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Impairments on Nonspatial Self-Ordered and Externally Ordered Working Memory Tasks after Lesions of the Mid-Dorsal Part of the Lateral Frontal Cortex in the Monkey

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Monkeys with lesions of the mid-dorsal part of the lateral frontal cortex, which extends above the sulcus principalis as far as the midline (MDL lesions), were shown to exhibit severe and long-lasting impairments on certain nonspatial working memory tasks: the self-ordered and externally ordered tasks (experiments 1, 2, 3, 5, 6, and 8). These tasks, which were modeled on similar ones previously used with patients, measure the capacity to monitor, within working memory, self-generated choices and the occurrence of externally ordered stimuli. Monkeys with lesions of the adjacent posterior dorsolateral frontal cortex, which surrounds the arcuate sulcus (PA lesions), performed as well as the normal control animals on these tasks. Experiments 4 and 5 showed that the critical variable accounting for the impairment on the self-ordered and externally ordered working memory tasks by monkeys with MDL lesions is the size of the set of stimuli that must be monitored. Furthermore, the MDL lesions did not affect basic recognition memory (experiment 6), or primacy and recency mnemonic effects [i.e., the capacity to discriminate between the initial (or final) items and other items in a list of stimuli (experiments 4 and 7), or the capacity to select from a set of stimuli on the basis of a learned fixed sequence (experiment 9)]. Thus, lesions of the mid-dorsal part of the lateral frontal cortex give rise to an impairment in working memory that depends on the size of the set of the stimuli that have to be monitored.

[Key words: frontal cortex, monkey, cortical lesion, working memory, lateral frontal cortex, prefrontal cortex]

Damage to the human lateral frontal cortex does not give rise to a general memory loss, but it severely impairs specific aspects of mnemonic performance (see Petrides, 1989, for a review). For instance, patients with lesions of the lateral frontal cortex perform well on many standard tests that are sensitive indicators of the memory disorder resulting from lesions of the mesial temporal lobe, but perform very poorly on the self-ordered working memory tasks that require monitoring of self-generated choices from a set of stimuli (Petrides and Milner, 1982). It has recently been demonstrated that, in monkeys, lesions confined to the mid-dorsal (MDL) part of the lateral frontal cortex, that is, the cortex that extends above the sulcus principalis as far as the midline, give rise to a striking impairment on a nonspatial self-ordered working memory task designed to be comparable in requirements to the self-ordered tasks originally used with patients (Petrides, 1988).

The demonstration of an impairment on a nonspatial mnemonic task after lesions of the mid-dorsal part of the lateral frontal cortex is of considerable interest because previous work had failed to demonstrate any impairments from lesions restricted to this part of the lateral frontal cortex. It has been known for a long time that lesions confined to the cortex lining the sulcus principalis result in severe impairments on certain *spatial* memory tasks, such as delayed alternation and delayed response (e.g., Mishkin, 1957; Gross and Weiskrantz, 1962; Butters and Pandya, 1969; Stamm, 1969; Goldman and Rosvold, 1970; Butters et al., 1971; Funahashi et al., 1993). Lesions, however, of the dorsal frontal cortex that spare the sulcus principalis do not cause an impairment in classical spatial delayed response (Goldman et al., 1971) and spatial delayed alternation tasks (Mishkin, 1957; Goldman and Rosvold, 1970), as well as in a spatial search task (Passingham, 1985a). In the 1970s, studies that utilized cooling of the cortex in the sulcus principalis found impaired performance on both a spatial delayed response and a nonspatial delayed matching-to-sample task (Fuster and Bauer, 1974; Bauer and Fuster, 1976), suggesting that this cortex may be involved in both spatial and nonspatial mnemonic function. Other work, however, showed that performance of the nonspatial delayed matching-to-sample task is not affected by lesions limited to the sulcus principalis, but that it is severely impaired by lesions of the ventrolateral frontal cortex that extends below it (Passingham, 1975; Mishkin and Manning, 1978). The results of the cooling experiments were therefore ascribed to spreading of the cooling effect to the ventrolateral frontal cortex that lies below the sulcus principalis. Furthermore, performance on *nonspatial* object alternation was also shown not to be markedly affected by lesions of the sulcus principalis (Mishkin and Manning, 1978) or by even more extensive lesions that included the cortex in the sulcus principalis and all of the dorsal cortex that lies above it (Mishkin et al., 1969). Studies of the activity of single cells in behaving monkeys also indicated the involvement of the cortex of the sulcus principalis in spatial mnemonic processing and that of the ventrolateral frontal cortex in nonspatial processing (see Goldman-Rakic, 1987; Wilson et al., 1993).

The above findings clearly established a role for the cortex that lies in the sulcus principalis in spatial working memory and

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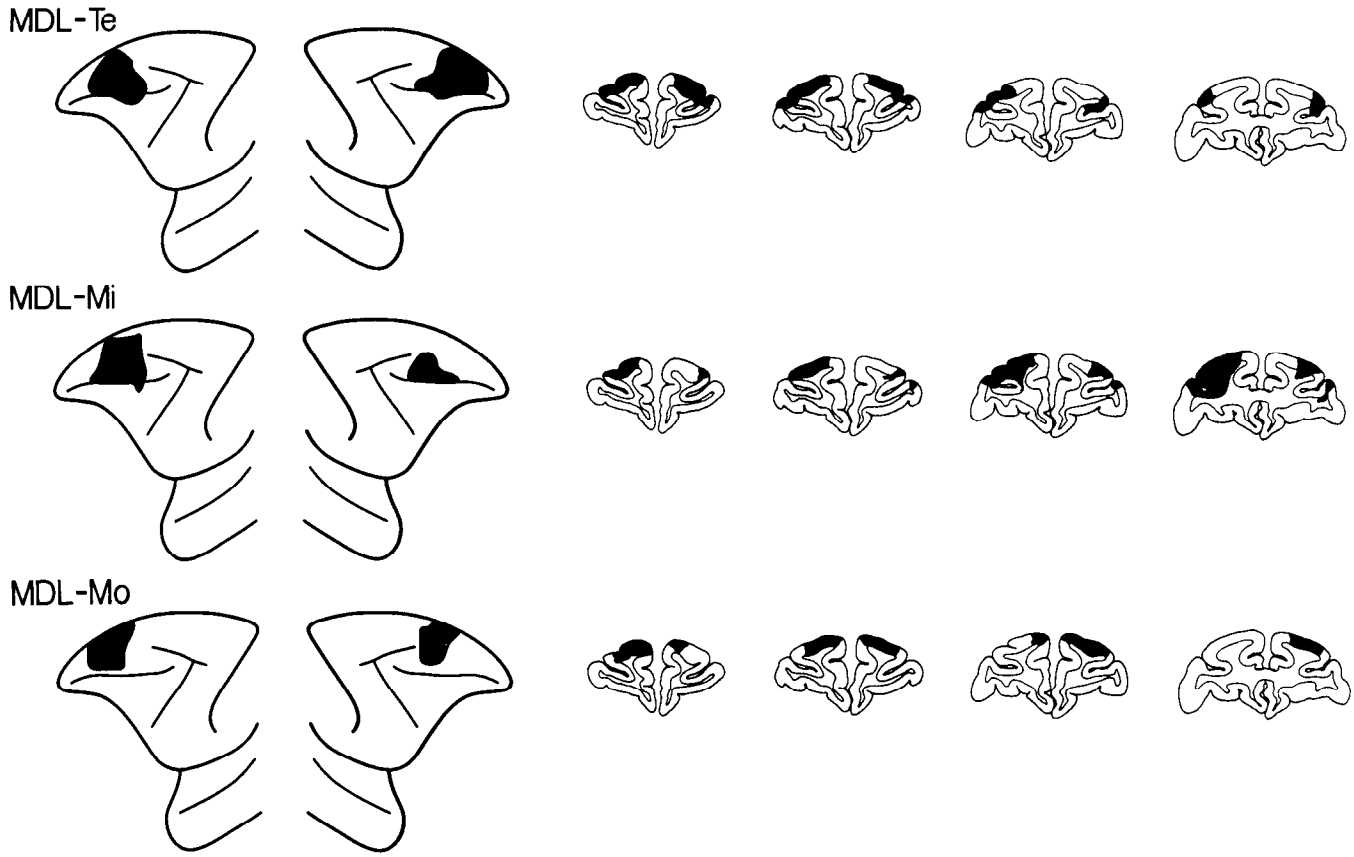

Figure 1. Extent of the lesions of the mid-dorsal part of the lateral frontal cortex (MDL lesions) depicted (*in black*) on standard diagrams of the lateral surface of the anterior part of the brain of the monkey, and on standard drawings of coronal sections. Left hemisphere is shown on the left side, both for the lateral surface diagrams and for the coronal sections. The approximate stereotaxic levels for the coronal sections shown are, from left to right, +36, +34, +32, +30. *Te, Mi,* and *Mo* refer to individual monkeys.

that of the ventrolateral frontal cortex in analogous nonspatial mnemonic processing. At the same time, however, these findings raised the question of whether the dorsal frontal cortex that extends above the sulcus principalis plays any role in mnemonic processing. Passingham (1978) suggested that the cortex that lies above the sulcus principalis may have a special role in the processing of movement information. This suggestion was based on the finding that monkeys with lesions that included the sulcus principalis and the cortex extending above it (Manning, 1978; Passingham, 1978), but not monkeys with lesions restricted to the cortex of the sulcus principalis (Passingham, 1978), were impaired on a motor task in which they had to discriminate between a few and many taps made on a response key. However, in a later study, no impairments were found after lesions *restricted* to the cortex that extends above the sulcus principalis on a task requiring reproduction of previously made movements (Passingham, 1986), suggesting that the originally reported impairment (Manning, 1978; Passingham, 1978) may have resulted from the combined damage of the sulcus principalis and the lateral frontal cortex extending above it.

At present, therefore, the only information available about the possible role of the frontal cortex that lies above the sulcus principalis in working memory is the recent demonstration that monkeys with MDL lesions are severely impaired on the nonspatial self-ordered task (Petrides, 1988). It must be emphasized here that, since the position of the visual stimuli varied randomly on each trial of this task, neither spatial nor motor (kinesthetic) solutions were possible. Thus, the severe impairment observed on the self-ordered task after MDL lesions must be reflecting a dysfunction in nonspatial working memory processing.

The present communication reports in full (experiment 1) the original study demonstrating a severe impairment on the nonspatial self-ordered working memory task after MDL lesions; this study has previously been reported only in abstract form (Petrides, 1988). The other eight experiments reported here were designed to answer a number of key questions raised by experiment 1. The following issues were addressed. First, is the deficit observed after MDL lesions restricted to the monitoring of self-generated responses, or is this impairment a more general one, encompassing, in addition, the monitoring of externally ordered stimuli? Second, what is the difference between the nonspatial self-ordered tasks that monkeys with MDL lesions fail and the nonspatial object alternation (Mishkin et al., 1969; Mishkin and Manning, 1978) and delayed matching-to-sample (Passingham, 1975; Mishkin and Manning, 1978) tasks whose performance was found not to be particularly affected by even extensive dorsolateral frontal lesions? Third, can monkeys with MDL lesions learn to select the stimuli of a recurring list according to a fixed order? In other words, can they learn a memory task in which the monitoring requirements within working memory are minimized by having each choice specified by the preceding one? Fourth, is the *nonspatial* memory impairment observed on the self-ordered task a long-lasting one? Resolution of these

