Perseveration and Strategy in a Novel Spatial Self-Ordered Sequencing Task for Nonhuman Primates: Effects of Excitotoxic Lesions and Dopamine Depletions of the Prefrontal Cortex

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Abstract

■ Damage to the prefrontal cortex disrupts the performance of self-ordered sequencing tasks, although the precise mechanisms by which this effect occurs is unclear. Active working memory, inhibitory control, and the ability to generate and perform a sequence of responses are all putative cognitive abilities that may be responsible for the impaired performance that results from disruption of prefrontal processing. In addition, the neurochemical substrates underlying prefrontal cognitive function are not well understood, although active working memory appears to depend upon an intact mesocortical dopamine system. The present experiments were therefore designed to evaluate explicitly the contribution of each of these abilities to successful performance of a novel spatial self-ordered sequencing task and to examine the contribution of the prefrontal cortex and its dopamine innervation to each ability in turn.

Excitotoxic lesions of the prefrontal cortex of the common marmoset profoundly impaired the performance of the self-ordered sequencing task and induced robust perseverative responding. Task manipulations that precluded perseveration ameliorated the effect of this lesion and revealed that the ability to generate and perform sequences of responses was unaffected by excitotoxic damage to prefrontal cortex. In contrast, large dopamine and noradrenaline depletions within the same areas of prefrontal cortex had no effect on any aspect of the self-ordered task but did impair the acquisition of an active working memory task, spatial delayed response, to the same degree as the excitotoxic lesion. These results demonstrate that a lesion of the ascending monoamine projections to the prefrontal cortex is not always synonymous with a lesion of the prefrontal cortex itself and thereby challenge existing concepts concerning the neuromodulation of prefrontal cognitive function. ■

INTRODUCTION

Damage to prefrontal cortex results in impaired performance on a variety of self-ordered sequencing tasks, while leaving more general mnemonic abilities intact. Thus, clinical studies have consistently demonstrated that patients with unilateral or bilateral damage to frontal lobe structures are impaired on a range of self-ordered sequencing tasks using both verbal and nonverbal stimuli (Owen, Downes, Sahakian, Polkey & Robbins, 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Petrides & Milner, 1982). This work is supported by a series of elegant experiments in nonhuman primates that suggest that areas within the dorsolateral prefrontal cortex may sustain some of the cognitive abilities required for the performance of analogous tasks (Passingham, 1985; Petrides, 1991a, 1991b, 1995). Recent functional activation studies employing positron emission tomography in human subjects provide additional support for this localisation (Owen, Evans, & Petrides, 1996; Petrides, Alivisatos, Evans, & Meyer, 1993) and have led Petrides to propose a two-stage model of working memory with both dorsal and ventral executive processing systems (see Petrides, 1994).

Cognitive Processes Required for the Performance of Self-Ordered Sequencing Tasks

The cognitive abilities underlying the performance of self-ordered sequencing tasks and the degree to which these abilities are disrupted by frontal lobe damage have been the subject of some interest. Because all self-ordered sequencing tasks require the subject to select a different exemplar from a given set of stimuli, on each of several successive occasions, at least three cognitive abilities may be required for successful performance. Firstly, the tasks may make considerable demands on active working memory because the subject is required

to retain and update a list of previous selections throughout the duration of each trial but must erase this information prior to the next trial. The term *active working memory* is used here to define a process by which information about one or more selections is actively held "on-line," within a short-term memory store, for the duration of each trial. Consequently, a failure of active working memory processes may precipitate the poor performance that follows damage to prefrontal cortex. Certainly the extensive experimental and clinical literature concerning the role of prefrontal cortex in classical tasks that make demands on active working memory processes, such as spatial delayed response, spatial and object delayed alternation, and delayed matching to sample with recurring stimuli would support such a proposal (Blum, 1952; Butters & Pandya, 1969; Freedman & Oscar-Berman, 1986; Goldman & Rosvold, 1970; Gross & Weiskrantz, 1964; Jacobsen, 1936; Mishkin, 1957; Mishkin & Manning, 1978; Mishkin, Vest, Waxler, & Rosvold, 1969; Passingham, 1975; Pribram & Mishkin, 1956; Pribram, Mishkin, Rosvold, & Kaplan, 1952; Verin et al., 1993).

A second possibility is that damage to the prefrontal cortex may impair performance on self-ordered sequencing tasks by disrupting an inhibitory control mechanism that may be necessary to avoid reselection of previously chosen exemplars. Indeed, the perseverative behavior observed after ventral prefrontal lesions in both human and nonhuman primate studies that do not have an obvious active working memory component, such as discrimination reversals, go-no-go discriminations, and the extinction of previously rewarded responses, suggests a lack of inhibitory control following damage to ventral areas of prefrontal cortex (Brutkowski, Mishkin, & Rosvold, 1963; Butter, Mishkin, & Rosvold, 1963; Butter, 1969; Iversen & Mishkin, 1970; Jones & Mishkin, 1972; Lawicka, Miskin, & Rosvold, 1975; Rolls, Hornak, Wade, & McGrath, 1994).

Lastly, a fundamental requirement for the successful performance of self-ordered sequencing tasks may be the ability to plan or organize a sequence of responses. To date, only a few studies have evaluated sequencing ability within a self-ordered task in nonhuman primates, and these studies provide conflicting data concerning the role of the prefrontal cortex in this ability. Thus, organized searching patterns have been observed using variants of the Hamilton Search Task in which the monkey was required to search for food reward in four fixed locations (Meyer & Settlage, 1958). Although these very simple organizational strategies were disrupted by large lesions of the dorsolateral prefrontal cortex (Meyer & Settlage, 1958) or anterior cingulate (Stern & Passingham, 1994), there was no evidence of an impairment in strategic organization on a sequencing task involving 25 locations, following lesions of dorsolateral prefrontal cortex (Passingham, 1985).

Nevertheless, the critical role played by organizational strategies in the performance of self-ordered sequencing tasks and the importance of an intact prefrontal cortex for the manifestation of this ability in humans is highlighted by a series of studies on patients with neurological or neurosurgical conditions. We have found that the performance of several patient groups and their respective control subjects is positively correlated with the degree to which they employ a repetitive searching strategy on a spatial self-ordered sequencing task (Owen et al., 1990, 1992, 1995). Importantly, patients with damage to prefrontal structures are less efficient in their use of this strategy (Owen et al., 1990) in contrast to patients with Parkinson's disease or temporal lobe excisions whose impairment may therefore be more purely mnemonic in character (Owen et al., 1992, 1995). A more complete analysis of strategic organization within spatial self-ordered sequencing tasks in both monkeys and humans will be required to resolve the role of the prefrontal cortex in this ability.

The Neurochemical Substrates of Prefrontal Cognitive Function

The neurochemical substrates underlying the performance of self-ordered sequencing tasks have received very little attention. There is some evidence implicating dopamine systems in the modulation of this ability because the controlled withdrawal of L-dopa therapy has been shown to exacerbate the impaired performance of patients with Parkinson's disease on a self-ordered spatial sequencing task (Lange et al., 1992). However, the exact substrate for this effect remains to be resolved because it is known that there is degeneration within the dopaminergic and noradrenergic projections to the prefrontal cortex in addition to disruption of the dopaminergic projections into striatum in Parkinson's disease (Agid, Javoy-Agid, & Ruberg, 1987). Given the considerable body of evidence suggesting that the dopamine neurones projecting into the prefrontal cortex regulate active working memory processes, it may be that the dopaminergic modulation of self-ordered sequencing observed in Parkinson's disease also occurs through this system (see Goldman-Rakic, 1992). This prediction is explicitly tested in the present experiment. Although there is also some evidence suggesting that noradrenergic systems may play a role in the age-related decline in active working memory (Arnsten, Cai, & Goldman-Rakic, 1988; Arnsten & Constant, 1992; Arnsten & Goldman-Rakic, 1985), the neurochemical determinants of inhibitory control and response sequencing have never been evaluated. Furthermore, the degree to which the proposed role for dopamine within active working memory can be generalized to other cognitive abilities localized within the prefrontal cortex remains unclear. Indeed, we have previously found dissociable effects of damage to the prefrontal cortex itself, or its dopamine innervation, on a primate analogue of the Wisconsin Card Sort Test, a standard clinical test of frontal lobe

function (Dias, Robbins, & Roberts, 1996a; Roberts et al., 1994).

A Novel Self-Ordered Sequencing Task

A major problem inherent in previous spatial self-ordered sequencing paradigms is the identification of the core effect of a given lesion from the evidence provided within the basic paradigm. For example, it is extremely difficult to dissociate a failure of active working memory from a failure of inhibitory control when both effects are likely to manifest as a return to a previously visited location. Furthermore as Passingham (1985) noted, it is as reasonable to assert that a particular search is disorganized because of a lack of active working memory or inhibitory control as it is to deduce that there is a lack of active working memory or inhibitory control because a given search appears disorganized. The paradigm described in the current work attempts to use the intrinsic flexibility of computer-controlled, touch-screen technology to circumvent these problems.

The task was developed from the spatial self-ordered sequencing task we have used extensively on human subjects to demonstrate both strategic and mnemonic working memory impairments (Morris et al., 1988; Owen et al., 1990, 1995). Spatial self-ordered searching ability was examined in a specially designed automated apparatus in which blue squares were presented simultaneously at various locations on a color visual display unit (Figure 1). A standard set of eight possible locations were used in all experiments. On each trial the monkey had to touch each square on the screen once, and once only, in a self-determined sequence in order to obtain reward. It is important to note that reinforcement was only available *after* the successful completion of a given trial and that all of the squares disappeared from the screen for 0.5 sec after each response. Furthermore, if the monkey responded to any square in a given trial on more than one occasion, that trial was immediately terminated and scored as incorrect.

In Experiment 1 the baseline performance of each monkey was assessed on a standard set of 60 novel trials in which each trial contained a different array of squares. The array of squares selected for each trial was therefore novel in that it appeared only once each day. Difficulty was gradually incremented through the session by increasing the number of squares on the screen from two to three to four and finally to five squares. The same standard set of trials was presented on each of the 10 days over which baseline performance was measured. The order in which the trials were presented on a particular day was identical for each monkey but was different for each of the 10 test sessions, with the stipulation that on each test session the first 15 trials contained sequences of two squares, followed by 15 trials with three, four, and finally five squares.

The basic task requires that the monkey conducts a self-ordered search through the array of squares on the screen and therefore requires varying degrees of active working memory, inhibitory control, and response-sequencing ability. Three additional experiments were then performed in which the basic paradigm was modified in an attempt to provide an assessment of any lesion effect on each ability in isolation.

Self-Ordered Sequencing in the Absence of Perseveration

The contribution of perseverative responding to impaired performance was specifically explored in Experiment 2 in which perseveration was explicitly prevented. Thus, in this version of the basic task, once a particular square had been touched, that square did not reappear again until *after* an alternative square had been touched (which would in turn not reappear until yet another square had been touched). Hence, although it was still possible to fail trials with three or more squares, by returning to a square that had already been touched within that trial, it was now *impossible* to fail a trial by perseverating (i.e., responding to the same square twice in succession). This modification to the basic paradigm provides an important additional advance over previous self-ordered sequencing tasks in that it facilitates an assessment of performance in the *absence* of the debilitating effects of perseveration.

Self-Ordered Sequencing in the Absence of Active Working Memory

Because the induction of perseveration may be due to a failure of active working memory or a failure of inhibitory control mechanisms, in Experiment 3 the basic paradigm was further modified to allow these two mechanisms to be dissociated. Specifically, the prediction that monkeys with lesions of the prefrontal cortex would fail the basic task because of a disruption in inhibitory control processes was explicitly tested in Experiment 3 by the provision of external cues to signal the location of each previous response within each trial. The active working memory load was removed by ensuring that once a square had been touched, it changed color from blue to yellow and remained yellow throughout the duration of that particular trial. This manipulation should reverse an impairment resulting entirely from a disruption of active working memory processes but should have little effect on an impairment due to a lack of inhibitory control. We can therefore infer that any perseveration still present after this modification to the basic task must result from a lack of inhibitory control.

