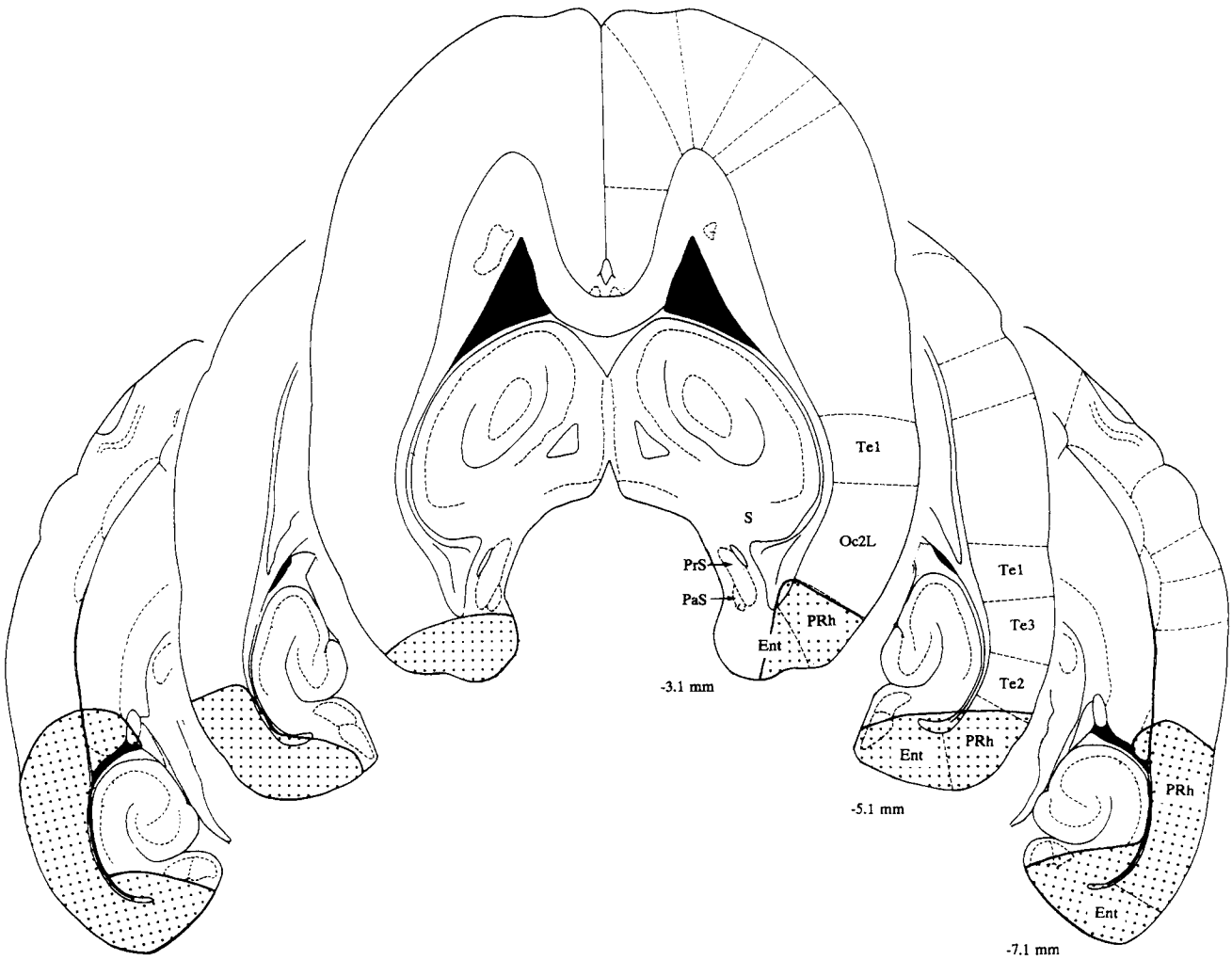

Figure 4. Representative lesion of the entorhinal–perirhinal cortex. (Ent = entorhinal cortex; Oc2L = occipital cortex, area 2; PaS = parasubiculum; PrS = presubiculum; PRh = perirhinal cortex; S = subiculum; Te1, Te2, Te3 = temporal cortex, areas 1—3, respectively. Numbers at the lower left of each section represent distance of representative sections from bregma. Adapted from *The Rat Brain in Stereotaxic Coordinates* [2nd ed., Plates 97, 105, and 113] by G. Paxinos and C. Watson, 1986, San Diego, CA: Academic Press. Copyright 1986 by Academic Press. Adapted by permission.)

required fewer trials to reach criterion performance than did any other rat in the group.

