Dissociable Effects of Frontal Cortical Lesions on Measures of Visuospatial Attention and Spatial Working Memory in the Rat

K.R. Bailey and R.G. Mair
Department of Psychology, University of New Hampshire, Durham, NH 03824, USA

Frontal cortex controls voluntary movement through projections to striatum that continue as parallel pallido-thalamic loops. In previous studies we found evidence of a double dissociation in rat striatum between visuospatial response time (RT) and radial maze delayed non-matching (DNM) tasks. Here we compare the effects of frontal cortical lesions on these tasks. We found that lesions involving sensorimotor areas in dorsolateral cortex affect RT for responding to visuospatial stimuli without affecting other measures of response speed or producing signs of attentional or sensory impairment. These deficits were equivalent to impairments observed with lesions in sensorimotor areas of dorsolateral striatum. Dorsal prefrontal lesions produced RT deficits indicative of attentional impairment that have not been observed with striatal or thalamic lesions. This suggests contributions of prefrontal cortex to attention independent of striatum and thalamus. Prefrontal lesions had significant but circumscribed effects on DNM consistent with effects of lesions in anatomically related areas of striatum or thalamus observed in earlier studies. These results are consistent with evidence implicating prefrontal cortex in aspects of spatial memory mediated by anatomically related pathways in the basal ganglia and thalamus.

Keywords: sensorimotor cortex, prefrontal cortex, striatum, voluntary movement, reaction time

Introduction

The frontal lobes support dissociable functions needed to produce and to guide intentional responding. Studies of anatomical connections suggest that frontal cortex in the rat is organized into subdivisions at least grossly similar to primates (Alexander et al., 1986; Groenewegen et al., 1990; Joel and Weiner, 1994). Thus dorsal lateral areas, including primary and secondary motor cortex in the rat, are the main targets of the ventrolateral thalamic nucleus (VL), have prominent connections with somatosensory and dorsal prefrontal cortex, and project heavily to sensorimotor areas in dorsolateral striatum. Ventral (limbic) prefrontal areas, including ventral prelimbic, infralimbic, medial orbital, lateral orbital and agranular insular cortex, are the main targets of medial and central segments of the mediodorsal nucleus (MD), have prominent connections with limbic areas (amygdala, entorhinal and perirhinal cortices, subiculum, chemosensory areas), and project heavily to ventral striatum. Dorsal prefrontal areas, including dorsal prelimbic and anterior cingulate cortex, are the main target of lateral and paralamellar segments of MD, have prominent connections with motor and sensory association cortices, and project heavily to dorsomedial striatum (Donoghue and Wise, 1982; Donoghue and Parham, 1983; Zilles and Wree, 1985; Groenewegen, 1988; McGeorge and Faull, 1989; Sesack et al., 1989; Neafsey, 1990; Uylings and van Eiden, 1990; Berendse et al., 1992; Wang and Kurata, 1998; Groenewegen et al., 1999; Groenewegen and Uylings, 2000).

Lesion studies have provided evidence for the functional heterogeneity of these areas of rat frontal cortex although the precise nature of this organization remains to be elucidated. Dorsal lateral damage has been associated with skilled motor impairments (Bures and Bracha, 1990; Whishaw et al., 1991; Whishaw and Coles, 1996). Lesions in dorsal and ventral areas of prefrontal cortex have been found to have distinct effects on delayed matching (DM) and non-matching (DNM) tasks used to measure working memory (Kolb et al., 1974; Seamans et al., 1995; Delatour and Gisquet-Verrier, 1996; Kesner et al., 1996; Floresco et al., 1997; Ragozzino et al., 1998). Other studies have shown dissociable effects of dorsolateral and medial prefrontal lesions on visuospatial response time (RT) (Muir et al., 1996). Medial prefrontal lesions affected the RT and accuracy of responding to brief visual stimuli in a manner suggestive of attentional impairment. Dorsolateral lesions increased RT without affecting accuracy under conditions consistent with a decisional impairment. Subsequent studies have confirmed the effects of prefrontal lesions on visually guided responding (Bussey et al., 1997; Passetti et al., 2000; Burk and Mair, 2001b; Chudasama and Mair, 2001) and have provided evidence of a further dissociation of visuospatial RT impairment between dorsal and ventral areas of medial prefrontal cortex (Passetti et al., 2002).

Lesion studies have also provided evidence for a parallel organization of function in striatum. Thus dorsolateral areas of striatum that are innervated by sensorimotor cortex have been associated with skilled motor deficits (Whishaw et al., 1986; Pisa and Cyr, 1990; Fricker et al., 1996). Visuospatial RT performance has been found to be similarly affected by bilateral lesions in dorsomedial striatum (Rogers et al., 2001) or by unilateral lesions of medial prefrontal cortex in one hemisphere and dorsomedial striatum in the other (Christakou et al., 2001). Lesions in ventral and dorsomedial striatum have been associated with prefrontal-like impairments of DM and DNM tasks (Dunnett, 1990; Seamans and Phillips, 1994; Dobrossy et al., 1996; Dunnett et al., 1999; Burk and Mair, 2001a; Mair et al., 2002). Recording of neural activity in rats performing a DM task have provided convergent evidence for the parallel involvement of prefrontal cortex and ventral striatum in working memory (Chang et al., 2002).

