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Medial Prefrontal Lesions in the Rat and Spatial Navigation: Evidence for Impaired Planning

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Rats with medial prefrontal cortical lesions were tested in a modified water maze navigation task. In Stage 1, the rats were trained to locate a hidden platform from a single start location. They were then subjected to a series of trials during which a second start position was used (Stage 2). In Stage 3, the rats had to navigate to a new goal location from the 2 experienced start positions. Stage 4 required the rats to navigate to the same goal as in Stage 3, starting from 4 distinct positions. Finally, a single probe trial with no platform was conducted. Rats with prefrontal lesions were impaired only during Stage 4. This deficit was specific to the 2 start positions newly introduced during this stage, suggesting a dysfunction of planning processes. This impairment might result from a working memory deficit, precluding the animal from forming an adequate representation of the whole course of movements required to reach the platform.

In human and nonhuman primates, lesions of the dorsolateral prefrontal cortex induce a complex pattern of deficits. These deficits can be adequately interpreted as resulting from a working memory impairment (Diamond & Doar, 1989; Fuster, 1989; Goldman-Rakic, 1990), that is, from a dysfunction in the short-term memory systems required for the manipulation of information (Baddeley, 1992; Squire, 1987). However, equally often is reported an inability of human patients or nonhuman primates with frontal lesions to shift behavior adequately when necessary, thus providing evidence for the hypothesis that the prefrontal cortex is involved in behavioral flexibility (Diamond & Goldman-Rakic, 1989; Milner, Petrides, & Smith, 1985).

In the rat (*Rattus norvegicus*), damage to the medial prefrontal cortex, an area homologous to the dorsolateral prefrontal cortex of primates (Groenewegen, 1988; Kolb, 1990; Krettek & Price, 1977; Uylings & van Eden, 1990), has been shown to result in inefficient navigational strategies in the Morris water maze task (Kolb, Sutherland, & Whishaw, 1983; Sutherland, Kolb, & Whishaw, 1982). This deficit complements those observed in spatial working memory tasks, such as the radial arm maze (Becker, Walker, & Olton, 1980) and spatial alternation (Granon, Vidal, Thinus-Blanc, Changeux, & Poucet, 1994; van Haaren, de Bruin, Heinsbroek, & van de Poll, 1985), and suggests a global impairment of rats with medial frontal lesions in spatial tasks (see Kolb, 1984, 1990, for reviews).

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Although the deficits induced by frontal lesions in rats in some of the spatial tasks mentioned above (e.g., radial arm maze and spatial alternation) can be easily interpreted as a result of a working memory impairment, it is more difficult to see how an impaired working memory would impede normal navigation. In fact, spatial navigation seems to involve only a minimal working memory component. Rather, it emphasizes two distinct aspects of behavior crucial for optimal performance. First, the animal must know the relative positions of the goal platform and its current start location with respect to the distal environment. Second, it must plan appropriate trajectories through the pool in order to reach the goal platform in the most efficient manner. Such planning processes must be in order so that the rat flexibly adapts to changing start positions across trials. Our past research has shown that rats with frontal lesions can use the spatial relationships of the environment to locate a goal location in simple mazes (Poucet, 1990; Poucet & Herrmann, 1990). It is thus possible to hypothesize that an appreciable fraction of their navigational impairment can be accounted for by difficulties in planning trajectories, rather than in processing spatial information.

The purpose of the present study was precisely to examine the latter hypothesis. More specifically, we asked how frontal rats adapt their trajectories when they confront a change either in the number and location of the start positions or in the location of the goal. Thus, the rats were first trained to locate a hidden platform in a circular water tank, starting from a constant start position. Once the rats had learned this relatively simple problem, they were then required to start from two opposite locations, including the one that had been used during the first phase. The third phase consisted of moving the hidden platform to the opposite quadrant in the water tank and requiring the rats to start from the same two locations as during the second phase. This phase emphasized the acquisition of new spatial information under constant conditions of complexity and served to examine the spatial bias for the former goal location. The last phase involved the same location for the goal platform as during the third phase but had four

distinct start positions (i.e., the two that had been previously used and two new start locations). At the end of testing, a single probe trial with the goal platform removed was conducted so we could examine the spatial bias of rats during searching behavior.

This experimental design allowed for predictions that were distinct according to the nature of the process impaired by frontal damage. For example, if frontal damage results in a specific spatial learning deficit, then performance of all stages, except Stage 1 (which minimized spatial processing), should be impaired. However, if frontal damage results in an inability to plan appropriate trajectories, our assumption was that the navigational impairment would become more evident as the task complexity increases. Therefore, frontal animals would display the greatest impairment during the last testing phase, when they have to flexibly adapt to multiple start positions in order to plan appropriate trajectories through the pool. Because our purpose was to focus on the navigational strategies, the measures of performance that were used relied on fine analyses of trajectories in addition to the gross measure provided by latencies to find the platform. Such analyses included measurements of the distance swum by the rats to reach the goal platform, of the spatial distribution of the rats' search relative to the goal (Gallagher, Burwell, & Burchinal, 1993), and of the dispersion of search during each trial.

Method

Subjects

Sixteen male Long-Evans rats (Janvier, St-Berthevin, France) approximately 120 days of age were used. Rats were housed in groups of 2 animals per cage in a temperature-controlled colony (20 ± 2 °C) on a natural light–dark cycle. They had food and water ad libitum at all times during testing. On receipt, the rats were handled daily for a period of 2 weeks before surgery.

Surgery

Rats were randomly assigned either to a group with lesions aimed at the prelimbic area (PL in Paxinos & Watson's [1986] terminology; Cg3 in Zilles's [1985] terminology) of the medial frontal cortex (hereinafter referred to as MFC, $n = 9$) or to a sham-operated group (CNT, $n = 7$). Rats were deeply anesthetized with an injection of pentobarbital (55 mg/kg ip) and placed in a Kopf stereotaxic apparatus (Roucaire Sud, S.A., Marseille, France). After a midline incision of the scalp, the skin and the muscles were retracted, and holes were drilled in the skull at appropriate locations. Radio frequency lesions of the prelimbic area were produced at the following stereotaxic coordinates relative to bregma (Paxinos & Watson, 1986): A/P = +3.0, +4.0, L = ±0.5, D/V = −3.5 from dura. Once the electrode was lowered at each of the placements, it was heated to 60 °C for 30 s using a Radionics RFG-4 radio frequency lesion generator (Roucaire Sud, S.A., Marseille, France). Control rats were anesthetized and had their scalp cut and sutured. Because all rats participated in another experiment, the time interval between surgery and behavioral testing for the present experiment was 1 month.

Apparatus

The apparatus was a 140-cm diameter circular pool with walls 60 cm high. The pool was filled with water (19 °C). The water was made opaque by the addition of powdered chalk that was stirred before each testing session and was changed every 5 days. Inside the pool was a small (11 cm × 11 cm) white platform (30 cm high) positioned such that its top surface was 1 cm beneath the water. The platform was initially located in the center of the arbitrarily defined north-east quadrant of the maze (see Figure 1). The pool was placed in a large (25 m^2) experimental room providing numerous extra-maze cues. No attempt was made to neutralize these cues. In all stages of this experiment, the position of the pool remained constant in the room. A video camera fixed to the ceiling of the room above the pool was connected to a video recorder and a monitor.