Perirhinal and entorhinal cortex. Subjects (PRERs, n = 7) were anesthetized and positioned in the custom-designed adjustable head holder described earlier. The temporal muscle was retracted from the portion of skull extending from the zygomatic arch to a point just anterior to the interaural line, and the underlying entorhinal and perirhinal cortices were exposed using a dental drill and fine-tipped rongeurs. Subpial aspiration of these cortical areas was performed under visual guidance with the aid of a dissecting microscope using a curved and blunted 20-gauge hypodermic needle. Two rats (PRER-shams) were prepared similarly, but no cortex was removed. Excessive bleeding during surgery was controlled by infusing the area with cold physiological saline. Gelfoam that had been soaked in physiological saline was then placed over the skull hole, the temporal muscle was replaced, and the wound was sutured and treated as described earlier. After training and histological preparation, the brain was sectioned in the horizontal plane, and every 10th section through the hippocampus was stained for acetylcholinesterase (AChE) activity.

A reconstruction of a representative lesion of the perirhinal and entorhinal cortices is shown in Figure 4. The entorhinal cortex and most of the perirhinal cortex were successfully aspirated in all subjects; the most rostral aspect of the perirhinal cortex remained intact bilaterally in all animals. The temporal neocortex was not damaged in any subject. One subject received unilateral damage to the CA1 subfield of the ventral hippocampus and to the presubiculum and parasubiculum. Two other subjects suffered inadvertent unilateral damage to presubiculum and parasubiculum; 1 of these subjects also received unilateral damage to the ventral dentate gyrus. Further light-microscopic evaluation revealed intense AChE staining in the molecular layer of the dentate gyrus of PRER subjects. This effect, which was observed throughout the entire septotemporal extent of the hippocampus, is consistent with that from previous anatomical studies showing that damage to the entorhinal cortex results in a degeneration