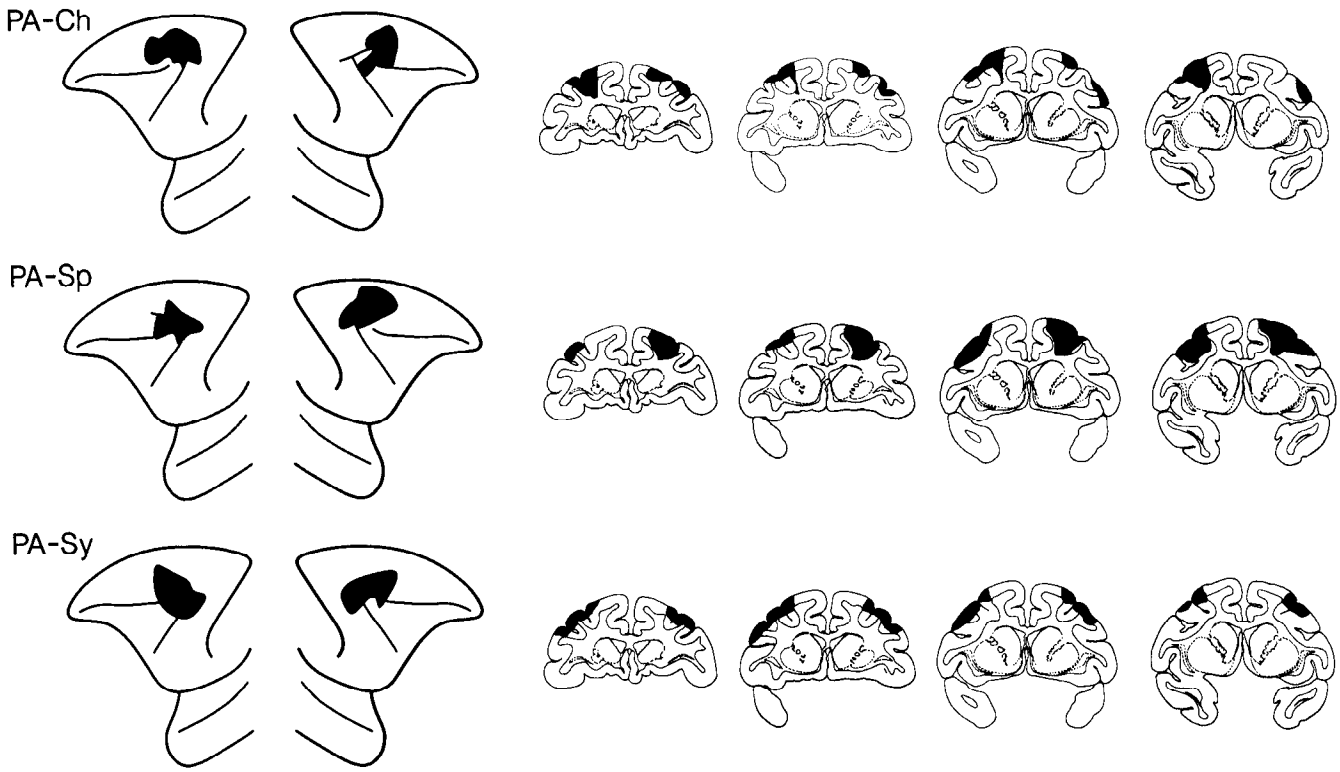

Figure 2. Extent of the periarcuate (PA) lesions, that is, the lesions of the posterior dorsolateral frontal cortex, depicted (*in black*) on standard diagrams of the lateral surface of the anterior part of the brain of the monkey, and on standard drawings of coronal sections. Left hemisphere is shown on the left side, both for the lateral surface diagrams and for the coronal sections. The approximate stereotaxic levels for the coronal sections shown are, from left to right, +26, +24, +22, +20. *Ch, Sp,* and *Sy* refer to individual monkeys.

issues should clarify significantly the understanding of the role of the mid-dorsal part of the lateral frontal cortex in mnemonic processing.

Experiment 1 of this series of experiments was reported at the 1988 annual meeting of the Society for Neuroscience in Toronto, Canada (Petrides, 1988).

Materials and Methods

Subjects and surgical procedure. The subjects were 10 male monkeys (*Macaca nemestrina*) weighing 4.5–9.5 kg at the time of surgery. Three monkeys were given one-stage bilateral ablation of the mid-dorsal (MDL) part of the lateral frontal cortex (see Fig. 1). These lesions were restricted within dorsal area 46 and area 9 of the dorsal lateral frontal lobe. They are referred to as mid-dorsal lesions because they were intended to extend from above the middle sector of the sulcus principalis to the midline, sparing the most rostral part of the dorsal lateral frontal cortex that is part of the frontopolar cortex (i.e., area 10). Posteriorly, these lesions were to spare the cortex surrounding the upper branch of the arcuate sulcus, as far as the midline (i.e., areas 8A, 8B, and rostral 6), as well as the cortex surrounding the posteriormost part of the sulcus principalis (in the concavity of the arcuate sulcus) that has connections very similar to those of the adjoining area 8A (Pandya and Kuypers, 1969; Pandya et al., 1971; Barbas and Mesulam, 1981). In making these lesions, great care was also taken not to damage or undercut the connections of the inferior frontal convexity, that is, the ventrolateral frontal cortex that lies below the sulcus principalis. Three animals were given a one-stage bilateral ablation of the periarcuate (PA) region, that is, the posterior part of the dorsolateral frontal cortex (Fig. 2). These lesions were to include the cortex surrounding and lying within the superior ramus, the spur, and the uppermost part of the inferior ramus of the arcuate sulcus. In other words, rostral area 6, which lies within the posterior bank of the arcuate sulcus, and area 8, within the anterior bank of the arcuate sulcus, were to be removed. In making these lesions, great care was taken not to damage or undercut the more rostrally located frontal cortex. Finally, four monkeys formed the unoperated normal control group (NC).

All operations were carried out by standard aseptic operating techniques for the subpial aspiration of cortical tissue. The animals were first anesthetized with ketamine (15 mg/kg, i.m.) and were then given the minimal dose of intravenous barbiturate (Nembutal) necessary to induce a deep state of anesthesia. Supplementary doses were administered during the operation as needed.

Histological procedure. At the completion of the present and other experiments (see Petrides, 1991a,b), the six operated animals were sacrificed with an overdose of Nembutal. The brains of the animals were removed and fixed in a 10% formalin solution. A macroscopic examination of the brains, which included drawings of the lesions as seen from the surface of the brain, was carried out. Frozen sections of the frontal lobe were then cut at 60 μm and every sixth section was kept for staining with thionin. A microscopic examination of the stained sections was conducted and drawings of the lesions were made (see Figs. 1, 2).

Preoperative testing. All testing was carried out in a Wisconsin General Testing Apparatus, which consists of a compartment where the monkey is held and a testing area. An opaque screen can be interposed between these two compartments to occlude the monkey's view of the testing area. The animals were tested for 5 d during each week, and were rewarded with banana-flavored food pellets for correct responses.

The aim of the present series of experiments was to examine the effect of selective lesions within the dorsal lateral frontal cortex on various aspects of *nonspatial* working memory. Certain nonspatial memory tasks can be very difficult for monkeys to learn, because, in trying to solve them, the animals initially adopt spatial strategies that interfere with learning. To encourage the monkeys to focus their attention on the visual characteristics of the stimuli and to ignore their location, all animals were first given, over a period of a several months, extensive training on visual discrimination tasks. The animals were then trained on various visual memory tasks. All these tasks were based on the same principle: on any given trial, the correct response (i.e., the response leading to reward) was to avoid selecting a stimulus that had been chosen on an

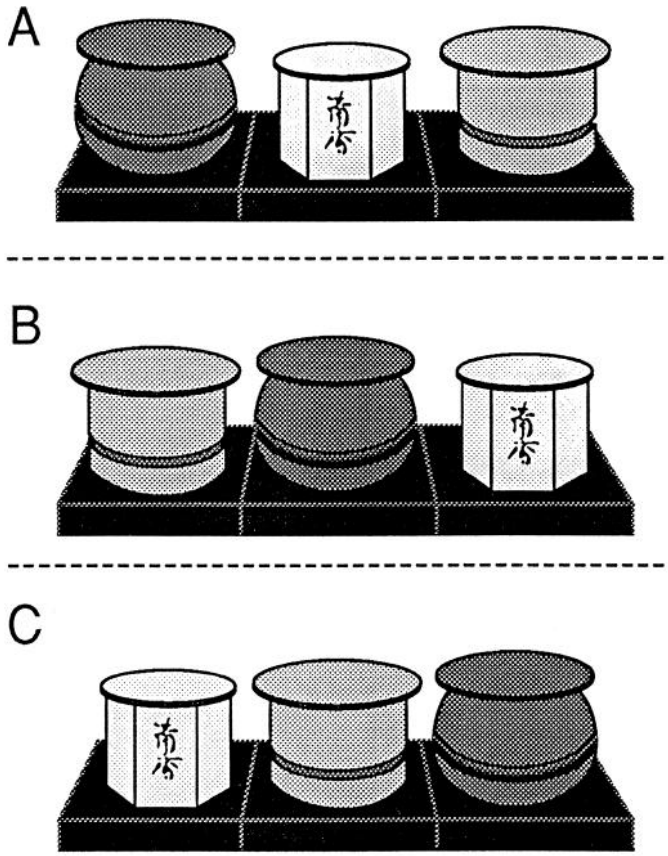

Figure 3. Schematic diagram of the experimental arrangement in the self-ordered task I (experiment 1). On each trial, three containers, which differed in color and shape, were presented in a horizontal row. The position of the three containers during the various trials was randomly determined. *A–C* illustrate examples of three different trials. Within each container, there was a block of wood on the top of which a food well had been carved. The food well, where the reward was placed, was therefore just beneath the cover of each container. The container could be opened by lifting its cover, which was fixed to the container by means of a small hinge.

earlier trial during that day's testing session, because reselection of that stimulus would not lead to reward. The first task administered in this part of the preoperative testing phase was the delayed nonmatching-to-sample task with trial-unique stimuli. This is a standard test of recognition memory, which monkeys learn readily. In this task, when the opaque screen was raised, the animal was faced with a single object, placed above a small white plaque covering the central food well of a testing board with three food wells. The animal was allowed to displace the plaque to retrieve the reward that was under it. Subsequently, after a delay of 10 sec, during which the opaque screen was interposed, the animal was presented with a choice between the object that he had previously seen and a novel object. These objects were placed over plaques covering the two lateral food wells. The relative position of the objects over the two food wells was determined according to a random but balanced order. The animal found the reward only if he displaced the novel object. Thirty such trials, each one with a different pair of objects drawn randomly from a pool of hundreds of small objects, were administered per day. Testing continued until the animal reached the learning criterion of at least 90% correct responses during 2 consecutive days of testing.

The animals were then trained on a self-ordered task in which they were required to monitor their choices from a set of three visual stimuli. In this task, the animals were first shown three objects placed in a row over the small white plaques covering the three food wells of the test board. Each one of these three objects covered a reward. The animal was allowed to displace any one of these three objects to obtain the reward that was hidden under it. After a 10 sec delay, during which the opaque screen was interposed, the animal was presented with a choice between the object that he had selected on the preceding trial and one of the other two objects that he had not selected. The animal now found the reward only if he chose the object that he had not previously selected, thus demonstrating memory of his earlier choice. This experiment has been published (see Petrides, 1991a, for details).

The next task administered preoperatively to these animals was also a self-ordered task requiring memory for self-generated choices. This task was modeled on the self-ordered tests originally used with patients (Petrides and Milner, 1982) and is described here in experiment 1 (see below for testing procedure).

When the animals had learned these preoperative tasks, they were allowed a 2 week rest period, and they were then retested on the delayed nonmatching-to-sample task and the two self-ordered tasks. All animals achieved the learning criterion within the minimum number of trials, demonstrating excellent retention of all tasks. As each animal completed its preoperative training, it was assigned, in turn, to one of the three groups described in the *subjects* section. The assignment of the animals to the groups was such as to match the three groups in terms of preoperative test scores. Surgery for the animals in the two operated groups (PA and MDL groups) was carried out at this stage. Postoperative performance on the second self-ordered task administered during the preoperative testing phase is presented in experiment 1. The experiments are presented in the order in which they were administered to the monkeys. After experiment 1, the monkeys were tested on the first self-ordered task administered preoperatively and a variation of the delayed nonmatching-to-sample task, and the results of this testing have been published separately (Petrides, 1991a). On completion of experiment 6 and before experiment 7, the animals were tested on a serial order memory task that has also been published separately (Petrides, 1991b). All animals were administered the same tasks, in the same order, and the time elapsed between tasks was the same for all groups.

Experiment 1: self-ordered task I

The purpose of this experiment was to examine the performance of monkeys with selective lesions within the mid-dorsal part of the lateral frontal cortex (MDL lesions) and the posterior dorsolateral frontal cortex (PA lesions) on a nonspatial mnemonic task that was formally comparable in cognitive requirements to the self-ordered working memory task that had previously revealed striking impairments in patients with frontal lobe damage (Petrides and Milner, 1982). In the self-ordered task that was used with patients, a different arrangement of the same set of stimuli was presented on each trial, and the subjects were required to select a different one of these stimuli until all stimuli had been selected. Therefore, to avoid selecting a stimulus more than once, the subjects were required to monitor constantly their previous selections within working memory. The self-ordered task for patients was adapted for work with the monkey in the following way. A different arrangement of three distinct containers were presented on each trial, and the animal was allowed to open any one of these containers to find the reward (Fig. 3). All three containers had a reward in them at the beginning of the daily testing session, but, on subsequent trials, if the animal opened a container that he had already selected, he found no reward. Thus, before each choice, the animal had to compare, from memory, his earlier selections to determine the stimuli that remained to be selected.