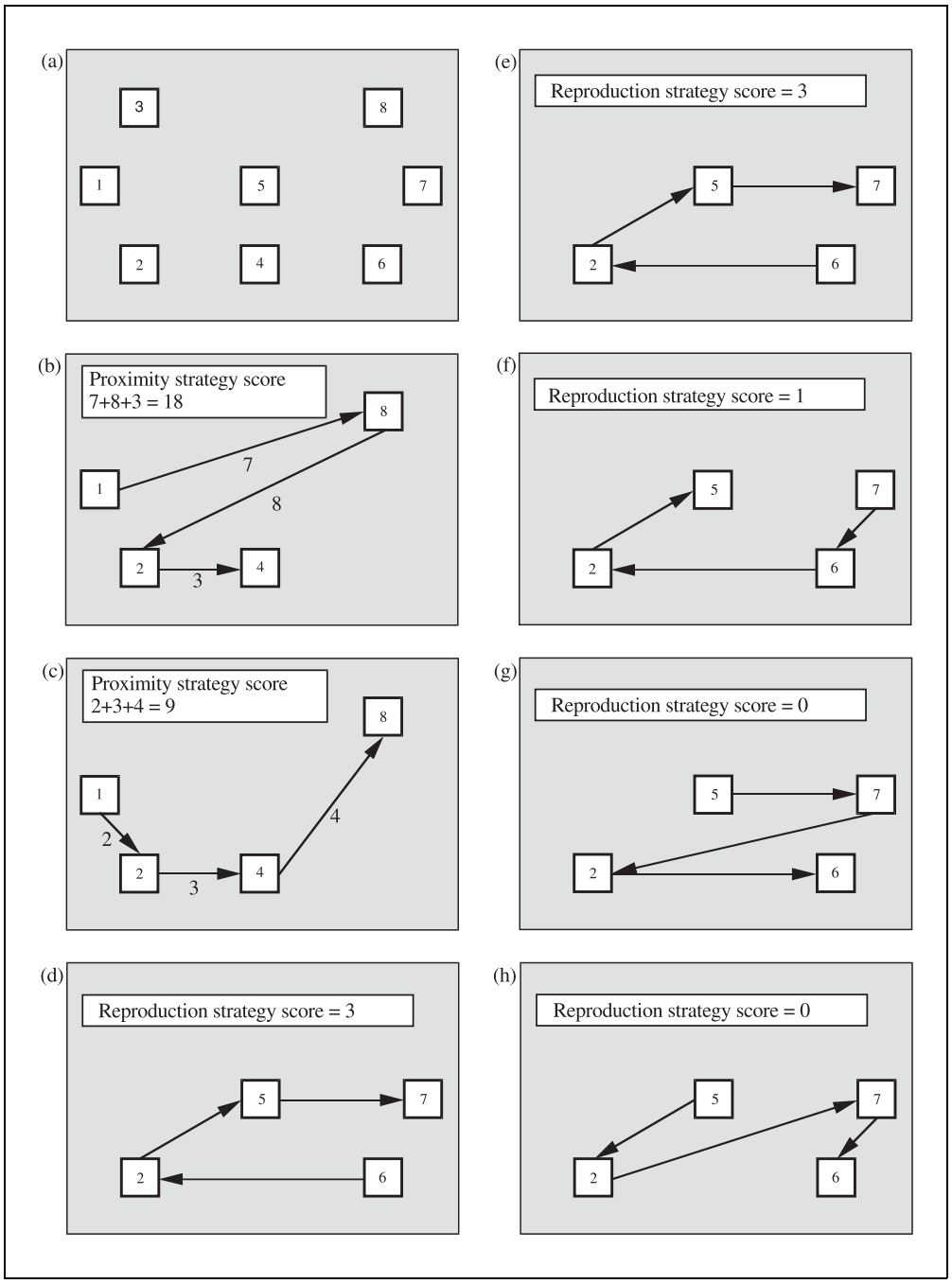

Figure 1. (a) Schematic diagram of the touch-sensitive screen used for the spatial self-ordered sequencing task showing the eight locations at which squares could appear. On any given trial an array consisting of two, three, four, or five squares would be presented and the monkey was required to touch each square on the screen once, and once only, to obtain reward. The three independent strategy scores were calculated as described below:

The proximity strategy score was calculated from the distance between each consecutive response within each correct solution, thereby providing a measure of the spatial "clustering" or "chunking" of responses within each particular trial. A separate score was calculated for trials containing three, four and five squares with mean values derived from all test sessions. Panels (b) and (c) demonstrate two solutions to a trial containing four squares. In panel (b) the first response is to square 1, followed by square 8, square 2, and finally square 4. This sequence of large moves results in a proximity strategy score of 18 as illustrated. In panel (c) a different response sequence of smaller moves through the same array of squares results in a smaller proximity strategy score of 9.

The reproduction strategy score was calculated from the number of novel sequences that were used to solve a given trial on each occasion that it was encountered during the 10 test sessions. For logistical reasons this analysis was limited to those trials containing four squares on which five correct solutions were obtained. There are 24 different correct response sequences available for a given trial containing four squares, which can be subdivided into six "families" of closely related sequences (CRS), each consisting of four sequences in which the response order remains constant but the starting position differs. A measure of the degree of reproduction is illustrated in the remaining panels. Note that although four different sequences are illustrated, only three are truly independent sequences because the sequences in panels (d) and (e) are exact reproductions, and (f) is a CRS. The degree of reproduction within a given trial was therefore calculated as follows: Exact reproduction of a given sequence, 3 pts. for each repetition [see (d) and (e) = 6]; 2 pts. for each repetition of a second novel sequence (not shown); repetition of a CRS, 1 pt for each repetition [see (f) = 1]; an additional 1 pt. for each repetition of the sequence with the most repetitions [(d) and (e) = 2]. The reproduction strategy score for the sequence illustrated was 9. When this analysis is conducted on five correct solutions, the maximum score that may be obtained is 20 pts.

The directional strategy score was also calculated from those four square trials in which there were five correct solutions and was simply the percentage of trials in which the first three responses could be classified as moving in a clockwise or counterclockwise direction. Panels (c) and (h) illustrate counterclockwise sequences, and panels (d), (e), (f), and (g) illustrate clockwise sequences. All three strategy measures are independent, because directional strategies do not always move from one square to the next nearest neighbor [contrast (d) and (f)] and so will not result in identical proximity scores. The reproduction strategy score is similarly independent of both proximity and direction scores.

Self-Ordered Sequencing in the Absence of Active Working Memory and Inhibitory Control: Strategic Organization

Strategic organization was specifically examined in Experiment 4 in which each square disappeared from the screen as soon as it was touched and did not reappear again until that particular trial had been completed. This modification of the basic task allows an analysis of the ability to organize and execute a sequence of spatial responses in the absence of any incorrect responses resulting from failures of active working memory or inhibitory control.

In summary, the present study assessed the relative contribution of active working memory, inhibitory control, and response sequencing to the successful performance of a novel self-ordered spatial sequencing task and evaluated the degree to which each ability was disrupted by excitotoxic lesions or dopamine depletion of the prefrontal cortex of the common marmoset.

RESULTS

Experiment 1: Self-Ordered Spatial Sequencing

Baseline Performance

Accuracy. All eight monkeys trained on the self-ordered spatial sequencing paradigm became proficient on the task within 12 months. The baseline performance on trials containing two squares was almost perfect and gradually declined as the number of squares in each trial and thus task difficulty increased (Table 1). One-way analysis of variance (ANOVA) confirmed that there was a highly significant effect of Difficulty (as measured by the number of squares in each trial) on task performance (percentage correct) during baseline testing ($F(3, 21) = 280.92, p < 0.0001$).

Strategy. A detailed analysis of the response sequences used within each trial strongly suggests that the monkeys were responding to the squares on the screen in an ordered rather than random fashion. Firstly, there was clear evidence that each monkey used only a very limited range of the available response sequences to respond correctly on each trial. For example on trials containing four squares, the monkeys used only 3.28 ± 0.21 of the 24 different sequences that were available to produce five correct solutions. Secondly, the sequences that were used to produce the five correct solutions were drawn from only 2.19 ± 0.16 of the six different closely related families (see Figure 1). These data resulted in a high reproduction strategy score of 12.2 ± 0.8. Thirdly, the proximity strategy score revealed that the monkeys did not respond randomly to the screen but instead frequently moved from one square to its nearest neighbor (see Figure 1), thereby generating low scores (60 to 70% of minimum possible scores) on this particular measure of strategy (Table 2).

There was no evidence that the monkeys were consistently moving across the screen in a single direction (e.g., left to right). The dominant strategy appeared to be for the monkey to move around the screen in either a clockwise or a counterclockwise direction. Thus, the directional strategy score revealed that six monkeys

Table 1. Performance on different versions of the self-ordered spatial sequencing task. Accuracy is expressed as mean percentage correct ±1 standard error of the mean (SEM) at each level of difficulty. Control values are the scores obtained for each monkey.

		Difficulty			
		2 squares	*3 squares*	*4 squares*	*5 squares*
Combined	Baseline	91.2 ± 1.3	72.7 ± 2.3	52.1 ± 2.4	24.6 ± 2.4
(*n* = 8)	Un-op	90.8 ± 1.6	71.2 ± 3.0	51.1 ± 2.6	25.6 ± 2.8
Control	Baseline	94.7 / 94.0	72.7 / 66.1	61.2 / 50.4	33.1 / 18.4
(*n* = 2)	Un-op	85.3 / 93.1	74.7 / 72.6	58.8 / 54.1	20.4 / 22.0
	Post L1	91.3 / 91.9	76.6 / 65.4	59.3 / 46.5	22.4 / 0.0
	Post L2	91.3 / 90.5	80.1 / 62.7	61.3 / 41.6	31.2 / 0.0
	Novel	89.3 / 88.8	77.4 / 64.5	50.0 / 42.1	26.9 / 0.0
Quinolinic	Baseline	91.3 ± 2.3	72.3 ± 5.8	48.5 ± 4.6	22.5 ± 2.1
acid	Un-op	89.1 ± 2.8	65.7 ± 6.2	46.6 ± 3.7	22.9 ± 6.1
(*n* = 3)	Post L1	55.4 ± 4.8	22.3 ± 2.2	8.3 ± 2.9	0.0
	Post L2	72.3 ± 10.5	29.6 ± 9.2	16.4 ± 6.7	0.7 ± 0.7
	Novel	66.1 ± 10.7	36.8 ± 14.4	13.8 ± 8.3	4.0 ± 4.0
6-OHDA	Baseline	88.9 ± 2.2	75.2 ± 2.2	53.2 ± 2.9	25.9 ± 5.1
(*n* = 3)	Un-op	93.5 ± 2.1	75.0 ± 4.7	52.1 ± 5.3	31.3 ± 2.8
	Post L1	90.3 ± 2.5	72.1 ± 3.3	51.2 ± 7.7	23.0 ± 6.4
	Post L2	92.4 ± 2.2	74.2 ± 5.6	58.0 ± 9.7	32.7 ± 14.3
	Novel	94.3 ± 0.9	71.3 ± 5.3	56.6 ± 9.2	35.1 ± 16.7

Table 2. Proximity strategy scores expressed as mean ± 1 SEM.

	Combined (n = 8)	*Control (n = 2)*	*Quinolinic acid (n = 3)*	*6-OHDA (n = 3)*
Baseline				
3 sq.	7.6 ± 0.1	8.2 / 7.6	7.5 ± 0.2	7.4 ± 0.2
4 sq.	11.9 ± 0.2	12.5 / 11.7	12.3 ± 0.1	11.5 ± 0.5
5 sq.	15.4 ± 0.4	16.1 / 14.6	15.4 ± 0.4	15.0 ± 1.0
Unoperated control				
3 sq.	7.5 ± 0.1	7.7 / 8.0	7.6 ± 0.2	7.3 ± 0.1
4 sq.	11.9 ± 0.3	12.1 / 11.7	12.4 ± 0.4	11.5 ± 0.6
5 sq.	14.8 ± 0.6	15.5 / 13.7	14.8 ± 0.9	14.8 ± 1.4
Post-surgery 1				
3 sq.	na*	7.8 / 7.7	7.6 ± 0.2	7.4 ± 0.1
4 sq.	na*	11.7 / 12.2	12.7 ± 1.2	11.4 ± 0.6
5 sq.	na*	14.6 / 13.0	–	13.7 ± 0.9

* na = not attempted.

moved in a clockwise direction and two monkeys moved in a counterclockwise direction on the majority (72.6 ± 4.6%) of correct solutions to trials containing four squares (Table 3). Although the consistency with which this approach was applied varied across animals, this strategy was clearly a key determinant of overall performance because in a separate analysis incorporating *all solutions* (correct and incorrect) to trials containing four squares, the degree to which a clockwise or counterclockwise strategy was applied was positively correlated with performance (coefficient of product-moment correlation, Pearson's $r = 0.766$, $p < 0.05$) (Figure 2). In simple terms, the level of performance was highest in those animals that consistently moved in one direction, clockwise or counterclockwise.

Perseveration. A detailed examination of the response sequences used for incorrect trials containing four squares revealed that the monkeys rarely made consecutive responses to the same square. This pattern of responding resulted in a perseveration score of 0.67 ± 0.05 when the baseline data for all monkeys were combined.