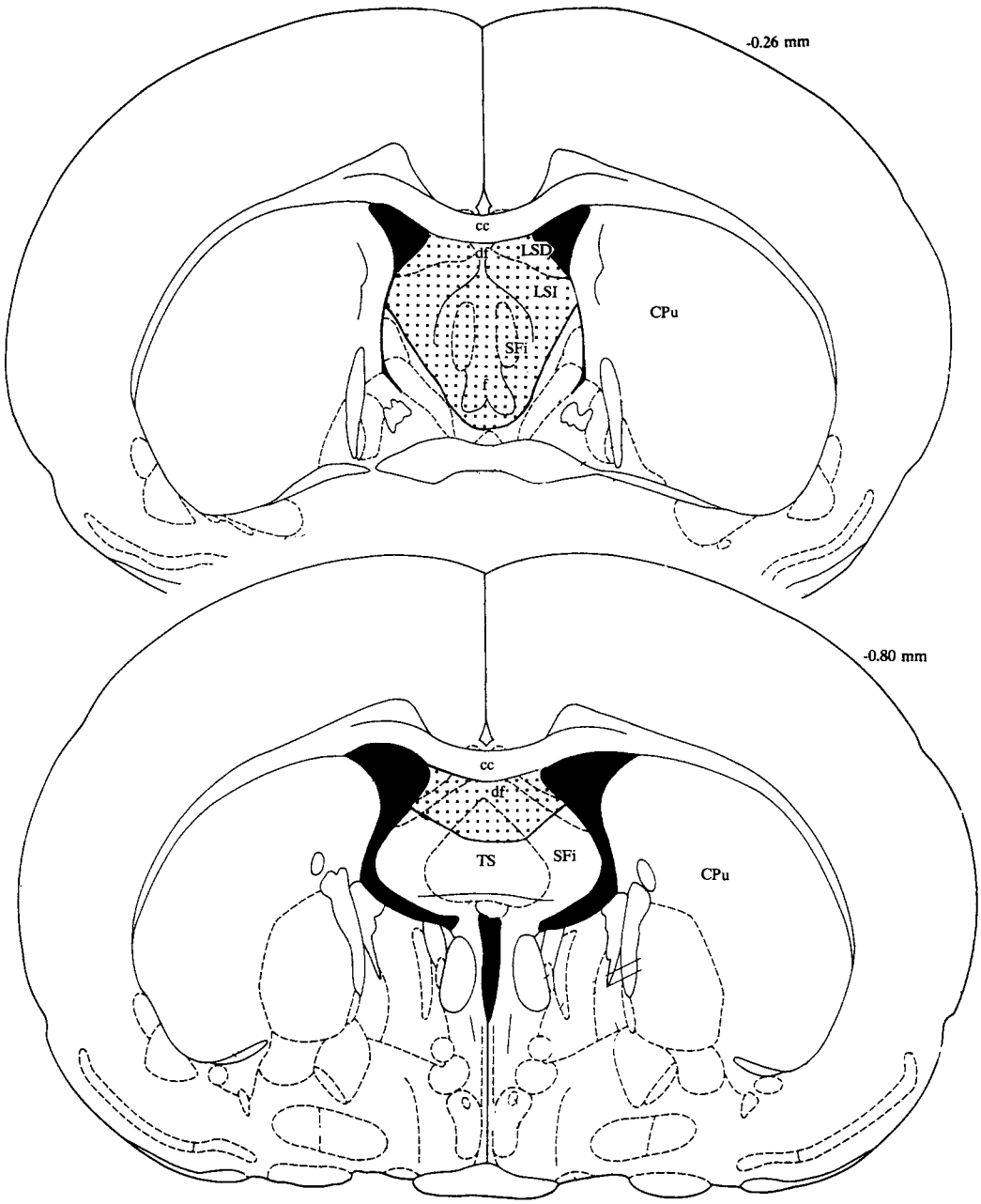

Figure 5. Representative lesion of the fornix. (cc = corpus callosum; CPu = caudate–putamen; df = dorsal fornix; f = fornix; LSD = lateral septal nucleus, dorsal; LSI = lateral septal nucleus, intermediate; SFi = septofimbrial nucleus; TS = triangular septal nucleus. Numbers at top right of each section represent distance of representative sections from bregma. Adapted from *The Rat Brain in Stereotaxic Coordinates* [2nd ed., Plates 18 and 21] by G. Paxinos and C. Watson, 1986, San Diego, CA: Academic Press. Copyright 1986 by Academic Press. Adapted by permission.)

of the outer molecular layer of the dentate gyrus and a sprouting of intact, presumably septal AChE-containing terminals into this region (Cotman, Matthews, Taylor, & Lynch, 1973; Lynch, Matthews, Mosko, Parks, & Cotman, 1972). There was no apparent correlation between the extent of unintended damage and cDNM performance. The subject with the most unintended damage (unilateral presubiculum, parasubiculum, and ventral dentate gyrus) performed at or above the mean for the entire PRER group in four of the six sessions that assessed performance under various combinations of delay and interference.

Fornix. Subjects (FXs, $n = 6$) were anesthetized and positioned in a Kopf stereotaxic instrument so that bregma and lambda were at equal heights. A Radionics radio-frequency lesion maker was used to produce lesions at the following coordinates in relation to bregma:

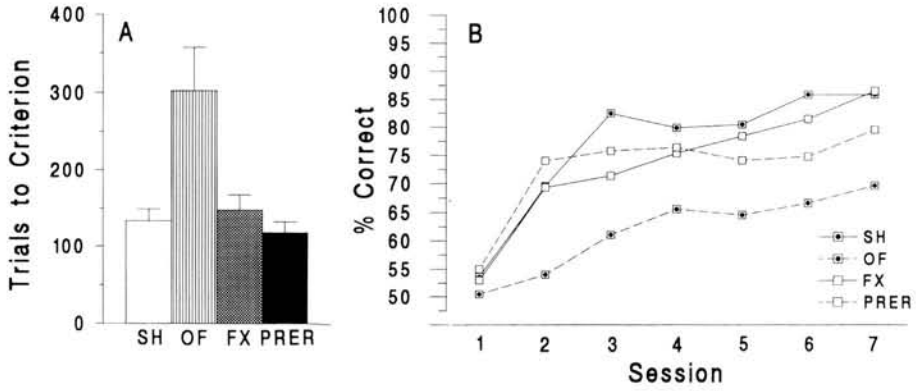

Figure 6. A: Average number of trials (±1 *SE*) required during acquisition to reach a performance criterion of 18 correct responses in 20 consecutive trials. B: Average percentage of correct responses across the first seven continuous delayed-nonmatching-to-sample acquisition sessions. (SH = sham-operated group; OF = orbital prefrontal cortex lesion group; FX = fornix lesion group; PRER = perirhinal and entorhinalx cortices lesion group.)

