Effect of Reversible Inactivation of Macaque Lateral Intraparietal Area on Visual and Memory Saccades

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Li, Chiang-shan Ray, Pietro Mazzoni, and Richard A. Andersen. Effect of reversible inactivation of macaque lateral intraparietal area on visual and memory saccades. *J. Neurophysiol.* 81: 1827–1838, 1999. Previous studies from our laboratory identified a parietal eye field in the primate lateral intraparietal sulcus, the lateral intraparietal area (area LIP). Here we further explore the role of area LIP in processing saccadic eye movements by observing the effects of reversible inactivation of this area. One to 2 μl of muscimol (8 mg/ml) were injected at locations where saccade-related activities were recorded for each lesion experiment. After the muscimol injection we observed in two macaque monkeys consistent effects on both the metrics and dynamics of saccadic eye movements at many injection sites. These effects usually took place within 10–30 min and disappeared after 5–6 h in most cases and certainly when tested the next day. After muscimol injection memory saccades directed toward the contralesional and upper space became hypometric, and in one monkey those to the ipsilesional space were slightly but significantly hypermetric. In some cases, the scatter of the end points of memory saccades was also increased. On the other hand, the metrics of visual saccades remained relatively intact. Latency for both visual and memory saccades toward the contralesional space was increased and in many cases displayed a higher variance after muscimol lesion. At many injection sites we also observed an increase of latency for visual and memory saccades toward the upper space. The peak velocities for memory saccades toward the contralesional space were decreased after muscimol injection. The peak velocities of visual saccades were not significantly different from those of the controls. The duration of saccadic eye movements either to the ipsilesional or contralesional space remained relatively the same for both visual and memory saccades. Overall these results demonstrated that we were able to selectively inactivate area LIP and observe effects on saccadic eye movements. Together with our previous recording studies these results futher support the view that area LIP plays a direct role in processing incoming sensory information to program saccadic eye movements. The results are consistent with our unit recording data and microstimulation studies, which suggest that area LIP represents contralateral space and also has a bias for the upper visual field.

INTRODUCTION

It is well known that patients with lesions in the posterior parietal lobe have difficulty moving their gaze to the contralesional space (for reviews see Andersen 1987; Lynch 1980). Reaction times are increased for saccades directed to the contralesional space, and the velocities are decreased (Braun et al. 1992; Nagel-Leiby et al. 1990; Sundqvist 1979). Bilateral lesions of the posterior parietal lobe produce what classically is known as Balint's syndrome (Balint 1909; Hecaen and Ajuriaguerra 1954). In this case, the patients are not able to shift their gaze from one direction to another, a symptom termed "psychic paralysis of gaze." Frequently associated with these oculomotor impairments in parietal patients are deficits in reaching and grasping movements (Jeannerod et al. 1994; Perenin and Vighetto 1988). These subjects mislocalized the object in space and were unable to preshape their hand in an adequate way to facilitate manipulative actions. More recently, the studies of some patients with selective lesions of the posterior parietal or occipitotemporal areas led Goodale et al. to suggest that instead of simply mediating the "where" function of the dorsal stream of the visual system the posterior parietal lobe is in general important for actions (Goodale and Milner 1992; Goodale et al. 1991). It is argued that this area controls the monitoring of moment-to-moment visual information to facilitate immediate motor outputs. Overall these results point to the posterior parietal lobe as an important structure for visuomotor control.

Similar to what was observed in humans, lesions of the posterior parietal lobe in nonhuman primates often result in various attentional and visuomotor deficits (for reviews see Andersen 1987; Lynch 1980; Stein 1989). Saccades directed to the contralesional space have a longer latency and in some cases are transiently impaired in accuracy (Lynch 1992; Lynch and McLaren 1989). Other studies demonstrate deficits in reaching and grasping that are reminiscent of what were found in human parietal patients (Faugier-Grimaud et al. 1985; Faugier-Grimaud et al. 1978; Gallese et al. 1994; Lamotte and Acuna 1978). These results suggest that the posterior parietal lobe may be important in integrating multiple modalities of sensory information and cognitive resources for movement planning (Andersen et al. 1997).

Along with these advances in behavioral and clinical studies, neuronal recordings in behaving primates identified several distinctive areas in the posterior parietal lobe that are important for visuomotor functions (Andersen et al. 1990; Colby and Duhamel 1991; Colby et al. 1993; Johnson et al. 1993; Kalaska et al. 1983; Sakata et al. 1995; Taira et al. 1990). Among them is an area in the posterior bank of the lateral intraparietal sulcus, the lateral intraparietal area (area LIP), which carries saccade activities and signals related to oculomotor planning (Barash et al. 1991a,b; Bracewell et al. 1996; Gnadt and Andersen 1988; Mazzoni et al. 1996a; Snyder et al. 1997; for review see also Andersen 1995). It was shown in these studies that LIP neurons discharged before visual saccades and also to memory saccades where no visual stimulus was available. In a memory double-saccade paradigm in which animals must remember the locations of visual stimuli but plan eye movements

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away from the visual stimuli most LIP neurons displayed sustained memory activities only for the upcoming intended eye movements (Mazzoni et al. 1996a). These results provide evidence that area LIP encodes motor intention for saccadic eye movements. Anatomic studies also show that area LIP is connected with other oculomotor centers, such as the frontal eye fields (FEF) and superior colliculus (SC), and thus constitutes an important node in the network of neural structures controlling saccadic eye movements (Andersen et al. 1990; Lynch et al. 1985).

To further explore how area LIP might play a role in processing saccadic eye movements, we reversibly inactivated this area and examined how saccadic eye movements might be impaired. Emphasis was also placed on how the effects compared with those observed after lesions of the FEF, SC, and other oculomotor structures. Preliminary results of part of this work were published in abstract form (Li et al. 1995).

METHODS

Surgery and animal care

Before behavioral training, aseptic surgeries for implanting the scleral search coil (Fuchs and Robinson 1966; Judge et al. 1980) and a head-holding device were performed under ketamine induction and pentobarbital anesthesia. Systemic antibiotics were administered before and after the surgery, and the monkeys were allowed full rest for ≥1 wk after surgery. NIH guidelines for the care and use of animals were closely followed.

Behavioral tasks and training procedures

Behavioral training began with visual fixation and visual saccade tasks. In the visual fixation task, the monkey was required to fixate a light spot (typically within a window of 2° in diameter), which appeared at different locations on the screen, to receive a juice or water reward. The duration of fixation required for successful performance was 1,800 ms in experimental sessions. Light spots were 0.5° in diameter and 45 cd/m^2 in luminance. Stimuli were back-projected from an optical bench, where their positions were controlled by a galvanometer system and electronic shutters to a tangent screen situated 57 cm in front of the animal. A video projector was used in later experiments.