Unoperated Control Performance

To facilitate comparisons across, as well as within, each experimental group, each monkey was removed from testing for 14 to 21 days immediately after the completion of the baseline sessions. This gap in the normal testing routine was equivalent to the time taken to recover from subsequent surgical procedures and therefore constituted an unoperated sham procedure for each animal.

Accuracy. When the performance of all eight monkeys was analyzed together as a single group, the unoperated control procedure (14- to 21-day testing holiday) had no effect on the performance of the self-ordered sequencing task (Table 1). Indeed, a two-way ANOVA again revealed a significant effect of task Difficulty on performance ($F(3, 21) = 514.3$, $p < 0.001$) but no effect of the unoperated control procedure ($F < 1$) and no interaction between Difficulty and the control procedure ($F < 1$).

Strategy. All three strategy measures indicated that the imposition of the unoperated control procedure had no effect on the strategy used to perform the self-ordered

Table 3. Direction strategy scores expressed as mean ± 1 SEM, except for control values which are the actual scores for each monkey.

	n	*Baseline*	*Unoperated control*	*Post-surgery 1*
Combined	8	72.6 ± 4.6	74.3 ± 5.4	na
Control	2	75.0 / 58.8	86.7 / 60.0	81.8 / 53.6
Quinolinic acid	3	65.8 ± 1.6	62.6 ± 5.5	–
6-OHDA	3	83.1 ± 8.9	86.5 ± 6.2	84.0 ± 13.5

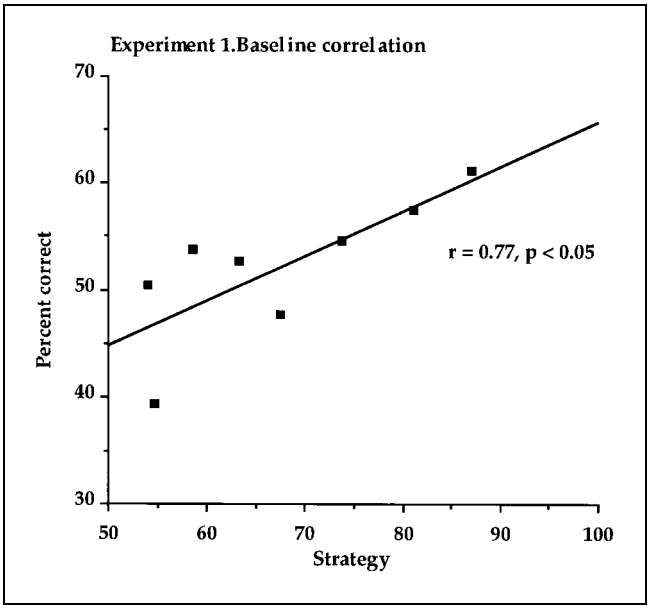

Figure 2. Positive correlation between performance and use of a directional strategy during baseline testing sessions for all eight monkeys during Experiment 1 (coefficient of product-moment correlation, Pearson's $r = 0.77, p < 0.05$). Performance is measured as the mean percentage correct on all trials containing four squares. Strategy is measured as the percentage of trials that were classified as proceeding in one direction (clockwise or counterclockwise, based on the first three responses in each trial) on the same set of trials containing four squares (see Figure 1).

sequencing task. Thus, there was no significant difference between reproduction strategy scores (baseline, 12.2 ± 0.8; unoperated control, 11.9 ± 0.9; $t = 0.54$, $df = 7$, *ns*) or directional strategy scores ($t = 0.58$, $df = 7$ *ns*) (Table 3) when these scores were compared from baseline and unoperated control sessions. Furthermore, Table 2 reveals that the proximity strategy score was also unaffected by the unoperated control procedure. A two-way ANOVA comparing the within-subject variables Surgery and Difficulty confirmed that there was an expected significant effect of task Difficulty on the proximity strategy score ($F(2, 14) = 281.6$, $p < 0.0001$) but no effect of Surgery ($F(1, 7) = 1.15$, *ns*) and no interaction between the two factors ($F(2, 14) = 2.51$, *ns*).

Perseveration. Perseveration remained a rare event following the unoperated control procedure because there was no significant difference between the perseveration scores obtained during baseline testing or after the unoperated control procedure when all eight monkeys were combined into a single group (baseline 0.67 ± 0.05; unoperated control 0.70 ± 0.05; $t = 0.65$, $df = 7$, *ns*).

Post-Operative Performance, Test 1

Accuracy. Infusions of quinolinic acid into the prefrontal cortex significantly impaired the performance of the self-ordered spatial sequencing task (Figure 3a). In contrast, infusions of 6-OHDA into the prefrontal cortex had

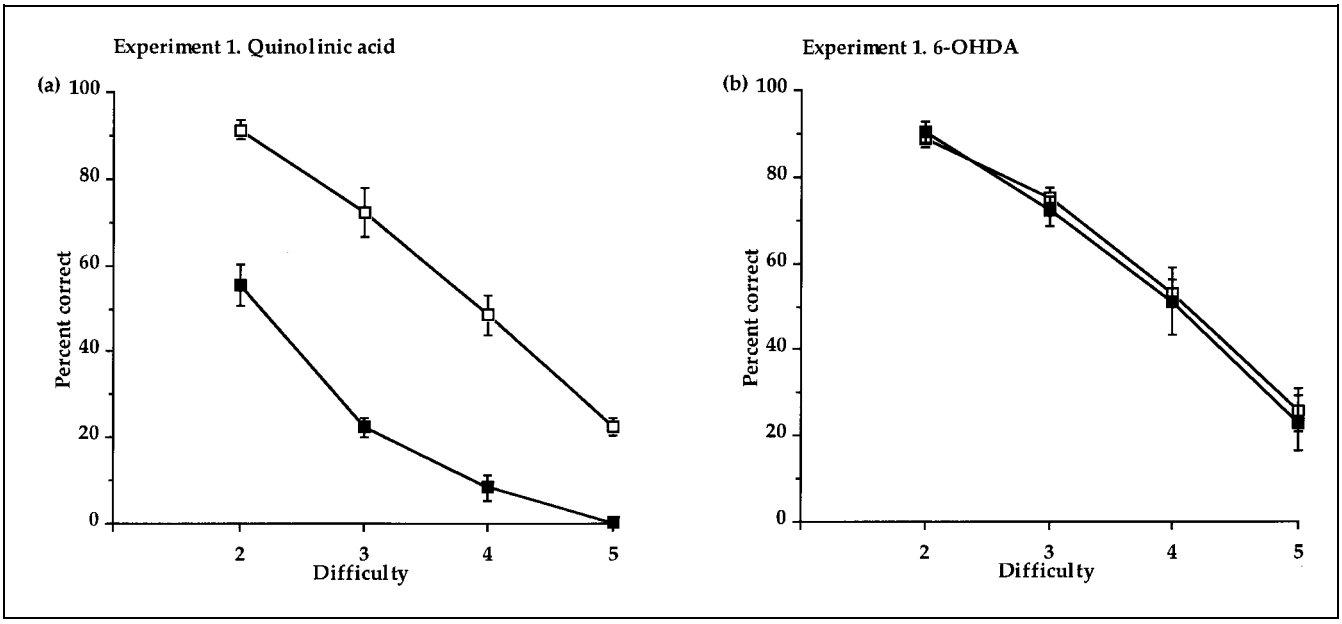

Figure 3. Effects of lesions of the prefrontal cortex on performance of the self-ordered spatial sequencing task during Experiment 1. Open squares represent baseline performance and the filled squares represent performance of the same monkeys on post-surgery test 1 ($n = 3$). Data presented are mean ± 1 SEM. (a) Effect of quinolinic acid lesions of the prefrontal cortex. Significant effect of Surgery ($F(1, 6) = 148.9$, $p < 0.01$) and Difficulty ($F(3, 6) = 104.5$, $p < 0.001$) with a significant Surgery × Difficulty interaction ($F(3, 6) = 17.0$, $p < 0.01$). Simple main effects confirm the monkeys bearing quinolinic acid lesions were impaired at all levels of Difficulty (2 sq.: $F(1, 2) = 47.6$; 3 sq.: $F(1, 2) = 97.2$; 4 sq.: $F(1, 2) = 545.4$; 5 sq.: $F(1, 2) = 120.9$; all $p < 0.05$). (b) Effect of 6-OHDA lesions of the prefrontal cortex. Significant effect of Difficulty ($F(3, 6) = 61.4$, $p < 0.001$) but no effect of Surgery ($F < 1$) and no interaction between Surgery and Difficulty ($F < 1$).

no effect on the performance of the self-ordered sequencing task (Figure 3b).

Strategy. The failure of the monkeys bearing quinolinic acid lesions of the prefrontal cortex to complete five correct trials containing four squares precluded a complete analysis of the effects of this lesion on all three strategy measures. However, a two-way ANOVA comparing the proximity strategy score obtained for trials containing three squares, using Lesion type (quinolinic acid or 6-OHDA) as a between-subject factor and Surgery (baseline or post-op 1) as a within-subject factor, revealed that there was no significant effect of either Lesion ($F(1, 4) = 1.88$, *ns*) or Surgery ($F(1, 4) < 1$) and no interaction between Lesion and Surgery ($F(1, 4) < 1$) (Table 2).

A separate analysis of the effects of prefrontal dopamine depletion on strategy indicated that there was no significant effect of the lesion on the reproduction strategy score (baseline, 13.7 ± 1.5; post-surgery 1, 13.2 ± 1.8; $t = 0.53$, $df = 2$, *ns*) or the directional strategy score (Table 3) ($t = 0.19$, $df = 2$, *ns*), although there was a small improvement in the proximity strategy scores following the lesion (Table 2). A two-way ANOVA, using Surgery and Difficulty as within-group factors, confirmed that there was a significant effect of both Surgery ($F(1, 2) = 281.9$, $p < 0.005$) and Difficulty ($F(2, 4) = 75.93$, $p < 0.001$) on the proximity strategy score but that the interaction between these two factors was not significant ($F(2, 4) = 4.7$, *ns*).

Perseveration. Infusions of quinolinic acid, but not 6-OHDA, into the prefrontal cortex induced profound increases in perseveration (Figure 4). Marked perseveration was also observed during the probe session, in which trials were not terminated by the first return to a previously touched square but were allowed to continue until each square had been touched or until a predetermined number of responses had been made to the screen. Thus, the proportion of perseverative responses (consecutive responses to the same square) was greater following quinolinic acid lesions of the prefrontal cortex than during baseline testing or after 6-OHDA lesions (Figure 5). A two-way ANOVA confirmed that there was a significant effect of Surgery ($F(1, 4) = 11.40$, $p < 0.05$) and a significant interaction between Lesion type and Surgery ($F(1, 4) = 16.81$, $p < 0.05$) with the effect of Lesion type just failing to reach significance ($F(1, 4) = 6.47$, $p = 0.064$). Further analysis of the simple main effects revealed that the interaction was again due to a significant effect of Surgery in those monkeys lesioned with quinolinic acid ($F(1, 4) = 27.95$, $p < 0.01$) and a significant effect of Lesion type (6-OHDA versus quinolinic acid) following surgery ($F(1, 7) = 20.05$, $p < 0.05$).

Moreover, there was also an increase in the number of consecutive responses that were made to a given square following quinolinic acid lesions of the prefrontal cortex. Not only was there an increase in the number of occasions on which two consecutive touches (baseline 4.7 ± 1.1, post-surgery 22.0 ± 6.7) and three consecutive touches occurred (baseline 1.3 ± 0.7, post-surgery 6.7 ± 0.3), but incidences of four and five consecutive touches were also recorded after quinolinic acid lesions of the prefrontal cortex. In contrast, there was no change in the number of consecutive responses made to a given square in control monkeys or those bearing 6-OHDA lesions of the prefrontal cortex. Control and 6-OHDA lesioned monkeys never responded to the same square on four or five consecutive occasions.

