The Role of Ventral and Orbital Prefrontal Cortex in Conditional Visuomotor Learning and Strategy Use in Rhesus Monkeys (Macaca mulatta)

Timothy J. Bussey, Steven P. Wise, and Elisabeth A. Murray
National Institute of Mental Health

Four rhesus monkeys (Macaca mulatta) were trained to learn novel sets of visuomotor associations in 50 trials or less, within single test sessions. After bilateral ablation of the orbital and ventral prefrontal cortex, the monkeys lost the ability to learn these associations within a session, although they could learn them when given several daily sessions. Thus, relatively slow, across-session visuomotor learning depends on neither the ventral nor orbital prefrontal cortex, but rapid, within-session learning does. The ablations also eliminated at least 2 response strategies, repeat-stay and lose-shift, which might account, in part, for the deficit in rapid learning. The deficit is unlikely to result from a failure of visual discriminative ability or working memory: The monkeys could discriminate similar stimulus material within a session, and reducing the working memory load did not improve within-session learning.

Conditional visuomotor learning requires the ability to form arbitrary associations between visual stimuli and responses (or response targets). In monkeys, associative learning of this type involves a distributed neural network that includes the premotor cortex (Halsband & Passingham, 1982; Petrides, 1982), the hippocampal system (Murray & Wise, 1996; Ridley & Baker, 1997; Rupniak & Gaffan, 1987; Wise & Murray, 1999), and projections from basal ganglia to frontal cortex through the thalamus (Canavan, Nixon, & Passingham, 1989). Normal learning rates require intact interactions between inferotemporal cortex (IT) and prefrontal cortex (PF), as demonstrated by experiments using a crossed disconnection procedure (Gaffan & Harrison, 1988; Parker & Gaffan, 1998) or transection of the uncinate fascicle, a major fiber bundle connecting IT and PF (Eacott & Gaffan, 1992). Selective lesions of dorsolateral PF also cause mild impairments in conditional visuomotor learning (Gaffan & Harrison, 1989).

The data concerning PF remain equivocal, however. The deficits reported after PF–IT crossed disconnection or uncinate fasciculotomy have been relatively modest, suggesting a minor or secondary role for PF in conditional visuomotor learning. On the other hand, recent neuroimaging studies have led to the suggestion that PF plays a central and necessary role in this form of associative learning (Toni & Passingham, 1999). Passingham and his colleagues have proposed that the ventral parts of PF are essential because only these regions have information about the stimulus, the response, and the outcome of that response (Passingham, Toni, & Rushworth, 2000), three items of information needed to form new visuomotor associations.

Thus, the present study tested the hypothesis that PF is necessary for conditional visuomotor learning. To test this hypothesis, we removed bilaterally the PF regions that receive object information from IT. Object-encoding areas in IT, particularly area TE and the perirhinal cortex (Buckley & Gaffan, 1997, 1998a, 1998b; Buckley et al., 1997; Buffal, Stefanacci, Squire, & Zola, 1998; Meunier, Bachevalier, Mishkin, & Murray, 1993; Murray & Bussey, 1999), project mainly to the ventral and orbital parts of PF (Carmichael & Price, 1996; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Pandya & Kuypers, 1969; Rempel-Clower & Barbas, 2000; Webster, Bachevalier, & Ungerleider, 1994). Thus, the present experiment involved removing ventral PF (PFv) and orbital PF (PFO) from both hemispheres in a single operation and evaluating the effects of this removal in a series of behavioral tests. If either PFv or PFO plays a necessary role in conditional visuomotor learning, then bilateral removal of these regions should yield impairments in the acquisition of novel conditional visuomotor associations.

In an earlier study focusing on the hippocampal system and amygdala (Murray & Wise, 1996), and during the present study, we found that the monkeys adopted various strategies that may promote conditional visuomotor learning. In view of renewed interest in PF as a neural substrate for strategies used by nonhuman...
Combining data from these two sets of subjects, we assumed that the displayed on the screen. Later shaping involved transferring that skill to the same information-processing functions; in both circumstances, an object-arbitrary relationship.

Method

Subjects

Four rhesus monkeys (Macaca mulatta), initially naive, were the subjects (S1–S4) of the present study. They ranged in weight from 5.1 to 8.5 kg at the time of surgery. The monkeys were housed individually and were fed a controlled diet of Purina Primate Chow (Purina Mills, St. Louis, MO), supplemented with fruit.

Apparatus

The monkeys were tested in a computer-controlled apparatus. Two of the monkeys, Subject 1 and Subject 2 (S1 and S2), were seated in a primate chair facing a 13-inch (33-cm) video monitor. The chair was placed in a testing cubicle that included a view of the monitor screen, a joystick (Measurement Systems, Norwalk, CT) mounted at waist level, and a small tube mounted at mouth level, through which rewards could be dispensed. The joystick was enclosed in a template that limited its movement to three directions, only one of which was possible at any given time. These three possible response directions formed a T shape, with the joystick’s origin at the junction. Visual stimuli were generated by the computer; each stimulus consisted of a superimposed pair of differently colored ASCII characters, one approximately 5.0 cm in height and the other approximately 3.5 cm in height. These complex visual stimuli, which were presented singly, always appeared at the center of the video screen. Reinforcement, consisting of approximately 0.3 ml aliquots of fruit juice or applesauce, was delivered through the tube directly into the monkey’s mouth.