Procedure

The stimuli used in the present experiment were three containers that differed from each other in terms of shape and color (Fig. 3). The same three containers were used for each daily testing session. When the opaque screen that separated the monkey's compartment from the testing area was raised, the animal faced a horizontal array of these three containers, each one having a reward (i.e., a banana-flavored food pellet) within it. The animal was allowed to open any one of the three containers to retrieve

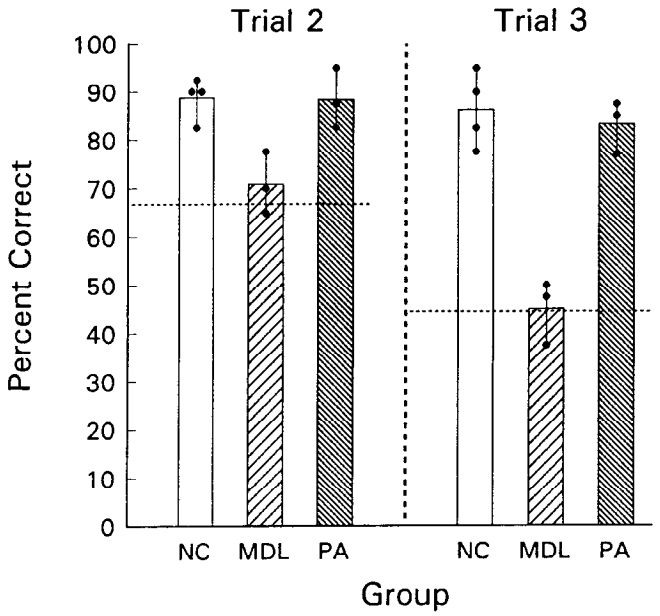

Figure 4. Mean percentage of correct responses made by the three groups on trials 2 and 3 of the self-ordered task I (experiment 1). The level of chance performance (trial 2 = 66.6%; trial 3 = 44.4%) is indicated by the *horizontal dashed line. Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

the reward that was in it, and the opaque screen was lowered to terminate the trial. The relative position of the three containers was then changed according to a random order and the screen was raised again, after a 10 sec intertrial interval, to allow the animal access to the three containers. If the animal responded correctly by opening one of the two containers that he had not previously selected, he found the reward that was in it. If, however, the animal made an error by opening the container that he had previously selected, he found no reward, and the screen was lowered to terminate the trial. The position of the three containers was again changed and the screen was raised, after the 10 sec intertrial interval, for the next trial. The daily test session continued in this manner until the animal had retrieved the reward from all three containers. Thus, if no errors were made, the daily test session would be completed after only three trials. Since no errors could be made on the first trial and the daily test session could be completed after only three consecutive trials, *performance measures were based only on the second and third trials administered.* Performance during each block of 10 consecutive days of testing was calculated. Preoperatively, the animals were trained until they achieved a performance criterion of at least 17 correct responses out of the 20 choices (i.e., 85% correct) that were made on trials 2 and 3 of a 10 d block of testing. This performance criterion (i.e., 85% correct) had to be maintained over three consecutive 10 d blocks of testing. Two weeks after surgery, the animals were retested on this task for 40 consecutive test ds, that is, four blocks of testing.

Results

Figure 4 shows the percentage of correct responses made by the various groups on trials 2 and 3 of the self-ordered task. It can be seen that the MDL group was performing close to the level expected by chance both on trial 2 and on trial 3. Note that, since on trial 1 of this task the monkey will have retrieved the reward from one of the three containers, the probability of being correct by chance on trial 2 is ⅔, or, 66.6%. The probability of being correct by chance on trial 3 breaks down as follows: the probability of being correct by chance on trial 3 having been wrong by chance on trial 2 (i.e., ⅔ × ⅓), plus the probability of being correct by chance on trial 3 having been correct by chance on trial 2 (i.e., ⅓ × ⅔), which is 44.4%. A Kruskal–Wallis ANOVA on the correct responses made on both trials 2 and 3 over the total 40 d of postoperative testing showed that there were significant differences among the three groups [$H(2) = 5.74$, $p < 0.05$]. The group with MDL lesions performed worse than both the normal control group (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$). The PA group, on the other hand, was not significantly different from the normal control group.

Table 1. Distribution of errors on trial 3 of the self-ordered task

Group	Percentage of repetitions of choice on trial 1	Percentage of repetitions of choice on trial 2
Normal		
NC1	38.8	61.1
NC2	28.6	71.4
NC3	50.0	50.0
NC4	50.0	50.0
Mean	41.8	58.1
Mid-dorsal		
MDL1	42.0	58.0
MDL2	57.1	42.8
MDL3	57.5	42.5
Mean	52.2	47.8
Periarcuate		
PA1	16.7	83.3
PA2	44.4	55.5
PA3	80.0	20.0
Mean	47.0	52.9

On trial 3, an error can be either a repetition of the correct choice made on trial 2 or a repetition of the choice made on trial 1. If animals had a tendency to perseverate their responses, a bias would have been expected in favor of repeating, on trial 3, choices made on trial 2 as compared with repeating choices made on trial 1. To find out whether there were any systematic differences in the distribution of responses among the three groups of animals, the proportion of errors on trial 3 that were repetitions of choices made on trial 1 and those that were repetitions of choices made on trial 2 were calculated. As can be seen in Table 1, there was no systematic tendency for the animals with MDL lesions to make errors by repeating choices made on trial 2. In fact, all three animals with MDL lesions distributed their errors evenly, indicating that they had no tendency to perseverate.

Comment

This experiment tested the effect of the MDL and PA lesions on performance of a nonspatial self-ordered working memory task that was designed to be comparable in requirements to the

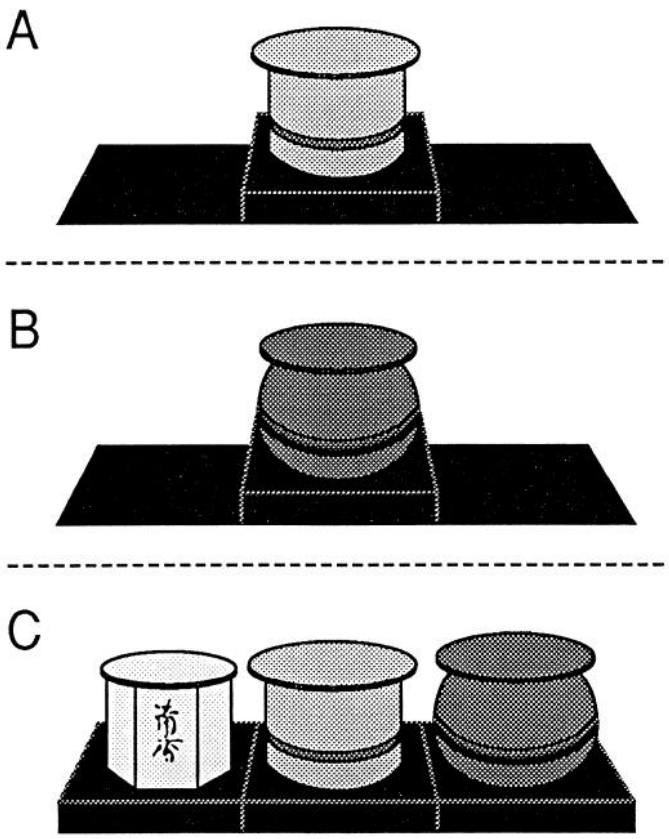

Figure 5. Schematic diagram of the experimental arrangement in the externally ordered task I (experiment 2). *A–C* represent the first three trials of the daily testing session. Two of the three containers, randomly selected, are shown on the first two presentation trials (*A* and *B*) and all three containers are shown together on the subsequent test trial (*C*).

self-ordered task that had previously been used with patients (Petrides and Milner, 1982). Lesions of the mid-dorsal part of the lateral frontal cortex caused a severe impairment, whereas lesions of the periarcuate cortex did not affect performance of this nonspatial mnemonic task. Analysis of the pattern of errors made by the animals with MDL lesions provided evidence that their impairment is not the result of perseverative tendencies in their choices.

Experiment 2: externally ordered task I

On completion of experiment 1, the animals were tested on another self-ordered task, which also required monitoring of self-generated choices from a set of visual stimuli, and on a recognition memory task. Performance on this other self-ordered task, which was the first self-ordered task administered to the animals preoperatively, and the recognition memory task has been reported separately (see Petrides, 1991a). In that study, the monkeys with MDL lesions were severely impaired on the self-ordered working memory task, but performed very well on the recognition memory task (Petrides, 1991a). The severe deficit observed on the two self-ordered tasks (experiment 1 and Petrides, 1991a) raised the following question: are animals with MDL lesions impaired only on working memory tasks that require monitoring of self-generated responses or is this impairment a more general one, involving, in addition, the monitoring of stimuli that are externally ordered? The present experiment addressed this question.

Procedure

The three containers that had been used in experiment 1 were also the stimuli used in this experiment. Each day, two of the three containers were randomly selected for presentation during the first and second trials of the testing session. These trials were therefore the presentation trials during which the animal saw two of the set of three stimuli. When the opaque screen was raised to initiate the first presentation trial, the animal saw, in the middle of the test board, one of the containers, and was allowed to open it to retrieve the reward that was in it (Fig. 5). The screen was then lowered, the container was replaced by another one, and, after a 10 sec delay, it was again raised to allow the monkey to retrieve the reward. The screen was lowered once more, and, when it was raised, after the 10 sec intertrial delay, to administer the test trial, the animal was now faced with all three containers. These were placed in a row on the test board. Only the container that had not been shown on the previous two trials had a reward in it, and, if the animal responded correctly by opening it to retrieve the reward, the daily testing session was terminated. Thus, testing could be terminated after only three trials. If the animal made an error by opening one of the two containers that were presented on the first two trials, the screen was lowered, the position of the three containers was changed according to a random order and the screen was raised, after the 10 sec intertrial interval, to initiate another test trial. This procedure was repeated until the animal opened the container with the reward. The animals were tested in this manner for 40 consecutive days.

Results and comment

The performance of the three groups of animals on the test trial, that is, the third trial administered per day, is illustrated in Figure 6. The monkeys with periarcuate lesions performed as well as the normal control animals. By contrast, the animals with lesions of the mid-dorsal part of the lateral frontal cortex performed close to the level expected by chance. Since only one of the three containers on the test trial had reward in it, the probability of performing correctly by chance is 33.3%.

A Kruskal–Wallis ANOVA on the overall correct responses, summed across all 40 test days, indicated significant differences among the three groups [$H(2) = 5.98$, $p < 0.05$]. The MDL group performed worse than both the normal control (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$). These results demonstrated that the deficit in the monitoring of self-generated responses, which was previously shown to result from lesions of the mid-dorsal part of the lateral frontal cortex (experiment 1 and Petrides, 1991a), is a more general impairment encompassing, in addition, the monitoring of externally ordered stimuli.

Experiment 3: externally ordered task II

Experiment 2 demonstrated a severe impairment in monkeys with lesions of the mid-dorsal part of the lateral frontal cortex when the animals were required to monitor an externally ordered set of stimuli. In experiment 2, the monkeys were first shown two of a set of three stimuli, and, during the test trial, they were required to select, from all three stimuli, the one that had not been presented on the first two trials. The purpose of

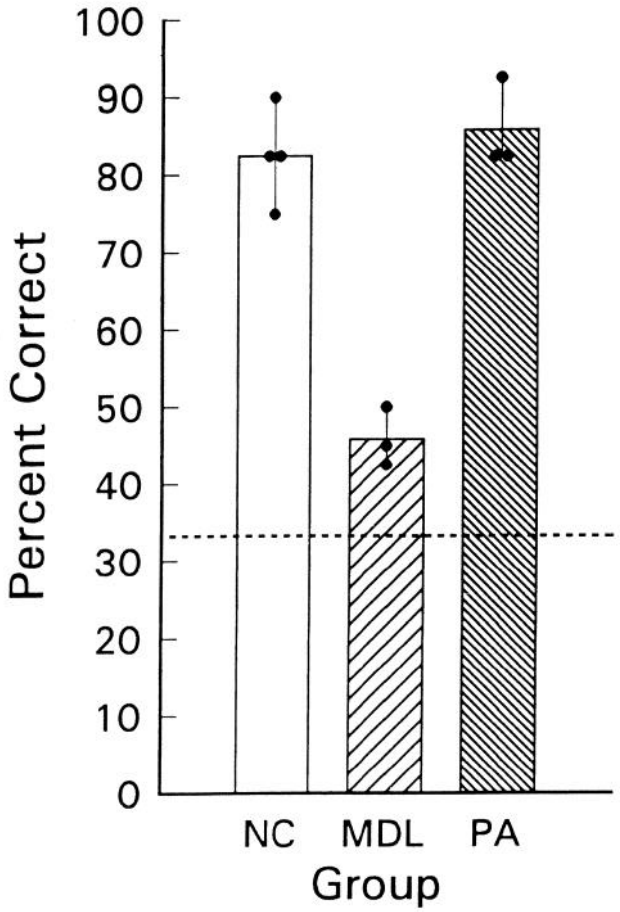

Figure 6. Mean percentage of correct responses made by the three groups of animals on the externally ordered task I (experiment 2). The level of chance performance (33.3%) is indicated by the *horizontal dashed line. Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

the present experiment was to examine whether the deficit observed after lesions of the mid-dorsal part of the lateral frontal cortex in experiment 2 could still be observed in a task that was identical in terms of mnemonic demands but that restricted the animal's choice, on the critical test trial, between two stimuli. It was necessary to examine the influence of this factor (i.e., the number of stimuli present on the critical test trials) on performance of the externally ordered nonspatial working memory task because of earlier reports that dorsolateral frontal lesions do not markedly affect performance on nonspatial delayed alternation or matching tasks (Passingham, 1975; Mishkin and Manning, 1978). In the latter tasks, the animals had to make choices between two stimuli. It could therefore be argued that animals with MDL lesions, perhaps because of some attentional impairment, may be overwhelmed when presented with a choice of three stimuli, whereas they can still function well when faced with only two stimuli.