In the visual saccade task, the monkey fixated on a light spot straight ahead for 1,200 ms and was required to make a saccadic eye movement within a time window of 350 ms to a peripheral target appearing randomly at 8 or 24 different locations. The monkey was required to stay at the peripheral target for another 1,000 or 1,200 ms within a space window of 8° in diameter to complete the task and receive a juice reward. A large window was used for the acquisition of the peripheral target to allow for possible targeting errors after muscimol injection. Target locations for saccades were arranged either in a circle (the 8-target array) or in three concentric circles (the 24-target array) of different radii (either 7, 12, and 18° or 10, 15, and 20°) and in eight different directions (in spacings of 45°), centered on the fixation point. The eight-target array was usually used for monkey LBZ, and different amplitudes were tested in successive blocks of experiments. The two 24-target arrays were routinely used in the experiments with monkey MRS. Training for the fixation and visual saccade tasks was completed within 1 wk.

The monkeys were next trained on the memory saccade task. In this task while the monkey was fixating straight ahead a light spot was flashed briefly (100 ms) at one of the 8 or 24 locations, and when the fixation point went off after a delay of 950 ms he was required to initiate a saccadic eye movement within 450 ms to the location where the target appeared before. The spatial window for the peripheral target was typically large, allowing for the upshift of end points constantly observed for memory saccades in the dark (Gnadt et al. 1991; White et al. 1994) and any possible targeting error in the muscimol experiments. The window was a circle of 8° in diameter for 7° saccades, 10 for 10° saccades, 14 for 12° saccades, 18 for both 15 and 18° saccades, and 20 for 20° saccades. The same performance criteria were used throughout the experiments for both the control and lesion sessions. Training for the memory saccade task took another 2–4 wk to complete. Both the training and experiments were carried out in otherwise total darkness in a room in which auditory noise was significantly reduced. The room light was turned on periodically (typically every 5 min) to prevent the monkey from becoming dark adapted or drowsy.

Monkeys usually performed 1,000–1,500 trials in each session daily in a period of 4–6 h. They were generally given a short break of 5–10 min between runs. The room light was turned on when the monkey was at rest.

Eye position monitoring and data collection

Eye position was monitored by a search coil system (Robinson 1963) and sampled at 500 Hz. Experiments started with a calibration run each day in which the animal-fixated stimuli presented at nine different locations, typically 20° apart in both the *x*- and *y*-axes, including the straight-ahead position. Daily calibration remained fairly constant within each experimental period.

Experiments were controlled by a PDP-11 computer early on and later by a PC-based system. In both the visual and memory saccade tasks after the fixation point came on the monkey was required to acquire fixation within 2 s, and a trial was declared to start if he continued to fixate for another 300 ms. Failure to acquire the fixation point or to fulfill the initial stay at the fixation light for the criterion duration (300 ms) was regarded as a MISS; the trial was aborted, and a new trial started over again. No data were collected in this case. When the monkey succeeded in acquiring fixation and managed to complete the rest of the task successfully, the trial was a HIT. The trial was an ERROR if the monkey failed to complete the task after the trial started. This could occur because he broke fixation, did not initiate a saccade within the preset time window, failed to land on the target location correctly, or failed to stay at the target location for the criterion duration. The data of the ERROR trials were collected up to the point where the error occurred and the trial ended.

Recording and reversible lesion

Both glass-coated, platinum–iridium and the commercial vinyl-coated tungsten electrodes, with impedance of 1–2 MΩ at 1 kHz, were used for the recordings. The electrodes were advanced through the dura with a guide tube. The electrode penetrations could be spaced with approximately a 1-mm resolution on both the *x*- and *y*-axes. Electrical signals were fed into an amplifier, and single units were isolated with a variable-delay window discriminator. Before the lesion experiments, recordings were carried out for a period of 2–6 mo with both the visual and memory saccade tasks. Area LIP was identified by typical neuronal activities in these two tasks (Andersen et al. 1990). Other physiological landmarks were also useful to ensure penetrations at proper locations to isolate units from area LIP. These landmarks included neuronal activities primarily related to reaching movements and somatosensory stimulation in the medial bank of the intraparietal sulcus and unit activities responding to motion stimuli deep in the sulcus (Colby et al. 1993; Johnson et al. 1993).

We used muscimol (Sigma, St. Louis, MO), a GABAa agonist, for the reversible lesions. The solution was made of 1 mg of muscimol in 125 μl of normal saline to achieve a concentration of 8 mg/ml. Pressure injection of muscimol was made with a Hamilton syringe, which was held by an adapted Narishigi microdrive. For most cases 1

TABLE 1. *Effect of muscimol lesion on* MISS *and* ERROR *rates*

		Monkey LBZ			Monkey MRS		
		Number of experiments	MISS rate, %	ERROR rate, %	Number of experiments	MISS rate, %	ERROR rate, %
				Visual saccade			
Contralesional	Control	8	6.2 ± 3.0	5.6 ± 1.7	4	7.2 ± 5.4	6.5 ± 2.2
	lesion	9	9.0 ± 5.7	5.7 ± 2.3	4	8.3 ± 3.6	7.4 ± 3.8
Ipsilesional	Control	8	7.6 ± 3.4	6.8 ± 2.1	4	8.9 ± 6.7	5.8 ± 1.8
	lesion	9	8.2 ± 2.5	4.2 ± 3.7	4	11.0 ± 4.9	6.0 ± 3.4
				Memory saccade			
Contralesional	Control	14	14.2 ± 5.6	9.1 ± 5.5	7	12.2 ± 8.8	14.6 ± 5.2
	lesion	14	21.7 ± 6.1*	36.7 ± 9.5**	6	36.6 ± 8.4**	20.2 ± 5.7*
Ipsilesional	Control	14	12.4 ± 3.3	11.6 ± 3.8	7	13.5 ± 6.7	9.9 ± 4.1
	lesion	14	14.4 ± 4.9	10.3 ± 7.2	6	11.3 ± 3.5	11.8 ± 6.4

Values are means ± SD. * $P < 0.01$; ** $P < 0.001$.

μl of muscimol was used. The maximum amount of muscimol used at one time was 3 μl, and $\leq$2 μl was used at one injection site in one given experiment. Normal saline was used for injection for the control experiments. The amount of normal saline used and method of injection were the same.

Histology

One monkey was euthanized after both hemispheres were explored in the recording and lesion experiments. The monkey was given an overdose of pentobarbital sodium and then perfused transcardially with heparinized saline followed by buffered formalin. Examination of the penetration marks on the surface of the brain showed that they were mostly concentrated on the lateral bank of the intraparietal sulcus. Sections of the brain 50 μm thick were cut and stained with neutral red for cytoarchitecture. The lesion marks created by muscimol injections were clearly visible and located in the lateral bank of the intraparietal sulcus.

Data analyses

Muscimol injections were done at most every other day during each experimental period. Performance during the days when no injections were made or when normal saline was used served as controls. Data collected for each muscimol experiment were usually compared with the control data pooled from 1 day before and 1 day after the lesion.