In summary, quinolinic acid lesions of the prefrontal cortex induced a marked impairment in performance of the self-ordered sequencing task, which was associated with a profound increase in perseveration. When the constraints on the production of perseveration, inherent in the basic task, were removed during the probe test, monkeys bearing quinolinic acid lesions continued to respond to the same square on more occasions, and to

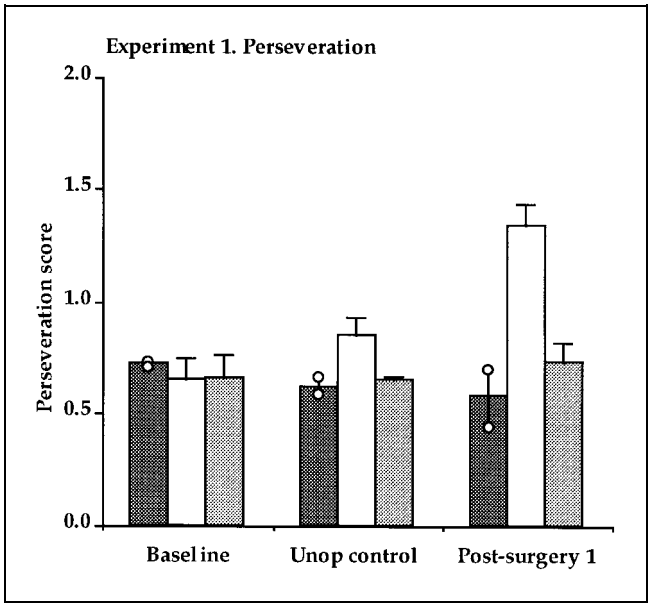

Figure 4. Effect of quinolinic acid (open bars) and 6-OHDA (lightly shaded bars) lesions of the prefrontal cortex on perseveration scores during the basic self-ordered sequencing task in Experiment 1. Bars represent mean perseveration scores (+ 1 SEM) with the exception of the control group (darkly shaded bars, $n = 2$) in which the open circles represent the actual scores achieved by each monkey. A two-way ANOVA comparing the baseline perseveration scores with those on post-operative test 1 for both lesioned groups confirmed that there was a significant effect of Lesion type (6-OHDA versus quinolinic acid) ($F(1, 4) = 16.60$, $p < 0.05$) and Surgery ($F(1, 4) = 11.69$, $p < 0.05$) and a significant Lesion type × Surgery interaction ($F(1, 4) = 8.11$ $p < 0.05$]. The interaction was due to a significant effect of Surgery in those monkeys bearing quinolinic acid lesions of the prefrontal cortex ($F(1, 4) = 19.64$, $p < 0.05$) and a significant effect of Lesion type (6-OHDA versus quinolinic acid) following surgery ($F(1, 7) = 21.42$, $p < 0.01$). Consecutive responses to the same square (scored as 2) indicate a higher degree of perseveration than responses to the same square that were separated by one (scored as 1) or two (scored as 0) correct responses to alternative squares.

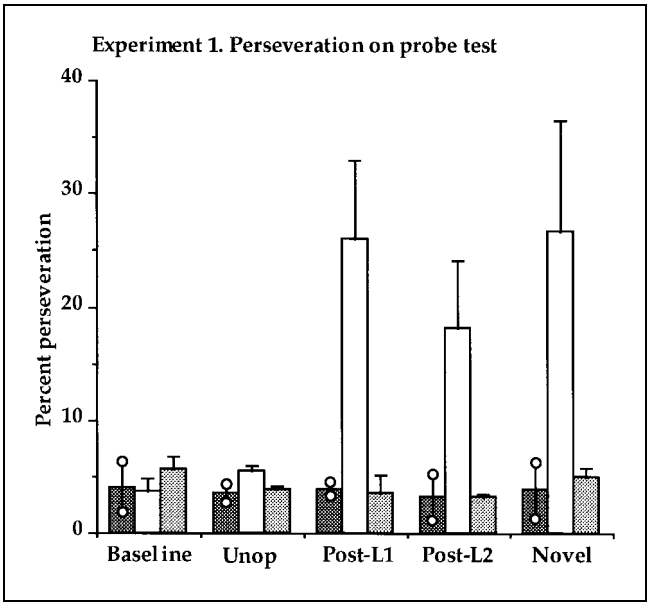

Figure 5. Effect of quinolinic acid (open bars) and 6-OHDA (lightly shaded bars) lesions of the prefrontal cortex on perseveration scores during the probe sessions on the self-ordered sequencing task in Experiment 1. Bars represent the percentage of responses that were classified as perseverative (consecutive responses to the same square) (mean + 1 SEM) with the exception of the control group (darkly shaded bars, $n = 2$) in which the open circles represent the actual scores achieved by each monkey.

a greater degree, than they had done prior to surgery. In contrast, infusion of 6-OHDA into the prefrontal cortex had no effect on either accuracy or perseverative responding.

Post-Operative Performance, Test 2

Accuracy. Quinolinic acid lesions of the prefrontal cortex induced a stable impairment in performance of the spatial self-ordered sequencing task. Thus, a two-way ANOVA using Surgery (baseline, post-op 1, post-op 2) and Difficulty as within-group factors confirmed that there was a significant effect of Surgery ($F(2, 4) = 35.06, p < 0.005$) and Difficulty ($F(3, 6) = 120.0, p < 0.0001$) and a significant interaction ($F(6, 12) = 4.68, p < 0.05$) between these two factors on accuracy (Table 1). Specific planned contrasts revealed that performance on post-operative test 2 was significantly worse than during the baseline test ($F(1, 2) = 73.09, p < 0.05$) but did not differ from post-operative test 1 ($F(1, 2) = 1.5$, *ns*). In contrast, a parallel analysis confirmed that there was no effect of Surgery on the performance of monkeys bearing 6-OHDA lesions of the prefrontal cortex ($F(2, 4) < 1$) and no interaction between Surgery and Difficulty ($F(6, 12) = <1$), although the effect of difficulty remained significant ($F(3, 6) = 45.18, p < 0.0005$) as expected (Table 1).

Perseveration. Quinolinic acid lesions of the prefrontal cortex induced a stable increase in perseveration (Figure 5). A two-way ANOVA contrasting data from the baseline and post-operative test 2 probe sessions confirmed that there was a significant interaction between Lesion type (6-OHDA versus quinolinic acid) and Surgery ($F(1, 4) = 10.67, p < 0.05$), although the effect of both Surgery ($F(1, 4) = 3.39$, *ns*) and Lesion type did not reach significance ($F(1, 4) = 3.39$, *ns*). Further analysis of the simple main effects revealed that the interaction was due to a significant effect of Surgery in those monkeys lesioned with quinolinic acid ($F(1, 4) = 15.45, p < 0.05$) and a significant effect of Lesion type (6-OHDA versus quinolinic acid) following surgery ($F(1, 7) = 11.65, p < 0.05$).

Strategy. The perseverative responding associated with quinolinic acid lesions of the prefrontal cortex precluded a full examination of the effects of this lesion on measures of strategy.

Acquisition of Novel Self-Ordered Sequences

Accuracy. The introduction of novel trial sequences confirmed the stable and long-lasting nature of the impaired performance following quinolinic acid lesions of the prefrontal cortex (Table 1). A comparison between the baseline and novel test performance of the quinolinic acid lesioned group confirmed there was a significant effect of Surgery ($F(1, 2) = 35.31, p < 0.05$) and Difficulty ($F(3, 6) = 55.58, p < 0.005$) but no interaction between these factors ($F(3, 6) = 1.2$, *ns*) following this lesion. Dopamine depletion from the prefrontal cortex continued to have no effect on the performance of the self-ordered sequencing task—no effect of Surgery ($F(1, 2) < 1$), significant effect of Difficulty ($F(3, 6) = 30.12, p < 0.0005$) with no interaction ($F(3, 6) = 1.25$, *ns*).

Perseveration. Monkeys lesioned with quinolinic acid, but not 6-OHDA, continued to demonstrate perseveration on probe sessions using novel trial sequences (Figure 5). Thus in parallel with earlier results there was a significant interaction between Lesion type (6-OHDA versus quinolinic acid) and Surgery ($F(1, 4) = 7.73, p < 0.05$), although the effect of either Surgery ($F(1, 4) = 6.39$, *ns*] or Lesion type ($F(1, 4) = 3.39$, *ns*) was not significant. Further analysis of the simple main effects confirmed that this interaction was due to a significant effect of Surgery in those monkeys lesioned with quinolinic acid ($F(1, 4) = 14.08, p < 0.05$) and a significant effect of Lesion type following surgery ($F(1, 7) = 10.02, p < 0.05$).

Experiment 2: Self-Ordered Spatial Sequencing in the Absence of Perseveration

Accuracy. The detrimental effect of perseveration on the performance of the basic version of the self-ordered

sequencing task was confirmed by the marked improvement in the performance of the quinolinic acid-lesioned monkeys when perseveration was expressly prevented (Figure 6a). Planned contrasts revealed that the performance of the lesioned monkeys during Experiment 2 test sessions was significantly better than their performance on the post-operative session 2 and was no longer significantly different from their performance on the baseline test sessions. Evidently the perseverative responding induced by quinolinic acid lesions of the prefrontal cortex did not mask an additional deficit on the self-ordered sequencing task.

A separate analysis strongly suggests that the improved performance of the quinolinic acid-lesioned

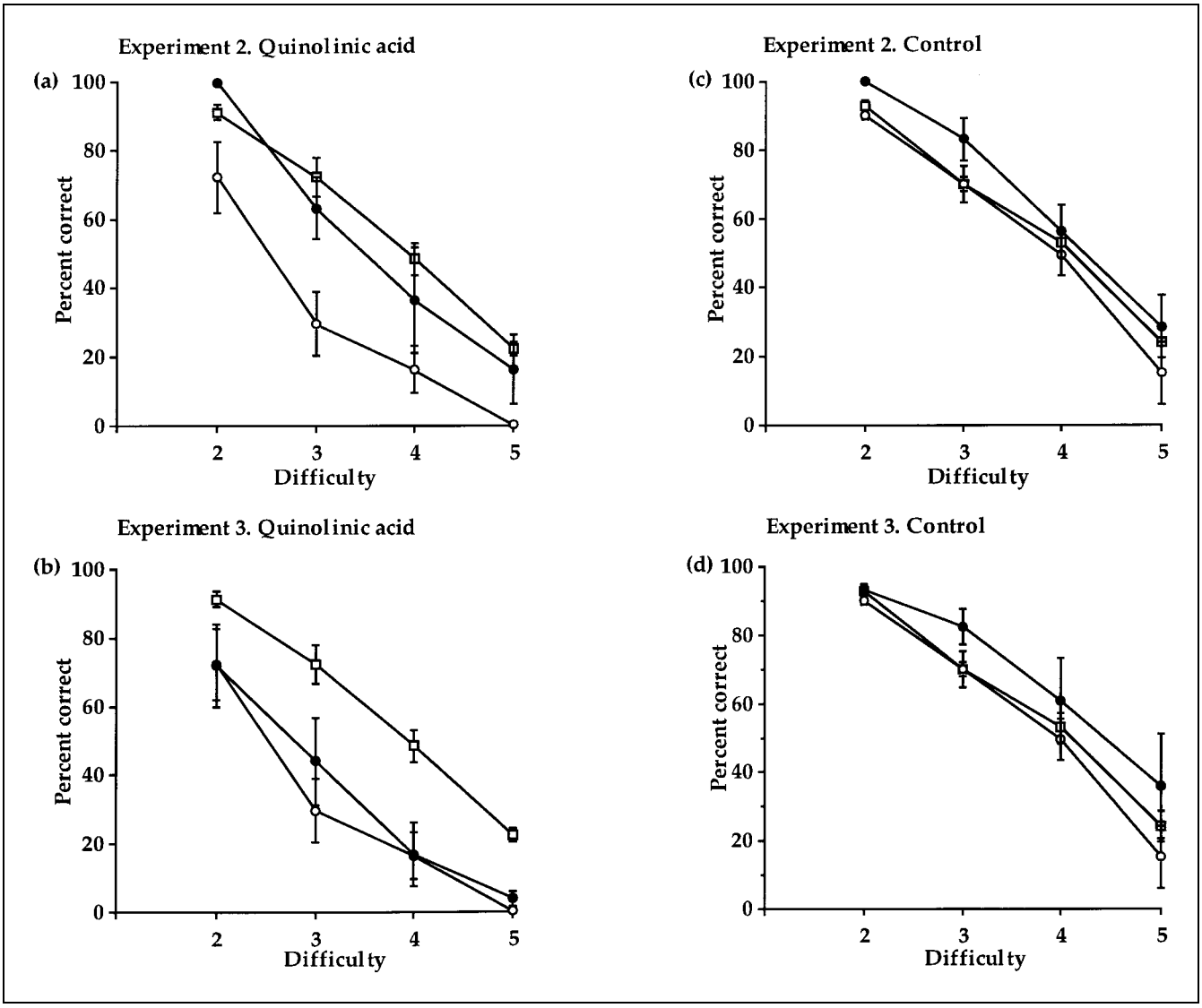

Figure 6. Effect of task modifications on performance of the self-ordered sequencing task. The performance during baseline testing (open squares) or following surgery (open circles) is always presented for comparison with the performance of the same monkeys during modified versions of the self-ordered sequencing task (filled circles). (a) *Experiment 2. Quinolinic acid.* A two-way ANOVA comparing performance of the quinolinic acid-lesioned monkeys during baseline, post-operative test 2, and Experiment 2 test sessions, across each level of difficulty, confirmed that there was still a significant effect of Difficulty ($F(3, 6) = 159.93, p < 0.0001$) and Surgery ($F(2, 4) = 30.32, p < 0.05$) on task performance with no interaction between these two factors ($F(1.86, ns)$. The performance of the lesioned monkeys during Experiment 2 test sessions was significantly *better* than their performance on the post-operative session 2 ($F(1, 2) = 75.69, p < 0.05$) and was no longer significantly different from their performance on the baseline test sessions ($F(1, 2) < 1$). (b) *Experiment 3. Quinolinic acid.* Significant effect of Difficulty ($F(3, 6) = 68.62, p < 0.0001$) and Surgery ($F(2, 4) = 29.40, p < 0.01$) with a significant interaction between these two factors ($F(6, 12) = 3.85, p < 0.05$). Performance on the externally cued test sessions was significantly *inferior* to that observed during baseline testing ($F(1, 2) = 19.41, p < 0.05$) and was not significantly different from that observed on post-operative test 2 ($F(1, 2) = 2.83, ns$). (c) *Experiment 2. Control.* Significant effect of Difficulty ($F(3, 6) = 109.49, p < 0.0001$) but no effect of Surgery ($F(2, 4) = 4.81, ns$) and no interaction ($F(1.37), ns$). (d) *Experiment 3. Control.* Significant effect of Difficulty ($F(3, 6) = 90.20, p < 0.0001$) but no effect of Surgery ($F(2, 4) = 1.37, ns$) and no interaction ($F(6, 12) < 1$).

