MACAQUE LATERAL INTRAPARIETAL AREA AND OCULOMOTOR BEHAVIORS

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ABSTRACT

Neurons in the primate lateral intraparietal area(area LIP) carry visual, saccade-related and eye position activities. The visual and saccade activities are anchored in a retinotopic framework and the overall response magnitude is modulated by eye position. It was proposed that the modulation by eye position might be the basis of a distributed coding of target locations in a head-centered space. Other recording studies demonstrated that area LIP is involved in oculomotor planning. These results overall suggest that area LIP transforms sensory information for motor functions. In this thesis I further explore the role of area LIP in processing saccadic eye movements by observing the effects of reversible inactivation of this area. Macaque monkeys were trained to do visually guided and memory saccades and a double saccade task to examine the use of eye position signal. Finally, by intermixing visual saccades with trials in which two targets were presented at opposite sides of the fixation point, I examined the behavior of visual extinction.

In chapter 2, I will show that lesion of area LIP results in increased latency of contralesional visual and memory saccades. Contralesional memory saccades are also hypometric and slower in velocity. Moreover, the impairment of memory saccades does not vary with the duration of the delay period. This suggests that the oculomotor deficits observed after inactivation of area LIP is not due to the disruption of spatial memory.

In chapter 3, I will show that lesion of area LIP does not severely affect the processing of spontaneous eye movement. However, the monkeys made fewer contralesional saccades and tended to confine their gaze to the ipsilesional field after inactivation of area LIP. On the other hand, lesion of area LIP results in extinction of the contralesional stimulus. When the initial fixation position was varied so that the retinal and spatial locations of the targets could be dissociated, it was found that the extinction behavior could best be described in a head-centered coordinate.

In chapter 4, I will show that inactivation of area LIP disrupts the use of eye position signal to compute the second movement correctly in the double saccade task. If the first saccade steps into the contralesional field, the error rate and latency of the second saccade are both increased. Furthermore, the direction of the first eye movement largely does not have any effect on the impairment of the second saccade. I will argue that this study provides important evidence that the extraretinal signal used for saccadic localization is eye position rather than a displacement vector.

In chapter 5, I will demonstrate that in parietal monkeys the eye drifts toward the lesion side at the end of the memory saccade in darkness. This result suggests that the eye position activity in the posterior parietal cortex is active in nature and subserves gaze holding.

Overall, these results further support the view that area LIP neurons encode spatial locations in a craniotopic framework and is involved in processing voluntary eye movements.

Contents

CHAPTER ONE

INTRODUCTION

A Brief History of the Posterior Parietal Lobe and the "Posterior Parietal Syndrome"

Modern conceptions of the function of the posterior parietal cortex(PPC) started with David Ferrier's well-known mistake(Glickstein, 1985; Hyvärinen, 1982) in the 1890's. Ferrier went on to stimulate other parts of the monkey's brain after confirming Fritz and Hitsig's discovery that electrically stimulating the pre-central gyrus of the dog led to movements of the contralateral limbs(Stein, 1991). When he stimulated the posterior part of the parietal lobe he found that the animal's eyes deviated contralaterally, and when he cauterized this area the animal behaved as if it was blind; so Ferrier concluded that the PPC contained the primary visual centers of the brain. This contradicted an earlier study of Herman Munk, who had then reported that the occipital, not the parietal, lobe housed the visual centers(Stein, 1991). As was pointed out by Glickstein, Ferrier's mistake was probably a result of lack of asepsis in surgery(Glickstein, 1985). After he was introduced to asceptic surgery, he was able to observe his animals for a much longer period of time and came to the conclusion that Munk had arrived at. On the other hand, he found that parietal lesion resulted in only apparent loss of vision temporarily but continued to cause poor reaching.

Eye movements were elicited by electrical stimulation of the parietal lobe by several other people later(see Hyvärinen, 1982, for a review).