This experiment was a variation of experiment 2. The stimuli were the three containers that were used in experiment 2. Two of these containers were first shown on two presentation trials, and, on the test trial that followed, the monkeys were faced with one of the two containers that had been shown on the presentation trials together with the container that had not been shown

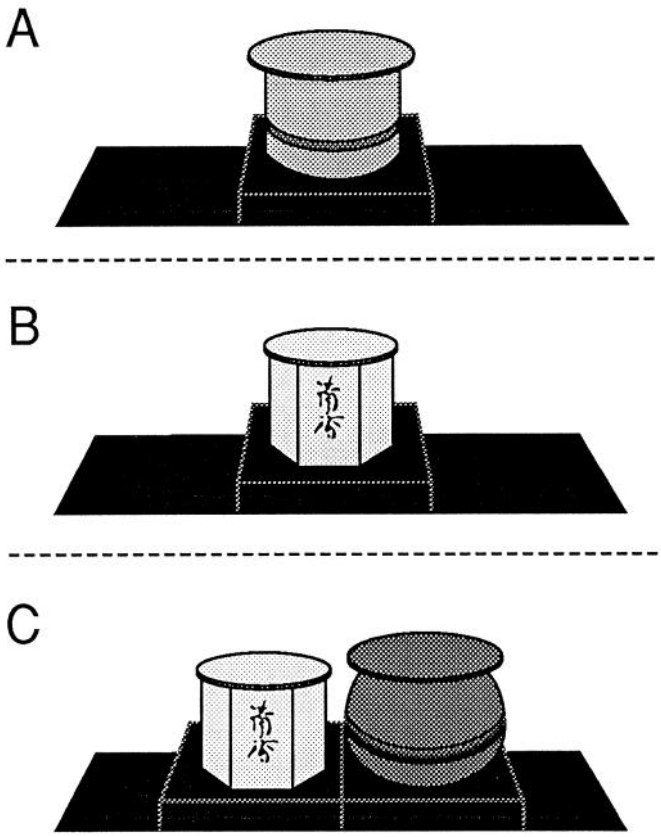

Figure 7. Schematic diagram of the experimental arrangement in the externally ordered task II (experiment 3). *A–C* represent three trials. Two of the three containers, randomly selected, are first shown on the two presentation trials (*A* and *B*). On the subsequent test trial (*C*), one of these containers is shown together with the container that was not shown on the presentation trials.

on those trials (Fig. 7). As in experiment 2, the animals were required to select the stimulus that had not been shown on these first two trials. Thus, if the number of stimuli at the time of making a choice were the critical factor giving rise to the deficit observed in experiment 2, the animals with MDL lesions should not be impaired in the present experiment. On the other hand, if the mnemonic requirements of experiment 2 were the critical factor for the observed defect after MDL lesions, a deficit should also be observed in the present experiment.

Procedure

The stimuli were the same three containers that had been used in experiments 1 and 2. As in experiment 2, during the daily test session, two of the three containers were randomly selected to be shown on the first two presentation trials. One of these containers was presented on the first trial and the other on the second trial. On each occasion the monkey was allowed to open the container to retrieve the reward that was in it. On the third trial, which was the critical test trial, one of the containers that had been shown on the first two presentation trials was randomly chosen and was paired with the container that had not yet been shown. The reward was in the container that had not been shown before and the animal was therefore rewarded if he selected it. The daily test session was terminated after the test trial. The monkeys were tested in this manner for 40 consecutive days. The raising and lowering of the opaque screen marked the ini-

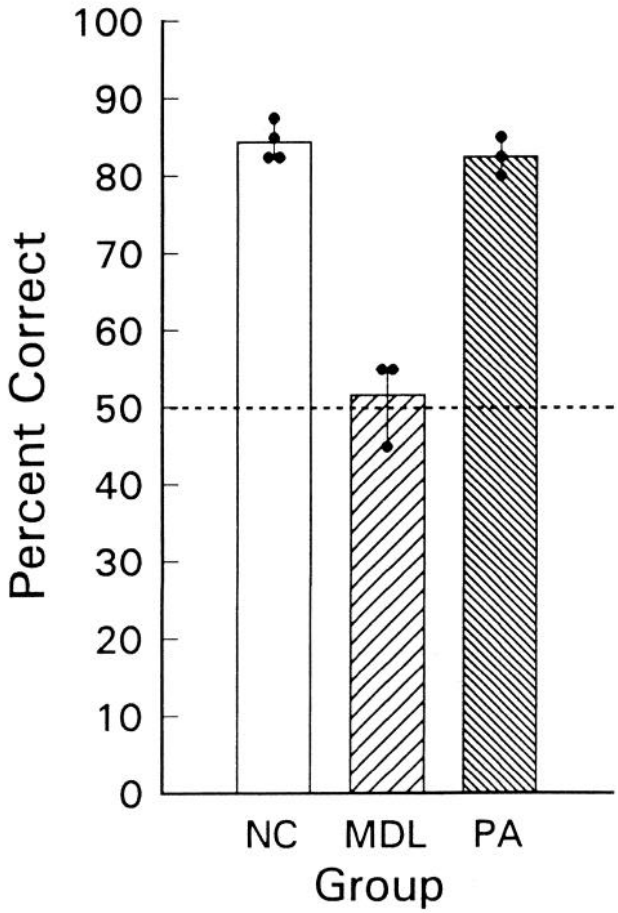

Figure 8. Mean percentage of correct responses made by the three groups of animals on the externally ordered task II (experiment 3). The level of chance performance (50%) is indicated by the *horizontal dashed line*. *Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

tiation and termination of each trial and the intertrial interval was 10 sec.

Results and comment

As can be seen in Figure 8, there were significant differences between the three groups of monkeys in their performance on the test trial [Kruskal–Wallis test: $H(2) = 6.12$, $p < 0.05$]. The group of monkeys with MDL lesions was impaired in comparison with both the normal control group (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$). Note that since on the test trial only one of the two containers had reward in it, the level of chance performance is 50% and that the performance of the MDL group is at chance. The present findings confirmed those of experiment 2 by demonstrating that monkeys with MDL lesions were impaired on a mnemonic task in which they had to monitor which ones from a set of three stimuli had occurred in earlier trials. Furthermore, these findings showed that the number of stimuli present on the test trials is not a critical factor determining whether an impairment will be observed after MDL lesions. Thus, the mnemonic requirements of the task, and not external variables such as the number of stimuli present at the time of choice, account for the impairment observed after such lesions.

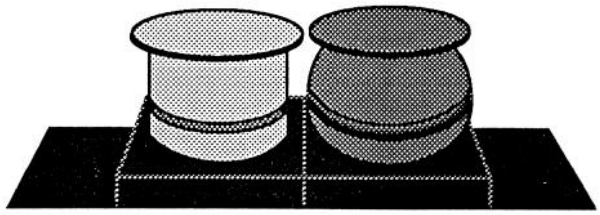

Figure 9. Schematic diagram of the experimental arrangement in the object alternation task (experiment 4). On each trial, two containers differing in color and shape were presented in a horizontal row. The relative position of the containers during the various trials was randomly determined.

Experiment 4: nonspatial object alternation

Experiments 1, 2, and 3 of the present communication and the experiment reported in Petrides (1991a) demonstrated a severe impairment on nonspatial working memory tasks after lesions limited to the mid-dorsal part of the lateral frontal cortex, yet earlier work had shown that monkeys with extensive dorsolateral frontal lesions (which included the cortex removed in the present MDL lesion, the cortex lining the sulcus principalis, the frontopolar cortex above the sulcus principalis, and area 8 in the concavity of the arcuate sulcus) were only mildly impaired on delayed object alternation, a nonspatial mnemonic task in which the animals were required to alternate their responses between two objects on successive trials (Mishkin et al., 1969). The purpose of this experiment was to confirm that the present animals with MDL lesions would show mild, if any impairments, on a nonspatial delayed object alternation task, as would be expected from the earlier work by Mishkin et al. (1969).

Procedure

All animals encountered this task for the first time postoperatively. No training was necessary to carry out this experiment because the basic principle for correct performance in object alternation is the same as that in all other experiments of this series: to obtain the reward, the animal must not return to a stimulus that he had responded to on the preceding trial. Two of the three containers that had been used in experiments 1, 2, and 3 were the stimuli in the object alternation task (Fig. 9).

Part I. In the first part of this experiment, the animals were tested for 10 trials per day. On each trial, when the screen was raised, the animal saw the two containers placed in a row side by side and was allowed to open one of them. The left/right position of these two containers was varied from trial to trial according to a random but balanced schedule (Gellermann schedule). On the first trial of the daily testing session, both containers had a reward hidden in them. On subsequent trials, however, the animal would not find the reward if he returned to the container that he had selected on the preceding trial; reward was now to be found by alternating between the two stimuli. The intertrial interval was 10 sec. Five consecutive days of testing completed part I of this experiment.

Part II. Testing in part II was identical to that of part I, except that now 30 trials were administered during the daily session. The animals were tested for 5 consecutive days. The intertrial interval was 10 sec.

Part III. In this part of the experiment, the monkeys were tested as in part I, that is, 10 trials of object alternation per day, except that now the intertrial delay was increased to 60 sec.

Results and comment

The mean performance of each group for each daily testing session is shown in Figure 10 and the scores of individual animals in Table 2. As can be seen, all three groups of animals were able to perform the object alternation task. The animals with MDL lesions performed slightly worse (about 70% correct) than the other two groups on the first 2 d of testing in part I, but this difference disappeared on subsequent days. The fact that performance was relatively poor only on the first few days was confirmed by a significant group × day effect [$F(8, 28) = 3.47$, $p = 0.023$] when the data of part I were subjected to an ANOVA. Tests of simple main effects showed that there were significant differences among the groups on day 1 [$F(2, 35) = 15.73$, $p < 0.001$] and day 2 [$F(2, 35) = 8.04$, $p = 0.001$]. Tukey HSD post hoc tests showed that the MDL group was significantly different from both the NC group ($p < 0.01$) and the PA group ($p < 0.01$). The NC and the PA groups were not significantly different from each other. The group [$F(2, 7) = 13.29$, $p = 0.004$] and day [$F(4, 28) = 3.88$, $p = 0.032$] main effects were also significant.

ANOVA carried out on the data of part II did not demonstrate any significant differences in the group or day main effects, or a group × day interaction. Finally, in part III, there was only a significant day effect [$F(4, 28) = 5.56$, $p = 0.009$], reflecting the fact that performance for all the groups improved across the 5 d of testing. There were, however, no differences among the groups as shown by the nonsignificant group [$F(2, 7) = 0.55$, NS] and group × day [$F(8, 28) = 1.02$, NS] effects. The significance levels reported above were obtained using the Greenhouse-Geisser conservative degrees of freedom.

This experiment showed that MDL lesions do not cause more than a mild and transient impairment on the delayed object alternation task. This finding is in agreement with the earlier work by Mishkin et al. (1969), which had shown that even large dorsolateral frontal lesions do not markedly affect object alternation performance. It is particularly noteworthy that, even when the intertrial interval was increased to 60 sec, as in part III of the present experiment, the performance of the animals with the MDL lesions was not significantly different from that of the control animals.