Behavioral Procedures

Each day, the rats were subjected to a single testing session, which consisted of four trials. On all trials, the rats were placed by hand into the water facing the wall of the pool. The swim path of each rat was monitored and recorded by means of the video camera mounted above the pool. Once a rat had reached the goal platform, it was allowed to remain there for 10 s before being returned to its home cage. If a rat did not locate the goal within 120 s, it was placed on the platform by the experimenter for 30 s. Because the experiment was run with squads of 4 rats, the intertrial interval for a given rat was approximately 5 min.

Figure 1 is a diagrammatic representation of the schedule that was used. Stage 1 consisted of five consecutive sessions during which the rats were trained to reach the platform location from a single start position (SP1) on all trials.

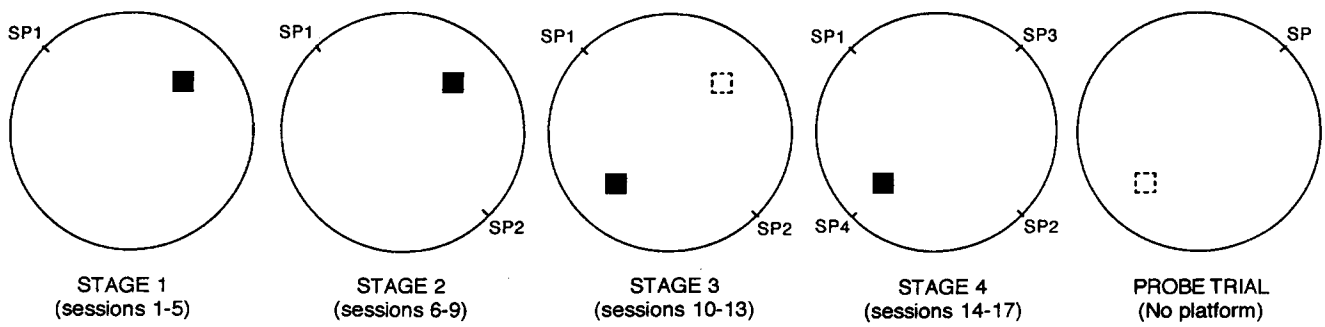

Figure 1. A diagrammatic representation of the experimental schedule. The goal platform location is indicated by a solid black square. The former location of the platform is shown as a white square delineated by hatched lines. Each session consisted of four trials. SP = start position.

During Stage 2 (four sessions), rats were required to reach the same platform location from a new start position, SP2, as well as from the previously experienced start position, SP1. Because SP2 was diametrically opposite to SP1 relative to the platform location, the distances between either start position and the platform location were equal (78 cm). On each session of Stage 2, the order of start positions was balanced such that the first, as well as the last, pair of trials involved both start positions, thus allowing assessment of the within-session time course of performance scores. For all rats, Session 1 of Stage 2 began with a trial using SP1 as the start position followed by a trial from SP2.

During Stage 3 (four sessions), the platform was relocated in the opposite (south-west) quadrant. The rats were tested with the same two start positions as during Stage 2. The same requirements for the within-session ordering of start positions were adopted.

Stage 4 (four sessions) involved the same platform location as Stage 3. However, four distinct start positions were used. They were the two that were used during Stages 2 and 3 (SP1 and SP2) plus two new start positions (SP3 and SP4). The mean distance from SP3 (108 cm) and SP4 to the platform location (31 cm) was approximately equal to the distance from SP1 and SP2, thereby allowing for a comparison of trials using the "old" start positions, SP1 and SP2, with trials using the "new" start positions, SP3 and SP4. On each session of Stage 4, the within-session order of start positions was balanced such that the first and last pair of trials each involved a new start position as well as an old one, thus allowing assessment of the within-session time course of performance scores. For all rats, Session 1 of Stage 4 began with a trial using the old start position SP1 followed by a trial from the new start position SP3. At the end of Stage 4, a single 120-s probe trial with the goal platform removed from the pool was conducted in order to examine the spatial bias of each rat's search.

Histology

At the completion of the experiment, all rats were given a lethal dose of pentobarbital. Rats with frontal lesions were transcardially perfused with 10% formalin, and their brains were removed and stored in 4% formalin 1 week before sectioning. Following fixation, the brains were cut into 40 μm coronal sections and stained with cresyl violet for visual inspection of lesion location and extent.

Behavioral and Statistical Analyses

The paths of all trials were filmed. After each session, the videotapes were read so that the trajectories were transformed into ASCII files with an image analyzer (Image PC, Grenoble, France) connected to the video recorder. Each file consisted of a series of pairs of integers (from 0 to 255), which represented the X–Y position coordinates of the rat while it was swimming. Sampling was done at 12.5 samples per second (i.e., each 80 ms). The files were then stored in a computer for off-line analysis. Programs were written to extract the raw data for each trial and calculate the *latency* (i.e., the time required to find the platform) and *path length* (i.e., the distance covered by the rat until it found the platform).

In addition to these two traditional measures of navigation performance, the cumulative distance to the goal was calculated on each trial (see Gallagher et al., 1993, for details). Briefly, the distance between the current position of the rat and the goal position was calculated for each even sample (separated from each other by 160 ms). Adding these distances provides a measure of the *cumulative search error*, which reflects deviations from an optimal path. To take into account the bias introduced by differences in distance to the goal from the various start positions at the periphery of the pool, however, a correction factor was adopted. It consisted of removing from the calculation of the total cumulative distance the portion of the path that, given the swimming speed of a given rat on a given trial, corresponded to the shortest path to the goal from the current start position (Gallagher et al., 1993).

The last measure (*search error dispersion*) was intended to reflect the dispersion of searching behavior independently from the distance swum by the rat. To this aim, the standard deviation δ of the cumulative search error was calculated for each trial according to the formula

$$\delta = \left[\sum_i d_i^2/(2n)\right]^{1/2} \quad \text{(Benhamou, 1989),}$$

where d_i is the distance (in centimeters) of the rat to the goal platform on each even sample, and n is the total number of samples used for the calculation (i.e., total number of even samples). The same correction factor as for the calculation of the cumulative search error was applied.

The data were analyzed using repeated measures analyses of variance (VAR3 program; Rouanet & Lépine, 1970). In addition to the effects of the main factors and their interactions, this program allows for planned contrasts and detailed analyses of the significant effects. One type of analysis was done with the data of each measure pooled over blocks of four trials within each session of each stage (Lesion and Session were the main factors). Another type of analysis was made to compare spatial performance from old and new start positions (Stages 2 and 4): The data were pooled according to the type of start position (old vs. new) for each session, and the analysis was conducted on the pooled data (main factors: Lesion, Session, and Start).

Results

Histology

The extent of maximal and minimal lesions in the medial frontal cortex is depicted in Figure 2. Typically, damage included the prelimbic area (Cg3 in Zilles's [1985] terminology) and a portion of the dorsal anterior cingulate cortex (Cg1). In no case was damage to the medial precentral cortex or to the medial-ventral orbital cortex observed.

Behavior

Stages 1 and 2. Both CNT and MFC rats quickly learned to reach the platform in a relatively efficient, though not optimal, manner when they were started from the constant location SP1 (Stage 1). The analysis of variance revealed no effect of lesion over successive sessions. The results of Session 5 (last session of Stage 1) are shown in Figure 3. The analysis of variance that was conducted on the data of this last session for each measure (i.e., latency, distance, cumulative search error, and search error dispersion) failed to reveal any significant effect of lesion (all Fs < 1), showing that both groups had reached comparable levels of spatial performance.

