The Cerebral Cortex of the Rat and Visual Attentional Function: Dissociable Effects of Mediofrontal, Cingulate, Anterior Dorsolateral, and Parietal Cortex Lesions on a Five-Choice Serial Reaction Time Task

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Dissociable effects of bilateral excitotoxic lesions of different regions of the rat neocortex, including medial prefrontal and anterior cingulate cortices, were investigated in a five-choice serial reaction time task that provides several indices of the accuracy and speed of attentional function. Whereas medial prefrontal cortical lesions impaired performance of the task as revealed by a reduction in choice accuracy, an increase in the latency to respond correctly to the visual target and enhanced perseverative responding, lesions of the anterior cingulate cortex specifically increased premature responding. By contrast, lateral frontal cortical lesions did not significantly disrupt baseline performance of the task, but rather increased the latency to respond correctly to the visual target during various behavioral manipulations, for example, when the length of the intertrial interval was varied unpredictably and during interpolation of distracting bursts of white noise. Lesions of the parietal cortex failed to disrupt any aspect of task performance investigated.

These behavioral effects in the five-choice task were compared with the effect of these same lesions on acquisition and retention of a one-trial passive avoidance task. The main finding from this paradigm was that lesions of the lateral frontal cortex produced a significant disruption to the retention of passive avoidance, which stands in marked contrast to the successful retention observed by animals of the other lesion groups. In addition, this pattern of results reveals that the "disinhibitory" effect of cingulate cortex lesions are relatively specific to the five-choice attentional task.

Finally, the results of the present study are compared with the findings of previous experiments using the five-choice task, which have examined the effect of selective manipulations of the ascending noradrenergic, cholinergic, dopaminergic, and serotonergic projections. In particular, the deficits in attentional function observed following cholinergic lesions of the nucleus basalis magnocellularis appear to be attributable to cholinergic denervation of the medial frontal cortex. These results are discussed in terms of the role of parallel distributed neural systems within the neocortex that mediate continuous attentional performance in the rat.

Recent studies have implicated the neocortical cholinergic projections of the nucleus basalis magnocellularis (nbM) in forms of visual attentional function in the rat (Robbins et al., 1989; Muir et al., 1992, 1994, 1995). Thus, AMPA-induced lesions of the nbM, which produce substantial reductions in choline acetyltransferase (ChAT) activity in neocortical areas, including medial prefrontal, anterior dorsolateral, cingulate, and parietal cortices, have been shown to impair the accuracy of detecting brief presentations of light occurring in one of five spatial locations (Muir et al., 1994, 1995), in a paradigm designed specifically to assess disturbances in visual attention (Carli et al., 1983; Robbins et al., 1993). These deficits in the five-choice serial reaction time task are reversible by cholinergic treatments, such as administration of nicotine or the anticholinesterase, physostigmine (Muir et al., 1995). However, the precise mechanisms underlying this change in visual attention remain unclear. For example, lesion-induced deficits may be the result of cholinergic denervation and thereby loss of cholinergic modulation of the neocortex, or depend instead upon damage to basal forebrain neurons that do not project to the neocortex. One way of clarifying this issue is to determine whether similar impairments in attentional function are produced by lesions of discrete cortical regions that are typically denervated by lesions of the cholinergic basal forebrain. Moreover, different aspects of the deficits induced by nbM lesions may be mediated by the different cortical areas to which the cholinergic neurons project.

While there is an extensive literature, especially using positron emission tomography (PET), with human subjects to delineate specific cortical neural networks associated with different forms of attentional function (Mesulam, 1981; Corbetta et al., 1991; Pardo et al., 1991), most of the studies using experimental animals have been concerned with assessment of attentional neglect following unilateral lesions (Cowey and Bozek, 1974; Crowne and Pathria, 1982; King and Corwin, 1990; Brown et al., 1991). However, the procedures used have generally not involved operant methods, but rather the use of clinical sensorimotor test batteries. In contrast, the five-choice task provides a test of attention, which has obvious analogies with the human Continuous Performance test of attention by Mirsky and Rosvold (1960) and Leonard's five-choice serial reaction time task much used in human experimental psychology (Leonard, cited in Wilkinson, 1963). Indeed, this task contains elements not only of a sustained attention paradigm, but also requires the animal to divide attention across five spatial locations. Furthermore, during certain manipulations to the basic paradigm, such as the interpolation of distracting bursts of white noise during the animals' performance of the task, there may be an additional high premium on selective attention mechanisms. Therefore, it is possible that lesions that impair either selective or divided attention may also produce, under particular circumstances, deficits on this task. Data from human PET studies would suggest that selective attention conditions activate lateral orbitofrontal and insular-premotor cortex, while divided attention conditions activate the anterior cingulate and dorsolateral prefrontal cortex (Corbetta et al., 1991). In addition, given that the parietal cortex has been implicated in visuospatial attentional processes (Mesulam, 1983; Posner et al., 1984), it would be expected that, in addition to frontal and cingulate cortices, this area of cortex may also be important for effective task performance.

Many previous studies of cortical function in rats have employed aspirative lesion methods (e.g., Kolb et al., 1974, 1982; Kesner and Holbrook, 1987; Sutherland et al., 1988), and thus may have compromised interpretation of precise functional localization due to inadvertent damage to fibers of passage and corticocortical connections. Consequently, the present study employed the excitotoxin quinolinic acid to produce fiber-sparing cell body lesions of the cortex. In order to dissociate the contributions of different neocortical regions, multiple measures of task performance were made. Previous studies investigating the role of various neurotransmitter systems on performance of this task have also utilized this approach and have revealed that each transmitter system affects quite

different components of the task. For example, while ceruleocortical noradrenaline loss severely disrupts accuracy when distracting bursts of white noise are interpolated into the task or if stimuli are presented unpredictably (Carli et al., 1983), increased mesolimbic dopamine release does not affect accuracy but, instead, increases the overall speed and probability of responding (Cole and Robbins, 1987) while mesolimbic dopamine depletion has the opposite pattern of effects (Cole and Robbins, 1989).

Furthermore, in addition to assessing attentional function, animals in the present study were also tested on acquisition and retention of a passive avoidance task. Although this paradigm has revealed deficits following AMPA-induced basal forebrain lesions (Page et al., 1991), it remains unclear whether these deficits are attributable to cholinergic denervation of the neocortex or are due to disruption of either the cholinergic projection to the amygdala or to noncholinergic neurons in the dorsal forebrain. It appears that relatively little is known about the effect of discrete cortical lesions on passive avoidance in the rat, despite the considerable body of literature concerned with other forms of learning and memory (Kolb et al., 1983; Kolb and Walkey, 1987; Kesner, 1989; Olton, 1989).

Materials and Methods

Animals

Male Lister hooded rats (Olac, Bicester, UK) were housed in pairs in a temperature-controlled (21°C) room, under natural daylight conditions, with water available ad libitum. Rats were food deprived and maintained at 90% of their free-feeding weight (MRC Diet 41B laboratory chow) throughout the experiment.