We recently observed a double dissociation in the effects of striatal lesions on radial maze DNM and visuospatial RT tasks (Mair et al., 2002). Lesions in ventral striatum had significant effects on radial maze DNM while sparing RT performance. Lesions in dorsolateral striatum increased choice RT while sparing DNM performance. In this report we describe four
studies conducted to determine whether a similar dissociation exists between frontal cortical areas that project to these regions of striatum. Experiment 1 compared the effects on radial maze DNM of relatively discrete NMDA lesions in primary motor (M1), dorsal anterior prefrontal (dAPF) and ventral prefrontal (vPF) cortex. None of these lesions were associated with significant DNM impairment. Experiment 2 was designed to test possible explanations for this result. We used training procedures for radial maze DNM that have proved sensitive to prefrontal lesions in previous studies (Porter et al., 2000) and included larger lesions aimed at dorsal prefrontal cortex (dPF) and at primary and secondary motor cortex (M1M2) for comparison to dAPF and vPF lesions. Experiment 3 compared the effects of M1, dAPF, vPF and dPF lesions on visuospatial RT performance. Because M1 lesions had no significant effect on performance experiment 4 examined the effects of larger M1M2 lesions on the RT task.

Materials and Methods

Subjects

One hundred and thirty-two male Long-Evans rats served as subjects. Thirty six were used for experiment 1, 40 for experiment 2, 40 for experiment 3, and 16 for experiment 4. The animals were experimentally naive and ~2 months old at the start of each experiment, 7–9 months old at the time of surgery, and 10–12 months old at the end of post-surgical training. They were caged singly on a 12 h light/dark cycle with all training occurring during the light phase. Access to water was restricted to training sessions and 30 min of free access at the end of the light phase each day (60 min on days when rats were not trained) so that water could be used as a reinforcer.

Apparatus

DNM was trained using automated eight arm radial mazes (Med Associates, Georgia, VT) and procedures described previously (Mair et al., 1998, 2002). Mazes were constructed of polycarbonate with eight arms (60 × 9 cm) connected to an octagonal hub (28 cm in diameter). Each arm had a motorized gate at the entrance to the hub, a well milled into the floor at the far end in which water was delivered as a reinforcement (by activation of miniature solenoid valves), and photocells positioned at each end to detect arm entries and responses to the well. Mazes were located in a windowless laboratory room and were remotely controlled by computer interface.

Radial Maze DNM Training

In experiment 1, DNM was trained using procedures that proved successful in demonstrating impairments in rats with striatal lesions (Mair et al., 2002). Rats were trained to perform varying- and recurring-choice DNM on alternate days. In both tasks rats receive water reinforcement for responding to the arm not reinforced on the preceding sample response. Recurring-choice DNM is designed to encourage an egocentric solution based on direction of turning or other body-centered cues. The same three arms (in a T-maze configuration) are used on all trials and external visual stimuli are minimized by covering the maze and turning lights out in the room. Trials begin with the rat in the start arm (the stem of the T). The sample phase begins with the gates to the start arm and to one of the goal arms (randomly selected) opening. Rats are given reinforcement (two 0.1 ml pulses of tap water) for responding to the goal arm (the sample for the trial) and returning to the central start arm where gates are closed to hold the rat for the duration of the retention interval (randomly selected as 0, 6, 12 or 24 s). At the end of the retention interval the choice phase begins with gates opening to the start arm and both goal arms. Reinforcement is given for responding to the S+ goal arm (not entered during the preceding sample phase) and then for returning to the start arm. Responses are scored as correct when rats enter the correct (S+) goal arm before entering the incorrect (sample) arm.

Varying choice DNM is designed to encourage an allocentric solution based on location relative to external stimuli independent of body orientation. There are two important differences between varying- and recurring-choice DNM. First, room lights are on and the mazes are uncovered to reveal numerous external visual cues in the varying-choice task. Second, the arms used as the sample, the S+, and to hold animals during retention intervals are selected at random from the eight arms of the maze. This is done to change the spatial configuration of these arms in an unpredictable fashion on every trial so that the direction of a correct response cannot be known until after the retention interval ends. Varying choice trials begin with rats trapped in the arm last reinforced on the preceding trial (which then serves as the sample for the next trial). Trials begin with the gates opening to that arm and to the holding arm (randomly selected from the seven alternatives). Rats are reinforced for entering the holding arm when gates are closed so that they are retained for the duration of the retention interval (randomly selected as 0, 6, 12 or 24 s). At the end of the retention interval the same two gates open again along with a third (randomly selected) gate to the S+ (or non-matching) arm for that trial. Reinforcement is given when rats enter the S+ arm. Responses are scored as correct when this is the first arm entered.

Prior to surgery rats were trained to perform recurring- and varying-choice DNM on alternate days until they reached a criterion of completing all 40 trials in a session at 85% correct averaged across delays for each of these tasks. After 2 weeks of recovery from surgery water availability was again restricted and rats were trained for 10 sessions (of 40 trials) each with the recurring- and varying-choice tasks, alternating between them on a session-by-session basis.

In experiment 2 rats were trained to perform recurring-choice DNM to a criterion of 85% correct (averaged across delays) before surgery using the procedures described for experiment 1. After 2 weeks of recovery from surgery water restriction was re-instituted and rats were trained for 30 additional sessions of recurring choice DNM. This was done to test whether the history of alternate varying-choice and recurring-choice training protected rats from the effects of prefrontal lesions in experiment 1 (see Porter et al., 2000).