monkeys was due to the abolition of perseverative responding because the same task modification had no effect on the performance of three monkeys who did not demonstrate enhanced perseveration on the basic task ("nonperseverative control" group; two controls + one monkey with dopamine depletion from the prefrontal cortex) (Figure 6c).

Experiment 3: Self-Ordered Spatial Sequencing in the Absence of Active Working Memory

Accuracy. The opportunity to use external cues to signal the location of previous responses, and so reduce the demands on active working memory within each trial, did not improve the performance of the quinolinic acid lesioned group (Figure 6b). Planned contrasts revealed that the performance on the externally cued test sessions was significantly inferior to that observed during baseline testing and was not significantly different from that observed during post-operative test 2.

Although an identical analysis on the performance of the control group revealed that this task manipulation did not significantly improve the performance of the group as a whole (Figure 6d), the performance of two of the three control monkeys was significantly improved by this task manipulation. Thus, a separate analysis of the performance of each monkey during the Experiment 3 revealed that they were performing significantly better than their mean level of performance during the baseline testing sessions (95% confidence limit). The performance of one control monkey was significantly improved on trials containing three squares (mean percent correct baseline: 66.1, Experiment 3: 87.0, $p < 0.05$), four squares (baseline: 50.4, Experiment 3: 81.0, $p < 0.05$), and five squares (baseline: 18.4, Experiment 3: 52.0, $p < 0.05$), and another was significantly improved on trials containing three squares (baseline: 72.7, Experiment 3: 88.0, $p < 0.05$) and five squares (baseline: 33.1, Experiment 3: 50.0, $p < 0.05$). In contrast, none of the three monkeys bearing quinolinic acid lesions of the prefrontal cortex significantly improved their performance during Experiment 3 relative to their mean level of performance during the baseline testing sessions.

Experiment 4: Self-Ordered Spatial Sequencing in the Absence of Active Working Memory and Inhibitory Control: Strategic Organization

Accuracy. In Experiment 4 it was impossible to commit an error because each square disappeared from the screen as soon as it was touched and did not reappear for the duration of that trial. As a consequence of this manipulation, the ability to organize and execute a series of spatial responses was assessed in the absence of incorrect responses due to failures of active working memory or inhibitory control. Accuracy scores are therefore meaningless and are not reported.

Strategy. Quinolinic acid lesions of the prefrontal cortex had no effect on the ability to organize or execute a sequence of spatial responses in the modified version of the self-ordered spatial sequencing paradigm in which incorrect responses were precluded. Indeed, all three strategy measures indicate that this lesion had no effect on strategic organization. For example, a two-way ANOVA comparing the reproduction strategy scores from baseline and Experiment 4 test sessions of both quinolinic acid-lesioned monkeys and the control group confirmed that although there was a significant effect of Surgery ($F(1, 4) = 7.84$, $p < 0.05$), there was no effect of Lesion type (control versus quinolinic acid) ($F(1, 4) < 1$) and no interaction between these two factors ($F(1, 4) < 1$) (Table 4). A similar analysis of the direction strategy scores confirmed that there was no effect of either Lesion type ($F(1, 4) < 1$) or Surgery ($F(1, 4) = 3.58$, *ns*) and no significant interaction between Lesion type and Surgery ($F(1, 4) < 1$) (Table 4). Finally, the proximity strategy scores obtained during Experiment 4 test session did not differ from those observed during baseline testing in the monkeys with quinolinic acid lesions of prefrontal cortex (baseline: 3 sq. = 7.7 ± 0.2, 4 sq. = 12.3 ± 0.1, 5 sq. = 15.4 ± 0.4; Experiment 4: 3 sq. = 7.9 ± 0.2, 4 sq. = 12.9 ± 0.2, 5 sq. = 17.3 ± 0.4). Thus, a two-way ANOVA confirmed that although there was a significant effect of Difficulty ($F(2, 4) = 4952.6$, $p < 0.0001$), there was no effect of Surgery ($F(1, 2) = 5.34$, *ns*) and no interaction between these two factors on proximity strategy scores ($F(2, 4) = 2.16$, *ns*).

Table 4. Strategy scores from baseline and Experiment 4 testing sessions. All scores are expressed as mean ± 1 SEM.

	n	*Baseline*	*Experiment 4*
Reproduction strategy scores			
Control	3	11.9 ± 0.9	7.9 ± 1.8
Quinolinic acid	3	10.6 ± 0.3	8.7 ± 0.5
Direction strategy scores			
Control	3	66.6 ± 4.7	75.5 ± 2.3
Quinolinic acid	3	65.8 ± 1.6	79.3 ± 10.0

Perseveration. Perseveration scores are not presented because consecutive touches to the same location within a given trial were precluded during this version of the basic task.

Summary of Results on the Self-Ordered Spatial Sequencing Task

Quinolinic acid lesions of the prefrontal cortex induced a large and stable impairment in the performance of the spatial self-ordered sequencing task that was characterized by a profound increase in perseverative responding. It is striking that the presurgery performance of monkeys bearing quinolinic acid lesions of the prefrontal cortex was reinstated in Experiment 2, when the basic task was modified to prevent perseverative responding. In contrast, the provision of external cues in Experiment 3, with the consequent reduction in the active working memory requirement, did not improve the performance of those monkeys with excitotoxic lesions of the prefrontal cortex. The data from experiment 4 demonstrate that the ability to organize and execute a series of spatial responses was not affected by quinolinic acid lesions of the prefrontal cortex when incorrect responses were precluded. In direct contrast, large depletions of dopamine and noradrenaline from the same areas of prefrontal cortex had no effect on performance of the self-ordered sequencing task.

Experiment 5: Spatial Delayed Response, an Index of Active Working Memory

In order to facilitate comparisons with previous studies that assessed the effects of frontal lesions or dopamine depletion on active spatial working memory, the monkeys in the current study were also examined using a traditional test of active spatial working memory, spatial delayed response. All control monkeys successfully reached the specified criteria at all levels of the spatial delayed response task. In contrast, monkeys bearing either quinolinic acid or 6-OHDA lesions of the prefrontal cortex were impaired on the acquisition of this task (Figure 7). Two of the three monkeys within the quinolinic acid-lesioned group failed to complete the distractor stage of the task within 300 trials.

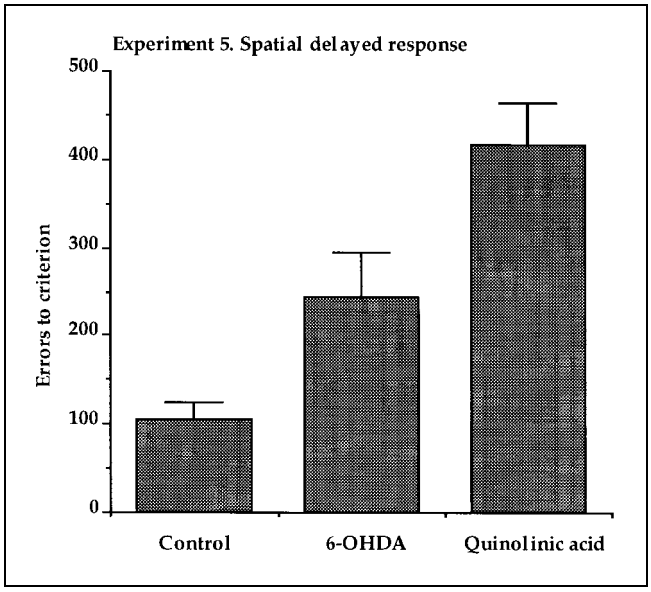

Figure 7. Effect of prefrontal cortex lesions on acquisition of spatial delayed response. Bars represent mean trials to criterion (+ 1 SEM). The control group (n = 4) also includes the two additional monkeys that were used for histochemical analysis. A one-way ANOVA revealed a significant effect of Lesion type ($F(2, 7) = 15.51$, $p < 0.005$). Preplanned comparisons confirmed that both quinolinic acid ($F(1, 7) = 32.38, p < 0.001$) and 6-OHDA ($F(1, 7) = 6.48, p < 0.05$) lesions significantly impaired the acquisition of this task. Spatial delayed response performance was evaluated in a specially designed "hand testing" apparatus (see Roberts et al., 1994). The delay period was incremented from 0 to 3 sec and then to 6 sec when the monkey selected the correct box on 8 out of 10 consecutive trials. The use of mediating responses during the delay period was explicitly prevented in a final stage in which the monkey was distracted away from the front of the transport cage by the delivery of a very small piece of marshmallow at the back of the cage. Incorrect trials were repeated until a correct response was obtained.

Lesion Assessment

Cortical Neurotransmitter and Metabolite Levels

Infusions of 6-OHDA into the prefrontal cortex induced large depletions of dopamine throughout this region (Table 5). Indeed, 12 months after surgery the largest and most consistent reductions were observed in lateral (B9), and medial (MF) prefrontal areas with slightly smaller reductions in the orbital (B10, B11) prefrontal cortex, supplementary/premotor cortex (B6–8), and primary motor cortex (B4). The reductions in adjacent cingulate and parietal areas were generally smaller and more variable and were not significant for the group as a whole. These data are in full agreement with our previous results using this lesioning procedure (see Roberts et al., 1994). Smaller reductions (4 to 35%) in the level of the dopamine metabolite dopamine 3,4-dihydroxyphenylacetic acid (DOPAC) were observed in all cortical areas following 6-OHDA lesions, although these reductions were not significant.

The noradrenaline uptake blocker talsupram only partially and variably protected the noradrenergic systems from the toxic effects of 6-OHDA, in agreement with previous results (see Roberts et al., 1994). The largest reductions were observed in lateral (B9), orbital (B10, B11) prefrontal areas and supplementary/premotor cortex (B6–8). Smaller and more variable reductions (50%) were observed in all other cortical areas, although only those in primary motor cortex (B4), posterior frontal (Fr2), and posterior cingulate areas (C3) were significant (see Table 5). Citalopram provided full protection for the serotonin afferents to the prefrontal cortex with the

Table 5. Tissue levels of catecholamines in frontal and parietal cortical regions in control and 6-OHDA lesioned marmosets. Mean levels ± 1 SEM expressed as ng/mg wet weight tissue.

