Behavioral Neuroscience
2012, Vol. 126, No. 6, 772–780

0735-7044/12/$12.00 DOI: 10.1037/a0030493

Impairment in Delayed Nonmatching to Sample Following Lesions of Dorsal Prefrontal Cortex

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The prefrontal cortex has been identified as essential for executive function, as well as for aspects of rule learning and recognition memory. As part of our studies to assess prefrontal cortical function in the monkey, we evaluated the effects of damage to the dorsal prefrontal cortex (DPFC) on the Category Set Shifting Task (CSST), a test of abstraction and set-shifting, and on the Delayed Nonmatching to Sample (DNMS) task, a benchmark test of rule learning and recognition memory. The DPFC lesions in this study included dorsolateral and dorsomedial aspects of the PFC. In a previous report, we published evidence of an impairment on the CSST as a consequence of DPFC lesions (Moore, Schettler, Killiany, Rosene, & Moss, 2009). Here we report that monkeys with lesions of the DPFC were also markedly impaired relative to controls on both the acquisition (rule learning) and performance (recognition memory) conditions of trial-unique DNMS. The presence and extent of the deficits that we observed were of some surprise and support the possibility that the dorsal prefrontal cortex plays a more direct role in learning and recognition memory than had been previously thought.

Keywords: dorsal prefrontal cortex, delayed nonmatching to sample, recognition memory, rule learning, rhesus monkey

The work of Jacobsen (1936) using nonhuman primates was among the first to implicate the prefrontal cortex (PFC) in cognitive function in an animal model. During the past 70 years, this work was extended to show that the prefrontal cortices subserve several aspects of cognitive function, including aspects of executive functions such as abstraction, cognitive flexibility, category shifting (Pribram, Mishkin, Rosvold, & Kaplan, 1952; Mishkin & Weiskrantz, 1958; Butter, Mishkin, & Mirsky, 1968; Butters & Panyda, 1969; Pohl, 1973; Mishkin & Manning, 1978; Oscar-Berman, 1978; Dias, Robbins, & Roberts, 1996; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Buckley et al., 2009: Mansouri, Tanaka, & Buckley, 2009; Moore, Schettler, Killiany, Rosene, & Moss, 2009; Tsujimoto et al., 2011) as well as conditional associative learning and working memory (Passingham, 1985; Petrides, 1985a, 1985b; Bachevalier & Mishkin, 1986; Gaffan & Harrison, 1989; Kojima, Kojima, & Goldman-Rakic, 1982; Petrides, 1991; Levy & Goldman-Rakic, 1999, 2000). Though the PFC has been implicated strongly with executive function and working memory, evidence for a role in rule learning and various aspects of recognition memory have also been well established. (Goldman-Rakic, 1991; Rowe & Passingham, 2001; Sakai, Rowe, & Passingham, 2002; Passingham & Sakai, 2004; Passingham, Rowe, & Sakai, 2005; Warden & Miller, 2010).

As part of our studies of prefrontal cortical function (see Moore et al., 2009), we assessed monkeys with lesions of the dorsal prefrontal cortex (DPFC) (including dorsolateral and dorsomedial aspects of the PFC, extending laterally from the ventral lip of sulcus principalis and to the dorsal lip of the cingulate sulcus) on the acquisition and delay conditions of trial-unique Delayed Nonmatching to Sample (DNMS). The acquisition phase of the DNMS task serves as a test of rule learning since it requires the monkey to learn to choose a novel object when presented together with a familiar one that had been originally presented 10 seconds earlier. The delay phase of the DNMS task serves as a test of recognition memory since the delay between the presentation of the sample stimulus and its representation with the novel one is lengthened from 10 sec, to increasingly longer intervals. In the present study, the administration of the DNMS task was virtually identical to that

This article was published Online First October 22, 2012.

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The research was supported by NIH Grant PO1-AG00001. We thank Jerry Edwards, Beverly Duryea-Steiger, and Dana Whitelaw for their valuable assistance with this project.

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used in previous studies assessing damage to various regions of the PFC (Bachevalier & Mishkin, 1986; Kowalska, Bachevalier, & Mishkin, 1991; Levy & Goldman-Rakic, 1999). It is important to note, however, that in all of these prior studies, monkeys were trained on the acquisition phase of the DNMS task to a stringent learning criterion prior to surgery, and then tested for retention of the task and performance on the delay phase after surgery. In contrast, in our study monkeys were administered the DNMS task for the first time after surgery, and thus acquired the task in the absence of a prefrontal cortex, a paradigm unlike the previous studies where the monkeys first learned the task with an intact prefrontal cortex and were then tested for retention of the task following damage to the prefrontal cortex, producing a different set of test conditions.