Visuospatial RT Training

The visuospatial RT task is a modification of the five-choice task (Carli et al., 1983) designed to minimize demands on vigilance by giving rats control over when trials begin and stimuli occur and to insure that they are in a consistent location optimal for observing at stimulus onset. RT trials begin with the lever extending. When the lever is pressed stimulus lights turn on in all seven response ports and the lever retracts. When the rat triggers the arm photocell, just before re-entering the hub, six of these lights turn off leaving the stimulus light on in the S+ port for an additional period of time (0.05, 0.11, 0.26, 0.58, 1.35 or 3.00 s). Reinforcement (two brief pulses of tap water) is delivered when rats respond to the S+ port first, within 3.0 s of crossing the arm photocell (the limited hold). The location and duration of the S+ stimulus is varied at random on a trial-by-trial basis. Responses are classified as errors of omission when rats fail to respond within the 3.0 s limited hold and errors of commission when they respond to an incorrect port first within this time constraint. RTs are measured for the runway response (from the lever press until the arm photocell is triggered) and the choice response (from when the arm photocell is triggered until the rat responds to a port). Previous
studies have shown that lesions of dorsolateral striatum increase choice but not non-delay RT (Mair et al., 2002).

The visuospatial RT task was shaped by placing rats in the hub with the retractable lever inserted at the entrance to the arm and lights turned on in each port. Individual lights were then turned off and rein-
forcement delivered when rats made a headpoke into a port with its light on. After reinforcements were delivered (and lights turned off) in all seven ports, the lever was extended to start the next trial. When the lever was then pressed, lights were turned on in all seven ports to signal the availability of reinforcement. Sessions ended after six trials (42 reinforcements including six in each of the seven ports) or after a period of 20 m. Training continued with this procedure until rats completed three daily sessions obtaining the maximum of 42 rein-
forcements within the 20 m limit. The lever was then moved to the far end of the arm and training continued until rats completed another three sessions obtaining the maximum of 42 reinforcements within 20 m. After this the task was modified so that lights turned off in six of the seven ports (randomly selected on each trial) when rats crossed the arm photocell after pressing the lever (before re-entering the hub). The remaining light stayed on for 3 s and reinforcement deliv-
ered when rats made a headpoke into the port while the light was still on (i.e. within 3 s of crossing the arm photocell). This task was trained in 45 m sessions until rats completed 96 trials with 90% correct for per cent correct over the last three sessions and assigned by block using a matching procedure to ensure the initial equivalence of groups. At the end of presurgical training, rats were rank ordered for per cent correct over the last three sessions and assigned by block randomization to a treatment. Surgeries were done with aseptic procedures. Rats were anesthetized (85 mg/kg ketamine and 8.5 mg/kg xylazine i.m.), placed in a stereotaxic instrument with the incisor bar set 3.3 mm below the interaural line, and an incision made and skin retracted to expose a surgical field over frontal cortex. For rats receiving lesions the skull was opened with a small trephine (2 mm in diameter) and lesions made by infusing 0.1 µl of a 150 mM NMDA solu-
tion between studies. The vPF lesions were associated with

| Table 1 Sites of injections (0.1 µl of 150 mM NMDA) |
|--------------------|---|---|---|
| **Lesion** | **AP** | **ML** | **DV** |
| M1 | 3.4 | 3.0-4.0 | 1.5 |
| | 2.5 | 3.0-4.0 | 1.5 |
| | 1.6 | 3.0-4.0 | 1.5 |
| vPF | 4.3 | 0.8-3.4 | 3.5 |
| | 3.4 | 0.8 | 4.0 |
| | 3.4 | 3.6 | 4.5 |
| | 2.5 | 0.8 | 4.5 |
| | 2.5 | 4.0 | 5.0 |
| daPF | 4.3 | 0.8 | 1.0, 2.0 |
| | 3.4 | 0.8 | 1.0, 2.0 |
| | 2.5 | 0.8 | 1.0, 2.0 |
| dPF | 4.7 | 0.8-2.0 | 1.0 |
| | 3.7 | 0.8 | 1.0, 2.0 |
| | 3.7 | 2.0 | 1.0 |
| | 2.7 | 0.8 | 1.0, 2.0 |
| | 2.7 | 2.0 | 1.0 |
| | 1.7 | 0.8 | 1.0, 2.0 |
| | 0.7 | 0.8 | 1.0, 2.0 |
| M1M2 | 3.7 | 1.8, 2.8, 3.8 | 1.5 |
| | 2.7 | 1.8, 2.8, 3.8 | 1.5 |
| | 1.7 | 1.8, 2.8, 3.8 | 1.5 |
| | 0.7 | 1.2, 2.2 | 1.5 |

Coordinates were measured in millimeters from bregma for antero-posterior (AP), on each side of midline for mediolateral (ML), and below the surface of cortex for dorsoventral (DV).

Formalin. This tissue was blocked in the plane of Paxinos and Watson (1998) using an RBM 4000C mold (ASI Instruments, Warren, MI), and sectioned frozen in the coronal plane at 30 µm. Every fifth section was mounted and stained with thionin.

We carried out quantitative analyses of lesions to compare areas damaged by different lesions and to test whether equivalent patterns of damage were produced by the same surgical procedure applied in different studies. We defined the most anterior section with cell bridges between ventral orbital cortex and the anterior olfactory nucleus as AP = 3.7, the most posterior section before the corpus callosum crossed midline as AP = 1.7, and the most anterior section in which the anterior commissure crossed midline as AP = 0.0 (Paxinos and Watson, 1998). Based on these landmarks, we measured the most anterior and posterior sections with bilateral damage to the intended target of each lesion. These landmarks were also used to identify sections at AP 3.2 for vPF and daPF lesions and AP 2.7 for M1 and for dPF and M1M2 lesions. These sections were used to determine the extent of cortex damaged in the coronal plane, inferred by measuring the linear extent of cortex spared (defined as having all layers intact).