The other 2 monkeys, S3 and S4, were placed in a testing cage in front of a 19-inch (48.3-cm) video monitor fitted with a touch-sensitive screen. Visual stimuli were of the same type as those used for S1 and S2, but a choice was indicated by touching a target box displayed in one of the corners of the touch-screen rather than by moving a joystick. Reinforcement consisted of a single 190-mg banana-flavored food pellet (Noyes, Lancaster, NH) delivered to a cup located directly under the monitor. In combining data from these two sets of subjects, we assumed that the joystick and touch-screen versions of the conditional motor task tap the same information-processing functions; in both circumstances, an object-like visual cue instructs a spatially directed movement on the basis of an arbitrary relationship.

Behavioral Procedures

The general behavioral methods used for shaping, preoperative testing, and postoperative testing are described below, followed by a detailed description of each task used in the present study.

Shaping. For S1 and S2, the shaping methods were as described in Murray and Wise (1996). Briefly, monkeys first learned to make joystick-controlled movements of a cursor on the video screen. The initial shaping involved rewarding cursor movement to a spatial target that was also displayed on the screen. Later shaping involved transferring that skill to the use of nonspatial stimuli (i.e., the superimposed ASCII-character stimuli described above) so that subjects could choose a joystick movement without any visual feedback regarding joystick position.

In the initial shaping for S3 and S4, an autoshaping procedure was used to associate visual stimuli with reward. An ASCII-character stimulus was displayed in the center of the screen for 10 s, immediately after which a reward pellet was delivered, followed by a variable intertrial interval ($M = 120$ s). If the monkey touched the stimulus before the end of the 10 s, the stimulus was immediately removed from the screen, and a food reward was delivered. During the second phase of shaping, a stimulus was displayed in the same manner, but now for 30 s, and delivery of the food reward was contingent on the monkey’s touches to the stimulus on the screen. If the monkey did not touch the stimulus within 30 s, the stimulus was removed from the screen and the trial advanced. Monkeys were required to complete successfully $\geq 49$ out of 50 possible trials for 2 consecutive days before proceeding to the main task.

Preoperative testing. Conditional visuomotor training consisted of the daily presentation of two or more problem sets, each consisting of three or four visuomotor problems to be solved concurrently. A problem, in this sense, consisted of a single stimulus-response association, in which a particular stimulus served as a discriminative stimulus for one, and only one, response. Monkeys were trained initially on a group of visuomotor problems, referred to as familiar problem sets (eight 3-problem sets for S1, four 3-problem sets for S2, and two 4-problem sets for S3 and S4). They were then trained across sessions on the familiar sets until performance was stable. The monkeys were also trained preoperatively on sets of novel visuomotor problems. These novel sets were presented for only $\sim 50$ trials (50 trials for S1 and S2, 48 trials for S3 and S4), and the monkeys were trained until they were able to solve the novel problem sets within that number of trials; this is referred to as within-session learning.

Monkeys were presented with ordered groups of consecutive sessions, which we termed testing cycles. For S1 and S2, a cycle consisted of five sessions with novel problem sets, followed by one session with the familiar problem sets. Preoperative data for S1 and S2 were gathered from three of these cycles presented immediately before surgery. We analyzed the last five sessions involving novel stimuli, all from the last cycle, and the last three sessions with familiar stimuli, one from each cycle. Monkeys S3 and S4 were trained to perform a matching-to-sample task (see below for details) in addition to the visuomotor tasks with novel and familiar problem sets. A testing cycle for these monkeys consisted of five sessions with novel visuomotor problems sets, two sessions with the familiar visuomotor problem sets, and one session of the matching-to-sample task. Preoperative data for S3 and S4 were gathered from the six testing cycles that immediately preceded surgery.

Postoperative testing. After surgery, the monkeys were tested for three (S1 and S2) or six (S3 and S4) cycles that were identical to those administered preoperatively. For both groups, the data were collected and analyzed in the same manner as before surgery. Additional postoperative data for S3 and S4 were collected on five tasks during subsequent training and testing sessions: (a) new visuomotor learning across sessions; (b) consecutive sessions of the matching-to-sample task; (c) concurrent pairwise visual discrimination learning within sessions; (d) a “simultaneous” version of the matching-to-sample task; and (e) a simultaneous version of the conditional visuomotor learning task, within sessions. Detailed methods for each of these tasks are given below.

Conditional visuomotor learning. The methods of Murray and Wise (1996) were used for S1 and S2. Briefly, monkeys were required to learn problem sets consisting of three visuomotor associations, in which each visual stimulus instructed one, and only one, of the three possible responses with the joystick. On each trial, a stimulus was selected from the current problem set and presented on the monitor screen, where it remained until the monkey completed a response. A correct response led to immediate activation of the reward dispenser and positive visual feedback, in which the stimulus remained on the screen (at its original central location) for 1 s. The trial was then terminated, and an intertrial interval ensued. An incorrect response led to the same intertrial interval, but without reward or the 1-s stimulus persistence. Such errors were followed by up to two additional presentations of the same stimulus as a correction procedure. Thus, a single behavioral trial consisted of an initial stimulus presentation plus one or two correction trials, if necessary. Just as for the initial presentation, a correct response on a correction trial led to delivery of reinforcement and the other
events listed above. Both S1 and S2 were given 50 trials (excluding correction trials) to solve a problem set of 3 conditional visuomotor problems, after which they were presented with a new problem set until eight (S1) or four (S2) sets had been completed within a daily testing session (yielding 400 trials per session and 200 trials per session, respectively, for S1 and S2). Testing on familiar problem sets followed the same procedures. As noted above, S1 learned 24 familiar visuomotor problems preoperatively, presented in eight sets of three stimuli, whereas S2 learned 12 familiar problems, presented in four sets of three stimuli.