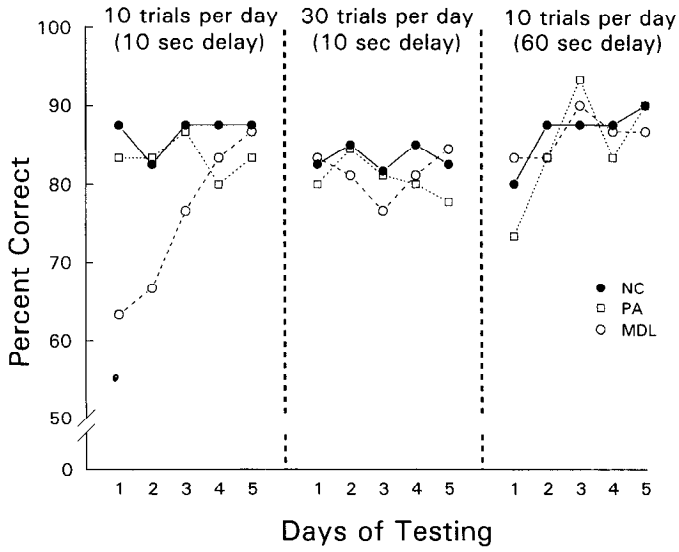

Figure 10. Mean percentage of correct responses made by the three groups of animals on the nonspatial object alternation task (experiment 4). The level of chance performance is 50%. *NC*, normal monkeys; *MDL*, monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA*, monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

Experiment 5: monitoring of two and three stimuli in a self-ordered task

In Experiment 1, the monkeys with MDL lesions exhibited a severe impairment on the self-ordered task in which they were required, on each trial, to select a different one of three recurring stimuli. It is important to note that in that experiment, the monkeys with MDL lesions were performing at chance even on the second trial. In other words, having selected just one of the three stimuli on trial 1, these animals were unable to perform correctly on the subsequent trial, 10 sec later (see Fig. 4). By contrast, these same monkeys performed well on the object alternation task (experiment 4) in which they alternated their responses between two stimuli, that is, a task that required memory of which one of the two stimuli had been chosen on

Table 2. Percentage correct performance per day in experiment 4

	10 trials per day (10 sec delay)					30 trials per day (10 sec delay)					10 trials per day (60 sec delay)				
Group	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5
Normal															
NC1	80.0	90.0	90.0	90.0	90.0	86.7	86.7	83.3	86.7	83.3	70.0	90.0	90.0	90.0	90.0
NC2	90.0	80.0	90.0	80.0	100.00	83.3	83.3	80.0	86.7	86.7	80.0	90.0	90.0	90.0	100.0
NC3	90.0	80.0	80.0	80.0	80.0	80.0	86.7	83.3	86.7	83.0	80.0	90.0	80.0	90.0	90.0
NC4	90.0	80.0	90.0	90.0	80.0	80.0	83.3	80.0	80.0	76.7	90.0	80.0	90.0	80.0	80.0
Mid-dorsal															
MDL1	60.0	60.0	80.0	80.0	90.0	80.0	80.0	76.7	80.0	86.7	80.0	90.0	90.0	90.0	90.0
MDL2	60.0	70.0	70.0	80.0	90.0	83.3	80.0	80.0	83.3	83.3	80.0	80.0	90.0	80.0	90.0
MDL3	70.0	70.0	80.0	90.0	80.0	86.7	83.3	73.3	80.0	83.3	90.0	80.0	90.0	90.0	80.0
Periarcuate															
PA1	80.0	80.0	80.0	80.0	80.0	76.7	86.7	83.3	83.3	73.3	70.0	80.0	100.0	90.0	90.0
PA2	90.0	80.0	90.0	80.0	80.0	83.3	86.7	80.0	80.0	76.7	70.0	80.0	90.0	80.0	90.0
PA3	80.0	90.0	90.0	80.0	90.0	80.0	80.0	80.0	76.7	83.3	80.0	90.0	90.0	80.0	90.0

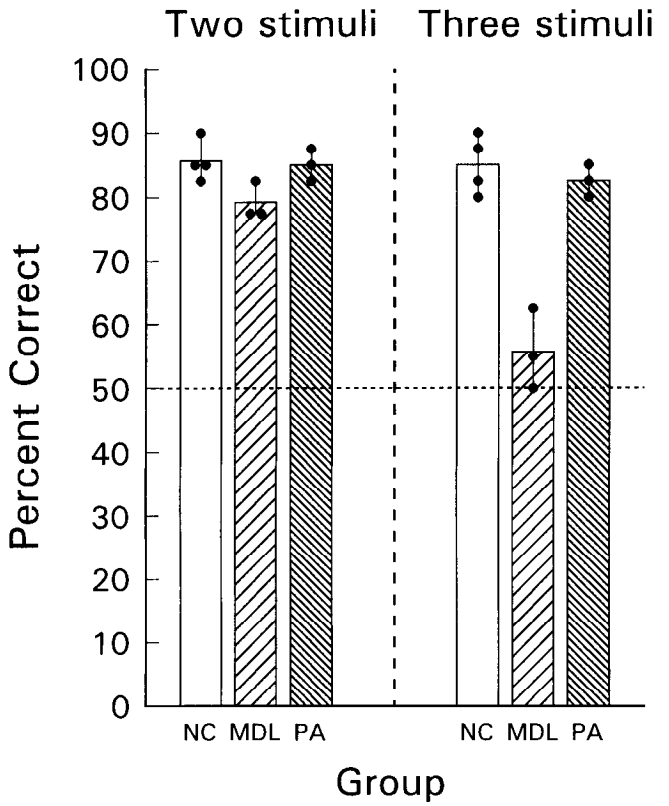

Figure 11. Mean percentage of correct responses made by the three groups of animals in the two-stimulus and the three-stimulus condition in experiment 5. The level of chance performance (50%) is indicated by the *horizontal dashed line. Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the posterior dorsolateral frontal cortex, that is, the periarcuate cortex.

the preceding trial. Note that in terms of the number of selected stimuli that had to be remembered during the delay interval, trial 2 of the self-ordered task (experiment 1) and all trials of the object alternation task (experiment 4) were identical: there was one selected stimulus to be remembered during the delay. Note further that in the object alternation task, this one stimulus had to be maintained in the face of increasing interference from the preceding trials administered that day, whereas in trial 2 of the self-ordered task there was no interference from preceding trials, making the difference in the performance of the MDL monkeys on the two tasks all the more remarkable.

The object alternation and the self-ordered tasks differ in terms of the monitoring requirements within working memory: the self-ordered task requires comparison of the selected stimuli against the three possible stimuli, whereas the object alternation task merely requires comparison with the one remaining stimulus. Thus, the number of chosen stimuli to be maintained in short-term memory and the length of the delay cannot be the critical variables accounting for the striking difference in performance on the two tasks by the animals MDL lesions. This difference in performance must therefore be attributed to the difference in the monitoring requirements of the tasks. This interpretation is tested directly in the present experiment in which the animals are presented with a self-ordered task in which two levels of monitoring within working memory are being compared, everything else being kept the same.

Procedure

In this experiment, the stimuli were small objects presented over small white plaques covering the food wells (10.5 cm apart) of a three-well black testing board. Two conditions of testing were compared in this experiment. In both conditions, there were only two trials administered per day, a presentation trial followed by a test trial, and the testing procedure was identical, except for the number of stimuli shown on the presentation trial. In the two-stimulus condition, two small objects were presented over two small white plaques covering two adjacent food wells of the testing board. In the three-stimulus condition, three small objects were also presented over small white plaques covering the three food wells of the testing board. In the presentation trial, every stimulus covered a reward that was hidden in the food well underneath the small white plaque. When the opaque screen was raised to initiate the presentation trial, the monkeys were allowed to displace any one of the stimuli to retrieve the reward, and the screen was then lowered. After a delay of 10 sec, it was raised again to administer the test trial. On the test trial, in both conditions, the monkey was faced with only two stimuli, placed over white plaques covering the two lateral food wells of the testing board. In the three-stimulus condition, the animal faced the stimulus that he had chosen on the presentation trial and one of the other two stimuli that he had not selected; the nonselected stimulus shown on the test trial was randomly determined. In the two-stimulus condition, the animal faced the same two stimuli that he had seen on the presentation trial. On the test trials of both conditions, only the stimulus not selected on the presentation trial covered a reward, and the monkey was therefore rewarded only if he uncovered that stimulus. The left/right position of the two stimuli was determined according to a random but balanced order (Gellermann schedule). The animals were first tested for 40 d on the two-stimulus condition, and then for another 40 d on the three-stimulus condition. The same two (or three) stimuli were used throughout testing in both conditions.

Results

Two-stimulus condition. As can be seen in Figure 11, the animals with the MDL lesions performed slightly worse than both the normal control animals and the animals with PA lesions. A Kruskal–Wallis ANOVA on the correct responses made by the three groups did not reach the accepted level of significance [$H(2) = 4.71, p < 0.092$]. A comparison of the MDL group with the normal control group (Mann–Whitney test) yielded a $U = 0.5$, $n_1 = 3$, $n_2 = 4$, $p < 0.057$ and a comparison of the MDL with the PA group a $U = 0.5$, $n_1 = 3$, $n_2 = 3$, NS. It is clear that the animals with the MDL lesions are only slightly, if at all, impaired on this task in comparison with the control groups. The results are similar to those obtained in the nonspatial object alternation task (experiment 4), suggesting that the demands of the present task, for the animals with MDL lesions, were comparable to those of the object alternation task.

Three-stimulus condition. A very severe impairment was evident in the three-stimulus condition (see Fig. 11). The animals with MDL lesions were performing at the level expected by chance. A Kruskal–Wallis ANOVA indicated significant differences between the groups [$H(2) = 5.98$, $p < 0.05$]. The MDL group was impaired relative to both the NC (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$).

Comment

In this experiment, the monkeys were allowed to select from a two- or a three-stimulus set on a presentation trial and, on a subsequent test trial they were faced with a choice between the stimulus they had selected and one of the stimuli that they had not selected. Note that in both conditions, the test trial was identical in terms of the delay intervening between it and the presentation trial, the need to remember the stimulus that was selected on the presentation trial, the reward that was hidden under the nonselected stimulus, and the form of presentation of the stimuli over the two lateral food wells. The only difference was in the size of the stimulus set that the monkeys had to consider in making their choice: the selected object was one of three possible ones in the three-stimulus condition and one of two stimuli in the other condition. This difference in the monitoring demands of the two conditions must therefore account for the striking difference in performance of the animals with MDL lesions, since everything else was kept constant on the test trials.

Experiment 6: recognition memory and monitoring of externally ordered stimuli

An earlier experiment compared the performance of the present animals on a self-ordered task in which they had to monitor their choices from a set of three stimuli and on a recognition memory task in which correct performance could be the result of familiarity discrimination (Petrides, 1991a). The animals with MDL lesions performed at chance on the self-ordered task, but were unimpaired on the recognition memory task. The purpose of the present experiment was to extend the earlier findings by comparing the performance of the monkeys with MDL lesions in two testing conditions that were identical in every respect, except that one required *monitoring of an externally ordered* set of stimuli and the other *recognition memory*. In both conditions, the animals were first shown two objects in succession, and, on a subsequent test trial, these two objects were presented together with a third object. In the *recognition* condition, new objects were used all the time and thus performance could be based on the ability to recognize the familiar stimuli. In the *monitoring* condition, however, the same set of three objects were used every day. Since all the objects were now familiar, performance had to be based on the ability to recall those specific objects from the familiar set that had occurred on the preceding two trials. Based on the findings of experiments 2 and 3, it was predicted that the animals with MDL lesions would be impaired in the monitoring condition; performance in the recognition condition was expected to be normal, as was the case in the earlier test of recognition memory administered to these monkeys (Petrides, 1991a).