Starting the rats from a new position in the pool (Stage 2) did not affect spatial navigation performance of either CNT or MFC rats. Figure 3 shows that both groups tended to improve on all measures relative to their scores at the end of Stage 1. The analysis of variance that was conducted on these data failed to reveal any effect of Lesion, all Fs(1–14) < 1.43, *ns*, Session, all Fs(3–42) < 2.04, *ns*, and Start, all Fs(1–14) < 3.46, *ns*. None of the interactions was significant: Lesion × Session,

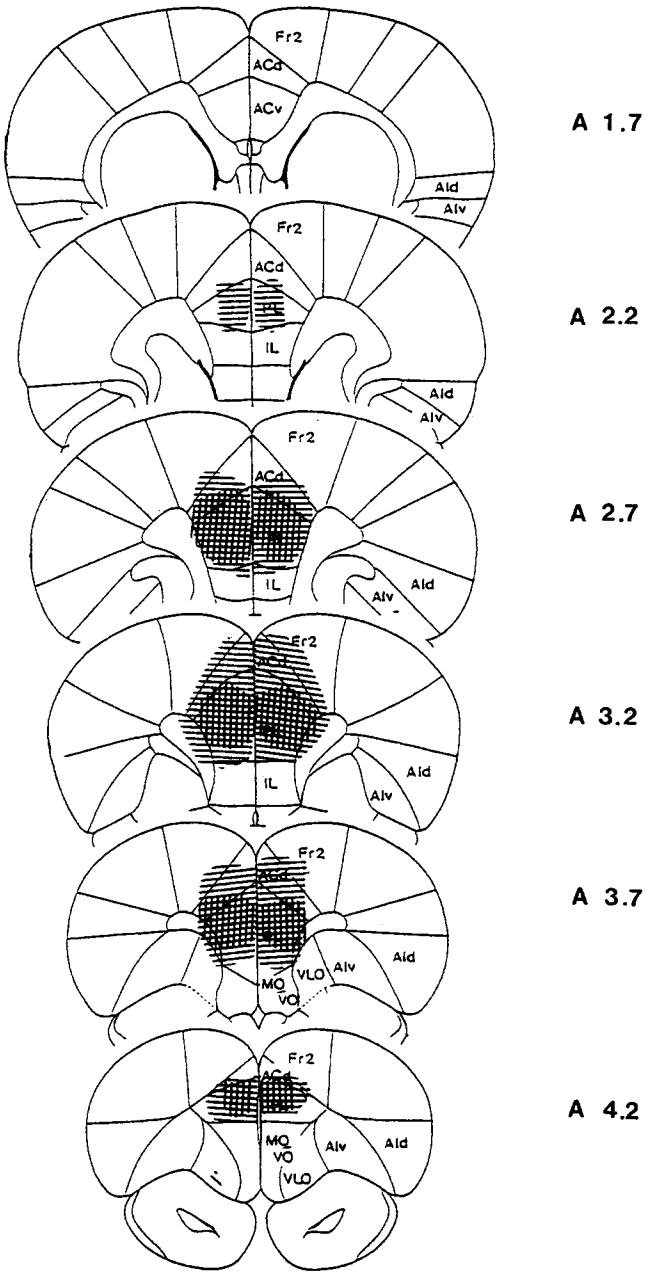

Figure 2. Location and extent of medial prefrontal lesions. From *The Rat Brain in Stereotaxic Coordinates* (Figures 5–12) by G. Paxinos and C. Watson, 1986, San Diego, CA: Academic Press. Copyright 1982 by Academic Press. Adapted with permission. Fr2 = frontal area 2; ACd = dorsal anterior cingulate area; ACv = ventral anterior cingulate area; PL = prelimbic area; IL = infralimbic area; AId = dorsal agranular insular area; AIv = ventral agranular insular area; MO = medial orbital; VO = ventral orbital; VLO = ventrolateral orbital.

all $Fs(3–42) < 1.31, ns$; Lesion × Start, all $Fs(1–14) < 3.27, ns$; Session × Start, all $Fs(3–42) < 1.71, ns$; Lesion × Session × Start interaction, all $Fs < 1$. More detailed analyses of the performance on Session 6 (first session of Stage 2) revealed that both CNT and MFC rats had no difficulty when transferred from the single-start condition of Stage 1 to the two-start condition of Stage 2, as shown by similar performance scores on each measure. None of the measures of spatial navigation was found to be significantly different in CNT and MFC rats, even when only the new start position SP2 was considered, all $Fs(1–14) < 1, ns$.

Stage 3. As shown by the increase in latencies, path lengths, cumulative search error, and search error dispersion, changing the platform location greatly altered the spatial navigation performance of both CNT and MFC rats. However, these alterations were of comparable extent in the two groups (Figure 4). Furthermore, the two groups rapidly learned the new platform location, as shown by the improvement of their scores on all measures. The analysis of variance conducted on the data of Stage 3 revealed a significant main effect of Session for all measures, all $Fs(3–42) > 7.35$, $p < .01$, but no significant effect of either Lesion, all $Fs(1–14) < 2.79$, *ns*, or Lesion × Session (all $Fs < 1, ns$).

To determine whether CNT and MFC rats differed in searching behavior with respect to the former platform location (used during Stages 1 and 2), the very first trial of Stage 3 was reanalyzed. Because latencies, distances, and cumulative search error could not be considered as valid indexes of search behavior, as all these measures were affected by the ease with which the rats found the new platform location, only the search error dispersion score (which does not depend on the distance traveled) was used. A comparison of the scores in search error dispersion in CNT and MFC rats yielded similar values of 22.6 and 24.1, respectively, $t(14) = 0.8$, *ns* (two-tailed), therefore suggesting that the two groups had comparable tendencies to concentrate their search around the former goal platform location.

Stage 4. Starting the rats from four start positions instead of two differentially affected the navigation performance of CNT and MFC rats. Figures 5 and 6 show, for each measure, the scores after they were pooled according to the type of start position (i.e., old vs. new). Although it is clear from these figures that both groups continued to display correct navigation when old start positions were used, the navigation performance of MFC rats was disrupted when they were placed at new start positions. This disruption was still visible on Session 17 (last session of Stage 4).