Trials with saccade latencies shorter than 100 ms were most likely a result of anticipation and were excluded from further analysis. The number of trials excluded comprised $\leq$0.5% for monkey LBZ and 1% for monkey MRS of the total number of trials collected in each block of experiment.

The saccade amplitude was computed by subtracting the starting point from the end point of a saccade. This subtraction was performed to take into account very slow drifts in the recording system that were occasionally observed in the experiments. The saccade beginning was defined as the time at which the velocity increased to >20°/s, and the saccade ending was defined as the time when the velocity decreased to <50°/s. The saccade latency was defined as the time it took for the saccade to be initiated after the fixation point went off. The saccade's peak velocity was computed with a two-point differencing mechanism with a temporal spacing of 2 ms (Bahill et al. 1982). The saccade duration was computed by subtracting the time when the saccade began from the time when the saccade ended.

RESULTS

A total of 14 lesions were performed in two hemispheres (10 lesions in the left and 4 in the right hemisphere) of monkey LBZ, and 6 lesions were performed in the right hemisphere of monkey MRS. Saccade amplitudes of 15° and of a combination of 10, 15, and 20° were routinely tested for both visual and memory saccade tasks. For several sessions, amplitudes of 7, 12, and 18° were also tested. Because the effects of muscimol lesion were generally similar in monkey LBZ and MRS, the results will primarily be illustrated by those obtained from monkey LBZ. The data obtained from the left and right hemispheres of monkey LBZ were also similar. They were thus combined, unless otherwise noted.

General performance

The general performance of the two monkeys in terms of the MISS and ERROR rates for the visual saccade task was not different after the injection of muscimol compared with the controls. However, in the memory saccade tasks a significant deterioration of performance for the contralesional saccades after muscimol injection was noted and was manifested as an increase of MISS and ERROR rates. The increase of the MISS rate was probably a result of decreased motivation of the monkey after many failures at the task. The increase of the ERROR rate occurred primarily as a result of the failure to stay on the target after acquiring fixation, to initiate a saccade within the time window, or to make a correct saccade to the target. We did not observe an irrepressible tendency in the monkey to make a saccade at the time when the target was presented in the ipsilesional field in the memory saccade task. Averages of the MISS and ERROR rates for ipsilateral and contralateral saccades in the control and lesion experiments are listed in Table 1 for both monkeys. Saccades were grouped into contralateral and ipsilateral according to the direction of their horizontal component. If the lesion was in the left hemisphere, for example, contralateral saccades would include those directed to up right, right, and down right and vice versa.

We will describe the results of muscimol injection on both the metrics and dynamics of saccadic eye movements. These effects usually took place within 10–30 min (85 min in 1 case with monkey LBZ) and disappeared within 5–6 h in most

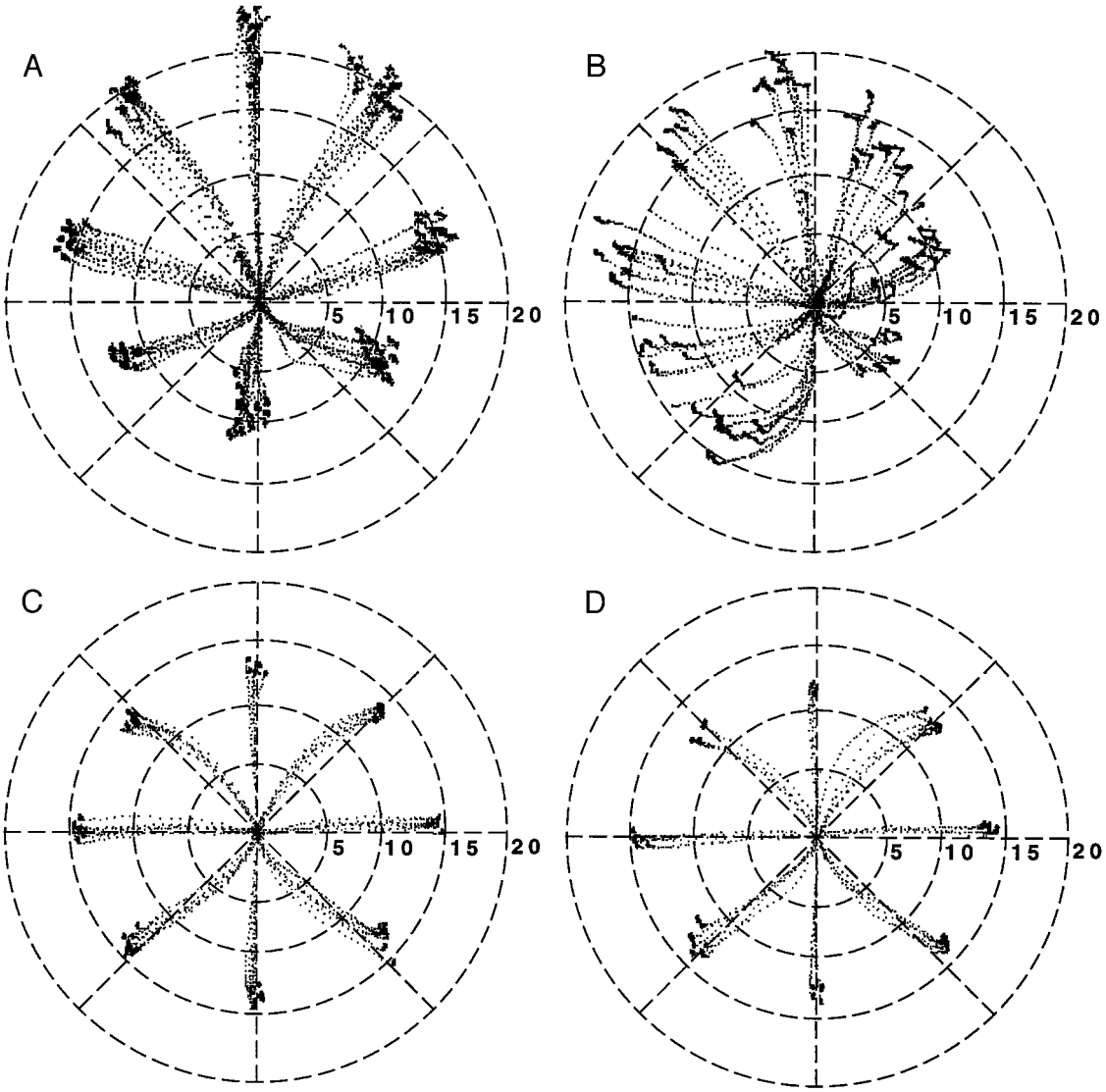

FIG. 1. The metrics of the memory and visual saccade in an experiment with monkey LBZ. The saccades were made to targets 15° away from the fixation point and in 8 directions. Six trials each are plotted for visual saccades, and 8–10 trials are plotted for memory saccades. The trajectories are all centered on the beginning of the saccades. Muscimol was injected in the left hemisphere. The end points of the memory saccades show a characteristic upshift, which can be seen for both the control (*A*) and lesion (*B*) experiments. The end points of the memory saccades in many directions were shifted to the left, resulting in hypometric contralesional saccades. The amplitudes for upward saccades were also reduced. On the other hand, the metrics of visual saccades after muscimol lesion (*D*) are not different from those of the controls (*C*). See text for further explanation.

cases, when the monkey could still perform the tasks reliably, and definitely when tested the next day.