Procedure

Recognition condition. In this condition, and in the monitoring condition (see below), the daily testing session consisted of only three trials: two presentation trials followed by a test trial. The intertrial interval was 10 sec. When the screen was raised to initiate the first presentation trial, the animal saw one object on a small white plaque covering the central food well of a testing board with three food wells (10.5 cm apart). When the animal had displaced the plaque and obtained the reward that was under it, the screen was lowered. On the second presentation trial, a different object was placed on the central food well and, after

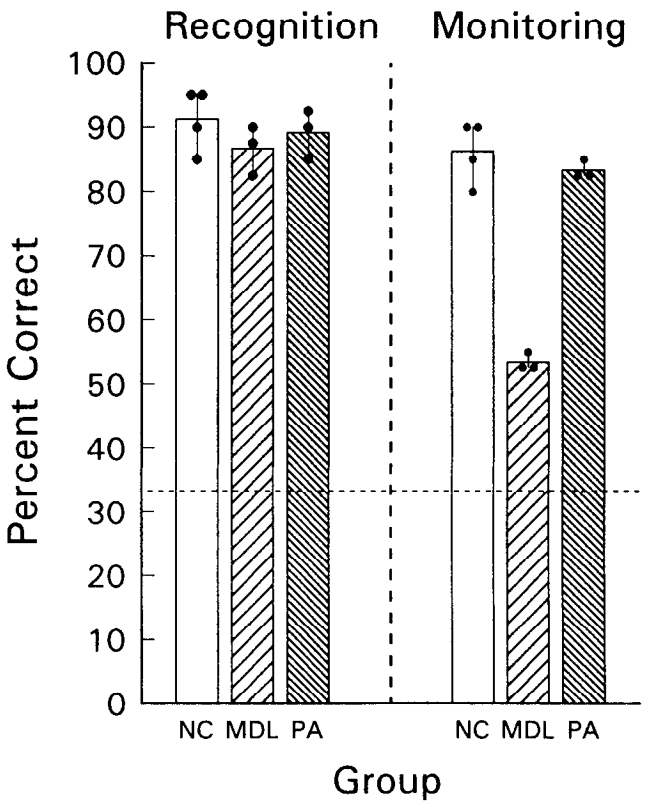

Figure 12. Mean percentage of correct responses made by the three groups of animals in the recognition and the monitoring conditions of experiment 6. The level of chance performance (33.3%) is indicated by the *horizontal dashed line. Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

the animal had obtained the reward that was under it, the screen was lowered to terminate the trial. A test trial was then administered during which the two objects shown on the preceding two trials were presented together with a new object. The position of these objects over the three food wells was randomly determined. The reward was now hidden under the novel object and, thus, the monkey was rewarded only if he selected that object. Different objects were used each day and these were drawn randomly from a pool of hundreds of small objects. The animals were tested for 40 consecutive days.

Monitoring condition. The testing procedure was identical to that of the recognition condition, except that now the *same* three objects were used throughout the experiment. The daily test session consisted of only three trials and the intertrial interval was 10 sec. During the first trial, one of the three objects, drawn randomly from the set of three stimuli, was presented on the central food well. On the second trial, one of the remaining two objects, again drawn randomly, was presented on the central food well. The objects presented on these two presentation trials covered a reward and the monkey was allowed to displace the object to obtain the reward. On the third trial, all three objects were presented together, but now only the object that had not been shown on the two presentation trials covered a reward. The position of the three objects over the three food wells was randomly determined. To perform well on the test trial, the animal had to recall which ones of the three stimuli had occurred

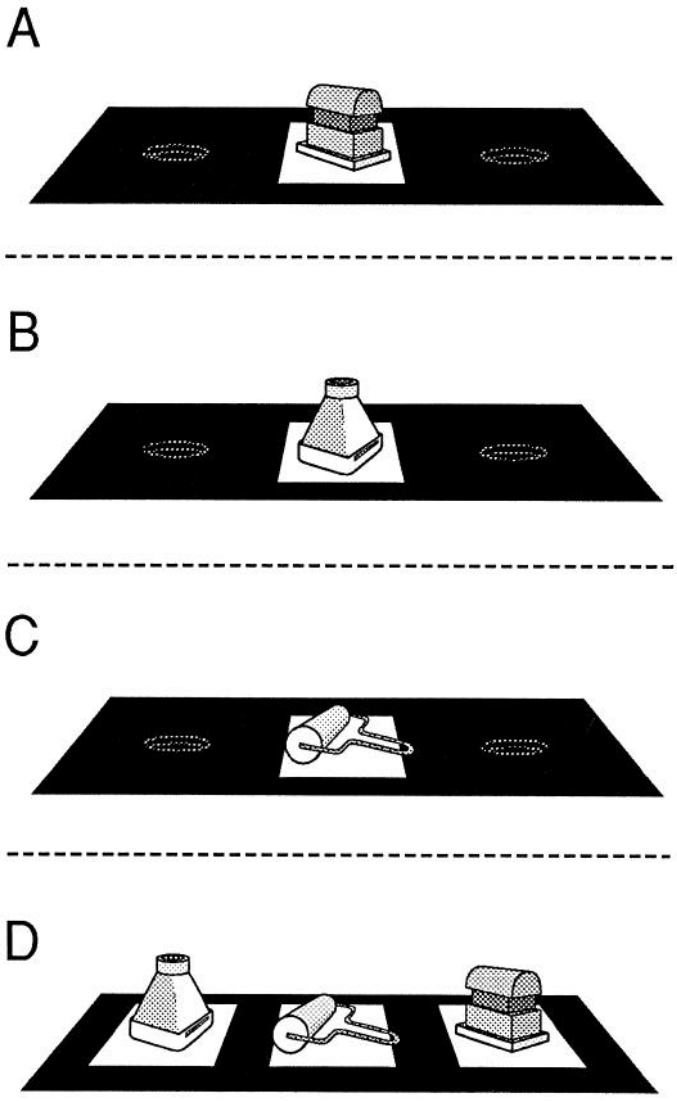

Figure 13. Schematic diagram of the experimental arrangement in experiment 7. *A–C* represent three presentation trials and *D* the test trial that follows. The order according to which the three objects are shown during the three presentation trials (*A–C*) was randomly determined. On the subsequent test trial (*D*), all three objects are shown together. The relative position of the objects over the three food wells in the test trial was randomly determined.

on the first two trials. Forty days of testing were administered in this manner.

Results

Recognition condition. The performance of the three groups of monkeys is shown in Figure 12. It can be seen that all groups performed well in the recognition memory condition. A Kruskal–Wallis ANOVA did not reveal significant differences in performance among the three groups [$H(2) = 1.92$, NS].

Monitoring condition. As can be seen in Figure 12, the group of monkeys with MDL lesions exhibited a severe impairment in this condition [$H(2) = 6.12$, $p < 0.05$]. The MDL group was impaired in comparison with the normal control group (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$).

Comment

The findings in the monitoring condition were similar to those of experiments 2 and 3. The monkeys with MDL lesions were severely impaired when their choices had to be based on memory of which stimuli from a familiar set had previously been presented. The deficit exhibited by these monkeys in the monitoring condition contrasted sharply with their excellent performance in the recognition condition in which they could base their choices on the ability to discriminate the familiar from the unfamiliar stimulus. This experiment is in agreement with the findings of Bachevalier and Mishkin (1986), who showed that dorsolateral frontal lesions do not affect recognition memory and replicated the earlier result with these same animals showing that their recognition memory was not affected by the lesion they had sustained in the mid-dorsal part of the lateral frontal cortex (Petrides, 1991a).

Experiment 7: primacy effect

On completion of experiment 6 and before the present experiment was carried out, all monkeys were trained on a serial order memory task in which they were required to monitor the order of occurrence of a set of stimuli (Petrides, 1991b). In this task, the monkeys saw a number of objects in sequence and were subsequently tested with two of these objects. In this test trial, the animals were required to select the object that had occurred earlier in the sequence. Monkeys with MDL lesions were severely impaired in order judgements, except when the pair of stimuli shown in the test trial included either the first or the last stimulus of the sequence. Thus, the animals with the MDL lesions were able to use primacy and recency mnemonic effects to make simple judgements of serial order, although they were otherwise completely unable to judge serial order. In the serial order task, different sets of objects were used in the various sequences presented to the monkeys. The purpose of the present experiment was to examine whether a normal primacy effect can also be observed after MDL lesions in a situation where the same stimuli recur constantly, thus increasing proactive interference.

Procedure

The stimuli used in this experiment were three small objects, and these three objects were used throughout testing (Fig. 13). In this task, three presentation trials were followed by a test trial. During each presentation trial, the animal saw one of the three objects on a small white plaque covering the central food well of a testing board with three food wells (10.5 cm apart). The animal was allowed to displace the plaque to obtain the reward that was hidden under it. The order in which the three objects were shown during the three presentation trials was randomly determined. On the test trial, which followed the presentation trials, the animal saw all three objects placed over small white plaques covering the three food wells. Only the object that had been shown on the first presentation trial now covered a reward and, therefore, the animal was rewarded if he selected that object. The relative position of the objects over the three food wells was randomly determined. Ten such sets of presentation and test trials were administered per day. A trial was initiated by raising the screen and terminated by lowering the screen and the intertrial interval was 10 sec. The animals were tested on this task for 40 consecutive days.

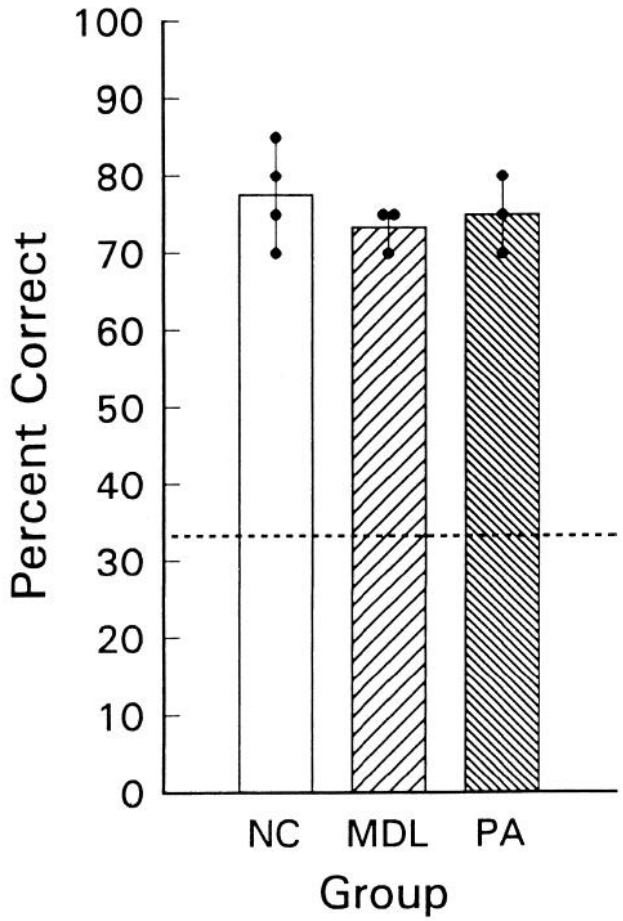

Figure 14. The mean percentage of correct responses made by the three groups in experiment 7. The level of chance performance (33.3%) is indicated by the *horizontal dotted line. Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

Results and comment

There were no significant differences between the three groups on this task [Kruskal–Wallis test: $H(2) = 0.89$, NS]. As can be seen in Figure 14, the monkeys with MDL lesions were able to perform just as well as the normal control monkeys and those with the PA lesions. These findings extend those previously obtained on the serial order task with these same animals (Petrides, 1991b) by showing that MDL lesions do not impair memory performance that can be based on the saliency of the first stimulus presented (i.e., primacy effect), even when proactive interference is increased by using a constantly recurring set of stimuli.

Experiment 8: retest on the self-ordered task

The purpose of this experiment, which was conducted approximately 3 years after operation, was to find out whether the monkeys with MDL lesions would still be impaired on the original self-ordered task despite the passage of time and the extensive testing that they had received on various nonspatial memory tasks.

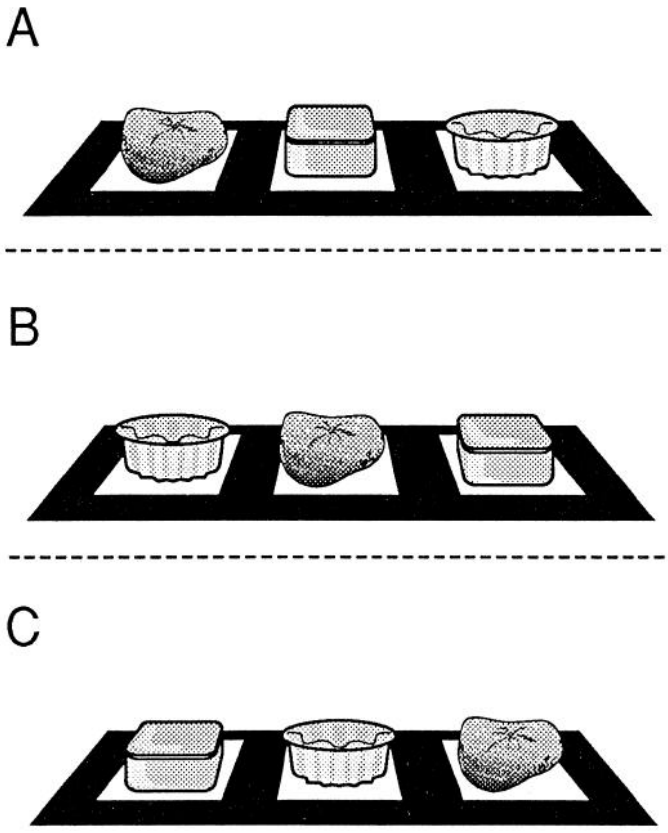

Figure 15. Schematic diagram of the experimental arrangement in the self-ordered task (experiment 8). On each trial, three objects differing in color and shape were presented in a row over small white plaques that covered the three food wells of the test board. The position of the three objects was randomly determined. *A–C* illustrate examples of three different trials.