Although none of the analyses of variance that were conducted on the four measures of navigation performance revealed a significant main effect of Lesion, all $Fs(1–14) < 3.42$, *ns*, all yielded a significant Lesion × Start interaction. The analysis of latencies yielded significant effects of Session, $F(3–42) = 4.01, p < .02$, Start, $F(1–14) = 4.76, p < .05$, and Lesion × Start, $F(1–14) = 9.63$, $p < .01$. The analysis of distances traveled revealed significant effects of Session, $F(3–42) = 3.76, p < .02$, and Lesion × Start, $F(1–14) = 6.61, p < .025$, but no effect of Start, $F(1–14) = 1.66$, *ns*. The analysis of cumulative search errors and search error dispersion scores yielded significant effects for Start, $F(1–14) = 9.08, p < .01$, and $F(1–14) = 8.39, p < .02$, respectively, and for the Lesion × Start interaction, $F(1–14) = 5.01, p < .05$, and $F(1–14) = 5.40$, $p < .05$, respectively. The effects of start position on the different measures of navigation performance were further

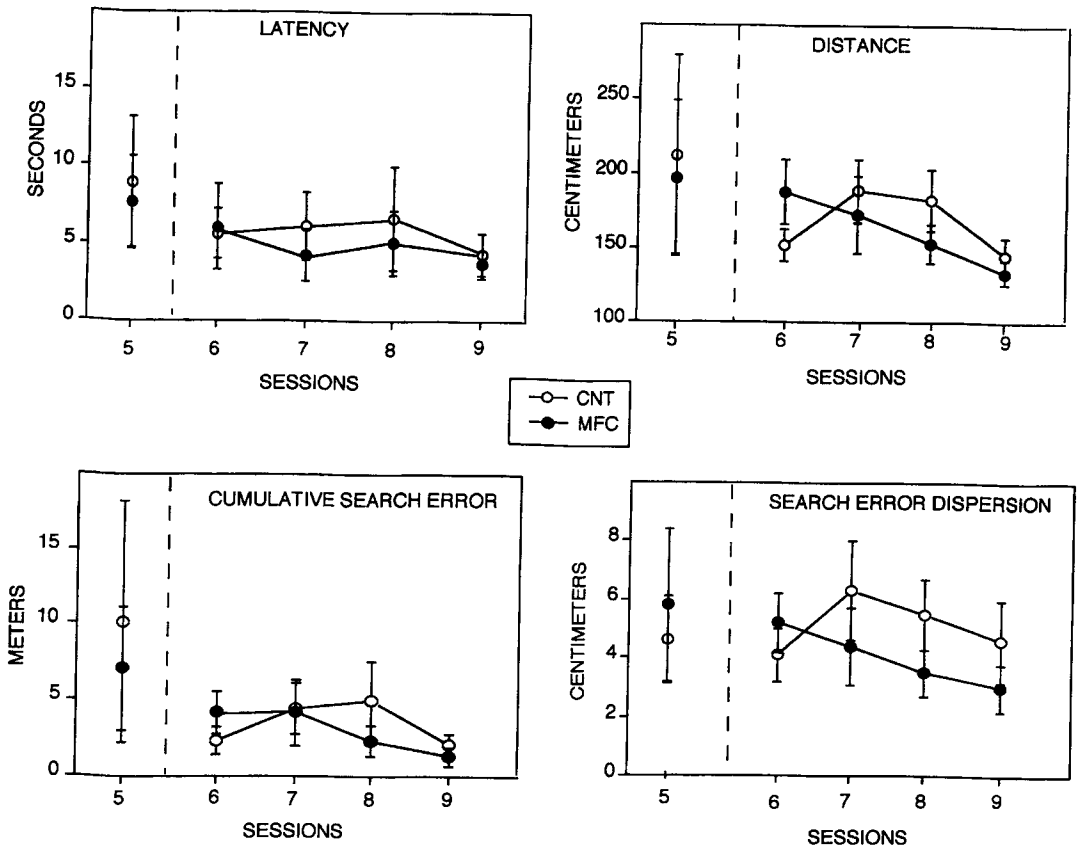

Figure 3. Navigation scores during Session 5 (last session of Stage 1) and Sessions 6–9 of Stage 2. Values are expressed as means plus or minus standard error. CNT = sham-operated group; MFC = medial frontal cortex.

confirmed by planned contrasts, which showed a significant effect of Lesion for new, all $Fs(1–14) > 4.81, p < .05$, but not for old start positions (all $Fs < 1$), and significant differences in navigation performance from new versus old start positions in MFC rats only, all $Fs(1–8) > 10.82, p < .02$. Accordingly, frontal lesions specifically altered navigation performance from the new start positions used in Stage 4 while leaving unchanged performance from the old start positions.

In addition, close inspection of the raw data and trajectories revealed that the trajectories of rats with frontal lesions were more disrupted when they were started from SP4 than when they were started from SP3. To provide further support for this observation, the scores on each measure were pooled over the four sessions of Stage 4 and plotted as a function of start position (Figure 7). The specific difficulty that rats encountered when started from SP4 was apparent only when the measures of cumulative search error and search error dispersion were considered. The analyses of variance revealed significant effects of Lesion, both $Fs(1–14) > 4.63, p < .05$, and Start, both $Fs(1–14) > 9.15, p < .01$, only for these two measures. In both cases, there was no significant Lesion × Start interaction, suggesting that both CNT and MFC rats experienced some difficulty when started from SP4, although to a different extent. The obvious explanation of the failure of latency and distance measures to yield significant start position effects lies in the fact that the distance from SP3 was greater than the distance from SP4 to the goal, therefore making the latency and distance measures from each start position incomparable.

Probe trial. The removal of the goal platform during the 120-s probe trial resulted in a tendency of both CNT and MFC rats to swim near its former location, as revealed by their similar cumulative search error scores (181 and 167, respectively), $F(1–14) = 2.82$, *ns*, and search error dispersion scores (19.0 and 18.7, respectively), $F(1–14) = 1.31$, *ns*. Representative swim paths of CNT and MFC rats are shown in Figure 8.

Discussion

A major result of the present study is that the prelimbic area of the medial frontal cortex appears to play a very limited role in the processing of spatial information required for successful navigation in the Morris water maze task. Rats with frontal lesions were clearly as capable as control rats of locating a hidden goal platform in the pool when starting from a constant position (Stage 1) and of flexibly adapting their trajectories when a new start position was used (Stage 2), an ability that suggests that they were using a real configural (i.e., spatial) solution rather than a single cue to guide their navigation behavior. Frontal rats were also found to be able to learn a new goal location (Stage 3) and to search for the platform in the vicinity of its former location (probe trial with no platform).