Surgical Procedures

Animals were anesthetized using Equithesin administered intraperitoneally (0.3 ml/100 gm) and placed in a Kopf stereotaxic instrument fitted with atraumatic earbars. A total of 35 rats received bilateral injections of 0.09 M quinolinic acid (Sigma, St. Louis, MO) and 19 sham-operated controls received infusions of 0.1 M phosphate buffer (pH 7.2). A volume of either 0.5 or 1.0 μl of quinolinic acid or the same volume of buffer alone was infused bilaterally over 90 sec via a 30-gauge cannula attached to a 5 μl precision sampling syringe (SGE, Baton Rouge, LA). The toxin was infused manually in volumes of 0.2 μl, followed by a 20 sec infusion period before the next 0.2 μl infusion. For animals receiving quinolinic acid lesions (n = 9) or sham lesions (n = 4) of the medial frontal cortex (MF), comprising areas Cg1, Cg3, and Fr2 according to the classification of Zilles (1985), 1.0 μl infusions were made at each of three placements presented in Table 1. For lesions of the anterior dorsolateral cortex (ADL; n = 9) and sham controls (n = 5), the infusion sites are listed in Table 1 and included Zilles' areas Fr1, Fr2, and Fr3. Cingulate cortex lesions (n = 8) were aimed at postgenu anterior cingulate cortex (Cg1, Cg2, and Fr2), and the respective sham-control lesions (n = 5) were made using a volume of 1.0 μl into each site, as for lesions of the MF and ADL. Finally, for lesions of the parietal cortex (PAR), 0.5 μl of quinolinic acid (n = 9) or vehicle solution (n = 5) was infused at each of the placements presented in Table 1, in order to include Zilles' areas Par1 and Par2. For each of the four cortical lesions, the incisor bar was set at 2.3 mm below the interaural line. Following infusion of the appropriate volume, the injection cannula was left in place for a further 2 min following each infusion.

Histology

Following completion of behavioral testing, animals were perfused with 0.9% saline followed by 10% formol saline. The brains were then stored in 30% sucrose until sections were cut at 60 μm thickness on a freezing microtome. Every fourth section through the region of the lesion was mounted on a glass slide for staining with cresyl violet. These sections were used to verify lesion placement and to assess the extent of lesion-induced neuronal loss.

Table 1
Stereotaxic coordinates used for lesions of the medial frontal (MF), anterior dorsolateral (ADL), anterior cingulate (CING), and parietal (Par) cortices

Region	Stereotaxic coordinates	Zilles areas
MF	AP + 2.4; L ± 0.5; DV −1.5 mm	Cg1, Cg3, Fr2
	AP + 3.1; L ± 0.5; DV −3.0, −1.5 mm	
	AP + 3.8; L ± 0.6; DV −1.5 mm	
ADL	AP + 3.0; L ± 3.5; DV −1.5, −0.5 mm	Fr1, Fr2, Fr3
	AP + 3.0; L ± 4.0; DV −2.0, −1.0 mm	
	AP + 4.0; L ± 3.0; DV −1.5, 0.5 mm	
CING	AP + 0.2; L ± 0.5; DV −2.0, −1.5	Cg1, Cg2, Fr2
	AP + 1.0; L ± 0.5; DV −2.5 mm	
PAR	AP − 0.8; L ± 5.0; DV −1.3 mm	Par1, Par2
	AP − 0.8; L ± 6.0; DV −1.8, −1.0 mm	
	AP − 1.3; L ± 5.3; DV −1.0 mm	
	AP − 1.3; L ± 6.0; DV −2.0, −1.0 mm	

AP, anterior–posterior; L, lateral; DV, dorsal–ventral.

General Behavioral Procedures

Apparatus

The test apparatus for these experiments consisted of three 25 × 25 cm aluminum chambers built in the Department of Experimental Psychology, University of Cambridge. The rear wall of each chamber was concavely curved and contained nine apertures, each 2.5 cm square, 4 cm deep, and set 2 cm above floor level. Illumination of each hole was provided by a standard 3 W bulb located at the rear of the hole. In addition, each hole had an infrared photocell beam monitoring the entrance and each hole could be blocked by a metal cover when not required (for details, see Carli et al. 1983).

The three chambers were individually housed within wooden sound-attenuating cabinets, ventilated by low-level noise fans, which also served to mask extraneous background noise. Each chamber was illuminated by a 3 W house light mounted in the center of the roof along side a small general purpose loud speaker. White noise could be delivered through the speaker by a purpose-built white noise generator.

Animals were placed in the chamber through a Perspex door located in the front wall. Directly below this door, animals obtained access to the food magazine by pushing a hinged Perspex panel monitored by a microswitch. Food pellets (45 mg, dustless, Bioserv. Inc., NJ) were dispensed automatically into the magazine. The distance from the magazine panel to each of the holes in the rear wall was 25 cm.

The apparatus and on-line data collection was controlled by means of a Control Universal (Cambridge, UK) Cube microcomputer system with software written in ONLIBASIC.

Behavioral Procedure

Rats were trained to discriminate a brief visual stimulus presented randomly in one of five spatial locations, as described previously (Carli et al., 1983; Robbins et al., 1989, 1993). The task used in the present study has obvious analogies with the Continuous Performance test of attention by Mirsky and Rosvold (1960). Thus it contains elements not only of a sustained attention paradigm, the animal being required to monitor the apertures for brief presentations of the visual target during the 30 min session, but also requires the animal to divide attention across five spatial locations. Furthermore, during certain manipulations to the basic paradigm, such as the interpolation of distracting bursts of white noise during task performance, there may be an additional high premium placed upon selective attention mechanisms.

The training procedure for this task began with two 15 min sessions with the response apertures covered with metal caps. During these sessions, the magazine panel was partially open and food pellets were placed in the tray. In the next two 30 min sessions, the metal caps were removed from five of the apertures (from left: 1, 3, 5, 7, 9) and several food pellets placed within each aperture as well as within the food tray. During the fifth session the test schedule was implemented.

At the beginning of each test session, the house light was illuminated and free delivery of a single food pellet to the magazine was made. The trial was initiated by the rat opening the panel to collect

this pellet. After a fixed 5 sec intertrial interval (ITI), the light at the rear of one of the apertures was illuminated for a short period (0.5 sec). Responses in this aperture during illumination and for 5 sec afterward (the limited hold period) were rewarded with the delivery of a food pellet and a correct response was recorded. Additional responses in the apertures were recorded as perseverative responses and resulted in a 5 sec period of darkness (time out). Further responding in the apertures during the time out restarted this period. Responses in a nonilluminated hole during the signal period (incorrect response) and failures to respond within the limited hold period (omission) were similarly punished with a period of darkness. Once again, responses made in an aperture during this period restarted the time out.

A response in the food panel after the delivery of a food pellet, or after the time out period, initiated the next trial. Additional responses in the panel during the ITI or time out periods were recorded but had no further consequences. Responses in the apertures during the ITI were recorded as anticipatory responses and resulted in a time out period of darkness, additional responses during this time restarting the time out period.

During any one session, the light stimulus was presented an equal number of times in each of the five holes in a random order. A daily session consisted of 100 trials or was terminated after 30 min of testing. The end of a test session was signalled by extinguishing all the lights. For the first session of training, the stimulus duration and limited hold periods were both set at 1 min, and the ITI and time out periods set at 3 sec. These variables were altered on subsequent trials according to the individual animal's performance, until the target set of task parameters could be instituted. The target parameters were as follows: stimulus duration, 0.5 sec; limited hold period, 5 sec; ITI and time out period, 5 sec. The animals were considered to have reached criterion when these target parameters were attained on five consecutive sessions with >80% correct responses and <20% omissions within the 30 min session time. Approximately 30 sessions were required for the animals to attain this criterion.

Performance of the task was assessed using the following behavioral measures:

Accuracy. This measures accuracy of responding in a divided attention task where attention is spread over a range of spatial locations. Accuracy of performance was measured as the proportion of responses that were correct (number of correct responses/total number of responses), expressed as a percentage. Thus, this measures errors of commission without including errors of omission. The difficulty in making this discrimination can be modulated by variations of stimulus intensity, variations of stimulus duration, and by temporal predictability of stimulus presentation.