Method

The subjects were eight, behaviorally naive, young adult (5–10 years of age), male rhesus monkeys (*Macaca mulatta*), weighing between 6.0 kg and 14.5 kg at the beginning of this study. All of the monkeys were obtained from a national primate research facility or breeding facility and had known birth dates and complete health records. Before entering the study, monkeys received medical examinations that included serum chemistry, hematology, urine analysis, and fecal analysis. In addition, all monkeys underwent MRI to ensure there was no occult neurological damage and to provide a baseline for lesion reconstruction. Results of the medical exams and MRIs revealed that all monkeys were healthy at the time of the study. While on study, monkeys were individually housed in colony rooms where they were in constant auditory and visual range of other monkeys in the Laboratory Animal Science Center (LASC) of Boston University School of Medicine. This facility is fully AAALAC approved and animal maintenance and research were conducted in accordance with the guidelines of the National Institutes of Health and the Institute of Laboratory Animal Resources *Guide for the Care and Use of Laboratory Animals* (2011). All procedures were approved by the Institutional Animal Care and Use Committee of the Boston University Medical Campus. Diet consisted of Purina Monkey Chow (Purina Mills, St. Louis, MO) supplemented by fruit with feeding taking place once per day, immediately following behavioral testing. All monkeys were fed 12–15 biscuits per day based on their weight. During testing, raisins or small pieces of apple were used as rewards; as there were 20 trials per day, monkeys received approximately 20–40 rewards each day. Water was available continuously. The monkeys were housed under a 12-hr light−dark cycle with cycle changes occurring in a graded fashion over the course of an hour. Following a quarantine period and acclimation to the colony room, four monkeys were randomly assigned to the surgical group for bilateral removal of the prefrontal cortex (PFC−1, 2, 3, 4), and the remaining four monkeys served as unoperated controls.

Surgical Procedures

Monkeys were sedated with ketamine hydrochloride (10 mg/kg) and cuff blood pressures and electrocardiograms were taken. An intravenous line was established via the saphenous vein and slow infusion of lactated Ringers solution was begun. A surgical level of anesthesia was induced with intravenous sodium pentobarbital (approximately 25 mg/kg) in titrated doses to effect. The monkeys were intubated and heart rate, respiration rate, and muscle tonus were continuously monitored throughout surgery to ensure that a deep surgical level of anesthesia was maintained. Body temperature was monitored and maintained with a heating pad.

After opening the skin and retracting fascia and muscle, a bone flap was opened bilaterally over the prefrontal cortex extending approximately 5 cm caudally from the frontal sinus and about 5 cm in width at its caudal margin. The dura was then opened and the cortical lesion accomplished in one stage by using a small glass pipette and subpial aspiration to separate the pia and its blood vessels from the underlying superficial layer of the cortex. This results in degeneration of the cortical gray matter without direct damage to underlying white matter tracks. As shown in Figures 1 and 2, the intended lesion was targeted to include all of area 46 in the banks and depths of the sulcus principalis as well as the more dorsally located area 9 beginning on the dorsal bank of sulcus principalis and continuing rostrally toward the frontal pole, first beneath the superior limb of the arcuate sulcus and to its tip and then extending medially to the cingulate sulcus. The lesion also targeted the adjacent parts of area 8 on the rostral lip of the arcuate sulcus. Care was taken to avoid extending the lesion into the bank of cingulate sulcus. Upon completion of the lesion within these boundaries, the dura was closed, the bone flap sutured back in place and the incision closed in layers.

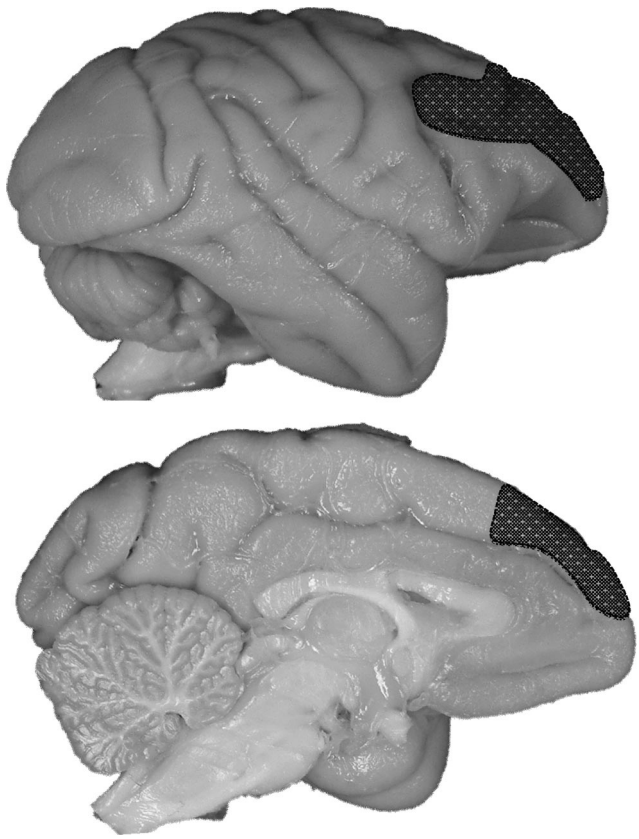

Figure 1. Lateral and medial view of the rhesus monkey brain. The intended area of the lesion is outlined.