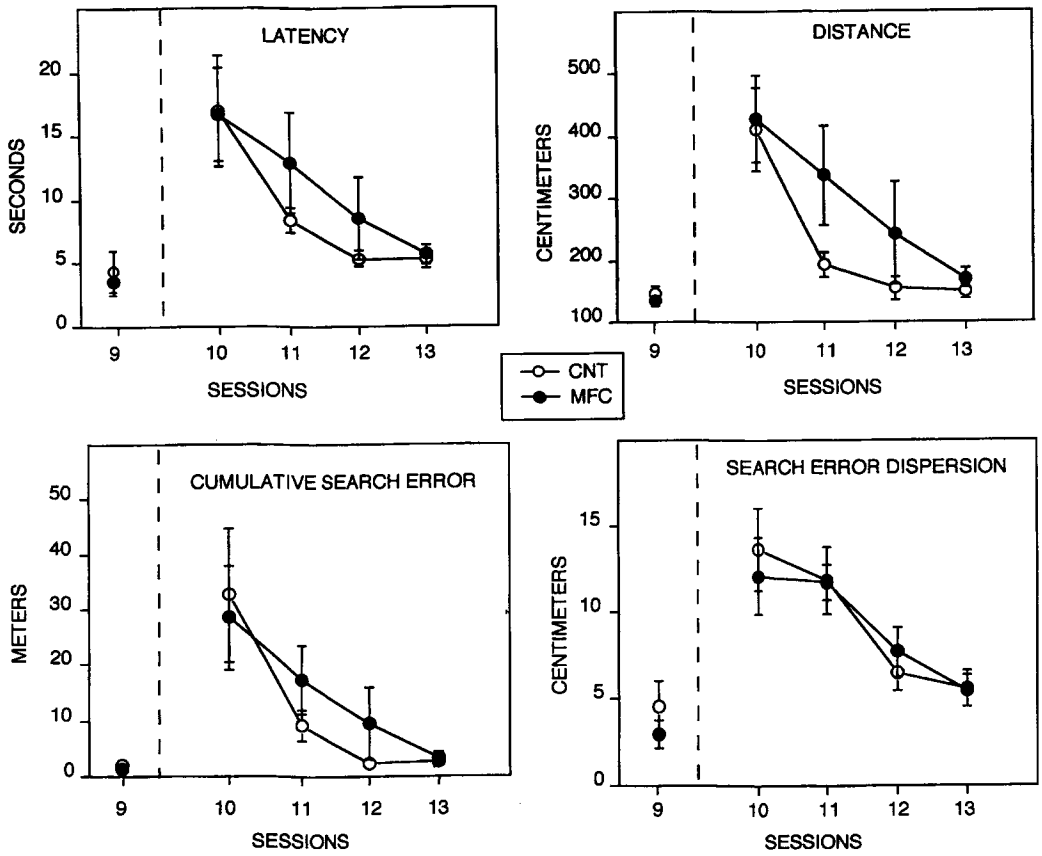

Figure 4. Navigation scores during Session 9 (last session of Stage 2) and Sessions 10–13 of Stage 3. Values are expressed as means plus or minus standard error. CNT = sham-operated group; MFC = medial frontal cortex.

Together these results provide little support to the notion that the frontal cortex would play a crucial function in spatial mapping, that is, in the acquisition of spatial knowledge about the environment (e.g., Kolb, Pittman, Sutherland, & Whishaw, 1982; Kolb et al., 1983). It is quite possible, however, that more extensive lesions of the frontal pole, for example, encroaching areas Fr1 and Fr2 (Kolb et al., 1982, 1983) or extending to more posterior parts of the cingulate cortex (Sutherland, Whishaw, & Kolb, 1988), would have resulted in a consistent spatial navigation impairment, resembling that produced by hippocampal lesions (Morris, Garrud, Rawlins, & O'Keefe, 1982; Morris, Hagan, & Rawlins, 1986) and therefore likely to be interpreted as a real spatial mapping impairment. It is important to realize that similar spatial impairments following frontal or hippocampal lesions would not be unexpected given the existence of direct functional connections from the temporal hippocampus to the prelimbic area of the frontal cortex (Jay, Glowinsky, & Thierry, 1989; Jay & Witter, 1991; Laroche, Jay, & Thierry, 1990; Swanson, 1981).

However, previous evidence has shown that, contrary to hippocampal damage, large lesions of the frontal cortex do not disrupt retention of spatial navigation in the water maze task (Sutherland, 1985) nor acquisition of spatially guided behavior in structured mazes such as the three-table task (Poucet, 1990). In addition, unlike rats with lesions to the hippocampal formation (Poucet, 1989; Save, Buhot, Foreman, & Thinus-Blanc, 1992; Save, Poucet, Foreman, & Buhot, 1992), rats with frontal lesions display almost normal behavioral reactions to spatial changes in their environment (Poucet, 1989), suggesting therefore an unaltered ability to build up spatial representations. Such evidence, when combined with the observation of near normal navigation in frontal rats during the first three phases of the present study and during the final probe trial, does not support the notion that these rats suffer from an overall impairment in processing spatial information. Rather, the data suggest that the navigational deficit resulting from frontal damage could be accounted for by the rats' inability to compute efficient trajectories when the task demands are increased, as is the case in the traditional procedure when four distinct start positions are imposed right from the start of navigation acquisition (Kolb et al., 1982, 1983).

Support for this conclusion is provided by the results of Stage 4 of the present study. During this phase, the rats were started from two positions that had never been used as start locations (although, presumably, they had been traversed during previous navigation trials) in addition to two experienced start positions. A marked disruption of navigation performance was observed in frontal rats when they were started from the new start positions but not when they were started from the experienced ones. Although such a disruption

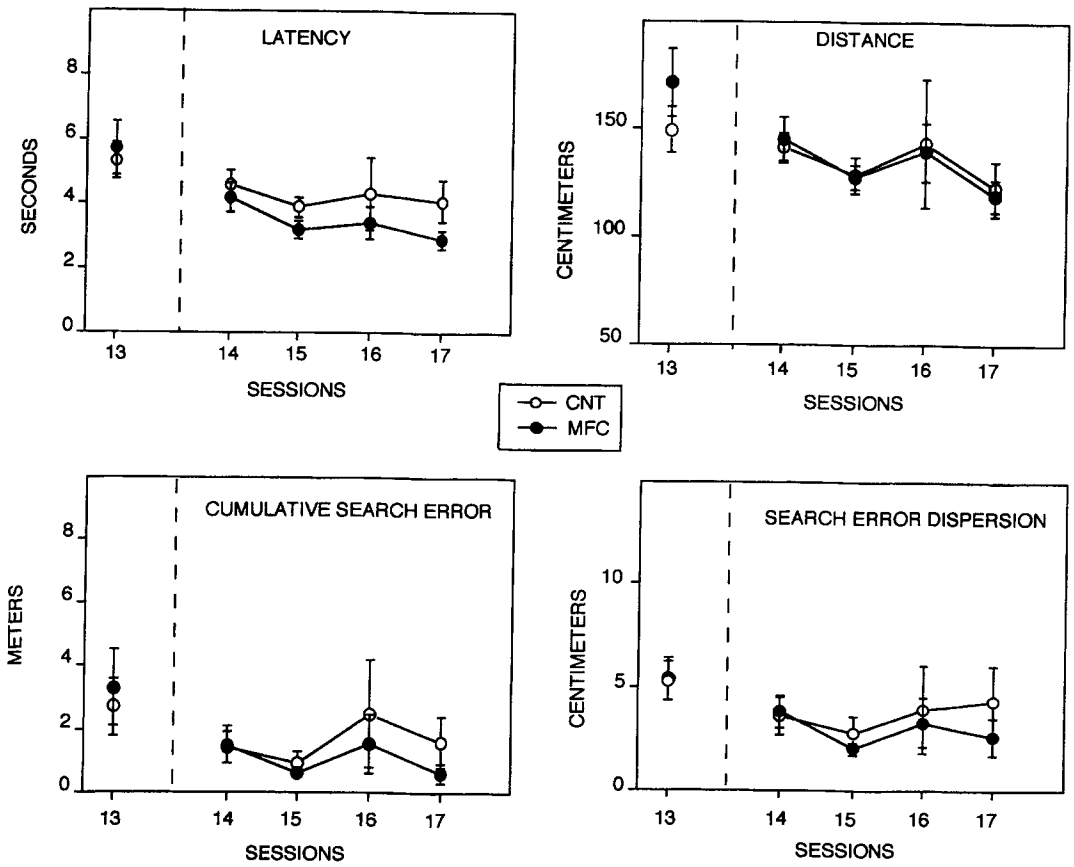

Figure 5. Navigation scores during Sessions 14–17 of Stage 4. Scores were obtained when the rats were started from "old" start positions SP1 and SP2 (Session 13 = last session of Stage 3). Values are expressed as means plus or minus standard error. CNT = sham-operated group; MFC = medial frontal cortex.

was observable from each of the two new start positions, it was even more pronounced when the rats were started from the start position closest to the goal, as evidenced by increased measures of cumulative search error and dispersion. The fact that the alteration of navigation performance was specific to the new start positions demonstrates that it did not result from an impaired knowledge of the goal platform position (as also confirmed by performance during the probe trial). Rather, the problem that frontal rats had to deal with when starting from the new start positions was to compute trajectories that sensibly differed both from those used during previous trials and from each other.