	Dopamine levels			*Noradrenaline levels*		
Region[a]	*Control*[c]	*6-OHDA*	*Percent depletion*[b]	*Control*[c]	*6-OHDA*	*Percent depletion*
B9	0.06 ± 0.01	0.01 ± 0.01	83.3**	0.17 ± 0.02	0.03 ± 0.01	82.4**
B10/11	0.07 ± 0.01	0.03 ± 0.01	57.1**	0.18 ± 0.03	0.03 ± 0.01	83.3**
MF	0.08 ± 0.07	0.02 ± 0.01	75.0*	0.19 ± 0.02	0.08 ± 0.06	57.9
B6-8	0.08 ± 0.01	0.03 ± 0.01	62.5*	0.18 ± 0.01	0.05 ± 0.01	72.2**
B4	0.11 ± 0.01	0.07 ± 0.01	36.4*	0.22 ± 0.02	0.10 ± 0.03	54.5*
C1	0.12 ± 0.02	0.05 ± 0.03	58.3	0.27 ± 0.05	0.12 ± 0.05	55.6
C2	0.08 ± 0.02	0.07 ± 0.01	12.5	0.24 ± 0.03	0.11 ± 0.05	54.2
C3	0.05 ± 0.01	0.04 ± 0.01	20.0	0.21 ± 0.03	0.09 ± 0.03	57.2*
Fr2	0.08 ± 0.01	0.05 ± 0.01	37.5	0.23 ± 0.02	0.10 ± 0.04	56.5*
Fr3	0.05 ± 0.01	0.03 ± 0.01	40.0	0.21 ± 0.03	0.08 ± 0.05	61.9

[a] B9, lateral prefrontal cortex; B10, 11, orbitofrontal cortex; MF, medial prefrontal cortex; B6/8, supplementary and premotor cortex; B4, primary motor cortex; C1, anterior cingulate cortex; C2, mid-cingulate cortex; C3, posterior cingulate cortex; Fr2, posterior frontal and anterior parietal cortex; Fr3, posterior parietal cortex.
[b] Mean levels that are significantly different from control values at 5% and 1% (Student's *t* test) are marked * and **, respectively.
[c] The control group (n = 4) was expanded to include two additional monkeys, which also performed the spatial delayed response task.

largest reduction (17%) occurring in medial prefrontal cortex.

Subcortical Neurotransmitter Levels

As expected, the lesioning procedure did not induce any significant alterations in the levels of dopamine, noradrenaline, or serotonin within the caudate nucleus, putamen, or nucleus accumbens.

Histological Assessment

Examination of the cresyl violet-stained coronal sections revealed that infusions of quinolinic acid into the prefrontal cortex induced extensive damage within lateral and orbital areas of the prefrontal cortex with a much smaller amount of more variable damage to medial areas (Figure 8). The lesion on the orbital surface extended from the frontal pole to the level of the anterior limit of the putamen. On the lateral surface the lesion incorporated most of the lateral surface from the frontal pole to the genu of the corpus callosum. There was almost total loss of cells within these areas accompanied by extensive gliosis. As intended, the cortex in the adjacent premotor area was spared.

DISCUSSION

The present investigation demonstrates that severe and long-lasting impairments in the performance of a novel spatial self-ordered sequencing task follow excitotoxic lesions encompassing both lateral and orbital regions of the prefrontal cortex of the common marmoset. In direct contrast, large combined depletions of dopamine and noradrenaline from within the same areas of prefrontal cortex had no effect on the performance of this task. Discrete modifications of the basic self-ordered sequencing task were then used to isolate the precise cognitive abilities required for the successful performance of this task and to reveal the degree to which each ability was dependent upon processing within the prefrontal cortex and the modulation of this processing by the ascending monoamine projections.

Specifically, we have established that the impaired performance that results from excitotoxic damage to the prefrontal cortex was characterized by the induction of profound perseveration. This perseveration was due to the disruption of an inhibitory control mechanism necessary to avoid the reselection of previously chosen stimuli. Because perseveration was not induced by monoamine depletions from within the prefrontal cortex, we can conclude that the substrate for this inhibitory control mechanism resides within the prefrontal cortex but that the ascending dopamine and noradrenaline projections to the prefrontal cortex do not modulate this cognitive ability. In contrast, the acquisition of spatial delayed response, a classic test of active working memory, was impaired by either excitotoxic lesions of the prefrontal cortex or monoamine depletions within this cortical area, in agreement with previous work (Brozoski, Brown, Rosvold, & Goldman, 1979; Dias, Robbins, & Roberts, 1996b; Roberts et al., 1994).

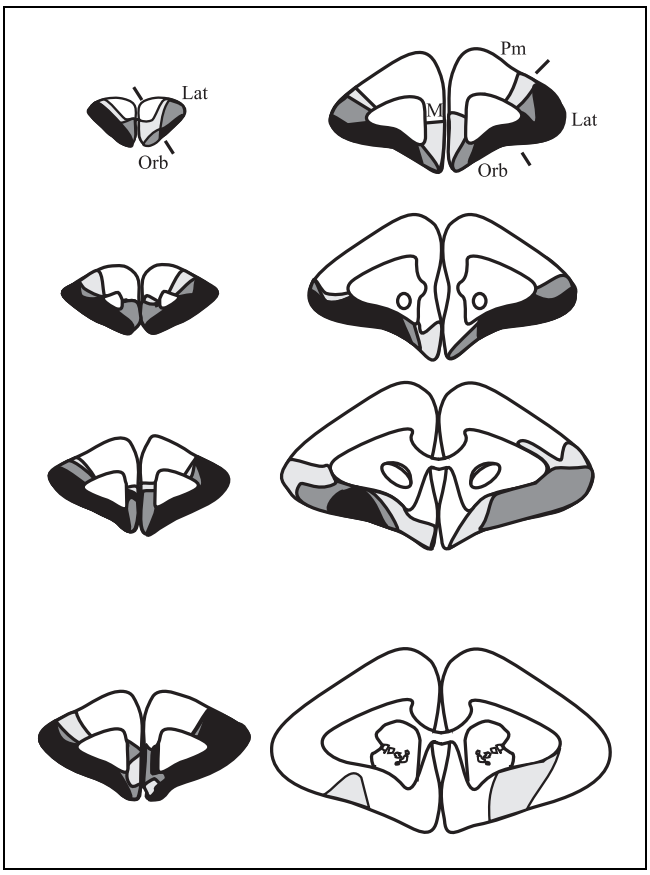

Figure 8. A schematic diagram of a series of coronal sections through the frontal lobe illustrating the extent of all three lesions induced by infusions of quinolinic acid into the prefrontal cortex. Dark shading depicts areas of cortex that were lesioned in all three monkeys, medium shading depicts areas of cortex that were lesioned in two monkeys, and light shading depicts areas of cortex that were lesioned in a single individual. Lat = lateral prefrontal cortex; Orb = orbital prefrontal cortex; Pm= premotor cortex; M = medial prefrontal cortex.

These results therefore confirm that active working memory is mediated by the prefrontal cortex and that this cognitive ability is modulated by the prefrontal monoamine systems, and they suggest that the amount of active working memory required to perform the basic self-ordered sequencing task was minimal. Because the ability to organize and execute a series of spatial responses within the current task was completely unaffected by either lesion, the neural substrate for this ability appears to be located outside the prefrontal cortex.

In summary, these results demonstrate that the prefrontal cortex plays a central role in the performance of tasks that require self-ordered sequencing and that the susceptibility of a given task to the disruptive effects of damage to the prefrontal cortex may ultimately depend upon the degree to which that particular task requires active working memory, inhibitory control, or response sequencing abilities. Finally and perhaps most importantly, the differential effects of excitotoxic lesions and monoamine depletion of the prefrontal cortex on self-ordered sequencing has important implications for current theories concerning the role of dopamine in prefrontal cognitive function.

Behavioral Analysis of Spatial Self-Ordered Sequencing

The spatial self-ordered sequencing task described in the present work was designed to be as similar as possible to a spatial self-ordered sequencing task that has been used extensively to measure the spatial working memory abilities in a wide range of neurological conditions (Morris et al., 1988; Owen et al., 1990, 1995). The task contains the essential elements of the original human task in that the subject is required to organize and perform a self-ordered search through an array of spatial locations on a touch-sensitive screen. The main difference is that the monkey is required to search once through a given array and obtains one reward at the end of each trial, whereas the human subject searches repeatedly through a given array to obtain several "rewards" within each trial. Nevertheless, the monkeys are clearly required to organize a self-ordered search through an array of spatial locations and subsequently must continuously monitor their choices and compare them to the selections remaining to be made so as to avoid returning to previously chosen locations. The task, in keeping with other self-ordered sequencing tasks, therefore requires varying degrees of active working memory, inhibitory control, and response sequencing.

Active Working Memory

The differential effect of excitotoxic lesions and monoamine depletion from the prefrontal cortex on the basic self-ordered sequencing task suggests that these lesions may have dissociable effects on active working memory. However, it is not completely clear that the present self-ordered sequencing task required a significant amount of active working memory. The extensive use of spatial strategies within the basic self-ordered sequencing task may be expected to reduce the amount of active working memory required because, to some degree, the next response was specified by the preceding response. There was therefore no need to remember the locations of all previous responses within a trial during the self-ordered sequencing task, and consequently the active working memory load was small. This contrasts with previous self-ordered tasks in which the use of simple strategies was either precluded by experimental instruction (Petrides & Milner, 1982) or design (Petrides, 1995). Moreover, the repeated searches inherent in the human self-ordered searching task probably require a significant amount of active working memory despite the use of strategic approaches (Owen et al., 1990).

In contrast, correct performance on the spatial delayed response task must have been guided by a representation of the location of the hidden food reward during the delay period because strategic planning cannot improve performance on this task. Spatial delayed response therefore clearly required active working memory to bridge the delay between the stimulus and choice phases of the task. The findings of the current study are therefore in complete agreement with the literature on the effects of prefrontal lesions or monoamine depletion on active working memory, in that both lesions disrupted the acquisition of spatial delayed response (Goldman-Rakic, 1992). The demonstration of the use of a spatial sequencing strategy within the self-ordered task and the consequent reduction in active working memory load within that task therefore probably accounts for the failure of the monoamine lesion to impair performance on the self-ordered task.

There is some evidence in rats, at least, that the behavioral changes that follow mesocortical dopamine depletion are only observed when the ascending noradrenergic system is preserved (Taghzouti et al., 1988; Tassin, Simon, & Glowinski, 1986). Because in the present study there was an equivalent loss of dopamine and noradrenaline in all areas of the prefrontal cortex, it might be argued that the noradrenergic lesion somehow prevented an effect of dopamine depletion on the self-ordered task. However, it is unclear how this proposed interaction could explain why the monkeys in the current study were able to perform normally on the self-ordered task while simultaneously showing impaired acquisition of the spatial delayed response task. Furthermore, the lesioned monkeys in the seminal demonstration of the detrimental effect of prefrontal dopamine depletion on spatial delayed alternation sustained noradrenaline (76%) and dopamine (87%) depletions that were comparable to those observed in the present study (Brozoski et al., 1979). Indeed, the possibility that the noradrenergic depletion contributed to these effects should not be overlooked in the light of the work of Arnsten and colleagues that suggests a noradrenergic substrate for these deficits in aged monkeys (Arnsten et al., 1988; Arnsten & Constant, 1992; Arnsten & Goldman-Rakic, 1985). In conclusion, it appears that while lesions of dopamine and noradrenaline prefrontal afferents impair the acquisition of spatial delayed response, a combined lesion of both systems had no effect on the performance of the self-ordered task.

Although it may be argued that disruption of the self-ordered task simply requires a greater level of dopamine depletion than disruption of spatial delayed response, the relative timing of these two experiments together with the level of dopamine depletion obtained within all areas of the prefrontal cortex in the present and previous studies (Roberts et al., 1994) argue against such a conclusion. Thus, it should be remembered that the self-ordered task that was unimpaired by the 6-OHDA lesion was administered within 3 weeks of surgery (when the neurochemical effects of the lesion would have been maximal), whereas the spatial delayed response task that was impaired by the 6-OHDA lesion was not administered until several months later. Indeed, dopamine levels were reduced by more than 75% in all areas of prefrontal cortex when analyzed 3 weeks after surgery (Roberts et al., 1994). Moreover, there is as yet no evidence linking specific areas of prefrontal cortex to spatial delayed response performance in the common marmoset, so regional variations in neurotransmitter depletion do not illuminate this issue.

Inhibitory Control

The process of inhibitory control was clearly evident in the performance of all monkeys once they had become proficient on the basic task. Indeed, the successful performance of the task when there were four or five squares on the touch-screen required considerable inhibitory control because after three touches, there was ample opportunity to return to locations that had already been touched. The very low level of perseveration within the basic paradigm and during the probe test sessions was confirmed by the finding that the performance of the control monkeys did not improve in Experiment 2 when the task was modified to preclude perseverative responding. It is therefore all the more striking that following excitotoxic prefrontal lesions more than 25% of all responses on the probe sessions were classified as perseverative, with as many as five consecutive responses occurring to the same square on some occasions. The dramatic improvement in the performance of these monkeys in Experiment 2 confirms the perseverative nature of the deficit induced by excitotoxic lesions. Again, the contrast between the effects of excitotoxic lesions and monoamine depletion is striking. That large frontal lesions should induce perseveration is not in itself particularly surprising given the literature on the induction of perseverative behavior in a number of different behavioral paradigms following damage to frontal structures (see Passingham, 1993). however, the present task allowed a powerful analysis of the precise nature of this perseverative behavior.