For S3 and S4, each trial began with the presentation of a single stimulus in the center of the monitor screen. This stimulus, chosen from a problem set of four stimuli, indicated which of the four target locations was correct on that trial. After the monkey had touched and maintained contact with the stimulus for 1.5 s, the stimulus was removed from the display, and four identical target boxes appeared, one in each corner of the monitor screen. If the monkey chose correctly, by touching the target box instructed by the visual stimulus for that trial, food reward was delivered, and a 3-s intertrial interval ensued. No positive visual feedback was given for correct responses. Touches to parts of the visual display outside the stimulus (during the stimulus presentation) or outside the target boxes (during the target box presentation) had no consequences. If the monkey chose incorrectly, no food was delivered, and an unlimited number of correction trials was presented, each separated by a 3-s intertrial interval. This correction procedure, which required that the monkey complete each trial with a correct response, thus differed from that used for S1 and S2. The unlimited correction procedure was instituted for S3 and S4 to overcome response biases, which S1 and S2 did not demonstrate. Reinforcement was delivered for correct responses on either the initial stimulus presentations or on correction trials. Both S3 and S4 were given 48 trials (not counting the correction trials) to solve one set of four conditional visuomotor problems, after which they were presented with a second problem set for 48 trials, thus yielding a total of 96 trials per daily session. Testing with familiar problem sets followed the same procedures. Presentation of one set of four familiar stimuli for 48 trials was followed by the other set of four familiar stimuli for an additional 48 trials.

New visuomotor learning across sessions. After a postoperative assessment of the ability of S3 and S4 to acquire novel visuomotor problems within 48 trials, we tested their ability to do so when given the same set of problems for an unlimited number of trials administered across sessions (i.e., over several days). Thus, the same four initially novel problems were presented in each 96-trial session, until each monkey attained a criterion of 90% correct in a single session. Other than repeating the problem set across sessions, this across-session learning task was identical to the within-session learning task described above.

Matching-to-sample. We tested S3 and S4 on a matching-to-sample task with a 0-s delay. In the test cycles administered before and after surgery, the sample was chosen randomly, on each trial, from among the same eight stimuli used for the familiar visuomotor association task. Each trial began with the presentation of the sample, an ASCII-character stimulus, at the center of the screen. The sample remained on the screen until the monkey touched it, at which time it disappeared and two choice stimuli simultaneously appeared at the same elevation as the sample, one on the left side of the screen and the other on the right. One of these two stimuli was the same as the sample stimulus; the other was a different stimulus drawn from the familiar set. The sample was rewarded for choosing the sample stimulus. The location of the correct stimulus (left or right) followed a pseudorandom order. The intertrial interval was 7 s, and no correction procedure was used. Each session consisted of 96 trials.

Because the monkeys were unable to relearn this version of the matching-to-sample task after surgery (see Results section), a second administration of matching-to-sample was given after completion of the six postoperative cycles mentioned above. This version of the task was identical to that described above, except that novel stimuli appeared on each trial, both within and across sessions. Use of trial-unique stimuli together with the administration of consecutive sessions of the matching-to-sample task was intended to facilitate relearning of the matching-to-sample rule.

Concurrent pairwise discrimination learning within sessions. Monkeys S3 and S4 were tested for the ability to acquire four 2-choice discrimination problems concurrently within a single 48-trial session. On a given trial, two stimuli appeared on the screen. One stimulus was designated the S+; the other, the S−. The stimuli remained on the screen until the monkey touched the S+ or the S−. A touch to the S+ was followed by the removal of the stimuli from the screen and delivery of a reward pellet. A touch to the S− resulted in removal of the stimuli from the screen and no reward delivery. A correction procedure involved representation of the same stimulus configuration, repeatedly, until the monkey responded correctly. The pair presented on a particular trial followed a pseudorandom order, and the intertrial interval was 3 s.

Simultaneous matching-to-sample. This task, given to S3 and S4, was nearly identical to the matching-to-sample task with familiar stimuli used earlier. That is, both the sample stimulus and the foil were chosen from the set of eight stimuli used for the familiar visuomotor association task. The simultaneous version of the task, however, was designed to minimize working memory demands. In this version, the sample stimulus remained on the screen, along with the two choice stimuli, until the monkey made a response to one of the two choice stimuli.

Simultaneous visuomotor learning within sessions. This task, given to S3 and S4, was nearly identical to the within-session visuomotor task described above. The simultaneous version of the task, however, was designed to minimize working memory demands. The instruction stimulus remained on the screen, along with the four boxes at the target locations, until the monkey made a response to one of the four target locations. As in the regular version of within-session learning for S3 and S4, each day, sets of four novel problems were presented for 48 trials, followed by a different set of four novel problems for an additional 48 trials.

Surgical Procedures

Anesthesia was induced with ketamine hydrochloride (10 mg/kg im) and maintained with isoflurane (1.0–2.0%, to effect). The monkeys received isotonic fluids through an intravenous drip. Aseptic procedures were used, and heart rate, respiration rate, body temperature, and expired CO2 levels were monitored throughout the procedure. Cranietomies were made in the appropriate location, and the dura mater was cut and reflected toward the orbit. One-stage, bilateral removals of PFv and PFe were then achieved by direct subpial aspiration of tissue, with the aid of an operating microscope. The lesion extended ventrally from just below the principal sulcus to the orbital surface and continued medially to the medial orbital sulcus (see Figure 1 and Figure 2). The boundaries of the lesion were the rostral extent of the principal sulcus, rostrally; the fundus of the ventral limb of the arcuate sulcus, caudally; the principal sulcus, dorsolaterally; and the medial orbital sulcus, ventromedially. Thus, the intended lesion included the cortex lining the anterior bank of the ventral limb of the arcuate sulcus, but not the cortex within either the principal sulcus or medial orbital sulcus. When the removals were complete, the wound was closed in anatomical layers. For 1 day before surgery and 1 week after, the monkeys received a treatment regimen of dexamethasone sodium phosphate (0.4 mg/kg im) and Di-Trin (0.1 ml/kg im, 24% w/v solution, Syntex Animal Health, West Des Moines, IA) to reduce inflammation and to protect against infection, respectively. For 3 days after surgery, the monkeys also received acetaminophen (40 mg) and Banamine (flunixin meglumine, 5 mg) as analgesics.