Speed. Two measures of speed of responding were used. The first was the latency to respond correctly, defined as the time between the onset of the visual stimulus and the point at which the animal's nose breaks the infrared beam of the lit hole. The second measure was magazine latency: the time between performance of a correct response and the opening of the magazine panel to collect the food pellet. These latencies can be interpreted to reflect either or both of motor or global motivational functions. However, if only one of the measures varies, more specific conclusions are possible. For example, if latency to respond is affected independently of magazine latency, this indicates possible changes in decisional mechanisms (e.g., speed/error trade-off. Moreover, if magazine latency is altered independently of response latency, then specific effects on incentive motivational mechanisms are likely.

Anticipatory Responses. The number of responses in the apertures during the ITI. This measure reflects deficits in inhibitory mechanisms of response preparation.

Perseverative Responses. Additional responses in the apertures following the initial response in an aperture. This measure also reflects inhibitory processes of response control, but is less related to response preparation.

Errors of Omission. The number of trials on which no response was made during the limited hold period. This measure reflects possible failures of detection and also motivational/motor deficits, depending on the overall pattern of effects.

Two weeks following surgery, the 54 animals used in this experiment were tested across 10 sessions on the standard schedule of the task. At the completion of these baseline test sessions, and having obtained stable performance on the task, a series of manipulations to the basic test schedule was instituted.

First, the stimulus duration was reduced to 0.25 sec during a single test session. Second, in order to assess the effect of stimulus unpredictability, animals were exposed to variations in the intertrial interval (ITI) duration: a short ITI schedule (1.5, 3.0, and 4.5 sec) and a long ITI schedule (4.5, 6.0, 7.5, and 9.0 sec), each preceded by a baseline session. Equal numbers of each intertrial interval were randomly presented during the 100 trial session.

Third, bursts (0.5 sec) of distracting white noise (105 dB as measured with a Dawe's sound level indicator) were interpolated at various points within the normal 5 sec ITI: 0.5, 2.5, 4.5, or 5.0 sec after the beginning of the ITI. In the latter case, the white noise was presented simultaneously with the visual target stimulus. Within this session, no noise was presented on 20% of the trials, these trials being randomly interspersed throughout the 100 trial session.

Finally, the baseline schedule was altered so that on 25% of the trials the stimulus was of normal brightness, and on the remainder of the trials the brightness was reduced to 6/8, 5/8, or 3/8 of the standard. The reductions were achieved by switching appropriate resistors into series with the stimulus bulbs. The stimuli were presented in random order, counterbalanced over trials and locations. This final behavioral challenge occurred approximately 16 weeks following surgery.

Passive Avoidance

Following the final manipulation on the five-choice attentional task, animals of the MF, ADL, and CING lesion groups were trained on "step-through" passive avoidance (PA) using the procedure of Fine et al. (1985), which allows the separate assessment of acquisition and retention impairments. Animals of the PAR group were not tested on this task because of time constraints and because this group was least expected to be impaired on the task.

The apparatus consisted of a 50 cm^2 aluminum box divided into two equal-sized compartments that were connected by a small guillotine door. The front compartment, which was brightly lit by two overhead 60 W bulbs, had an open roof and a Perspex front wall for observation. The rear compartment had a closed roof, no illumination, and an electrified grid floor.

Animals were habituated to the apparatus over 2 d repeated testing, during which time the connecting door was open and the animals were encouraged to move from the brightly lit front compartment to the darker rear compartment within an accepted "step-through" latency of 15–20 sec. During acquisition training, upon entering the rear compartment, the separating door was lowered and the rat immediately received a 1 sec, 0.5 mA scrambled footshock. The rat was left for 30 sec before being removed from the rear compartment and placed in a holding cage. Two minutes later, the rat was retested in the same manner as above; successful acquisition of PA was recorded when the rat remained in the front compartment for 120 sec. If this criterion was not met, upon entering the rear compartment a second time, the door was lowered and the rat received a 1.5 sec, 0.5 mA shock.

Retention of PA was tested 96 hr later. Each animal was placed in the front compartment and retention of the PA response was recorded as the latency, up to a maximum of 300 sec, to step through into the rear of the compartment.

Statistical Methods

Data for each variable for the five-choice attentional task were subjected to analysis of variance (ANOVA) using the GENSTAT (Rothamsted, UK) statistical package. Further post hoc comparisons were made using the Newman-Keuls test. Skewed data, which violate the distribution requirement of the ANOVA, were subjected to arcsine, square root, or logarithmic transformation as recommended by Winer (1971).

Retention of the passive avoidance task was analyzed using the Kruskal-Wallis nonparametric analysis of variance. The Information Statistic, a method for determining the significance of inhomogeneity in contingency tables analogous to chi-squared, but suitable for small cell samples (Kullback, 1968; Robbins, 1977), was used for contingency table analysis of the numbers of animals reaching the acquisition and retention criterion for PA.

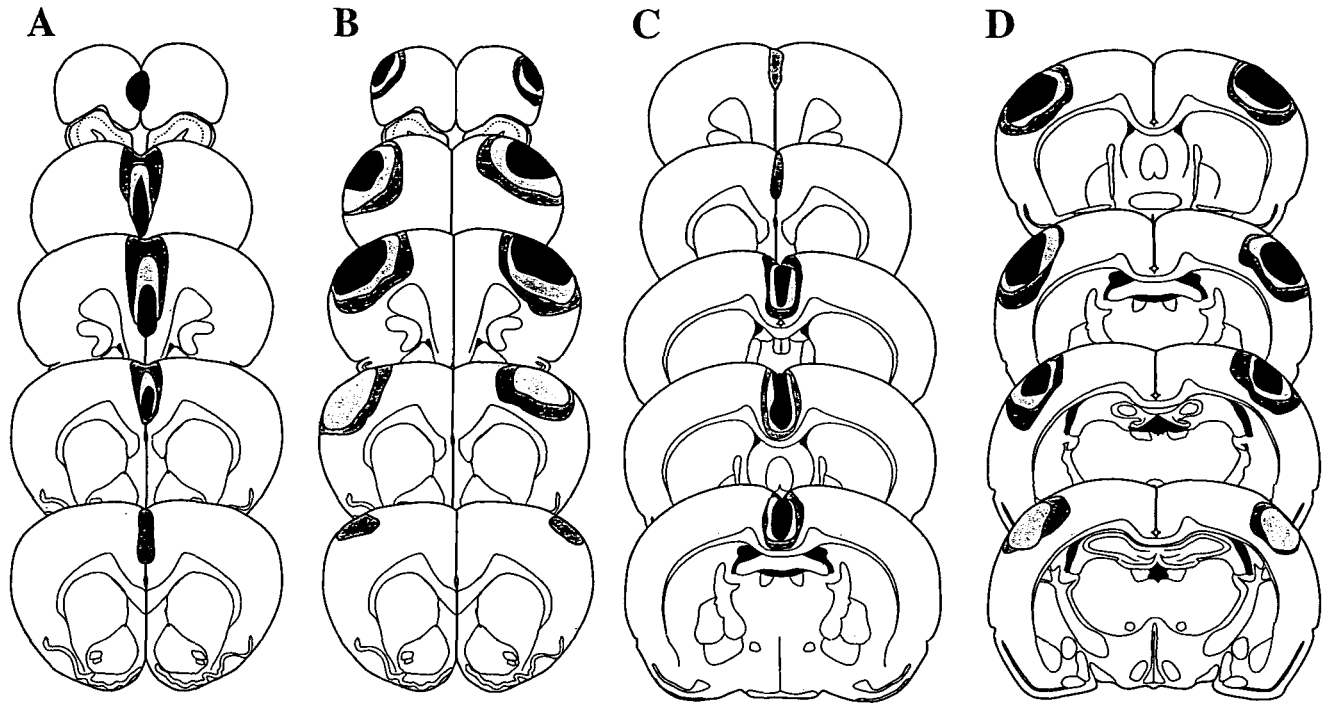


Figure 1. Reconstructions of the lesions for the four cortical groups at various anterior–posterior levels (coronal sections are shown at various levels from the interaural line of Paxinos and Watson (1986), and show representative lesions of the smallest, medium, and largest lesion within each group). *A*, Medial frontal (MF) (14.20–10.60 mm from the interaural line according to Paxinos and Watson, 1986). *B*, Anterior dorsolateral (ADL) (14.20–10.60 mm from the interaural line). *C*, Anterior cingulate (CING) (11.70–7.70 mm from the interaural line). *D*, Parietal (PAR) (8.70–6.20 from the interaural line). *Black shading refers to the smallest lesion in each group, light shading* refers to the medium-sized lesion within each group, and the *middle shading* shows the extent of the largest lesion of each group.