Results

Histological Analyses

After completion of behavioral training, rats in each of the lesion groups were killed under deep anesthesia (100 mg/kg ketamine and 10 mg/kg xylazine i.m.) by transcardiac perfusion of normal saline followed by 5% (v/v) neutral-buffered formalin. Brains were cryoprotected by subsequent immersion in solutions of 10% glycerin/4% neutral-buffered formalin and then 20% glycerin/4% neutral-buffered formalin. This tissue was blocked in the plane of Paxinos and Watson (1998) using an RBM 4000C mold (ASI Instruments, Warren, MI), and sectioned frozen in the coronal plane at 30 µm. Every fifth section was mounted and stained with thionin.

We carried out quantitative analyses of lesions to compare areas damaged by different lesions and to test whether equivalent patterns of damage were produced by the same surgical procedure applied in different studies. We defined the most anterior section with cell bridges between ventral orbital cortex and the anterior olfactory nucleus as AP = 3.7, the most posterior section before the corpus callosum crossed midline as AP = 1.7, and the most anterior section in which the anterior commissure crossed midline as AP = 0.0 (Paxinos and Watson, 1998). Based on these landmarks, we measured the most anterior and posterior sections with bilateral damage to the intended target of each lesion. These landmarks were also used to identify sections at AP = 3.2 for vPF and daPF lesions and AP = 2.7 for M1 and for dPF and M1M2 lesions. These sections were used to determine the extent of cortex damaged in the coronal plane, inferred by measuring the linear extent of cortex spared (defined as having all layers intact).

Histological Findings

The damage produced by the NMDA infusions was character-
ized by tissue loss surrounded by areas of gliosis marked by a lack of neurons and proliferation of glial cells (Figs 1 and 2). All lesions affected their intended targets with little apparent vari-
ation between studies. The vPF lesions were associated with...
unintended damage in more dorsal areas adjacent to the tracks of the cannulas used to infuse the NMDA solution (Fig. 1).

Quantitative analyses confirmed these impressions. The average anterior and posterior limits of the lesions were equivalent to or extended slightly beyond the sites at which NMDA infusions were aimed. ANOVA showed only one case where differences between the anterior or posterior limits for a given lesion differed between studies. The anterior limit of the M1 lesion averaged 3.9 mm anterior to bregma in experiment 1 and 4.1 mm in experiment 3, $F(1,15) = 5.191, P = 0.0378$. Both these measures were in front of the most anterior target site for infusing NMDA (3.4 mm from bregma). Given the small size of this difference and the normal performances of M1-lesioned animals in both experiments (see below), this discrepancy does not appear to have had an important impact on the results.

Measurements of the extent of cortical damage in the coronal plane (Figs 1 and 2) confirmed the consistency with which lesions damaged tissue within the intended lesion sites. ANOVAs comparing these results across experiments showed no significant differences for any of these lesions between the different studies in which they were made. The daPF, vPF and M1 lesions made in the first three experiments showed little overlap with each other, beyond the unintended damage along the cannula tracks dorsal to the vPF lesions (Fig. 1). The daPF lesion consistently damaged the M2, Cg1 and dorsal PrL areas in Paxinos and Watson (1998). The vPF lesion produced consistent damage in the IL, ventral PrL, AIV and orbital areas. The M1 lesion damaged M1 cortex and laterally adjacent areas of S1 cortex. The dPF lesion affected all areas damaged by the daPF lesion and additionally affected more lateral areas of M2.
cortex, more anterior areas of M2 and FrA cortex, and more posterior areas of M2, Cg1 and Cg2 cortex. The M1M2 lesion involved areas damaged by M1 lesions but additionally damaged more anterior, medial, and posterior regions of both M1 and M2 cortex. There was overlap of ~0.6 mm within M2 cortex between the areas damaged by the dPF and M1M2 lesions.

Behavioral Findings

Experiment 1 — Effects of Frontal Cortical Lesions on Recurring- and Varying-choice DNM Trained Alternately

Table 2 presents a summary of the main results of all four experiments. The cortical lesions in experiment 1 did not substantially affect either DNM task. All groups tended to perform better for varying- than for recurring-choice DNM and showed signs of temporal decay, with higher per cent correct at shorter retention intervals. These trends were confirmed by a three factor ANOVA showing significant effects for task (recurring versus varying choice DNM), $F(1,31) = 54.579, P < 0.0001$; and delay, $F(3,93) = 142.627, P < 0.0001$; but not for group (control, vPF, daPF or M1), $F < 1$.

The rate of temporal decay was greater for recurring than varying choice DNM but did not appear to differ between groups. These trends were confirmed by a significant interaction between task and delay, $F(3,93) = 586.406, P < 0.0001$; but not between group and delay, $F < 1$. The interactions between task and group, $F(3,31) = 1.958, P = 0.1409$, and between task, delay, and group were not significant, $F < 1$.