Histology

At the completion of the experiment, S1 and S2 received ketamine followed by a lethal dose of sodium pentobarbital (100 mg/kg ip). They
Figure 1. Extent of the ventral and orbital prefrontal cortex ablations. Coronal sections from a standard rhesus monkey brain showing the location and extent of the intended lesion (middle) and extent of the lesions shown on sections from matching levels in S1 (left) and S2 (right). Numerals indicate the distance (in millimeters) from the interaural plane. The region in which tissue has been removed is indicated with heavy black lines. S = subject; AsD = dorsal limb of the arcuate sulcus; AsV = ventral limb of the arcuate sulcus; Cs = cingulate sulcus; los = lateral orbital sulcus; mos = medial orbital sulcus; ps = principal sulcus; tp = temporal pole.

were perfused transcardially with 0.9% (wt/vol) saline followed by a solution of aldehyde fixatives. The brains were removed from the cranium, photographed, and cryoprotected in a solution of 20% glycerol and 10% Formalin (vol/vol). Tissue was sectioned in the coronal plane at 50 μm on a freezing microtome. Every fifth section was mounted on gelatin-coated slides, demyelinated, and stained with thionin. The lesions were plotted onto standard drawings of brain sections and reconstructed onto ventral and lateral views of the brain. Testing of S3 and S4 continues. The extent of their lesions has been evaluated through T1-weighted structural magnetic resonance (MR) imaging.

The lesions, which involved both Pfv and Pfo, were generally as intended. Figure 1 shows representative sections through the lesions in S1 and S2, together with sections from a standard rhesus monkey brain illustrating the intended location and extent of the lesion. Figure 2 shows the extent of the lesions in the same 2 monkeys, reconstructed onto lateral and ventral views of the brain. There was no obvious difference between

Figure 2. Extent of the ventral and orbital prefrontal cortex ablations. Reconstructions of the lesions (shaded regions) from the coronal sections in S1 (A) and S2 (B) onto lateral (top) and ventral (bottom) views of a standard rhesus monkey brain. Numerals indicate the distance (in millimeters) from the interaural plane. S = subject.
the extent of the lesions in S1 and S2, nor was there evidence of unintended damage to other structures. The lesions in S3 and S4, as assessed from a coronal series of MR images at 1-mm intervals, closely matches the lesions in S1 and S2. There was no evidence of damage outside PFv or PFo. The areas included in the removal correspond, very roughly, to Walker’s Areas 11, 12, 13, and 45, as indicated by reference to sulcal landmarks. However, because we did not attempt a cytoarchitectonic analysis of the remaining tissue, we will continue to use the more general anatomical terms, PFv and PFo, to refer to the areas removed.

Results

Conditional Visuomotor Learning

With the exception of the first trial, all noncorrection trials were divided into two main trial types: trials on which the instruction stimulus remained the same as that on the previous trial (repeat trials) and trials on which it differed from that on the previous trial (change trials).

Within-session learning. After a single-stage bilateral removal of PFv and PFo (PFv+o), the monkeys could no longer learn new conditional visuomotor associations within sessions (see Figure 3). Whereas before surgery, monkeys showed rapid within-session learning, after surgery, all subjects performed near chance levels. Data from the 4 monkeys were combined by grouping into 12 blocks of four trials each (see Figure 3A). These data were analyzed with analysis of variance (ANOVA), with three within-subject (repeated) measures: lesion, trial type (repeat or change), and block, for each monkey. There was a significant main effect of lesion, F(1, 3) = 61.2, p = .004, and a significant Lesion × Block interaction, F(11, 33) = 5.8, p < .0001. In addition, there was a significant Lesion × Trial Type interaction, F(1, 3) = 28.0, p = .013. Post hoc Newman–Keuls analysis revealed a significant effect of lesion for both the repeat trials (p < .01) and the change trials (p < .01). There was a significant difference between performance on repeat and change trials preoperatively (p < .01), but not postoperatively. Because the three-choice (S1 and S2) and four-choice (S3 and S4) versions of the task were associated with different levels of chance performance, Figure 3A shows the degree to which the group improved performance from chance levels. Figure 3B shows the asymptotic performance of each monkey, taken from the last 6 blocks of trials (i.e., Trials 25–48 of Figure 3A). It should be noted that the differing levels of chance performance had little effect on the behavioral measures.

Repeat–stay and change–shift strategies. Preoperative performance levels were very high on repeat trials almost immediately on presentation of the new problems (see Figure 3A), and, compared with change trials, there was little room for improvement as the session progressed. Postoperatively, there was no significant difference in performance for repeat versus change trials (see Figure 3A and Figure 3B).