Results

Histology

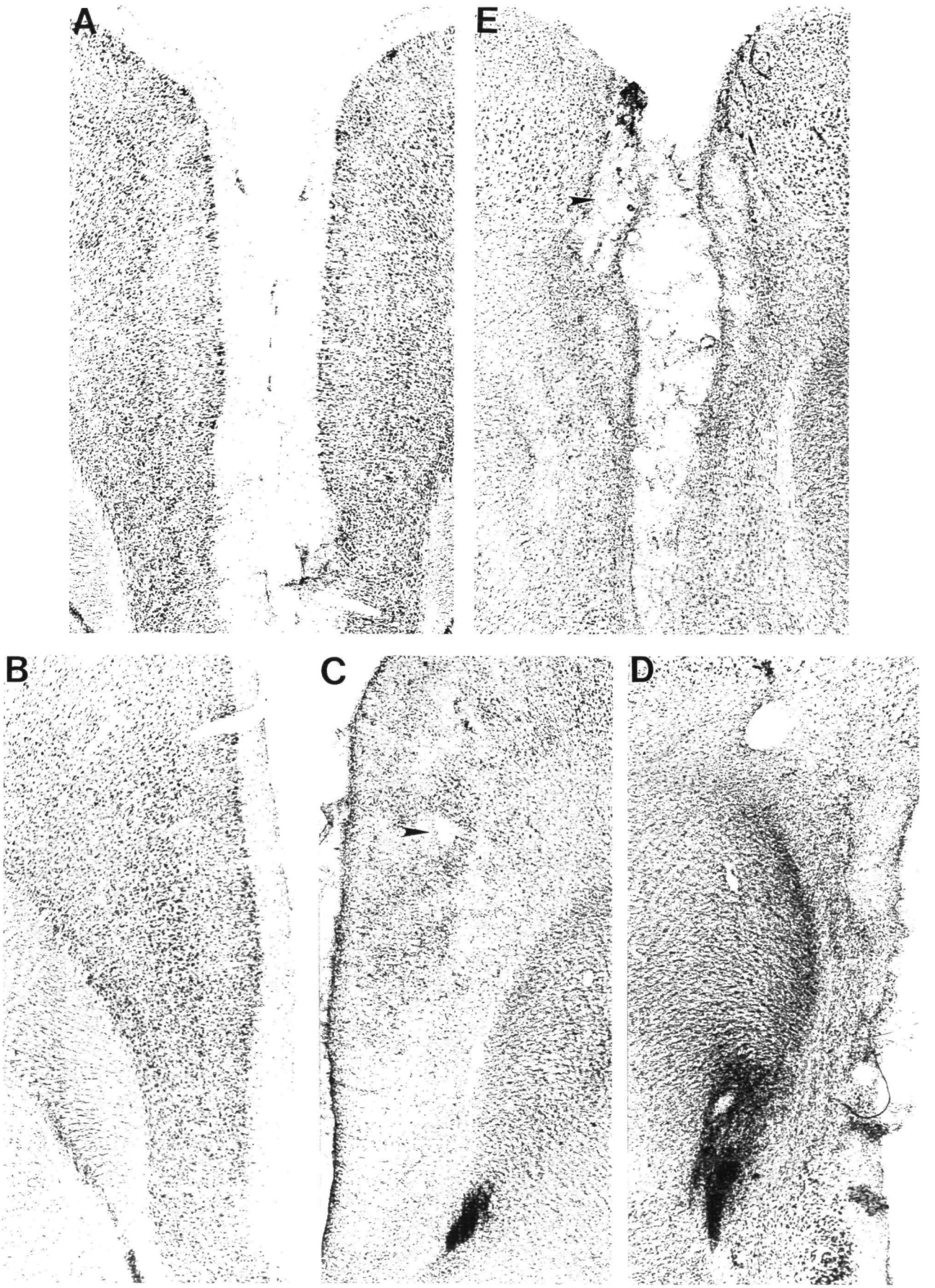
Figure 1 shows the extent of the lesioned areas in the four cortical lesion groups. Depicted are representative cases of the smallest, medium, and largest lesion for each lesion group as determined by projecting each lesion onto standardized sections of rat brain that were redrawn from Paxinos and Watson (1986). Examination of the cresyl violet-stained material revealed that one animal of the MF group and two animals of the ADL lesion group presented with either a unilateral or a very small, incomplete lesion and were thus discarded from the behavioral analysis. In all other cases, the area of destruction was centered on the appropriate target region for that particular lesion group. Medial frontal lesions in one case only extended posterior to the genu of the corpus callosum. Cingulate cortex lesions primarily did not extend anterior to the genu of the callosum and never encroached upon the posterior cingulate cortex. Dorsolateral cortical lesions were centered primarily on areas Fr1, Fr2, and Fr3, while lesions of parietal cortex were centered upon area Par1, according to the nomenclature of Zilles (1985). In many instances, the deeper layers of the cortex were spared, especially layer six and sometimes layer 5. However, overlying cortical layers were completely destroyed. Figure 2 shows the typical form of a quinolinate-induced cortical lesion, in this case of the medial prefrontal cortex. It can be seen that the lesion extends the full depth of the cortex in two cases (2*C,D*), but spares the deepest layers in a third case (2*E*). Vacuolation is often seen in the lesioned area (e.g., Fig. 2*C,E*), indicating the massive neuronal loss following infusions of quinolinate, which is not always associated with uniform gliosis (also clearly visible in more ventral parts of the lesion in Fig. 2*E*). Infralimbic cortex was not destroyed in the majority of cases following infusions of quinolinate into the medial prefrontal cortex.

Behavioral Results

Two Weeks Postlesion Surgery

As shown in Figure 3*A*, quinolinic acid lesions of the medial frontal cortex (MF) significantly reduced choice accuracy [$F(4,46) = 14.78, p < 0.001$], an effect that remained constant throughout the 10 d postoperative testing period. Newman-Keuls post hoc comparisons revealed that accuracy of performance by these animals was significantly different from both sham controls ($p < 0.05$) and the performance shown by the other lesion groups ($p < 0.05$). This reduction in accuracy of performance by the MF group was accompanied by a significant lengthening of the latency to respond correctly to the visual stimulus [$F(4,46) = 10.85, p < 0.001$] (see Fig. 3*B*). A significant main effect of lesion on errors of omission was also observed [$F(4,46) = 3.22, p < 0.05$]. Newman-Keuls post hoc analysis revealed this to be due to animals of the CING lesion group making significantly fewer omissions than animals of the other groups ($p < 0.05$). Importantly, animals of all groups did not respond with omissions above that considered acceptable (20%) in performing this task (shams = 16.2; MF = 20; ADL = 17.4; CING = 8.7; PAR = 15.4%).

Perseverative responses were, however, significantly increased in both the MF and CING lesioned groups ($p < 0.05$), an effect that did not reduce significantly over test sessions [$F(4,46) = 4.1, p < 0.0$] (see Fig. 3*D*). A lesion × session interaction was, however, obtained for anticipatory responding [$F(36,414) = 1.74, p < 0.01$]. Newman-Keuls post hoc comparisons revealed that anticipatory responding by animals of the CING lesion group was significantly elevated compared with that of sham controls and the other lesion groups



on the first day of testing ($p < 0.01$) and, although declining over days, remained significantly increased relative to all other groups on the final baseline test session (see Fig. 3*C*).