Metrics

After muscimol injection, the memory saccades toward the contralesional side became hypometric. This disruption of metrics affected all contralateral saccades and did not show a significant amplitude dependence. In monkey MRS ipsilateral saccades were also significantly hypermetric compared with the controls. In other words the end points of memory saccades in all directions were shifted to the ipsilesional side, although to different degrees. For both monkeys, the amplitudes of upward saccades were also reduced in many injections. On the other hand, the metrics of the visual saccades were relatively intact. Figure 1 shows the eye traces for 15° visual and memory saccades taken from one typical experimental set with monkey LBZ. The injection site in this case was in the left hemisphere. The rightward and upward memory saccades were hypometric, whereas the visual saccades were fairly normal. In this case the scatters of the end points of the memory saccades were also larger after muscimol lesion. Figure 2 shows in *x-y* plots the average shifts of the end points for 15° memory saccades across all 10 lesion experiments in the left hemisphere and 4 lesions in the right for monkey LBZ and all 6 experiments in the right hemisphere for monkey MRS. The change in amplitude was significant in both monkeys [$P < 0.001$, analysis of varaince (ANOVA)], and the magnitude of change varied with the directions of saccades ($P < 0.001$,

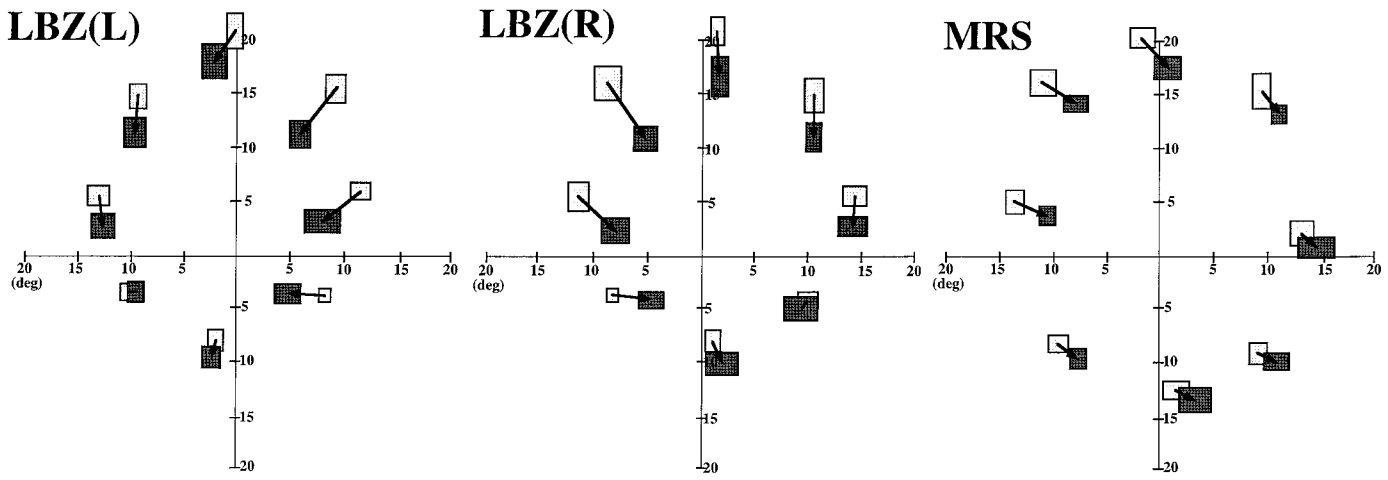

FIG. 2. The effect of lateral intraparietal area (area LIP) lesion on the metrics of memory saccades, averaged from all lesion experiments in the left (L) and right (R) hemispheres of monkey LBZ and in the right hemisphere of monkey MRS using saccades of 15° amplitude. For both monkeys, the contralesional saccades are consistently hypometric. For monkey MRS, the end point of ipsilesional saccades is also shifted to the ipsilesional side, although to a lesser degree. Also the amplitudes of upward saccades are reduced in both monkeys. The center of each box is the average end point of the saccades, and the width and height of each box are the SDs of the *x* and *y* components of the end points. Arrows show the change of the metrics as a result of the lesion. □: control; ■: lesion.

ANOVA). The contralesional saccades showed a larger reduction in amplitude than the ipsilesional saccades. For both monkeys in many cases (6/9 injection sites for monkey LBZ and 3/4 for monkey MRS) the upward saccades were also reduced in amplitude. We computed the ratio of saccade amplitude between the results of the lesion and control for both contralesional and ipsilesional saccades in each experimental session. For instance, a ratio of 0.85 denoted a 15% reduction in amplitude. The results were averaged across all sessions. They are listed in Table 2 for both visual and memory saccades, organized according to the saccade amplitude.

Corrective saccades were rarely seen in either task, and the frequency did not seem to be different between the lesion and control experiments.

Latency

After muscimol injection, the latencies for both visual and memory saccades directed to the contralesional space increased. Although latency sometimes also increased for ipsilesional saccades (particularly in the memory saccade task), the deficit was much more pronounced for contralesional saccades. In many cases there was also an increase of latency for sac-

TABLE 2. *Change in amplitude*

	Monkey LBZ			Monkey MRS		
Amplitude, deg	Contralesional	Ipsilesional	Number of lesions	Contralesional	Ipsilesional	Number of lesions
			Memory saccade			
7	0.84 ± 0.07	1.00 ± 0.08	7	0.83 ± 0.12	1.03 ± 0.08	4
10	0.82 ± 0.05	1.02 ± 0.03	10	0.89 ± 0.04	1.09 ± 0.08	6
12	0.76 ± 0.09	0.94 ± 0.05	7	0.84 ± 0.07	1.10 ± 0.09	4
15	0.68 ± 0.11	0.92 ± 0.06	14	0.86 ± 0.05	1.05 ± 0.07	6
18	0.70 ± 0.10	0.92 ± 0.06	7	0.82 ± 0.09	1.06 ± 0.11	4
20	0.71 ± 0.08	0.95 ± 0.05	10	0.84 ± 0.05	1.05 ± 0.04	6
Average	0.75 ± 0.08	0.96 ± 0.05		0.85 ± 0.07	1.06 ± 0.08	
			Visual saccade			
7	1.04 ± 0.06	0.97 ± 0.04	4	1.03 ± 0.04	0.97 ± 0.03	4
10	1.00 ± 0.02	0.95 ± 0.05	7	1.04 ± 0.05	0.95 ± 0.06	4
12	1.01 ± 0.04	1.02 ± 0.05	4	0.99 ± 0.05	1.02 ± 0.06	4
15	0.97 ± 0.04	0.99 ± 0.03	9	1.06 ± 0.09	0.99 ± 0.04	4
18	0.98 ± 0.04	1.01 ± 0.07	4	0.98 ± 0.04	1.01 ± 0.05	4
20	1.01 ± 0.06	1.01 ± 0.03	7	1.01 ± 0.04	1.01 ± 0.06	4
Average	0.99 ± 0.04	0.99 ± 0.04		1.02 ± 0.05	1.00 ± 0.05	

Values are means ± SD. Change of saccade metrics is shown as a ratio of post/pre-injection amplitude. Total numbers of lesions were different for different saccade amplitudes because the number of experiments in which saccades of different amplitudes were tested was not the same.