Experiment 2 — Effects of Frontal Cortical Lesions on Recurring Choice DNM Trained Exclusively

This study was conducted to test possible explanations for the normal performance of lesion groups in experiment 1. The dPF lesion was the least accurate performing the DNM task, averaging 74.4% correct, compared to 76.8% for the daPF, 77.2% for the vPF, 79.3% for the M1M2, and 81.9% correct for the control groups. There were no apparent differences in the rates of temporal decay between groups (Fig. 3). The effects of the NMDA dPF lesion resembled previous results for radio-frequency (RF) dPF lesions in rats trained using similar procedures (Porter et al., 2000). In this earlier study, RF dPF lesions produced delay-independent impairments of recurring choice DNM averaging 68.9% correct compared to 78.5% correct for controls. These results suggest that the limited size of prefrontal lesions in experiment 1 may have contributed to the normal performance of the lesion groups.

An ANOVA showed significant effects of treatment group, $F(4,35) = 5.700, P = 0.0012$, and retention interval, $F(3,105) = 200.480, P < 0.0001$, that did not interact significantly with each other, $F(12,105) = 1.454, P = 0.1537$. Comparison of each of the lesion groups using Fishers Protected Least Significant Difference (PLSD) test (Statview, SAS Institute, Cary, NC) ($\alpha = 0.05$) showed significant differences between controls and the daPF, vPF and dPF groups and between the dPF and M1M2 group. The control and M1M2 groups did not differ significantly by this measure. The significant effects of daPF and vPF lesions suggest that training procedures may have also contributed to the normal performance of these lesion groups in experiment 1.

Experiment 3 — Effects of Frontal Cortical Lesions on Visuospatial RT Performance

The dPF lesion affected both the speed and accuracy of responding (Fig. 4). Accuracy increased at longer stimulus
durations, with all groups performing essentially without error at the 1.33 and 3.00 s durations. These trends were confirmed by an ANOVA showing significant effects for group, $F(4,34) = 17.505, P < 0.0001$; stimulus duration, $F(5,170) = 1405.580, P < 0.0001$; and for the interaction between these factors, $F(20,170) = 9.570, P < 0.0001$. Because of this interaction, Fishers PLSD test ($\alpha = 0.05$) was carried out at each duration to compare treatment groups. These analyses showed that the dPF lesion produced significant impairment compared to M1, daPF and controls at the 0.05, 0.11, 0.26 and 0.58 s durations. The vPF lesion produced impairment compared to the M1 and control groups at the 0.11 and 0.26 s durations. There were no significant differences between the daPF, M1 and control groups at any duration.

The dPF and vPF lesions increased choice RT most noticeably at longer stimulus durations (Fig. 4). This trend was confirmed by an ANOVA showing significant effects of group, $F(4,34) = 5.105, P = 0.0025$; stimulus duration, $F(5,170) = 65.657, P < 0.0001$; and for the interaction of these factors, $F(20,170) = 6.806, P < 0.0001$. Because of this interaction, Fishers PLSD test ($\alpha = 0.05$) was carried out at each duration to compare treatment groups. These analyses showed that the

Figure 4. Effects of cortical lesions on the standard visuospatial RT task. In experiment 3 the dPF lesion had significant effects on choice accuracy and RT that varied with stimulus duration and effects on runway RT that did not. M1 lesions had no significant effects on performance. The effects of dPF lesions on accuracy were significant at shorter (0.05, 0.11, 0.26 and 0.58 s) durations. The effects of this lesion of choice RT were significant at the longer (0.58, 1.33 and 3.00 s) durations. In experiment 4, M1M2 lesions had significant effects on choice accuracy and RT at all stimulus durations examined. M1M2 lesions had no significant effect on runway RT. See Results for details. Error bars represent standard error of the mean.
dPF and vPF lesions had significant effects compared to the M1, daPF and control groups at the 0.58, 1.33 and 3.00 s durations. The cortical lesions also increased runway RT. An ANOVA showed a significant effect for group, $F(4,34) = 3.781$, $P = 0.0120$; but not for stimulus duration, $F(5,170) = 1.365$, $P = 0.2399$; or for the interaction of these factors, $F(20,170) = 1.351$, $P = 0.1537$. Comparison of lesion groups with Fishers PLSD test ($\alpha = 0.05$) showed significant effects on runway RT for the dPF, vPF and daPF groups compared to either the control or M1 groups.

The impairment of response accuracy by the NMDA dPF lesion was exacerbated when background illumination was increased to reduce stimulus salience. This effect was most noticeable at the 0.58, 1.33 and 3.00 s stimulus durations where performance was highly accurate for all groups in the dim or no house light conditions (Fig. 5). At shorter durations, where the dPF group was significantly impaired in the no light condition, the effects of background illumination appeared to be constrained by a floor effect (see Figs 4 and 5). These results provide a precise verification of findings for RF dPF lesions with the same manipulations of salience (Burk and Mair, 2001b).