However, following this 10 d assessment of performance, it was apparent that the deficits observed in choice accuracy and response latency were showing gradual behavioral recovery. All animals therefore received additional baseline sessions on the task in order to obtain a stable baseline upon which to initiate the behavioral "challenges." After these additional sessions, sham and lesion animals did not significantly differ in their performance of the task on any behavioral measure recorded except for anticipatory responding, the CING lesion group continuing to show a significant increase in such behavior. Consequently, the behavioral manipulations described in Materials and Methods could be instituted beginning with reductions in the duration of the visual target.

Effect of Varying the Stimulus Duration

As shown in Figure 4*A*, reducing the stimulus duration to 0.25 sec resulted in a significant reduction in the accuracy of performance by all animals, irrespective of group [$F(1,46) = 184.48$, $p < 0.001$]. This measure was not differentially affected by the different cortical lesions, although animals of the MF group showed a trend toward a more substantial reduction in accuracy of responding when the stimulus duration was 0.25 sec. There was, however, a significant lesion × stimulus duration interaction effect on the latency to respond correctly to the visual target [$F(4,46) = 4.20, p < 0.01$]. Newman-Keuls post hoc comparisons revealed a significant increase in the response latency of both the MF and ADL lesion groups when the stimulus duration was reduced (0.25 sec), compared to performance during the baseline (0.50 sec) stimulus condition ($p < 0.05$). Although under baseline conditions the response latencies of MF and ADL animals were equivalent to those of Sham, CING, and PAR groups, presentation of the stimulus for 0.25 sec significantly lengthened the correct latency of MF and ADL animals compared to performance of the other groups (see Fig. 4*B*). Furthermore, this effect was significantly greater in the MF lesion group ($p < 0.05$).

Once again, animals of the CING lesion group made significantly fewer errors of omission than animals of the other groups [sham = 15.1; MF = 16.6; CING = 19.5; CING = 7.2; PAR = 18.5], an effect that was independent of stimulus duration [$F(4,46) = 3.74, p < 0.01$]. In addition, animals of the CING group continued to make more anticipatory responses than animals of the other groups ($p < 0.01$), and this level of responding also significantly increased in this group when the stimulus was reduced to 0.25 sec duration [$F(4,46) = 12.82, p < 0.001$] (see Fig. 4*C*). There was no effect of this manipulation or the lesions on perseverative responding.

Effect of Variable Intertrial Intervals

Short ITIs (1.5-4.5 sec). Unpredictable presentation of short ITIs did not significantly disrupt the accuracy of performance for any of the cortical regions lesioned, these animals performing at the same level of accuracy as the Sham group at all ITIs tested [$F(8,92) = 1.12, p > 0.05$]. However, animals of the MF and ADL groups took significantly longer than either the Sham, CING, or PAR groups ($p < 0.05$) to respond correctly to the visual stimulus [sham = 0.75; MF = 1.04; ADL = 0.99; CING = 0.66; PAR = 0.81 sec], an effect that was independent of the length of the ITI [$F(4,46) = 6.96, p < 0.01$]. Indeed, when MF and ADL animals and their sham controls were presented with a single session of ITIs of 1.5 sec for the entire 100 trials, there was no significant effect of either lesion on response latency [$F(2,21) = 0.74, p > 0.05$], indicating the importance of the unpredictability of stimulus presentation in producing the deficit during the previous test session.

Unpredictable presentation of the ITI significantly increased ITI errors of omission [$F(2,92) = 148.78, p < 0.001$], animals of all groups showing a significant reduction in the number of omitted responses as ITI length increased (1.5 sec = 13.32; 3.0 sec = 7.10; 4.5 sec = 4.82 omissions). Furthermore, there was also a significant main effect of lesion on this measure, animals of the CING group making significantly fewer omissions than animals of the other groups [$F(4,46) = 8.22$, $p < 0.001$]. The CING group also continued to show a significant ($p < 0.01$) increase in number of anticipatory responses [$F(4,46) = 6.97, p < 0.001$] across all ITIs but had no effect on perseverative responding.

Long ITIs (4.5-9.0 sec). Choice accuracy was not significantly affected by unpredictable presentation of long intertrial intervals [$F(4,46) = 2.11, p > 0.05$]. However, similar to the result obtained for short ITIs, the latency to respond correctly to the visual stimulus was significantly increased across all ITIs presented in this test session in both the MF and ADL lesion groups]$F(4,46) = 3.28, p < 0.05$] (sham = 0.59; MF = 0.72; ADL = 0.75; CING = 0.62; PAR = 0.61 sec). There was no effect of the lesions on either errors of omission or perseverative responding, but once again animals of the CING lesion group showed a significant increase ($p < 0.01$) in anticipatory responding across all ITIs presented compared to the performance of animals of the other groups [$F(4,46) = 5.94, p < 0.001$] (sham = 14.1; MF = 11.0; ADL = 9.4; CING = 30.0; PAR = 13.3 responses). Furthermore, all animals regardless of lesion group, showed a significant increase in anticipatory responding as the ITI lengthened [$F(3,138) = 121.1, p < 0.001$].

Effects of Interpolated Bursts of White Noise

Interpolating bursts of white noise (105 dB) revealed only a strong trend for performance to be disrupted in the MF lesioned group by this distractor as measured by choice accuracy [$F(4,46) = 2.56, p > 0.05$ (sham = 85.2; MF = 75.9; ADL = 80.5; CING = 80.4; PAR = 80.6%). However, there was a significant effect of this manipulation on latency to respond correctly, which was dependent upon the locus within the ITI at which the noise was interpolated [$F(16,184) = 2.12, p < 0.01$]. Post hoc comparisons revealed that animals of the MF lesion group showed an increase in response latency ($p < 0.05$) when the noise was interpolated immediately prior to the presentation of the visual target (4.5 sec), while animals of the ADL lesion group were disrupted when the noise was presented 2.5 sec after the start of the ITI ($p < 0.05$). Animals of the CING lesion group continued to show a significant increase in anticipatory responding that was independent of where within the ITI the noise was interpolated [$F(4,46) = 3.10, p < 0.05$], and also showed a significant increase in perseverative responding [$F(4,46) = 2.84, p < 0.05$]. The remaining behavioral measures were not significantly effected by this manipulation.

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Figure 2. Photomicrographs of cresyl violet-stained sections through the medial prefrontal cortex of control (*A* and *B*) and quinolinate lesioned (*C–E*) subjects. Marked neuronal loss is evident in all three lesioned subjects (*C–E*). In two cases, the lesions extends through the depths of the cortex (*C, D*), whereas the deepest layers of the prefrontal cortex are relatively spared in *E*. Vacuolation in the lesioned areas is not uncommon in the lesioned areas (e.g., *arrows in C and E*) and gliosis is often very marked (see especially *E*).