Reszo Balint provided the first detailed account of a variety of visuomotor abnormalities due to posterior parietal lesion(Balint, 1909; Stein, 1991). His patient was shown in autopsy to have bilateral lesions in the posterior parietal lobes. Three major symptoms were noted in Balint's patient: first, impaired visual guidance of movement, which Blint termed optic ataxia - the patient was unable to direct his hand to visually presented object; second, psychic paralysis of gaze - the subject had great difficulty moving his eyes from one place to another, and this disturbance was particularly grave for locations in the visual periphery; third, difficulty in spatial attention - the patient could only attend to the space on the right most of the time. Together, these behavioral deficits are nowadays known as Balint's syndrome. Following Balint, Holmes described six patients with disturbances in visual orientation following gunshot wounds that involved bilateral posterior parietal lobes(Holmes, 1918). The patients were disoriented, missed visual targets when reaching out for them, and were unable to find their way around and judged where they were in relation to surrounding objects. Holmes concluded that the damage to the inferior parietal lobule disrupting the association pathway connecting the occipital visual areas with the rest of the brain might account for these behavioral deficits(Stein, 1991). Finally, Gerstmann described in 1924 a patient with lesion in the left angular gyrus. Among other symptoms, the deficits related to finger agnosia and right/left confusion observed in this patient suggested for the first time that, other than a representation of the external space, the functions of the PPC might also include a spatial schema of one's own body. In other words, the PPC might contain the neural substrate for the behaviors in the peripersonal space(Stein, 1991). The studies by Denny-Brown et al. documented the phenomenon of visual extinction in parietal lesions(Denn-Brown et al., 1952).

Later studies revealed a myriad of symptoms in humans with parietal lesions and to a large extent confirmed Balint's original findings(see Lynch, 1980; Hyvärinen, 1982; Andersen, 1987, for reviews). These behavioral deficits could be subsumed under two general categories: visuomotor impairment and unitlateral neglect. The former includes defective eye and limb movement under visual guidance.

Deficits in eye movement could include fixity of gaze, slowness in moving gaze from one direction to another and inability to maintain gaze in the contralesional(mostly left) space. Abnormal visual search pattern could also be conspicuous; subjects would confine their gaze in the ipsilesional space most of the time. These defects in eye movements may altogether be described as ocular motor apraxia. In the reaching disturbance, the patients can not correctly reach toward a target under visual guidance. Several attemps at exploring the path around are usually required before the subjects could correctly get to the target. In most of these patients this defect has affected reaching with either hand into the contralesional hemifield during fixation of gaze. Thus the defect presumably affects a mechanism which ties the reaching movement to the visual coordinate of the target. Such disturbance has occasionally been termed "optic apraxia." On the other hand, the performance of a movement which does not require visual guidance, such as buttoning a shirt and bringing a cigarette to the mouth, could very well be spared.

Another symptom commonly encountered in parietal lesion is inattention towards the contralateral body half and visual space. Patients with a right parietal lesion often ignore the objects on the left and behave as though the left side of his body does not exist. This symptom classically is demonstrated in the line bisection and letter cancellation tasks, in which the patients choose to bisect the line to the right of the midpoint and do not pick out the letters in the left half of the workspace. The mechanism underlying unilateral neglect has long been a focus of debate. Bisiach et al. demonstrated in a scene recall task that parietal patients had difficulty recollecting the left-sided scence based on current viewpoint(Bisiach and Luzzatti, 1978). They also found that these patients neglected the left side of an image they had to reconstruct from stimuli appearing successively in time in a narrow vertical slit(Bisiach et al., 1979). These results suggest that in the parietal patients with unilateral neglect the *access* to the representation of the contralateral space is disrupted(see Bisiach and Vallar, 1988, for a review).

A Heterogeneity of Different Areas in the Posterior Parietal Lobe

Recent physiological and anatomical studies have identified many cortical areas in the macaque monkey. In particular, approximately 30 cortical areas have been identified to be primarily visual(Felleman and Van Essen, 1991). Further functional differentiation of these visual areas has been made based on the behavioral deficits observed following selective cortical lesion(Mishkin et al., 1983; Ungerleider and Mishkin, 1982). In essence, it is found that object discrimination is impaired after lesion of the temporal areas whereas responses contingent upon location information are impaired after lesion of the parietal areas. These results suggest that visual information is funneled through the striate and pre-striate areas into two different functional streams - what(ventral) and where(dorsal) pathways. The posterior parietal areas mainly mediate space perception(where pathway), while the temporal cortices process visual information for pattern perception(what pathway).