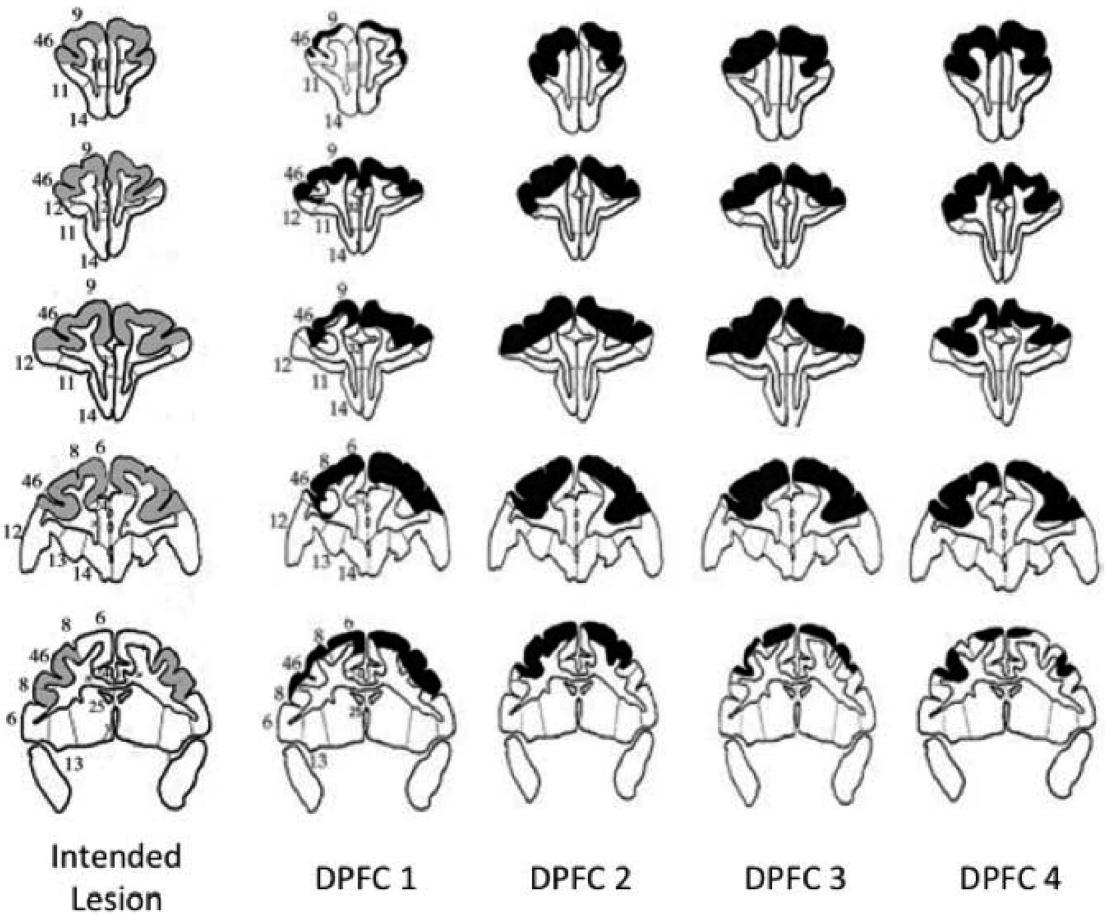

Figure 2. Lesion reconstructions of all four monkeys in the DPFC lesion group (from Moore et al., (2009). Numerals indicate Walker cortical areas as modified by Petrides and Pandya (1999).

At the conclusion of surgery, the monkeys were administered 600,000 units of Bicillin-LA intramuscularly to guard against infection, extubated and maintained in an incubator until they emerged from anesthesia. They were administered analgesic to treat postoperative pain (Banamine IM, 1.0 mg/kg). Analgesia was continued for 48 to 96 hours or longer if needed as determined by the veterinary staff. One week after surgery, the skin sutures were removed.

MRI

Prior to behavioral testing, which began 3 to 4 weeks postoperatively, all monkeys underwent a MRI scan in order to characterize the locus and extent of the lesion. For all MRI procedures, monkeys were anesthetized with a mixture of ketamine and xylazine and their head was stabilized using an MRI compatible stereotactic machine. A coronal T1 weighted high-resolution anatomical scan (3-D SPGR with slice thickness of 1.5 mm) as well as an axial T2 weighted scan were acquired on a GE 1.5 Tesla Signa scanner.

Behavioral Training

Preoperative familiarization. Preoperatively all monkeys were initially familiarized with behavioral testing in a Wisconsin General Testing Apparatus (WGTA). All monkeys were trained only to displace a single gray plaque placed pseudorandomly over one of the three food wells to obtain a reward. Raisins or small pieces of apples were used as rewards during testing. Monkeys were trained until they responded for 20 consecutive trials on two successive days.