Several interpretations of this reduced ability to compute new trajectories can be proposed. It should be noted, however, that several of these interpretations are probably not mutually exclusive, as they emphasize the contribution of the frontal cortex to a set of processes that are very likely to be related to each other.

The simplest explanation states that frontal lesions would result in an impaired ability of the rat to change behavior when such changes are required by the circumstances. Behavioral rigidity has been previously shown to be associated with medial frontal lesions and is usually exemplified as a tendency to perseverate when a shift of the correct response is required (e.g., Becker & Olton, 1980; Divac, 1971; see Kolb, 1984, 1990, for reviews). In the present study, a nonsignificant trend for frontal rats to acquire the new spatial location at a lower rate when compared with normal rats was observed in Stage 3 (see latency, distance, and cumulative search error measures in Figure 4). In contrast, a significant impairment was found for all measures recorded from the new start positions of Stage 4. This pattern of results could be taken to indicate that the effects of "behavioral rigidity," hardly observable during Stage 3, were amplified in Stage 4 as a result of the greater complexity of the task. The behavioral rigidity explanation, however, would fail to account for the normal transfer of navigation observed during Stage 2, which involved a situation of similar complexity as compared with Stage 3.

Another recently proposed explanation that could account for the present results stresses that rats with frontal lesions would suffer from an impaired attentional ability, precluding them to pay attention to several stimuli simultaneously (Olton, Wenk, Church, & Meck, 1988). Although it is true that, in principle, such a process might be necessary for the emergence of a coherent representation of space (which presumably requires simultaneous processing of spatial information), it is difficult to see why it would be more crucial in Stage 4 as opposed to the others. However, because the four-start condi-

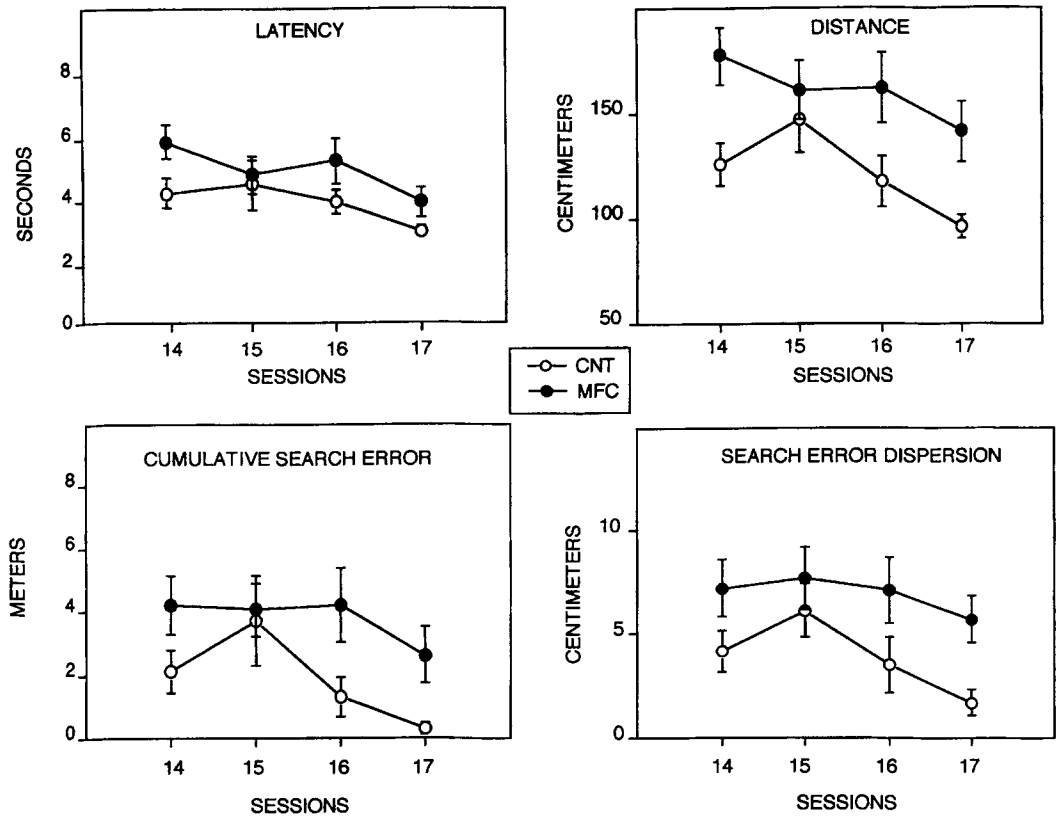

Figure 6. Navigation scores during Sessions 14–17 of Stage 4. Scores were obtained when the rats were started from "new" start positions SP3 and SP4. Values are expressed as means plus or minus standard error. CNT = sham-operated group; MFC = medial frontal cortex.

tion of Stage 4 indubitably required the rat switching its attentional focus about its current location more flexibly than the two-start condition of Stage 3, the possibility cannot be definitively ruled out that a rat with a frontal lesion had an increased difficulty in simultaneously paying attention to its current location and to the platform goal location.

The last interpretation is probably the less direct one. In spite of its indirectness, however, it receives support from previous work in primates. More specifically, it proposes that the frontal cortex of the rat is the locus of a working memory system that is necessary for planning complex sequences of behavior, such as those represented by the computation of spatial trajectories in the water navigation task. A very similar hypothesis has been put forward to account for the deficits displayed by nonhuman and human primates following frontal damage (e.g., Fuster, 1989; Goldman-Rakic, 1987; Milner et al., 1985). Basically, these researchers' hypothesis is that the flexible planning of any complex behavior requires that, at some point, pieces of information must be held in a temporary memory store so they can be assembled for the full sequence of actions to emerge. Once the planned sequence has been performed, the memory store is reset (hence its appellation of working memory) so that a new action can be planned. In this view, working memory thus permits the manipulation of stored information, and frontal lesions would impede such manipulation by altering working memory function (Goldman-Rakic, 1992). This hypothesis is well supported in primate studies (for reviews, see Fuster, 1989, and Goldman-Rakic, 1990).