More recent works by Goodale et al. and Milner et al. suggest that the posteior parietal cortex does not just process location information, but is also intricately involved in spatial actions(Goodale et al., 1991; Milner et al., 1991). They described a patient with visual agnosia, who, despite an inability to recognize the size, shape and orientation of an object, showed accurate visual guidance of hand movement. Imaging studies revealed a lesion focus mainly in the lateral occipital area. In contrast, patients with optic ataxia as a result of parietal lesion were unable to adjust the orientation of their hand to that of a target, even though they do not overtly manifest any disturbance in space or object perception(Perenin and Vighetto, 1983; 1988).

Along with these behavioral and clinical studies, recordings in behaving primates over the last decade or so have identified many different areas in the posterior parietal lobe(Andersen et al., 1995; Colby and Duhamel, 1991; Sakata and Kusunoki, 1992; see Mountcastle, 1995, for a brief history of earlier exploration of this part of the brain).

Area 5 on the medial bank of the intraparietal sulcus projects to the dorsal premotor areas and carries visuomotor signals related to planning for reaching movement(Kalaska et al., 1983; Kalaska et al., 1990; Kalaska and Crammond, 1995). The activities of area 5 neurons are not modulated by different loads for a given direction of movement and do not differentiate between the Go and NoGo conditions(as the neurons in the premotor cortex) in a delayed movement task. These findings suggest that area 5 is involved in the processing of the information about the location of external stimuli for the guidance of limb movements(Kalaska and Crammond, 1995).

Sakata et al. found in the anterior end of the intraparietal sulcus(anterior intraparietal area, area AIP) neurons related to hand manipulation(see Sakata et al., 1995, for a review). Neurons could predominantly respond to the hand actions("motor-dominant" cells) or to the fixation of the object for manipulation("visual-dominant" cells). The motor dominant cells are activated to a specific movement both in the light and in darkness. Another group of cells are activated either when the animajs fixate or manipulate the objects and they show the same object specificity in both conditions. Furthermore, lesion of area AIP led to selective impairment of hand preshaping(Gallese et al., 1994). These results suggest that this area plays an important role in matching the pattern of hand movement to the visuospatial characteristics of the object to be manipulated. With its reciprocal connection with area F5 in the premotor cortex, area AIP is a crucial node in the cortical networks mediating visual guidance of hand actions.

The ventral intraparietal area(or area VIP), situated in the fundus of the intraparietal sulcus and connected with areas MT and MST, contains neurons activated to motion stimuli(Colby et al., 1993). The neuronal responses are directionally selective. Moreover, neurons in this area have somatosensory and visual receptive fields that are often spatially congruent. Some neurons in this area prefer ultra-near(within 5 cm of the monkey's face) visual stimuli. Such bimodal neurons have also been demonstrated in earlier studies to exist in area 7b in the anterolateral part of the intraparietal sulcus(Leinonen et al., 1979a; Leinonen and Nyman, 1979b). It is suggested that one function of area VIP may be to detect and localize visual stimuli near the face and contribute to mouth and eye/hand coordination. It is also possible that through its connection with premotor area F4, area VIP is in general important for visuomotor functions in the near peri-personal space.

Another area in the posterior parietal cortex that subserves important visuomotor functions is area PO(parietal-occipital area) in the anterior bank of the parieto-occipital sulcus(Allman and Kaas, 1976; Colby et al., 1988; Covey et al., 1983; Galletti et al., 1991; 1995). Recording studies show that area PO receives retinotopically organized inputs from striate and pre-striate areas. The upper space is represented medially and the lower space laterally, with an emphasis on the visual periphery. The findings that the visual responses of many neurons in this area are retinotopically organized and modulated by eye position suggest that this area is engaged in the encoding of the extrapersonal visual space in an egocentric framework(Galletti et al., 1991; 1995). The emphasis on the respresentation of the visual periphery suggests that area PO might be important for visually guided reaching movements using ambient vision. Indeed, a direct projection from area PO to the dorsal premotor area has recently been identified(Tanné et al., 1995).