A three-factor (group $\times$ stimulus duration $\times$ salience condition) ANOVA confirmed these trends. As in the preceding sessions (above) there were significant effects on per cent correct of group, $F(4,34) = 16.934$, $P < 0.0001$; stimulus duration, $F(5,170) = 1935.022$, $P < 0.0001$; and the interaction of group and duration, $F(20,170) = 4.346$, $P < 0.0001$. The effect

![Graphs showing percent correct vs. stimulus duration for different conditions](https://academic.oup.com/cercor/article-abstract/14/9/974/360515/fig)
of the salience condition (no, dim or bright house light) was also significant, F(2,68) = 137.929, P < 0.0001; and interacted significantly with the effects of duration, F(10,340) = 11.581, P < 0.0001 and the combination of group and duration, F(40,340) = 3.471, P < 0.0001. Because of the significance of the three-way interaction we compared the effects of the salience manipulations at each duration with two factor group \times salience ANOVAs. These analyses showed significant interactions between group and salience at the 1.33 [F(8,68) = 7.627, P < 0.0001] and the 3.00 s [F(8,68) = 6.065, P < 0.0001] durations consistent with the increased impairment of the dPF group in the bright house light condition at these durations. There was also a significant group \times salience interaction at the 0.11 s duration [F(8,68) = 2.234, P = 0.0352]. This interaction is consistent with the floor effect essentially eliminating lesion effects during training with the bright house lights at short durations (Fig. 5).

As in previous studies (Burk and Mair, 2001b; Mair et al., 2002) these manipulations of salience affected choice and runway RTs similarly for all treatment groups. For runway RT a two-factor ANOVA showed a significant effect for salience condition, F(2,68) = 10.659, P < 0.0001, and an effect approaching significance for group, F(4,34) = 2.508, P = 0.0607, that did not interact significantly [F(8,68) = 1.570, P = 0.1510]. For choice RT a two-factor ANOVA showed significant effects for treatment group, F(3,34) = 5.998, P = 0.0099; salience condition, F(2,68) = 206.452, P < 0.0001; and for the interaction of these factors, [F(8,68) = 2.248, P = 0.0341]. For both runway and choice RT, comparisons between treatment groups with Fishers PLSD test demonstrated the same differences observed for the standard task. While the salience manipulations had significant effects on both runway and choice RT, these effects did not alter the relative impact of cortical lesions on these measures.

Experiment 4 — Effects of Larger Sensorimotor Cortical Lesions on Visuospatial RT Performance

The results of experiment 3 showed no significant effect of the M1 lesion on visuospatial RT performance. Experiment 4 was carried out to determine whether a lesion causing more extensive damage to M1 and M2 cortex would produce RT deficits resembling those observed with sensorimotor striatal lesions (Mair et al., 2002). The M1M2 lesion decreased choice accuracy, increased choice RT, and had relatively little effect on runway RT (Fig. 4). These trends were confirmed by ANOVA. For per cent correct of choice responses there were significant effects of treatment group, F(1,14) = 12.945, P = 0.0029; stimulus duration, F(5,70) = 500.898, P < 0.0001; and for the interaction between these factors, F(5,70) = 9.009, P < 0.0001. For correct choice RT, there were significant effects for treatment group, F(1,14) = 16.841, P = 0.0011; stimulus duration, F(5,70) = 20.039, P < 0.0001; and for the interaction between these factors, F(5,70) = 2.417, P = 0.0443. Analyses of choice responses at each stimulus duration showed a significant decrease in per cent correct (Fs > 7, Ps < 0.02) and increase in RT (Fs > 14, Ps < 0.0022) for the M1M2 group at every duration. For runway RT there was no significant effect of treatment group and no interaction between treatment and stimulus duration (Fs < 1).

Varying background illumination to change stimulus salience affected each of these measures without notably altering the effects of the M1M2 lesion (Fig. 5). For per cent correct there were significant main effects for stimulus duration, F(5,70) = 45.683, P < 0.0001; and salience condition, F(2,28) = 243.970, P < 0.0001; and an effect of treatment group that approached significance, F(1,14) = 4.094, P = 0.0626. There were significant interactions between duration and salience, F(10,140) = 9.943, P < 0.0001; and between duration, salience, and group, F(10,140) = 1.941, P = 0.0445. The other interactions were not statistically significant. As in experiment 3 we explored this three-way interaction by comparing results at each duration. The results of these analyses showed a significant group by salience interaction only at the 0.11 s duration, F(2,28) = 7.387, P = 0.0027, where the effects of the salience manipulation was greater for controls than for the M1M2 group (Fig. 5). At the three longest durations where the effects of the dPF lesion were exacerbated by the bright house light the interactions between salience and group were not significant, Fs < 1. For choice RT, there were significant effects of treatment group, F(1,14) = 9.113, P = 0.0092; and salience, F(2,28) = 40.088, P < 0.0001; that did not interact (F < 1). Runway RT was also affected by salience, F(2,28) = 30.610, P < 0.0001, although there was no effect of group (both averaged 0.79 s, where there had been a non-significant difference of 0.90 versus 0.83 s during initial postsurgical training) and no interaction between group and salience (Fs < 1).

Discussion

The cytoarchitectonic features of frontal cortex are poorly differentiatied in the rat. Nevertheless there appears to be heterogeneity in cognitive functions of frontal areas as defined by anatomical connections. The present results reveal dissociable patterns of impairment for lesions involving dorsolateral motor areas innervated by the VL thalamic nucleus and prefrontal areas innervated by the MD nucleus. We found that recurring choice DNMs was affected significantly by prefrontal but not by M1M2 lesions involving adjacent areas of dorsolateral cortex. M1M2 lesions affected the speed and accuracy of visually guided choice responses, while sparing the speed of runway responses in the RT task. Prefrontal lesions had distinct effects on visually guided responding that were sensitive to manipulations of stimulus duration and background illumination in the RT task.