anterior–posterior (AP) = −0.3, lateral (L) = 0.7, dorsal–ventral (DV) = −3.8, bilateral; AP = −0.8, L = 1.7, DV = 4.0, bilateral; and at 10° to the midline: AP = −0.3, L = 0.7, DV = −3.9. Six other subjects (FX-sham) received sham surgery; that is, they were prepared similarly, but no lesion was made. In 3 of these rats, the electrode was lowered to the just-listed coordinates, but no current was applied; the other 3 rats were prepared similarly, but the electrode was not lowered into the brain. After training and histological preparation as described earlier, the brain was sectioned coronally, and every fifth section through the fornix and hippocampus was stained for AChE activity.

A typical fornix lesion is reconstructed in Figure 5. In addition to the complete ablation of the fornix, the adjacent anterior aspects of the lateral and triangular septal nuclei and the septofimbrial nucleus were damaged in all subjects. No other areas were damaged in any subject. Inspection of the AChE-stained sections revealed an absence of cholinergic activity throughout the entire hippocampus in all subjects, which is characteristic of complete fornix damage (for representative figures see Eichenbaum et al., 1986, 1988).

Apparatus and Training Procedure

All training was conducted in the same behavioral chamber that was used in Experiment 1. The procedure that was used to assess the acquisition of the cDNM task and the effect of increased memory delay and interitem interference was identical to that of Experiment 1, with the following exceptions. First, individual acquisition sessions consisted of 50 trials instead of 100 trials to accommodate a greater number of subjects in daily training sessions. Second, only odor set sizes of 16 and 8 were used to assess the effect of increased interference on cDNM performance; thus, one 50-trial session was run at each of the six unique combinations of delay and interference. Odor sets of 4 and 2 were not used because the results of Experiment 1 indicated that, at levels of interference associated with these parameters, any impairment resulting from the lesions would likely be obscured by a floor effect.

Statistical Analysis

All data were analyzed using parametric analyses of variance (ANOVAs), with repeated measures when appropriate. In the event of a significant group effect or a significant interaction, post hoc comparisons were conducted using Tukey's least significant difference procedure with an alpha of .05.

Results

Because the three groups of sham-operated control subjects (OF-shams, PRER-shams, and FX-shams) did not differ in either their acquisition of the cDNM task as measured by both the number of trials to criterion, $F(2, 8) = 2.04$, *ns*, and by the average percentage of correct across the first seven acquisition sessions, $F(2, 8) = 2.76$, *ns*, or their performance across the various levels of memory delay and interference, $F(2, 8) = 0.31$, *ns*, all performance scores for these groups were combined for subsequent statistical analysis and comparison to the three groups of subjects with circumscribed lesions (OFs, PRERs, and FXs). The 11 sham-operated control subjects will hereafter be collectively referred to as group SH. One of the OF rats died after acquiring the task but before all subsequent training was completed. This animal's data were excluded from the present analyses.

The acquisition data for the four groups appear in Figures 6A and 6B. A single-factor ANOVA on the number of trials to reach a criterion of 18 correct responses in 20 consecutive trials (Figure 6A) revealed a significant difference between the groups, $F(3, 35) = 13.6$, $p < .001$. Subsequent post hoc comparisons revealed that the OF group was significantly impaired in relation to each of the other groups; no other paired comparisons reached statistical significance. The percentage of correct responses across the first seven acquisition sessions appears in Figure 6B. Data from only the first seven sessions are plotted and analyzed statistically because subsequent data for several subjects were not available; these animals had met the performance criterion of 85% correct for two consecutive sessions and had moved on to sessions with longer delays and increased interference. A two-way ANOVA with repeated measures revealed a significant difference between experimental groups, $F(3, 25) = 8.07$, $p < .001$, and between sessions, $F(6, 150) = 35.3$, $p < .001$; the Group ×