On repeat trials, the monkeys could duplicate the response made on a previous, successful trial, a strategy termed repeat–stay (Wise & Murray, 1999). Use of the correction procedures ensured that the monkeys almost always obtained reward by the end of a trial, enabling the repeat–stay strategy to improve the monkey’s overall performance independent of conditional visuomotor learning. A change–shift strategy was also available to the monkeys, according to which they altered their response whenever the stimulus changed from a previous, successful trial. For example, if a monkey had just made a correct response to the upper right target, on the basis of Instruction Stimulus A, then on a change trial (involving stimuli other than A) the monkey could select any response other than “upper right” to improve its chances of success. Like repeat–stay, this strategy can be applied in the absence of any knowledge about specific visuomotor associations. The change–shift strategy, however, eliminated only one potential response, whereas the repeat–stay strategy provided a unique solution. The
monkeys' use of these strategies has at least two consequences: Performance on change trials can be used to evaluate learning of the visuomotor associations per se, independent of a generalized strategy such as repeat-stay; and strategy use can be approximated by measuring the difference between performance on repeat and change trials. Thus, we defined a strategy score that was based on the difference in performance between these two trial types. Because, preoperatively, the effect of these generalized strategies became less apparent as the monkeys learned the visuomotor associations, the strategy score was calculated for the first two blocks of four trials, before substantial learning could have taken place (see Figure 3A). To compensate for the differences between three- and four-choice tasks, the strategy score was based on the differences expected if the monkeys used both strategies perfectly:

\[ SS = \frac{X(C_1 - R_1 C_2 - R_2)}{P} \]

where \( SS \) is strategy score; \( C_1 \) and \( R_1 \) are percentage of error for change and repeat trials on Block \( i \), respectively; and \( P \) is the ideal percentage difference between repeat and change trials (50.0\% for a three-choice task and 66.7\% for a four-choice task). A score of 1 indicates perfect application of the strategy; a score of 0 results from no difference between performance on repeat and change trials. As shown in Figure 4 (left), the PFv+o lesions severely reduced the monkeys’ strategy scores, \( F(1, 3) = 30.2, p = .012 \). For comparison, Figure 4 (right) shows a comparable analysis for data obtained from monkeys trained in the same manner as S1 and S2, before and after ablations of the hippocampus and subjacent cortex (Murray & Wise, 1996). Monkeys with such lesions were severely impaired in the ability to acquire novel visuomotor associations (not illustrated) but remained proficient at applying the repeat-stay and change-shift strategies.

**Lose-shift strategy.** In addition to the repeat-stay and change-shift strategies, the monkeys used a lose-shift strategy during correction trials. According to this strategy, a different response was selected after failure to obtain reward, that is, after an error. (Lose-shift differs from change-shift because, in the former, a different response follows failure on the previous trial, whereas in the latter, it follows a success.) To measure the use of the lose-shift strategy, we analyzed the second and third responses made on a given trial (i.e., the first and second correction trials). Adherence to the lose-shift strategy was reflected in a relatively large performance improvement on second and third responses, when the monkeys avoided repeating an incorrect response. As shown in Figure 5, PFv+o removal significantly reduced the application of the lose-shift strategy: third ≠ first, \( F(1, 3) = 26.4, p = .014 \); third ≠ second, \( F(1, 3) = 87.0, p = .0026 \); and second ≠ first, \( F(1, 3) = 329.9, p = .0004 \). The monkeys largely avoided repeating the incorrect response preoperatively, but, postoperatively, response repetition was near chance levels. Response perseveration was not observed (see Figure 5). Indeed, after surgery, responses appeared to be distributed nearly randomly.

**Conditional Visuomotor Retention**

Retention of familiar visuomotor conditional problems was assessed for at least three sessions in all 4 monkeys. When more than three postoperative testing sessions had been given, the first three were used for analysis. As shown in Figure 6, the PFv+o lesion significantly impaired the retention of familiar, preoperatively learned visuomotor associations, \( F(1, 3) = 15.5, p = .001 \). The monkeys, as a group, did not perform significantly above chance levels postoperatively, \( t(3) = 2.15, p > .05 \).

**Matching-to-Sample Retention**

We also tested S3 and S4 for their ability to perform a matching-to-sample task that they had acquired preoperatively, to a criterion of 90% correct. The initial six postoperative testing cycles used the same set of eight stimuli as was used preoperatively, and the sample stimulus was selected randomly from this set on each trial. Both monkeys performed at near chance level for all 6 postoperative retention-test sessions presented during the standard testing cycles (see Method section). These monkeys were subsequently given an additional 20 consecutive sessions of the matching-to-sample task, with trial-unique stimuli. We reasoned that if monkeys were having difficulty mastering and implementing several response rules concurrently, as was required during the standard testing cycles, or if there was interference engendered by using the same stimuli in two different tasks, then training on only the matching-to-sample task and using novel stimuli might help them reacquire the rule. Even with this extensive postoperative training, neither S3 nor S4 showed evidence of relearning the matching-to-sample task. The scores for the 2 monkeys on the 20th day of testing were 49% and 44% error for S3 and S4, respectively (chance performance = 50%). Examination of tables of the bino-
Across-Session Conditional Visuomotor Learning

When they were given the opportunity to acquire conditional visuomotor problems across sessions, both S3 and S4 demonstrated significant learning (see Figure 7). On the first two or more sessions of acquisition, neither of the monkeys performed significantly differently from chance (75% error) on either repeat or change trials. In contrast, by the final session of acquisition, neither of the monkeys performed significantly differently from chance levels of performance. Asterisks indicate a significant difference between PRE and POST performance, *p < .05; **p < .01; ***p < .001.