Effects of Dorsolateral Frontal Lesions

The dissociations observed for the RT task are consistent with evidence that dorsolateral areas play a critical role in sensorily-guided motor function and medial prefrontal areas in sensory attention (Brown et al., 1991; Mair et al., 1996; Bussey et al., 1997; Birrell and Brown, 2000). M1M2 lesions increased choice RT without affecting runway RT. Runway and choice responses were initiated by the behavior of rats and involved similar travel distances within the RT apparatus. Thus the normal runway RT seems inconsistent with a general deficit in vigilance, response initiation, or motor speed. Choice responses additionally required rats to detect and then respond to the location of a luminance cue. M1M2 lesions had significant effects on choice accuracy and RT at all stimulus durations and these effects did not change appreciably when the difficulty of detecting stimuli was increased by bright house lights. Our results thus demonstrate a deficit in guiding responses based on the location of luminance cues even when demands on attention and sensory function are minimized by presenting
discriminative stimuli for the duration of the limited hold (3.0 s) and turning house lights off.

Muir et al. (1996) also observed an increase in visuospatial RT with dorsolateral frontal lesions, however they found significant impairment only with decreased stimulus duration (0.25 versus 0.5 s), variable intertrial intervals, or interpolated white noise: conditions judged to affect decisional processes. They also found significant effects of stimulus illumination on response accuracy that did not interact with the effects of their dorsolateral lesions. We carried out a more fine grained analysis, comparing stimulus durations ranging from 0.05 to 3.0 s. We found significant effects of duration that interacted with the effects of the M1M2 lesion. Unlike Muir et al., we observed significant effects of M1M2 lesions on speed and accuracy at all durations tested. Our results are consistent with Muir et al. (1996) in finding no interaction between dorsolateral lesions and manipulations making stimuli more difficult to discriminate (decreasing stimulus illumination in their study and increasing background illumination in ours).

We found no effect of M1 lesions on any of our measures of visuospatial RT. Since M1M2 lesions involved larger regions of both primary and secondary motor cortex, their effects on the RT task could be ascribed to the extent of damage in either of these areas. In previous work, we have found a similar pattern of visuospatial RT impairment with lesions in dorsolateral areas of striatum that are innervated by sensorimotor cortex (McGeorge and Faull, 1989). Dorsolateral striatal lesions decreased the speed and accuracy of choice responses without affecting runway RT or sensitivity to manipulations of background illumination (Mair et al., 2002). These lesions have also been found to spare recurring choice radial maze DNM (Mair et al., 2002). Our results thus demonstrate a close correspondence between the functions affected (and spared) by lesions in sensorimotor cortex and its projection areas in dorsolateral striatum. Others have reported that lesions in these areas of cortex and striatum have comparable effects on measures of skilled motor function (Whishaw et al., 1986; Bures and Bracha, 1990; Pisa and Cyr, 1990; Whishaw et al., 1991; Whishaw and Coles, 1996; Fricker et al., 1996). These results seem consistent with our findings suggesting a role for motor cortex and its striatal projection areas in the capacity to generate and control intentional actions guided by external stimuli (see also Alexander et al., 1986; Georgopoulos, 1995; Graybiel, 1995; Sanes and Donoghue, 2000; Doyon et al., 2003).

Effects of Prefrontal Lesions

Prefrontal cortex has been implicated in a broad range of executive functions that are important for encoding and retrieving information in memory, controlling attention, and selecting or formulating actions (Fuster, 1989; Goldman-Rakic, 1998; Petrides, 1998; Robbins, 1998; Duncan and Owen, 2000). We examined two aspects of prefrontal function. Experiments 1 and 2 corroborated earlier reports that prefrontal lesions impair the recurring-choice DNM while sparing the varying-choice DNM (Porter and Mair, 1997; Porter et al., 2000). Comparison of vPF, dPF and dPF lesions in experiment 2 provides no indication that any particular area of prefrontal cortex is specifically important for this task.

It is not certain why the recurring-choice task was spared in experiment 1. Porter et al. (2000) found that prefrontal lesions spared recurring choice DNM when rats were first given extensive training with the varying choice procedure: an effect they ascribed to the development of an allocentric response strategy during varying choice training. Thus it seems possible that concurrent training with varying and recurring choice procedures in experiment 1 may have similarly protected rats from impairment. The impairments associated with vPF and dPF lesions when training was restricted to recurring-choice DNM in experiment 2 are consistent with this possibility. Other studies have shown that prefrontal lesions affect delayed conditional discriminations between response alternatives distinguished by egocentric spatial cues (Larsen and Divac, 1978; Kesner et al., 1989, 1996; Dunnett, 1990; King and Corwin, 1992; Broersen, 2000; de Bruin et al., 2001; Ragozzino and Kesner, 2001). Recordings in awake behaving rats have confirmed that prefrontal lesions do not code allocentric information but exhibit responses correlated with memory-related behavioral events or egocentric (right/left) aspects of space (Jung et al., 1998, 2000; Pratt and Mizumori, 2001; Chang et al., 2002).

The results of experiment 3 showed that excitotoxic dPF lesions, involving prelimbic, cingulate, and medial areas of secondary motor cortex, affected the accuracy of the RT task only when luminance cues were made difficult to detect by either reducing stimulus duration (Fig. 4) or increasing background illumination (Fig. 5). The effect of dPF lesions on choice RT also varied with stimulus duration in a manner suggestive of slow sensory processing or attentional impairment (Fig. 4). At longer stimulus durations (1.33 and 3.00 s) dPF lesions spared response accuracy but increased correct choice RT by an average of 0.37 s. At short durations (0.05, 0.11, 0.26 s) dPF lesions affected choice accuracy but not RT. Thus when inspection time was limited dPF animals demonstrated a spared capacity to execute correct choice responses as quickly as controls. When allowed more time to inspect stimuli, they took longer to respond but were apparently able to take advantage of this increase and respond without error.