Finally, the lateral intraparietal area(area LIP) is located in the lateral(or posterior) bank of the intraparietal sulcus(Andersen et al., 1990). Neurons in this area were found to respond to visual stimuli and saccadic eye movements. The saccade-related activities are mostly pre-saccadic(Barash et al., 1991a). Furthermore, in a memory saccade task, cells display sustained memory activity during the delay period(Barash et al., 1991b; Gnadt and Andersen, 1988). These results suggest that area LIP is another visuomotor structure in the posterior parietal lobe. We will provide a detailed overview of the anatomical connections and physiological findings of this area in the next section.

In sum, a heterogeneity of different areas in the posterior parietal lobe seems to derive spatial information from different sensory modalities and, through their projections to the premotor and motor areas, controls different sensorimotor actions. Parallel circuits for reaching and grasping movements linking the inferior parietal lobule and the premotor areas, for example, appear to be identified(Matelli et al., 1994): The VIP - area F4 pathway is involved in the control of reaching movement, and the AIP - area F5 pathway in the control of grasping movement. Both of these actions would most likely occur in the peripersonal space. On the other hand, the area LIP - FEF connection is probably involved in the oculomotor exploration of the environment in the extrapersonal space(Rizzolatti et al., 1983). More studies are required to further characterize these parallel functional pathways.

The Macaque Lateral Intraparietal Area(area LIP)

Anatomy

Area LIP was first described as the portion of the lateral bank of the intraparietal sulcus which projects to the frontal lobe(Andersen et al., 1985). This part of the brain was designated area LIP to distinguish it from the ventral intraparietal area(area VIP), which abuts area LIP's ventral border(Maunsell and Van Essen, 1983), and area 7a located on the lateral convexity of the lateral intraparietal sulcus. The anatomical distincition of area LIP from area 7a is largely based on the finding that area LIP has a heavy projection to the area 8 and the superior colliculus(SC) while area 7a does not(Andersen et al., 1985, 1990; Asanuma et al., 1985; Barbas and Mesulam, 1981; Lynch et al., 1985; Seltzer and Pandya, 1980).

Visual inputs to area LIP come from the pre-striate areas, including V3, V3A, V4, MT and DP, and probably also through connections with other parietal areas such as PO and 7a, and areas in the temporal lobe(Andersen et al., 1990; Baizer et al., 1991; Colby et al., 1988; Felleman and Van Essen, 1991).

Area LIP is reciprocally connected with many other oculomotor structures such as the frontal eye field(FEF)(Andersen et al., 1990; Blatt et al., 1990; Huerta et al., 1987a; Petrides and Pandya, 1984; Schall et al., 1995; Stanton et al., 1995), the superior colliculus(Leichnetz et al., 1984; Lynch et al., 1985), the supplementary eye field(SEF)(Andersen et al., 1990; Huerta and Kaas, 1990), and the dorsolateral prefrontal cortex(DLPFC)(Andersen et al., 1990; Blatt et al., 1990; Petrides and Pandya, 1984). It also projects heavily to the pontine nuclei in the brain stem(Glickstein et al., 1985; May and Andersen, 1986), but this pathway is seldom explored in physiological studies. Unlike the projections from the FEF(Huerta et al., 1987a, 1987b), the SEF(Huerta and Kaas, 1990; Huerta et al., 1987; Shook et al., 1990; Stanton et al., 1988b) and the SC(see Sparks and Hartwich-Young, 1989, for a review), however, the projections from area LIP to the brain stem do not appear to terminate in the area where the premotor circuitry for eye movements is located(Leichnetz et al., 1984; Weber and Yin, 1984). The projection from area LIP is largely localized in an area more lateral in the pons than that from the FEF. From there onward, these two projections might converge at the level of the cerebellum(Leichnetz et al., 1984).