Figure 7. Across-session conditional visuomotor learning. The percent improvement from chance is shown for each monkey across sessions of acquisition. The mean percentage of improvement from chance is indicated by the bars, with error bars representing the standard error of the mean. Asterisks indicate a significant difference from chance levels (p < .05).

Concurrent Visual Discrimination

To test whether the deficit in visuomotor learning could be attributed to an inability to discriminate visual stimuli, we trained S3 and S4 on a series of four concurrent pairwise discriminations. By the end of this training, they were able to learn these novel four-pair discriminations within a single 48-trial session. Data averaged across the final 10 testing sessions show that these monkeys were able to rapidly learn a novel set of visual discriminations with stimulus material similar to that used for the conditional visuomotor learning task (see Figure 8).

Simultaneous Matching-to-Sample and Visuomotor Learning

To assess whether the observed impairments in matching-to-sample and within-session visuomotor learning were due to the working memory requirements of these tasks, we tested S3 and S4 on simultaneous versions of these two tasks. For the data described above regarding S3 and S4, the sample for the matching-to-sample task was removed from the display immediately after the monkeys touched the sample, which triggered the presentation of the choice stimuli. In a similar manner, in the conditional visuomotor task for S3 and S4, the instruction stimulus disappeared as soon as the monkey touched it, at which time the four potential response targets appeared. The goal of the simultaneous versions of these tasks was to reduce the working memory load, which was already slight. This was accomplished by allowing the sample (for the matching-to-sample task) or the discriminative cue (for the conditional visuomotor task) to remain on the display, along with the choice stimuli, until the monkey made a choice response. The conditional visuomotor task performed by S1 and S2 was also simultaneous in this sense; the stimulus remained on the screen until the response was completed, and for an additional 1 s if the response was correct.

Twenty sessions each of the simultaneous versions of the matching-to-sample task and the conditional visuomotor tasks were given to S3 and S4. Despite the decrease in working memory load and use of familiar stimuli across sessions, no improvement in performance was seen across the 20 testing sessions for the matching-to-sample task. On the 20th session of simultaneous
Thus, as with the findings for the matching-to-sample task, the visuomotor learning. choice did not ameliorate the deficit on within-session conditional persistence of the instructional cue at the time of the response significantly from chance: one-sample test, \( t(3) = 0.49, p = .66 \).

These scores did not differ from chance performance. Thus, the persistence of the binomial distribution reveals that these scores do not significantly differ from chance levels of performance within such sessions (see Figure 3A, squares). They could, however, learn these associations over the course of several sessions consisting of several hundreds of trials (see Figure 7A and Figure 7B). This latter finding rules out the hypothesis that either PFv or PFo alone, or PFv+o, are necessary for conditional visuomotor learning. These parts of PF are necessary, however, for the impressive rates of learning observed in experienced rhesus monkeys (see Figure 3A). Although the ablations made in this study were substantial, encompassing both PFv and PFo in both hemispheres, it remains possible that still larger PF lesions might yield a complete inability to learn visuomotor associations, both within and across sessions.

The retention of conditional visuomotor problems was also severely disrupted after PFv+o removal (see Figure 6). Although the deficit appeared to be milder in a preliminary report that presented data from S1 (Murray, Bussey, & Wise, 2000), the data presented there included across-session relearning of the familiar associations, such as that seen across sessions for novel problems in the present study (see Figure 7). The monkeys' severe impairment in retention of visuomotor associations contrasts with the results of Wang, Zhang, and Li (2000), who reported that bicuculline injections into PFv fail to disrupt performance on highly familiar visuomotor problems. The fact that Wang et al. studied the effects of smaller disruptions of PF function than we did and that the disruptions were temporary might account for this discrepancy.

**Neural Basis of Conditional Motor Learning**

One source of the deficit could, in principle, have been an inability to discriminate or categorize the visual stimuli. Previous matching-to-sample, scores were 58% and 40% error for S3 and S4, respectively (chance = 50%). Examination of tables of the binomial distribution reveals that these scores do not significantly differ from chance performance. Thus, the persistence of the sample at the time of the choice did not enable the monkeys to overcome their deficit on the matching-to-sample task. On the 20th postoperative session of simultaneous visuomotor learning, with novel problem sets every 48 trials, scores were 69% and 68% error for S3 and S4, respectively (chance = 75%). With new problem sets used for every 50 trials, scores were 58% and 79% error for S1 and S2, respectively (chance = 67%). These scores did not differ significantly from chance: one-sample \( t \) test, \( t(3) = 0.49, p = .66 \).

Thus, as with the findings for the matching-to-sample task, the persistence of the instructional cue at the time of the response choice did not ameliorate the deficit on within-session conditional visuomotor learning.

**Discussion**

Removal of PFv+o had a dramatic effect on rapid conditional visuomotor learning. Preoperatively, the monkeys could consistently learn a novel, concurrent set of visuomotor associations in less than 50 trials (see Figure 3A, circles). Postoperatively, the monkeys could no longer do so; indeed, they could not improve on chance levels of performance within such sessions (see Figure 3A, squares). They could, however, learn these associations over the course of several sessions consisting of several hundreds of trials (see Figure 7A and Figure 7B). This latter finding rules out the hypothesis that either PFv or PFo alone, or PFv+o, are necessary for conditional visuomotor learning. These parts of PF are necessary, however, for the impressive rates of learning observed in experienced rhesus monkeys (see Figure 3A). Although the ablations made in this study were substantial, encompassing both PFv and PFo in both hemispheres, it remains possible that still larger PF lesions might yield a complete inability to learn visuomotor associations, both within and across sessions.