Postoperative testing. Though changes in overt behaviors can occur following lesions to the PFC, throughout the postoperative period we did not see any overt changes in the disposition or day-to-day behavior/demeanor of any of the monkeys in this study. The monkeys continually demonstrated efficient attention and did not display evidence of abnormal disinhibition, perseveration, or hyperactivity.

Delayed nonmatching to sample (DNMS). Three to 4 weeks following surgery, all monkeys began the acquisition phase of the Delayed Nonmatching to Sample task in the WGTA. The DNMS task assesses the subject's ability to identify a novel from a familiar stimulus and was administered in two parts. First, in the basic task or acquisition phase, there is a short delay (10 seconds) between the sample and the nonmatch portion of each trial, the monkey over time and trials acquires the rule that was necessary for the successful completion of this task—that is, the "novel" stimulus is always rewarded. Once criterion was reached on the basic task, (90% correct over 100 trials) the monkey was tested in

stages on two delay conditions with the intratrial interval set at two minute and then ten minute delays.

DNMS basic task. The trial begins with a sample object presented over the central baited food well. The monkey was permitted to displace the object and obtain the reward. The door was then lowered, and the original, now familiar, sample object was placed over an unbaited lateral well and a new, novel, unfamiliar object is placed over the other lateral well that was baited. Ten seconds after the original sample trial, this choice trial was begun and the monkey must choose the unfamiliar, novel object in order to obtain the reward. Twenty seconds later, the next trial was initiated with a new, novel sample object presented over the baited central well followed 10 seconds later by another recognition trial using that second sample object and another new novel object. The position of the two objects on successive recognition trials was varied from left to right lateral wells in a predetermined pseudorandom order. A noncorrection procedure was used, and 20 trials per day were given until the monkey reaches a learning criterion of 90 correct responses in 100 consecutive trials or a maximum of 1,500 trials. Objects were drawn from a pool of 600 "junk" objects, and paired so that in each daily session of 20 trials, 40 of the objects were used. Once all of the initial pairings were used, (30 days of 20 trials per day), the 600 objects were randomly recombined to produce new pairs so that the pairings presented continued to be new and unique on each trial.

DNMS delays. Following administration of the basic task, the 10-sec delay between the presentation of the sample object and the recognition trial was increased, in stages, first to two minute and then to ten minute. Ten trials a day for 10 days at each delay interval were given with the monkey remaining in the testing apparatus during the delay interval. A total of 100 trials were given over 10 days at each of the two delays.

Perfusion and Lesion Reconstruction

Following completion of testing on the DNMS task, monkeys were tested on other tasks that are reported elsewhere (Moore et al., 2009). After all testing was completed, monkeys were sedated with Ketamine (10 mg/kg) and were then given an overdose of sodium pentobarbital and were killed by exsanguination during transcardial perfusion of the brain with 4% paraformaldehyde. Following perfusion, both hemispheres of the brain were blocked in situ in the coronal stereotactic plane for serial sectioning and transferred to cryoprotectant solution to eliminate freezing artifact (Rosene, Roy, & Davis, 1986). The cryoprotected blocks were then flash frozen and stored at −80 °C until they were cut on a microtome into eight interrupted series of 30-μm-thick frozen sections and one 60-μm-thick series. The 60-μm series and one 30-μm series were immediately mounted on microscope slides, stained with thionin, and used to reconstruct the lesions.

For lesion reconstructions, each monkey's preoperative T1 weighted MRI scans were used with a standard rhesus monkey brain template to create an individualized coronal section atlas of the frontal lobe from the arcuate sulcus to the rostral extent of the frontal pole. Walker's cytoarchotechtonic areas (as revised by Barbas & Pandya, 1989) were marked on each section of this individualized atlas. Area measurements (mm^2) were determined for each of the cytoarchotechtonic areas on each section of the individualized map using NIH Image J software.

To reconstruct the lesions, thionin-stained sections throughout the rostral/caudal extent of the lesion were superimposed onto the atlas sections and the extent of the lesion was marked. The borders of lesions were then checked at higher power under the light microscope and adjusted accordingly. Each section was then scanned into the computer and NIH Image J software was used to obtain area measurements of the lesion. The percent of cortical tissue damaged for each cytoarchitectonic area was then calculated by dividing each area of damage by the baseline area established on the preoperative MRI slices. These relative lesion sizes are shown in Figure 2 and the percent of tissue damaged is presented in Table 1.

Data Analysis

Acquisition scores for the DNMS basic task, both trials and errors to criterion, were analyzed separately with one-way analyses of variance. Performance scores for 2- and 10-min delays were based on the percentage of correct responses for each delay condition. These scores were analyzed with a two-way, repeated measures analysis of variance with group as a between-subjects variable and delay as a within-subjects variable.