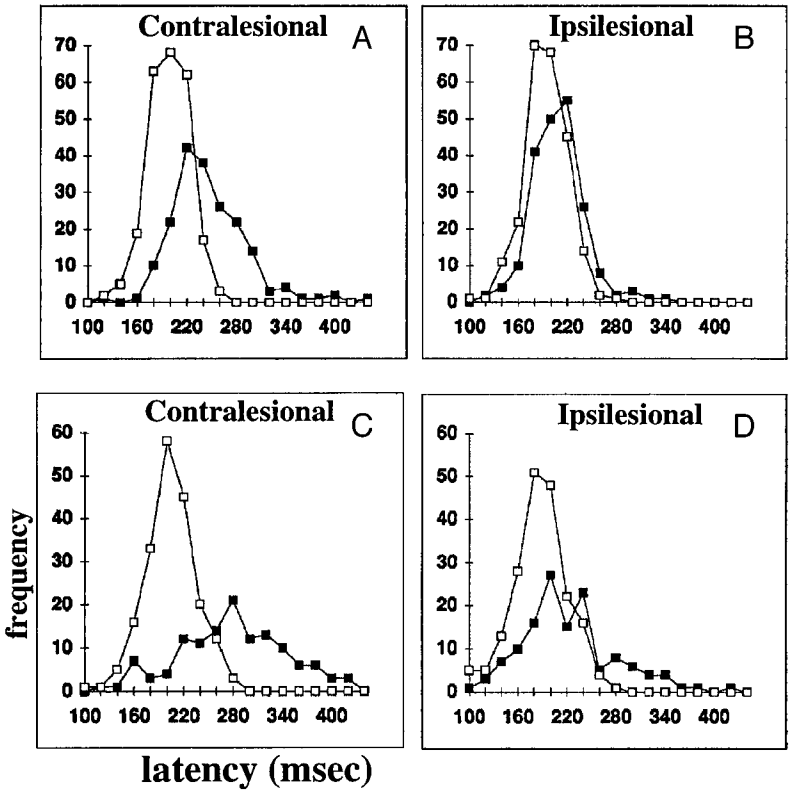

FIG. 3. The effect of area LIP lesion on saccade latency. Data were taken from an experiment of both visual and memory saccades from monkey LBZ. The latency increased for both contralesional and ipsilesional visual (*A* and *B*) and memory (*C* and *D*) saccades after muscimol injection, but the effects on the contralesional saccades were much greater. □: control; ■: lesion. See text for statistics of the differences between the lesion and control data.

cades directed to the upper space. A typical set of data of 15° visual and memory saccades from one control and lesion experiment with monkey LBZ is shown in Fig. 3. Both the ipsilesional and contralesional (visual and memory) saccades increased in latency in this experiment, but the impairment was more severe for contralesional saccades. In this case the average latencies were (lesion vs. control, in ms) ipsilesional visual, 210 versus 198 m; contralesional visual, 241 versus 202 ms [ANOVA for interaction: $F(1, 859) = 14.8$, $P < 0.001$]; ipsilesional memory, 224 versus 197 ms; contralesional memory, 281 versus 209 ms [ANOVA for interaction: $F(1, 634) = 21.2$, $P < 0.001$]. Table 3 lists the average change of latency (lesion minus control, in ms) for contralesional and ipsilesional saccades for both monkeys. The latency change was computed

TABLE 3. *Change in latency*

	Monkey LBZ, ms			Monkey MRS, ms		
Amplitude, deg	Contralesional	Ipsilesional	Number of lesions	Contralesional	Ipsilesional	Number of lesions
			Memory saccade			
7	43 ± 12	18 ± 16	7	28 ± 19	8 ± 21	4
10	35 ± 21	9 ± 13	10	42 ± 14	12 ± 14	6
12	52 ± 23	20 ± 17	7	35 ± 20	10 ± 29	4
15	56 ± 29	16 ± 10	14	40 ± 21	23 ± 24	6
18	51 ± 18	15 ± 15	7	49 ± 24	20 ± 28	4
20	59 ± 29	11 ± 18	10	40 ± 26	12 ± 12	6
Average	50 ± 23	14 ± 14		39 ± 21	14 ± 20	
			Visual saccade			
7	28 ± 20	−1 ± 12	4	35 ± 11	7 ± 19	4
10	34 ± 19	6 ± 10	7	33 ± 23	9 ± 14	4
12	36 ± 28	0 ± 23	4	40 ± 13	1 ± 15	4
15	35 ± 9	9 ± 8	9	42 ± 12	2 ± 19	4
18	35 ± 22	2 ± 20	4	39 ± 8	11 ± 21	4
20	43 ± 23	7 ± 21	7	34 ± 19	19 ± 20	4
Average	36 ± 19	5 ± 15		37 ± 14	8 ± 18	

Values are means ± SD and listed according to saccade amplitude.

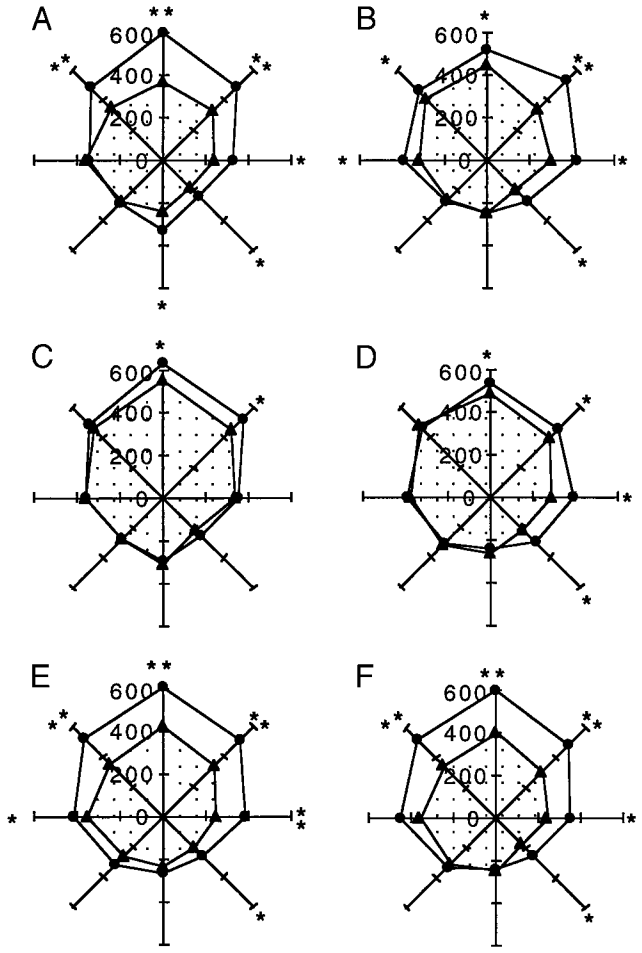

FIG. 4. The effect on saccade peak velocity after area LIP lesions. Data were taken from 6 different experiments on memory saccades with muscimol injected at different coordinates in the left hemisphere. All but 1 experiment used 15° saccades. The velocities of the saccades in 8 different directions are organized in a polar plot, with their values represented by the distance from the center. Control data were blank, and lesion data were stippled. It can be seen that the contralesional (right side of plot) and upward saccades are affected in most cases. *: $P < 0.01$; **: $P < 0.001$.