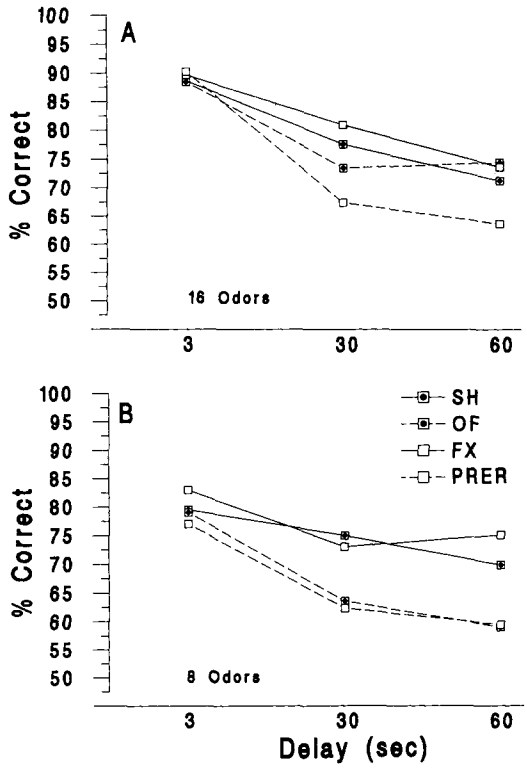

Figure 7. A: Average percentage of correct responses across varying memory delays when individual trial stimuli were chosen from a set of 16 odors. B: Same as in A, but when individual trial stimuli were chosen from a set of 8 odors. (SH = sham-operated group; OF = orital prefrontal cortex lesion group; FX = fornix lesion group; PRER = perirhinal and entorhinal cortices lesion group.)

Session interaction did not reach statistical significance, $F(18, 150) = 1.16$, *ns*. Post hoc comparisons for each session revealed that the OF group performed significantly more poorly than did all other groups in Sessions 2–7.

Percentage of correct performance across different memory delays and levels of interference appear in Figures 7A and 7B, respectively. A three-way ANOVA with repeated measures revealed a significant difference between experimental groups, $F(3, 24) = 3.45$, $p < .05$, and a significant difference in performance across both the various delays, $F(2, 48) = 104.3$, $p < .001$, and the various levels of interference, $F(1, 24) = 16.2$, $p < .001$. A significant Group × Delay interaction was also found, $F(6, 48) = 3.57$, $p < .005$; no other interactions reached statistical significance. An analysis of the simple main effects indicated that, when tested with 16 odors, the groups did not differ at the 3-s delay, $F(3, 24) = 0.1$, *ns*. By contrast, significant group effects were observed in the 16-odor, 30-s delay condition, $F(3, 24) = 3.8$, $p < .05$; post hoc comparisons revealed that the SH, OF, and FX rats performed similarly at all delays but were superior to PRER rats at the 30- and 60-s-delay conditions.

No group effect was observed in the 8-odor condition when the delay was 3 s, $F(3, 24) = 0.3$, *ns*, but the groups did differ when the delay was either 30 or 60 s, $F(3, 24) = 3.6$, $p < .05$, and $F(3, 24) = 4.9$, $p < .01$, respectively. As in the 16-odor condition, post hoc comparisons revealed that the performance of the SH and FX rats was statistically indistinguishable and was significantly better than that of the PRER rats at both the 30- and 60-s delays. Further pairwise comparisons indicated that the SH and FX rats also outperformed the OF rats when the delay was either 30 or 60 s. At this increased level of interference, the OF and PRER subjects did not differ at any delay.

Discussion

Orbital Prefrontal and Parahippocampal Cortical Areas Play Complementary Roles in Recognition Memory in Rats and Monkeys

In this second experiment, lesions of the orbital subdivision of the prefrontal cortex resulted in a disproportionate impairment in acquisition of the cDNM task; a deficit in retention across longer delays appeared only under conditions of increased interitem interference. By contrast, combined lesions of the entorhinal and perirhinal cortices did not affect cDNM acquisition but resulted in a rapid forgetting of specific odor stimuli that was characterized by a selective, delay-dependent deficit in retention. Finally, transection of the fornix did not result in impairment in either acquisition or retention in cDNM. Each of these findings corresponds quite closely to the patterns of performance in DNMS after lesions of similar brain areas in monkeys. When combined with the results of previous studies on primate and rodent spatial and visual memory, the present functional dissociation between the prefrontal and parahippocampal cortical areas in rule acquisition and memory maintenance, respectively, indicate common and complementary roles for these systems in memory processes across species and across tasks; the findings that support each of these conclusions are discussed in the following sections.