Procedure

On each trial of this experiment, when the screen was raised, the animals were faced with a horizontal array of three small objects. These objects were placed over small white plaques, each one covering one of the three food wells (10.5 cm apart) of the testing board (Fig. 15). On the first trial, all three objects covered a reward and the animal was allowed to displace any one of the three plaques to obtain the reward that was under it. On subsequent trials, the same three objects were presented, but with their relative positions changed according to a random order. Only the objects that had not been selected on the preceding trials covered a reward. This procedure was continued until each one of the three objects was selected once, thus completing a set of trials. Three different objects were then used to administer another set of trials in the same manner. Five such sets of trials completed the day's testing. The animals were tested for 50 d on this experiment. Different objects were used on each of these 50 d of testing. As in all other experiments in this series, raising of the screen initiated a trial and lowering it terminated that trial. The intertrial interval was 10 sec.

Results and comment

Figure 16 shows the combined performance on trials 2 and 3 during each one of five 10 d blocks of testing. A Kruskal–Wallis test on the performance of the three groups over the total 50 d of testing revealed significant differences [$H(2) = 5.74, p < 0.05$].

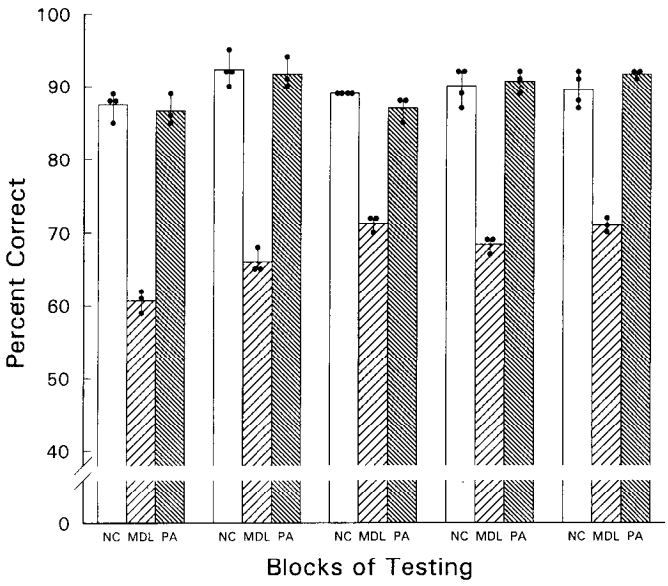

Figure 16. Mean percentage of correct responses made by the three groups of animals on the self-ordered task (experiment 8). Since responses on trial 1 will always be correct, performance measures are based only on trials 2 and 3. *Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

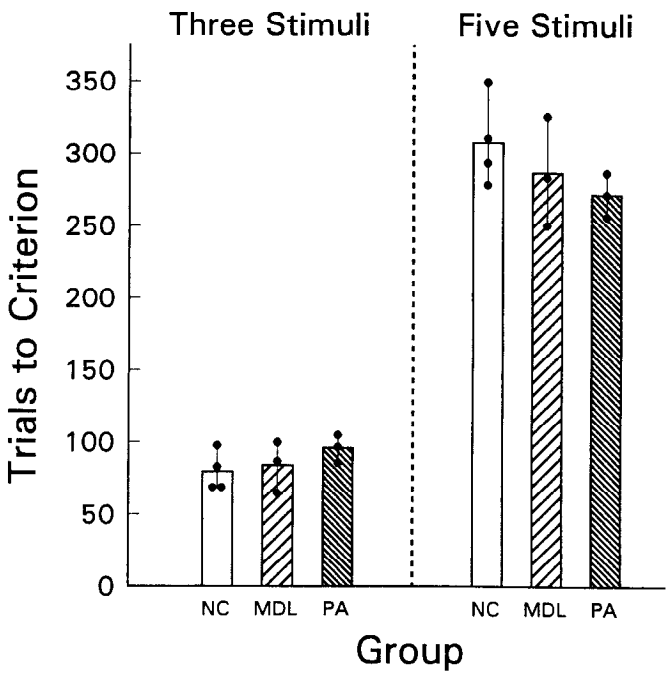

Figure 17. Mean number of trials to achieve criterion by the three groups of animals on the fixed order task with three stimuli and the fixed order task with five stimuli in experiment 9. *Solid circles* indicate the scores of individual animals in each group. *NC,* normal monkeys; *MDL,* monkeys with lesions of the mid-dorsal part of the lateral frontal cortex; *PA,* monkeys with lesions of the periarcuate cortex, that is, the posterior dorsolateral frontal cortex.

The animals with the MDL lesions were impaired in comparison with the normal control group (Mann–Whitney test: $U = 0$, $n_1 = 3$, $n_2 = 4$, $p = 0.028$) and the PA group ($U = 0$, $n_1 = 3$, $n_2 = 3$, $p = 0.05$). The present results confirmed those obtained in experiment 1, but, more importantly, demonstrated the long-lasting nature of the impairment on the self-ordered task after MDL lesions. It must be pointed out that this experiment was carried out approximately 3 years after experiment 1 and that the animals had been tested extensively during this period on various nonspatial mnemonic tasks. In all these tasks, the same principle applied, namely, the avoidance of objects that had been selected before. Despite this extensive training and the fact that the animals with MDL lesions had repeatedly shown that they could apply this principle (e.g., object alternation in experiment 4, two-stimulus condition in experiment 5, etc.), they were still impaired on the self-ordered task when tested approximately 3 years later.

Experiment 9: selection of stimuli according to a fixed order

In the present series of experiments, monkeys with MDL lesions were impaired on nonspatial working memory tasks in which they had to monitor their selections (experiments 1, 5, and 8, and Petrides, 1991a) or the occurrence of stimuli from a given set (experiments 2, 3, and 6). It is important to note that, in these tasks, the animals not only must maintain an on-line record of the stimuli that they have chosen (self-ordered tasks) or have occurred (externally ordered tasks), but they must also continually compare these stimuli against those that remain to be selected (self-ordered tasks) or to occur (externally ordered tasks).

Experiments 4 and 5 demonstrated that neither the memory of the selected stimuli nor the length of the delay can account for the impairment on the self-ordered and the externally ordered tasks after MDL lesions; it is, rather, the size of the set of the stimuli that must be monitored in working memory that accounts for this impairment. This monitoring process is, of course, taxed in situations, like the above, where any one of a set of stimuli can occur, and, therefore, the animal must constantly monitor what has occurred against the expected set.

If the above interpretation is correct, animals with MDL lesions should *not* be impaired on tasks in which they would have to learn to select a set of stimuli always in the same *fixed* order. Such a task would not challenge monitoring mechanisms within working memory since each response would be totally determined by the preceding one. In a fixed order task, the animal does not have to consider the total set of possible responses and to compare what has occurred against this set, since he is merely performing an acquired chain of responses. Provided that the monkey can maintain in short-term memory the stimulus that was shown on the preceding trial, performance can be normal. The present experiment examined this prediction. The monkeys were trained on a three- and a five-set fixed order task in which they had to learn to select the stimuli in a predetermined sequence.

Procedure

Part I. The stimuli were the same three containers that had been used in experiments 1 and 2 (see Fig. 3). These containers were arbitrarily designated as A (the yellow one), B (the red one), and C (the blue one), denoting the order in which the animals had to learn to select them on successive trials during the daily testing session. When the opaque screen was raised to initiate a trial, the monkey saw the three containers arranged in a horizontal

row. The relative position of these three stimuli on each trial was randomly determined. The animal was allowed to open one of the three containers on a given trial in order to find the reward. When the animal had made his choice, the screen was lowered and another trial was administered after a 10 sec intertrial delay.

On the first trial, only the container designated as A (i.e., the yellow one) had a reward hidden in it. If the animal made an error, that is, if he did not choose container A, the reward remained in this container on the subsequent (correction) trials until the animal had retrieved it. On the next trial(s), the reward was hidden in container B (i.e., the red one), again until the animal had discovered it. The reward was finally hidden in container C (i.e., the blue one), and the daily testing session was terminated when container C was selected, that is, when all three rewards had been retrieved. Thus, the daily testing session could be terminated after only three trials if the animal responded correctly on every trial. Each animal was tested until he reached the learning criterion of no errors over 10 consecutive days.

Part II. The same task was administered as in part I, except that now five stimuli were used. These stimuli were five small objects presented to the animals in a horizontal row and placed over small white plaques that covered five food wells (7.6 cm apart) on a black testing board. The five stimuli were arbitrarily designated as A, B, C, D, and E to denote the order in which the animals would have to learn to select them. As in part I, all stimuli were presented on every trial, but their relative position over the five food wells varied randomly from trial to trial. When the screen was raised to initiate a trial, the animal was allowed to displace one of the objects and the screen was lowered to terminate the trial. The intertrial interval was 10 sec. At the beginning of the daily testing session, the reward was under object A, and remained under that object on subsequent trials until it was retrieved. The reward was then hidden under object B until it was retrieved, and testing continued in this manner until the reward was retrieved from all five objects. Thus, the daily testing session could be terminated after only five trials if no errors were made. Learning of the task was considered complete when the animal made no errors during 10 consecutive daily test sessions.

Results and comment

As can be seen in Figure 17, there were no differences among the three groups in the number of trials necessary to reach the learning criterion either in part I, the three-stimulus task [Kruskal–Wallis test: $H(2) = 1.43$, NS] or in part II, the five-stimulus task [$H(2) = 2.52$, NS]. The learning curves of the animals were similar across groups. The results of this experiment demonstrated that monkeys with MDL lesions can learn, at a normal rate, a task in which they have to select stimuli from a set according to a fixed order and, having learned it, can perform at a very high level. It must be emphasized that the nature of the stimuli, the mode of display of the stimuli, the reward, and the intertrial delays used in this experiment were the same as those used in the self-ordered (experiments 1, 5, and 8) and the externally ordered (experiments 2, 3, and 6) tasks, that is, tasks in which these animals manifested a profound impairment. In the fixed order task, unlike the self-ordered or externally ordered tasks, the monitoring requirements are radically reduced since the animal is following a fixed sequence of responses. It is important to note that the fixed order experiment is analogous to the classical list learning experiments carried out with human subjects where a sequence of stimuli is learned by rote. In contrast to this, in the recently devised self-ordered and externally ordered tasks, the monitoring requirements within working memory are maximized by allowing flexible selections of stimuli.

Discussion

The present investigation demonstrated severe and long-lasting impairments on the self-ordered and externally ordered *nonspatial* working memory tasks after lesions limited to the mid-dorsal (MDL) part of the lateral frontal cortex (experiments 1, 2, 3, 5, 6, and 8). These lesions involved the middle portion of the dorsal frontal cortex that extends above the sulcus principalis as far as the midline (i.e., dorsal area 46 and area 9), but spared its rostralmost part (area 10) and the posterior dorsolateral cortex (area 8). These results provide the first demonstration of a severe nonspatial mnemonic impairment after lesions confined to the mid-dorsal frontal cortex. Earlier work had shown that even lesions of the entire dorsal frontal cortex above the sulcus principalis do not impair performance on the traditional spatial delayed response (Goldman et al., 1971) and spatial delayed alternation (Mishkin, 1957; Goldman and Rosvold, 1970) tasks; nor do such lesions impair performance on a nonspatial analog of these tasks, such as the delayed object alternation (Mishkin et al., 1969). Furthermore, although lesions of the dorsal frontal cortex in combination with lesions of the sulcus principalis (Manning, 1978; Passingham, 1978) and the premotor cortex (Mishkin et al., 1977) were reported to yield impairments on tasks requiring kinesthetic discrimination, lesions confined to the dorsal frontal cortex above the sulcus principalis have not yielded such impairments (Passingham, 1985b).