for each experimental session and averaged across all experiments. The latency of the upward saccades also significantly increased (average increase of latency: monkey LBZ, visual, 39 ms, and memory, 49 ms; monkey MRS, visual, 31 ms, and memory, 52 ms), whereas that of downward saccades remained statistically the same.

Velocity

Figure 4 shows the results of six experiments at different injection sites in the left hemisphere of monkey LBZ in which the peak velocities for memory saccades toward the contralesional and upper space decreased. Similar results were obtained from injections in the right hemisphere of monkey LBZ and from monkey MRS. Figure 5, *A* and *B*, plots the main sequences of the relationship between the peak velocity and saccade amplitude for contralesional and ipsilesional saccades, respectively, for one experiment in the memory saccade task from monkey LBZ. The peak velocities of saccades obtained in the lesion experiment were generally lower than those of the control. On the other hand, the velocities of visual saccades remained unchanged after muscimol lesion. The main sequences for visual saccades from one experiment are shown in Fig. 5, *C* (contralesional) and *D* (ipsilesional). These data were obtained on the same day as were those for memory saccades. In a further analysis we compared the velocities of both visual and memory saccades for three different amplitudes (7, 12, and 18°) between the control and lesion data. Data were combined with horizontal saccades, whose amplitudes were approximately of these magnitudes (≤0.2°), from all of the experiments. It was found that for all the three amplitudes the velocity of memory saccades was significantly reduced after muscimol lesion. These results are shown in Table 4.

Duration

Figure 6 plots the main sequences of saccade duration with respect to the saccade amplitude for both visual and memory saccades for the same set of control and lesion data shown in Fig. 5 for saccade velocity. Similar to the velocity data, the duration increased with the amplitude of the saccade but appeared to show a greater variance. This relationship remained relatively intact after muscimol injection. We compared the duration of the same set of data (horizontal saccades of 7, 12, and 18° of amplitude) that was used for the comparison of velocity. The results are shown in Table 5. It could be seen that

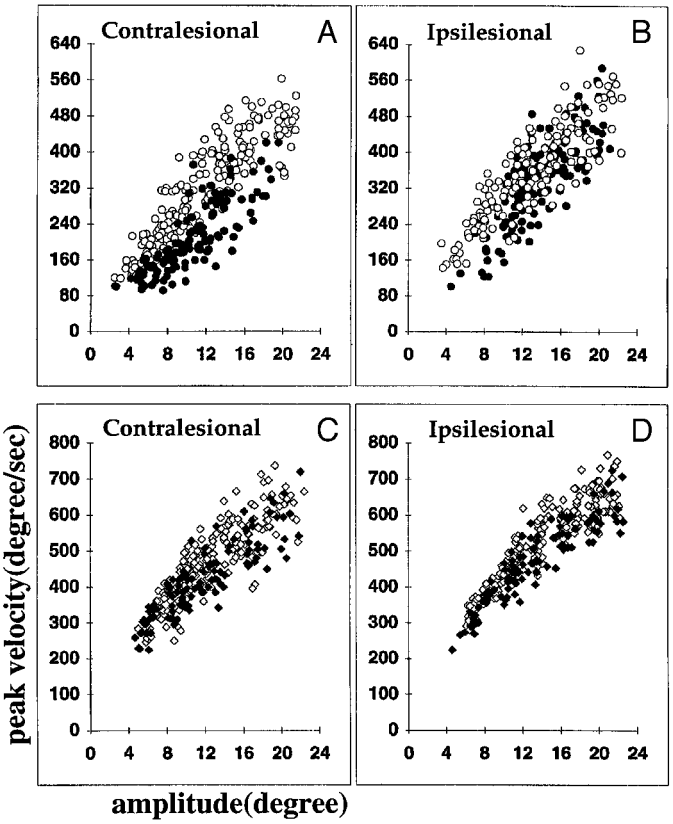

FIG. 5. The main sequences of the relationship of peak velocity vs. amplitude for both visual and memory saccades from an experiment with monkey LBZ. The ○ and ◇: control data; ● and ◆: lesion data. ○ and ●: memory saccades (*A* and *B*). ◇ and ◆: visual saccades (*C* and *D*). After muscimol injection, the contralesional memory saccades (*A*) are reduced in velocity, whereas those of ipsilesional saccades and visual saccades in both directions did not seem to be impaired. Vertical scales are different for visual and memory saccades.

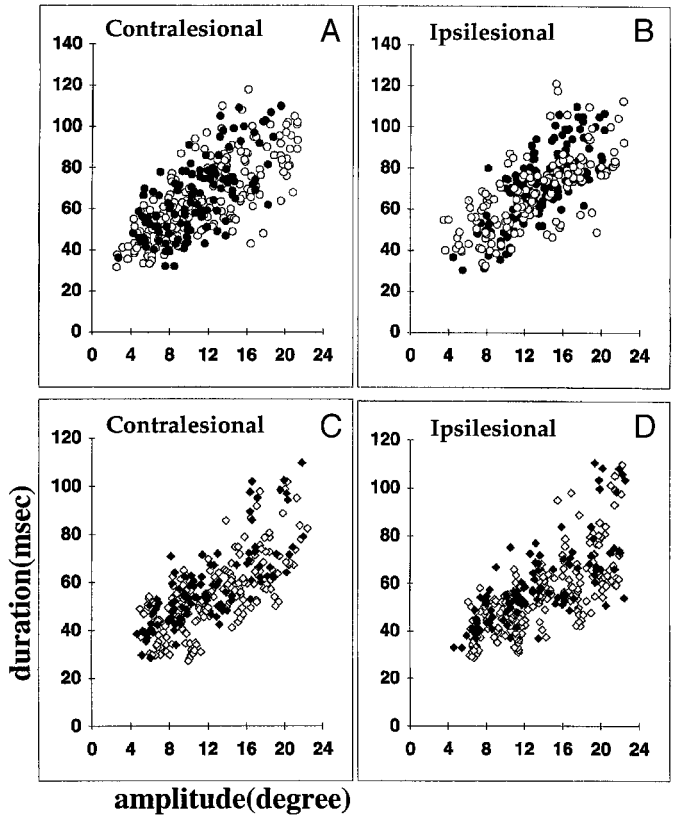

FIG. 6. The main sequences of the relationship of saccade duration vs. amplitude. Data were taken from the same set of data as shown in Fig. 5. The saccade duration increases with the amplitude, but the scatter is greater than that of peak velocity vs. amplitude. This relationship appears to remain intact for both visual and memory saccades after muscimol lesions. Convention for the symbols is the same as in Fig. 5. See text for statistics and further explanation.

for both visual and memory saccades the duration in general remained unchanged.