Firstly, unlike the classical tasks in which prefrontal lesions induce perseverative behavior in which the subject must withhold responding to one particular stimulus within the environment (e.g., reversal learning, extinction, or go-no-go paradigms), in the current task there were often several alternative stimuli very close to the location to which the monkeys were perseverating. Furthermore, the monkeys were rewarded after the successful conclusion of a given trial rather than after each individual response. The pattern of perseveration observed in the current study appears to be most similar to that described as "stuck-in-set" perseveration by Sandson and Albert (1984), which manifests as the inappro-

priate maintenance of a current category or framework. The finding that this type of perseveration is most common after frontal lobe pathology would appear to support this classification. However, it is possible that some aspects of "continuous" perseveration (inappropriate repetition without interruption) associated with damage to basal ganglia may be seen in the performance of the lesioned monkeys during the probe sessions (Sandson & Albert, 1984).

The induction of perseveration within the monkey paradigm following damage to the prefrontal cortex is reminiscent of some aspects of the performance of a frontal patient group on the human version of this task. Thus, in the human task it is possible to commit a "within search" error by returning to a location that has already been searched and has been found to be empty. An error of this nature is clearly a fundamental error within the human task and may possibly be the human equivalent of the perseverative errors observed in the present experiments. It may therefore be significant that the only patient group to show an increase in the number of within search errors contains those with frontal pathology (Owen et al., 1990).

The monkeys bearing excitotoxic lesions of prefrontal cortex in the present experiment were unable to make use of the external (inhibitory) cues provided in Experiment 3 to improve their post-lesion performance. This result confirms that these monkeys had problems when they were required to inhibit an inappropriate response and further confirms that a failure of active working memory cannot account for the deficit in these monkeys because there was no active working memory requirement in this version of the task.

The lesions in the present study were designed to encompass both lateral (B9) and ventral (B11–14) prefrontal areas, sparing more dorsal areas (B6, B8) of the frontal lobe, as defined by Brodmann (Brodmann, 1909). However, although the perseveration induced by excitotoxic lesions of the prefrontal cortex in the present experiment is reminiscent of lesions invading more ventral areas of prefrontal cortex in Old World monkeys (see Mishkin, 1964), it should be noted that this group was also impaired on the spatial delayed response task, which is more commonly associated with damage to dorsolateral prefrontal cortex (see Passingham, 1993). Because the subregions within the prefrontal cortex of the marmoset are less well defined than they are in Old World monkeys, the precise regions that were damaged by the lesion await further clarification. A precise anatomical determination of the subdivisions within the marmoset prefrontal cortex is currently underway within our laboratory.

Although the inappropriate repetition of a motor response in the current task reflects a lack of inhibitory control, it should be stressed that there are manifestations of a lack of inhibitory control that do not present as motor response perseveration. Human infants prior to the maturation of the prefrontal cortex fail an object retrieval paradigm in which a strong prepotent response to reach directly along their line of sight to retrieve a desired object must be inhibited. Diamond has demonstrated that this impairment represents a lack of inhibitory control in the absence of motor perseveration (Diamond, 1990). Monkeys with lesions of the prefrontal cortex show similar impairments on a nonhuman primate version of this task (Diamond, 1990; Dias et al., 1996b) and on a lever manipulation task (Crawford, Fulton, Jacobsen, & Wolfe, 1948; Jacobsen, Wolf, & Jackson, 1935). Indeed, we have recently demonstrated that discrete lesions within the prefrontal cortex can dissociate a lack of inhibitory control at an affective level from a lack of inhibitory control at an attentional level of cognitive processing using a visual discrimination paradigm (Dias et al., 1996a). These results suggest that inhibitory control mechanisms may be required at various levels of cognitive processing within the prefrontal cortex.

Strategy Utilization

A key finding arising from the present study was that successful performance on the self-ordered task was supported by, and indeed significantly correlated with, the use of a repetitive searching strategy in which the monkeys tended to approach the squares within a given array in an ordered manner (Figure 2). It is important to note that the monkeys did not simply reproduce an identical response sequence on each occasion that a given array of squares was encountered, but instead, using a variety of starting positions, they moved through a given array in a clockwise or counterclockwise direction. An important advantage conferred by the adoption of such a strategy is the flexibility observed in the data in Table 1, which clearly demonstrate that the introduction of novel trial sequences did not affect the accuracy of the performance of the control monkeys. Thus, the monkeys appeared to apply an overall rule or algorithm to solve each novel variant of the basic task.

This finding has important parallels within the human self-ordered spatial searching paradigm because the use of this repeated searching strategy has been consistently found to be correlated with successful performance on this task. Moreover, although patients with Parkinson's disease (Owen et al., 1992), temporal lobe damage (Owen et al., 1995), Huntington's disease (Lange, Sahakian, Quinn, Marsden, & Robbins, 1995), and Alzheimer disease (Sahgal et al., 1992) are, to varying degrees, impaired on the performance of this task, only patients with frontal lobe damage (Owen et al., 1990) or schizophrenia (Pantelis et al., 1996) have so far been demonstrated to have significantly reduced strategy scores.

The degree to which monkeys with prefrontal lesions can organize and perform a sequence of spatial responses is clearly an important issue. A significant aspect

of the current work, then, is that the flexibility inherent in the use of the touch-screen technology allowed the dissociation of the effects of perseveration and behavioral disorganization on the performance of the self-ordered task. Thus, whereas in the basic paradigm, the induction of perseverative responding prevented an analysis of the ability to organize and perform a sequence of responses, this was not the case in Experiment 4, which clearly shows that in the absence of the debilitating effect of perseveration, the monkeys with prefrontal lesions did not differ from their prelesion scores on three independent measures of response sequencing ability. Thus it can be concluded that, in this task at least, prefrontal lesions do not produce disorganized behavior when the confounding influence of lesion-induced perseveration is removed. Moreover, these results suggest that although the prefrontal cortex is not required for the implementation of previously acquired strategies, damage to the prefrontal cortex can disrupt the expression of strategic organization. It should be remembered that the patients with frontal lobe damage and schizophrenia who showed impaired strategic abilities on the human self-ordered spatial searching task were required to generate and implement a strategy rather than just implement a previously learned strategy, as was the case in the present experiments (Owen et al., 1990; Pantelis et al., 1996). This factor may have contributed to the strategic deficits observed in these patient groups that were not observed after frontal lesions in the present experiment.

This analysis is certainly consistent with the results of recent functional activation studies that have examined the pattern of regional blood flow in visuomotor sequencing tasks. For example, activation foci were consistently observed in midventrolateral prefrontal cortex in tasks in which the subject had to reproduce a sequence of spatial moves from memory. Critically, this activation foci was still observed even when the sequence had been learned prior to the scan and was just reproduced during the scan (fixed spatial sequence condition) (Owen et al., 1996). Moreover, midventrolateral foci were only observed in a visuomotor skill learning task when the subjects had acquired explicit knowledge of the embedded sequence that was presented in a highly practiced condition (Doyon, Owen, Petrides, Sziklas, & Evans, 1996).

Although strategic impairments have been reported in the Hamilton Searching Task following large dorsolateral lesions of the prefrontal cortex (Meyer & Settlage, 1958), closer inspection of these data reveal that rigid searching strategies developed prior to surgery in that study and that the subsequent impairments were extremely mild. Moreover, monkeys with dorsolateral prefrontal lesions continued to make errors on the Hamilton Task even when their searching strategy was no longer inferior to that seen in control animals (Harlow, Akert, & Schiltz, 1964). These results are therefore in broad agreement with the finding that lesions of the sulcus principalis did not impair strategic organization on a searching task involving 25 locations (Passingham, 1985). Although a disruption of strategic organization has been reported after lesions restricted to the anterior cingulate cortex or nucleus accumbens on a variant of the Hamilton Searching Task, as discussed above it is not possible to dissociate the effects of erroneous responses due to a disruption of active working memory/inhibitory control mechanisms from those due to disorganization in studies of this type (Stern & Passingham, 1994).

Although the important results in the present study suggest that the ability to organize and implement the required sequences had, to some degree, become automatic and thus liberated from the requirements of prefrontal cortical processing, it is also clear that the implementation of these sequences could be disrupted by prefrontal lesions during the basic task. The conceptualization is consistent with the initial specification of Norman and Shallice's (1980) model of the Supervisory System, which has been viewed as an information-processing analogue of prefrontal cognitive function. Thus the reproduction of a given response sequence would be a relatively automatic task, triggered by stimuli within the environment activating appropriate well-learned schemas *via* a process of contention-scheduling. Shallice has argued that when a trigger in the environment is particularly salient, and contention-scheduling is unmodulated by the supervisory system, behavior will be controlled by that one dominant schema and would therefore resemble stuck-in-set perseveration (Shallice, 1982; Shallice & Burgess, 1996). The similarity between this theoretical account and the effects of excitotoxic lesions of the prefrontal cortex in the present experiment is certainly compelling. Indeed, it predicts that removing the most salient stimuli (i.e., the square that has just been touched) from the environment during the period in which it exerts excessive control over the response output should release that control and allow other schemas to become active and thus allow normal behavior to proceed. This was precisely the outcome observed in Experiment 2.

The Role of Dopamine in Prefrontal Cognitive Processing

The present results also provide additional support for our earlier work on the consequence of prefrontal dopamine depletion on attentional set-shifting. This analogue of the Wisconsin Card Sort Test is another cognitive task that is disrupted by frontal lobe damage in both marmosets and humans but is not impaired by substantial prefrontal dopamine depletions (Dias et al., 1996a, 1996b; Owen et al., 1990). Indeed, performance on the critical stage of this task was actually improved following prefrontal dopamine depletion (Roberts et al., 1994). Thus, despite electrophysiological evidence in rats that

dopamine has an inhibitory action within prefrontal areas (Ferron, Thierry, Le Douarin, & Glowinski, 1984; Sesack & Bunney, 1989), we have so far demonstrated that in the primate prefrontal cortex dopamine depletion does not produce the same behavioral effect as cortical damage within this region on three forms of behavior: attentional set-shifting, visual discrimination reversal learning, and self-ordered sequencing (Dias et al., 1996b; Roberts et al., 1994; present results). Moreover, it is also clear that the only paradigm in which dopamine depletion mirrors the effect of damage within the prefrontal cortex itself is spatial delayed response.

Ultimately, the role of dopamine and the other neurotransmitter systems within the prefrontal cortex will *only* be understood when the precise cognitive processes required by all tasks sensitive to prefrontal damage have been established and the contributions of each neurotransmitter system have been fully evaluated across the full range of cognitive abilities.

Materials and Methods

Subjects

Eight common marmosets (*Callithrix jacchus*) (six females and two males) obtained from the Clinical Research Centre, Harrow, U.K., took part in this study. The monkeys were between 2 and 3 years old at the start of the study and were housed individually throughout. On test days the monkeys were given access to water and 20 grams of primate diet (MP. E1, Special Diet Services, or SDS, Withams, Essex, U.K.) and two pieces of carrot for a period of 2 h in the afternoon. At weekends, this diet was supplemented with fresh fruit, eggs, peanuts, bread, and marmoset jelly (SDS). All procedures were performed in accordance with the Project and Personal Licences held by the authors under the Animals (Scientific Procedures) Act 1986.

Experiment 1: Self-Ordered Spatial Sequencing

Apparatus

Spatial self-ordered sequencing was examined in a specially designed automated apparatus located within a wooden sound-attenuated box. The monkeys were transported to the apparatus within a Perspex transport cage. One side of the transport cage was removed to allow the monkey access to the screen of a high-resolution color VDU (Microvitec, M1440, Bradford, U.K). The monkey was able to touch the screen by reaching through an array of vertical metal bars. A touch-sensitive screen (Microvitec, Touchtec 501) was attached on the front of the VDU to monitor the location of responses to the screen. Liquid reinforcement (banana milkshake) was delivered via a peristaltic pump to a metal licking spout mounted on the bars in a central position. Licking was continuously monitored by an infrared detector within the licking spout. Two loudspeakers (R.S components) were located to the left and right of the touch screen. The testing box was illuminated by a 3-W bulb located above the Perspex transport cage. An illustration of this apparatus and a detailed account of the preliminary touch screen training procedure can be found in Roberts, Robbins, & Everitt (1988) and Roberts et al. (1992). All visual stimuli were generated by an Acorn BBC Master microcomputer and were presented on the VDU at various locations. The experimental contingencies including the recording of response locations, response latencies, and lick latencies were controlled by the computer using programs written in Spider control language (Paul Fray Ltd., Cambridge, U.K).