The posterior parietal cortex as a whole derives most of its thalamic input from the lateral posterior and pulvinar nuclei(Schmahmann and Pandya, 1990). There are differences, however, both in the sites of origin and the relative strength of projections from the different subregions of these nuclei to the superior versus the inferior parietal lobule(IPL). Overall, the thalamic connection of the mid- to caudal inferior parietal lobule is mainly with the medial and lateral pulvinar nuclei(Asanuma et al., 1985; Patrick Hardy and Lynch, 1992; Schmahmann and Pandya, 1990). A less prominent but significant input to the multimodal areas in the IPL comes from the ventral lateral(VL) nucleus. This latter connection suggests that the cerebellum may have some modulatory influences on the multimodal neuronal activities in the IPL, since the VL nucleus is known to receive inputs from a variety of areas of the cerebellum via the deep cerebellar nuclei. Other studies demonstrate that area LIP may receive a denser projection from the lateral pulvinar nucleus than area 7a, whose thalamic input is exclusively from the medial pulvinar nucleus(Asanuma et al., 1985; Patrick Hardy and Lynch, 1992). Physiological properties of these thalamic structures have largely not been explored. It is thus difficult to come up with a functional explanation for these connections.

The pattern of anatomical connections of area LIP overall suggests that it is functionally located at the interface of visual and motor areas.

Unit recording and microstimulation

Unit recordings from area LIP using the memory saccade task demonstrate that this extrastriate area contains both visual, memory and saccade-related activities(Andersen et al., 1990; Barash et al., 1991a; Barash et al., 1991b). Most of the saccade-related activities are pre-saccadic, in contrast to area 7a, where the activities are mostly post-saccadic(Barash et al., 1991a). The spatial tuning of area LIP cells is typically broad, with a 50% activity-width of approximately 90 degrees(Barash et al., 1991b). The directional tunings of visual, memory and saccade-related activities are for the majority of cells very well aligned. The amplitude tuning of area LIP neurons have not been systematically explored.

The memory activity in the delay period, in which the monkey was instructed to withdraw his response, has been shown in several studies to reflect the intended movement(Barash et al., 1991b; Bracewell et al., In press; Gnadt and Andersen, 1988; Mazzoni et al., In press). For example, in a double saccade task, in which the monkey was trained to saccade to a memorized target and then back to the original point of fixation, it was found that area LIP neurons fire contingent upon the impending eye movement(Gnadt and Andersen, 1988). In another double saccade task, in which the monkey was required to make two consecutive saccades to targets that were briefly flashed while the monkey was fixating, most LIP neurons encoded the upcoming saccade and did not carry sensory activity for the spatial location(Mazzoni et al., In press). It is demonstrated in these studies that the visual receptive fields and motor fields of area LIP neurons usually overlap, and, more importantly, most LIP neurons have little or no activity for the visual targets in their receptive fields if the task does not require eye movements into their motor fields(Andersen, 1995). Such activities for motor intention are also demonstrated for auditory saccades(Mazzoni et al., 1996). This finding lends further support to the view that the activity of area LIP neurons in the delayed period is most likely not sensory in nature. Overall, these results suggest that area LIP is involved in integrating spatial information from multiple sensory modalities for movement planning, and neuronal activities in this area are organized in motor coordinate.

Another line of research focuses on the coordinate frame of the representation of spatial locations in area LIP(Andersen et al., 1985; Andersen et al., 1990; Zipser and Andersen, 1988; see also Andersen, 1995, for a review). Recording studies of this area demonstrate that spatial locations are not represented explicitly at a single-cell level using a receptive field in space. The receptive fields of the area LIP neurons do not shift their retinal locations when the eye position changes. Rather, the visual and eye position signals interact to form "gain fields" in which the amplitude of the visual response is modulated by eye position. The location of a target in head-centered coordinate could then be determined by the activity of a population of such cells. In other words, the representation of space can be considered to be distributed in this area over many neurons. Such gain field modulation has also been demonstrated for head position signals - vestibular information and neck proprioception contribute to the formation of a body-centered space(Brotchie et al., 1995; Snyder et al., 1994; see also Andersen, 1995, for a review). Furthermore, it is shown in a study that the memory activity of area LIP neurons in a delayed auditory saccade task can be encoded in a head-centered, eye-centered or some intermediate coordinate frame(Stricanne et al., In press). The result that different coordinate frames exist in area LIP provides another evidence for the hypothesis that this area is involved in sensorimotor transformation. These results overall suggest that spatial locations are initially registered in area LIP in a craniotopic coordinate by combining retinal and eye position signals. The signals from area LIP are then relayed to different motor structures for specific motor outputs. Other studies further demonstrate that the movement fields of area LIP neurons are organized in a 3-D space and the modulation of neuronal activities by eye position may extend to the dimension of depth as well(Gnadt and Mays, 1994).