Muir et al. (1996) also report that mediofrontal lesions affect the speed and latency of responding in a similar RT task. They found that reducing stimulus duration from 0.5 to 0.25 s (between sessions) exacerbated deficits in response latency (significantly) and accuracy (non-significantly) and that making stimuli more difficult to discriminate (by reducing stimulus brightness) affected overall performance without exacerbating lesion effects. We tested a wider range of stimulus durations within sessions and found that increasing stimulus to much longer durations (1.33, 3.0 s) eliminated the effects of dPF lesions on accuracy while exacerbating the effects on response latency (Fig. 4). Testing at longer durations also revealed significant effects of reducing stimulus discriminability (by increasing background illumination) on response accuracy (Fig. 5). Passetti et al. (2002) have recently confirmed the effects of prefrontal lesions on visually guided responding in the five-choice task while providing evidence of a distinction between the effects of dorsal and vPF lesions. They found that lesions involving ventral areas increased perseverations, defined as repeated responses to a port before returning to the magazine for reinforcement. Prefrontal lesions have also been found to increase premature responses in the five-choice task, defined as responding to a port after a magazine response but before presentation of a stimulus (Muir et al., 1996; Passetti et al., 2002).

The training procedures for the present RT task eliminate the possibility of premature or perseverative responses as defined
in these studies. Premature responses are prevented by initiating trials with a lever press at the end of the runway and then triggering stimulus events as rats re-enter the hub. Perseverative responses are avoided by delivering reinforcement in the port as soon as a correct response is made and then immediately extending levers at the end of the arm to signal the start of the next trial. Eliminating the possibility of premature and perseverative responding is advantageous in avoiding possible confounds that might contribute to an overall picture of impairment but that are not directly related to sensory or attentional function (making multiple extra responses prior to reinforcement or making responses to ports prior to or during the presentation of discriminative stimuli). This could also be considered a disadvantage in limiting the sensitivity of the RT task to these other sources of impairment. We observed significant effects of ventral (vPF) lesions on choice accuracy and RT that were not observed for dorsal anterior (daPF) lesions. Post hoc testing revealed significant differences between these groups for choice RT.

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The results of experiments 1 and 2 are consistent with evidence that the contributions of prefrontal cortex to memory depend on the integrity of basal ganglia–thalamic connections. Lesions in dorsomedial or ventral areas of striatum have been associated with delay-independent impairment of the present recurring-choice DNM task (Mair et al., 2002) as well as DM trained with retractable levers that are qualitatively similar to results for prefrontal cortex (Dunnett, 1990; Burk and Mair, 2001a; Mair et al., 1998). Lesions of anatomically-related areas in ventral pallidium have been found to affect the DM task (Mair et al., 2003) and in medial thalamus both the DM and recurring-choice tasks (Burk and Mair, 1998; Mair et al., 1998). Seamans et al. (1995) compared the effects of temporarily inactivating dorsal and ventral regions of prefrontal cortex on a delayed foraging task trained in radial mazes. Although there were differences in the types of errors produced, both treatments affected delayed foraging when tissue was inactivated prior to testing: a result consistent with a deficit in retrieval. Phillips and his colleagues have provided direct evidence for the involvement of the basal ganglia and thalamus in these deficits by showing similar impairments following temporary inactivation of nucleus accumbens, ventral pallidium, and mediodorsal thalamus or crossed inactivation of prefrontal cortex and accumbens or prefrontal cortex and mediodorsal thalamus (Seamans and Phillips, 1994; Floresco et al., 1999,a,b).

Our results suggest a role for prefrontal cortex in sensory attention that is not dependent on connections with striatum or thalamus. We have found RF (Burk and Mair, 2001b) and excitotoxic (present results) lesions of dPF cortex to impair the accuracy of visually guided responding only when demands on attention are increased by either reducing stimulus duration or increasing the level of background illumination. By contrast lesions in areas of ventral or dorsomedial striatum, innervated by dPF, have not been found to have significant effects on visuomotor RT performance or to exacerbate the effects of stimulus duration or salience on performance (Mair et al., 2002). Similarly, Burk and Mair (2001b) found that lesions involving the intralaminar and mediodorsal thalamic nuclei increased choice RT, but did not affect response accuracy or sensitivity to manipulations of stimulus duration or background illumination. These results suggest that the contributions of prefrontal cortex to these aspects of attention do not depend on connections with thalamus or striatum. These results contrast with reports of similar effects on visually guided responding in the five-choice task with bilateral lesions in medial frontal cortex (Muir et al., 1996) or dorsomedial striatum (Rogers et al., 2001), or crossed lesions between these sites (Christakou et al., 2001). However these impairments included measures of non-attentional function, such as perseverative and premature responding. Our results seem consistent with evidence that at least some of the contributions of prefrontal cortex to sensory and attentional function are related to distributed cortical networks connecting modality-specific and associative areas of cortex (Rao et al., 1997; Mesulam, 1998; Knight and Grabowecky, 2000; Fox et al., 2003).

Notes
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Address correspondence to Robert G. Mair, Department of Psychology, University of New Hampshire, Durham, NH 03824, USA. Email: rgm@cisunix.unh.edu.

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