The orbitofrontal cortex is preferentially involved in learning the rules that govern odor-guided cDNM performance. Our findings on the effects of orbital prefrontal cortex lesions are consistent with the hypothesis that areas within the prefrontal cortex are critical to the initial acquisition of rules that govern performance. This interpretation is similar to that offered by Winocur and Moscovitch (1990), who found that lesions of the medial prefrontal cortex impaired rats' acquisition of the "general rules and some cognitive skills" (p. 549) that are critical to maze learning but did not impair memory for specific mazes once learned. The results of the present study extend these findings to the rodent orbital prefrontal cortex with regard to an odor-guided recognition memory task. Furthermore, the combined findings from both studies support the suggestion of Eichenbaum et al. (1983) and others (e.g., Kolb, 1990) that there exist functionally distinct areas within the rodent prefrontal cortex. Specifically, although the medial prefrontal cortex is involved preferentially in acquiring spatial rules, the orbital prefrontal cortex contributes disproportionately to learning the rules involved in olfactory learning and memory tasks. In many tasks, a failure to learn the rules that are necessary for successful performance is manifested in

increased perseverative errors; consistent with the view that each of these prefrontal areas is involved in learning task procedures are findings indicating that each of the modality-specific deficits is associated with increased perseverative errors in both rats and primates (Eichenbaum et al., 1983; Kowalska et al., in press). In our view, the interpretation that areas of the prefrontal cortex are disproportionately involved in learning the rules that govern performance is compatible with the suggestion that in monkeys the prefrontal cortex participates in working memory processes (Goldman-Rakic, 1990; Passingham, 1985). Indeed, this suggestion was based on the finding that monkeys with lesions of the prefrontal areas bordering the principal sulcus are severely impaired in acquiring spatial delayed response and delayed alternation tasks, even when short delays are used during training (Goldman & Rosvold, 1970; Goldman et al., 1971).

It is important to note that in both our study and that of Winocur and Moscovitch (1990) rats with prefrontal cortical damage could eventually acquire their respective tasks. This ultimate, albeit considerably retarded, acquisition of task rules could be due either to incomplete lesions of the respective prefrontal area or alternatively to the accommodation of this role by other brain systems.

The perirhinal and entorhinal cortices are critical to recognition memory. The present data indicate that although damage to the perirhinal and entorhinal cortices in rats has no effect on cDNM acquisition it selectively impairs recognition memory at long delays. These data are consistent with the effects of medial temporal lobe damage that includes part of the parahippocampal area in primates: DNMS acquisition is spared when short delays are used (0.5 s: Alvarez-Royo, Zola-Morgan, & Squire, 1991; 1.0 s: Overman, Ormsby, & Mishkin, 1990), but later performance declines progressively as the memory delay is extended. These findings help clarify the role of separate components within the hippocampal system in recognition memory and other types of hippocampal-dependent learning and memory. In the present study, lesions of the entorhinal and perirhinal areas, but not of the fornix, produced abnormally rapid forgetting in rats. This pattern of poor performance, which appears selectively at longer delays, is similar to the deficit after lesions of the homologous areas in primates, although the magnitude of effect in the present study is not as dramatic as that reported in monkeys (Gaffan & Murray, 1992; Murray, 1991; Zola-Morgan et al., 1989a). This difference can perhaps be attributed to the fact that in the present study the lesion spared the anterior-most part of the perirhinal cortex. A similar argument has been advanced by Zola-Morgan, Squire, Amaral, and Suzuki (1989; see also Murray, 1991) to explain the mild DNMS deficits that were observed after partial lesions of the perirhinal and entorhinal cortices in a study reported by Murray and Mishkin (1986). In addition, more dramatic delay-dependent deficits might have been observed in the present study had performance been assessed at longer delays. These accounts are not mutually exclusive.

Regardless of the explanation for differences in the magnitude of impairment after lesions of the parahippocampal area in rats and monkeys, in both species this damage results in more severe deficits in recognition memory than do lesions of other components of the hippocampal system. In the present study, lesions of the fornix had no effect on either acquisition or performance of cDNM across long delays. Lesions that are limited to the hippocampus also have little if any effect on performance by rats in DNMS tasks that use trial-unique objects or maze arms as cues (Aggleton et al., 1986; Mumby et al., 1992; Rothblat & Kromer, 1991). In monkeys, aspiration of the hippocampus that spares most of perirhinal and entorhinal cortices (Mishkin, 1978; Murray & Mishkin, 1984; Zola-Morgan et al., 1989b), stereotactic lesions of the hippocampus alone (Clower, Alvarez-Royo, Zola-Morgan, & Squire, 1991), or lesions of the fornix (Gaffan et al., 1984; Zola-Morgan et al., 1989b) results in only modest DNMS impairments. Thus, these data collectively indicate that parahippocampal areas play a decidedly prominent role in memory maintenance.