Neurological testing for attention and other visuomotor functions

Overt spatial neglect during the period of muscimol action was tested by bringing a piece of apple to the monkey from various directions. The monkey was sitting in a primate chair, secured only by a chest plate across and over his shoulders. No head restraint was imposed, so the monkey was free to turn his head to either side. No overt spatial neglect as a result of muscimol lesion was observed; the monkeys were able to fixate on the apple, visually track it often by using combined head and eye movements, and grasp the apple when it came within reaching distance. This was the case when the apple was presented in the contralesional space and moved in the ipsilesional direction across the midline or vice versa. Testing was done in both the near peripersonal and far space, and similar results were obtained. Presentation of a piece of apple in the peribuccal space (both ipsilesional and contralesional side) evoked precise mouth-grasping movements.

Although no overt spatial neglect was observed, the monkeys did display extinction of contralesional visual stimuli after muscimol lesion. In a behavioral paradigm in which targets were presented on both sides of the fixation the monkeys almost always made a saccade to the ipsilesional target and ignored the contralateral stimulus (Li and Andersen 1997). Such results were in agreement with the findings in monkeys whose posterior parietal cortices were chronically lesioned (Lynch and McLaren 1989). Details of this experiment will be reported in another study.

No somatomotor neglect was observed after the injection of muscimol, as was evidenced by the monkeys' ability to scratch themselves vigorously on either side of their bodies (scratching could easily be initiated by spraying some water onto their bodies) and their ability to reach and grasp a piece of apple presented to them with either hand. Their power grip was also normal as they could firmly grasp and pull the experimenter's finger. The monkeys also did not show any impairment of prehension. They were able to preshape their hand by effectively opposing the fingers when they reached for an object, usually a peanut or a small piece of apple or carrot.

Smooth pursuit eye movements were not tested systematically, but informal examination at many times showed that the animals were able to follow a piece of food in the experimenter's hand smoothly across different parts of the space. Also the monkeys were able to pursue the object no matter where the movement was initiated or in what direction it was moving. No abnormal body postures appeared to be present. Overall, other

TABLE 4. *Saccade peak velocity*

	Monkey LBZ					Monkey MRS			
	Contralesional		Ipsilesional			Contralesional		Ipsilesional	
Amplitude, deg	Control	Lesion	Control	Lesion	Amplitude, deg	Control	Lesion	Control	Lesion
				Memory saccade					
7	212 ± 40	156 ± 24*	234 ± 48	219 ± 33	7	222 ± 42	176 ± 33*	216 ± 40	222 ± 61
12	371 ± 62	296 ± 48*	390 ± 67	405 ± 60	12	384 ± 52	315 ± 78*	378 ± 81	379 ± 72
18	550 ± 84	411 ± 67*	581 ± 53	590 ± 82	18	562 ± 57	436 ± 79*	560 ± 76	556 ± 53
				Visual saccade					
7	240 ± 39	229 ± 54	245 ± 45	251 ± 47	7	248 ± 43	231 ± 77	250 ± 51	239 ± 73
12	382 ± 56	375 ± 27	393 ± 51	387 ± 66	12	389 ± 53	379 ± 67	380 ± 44	388 ± 69
18	606 ± 73	583 ± 96	620 ± 49	609 ± 78	18	610 ± 69	606 ± 64	621 ± 68	630 ± 68

Values are means ± SD. * $P < 0.001$.

TABLE 5. *Saccade duration*

	Monkey LBZ					Monkey MRS			
	Contralesional		Ipsilesional			Contralesional		Ipsilesional	
Amplitude, deg	Control	Lesion	Control	Lesion	Amplitude, deg	Control	Lesion	Control	Lesion
					Memory saccade				
7	44 ± 11	49 ± 14	42 ± 14	44 ± 18	7	42 ± 17	46 ± 12	45 ± 13	49 ± 10
12	61 ± 20	66 ± 17	55 ± 15	62 ± 13	12	63 ± 22	62 ± 23	59 ± 18	65 ± 25
18	78 ± 29	85 ± 33	78 ± 28	85 ± 34	18	78 ± 18	82 ± 26	76 ± 24	84 ± 36
					Visual saccade				
7	40 ± 12	42 ± 11	42 ± 9	39 ± 10	7	39 ± 8	43 ± 15	40 ± 14	41 ± 13
12	58 ± 16	57 ± 17	55 ± 12	54 ± 13	12	59 ± 20	61 ± 18	58 ± 27	62 ± 22
18	76 ± 20	79 ± 21	78 ± 19	74 ± 22	18	80 ± 31	79 ± 33	81 ± 34	86 ± 37

Values are means ± SD. * $P < 0.001$.

than the oculomotor deficits resulting from the muscimol lesion, the monkeys did not at any time during the experiment exhibit any overt signs of other motor deficits. However, it must be emphasized that careful measurements are needed to determine if quantitative changes in these behaviors might have resulted from LIP lesions.

DISCUSSION

Recordings from area LIP

Unit recordings from area LIP with a memory saccade task demonstrate that this extrastriate visual area contains visual, memory, and saccade-related activities (Andersen et al. 1990; Barash et al. 1991a,b). Most of the saccade-related activities are presaccadic in nature, in contrast to area 7a, where these activities are mostly postsaccadic (Barash et al. 1991a). Spatial tuning of the saccade-related activities of area LIP cells is typically broad, with a bandwidth of ~90° (Barash et al. 1991b). The memory activities in the delay period, in which the monkey was instructed to withhold his response, were shown in other studies to reflect the intended movement (Barash et al. 1991b; Bracewell et al. 1996; Gnadt and Andersen 1988; Mazzoni et al. 1996a). It was demonstrated in these studies that the visual receptive fields, memory, and motor fields of LIP neurons usually overlapped, and more importantly a majority of LIP neurons had little or no activity for the visual targets during delay periods if the task did not require eye movements into their motor fields (Andersen 1995). It was further shown in a more recent study in which the eye and reaching movements were dissociated that the delay period motor intention activities observed for most LIP neurons were specific to eye movement planning (Snyder et al. 1997). Such activities for motor intention were also demonstrated for auditory saccades (Mazzoni et al. 1996b), which lends further support to the view that the activity in the delay period for a majority of LIP neurons is not related to visual sensory memory but rather related to movement planning. Platt and Glimcher (1997) have shown that, although visual stimuli are represented in LIP, attention to a target for an instruction does not enhance the response of LIP cells, but selection of a target for an eye movement does. These results are again consistent with area LIP playing a distinct role in the planning of saccades.