Preoperative Training

Each monkey was trained to touch a blue square stimulus presented in any one of eight possible locations on the touch screen (see Figure 1). Correct responses were signaled by the disappearance of the stimuli and the onset of a tone that continued throughout a 5-sec period, during which reinforcement was available. Delivery of reinforcement (3 to 5 sec of banana milkshake) was contingent upon the monkey licking at the reinforcement spout during this period. Each trial was preceded by a 3-sec intertrial interval. Once this ability had been acquired, a second square was then added so that each trial now consisted of two squares. The first response to either square now resulted in that square changing color from blue to yellow and the onset of a tone for 0.1 sec. All the squares then disappeared from the screen for a further 0.5 sec before reappearing in exactly the same locations but now all colored blue again. The monkey now had two alternatives. A response to the same (previously touched) square was incorrect and resulted in termination of that trial, signaled by the removal of all squares from the screen and the onset of a 5-sec time-out period, during which the house light was turned off. A response to the other (previously untouched) square was correct and resulted in both squares turning yellow for 0.1 sec together with the onset of a tone that continued throughout the period during which reinforcement was available. Following an intertrial interval, subsequent trials commenced with the presentation of a novel array of two squares, again at sites randomly selected from the eight possible locations (Figure 1).

As the performance of each monkey improved, the number of squares presented on each trial was incremented up to a maximum of five squares. However, the task requirements remained the same for all trials because on each trial the monkey had to touch each square on the screen once, and once only, in a self-determined sequence in order to obtain reward. It is important to note that reinforcement was only available *after* the successful completion of a given trial. Furthermore, if the monkey responded to any square in a given trial on more

than one occasion, that trial was immediately terminated and scored as incorrect. Similarly, if the monkey failed to touch all of the squares in a given trial within 30 sec, that trial was scored as an omission and was also not rewarded. When each monkey was performing the more difficult five-square problems at greater than 20% correct, the baseline performance of each monkey was assessed.

Baseline Performance

The baseline performance of each monkey was assessed on a standard set of 60 trials, consisting of 15 novel trials with two, three, four, and finally five squares. The same standard set of trials was presented on each of the 10 days over which baseline performance was measured. The order in which the trials were presented on a particular day was identical for each monkey but was different for each of the 10 test sessions, with the stipulation that on each test session the first 15 trials contained sequences of two squares, followed by 15 trials with three, four, and finally five squares.

After completion of the tenth test session, a probe test was administered for 1 day only. The probe session consisted of a repeat of the third baseline session, with the exception that a given trial did not terminate after the first incorrect response. This manipulation of the paradigm was specifically designed to allow an assessment of the responses that would normally follow an incorrect response, should that have been possible in the standard task (i.e., would the monkey continue to search for the correct square or would he or she continue to respond to a particular square). Reinforcement was provided as in previous trials, once all of the squares within a trial had been touched. A limit was placed on the maximum number of responses that were permitted during each trial (twice the number of squares on screen + 1), thus ensuring that it was still eventually possible to fail a given trial and thereby trigger the normal trial termination sequence.

Unoperated Control Procedure

Once baseline testing had been completed, all testing was suspended for 14 to 21 days. Each monkey was then retested on the standard batch of 60 trials until each of the 10 test sessions and another probe session had been completed. This provided unoperated control data for each animal and so facilitated comparisons across as well as within each experimental group. Each monkey was then allocated to an experimental group such that the performance of each group was equated as far as possible. The monkeys then underwent the appropriate surgical procedure (quinolinic acid-lesion group n = 3, 6-hydroxydopamine (6-OHDA) lesion group n = 3, sham-operated group n = 2).

Behavioral Measures

In the self-ordered sequencing paradigm the following behavioral measures were calculated at each stage of the testing protocol:

1. *Accuracy.* The number of correct solutions was separately calculated for all trials containing two, three, four, and five squares within each of the 10 test sessions. Mean scores were then derived from the data from all 10 test sessions.

2. *Strategy.* Three independent strategy measures were computed (see Figure 1). A *proximity* strategy score provided a measure of the spatial "clustering" or "chunking" of responses within each particular trial. A *reproduction* strategy score provided a measure of the degree of repetition used to solve a given trial. A *directional* strategy score provided a measure of the degree to which each solution could be classified as moving in a clockwise or counterclockwise direction.

3. *Perseveration.* Because each incorrect trial must, by definition, include two responses to one of the squares, a perseveration score was derived from the number of correct responses made between these two responses to the same square (Figure 1).

Surgery

All surgical procedures were performed on anaesthetized monkeys (pentobarbitone 30 mg/kg/ip) held in a standard stereotaxic frame using a head holder with specially modified incisor and zygoma bars. Because the subregions within the prefrontal cortex of the marmoset are less well defined than they are in Old World monkeys, the lesions were designed to encompass both lateral and orbital prefrontal areas as defined by Brodmann (Brodmann, 1909) and described in our previous work (Dias et al., 1996a, 1996b).

Excitotoxic Lesion of Prefrontal Cortex

Neurons within the prefrontal cortex were selectively destroyed by injecting 0.6 to 1.5 µl of a 0.09M solution of quinolinic acid (Sigma, in 0.1M phosphate buffer pH 7.0) bilaterally into 10 sites within the prefrontal cortex. Each infusion was made over 100 sec through a stainless steel cannula (30 gauge) attached to either a 2- or 10-µl precision sampling syringe (Precision Sampling Co., Baton Rouge, LA, USA). The following stereotaxic coordinates were used: AP + 16.0, LM ± 2.0, ±4.0; AP + 16.5, LM ± 3.0; AP 17.75, LM ± 2.0; AP 18.5, LM ± 2.0; and AP 20.0, LM ± 3.0. Additional injections were placed at the following sites with the injection cannula angled 10° from the vertical: AP 16.0, LM ± 6.2; or 8° from absolute vertical AP 16.75, LM ± 5.9; AP 17.5, LM ± 5.6; AP 18.25, LM ± 5.3; AP 19.0, LM ± 4.6 (after Stephan et al., 1980). Single injections between 0.5 and 1.0 mm from the floor

of the skull were made at each of the above sites. The precise dorso-ventral coordinates were determined individually for each monkey and depended upon the thickness of the cortex at each site. The above surgery was performed in a two-stage process in which the lateral and orbital prefrontal areas of opposite hemispheres were targeted during the same operation; the lateral and orbital prefrontal areas on the contralateral side were targeted 2 weeks later.

Dopamine Depletion from Prefrontal Cortex

The dopamine innervation of the prefrontal cortex was selectively destroyed by using 2 μl of a 6 μg/μl solution of 6-hydroxydopamine hydrobromide (Sigma; in 0.01% ascorbic acid) bilaterally into 15 sites within the prefrontal cortex. Each infusion was made over 100 sec through a stainless steel cannula (30 gauge) attached to a 10 μl precision sampling syringe. The following stereotaxic coordinates were used: AP + 16.5, LM ± 1.5, ±3.0, and ±5.0 and AP + 18.5, LM ± 1.0, ±2.5, and ±4.0. Two or three injections were made at each of the above sites. The precise dorso-ventral coordinates were individually calculated for each monkey and were 0.5 mm below the surface, 0.5 mm above the floor of the skull, and, when the thickness of the cortex warranted, a third injection was placed equidistant from the preceding two. The monoamine oxidase inhibitor pargyline (Sigma, 50 mg/kg/ip) was administered 20 min prior to the anaesthesia. In an attempt to protect the noradrenergic and serotonergic innervation of the prefrontal cortex, the noradrenergic antagonist talsupram (Lundbeck, Copenhagen, Denmark, 15 mg/kg/sc) (Arnt et al., 1985) and the serotonergic antagonist citalopram (Lundbeck, Copenhagen, Denmark, 5 mg/kg/sc) (Hyttel, 1992) were administered 30 min prior to the injection of 6-OHDA. This treatment regime was found to reduce dopamine concentrations in the prefrontal cortex to between 75 to 90% of normal levels 3 weeks after surgery, and it prevented similar reductions in noradrenaline and serotonin concentrations. The concentration of dopamine in the prefrontal cortex continued to be reduced by between 56 and 81% 18 months after surgery (Roberts et al., 1994).

Sham Surgery

The sham-operated control animals received vehicle infusion (0.01% ascorbic acid) bilaterally into the 15 sites within the prefrontal cortex that were used for the prefrontal dopamine depletion described above. All experimental procedures, with the obvious exception of the addition of 6-OHDA to the vehicle solution, were duplicated including the administration of pargyline, talsupram, and citalopram.

Post-Operative Testing

Following a post-surgical recovery period the performance of each monkey was assessed according to the following protocol:

1. *Post-operative test 1.* Retention of baseline performance using the standard set of 60 trials for each of the 10 test sessions and a probe session.
2. *Post-operative test 2.* Repeat of the standard set of 60 trials used for each of the 10 test sessions and a probe session to examine the long-term stability of any lesion effects.
3. *Novel trials test.* This version of the basic task specifically examined the ability to generate novel response sequences and therefore consisted of a set of 60 completely novel trials, again tested for 10 test sessions and a probe session. Thus, this version of the basic task examined the ability to generate a novel response sequence when exposed to an array of squares that was randomly generated on each trial.

Experiment 2: Self-Ordered Spatial Sequencing in the Absence of Perseveration

This modification to the basic paradigm was expressly designed to enable an assessment of the contribution of perseverative responding to any impairments observed on the basic task. The test consisted of the standard set of trials with the exception that perseveration (consecutive responses to the same square) was rendered impossible. Thus, when a particular square was touched, that square did not reappear on the screen *until* an alternative square had been touched (which would in turn not reappear until yet another square had been touched). Thus, it was still possible to fail trials with three or more squares by returning to a square that had already been touched within that trial, but it was now *impossible* to fail a trial by perseverating (i.e., responding to the same square twice in succession). Performance on this test was evaluated for five sessions.

Experiment 3: Self-Ordered Spatial Sequencing in the Absence of Active Working Memory

This modification to the basic paradigm was especially designed to assess the ability to use external cues to signal where previous responses had been made within each trial. The standard set of trials was used with the exception that once a square had been touched, it changed color from blue to yellow as normal but then always reappeared colored yellow during the performance of that particular trial. Clearly, in this version of the basic task, memory for the location of previous responses within a given trial is not required. Performance on this test was examined over five sessions.

Experiment 4: Self-Ordered Spatial Sequencing in the Absence of Active Working Memory and Inhibitory Control: Strategic Organization

This modification to the basic paradigm was specifically designed to assess the ability to organize and execute a sequence of spatial responses in the absence of any confounding perseverative or mnemonic impairments. The test consisted of the standard batch of trials with the exception that responses to *all* previously touched squares were impossible. Thus, when a particular square was touched, it disappeared and did not reappear again until the trial had been completed. Thus, in this version of the basic task it was not possible to make an incorrect response, although omissions could still occur. Performance on this test was evaluated for five sessions.

Experiment 5: Spatial Delayed Response

The apparatus used and the preliminary training required to assess the acquisition of spatial delayed response have been described in detail on previous occasions and are briefly described in the legend for Figure 7 (see Roberts et al., 1994).

Assessment of Lesions

Measurement of Monoamines

All marmosets that had received 6-OHDA and the sham-operated control monkeys were deeply anaesthetized with pentobarbitone and their brains were removed to an ice-cold metal dissecting plate. A comprehensive range of cortical areas and subcortical structures were dissected. A full description of the dissection procedure can be found in Roberts et al., (1994). All tissue samples were analyzed using high-performance liquid chromatography, with electrochemical detection. The concentrations of dopamine, noradrenaline, serotonin, and selected metabolites were compared to those in the corresponding areas of the sham-operated control animals (see Roberts et al., 1994). The two additional monkeys that were also tested on the spatial delayed response task were included in the control group.

Histological Evaluation

All marmosets that had received quinolinic acid were deeply anaesthetized with pentobarbitone and perfused transcardially with phosphate buffer (0.1M, pH 7.3) followed by 4% paraformaldehyde (pH 7.3). Each brain was then removed and stored in fixative overnight before being transferred to 30% sucrose solution. The tissue was sectioned 4 days later at 60 μm, and every third section was mounted and stained with cresyl violet. A microscopic examination of the degree of neuronal cell loss and gliosis was then conducted, and the extent of each lesion was mapped onto standard drawings of coronal sections.

Statistical Methods

All behavioral results were subjected to analysis of variance for repeated measures using the CLR ANOVA 2.0 package (Apple Macintosh Inc.).

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