Our contention here is that the overall pattern of results yielded by the present study as well as by previous research provides converging support for a similar explanation in rats. First, a growing amount of evidence shows that rats with frontal lesions are impaired at virtually any delay-type task in which an interval is imposed between some stimulus and the corresponding associated response. Such tasks include delayed alternation (Divac, Wikmark, & Gade, 1975; Larsen & Divac, 1978; van Haaren et al., 1985) and delayed matching and non-matching-to-sample (Brito & Brito, 1990; Brito, Thomas, David, & Gingold, 1982; Kolb, Buhrman, & McDonald, 1989; Herrmann, Poucet, & Ellen, 1985; Poucet, 1990; Poucet & Herrmann, 1990). The lesion evidence is complemented by a few electrophysiological studies that have reported increased neuronal firing of single units in the frontal cortex during the delay period of delay-type tasks (e.g., Batuev, Kursina, & Shutov, 1990; Sakurai & Sugimoto, 1986). Second, we have recently demonstrated that the frontal lesion-induced working memory impairment is larger in spatial matching than in non-matching-to-sample when the sample is a spatial location and the response is a spatial response (Granon et al., 1994), whereas others have shown a larger impairment in non-

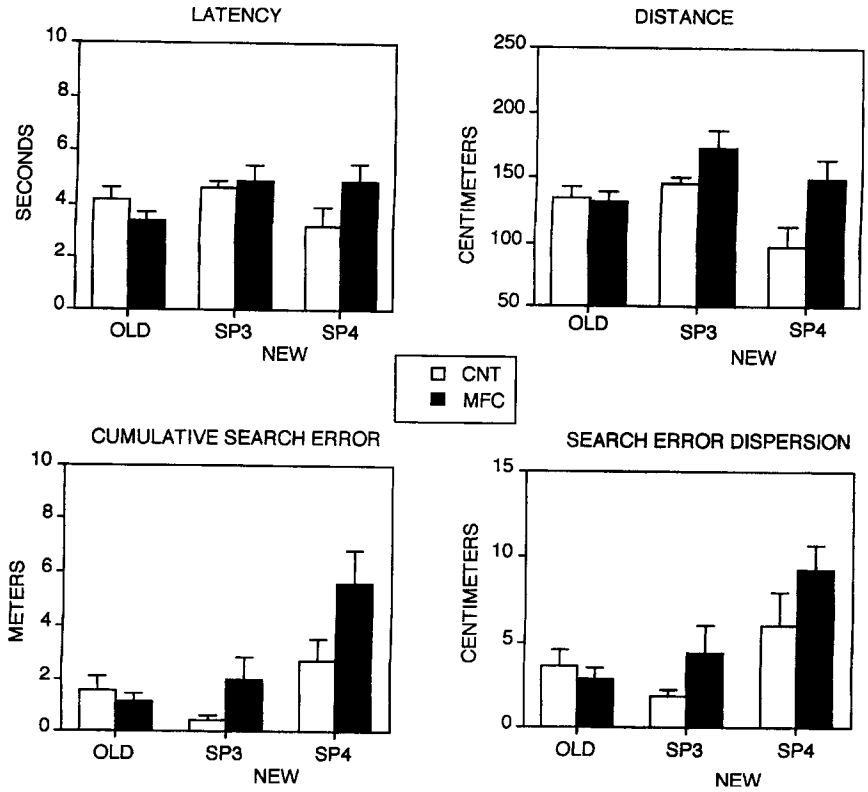

Figure 7. Navigation scores from each of the two "new" start positions, SP3 and SP4, during Stage 4. Values are expressed as means plus or minus standard error. For comparison, the mean navigation scores obtained from the "old" start positions are also shown. CNT = sham-operated group; MFC = medial frontal cortex.

matching-to-sample than in matching-to-sample when the sample is a light and the response is a lever press (Dunnett, 1990). These apparently incoherent results can be explained if one considers the relative difficulty of each task: Within each study, the working memory deficit is exacerbated in the task that is the most difficult for the rat to acquire (see Granon et al., 1994, for a discussion). This point merely suggests that the frontal cortical working memory system does not function separately from other processing systems, such as the attentional processes required for acquiring complex associations. Extending the latter notion to the present results, it can be admitted that computing trajectories from four start positions (Stage 4) rather than computing trajectories from two start positions (Stage 3) puts more demands on the processing systems that deal with planning trajectories, and in particular on a frontal cortex-dependent working memory system.

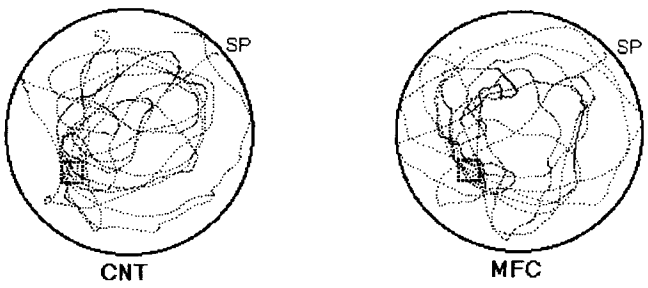

Figure 8. Representative swim paths of sham-operated group (CNT) and medial frontal cortex (MFC) rats during the probe trial with no platform. The former location of the platform is shown as a white square delineated by hatched lines. In these two examples, the cumulative search error scores yielded values of 179 m and 184 m for CNT and MFC, respectively; search error dispersions were 19.69 and 19.47, respectively. SP = start position.

Although it might seem speculative to put forward similar hypotheses about the role played by the prefrontal cortex in the rat and in primates, the fact that similarities can be found at both behavioral and anatomical levels supports a certain degree of functional homology. In both primates and rats, the frontal cortex appears to serve a special function that is most evident when the subject has to adapt quickly to changing conditions in complex situations. The additional observation that both rats and humans with frontal damage have problems in the temporal structuring of information and in the mediation of prospective codes, that is, in the use of past experiences to set up expectancies and anticipations (Kesner, 1989; Kesner & Holbrook, 1987; Petrides & Milner, 1982), provides further support for a special function of the frontal cortex in planning that could be shared across several species. A more precise assessment of the extent of this homology will have to wait for

additional studies of frontal cortical function. In particular, it seems to us that there is a need for more data about the behavioral correlates of neuronal firing in the rat frontal cortex during delay-type tasks as well as during complex problem solving such as that involved in spatial navigation.

References

Baddeley, A. (1992). Working memory. *Science, 255,* 556–559.

Batuev, A. S., Kursina, N. P., & Shutov, A. P. (1990). Unit activity of the medial wall of the frontal cortex during delayed performance in rats. *Behavioural Brain Research, 41,* 95–102.

Becker, J. T., & Olton, D. S. (1980). Object discrimination by rats: The role of frontal and hippocampal systems in retention and reversal. *Physiology and Behavior, 24,* 33–38.

Becker, J. T., Walker, J. A., & Olton, D. S. (1980). Neuroanatomical bases of spatial memory. *Brain Research, 200,* 307–321.

Benhamou, S. (1989). An olfactory orientation model for mammal's movements in their home range. *Journal of Theoretical Biology, 139,* 379–388.

Brito, G. N. O., & Brito, L. S. O. (1990). Septo-hippocampal system and the prelimbic sector of frontal cortex: A neuropsychological battery analysis in the rat. *Behavioural Brain Research, 36,* 127–146.

Brito, G. N. O., Thomas, G. J., Davis, B. J., & Gingold, S. I. (1982). Prelimbic cortex, mediodorsal thalamus, septum, and delayed alternation in rats. *Experimental Brain Research, 46,* 52–58.

Diamond, A., & Doar, B. (1989). The performance of human infants on a measure of frontal cortex function, the delayed response task. *Developmental Psychobiology, 22,* 271–294.

Diamond, A., & Goldman-Rakic, P. S. (1989). Comparison of human infants and rhesus monkeys on Piaget's AB task: Evidence for dependence on dorsolateral prefrontal cortex. *Experimental Brain Research, 74,* 24–40.

Divac, I. (1971). Frontal lobe system and spatial reversal in the rat. *Neuropsychologia, 9,* 171–183.

Divac, I., Wikmark, R. G. E., & Gade, A. (1975). Spontaneous alternation in rats with lesions in the frontal lobes: An extension of the frontal lobe syndrome. *Physiological Psychology, 3,* 39–42.