Results

Lesion Reconstructions

The results of the lesion reconstructions are tabulated in Table 1 and illustrated in drawings in Figure 2 and representative thionin sections from 1 monkey in Figure 3. These results show that, as intended, all monkeys had nearly complete damage to areas 46 and 9 where damage ranged from a low of about 71% up to a high of almost 95% of each area. In addition there was significant damage to area 8, largely on the surface and rostral bank of the arcuate suclus, and this ranged from about 44% up to almost 66%. There was also some encroachment of the lesion into areas 6, 10, 12 where the damage ranged from as little as 4% up to 32%. Due to the small group size in this study and the relative homogeneous performance on the DNMS task, it was not possible to determine if the variability in extraneous damage in areas 6, 10, 12 was related to individual impairment on the DNMS task.

DNMS Basic Task

Individual data for both trials and errors to criterion for the DNMS basic task are shown in Table 2. Monkeys in the control

Table 1
Extent of Damage in Four Monkeys With Lesions of Prefrontal Cortex by Cytoarchitectonic Areas

Monkey	Area 46	Area 8	Area 9	Area 10	Area 12	Area 6
DPFC 1	70.8	65.73	79.27	4.03	18.30	31.63
DPFC 2	89.92	53.64	85.54	20.13	17.26	32.29
DPFC 3	87.47	45.70	84.30	24.35	3.18	31.55
DPFC 4	94.33	43.92	90.34	30.29	2.99	22.18

Note. (From Moore, Schettler, Killiany, Moss, & Rosene, 2009.) Values represent percent of damaged tissue bilaterally based on comparison of thionin-stained sections with preoperative MRI scans.

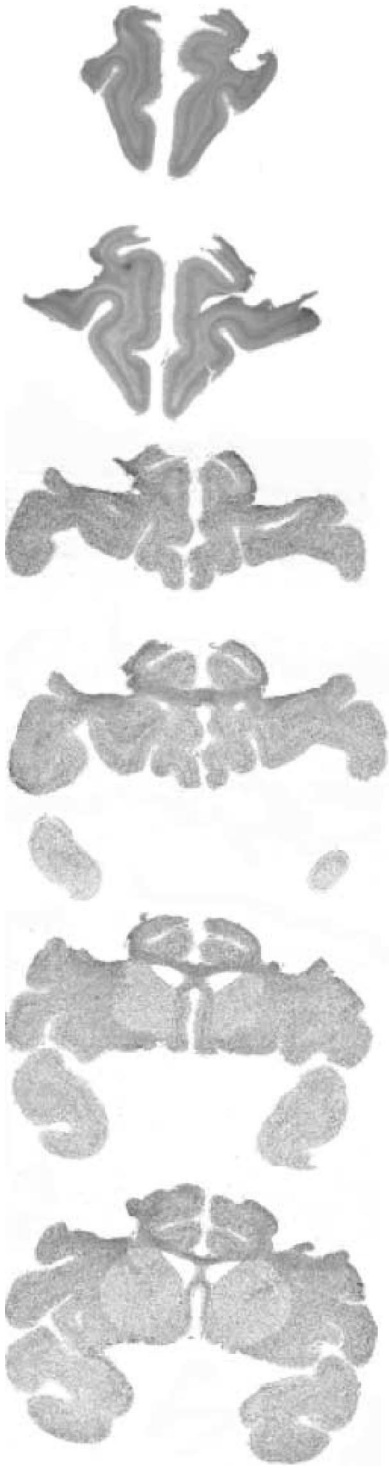

Figure 3. Representative thionin sections from one monkey in the study. Level of sections approximately match those shown in Figure 2.

group learned the basic task within an average of 213 trials, whereas monkeys in the lesion group required an average of 990 trials. Data for both trials and errors to criterion are shown in Figures 4 and 5. Separate one-way analyses of variance demonstrated that there was a significant difference between the control and lesion groups on the number of trials [$F(1, 6) = 53.70$, $p = .0003$] and also in the number of errors [$F(1, 6) = 50.16$, $p = .0004$] to criterion on the postoperative acquisition of the DNMS task.

DNMS Delays

As shown in Table 2, monkeys in the control group performed at an 88% level of accuracy on the 2-min delay condition of the DNMS task, whereas those in the DPFC group performed at a 74% level of accuracy. On the 10-min delay, performance of the control group dropped slightly to 82% accuracy, while that of the DPFC group declined to levels of only 66%. Separate two way repeated measures analysis of variance revealed a significant overall effect of group [$F(1, 16) = 15.43$, $p = .008$], and delay [$F(1, 16) = 29.4$, $p = .002$] for the total percent correct for delay trials (see Figure 6). There was no significant group-by-delay interaction [$F(1, 6) = 1.35$, $p = .289$] for the total percent correct for delay trials.