The retention of conditional visuomotor problems was also severely disrupted after PFv+o removal (see Figure 6). Although the deficit appeared to be milder in a preliminary report that presented data from S1 (Murray, Bussey, & Wise, 2000), the data presented there included across-session relearning of the familiar associations, such as that seen across sessions for novel problems in the present study (see Figure 7). The monkeys' severe impairment in retention of visuomotor associations contrasts with the results of Wang, Zhang, and Li (2000), who reported that bicuculline injections into PFv fail to disrupt performance on highly familiar visuomotor problems. The fact that Wang et al. studied the effects of smaller disruptions of PF function than we did and that the disruptions were temporary might account for this discrepancy.
results suggest that PF may be important for visual discrimination and categorization (Freedman, Riesenhuber, Poggio, & Miller, 2001; Gaffan, Murray, & Fabre-Thorpe, 1993; Passingham, 1972). Monkeys S3 and S4, however, were able to learn a four-pair concurrent visual discrimination within a single session, reaching levels above 80% correct within 48 trials. This performance level demonstrates substantial discrimination learning within a single session, which indicates that the deficit in within-session conditional visuomotor learning cannot be attributed to an impairment in visual discrimination abilities. We did not study a control group of subjects on this task, and so we cannot rule out the possibility that removal of PFv+o caused a deficit in learning to discriminate visual stimuli. However, the dramatic nature of the within-session deficit in visuomotor learning, coupled with the monkeys’ clear ability to learn visual discriminations within a session of similar length, indicates that neither visuoperceptual deficits nor categorization deficits are likely to explain the impairment in rapid visuomotor learning.

One might also posit that response perseveration was the cause of the impairment in conditional visuomotor learning. However, our error analysis indicates that, postoperatively, monkeys were no more likely to emit one response over another after an error (see Figure 5). In other words, response selection was essentially random, and there was no evidence of perseveration.

The present data thus show that monkeys with bilateral removal of PFv+o are impaired in several cognitive capacities and that these impairments cannot be accounted for by visuoperceptual deficits or response perseveration. The deficits include the acquisition of new visuomotor associations, the retention of preoperatively learned familiar visuomotor associations, and the retention of preoperatively learned strategies. Interactions among these deficits seem likely. For example, disruption of the various strategies that promote problem solving, such as repeat–stay and lose–shift, may have contributed to the deficit observed in learning the individual associations. Preoperative learning may have been similarly speeded by application of these strategies. It should be noted that, because the monkeys were given correction trials, they were receiving the same number of reinforced visuomotor associations per session, preoperatively and postoperatively. The main difference after surgery, however, was in the rate at which the successes occurred and the number of failures that intervened between successes. Perhaps the application of the strategies speeds visuomotor learning by decreasing the time or the number of responses between successful outcomes.

The finding that, postoperatively, the monkeys could neither use nor reacquire preoperatively learned strategies (see Figures 3, 4, and 5) accords with other evidence, from both macaques and marmosets, that implicates PF in the learning and implementation of strategies (Collins et al., 1998; Harlow & Settlage, 1947; Parker & Gaffan, 1997). The monkeys’ deficits are also consistent with a role for PF in learning response rules (Passingham, 1993; Wise, Murray, & Gerfen, 1996), a concept related to response strategies. The deficit observed here on matching-to-sample tasks has been reported previously (Rushworth, Nixon, Eacott, & Passingham, 1997), although it has usually been interpreted in terms of problems with visual recognition memory (Kowalska, Bachevalier, & Mishkin, 1991) or selective attention (see Miller, Erickson, & Desimone, 1996). However, an alternative interpretation—that the performance deficit is caused by the failure to recall a preoperatively learned response rule or strategy—is supported by the finding that, after retraining on the rule, the matching- or nonmatching-to-sample tasks can again be successfully performed (Kowalska et al., 1991; Rushworth et al., 1997). In the present study, however, the monkeys were unable to relearn the matching-to-sample rule, a finding that might be attributable to the fact that the lesion included both PFv and PFo, as opposed to the more restricted lesions (PFv) used in the earlier studies. An alternative possibility is that the inability to relearn the rule might have resulted from the same disability evidenced by the loss of strategies such as repeat–stay. The matching-to-sample task requires the use of a behavior-guiding rule or strategy that might be expressed as follows: On the choice test, choose either the familiar stimulus (trial-unique matching-to-sample) or the stimulus seen most recently (matching-to-sample with a small set of stimuli). If that strategy depends on some of the same neural substrates as the repeat–stay and lose–shift strategies, the inability of the present subjects to relearn the matching-to-sample task after surgery could have resulted from a general disruption of strategy-based behavior.

Another potential basis for the observed disability in rapid visuomotor learning could be a failure of working memory, especially as needed to support the response strategies described above. Each of the strategies considered here requires that the monkeys remember the stimuli or responses from the recent past. For example, application of the repeat–stay strategy requires that the monkeys recognize that the instruction stimulus on the current trial matches that from the previous trial. Therefore, disruption of some specialized form of working memory by PFv+o removal might prevent the application of the repeat–stay, change–shift, and lose–shift strategies. To the extent that those strategies underlie the rapid visuomotor learning observed preoperatively, such deficits might account for the dramatic slowing in learning rate caused by the lesion. Furthermore, one might argue that working memory for some combination of events, especially the stimulus, the response, and the reward outcome, needs to be maintained for rapid learning to occur. This interpretation would be consistent with the view that the principal role of PF involves keeping information “on-line” during a trial, for manipulation and for the guidance of future responses (Goldman-Rakic, 1994, 1995, 1996). However, decreasing the working memory load, as was accomplished by the simultaneous version of the conditional visuomotor task, did not ameliorate the deficits. In the simultaneous version of the task, the stimulus, response, and outcome information were all available simultaneously as soon as the monkeys completed their responses. Yet, all 4 monkeys continued to perform near chance levels within each session of the simultaneous visuomotor conditional task. This finding suggests that an impairment in working memory alone cannot account for the deficits that follow PFv+o lesions. Our conclusion accords with that of Rushworth et al. (1997), who found that monkeys with bilateral damage to PFv showed deficits that could not be accounted for in terms of working memory dysfunction.