In the self-ordered and externally ordered nonspatial tasks used in the present investigation, the arrangement of the stimuli varied randomly on each trial, making it impossible for the animals to use either spatial or motor (kinesthetic) coding of the responses to the stimuli. Thus, solution of these tasks had to be based entirely on memory of the visual stimuli and neither a spatial nor a motor explanation could account for these impairments. Furthermore, it should be pointed out that the type of stimuli used and their arrangement (i.e., two or three stimuli arranged in a horizontal row) were the same in both the experimental tasks (i.e., the self-ordered and externally ordered tasks), which animals with MDL lesions failed, and the control tasks (e.g., object alternation, fixed order task, etc.) on which these same animals succeeded. Thus, poor performance on any one task could not be explained by a general perceptual or attentional impairment.

Experiment 1 demonstrated that lesions of the mid-dorsal frontal cortex, but not lesions of the adjacent posterior dorsolateral frontal cortex (i.e., area 8 and rostral area 6), impair performance of the self-ordered task. This nonspatial mnemonic task was modeled on a test that had previously proved to be an extremely sensitive indicator of damage to the human frontal cortex (see Petrides and Milner, 1982). In the self-ordered task, the monkeys were shown, on each trial, a set of three visual stimuli and were allowed to select one of these stimuli. Across trials, the animals were required to monitor their selections from this set so that no stimulus would be chosen more than once. The impairment on the self-ordered task was both severe and long-lasting, as shown by the fact that it could be demonstrated both soon after the MDL lesions (experiment 1) and 3 years after the operation (experiment 8).

Experiments 2, 3, and 6 demonstrated that the impairment

observed after MDL lesions is not limited to the monitoring of self-generated choices, but that it is a more general impairment that includes the monitoring from working memory of externally ordered stimuli. In the externally ordered tasks (experiments 2, 3, and 6), the monkeys were first shown, during forced-choice presentation trials, two stimuli from a known set of three, and, on the subsequent test trial, they had to select the stimulus that had not yet been presented. Thus, correct performance required monitoring, across trials, of the occurrence/nonoccurrence of stimuli from a known set. A related question whether the mid-dorsal part of the frontal cortex is also involved in the monitoring of externally ordered stimuli that need no overt response from the subject was recently answered in the affirmative in a functional activation study with positron emission tomography (Petrides et al., 1993b). This study demonstrated clear activation within the human mid-dorsal frontal cortex during the performance of an externally ordered task requiring no overt response from the subject.

The striking impairment observed after MDL lesions on the nonspatial self-ordered (experiments 1, 5, and 8) and externally ordered (experiments 2, 3, and 6) working memory tasks stood in sharp contrast to the earlier report that monkeys with large lesions that included the cortex of the sulcus principalis and all of the dorsal cortex as far as the midline were not markedly impaired on another nonspatial working memory task, the delayed object alternation (Mishkin et al., 1969). In agreement with this earlier report, the present monkeys with the MDL lesions, who had performed so poorly on the self-ordered and externally ordered nonspatial mnemonic tasks in experiments 1, 2, 3, 5, 6, and 8, performed only slightly worse than the control animals during the first 2 d of testing on delayed object alternation, and were subsequently completely unimpaired (experiment 4).

How does delayed object alternation differ from the self-ordered and externally ordered tasks? Correct performance of all these nonspatial working memory tasks requires that the animal remember, during the intertrial interval, the stimulus that was presented (or chosen) on the preceding trial. In other words, all these tasks require maintenance of information during the intertrial delay, as well as the ability to categorize a selection as having been executed or not. If the impairment on the self-ordered and externally ordered tasks after MDL lesions reflected a simple failure to maintain a particular piece of information during the delay or a failure to categorize choices as being completed or not, then a severe impairment should also have occurred on the object alternation after such lesions. This was clearly not the case: the animals with the MDL lesions performed well on the object alternation task even with 60 sec intertrial delays and despite the high interference resulting from the continuous recurrence of the same two stimuli during the daily test session (experiment 4). Furthermore, a recent study has shown that even when the intertrial delay in object alternation is increased until the performance of normal animals falls to chance, the performance of animals with MDL lesions declines at the same rate as that of the normal control subjects (Petrides, unpublished experiments).

What then is the origin of the increased memory challenge in the self-ordered and externally ordered tasks in comparison with the object alternation task for the animals with MDL lesions? In the self-ordered and externally ordered tasks, every effort was made to minimize proactive interference from preceding trials by administering only a few trials per day, but to increase the monitoring demands within working memory. The monitoring demands within working memory (i.e., verification of what has occurred against what remains to occur) increase as the number of possible choices increases in a mnemonic task that allows flexible selections of stimuli. For instance, in the self-ordered task, even after a single response, the subject must compare his selection against all three possible choices in order to perform correctly. By contrast, in comparison with the self-ordered and externally ordered tasks, the object alternation task maximizes proactive interference from preceding trials because several trials are administered one after the other, but it has minimal monitoring requirements since the response on each trial is completely specified by the memory of the preceding event. Thus, provided that the animal can remember the stimulus that has occurred on the immediately preceding trial and can follow the fixed sequence of alternating between the two stimuli, performance can be correct.

Experiment 5 tested the hypothesis that the difference in difficulty between the object alternation task and the self-ordered and externally ordered tasks for the animals with MDL lesions is due to the greater number of stimuli that must be monitored in the two latter tasks. In experiment 5, the animal was allowed to choose, during a single daily presentation trial, one out of two or three stimuli, and was subsequently tested for memory of the selected stimulus. Only one test trial was administered per day to eliminate the potentially interfering effects from preceding trials (i.e., proactive interference) and, regardless of whether on the presentation trial two or three stimuli were shown, on the test trial the animal was faced with a choice between only two stimuli: the stimulus that had been previously selected and a stimulus that had not been selected. In this manner, the test trials were identical in every respect (i.e., number of stimuli present, display of the stimuli, response required, etc.), and the only factor that varied in the experiment was the size of the set of the stimuli from which the original choice had been made. Animals with MDL lesions performed well when the stimulus had been selected from a two-stimulus set, but performed at chance when the set of the possible stimuli was increased to three, suggesting that the source of their impairment in the self-ordered and externally ordered tasks was the number of potential choices that had to be monitored.

Experiment 9 also indicated that the impairment in the self-ordered and externally ordered tasks after MDL lesions was due to their increased monitoring requirements within working memory. In this experiment, the monkeys with MDL lesions were able to learn, at a normal rate, to select the various stimuli of a set according to a fixed order. The same set of stimuli was presented on each trial and the animal was required to select one of these stimuli per trial until all had been selected. Unlike the self-ordered task, however, the animal was required to learn to select the stimuli of the set always in the same fixed order. Thus, on each trial, performance was based on a learned sequence (i.e., a chain of responses), the stimulus to be selected being completely determined by the response that occurred just before the delay. In other words, correct performance was minimally dependent on monitoring within working memory since it was based on the execution of a well-learned chain of responses. Note that the fixed order task is analogous in cognitive requirements to the object alternation task where, once the rule of alternating has been learned, each choice is completely determined by the preceding one. By contrast, the self-ordered and externally ordered tasks, by allowing flexible selections of stim-

uli, maximize the monitoring requirements within working memory since no choice is ever completely specified. It is interesting to note that an earlier study showed that monkeys with extensive dorsolateral frontal lesions could learn, at a normal rate, fixed sequences of movements (Passingham, 1985b).

There are a wealth of data showing that lesions of the cortex lining the sulcus principalis result in impairments on various spatial working memory tasks (Goldman-Rakic, 1987). It is now clear that *basic mnemonic processing is not affected* by lesions of the dorsal part of the lateral frontal cortex that lies above the sulcus principalis. Such lesions do not affect basic recognition memory, that is, the capacity to discriminate between familiar and unfamiliar stimuli (Bachevalier and Mishkin, 1986; Petrides, 1991a; experiment 6), nor do they affect primacy (experiment 7 and Petrides, 1991b) and recency (Petrides, 1991b) mnemonic effects, that is, the capacity to discriminate between the initial (or final) items and other items in a list of stimuli. These lesions, however, cause a severe impairment in working memory that is related to the number of possible choices that the animals have to monitor. A recent study of regional cerebral blood flow with positron emission tomography in human volunteer subjects performing various working memory tasks lends further support to the above analysis (Petrides et al., 1993a). In that study, subjects were scanned as they performed a visual nonspatial self-ordered task and a visual control task. Every aspect of the control task (e.g., the nature of stimuli, mode of presentation of the stimuli, mode of response, etc.) was the same as that in the self-ordered task, except for the greater monitoring requirements of the latter task. When activation during the performance of the control task was subtracted from activation during the self-ordered task, specific activation within the human mid-dorsal part of the lateral frontal cortex was observed (Petrides et al., 1993a).

References

Bachevalier J, Mishkin M (1986) Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. Behav Brain Res 20:249–261.

Barbas H, Mesulam M-M (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. J Comp Neurol 200: 407–431.

Bauer RH, Fuster J (1976) Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. J Comp Physiol Psychol 90:293–302.

Butters N, Pandya DN (1969) Retention of delayed-alternation: effect of selective lesions of sulcus principalis. Science 165:1271–1273.

Butters N, Pandya DN, Sanders K, Dye P (1971) Behavioral deficits in monkeys after selective lesions within the middle third sulcus principalis. J Comp Physiol Psychol 76:8–14.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1993) Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas." J Neurosci 13:1479–1497.

Fuster JM, Bauer RH (1974) Visual short-term memory deficit from hypothermia of frontal cortex. Brain Res 81:393–400.

Goldman PS, Rosvold HE (1970) Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. Exp Neurol 27: 291–304.

Goldman PS, Rosvold HE, Vest B, Galkin TW (1971) Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. J Comp Physiol Psychol 77:212–220.

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and the regulation of behavior by representational memory. In: Handbook of physiology, Sec 1, The nervous system, Vol 5 (Plum F, Mountcastle V, eds), pp 373–417. Bethesda, MD: American Physiological Society.

Gross CG, Weiskrantz L (1962) Evidence for dissociation of impairment on auditory discrimination and delayed response following lateral frontal lesions in monkeys. Exp Neurol 5:453–476.

Manning FJ (1978) Dorsolateral prefrontal cortex lesions and discrimination of movement-produced cues by rhesus monkeys. Brain Res 149:77–88.

Mishkin M (1957) Effects of small frontal lesions on delayed alternation in monkeys. J Neurophysiol 20:615–622.

Mishkin M, Manning FJ (1978) Non-spatial memory after selective prefrontal lesions in monkeys. Brain Res 143:313–323.

Mishkin M, Vest B, Waxler M, Rosvold HE (1969) A re-examination of the effects of frontal lesions on object alternation. Neuropsychologia 7:357–363.

Mishkin M, Pohl W, Rosenkilde CE (1977) Kinesthetic discrimination after prefrontal lesions in the monkey. Brain Res 130:163–168.

Pandya DN, Kuypers HGJM (1969) Cortico-cortical connections in the rhesus monkey. Brain Res 13:13–36.

Pandya DN, Dye P, Butters N (1971) Efferent cortico-cortical projections of the prefrontal cortex in the rhesus monkey. Brain Res 31: 35–46.

Passingham RE (1975) Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). Brain Res 92:89–102.

Passingham RE (1978) Information about movements in monkeys (*Macaca mulatta*) with lesions of dorsal prefrontal cortex. Brain Res 152:313–328.

Passingham RE (1985a) Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. Behav Neurosci 99:3–21.

Passingham RE (1985b) Prefrontal cortex and the sequencing of movement in monkeys (*Macaca mulatta*). Neuropsychologia 23:453–462.

Passingham RE (1986) Cues for movement in monkeys (*Macaca mulatta*) with lesions in premotor cortex. Behav Neurosci 100:695–703.

Petrides M (1988) Performance on a nonspatial self-ordered task after selective lesions of the primate frontal cortex. Soc Neurosci Abstr 14:2.

Petrides M (1989) Frontal lobes and memory. In: Handbook of neuropsychology, Vol 3 (Boller F, Grafman J, eds), pp 75–90. New York: Elsevier.

Petrides M (1991a) Monitoring of selections of visual stimuli and the primate frontal cortex. Proc R Soc Lond [Biol] 246:293–298.

Petrides M (1991b) Functional specialization within the dorsolateral frontal cortex for serial order memory. Proc R Soc Lond [Biol] 246: 299–306.

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

Petrides M, Alivisatos B, Evans AC, Meyer E (1993a) Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 90:873–877.

Petrides M, Alivisatos B, Meyer E, Evans AC (1993b) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 90:878–882.

Stamm J (1969) Electrical stimulation of frontal cortex in monkeys during delayed-response performance. J Comp Physiol Psychol 67: 535–546.

Wilson FAW, O Scalaidhe SPO, Goldman-Rakic PS (1993) Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 260:1955–1958.