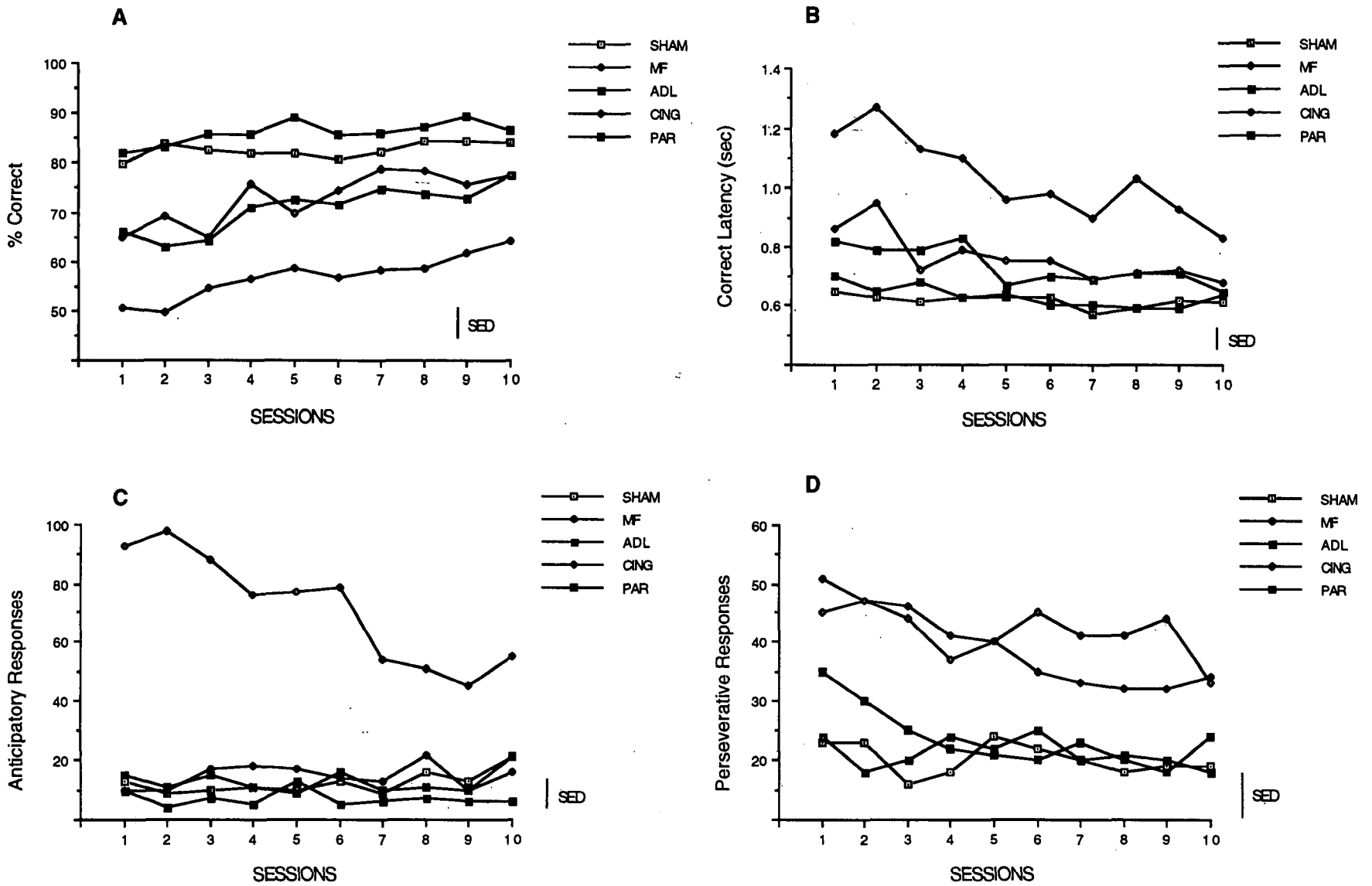

Figure 3. Performance of sham controls (*SHAM*), medial frontal (*MF*), anterior dorsolateral (*ADL*), anterior cingulate (*CING*), and parietal (*PAR*) lesion groups on the baseline schedule of the five-choice serial reaction time task 2 weeks after surgery. *A*, Choice accuracy. *B*, Correct response latency. *C*, Anticipatory responding. *D*, Perseverative responding (1 SED refers to 1 standard error of the differences between the means and is derived from the interaction of lesion group and sessions in the analysis of variance).

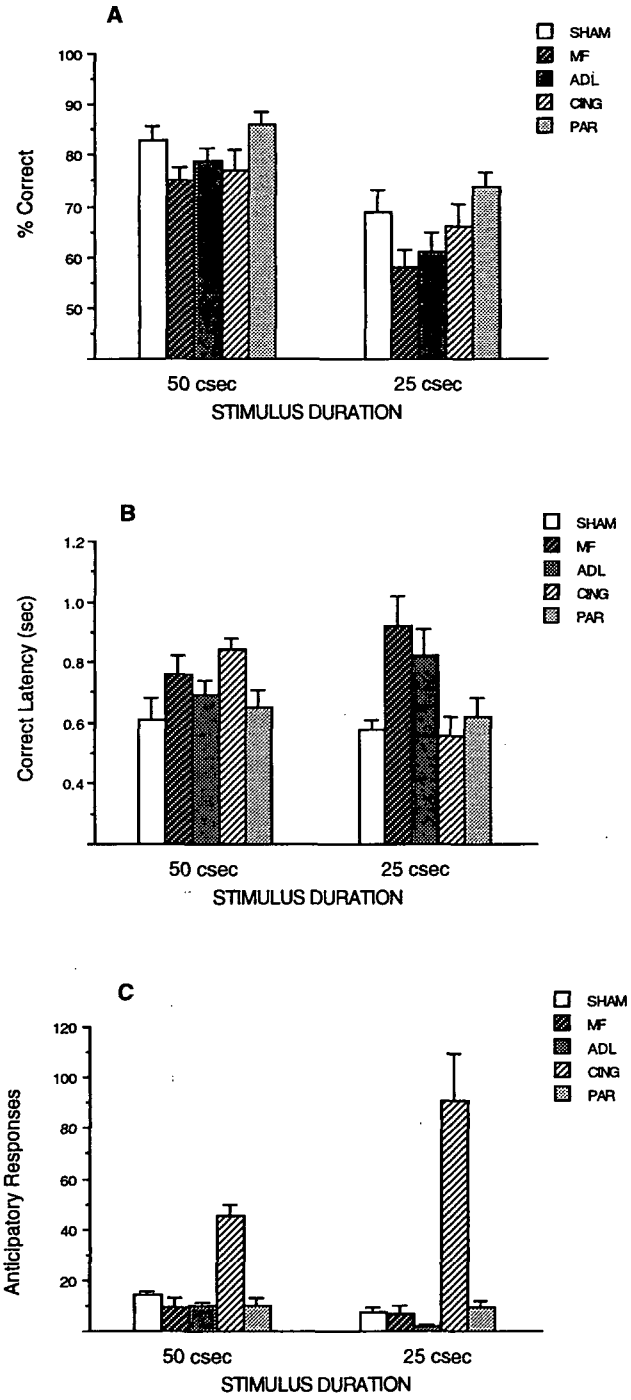

Figure 4. Effect of manipulating the duration of the visual stimulus on task performance. *A*, Choice accuracy. *B*, Correct response latency. *C*, Anticipatory responding (mean + SEM).

Effects of Varying Brightness of the Discriminanda

Reducing the illuminance of the stimuli produced a monotonic decline in accuracy of task performance [$F(4,46) = 41.41, p < 0.001$]. There was, however, no tendency for the accuracy of the lesioned groups to be differentially affected by this manipulation [$F(4,46) = 2.63, p > 0.05$]. A similar effect was observed for correct response latency with a main effect of Level of Brightness [$F(4,46) = 4.12, p < 0.01$]. The CING lesion animals continued to respond with a small but significant increase in anticipatory responding compared to sham control and animals of the MF, ADL, and PAR lesion groups, even 16 weeks following lesion surgery [$F(4,46) = 4.83, p < 0.01$].

Passive Avoidance

There was no effect of the lesion on acquisition of PA ($\chi^2 = 4.69$, df = 3, $p > 0.05$), seven out of eight animals of the MF group, eight out of eight of the CING group, and seven out of seven animals of the ADL lesion groups exhibiting one trial learning of the PA response compared to six out of eight animals of the sham control group.