Dissociable Functions of the Parahippocampal Areas and the Hippocampus in Declarative Memory

The conclusion that parahippocampal areas might subserve memory maintenance cannot explain why selective lesions of other components of the hippocampal system (hippocampus or fornix, as well as the parahippocampal areas) typically result in severe deficits in both rats and monkeys on recognition memory tasks that involve spatial cues (Olton et al., 1979; Mahut, 1972; Murray et al., 1989) and on learning over a large range of other paradigms including conditional (e.g., Ross, Orr, Holland, & Berger, 1984; Saunders & Weiskrantz, 1989), contextual (e.g., Gaffan & Harrison, 1989; Hirsh, 1974), and concurrent (Moss, Mahut, & Zola-Morgan, 1981; Wible & Olton, 1988) discriminations, spatial working memory (e.g., Olton & Feustle, 1981; Olton, Walker, & Gage, 1978; Olton, Walker, & Wolf, 1982), place learning (Eichenbaum et al., 1990; Gaffan & Harrison, 1984, 1988; O'Keefe, Nadel, Keightly, & Kill, 1975), and some other examples of discrimination learning (e.g., Eichenbaum et al., 1988). What distinguishes this set of learning paradigms from recognition tasks that involve memory for specific items is that each of the former paradigms requires the processing and permanent storage of critical relations among perceptually independent items, whereas nonspatial cDNM and DNMS tasks require only the capacity for temporary storage of representations for individual percepts.

One possible explanation for this pattern of findings is based on the hypothesis that there are two kinds of functional distinctions between the hippocampal-dependent and hippocampal-independent memory systems (Eichenbaum et al., 1992). According to this account, the hippocampal memory system differs from hippocampal-independent systems in both the nature of memory representation that it supports and the operating characteristics that determine the strength and persistence of memories for single experiences. As an extension of this account, we suggest that, although the parahippocampal areas are sufficient to support a strong and persistent memory trace for single experiences, the entire hippocampal system and its subcortical and cortical pathways are required for the relational processing on which permanent declarative memory representations rely. This view accounts for the observations that significant disruption of any one of the

components within the hippocampal circuit is sufficient to compromise the integrative processing that is demanded by conditional, contextual, and place learning and for working memory in some circumstances and that lesions sparing the parahippocampal areas leave intact a capacity for creation and intermediate-term maintenance of memory traces sufficient to support simple recognition memory performance. Also consistent with our account are recent data indicating that the activity of neurons in area CA1 during performance of the cDNM task described in this article reflects not the temporary storage of individual items across a memory delay but rather the outcome of comparisons among discrete stimuli that constitute the match–nonmatch decision (Otto & Eichenbaum, 1992a). Conversely, the firing patterns of cells in both inferotemporal (Baylis & Rolls, 1987; Fuster & Jervey, 1981; Miller, Li, & Desimone, 1991; Miyashita & Chang, 1988) and parahippocampal (Brown, Wilson, & Riches, 1987) cortical areas likely reflect short-term information storage. Thus, converging neuropsychological and electrophysiological data suggest that the hippocampus and associated parahippocampal areas may play distinguishable, and presumably interactive, roles in functional memory storage. Although many details remain to be resolved with regard to the circumstances requiring relational processing and those requiring only persistence of individual representations, our hypothesis accounts for an accumulating set of data that distinguish the functions of the parahippocampal cortex from those of other areas within the hippocampal system and is consistent with the recent suggestion that the parahippocampal areas may be more involved in recognition memory processes than is the hippocampus itself (Brown et al., 1987).

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1993 APA Convention "Call for Programs"

The "Call for Programs" for the 1993 APA annual convention appears in the October issue of the APA Monitor. The 1993 convention will be held in Toronto, Ontario, Canada, from August 20 through August 24. Deadline for submission of program and presentation proposals is December 10, 1992. Additional copies of the "Call" are available from the APA Convention Office, effective in October. As a reminder, agreement to participate in the APA convention is now presumed to convey permission for the presentation to be audiotaped if selected for taping. Any speaker or participant who does not wish his or her presentation to be audiotaped must notify the person submitting the program either at the time the invitation is extended or prior to the December 10 deadline for proposal submission.