Discussion

Two principal findings emerged from this study: 1) Relative to the control group, monkeys with lesions of the DPFC were significantly impaired in the initial acquisition of the DNMS task (i.e., learning to choose a novel from a familiar stimulus); and 2) Monkeys with lesions of the DPFC evidenced a degradation in performance relative to controls when delays were increased between the sample and recognition trials. These findings are discussed in separate sections below.

Acquisition of Delayed Nonmatching to Sample

Monkeys with DPFC lesions required an average of 990 trials to acquire the DNMS task, a level over four times greater than that of monkeys in the control group. In fact, this level of impairment is even greater than that observed in monkeys with selective hippocampal lesions who required an average of 650 trials to acquire the DNMS task postoperatively (Beason-Held, Rosene, Killiany, & Moss, 1999). The severity of this effect was striking, and somewhat surprising given previous findings that suggested that the locus for impairment of acquisition of the DNMS task is the more ventral, but not dorsal, aspects of prefrontal cortex (Bachevalier & Mishkin, 1986; Kowalska et al., 1991). Bachevalier and Mishkin (1986) found that monkeys with damage to the ventromedial prefrontal cortex, but not the dorsal prefrontal cortex, were markedly impaired in postoperative relearning of the basic DNMS task relative to controls. Kowalska et al. (1991), using the same experimental paradigm as that of Bachevalier and Mishkin (1986), found that monkeys with lesions of the inferior convexity alone or in combination with the dorsal prefrontal cortex, evidenced a moderate degree of impairment on the postoperative retention of the DNMS task. Finally, Levy and Goldman-Rakic (1999) showed that monkeys with lesions restricted to either the dorsal prefrontal cortex (areas 46 and 8a) or the dorsomedial prefrontal cortex (areas 9 and 8b), were unimpaired on the postoperative retention of the DNMS task.

The lesions in the present study were larger than those in the monkeys in the dorsal group of Levy and Goldman-Rakic (1999)

Table 2
Trials and Errors for Acquisition of DNMS, % Correct Performance on the Two Delay Conditions, and % Loss Across Delays for Each of the Control and Lesion Monkeys

Monkey	Acquisition trials	Acquisition errors	Two minute delay	Ten minute delay	% Loss between delays
Control 1	200	52	0.83	0.79	4.8
Control 2	180	35	0.85	0.74	12.9
Control 3	210	60	0.90	0.88	2.2
Control 4	260	60	0.92	0.87	5.4
Mean	212.5	51.8	0.88	0.82	6.3
DPFC 1	960	247	0.70	0.61	12.9
DPFC 2	940	277	0.79	0.72	8.9
DPFC 3	1280	393	0.80	0.67	16.5
PFC 4	780	258	0.67	0.62	7.5
Mean	990.0	293.8	0.74	0.66	11.5

and of those of the dorsal group of Bachevalier and Mishkin (1986). Unfortunately, a direct comparison of the lesion sizes across these studies is not possible, as the percent of damaged tissue is not presented in these other publications. However, it would not appear that the striking magnitude of behavioral effects found in the present study could be attributed solely to the size of lesion. We believe the experimental paradigm represents a more parsimonious explanation to account for the differences in performance on the DNMS task.

Monkeys in the studies cited above learned the rule of nonmatching of the DNMS task to a stringent learning criterion prior to surgery (i.e., with an intact prefrontal cortex). They were then retested on the already learned DNMS task following damage to the prefrontal cortex (i.e., postoperative retention of the preoperatively learned task). In the present study, monkeys first learned the DNMS task without the benefit of an intact prefrontal cortex (i.e., postoperative acquisition). The difference in the two paradigms should not be dismissed as an inconsequential difference in procedure, but rather should be viewed in the context of two very different brain states under which the DNMS task was acquired as has been postulated in the past to account for diverse findings about hippocampal lesions. Based on our findings, an intact DPFC is essential for the initial learning of the DNMS task, but as shown convincingly by the previous studies discussed above, it is not necessary for postoperative retention of the task. It would follow that once the DNMS task is learned with an intact DPFC, the representation of the nonmatching rule must be distributed or localized to other cortical and/or subcortical neural circuitries.

Performance on DNMS Delays

The severity of deficits on the DNMS task by this group of monkeys is underscored not only by the impairment in acquiring

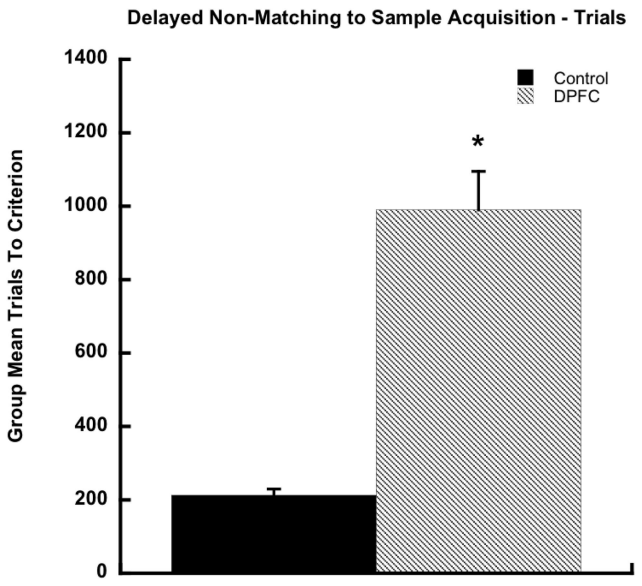

Figure 4. Group mean trials to criterion on the acquisition of the delayed nonmatching to sample task. Asterisk indicates a significant group difference ($p < 0.0003$).