Retention of PA was tested 96 hr later, where the step-through latency was recorded to a maximum of 300 sec, at which time successful retention was recorded. Overall analysis revealed that there was no significant effect of the lesion on this measure ($H = 6.76$, df = 3, $p > 0.05$). However, analysis carried out in terms of the number of rats successfully attaining the 96 hr retention criterion (> 300 sec) and those stepping through prior to the 300 sec revealed a significant effect of the lesion on this measure ($\chi^2 = 8.53$, df = 3, $p < 0.05$). Following partitioning of this main effect, it was found that animals of the ADL lesion group showed significantly ($\chi^2 = 5.47$, df = 1, $p < 0.05$) worse retention of PA than animals of the other groups, with only three out of seven (43%) showing successful retention in this group compared to six out of eight (75%) sham controls, seven out of eight (88%) animals of the MF group, and eight out of eight (100%) animals of the CING group showing successful retention.

Discussion

The results of this study very clearly show dissociable effects of discrete cortical lesions on performance of the five-choice attentional task, both during performance of the basic task and during various manipulations to the task. Lesions of the medial frontal cortex produced behavioral impairments immediately postoperatively, as shown by a reduction in choice accuracy, an increase in correct response latency, and an increase in perseverative responding. Lateral frontal cortical lesions did not significantly disrupt baseline performance of the task but rather produced a significant increase in the latency to respond correctly to the visual target during various behavioral manipulations. By contrast, lesions of the anterior cingulate cortex produced a selective and profound increase in anticipatory responding that was observed throughout the course of the experiment, while parietal cortex lesions failed to disrupt any aspect of task performance investigated.

Comparison with BF Lesions

A consistent finding following quisqualate- and AMPA-induced lesions of the BF is a significant reduction in choice accuracy and an increase in correct response latency on performance of this task (Robbins et al., 1989; Muir et al., 1992, 1994, 1995). In addition to these impairments, discrete lesions of the magnocellular cholinergic neurons of the nucleus basalis using AMPA also result in a significant increase in perseverative responding (Muir et al., 1994, 1995). In the present study, precisely this same pattern of behavioral effects was observed in those animals that had received quinolinic acid lesions of the medial frontal cortex but not in any of the other lesioned groups examined. These behavioral effects could not easily be attributed to damage to the frontal eye fields since this region appears to be situated more posteriorly to the site of the lesions in the present study (see Uylings and van Eden, 1990). Furthermore, the magnitude of the behavioral impairments observed in the medial frontal lesion group were remarkably similar to those observed following AMPA-induced lesions of the BF. This suggests strongly that the deficits in visual spatial attention following AMPA lesions of the BF were primarily the result of cholinergic denervation of the medial

frontal cortex. The importance of the cholinergic innervation of this cortical area for efficient spatial attentional function is further supported by the recent finding that infusion of the muscarinic antagonist, scopolamine, into the medial frontal cortex produced a parallel pattern of behavioral impairments to those observed following quinolinate-induced medial frontal cortex lesions or AMPA lesions of the basal forebrain (Muir, Everitt, and Robbins, unpublished observations). Support for the attentional nature of the scopolamine-induced deficits on this task is provided by the delay-independent effects produced by intramedial frontal cortical infusion of the drug (Dunnett et al., 1990).

The most distinctive effect observed in the anterior cingulate cortex lesioned animals (CING) in the attentional paradigm was an increase in premature, anticipatory responses prior to the occurrence of the visual stimuli, suggesting that this area has an important role in behavioral inhibition. However, cholinergic denervation of this area does not appear to be responsible for this long-lasting effect, as increases in anticipatory responding observed following AMPA lesions of the BF (Muir et al., 1994, 1995) are transient, unlike the long-lasting effects on this measure observed in the CING group. Furthermore, results of a recent study (Muir, Everitt, and Robbins, unpublished observations), revealed that AMPA lesions of the vertical limb of the diagonal band of Broca (VDB), which cholinergically denervate this area of cingulate cortex, also had no effect on this measure of performance of the five-choice task even though this lesion did affect the acquisition of a conditional visual discrimination task (Muir, Everitt, and Robbins, unpublished observations).

The main effect of lesions to the anterior lateral frontal cortex was a significant lengthening of correct response latency during various manipulations to the basic task, for example, when the length of the ITI was varied unpredictably and during interpolation of bursts of white noise into the ITI. These changes in latency resemble in part those observed in previous studies (Robbins et al., 1989; Muir et al., 1992) following quisqualic acid induced lesions of the nbM that resulted in significant reductions of cholinergic markers in this region of the cortex. Furthermore, this lesion produced a significant deficit in retention of passive avoidance (PA), with only 43% of animals of the ADL group showing successful retention, which stands in marked contrast to the successful retention observed by animals of the other lesion groups. Page et al. (1991) reported that AMPA lesions of the nbM resulted in successful task retention in only 41% of these lesioned animals, markedly similar to the low success rate reported here for ADL animals. While it is indeed possible that the effects of the nbM on PA may be mediated by denervation of the amygdala, given that lesions of the basolateral amygdala also impair PA (Dunn and Everitt, 1988), the results of the present study suggest that the area of lateral frontal cortex lesioned in the present study may also be important.

Behavioral Nature of the Deficits

The behavioral effects of quinolinic acid lesions of the medial frontal cortex on task performance are consistent with attentional dysfunction observed in patients with frontal lobe pathology (Shallice, 1982). Indeed, we have previously suggested that the greater disruption of task performance observed following AMPA-induced lesions of the BF, compared to performance following quisqualate lesions, may be at least partly attributable to the larger reduction in medial frontal cortex ChAT activity obtained with the former lesion (Muir et al., 1994a). Furthermore, given the recent localization of sustained attention to sensory input within the frontal cortex in human subjects using PET, particularly along the dorsolateral convexity corresponding to Brodmann's areas 8, 9, 44, and 46 (Pardo et al., 1991), the vigilance required in performance of the five-choice task would be expected to require the integrity of the frontal cortex.

There is good reason to suggest at least some degree of homology between the medial frontal cortex in the rat and the dorsolateral prefrontal cortex of primates. For example, according to the terminology of Zilles, area Cg1 has strong reciprocal connections with the lateral portion of the MD nucleus of the thalamus. This resembles the parvocellular portion of this nucleus in the primate, the dorsolateral cortex of the primate receiving reciprocal connections with the parvocellular part of the MD (for review, see Uylings and van Eden, 1990). Like the primate dorsolateral cortex, this area also has close connections with parietal cortex (van Eden et al., 1992). In addition, there are certain functional characteristics of the dorsolateral PFC of the monkey that also appear to be present in the rat. For example, investigations in monkeys have revealed that within this area of PFC, there are several neuronal types that regulate their activity in concert with the delay period of spatial delayed-response tasks (Fuster, 1989; Goldman-Rakic, 1990). Similar delay-activated cells have also recently been demonstrated in the rat medial prefrontal cortex (Batuev et al., 1990).