Overall, results from research along different lines support the view that area LIP is functionally situated between sensory and motor cortex. Thus this area is involved in encoding spatial locations through distributed activities over a population of cells (Andersen 1995). Also the activities related to intended movements represent an intermediate stage of the sensorimotor pathway in which the sensory signals go "over the hump" to become intentions and plans to make movement (Andersen 1995).

Overview of the effects of area LIP lesion

After the injection of muscimol into area LIP, we showed that both the metrics and dynamics of saccadic eye movements were affected. The effect on metrics was mainly a reduction of the amplitude of contralesional and upward memory saccades. The latencies of both the visual and memory saccades directed to the contralesional and upper space increased, and the velocities of the memory saccades decreased when compared with controls. These results were spatially selective and consistent across many individual lesion experiments in different monkeys; thus they could not be explained by some daily variation of performance or other effects such as fatigue or a general decrease of arousal.

The effects on oculomotor behaviors obtained in this study generally agree with those that were observed after chronic lesion of the posterior parietal lobe in humans and nonhuman primates (Braun et al. 1992; Lynch and McLaren 1989; Nagel-Leiby et al. 1990). They were also similar in quality to the results seen after the FEF or SC was inactivated, although the effects obtained after lesioning of these two structures were in general more severe (Dias et al. 1995; Hikosaka and Wurtz 1986; Sommer and Tehovnik 1997). On the other hand, our results did not show a clear topography in the deficits of the saccadic eye movements, as was demonstrated for the SC (Hikosaka and Wurtz 1986; Lee et al. 1988), although for some lesions the effect seemed primarily to be restricted to a particular quadrant in the contralesional space. Instead, all saccades to the contralesional space were affected most of the time after lesioning of area LIP. This finding is consistent with the recording data that show that there is at best a rough topography in this area (Andersen et al. 1990; Blatt et al. 1990). In many cases the upper visual space was involved along with the

contralesional field, in that the latencies for the upward saccades were increased and the amplitudes and the velocities of the upward memory saccades were reduced. Consistent with this latter finding is our previous demonstration from unit recordings and a microstimulation study that there is a representational bias of the upper visual space in area LIP (Li and Andersen 1994; Thier and Andersen 1996). This finding might be related to the functional asymmetry of the different parts of the visual space. It was suggested that the upper visual space is more related to visual scanning and saccadic exploration, whereas the lower visual field is more relevant to visually guided arm and hand movements (Previc 1990).

That both the metrics and dynamics of saccadic eye movements are affected after lesioning of area LIP is consistent with its role in integrating location information for movement planning. Because area LIP is involved in encoding target locations, inactivation of this area would result in some aberrant spatial signals being relayed to other oculomotor structures and hence disrupt saccade metrics. On the other hand, it appears that the information about saccade metrics is probably also registered in other structures (most likely the SC), resulting in only a modest effect. Other evidence suggests that movement planning or other cognitive factors might alter the characteristics of saccade dynamics (Ebisawa 1995; Enright and Hendriks 1995; Epelboim et al. 1994). It was found, for example, that the main sequences of saccades obtained while subjects were reading meaningful sentences differed from those obtained from reading strings of symbols matched in structural complexity (Ebisawa 1995). The peak velocities of saccades were higher and the durations were shorter in the former than in the latter condition. These studies demonstrated that eye movement dynamics could be altered by the cognitive or visuomotor strategies employed by subjects in a behavioral task.

The impairment of the latency for visual and memory saccades is also consistent with studies showing that the initiation of a saccade is an elaborate decision process (Carpenter 1988), presumably involving target selection and motor triggering. It was argued that the delay in initiating a saccade has to do with the task of deciding where to look, given that we are constantly surrounded with a wide variety of objects. It thus seems that the result of increased saccade latency after lesioning of area LIP lends further support to the view that area LIP is involved in the decision process of making a saccadic eye movement (Shadlen and Newsome 1996).

The results obtained from this study suggest that area LIP is not simply involved in processing sensory information, as are many early visual areas. Lesioning of area LIP did not create perceptual scotomas; after lesioning of area LIP the monkeys were still able to see the stimulus in the contralesional field and could successfully make saccadic eye movements to visible targets with no loss in accuracy.

Area LIP contrasted with other oculomotor areas

Lesioning of either the SC or the FEF appears to result in larger deficits than those obtained in the lesioning of area LIP. It was shown that after reversible inactivation of the SC the saccades directed to the affected movement field were hypometric, reduced in velocity, and usually increased in latency. Similar results were obtained for visual and memory saccades, but there was a greater impairment in the accuracy of memory saccades (Hikosaka and Wurtz 1985, 1986). Chronic ablation of the FEF resulted in impairment in learning memory saccades (Deng et al. 1987). Acute inactivation of the FEF also produced severe effects on both the visual and memory saccades (Dias et al. 1995; see also Sommer and Tehovnik 1997). After FEF lesions the monkey tended to look to the ipsilesional side of the fixation target, and both the accuracy and latency of visual and memory saccades were impaired.

Anatomically, unlike the FEF, SEF, or SC, area LIP does not project directly to the identified mesencephalic or pontine premotor structures for eye movements (Huerta and Kaas 1990; Huerta et al. 1986, 1987; Leichnetz et al. 1984a,b; Sparks and Hartwich-Young 1989; Stanton et al. 1988). The projection from area LIP to eye movement structures is mainly restricted to the lateral basilar pons, the FEF, and the SC (Leichnetz et al. 1984a,b; Weber and Yin 1984). Physiological studies further illustrated the functional differences between these oculomotor areas. Electrical microstimulation of area LIP evoked eye movements at higher threshold compared with FEF or SC (Bruce et al. 1985; Kurylo and Skavenski 1991; Robinson 1969; Shibutani et al. 1984; Thier and Andersen 1996), suggesting that area LIP might be more removed from the motor neurons than these other structures. Furthermore, lesioning of the SC along with neighboring projection fibers from the FEF silenced the effects of stimulation of the posterior parietal lobe (Keating and Gooley 1988b). This and other studies suggest that eye movement signals from area LIP are primarily relayed through the FEF, SEF, and/or SC before they reach the premotor circuitry in the brain stem (Keating and Gooley 1988a; Schiller et al. 1980). Thus after area LIP is lesioned these other structures likely have access to signals required for initiating saccadic eye movements, rendering the effects of lesioning smaller, compared with those observed when FEF and/or SC are directly lesioned.

In summary, the results obtained in this study provide further evidence that area LIP is involved in processing saccadic eye movements. That lesioning of this area results in greater impairment of memory saccades is consistent with a more cognitive role of area LIP in processsing visual signals for the purpose of making saccades.

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