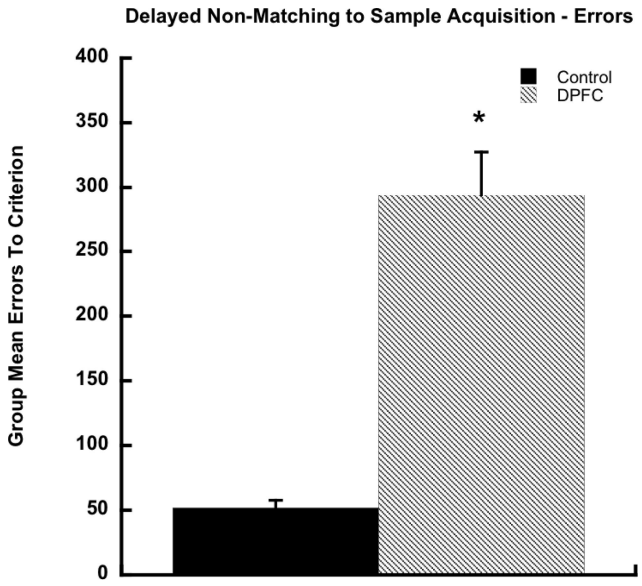

Figure 5. Group mean errors to criterion on the acquisition of the delayed nonmatching to sample task. Asterisk indicates a significant group difference ($p < 0.0004$).

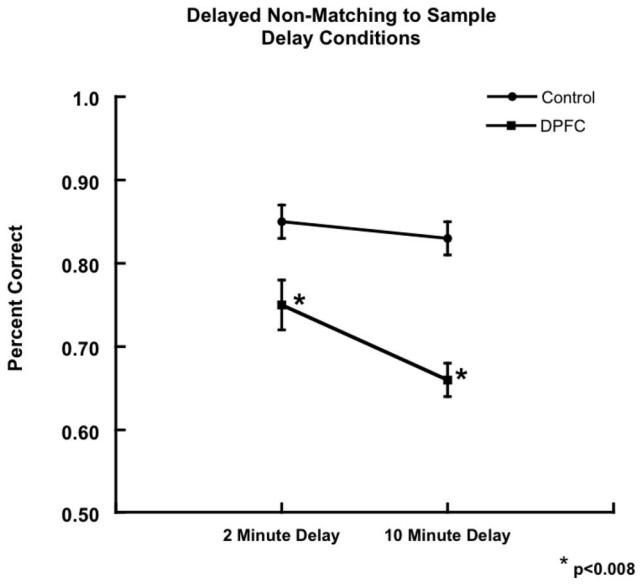

Figure 6. Group mean percent correct on the two delay conditions of the delayed nonmatching to sample task. Asterisk indicates a significant group difference ($p < 0.008$).

the rule of nonmatching, but also by poor performance when either short (2 min) or longer (10 min) delay intervals were interposed between the sample and recognition presentations. This reduction in accuracy by the monkeys with lesions of the DPFC occurred in spite of the fact that they had eventually learned the basic task to the same learning criterion as controls though admittedly with different neural systems. There are several possible explanations for this finding: First, the subjects may have a bona fide memory impairment (i.e., failing to remember which object had been seen before) as has been classically attributed to damage to hippocampus or adjacent medial temporal lobe structures (Zola-Morgan & Squire, 1985, 1986; Meunier, Bachevalier, Mishkim, & Murray, 1993; Beason-Held et al., 1999; Buffalo, Ramus, Squire, & Zola, 2000) and has been posited as the basis for the deficit on the DNMS task following removals of the ventromedial prefrontal cortex (Kowalska et al., 1991). A second possibility is that the monkeys with damage to the DPFC have difficulty with some aspect of rule-dependent processing (i.e., utilization of the nonmatching rule acquired with a damaged DPFC) that is exacerbated by the demands of the delay condition. A third possibility is that both processes, memory and rule learning, are affected by damage to the DPFC.