The finding that there remains a dramatic impairment in within-session simultaneous conditional visuomotor learning has an additional implication. The deficits on the simultaneous visuomotor task were observed in sessions given after the monkeys had demonstrated their ability to learn visual discriminations within a
session. Thus, the relatively spared within-session visual discrimination learning does not simply reflect a time-dependent recovery of function, such as, for example, the monkeys improving their ability to respond to visual stimuli of the type used here. The severe deficit in conditional visuomotor learning persisted, even after a demonstration of relatively good performance on visual discrimination learning, up to 18 months after surgery.

The present results are consistent with and complementary to those reported with other methods. Wang et al. (2000) disrupted the activity of PFv while monkeys learned novel conditional motor problem sets. They found that bicuculline, but not saline, injections into PFv temporarily impaired the monkeys’ ability to solve conditional visuomotor problems. These investigators attributed much of this deficit to an inability to apply win-stay, lose-shift, and change-shift strategies. The findings of Wang et al. thus confirm the within-session impairments reported here and the loss of specific strategies for task performance and learning. Their findings point to the PFv component of our ablation as a primary cause of the deficit reported here in conditional visuomotor learning and show that short-term, reversible disruption of PFv activity is sufficient to cause the impairment.

Relation to Neurophysiological Findings

Miller and his colleagues have found neuronal activity changes in PFv during the learning of conditional visuomotor associations and their reversals, especially regarding the directional selectivity of individual PFv neurons (Asaad, Rainer, & Miller, 1998; see also Li, Inase, Takashima, & Iijima, 1997). Similar findings have been reported for PFo (Tremblay & Schultz, 2000). Nothing in the present study should be construed as implying that these changes in neuronal activity have less importance because the areas in which these are located are not necessary for learning conditional visuomotor associations (as shown by the across-session learning illustrated in Figure 7). The finding that these areas are needed for the fastest, most efficient visuomotor learning suggests that their importance lies in that domain.

Role of PF Versus Premotor Cortex

It remains to be seen whether the slower across-session learning that survives PFv+o lesions is associated with similarly slow learning-related changes in neuronal activity in other regions. One likely candidate for such slow changes is the premotor cortex, which, like PFv and PFo, contains neurons that exhibit learning-related changes in activity during visuomotor learning (Mitz, Goldschalk, & Wise, 1991). In addition, lesions of the premotor cortex impair slow across-session conditional visuomotor learning (Petrides, 1982), as well as the postoperative retention (or relearning) of single two-choice conditional visuomotor problems (Halsband & Passingham, 1982). Because PFv+o receives most of the frontal lobe’s input from IT, including the perirhinal cortex (Carmichael & Price, 1996; Cavada et al., 2000; Pandya & Kuypers, 1969; Rempel-Clower & Barbas, 2000; Webster et al., 1994), it seems likely that the PFv+o lesion disrupted the flow of information from these visual areas to other regions of frontal cortex such as premotor cortex.

Role of PF Versus Hippocampus

The role of the hippocampal system in learning conditional visuomotor associations has been reviewed in detail (Wise & Murray, 1999). Like lesions of PFv+o, lesions of the hippocampal system lead to deficits in the rapid learning of novel conditional visuomotor associations (Gaffan & Harrison, 1989; Murray & Wise, 1996; Rupniak & Gaffan, 1987). However, unlike PFv+o lesions, damage to the hippocampal system leaves the repeat–stay and lose–shift strategies relatively intact (see Figure 4 in the present study and Figures 5 and 7 in Wise & Murray, 1999). Furthermore, bilateral aspiration removal of the hippocampus and nearby structures, unlike PFv+o removal (see Figure 6), completely spares performance on well-consolidated familiar conditional visuomotor associations (Murray & Wise, 1996; Figure 4 in Wise & Murray, 1999). These findings suggest that PF and the hippocampal system make different contributions to rapid visuomotor learning, with PF playing a larger role in the application of strategies and in the retrieval of familiar associations (Murray et al., 2000; Passingham, 1993; Wise et al., 1996).

Role of PF in Other Types of Conditional Associations

Conditional visuomotor associations are only one aspect of associative memory, and there is no reason to believe that the role of PF is confined to acquiring associations between instruction cues and movements. Indeed, there is evidence that PF’s role in conditional visuomotor associations is a special case of a more general involvement in conditional associative learning (Petrides, 1985, 1987, 1997). PF is needed for other types of conditional associations, for example, when both the conditional cue and the response consist of nonspatial visual stimuli, which is often termed visual–visual conditional association or paired-associate learning (Eacott & Gaffan, 1992; Gutnikov, Ma, & Gaffan, 1997). Parker and Gaffan (1998) have also pointed to a role for PF in conditional associations, using the arrival or nonarrival of a food pellet reward as the conditional cue. These data thus support a fairly general role for PF in the acquisition of conditional associations, one that encompasses at least visual–motor, visual–visual, and reward–visual associations.

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