It can be argued that the task used in the present study has some affinity with such spatial delayed-response tasks, given that the brevity of the stimulus requires the animal to respond in the absence of the target stimulus. However, we would suggest that the deficits observed in the present study are due to disruption of attentional, rather than mnemonic, function on the basis of several findings. First, the period of time between offset of the visual stimulus and the animal performing its response is usually very short, suggesting that the animals have oriented toward the stimulus before the stimulus has disappeared. Second, Dunnett (1990) has shown that aspirative lesions of the medial prefrontal cortex, which included those areas of pregenual cortex lesioned in the present study, produced nonspecific delay-independent deficits in performance of a version of a delayed response task, termed delayed matching to position. These aspirative lesions included not only area Cg1, but also area Cg3, which was included within the lesioned area in the present study. In several animals performing the delayed matching to position task, where damage did not include Cg3, Dunnett (1990) found delay-dependent deficits, suggesting that inclusion of Cg3 in the lesion masked the delay-sensitive effects of the more focal lesions. Indeed, the area delineated as Cg3 within the MF cortex differs from the rest of the medial prefrontal cortex in that its afferents from the MD nucleus come from the medial rather than from the lateral subnucleus (Krettek and Price, 1977; van Eden, 1986). Area Cg3 also has direct connections with structures such as the amygdala, nucleus accumbens, and the hippocampus (Swanson, 1981; Sesack et al., 1989; Hurley et al., 1991) and this subregion thus has some affinity with orbitofrontal areas of primate prefrontal cortex (Uylings and van Eden, 1990).

The load placed upon sustained attention in this task could be increased by reducing the duration of the visual stimulus, and this manipulation produced a significant slowing of correct response latency and a strong trend for a reduction in choice accuracy in animals with lesions of the medial frontal cortex. This does not appear to be a simple sensory effect as explicit variation of stimulus intensity failed differentially to affect the groups. Additional evidence for the attentional nature of this deficit comes from the observation that following unpredictable presentation of the target stimuli, correct response latency was significantly lengthened in the MF lesion group. It seems clear that this increase in correct response latency is due to the temporal uncertainty associated with

this manipulation, rather than reducing the rate of presentation of the visual stimuli, given that a similar impairment was observed following presentation of both shortened and longer ITIs and that a single session of very brief (1.5 sec) ITIs did not significantly disrupt task performance.

Furthermore, when a premium was placed upon selective attentional ability (resistance to distraction) by interpolating distracting bursts of white noise during the session, animals of the MF group showed a significant disruption in task performance when the distractor was presented immediately prior to the presentation of the visual stimulus, as measured by a significant increase in correct response latency. For a number of reasons, this lengthening of response latency, which was observed in the MF group on the baseline schedule of the task, as well as during manipulations of the basic paradigm, appears to be related to decisional processes involved in the selection of the correct response following presentation of the stimulus, rather than due to motivational or visual dysfunction. First, the latency to collect food reward was not lengthened in MF-lesioned animals, and there was no significant increase in errors of omission, which would be expected to occur as a result of reduced motivation. Second, there was no effect of the lesion on basic activity levels measured over a 12 hr period (Muir, Everitt, and Robbins, unpublished observations). Third, the visual capacity of the animals was unaffected by the lesion, as shown by the equivalent behavioral performance of control and MF animals when the brightness of the stimulus was reduced.

A similar lengthening of correct response latency was also observed in animals that received lesions of the lateral frontal cortex. This impairment on the task was observed during various behavioral manipulations such as varying the length of the ITI, reducing the duration of the visual target, and interpolating bursts of white noise, but was not observed on the standard baseline schedule of the task. Thus, the lengthening of the latency to respond correctly to the visual stimulus by this group and animals of the medial frontal lesion group appears to represent a lengthening of the decisional process, which may occur as a result of an inability to attend efficiently to the relevant stimuli in the environment. This may, in turn, be exacerbated by an abnormal distraction toward irrelevant sensory stimuli such as white noise. Given that this lengthening of response latency is not associated with an increase in errors during performance of the task, this change in latency may reflect a speed/accuracy tradeoff strategy by which the animals can maintain their accuracy of performance during certain task manipulations.

An important consideration is the possibility that lesions of the lateral frontal cortex may have disrupted motor cortical functions, given that these lesions included the primary motor cortex (Zilles' area Fr1). However, if this were the case, it is difficult to explain the lack of effect of the lesion immediately postsurgery on the measure of correct response latency and latency to collect food reward. Instead, it is more likely that these latency effects represent some form of response preparation, perhaps as a consequence of disruption of premotor function (see Brown et al., 1991). Indeed, these lesions included a large portion of area Fr2, which can be distinguished from area Fr1, with which it is directly connected, particularly by the fact that only Fr2 receives input from the MD nucleus of the thalamus (Donoghue and Parham, 1983). On the basis of anatomical data, it has, in fact, been suggested that Fr2, together with Cg1 within the medial prefrontal cortex, incorporate characteristics of the primate premotor cortex, or an 'amalgam' of functions comprising premotor and supplementary motor functions (Goldberg, 1985; Neafsey et al., 1986; Passingham et al., 1988; Conde et al., 1989; Reep et al., 1990) in addition to the presence of anatomical and functional features of dorsolateral PFC of the monkey described above.

In contrast to these effects on correct response latency observed in lateral frontal cortex-lesioned animals and the substantial effects obtained on choice accuracy and correct response latency following lesions of the MF cortex, quinolinic acid lesions of the postgenual anterior cingulate cortex failed to significantly affect these performance measures on the baseline schedule of the task, or during any of the behavioral manipulations to the basic paradigm. The profound behavioral effect observed as a result of these anterior CING lesions was an increase in premature, anticipatory responding. This increase in anticipatory responding was long-lasting, being present throughout the course of the experiment and still apparent 16 weeks following the lesion. Given the evidence that cholinergic denervation of this area has failed to produce such effects on anticipatory responding (Muir, Everitt, and Robbins, unpublished observations), it seems more likely that this effect on task performance may be attributable, for example, to disruption of serotonergic projections in this area, on the basis of recent evidence, which has shown that profound depletion of forebrain serotonin produces a similar long-lasting increase in premature responding (Harrison et al., 1993).

Using PET activation methodology, investigations of the functional anatomy of attention using the Stroop test have reported activation of the anterior cingulate during performance of the incongruent condition of the task (Pardo et al., 1990; Bench et al., 1993). This has led to the suggestion that this area of cortex is important for response selection, in particular, in the inhibition of prepotent response tendencies (Posner and Petersen, 1990). Clearly, the results of the present study would support this suggestion, given the substantial increase in premature responding observed throughout the duration of the experiment. However, it is important to note that not all forms of anticipatory responding are impaired by lesions of the anterior cingulate cortex, as animals of the CING group were not significantly impaired in either acquisition or retention of the passive avoidance task.

There was no significant effect in the present study of lesions to the parietal cortex on attentional function. This at first seems quite surprising, given that parietal cortex has been implicated in visuospatial attentional processes (Mesulam, 1983; Posner et al., 1984). However, the area of parietal cortex typically associated with such functions is the posterior association cortex commonly referred to as Krieg's area 7 (Krieg, 1946). In the present study, this area of parietal cortex was not removed by the lesion, as we were concerned to remove that area of parietal cortex that we have previously shown to sustain a 70% reduction in ChAT activity following AMPA lesions of the basal forebrain. There is also a major problem in identifying the rat analog of the posterior parietal cortex in primates, although there is a region from -4 to -6 mm from bregma, which has been suggested to be comparable to some extent with Krieg's area 7 (Zilles, 1985). However, this region, which consists of part of Zilles' areas Oc2ML and Oc2L, is also classified as secondary visual cortex and thus the extent to which lesions to this area of cortex may affect visual functioning, rather than spatial attentional function, requires clarification. Further studies that attempt to identify more refined subdivisions of this cortical region are obviously required, but it is by no means certain that parietal cortex lesions would disrupt those particular facets of attentional processes examined in this study. Using an analog of the human continuous performance test we have shown that different aspects of task performance depend upon discrete neocortical regions, which normally interact in parallel distributed neural networks to allow optimal performance on

this task. It is striking that lesions of the cholinergic basal forebrain and lesions of serotonergic and noradrenergic afferents to the neocortex lead to dissociable deficits as large as those produced by the selective cortical lesions. Presumably, these modulatory systems have quite specific functions in the control of different attentional processes mediated by specific anterior cortical mechanisms.

Notes

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