We realize that the distinction between these possibilities is indeterminate in the framework of the present study, but data from single unit studies of prefrontal cortex are beginning to shed some light on the issue. It has been shown that neurons in widespread regions of the PFC in the macaque appear to encode object identity during delay periods (Xiang & Brown, 2004; Warden & Miller, 2010). Similarly, several studies have identified cells in the PFC as encoding abstract rules or reflecting the guidance of behavior for learned rules (Hoshi, Shima, & Tanji, 1998; White & Wise, 1999; Asaad, Rainer, & Miller, 2000; Wallis, Anderson, & Miller, 2001; Wallis & Miller, 2003; Tsujimoto et al., 2011), as well as for assigning behavioral relevance to stimuli and task-related events (Miller et al., 1996; Everling, Tinsley, Gaffan, & Duncan, 2006). Together these single unit findings are consistent with the role of the PFC in memory and guidance of rule learning capacities. Recent work by Tsuijimoto et al. (2011) provides more insight into region-specific roles of neurons in the PFC. They have found that neurons in the dorsal and orbital aspects of the PFC in the monkey both contribute to behaviors guided by abstract response strategies, but do so differently, with the former related more to encoding a response based on a strategy, and the latter more related to encoding a strategy. Such fine-grained analysis of prefrontal cortical neuron activity is needed as this will be crucial to understanding the nature of the deficit evidenced by monkeys with lesions of the DPFC on the delay condition of the DNMS task.

Lesion Size and Location

The most striking methodological difference between the current study and previous studies investigating the role of the DPFC in performance on the DNMS task is the lack of preoperative training on the task. However, there is also a difference in the size and location of the lesions between studies. The lesion in the present study is relatively large and includes dorsolateral and dorsomedial aspects of the PFC and slight damage to areas 6, 10, and 12, while the lesions in other studies are smaller in comparison and are more limited to areas 9 and 46. This opens up the possibility that cortical regions included in this study but spared in prior studies are responsible for the deficits observed. However, a review of the literature does not support this view. Studies have demonstrated that damage to area 6 can cause impairments in sensory conditional motor learning, explicit learning, and perhaps abstract learning (Kantak, Mummidisetty, & Stinear, 2012; Kayser & D'Esposito, 2012; Halsband & Freund, 1990). However, Amiez, Hadj-Bouziane, and Petrides (2012) suggest that the dorsal premotor area is more involved in the development of associations during sensory conditional motor learning while the DPFC is more involved in determining the correct response to an individual trial and therefore the slight damage in this area is not likely the cause of the significant impairment on the DNMS task observed in the present study.

Imaging studies with humans have demonstrated activation of areas 10 and 12 during the encoding phase of the DNMS task and therefore damage to these areas may have contributed to the impairment of task performance (de Zubicaray, McMahon, Wilson, & Muthiah, 2001; Elliott & Dolan, 1999). While areas 6, 10, and 12 do serve a role in learning and likely some aspects of the acquisition of the DNMS task, it is unlikely that the slight damage to these areas that occurred in the monkeys in this present study would solely account for the significant impairment observed relative to other studies with lesions isolated to areas 9 and 46.

One cortical area that was not included in the lesions in this and in many of the other studies of prefrontal cortex is the orbitofrontal cortex, a region known to be involved in visual recognition memory (Meunier, Bachevalier, & Mishkin, 1997; Bachevalier & Mishkin, 1986; Mishkin, 1964), and specifically when familiar objects are used in testing (Schon, Tinaz, Somers, & Stern, 2008). Meunier et al., 1997 reports a level of performance on postoperative reacquisition of DNMS that is similar to the postoperative acquisition performance of the monkeys in the present study. However, again due to the difference in preoperative training, it is difficult to

directly compare the effects of the lesions in different regions of the PFC on the DNMS task.

Conclusions

The main finding of this study was that monkeys with extensive damage to the DPFC were impaired in the acquisition of the DNMS task, a deficit that has been typically reported following damage to the hippocampal formation when a postoperative acquisition paradigm is used (Zola-Morgan & Squire, 1986; Beason-Held et al., 1999). Together with recent findings in humans that both the prefrontal cortex and hippocampal formation are activated in various visual recognition memory paradigms (e.g., Kirwan, Wixted, & Squire, 2008; Trivedi et al., 2008), it is tempting to posit that both structures may participate in mediating recognition memory, at least that required in performing the DNMS task. Even more intriguing is the possibility that the two regions not only participate in subserving these functions (see Corkin, 2001), but that they do so in an interdependent fashion. Support for the notion of a functional relationship between the medial temporal lobe and prefrontal cortex has, in fact, begun to accumulate. Using postoperative retention paradigms, Gaffan, Easton, and Parker (2002) demonstrated impairments in object associative learning following crossed lesions of frontal and inferotemporal cortices in the monkey, and Bussey, Wise, and Murray (2002) has observed deficits in conditional visuomotor associations following crossed unilateral lesions of the orbital and ventral prefrontal cortices together with the inferotemporal cortex in the monkey. The nature of the interaction between the prefrontal cortices, and the medial temporal lobe in memory and rule learning, await further delineation.

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Received June 2, 2012
Revision received September 17, 2012
Accepted September 18, 2012 ■