Dunnett, S. B. (1990). Role of prefrontal cortex and striatal output systems in short-term memory deficits associated with ageing, basal forebrain lesions, and cholinergic-rich grafts. *Canadian Journal of Psychology, 44,* 210–232.

Fuster, J. M. (1989). *The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe.* New York: Raven Press.

Gallagher, M., Burwell, R., & Burchinal, M. (1993). Severity of spatial learning impairment in aging: Development of a learning index for performance in the Morris water maze. *Behavioral Neuroscience, 107,* 618–626.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In F. Plum (Ed.), *Handbook of physiology, Section 1: Nervous system, Vol. 5: Higher functions of the brain* (pp. 373–417). Bethesda, MD: American Physiological Society.

Goldman-Rakic, P. S. (1990). Cortical localization of working memory. In J. L. McGaugh, N. M. Weinberger, & G. Lynch (Eds.), *Brain organization and memory: Cells, systems and circuits* (pp. 285–300). New York: Oxford University Press.

Goldman-Rakic, P. S. (1992, September). Working memory and the mind. *Scientific American,* 73–79.

Granon, S., Vidal, C., Thinus-Blanc, C., Changeux, J.-P., & Poucet, B. (1994). Working memory, response selection, and effortful processing in rats with medial prefrontal lesions. *Behavioral Neuroscience, 108,* 883–891.

Groenewegen, H. J. (1988). Organization of the efferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neuroscience, 24,* 379–431.

Herrmann, T., Poucet, B., & Ellen, P. (1985). Spatial problem-solving in the rat following medial frontal lesions. *Physiological Psychology, 13,* 21–25.

Jay, T. M., Glowinsky, J., & Thierry, A.-M. (1989). Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. *Brain Research, 505,* 337–340.

Jay, T. M., & Witter, M. P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phasoleus vulgaris*-Leucoagglutinin. *Journal of Comparative Neurology, 313,* 574–586.

Kesner, R. P. (1989). Retrospective and prospective coding of information: Role of the medial prefrontal cortex. *Experimental Brain Research, 74,* 163–167.

Kesner, R. P., & Holbrook, T. H. (1987). Dissociation of item and order memory in rats following medial prefrontal lesions. *Neuropsychologia, 25,* 653–664.

Kolb, B. (1984). Functions of the frontal cortex of the rat: A comparative review. *Brain Research Reviews, 8,* 65–98.

Kolb, B. (1990). Prefrontal cortex. In B. Kolb & R. C. Tees (Eds.), *The cerebral cortex of the rat* (pp. 437–458). Cambridge, MA: MIT Press.

Kolb, B., Buhrman, K., & McDonald, R. (1989). Dissociation of prefrontal, posterior parietal, and temporal cortical regions to spatial navigation and recognition memory in the rat. *Society for Neuroscience Abstracts, 15,* 607.

Kolb, B., Pittman, K., Sutherland, R. J., & Whishaw, I. Q. (1982). Dissociation of the contributions of the prefrontal cortex and dorsomedial thalamic nucleus to spatially guided behavior in the rat. *Behavioural Brain Research, 6,* 365–378.

Kolb, B., Sutherland, R. J., & Whishaw, I. Q. (1983). A comparison of the contributions of the frontal and parietal association cortex to spatial localization in rats. *Behavioral Neuroscience, 97,* 13–27.

Krettek, J. E., & Price, J. L. (1977). The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *Journal of Comparative Neurology, 17,* 157–192.

Laroche, S., Jay, T. M., & Thierry, A.-M. (1990). Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. *Neuroscience Letters, 114,* 184–190.

Larsen, J. K., & Divac, I. (1978). Selective ablations within the prefrontal cortex of the rat and performance of delayed alternation. *Physiological Psychology, 6,* 15–17.

Milner, B., Petrides, M., & Smith, M. L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology, 4,* 137–142.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297,* 681–683.

Morris, R. G. M., Hagan, J. J., & Rawlins, J. N. P. (1986). Allocentric spatial learning by hippocampectomised rats: A further test of the "spatial mapping" and "working memory" theories of hippocampal function. *Quarterly Journal of Experimental Psychology, 38B,* 365–395.

Olton, D. S., Wenk, G. L., Church, R. M., & Meck, W. H. (1988). Attention and the frontal cortex as examined by simultaneous temporal processing. *Neuropsychologia, 26,* 307–318.

Paxinos, G., & Watson, C. (1986). *The rat brain in stereotaxic coordinates* (2nd ed.). San Diego, CA: Academic Press.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia, 20,* 249–262.

Poucet, B. (1989). Object exploration, habituation and response to a spatial change in rats following septal or medial frontal cortical damage. *Behavioral Neuroscience, 103,* 1009–1016.

Poucet, B. (1990). A further characterization of the spatial problem-solving deficit induced by lesions of the medial frontal cortex in the rat. *Behavioural Brain Research, 41,* 229–237.

Poucet, B., & Herrmann, T. (1990). Septum and medial frontal cortex contribution to spatial problem-solving. *Behavioural Brain Research, 37,* 269–280.

Rouanet, H., & Lépine, D. (1970). Comparisons between treatments in a repeated measurement design: ANOVA and multivariate methods. *British Journal of Mathematical and Statistical Psychology, 23,* 146–163.

Sakurai, Y., & Sugimoto, S. (1986). Multiple unit activity of prefrontal cortex and dorsomedial thalamus during delayed go/no-go alternation in the rat. *Behavioural Brain Research, 20,* 295–301.

Save, E., Buhot, M.-C., Foreman, N., & Thinus-Blanc, C. (1992). Exploratory activity and response to a spatial change in rats with hippocampal or posterior parietal cortical lesions. *Behavioural Brain Research, 47,* 113–127.

Save, E., Poucet, B., Foreman, N., & Buhot, M.-C. (1992). Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or dorsal hippocampus. *Behavioral Neuroscience, 106,* 447–456.

Squire, L. R. (1987). *Memory and brain.* New York: Oxford University Press.

Sutherland, R. J. (1985). The navigating hippocampus: An individual medley of movement, space, and memory. In G. Buzsaki & C. H. Vanderwolf (Eds.), *Electrical activity of the archicortex* (pp. 255–279). Budapest, Hungary: Akademiai Kiado.

Sutherland, R. J., Kolb, B., & Whishaw, I. Q. (1982). Spatial mapping: Definitive disruption by hippocampal or medial frontal cortical damage in the rat. *Neuroscience Letters, 31,* 271–276.

Sutherland, R. J., Whishaw, I. Q., & Kolb, B. (1988). Contributions of cingulate cortex to two forms of spatial learning and memory. *Journal of Neuroscience, 8,* 1863–1872.

Swanson, L. W. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Research, 217,* 150–154.

Uylings, H. B. M., & van Eden, C. G. (1990). Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Progress in Brain Research, 85,* 31–62.

van Haaren, F., de Bruin, J. P. C., Heinsbroek, R. P. W., & van de Poll, N. E. (1985). Delayed spatial response alternation: Effects of delay-interval duration and lesions of the medial prefrontal cortex on response accuracy of male and female Wistar rats. *Behavioural Brain Research, 18,* 41–49.

Zilles, K. (1985). *The cortex of the rat: A stereotaxic atlas.* Berlin, Germany: Springer-Verlag.

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