Electrical microstimulation of area LIP evokes saccadic eye movement, but at a threshold relatively higher than that in stimulating the SC and FEF(Bruce et al., 1985b; Kurylo and Skavenski, 1991; Marrocco, 1978; Robinson, 1969; Shibutani et al., 1984; Thier and Andersen et al., In press). Saccades could not be evoked by the stimulation of the PPC after the ablation of the SC(Keating et a., 1983). The dynamic characteristics of the saccades elicited are similar to those of memory saccades(Thier and Andersen, In press). The saccades evoked are typically of fixed direction but the saccade amplitude is modulated by the starting eye position. The modulation of eye position is similar to the gain field observed in recording studies(Goodman and Andersen, 1991; Thier and Andersen, In press). Therefore, the results of the microstimulation experiments provide another evidence that, with distributed activities in a population of neurons, area LIP encodes spatial locations in a head-centered coordinate.

An Overview of Other Cortical and Subcortical Saccade Areas

One important way to understand how area LIP is involved in processing saccadic eye movement is to contrast its role with those of other oculomotor areas. I will in this section provide a brief overview of some physiological and anatomical studies of these other saccade centers. Emphasis will be placed on the lesion experiments.

Superior colliculus

The intermediate and deep layers of the primate superior colliculus receive afferent projections from several cortical areas, including the frontal eye field(FEF), supplementary eye field(SEF), dorsolateral prefrontal cortex(DLPFC), and area LIP(Huerta et al., 1987a; Lynch et al., 1985; Shook et al., 1990; Stanton et al., 1988b). Output neurons in this area are topographically organized according to their movement field and project directly to the premotor circuitry in the pontine reticular formation in the brain stem. Collicular neurons are active for visually guided, self-generated and, for most of the cells, spontaneous saccades. Eletrical microstimulation of this area elicits saccadic eye movements at low threshold and with a short latency(see Sparks and Hartwich-Young, 1989, for a review).

In chronic lesion experiments, it was found that the ablation of superior colliculus produced relatively small deficits in saccadic eye movements. The frequency of spontaneous saccades decreased, saccadic reaction times increased, velocity decreased and accuracy suffered only to a modest extent (Albano and Wurtz, 1982; Mohler and Wurtz, 1977; Schiller et al., 1980; see Sparks and Hartwich-Young, 1989, for a review). During fixation of a visual target, the lesioned animal was less easily distracted by peripheral stimuli(Albano and Wurtz, 1982). Reversible inactivation of this structure, either with cooling or pharmacological agents such as lidocaine and muscimol, however, resulted in larger deficits. The saccades directed to the affected movement field were hypometric, reduced in velocity and usually increased in latency(Hikosaka and Wurtz, 1985; Hikosaka and Wurtz, 1986; Keating and Gooley, 1986). Similar results were obtained for visual and memory saccades, but there was a greater impairment in the accuracy of the memory saccades. Lee et al. demonstrated in an ingenious experiment that, after inactivation of a small area in the colliculus, the velocity of the saccades directed to the affected location was reduced and the metrics was disrupted in a way according to a weighted averaging scheme of local neuronal activities(Lee et al., 1988). Overall, these results suggest that superior colliculus is involved in processing the metrics and dynamics of both visual and memory saccades.

Striate cortex

Other than an indirect input coming through the pulvinar from the superior colliculus, area LIP receives most of its visual inputs relayed from the striate cortex(Asanuma et al., 1985; Benevento and Standage, 1983; Patrick Hardy and Lynch, 1992). Lesion of the striate cortex, either with chronic ablation or reversible inactivation, seems to affect primarily the sensory processing of the visual stimuli. Monkeys fail to detect the stimulus in the resulting scotoma or to process accurately the speed of a moving stimulus in order to initiate a correct saccade to the target(Mohler and Wurtz, 1977; Segraves et al., 1987; see also Newsome et al., 1985, for a similar effect of lesion of area MT on saccadic eye movement). Under impoverished stimulus conditions, a slight increase of the scatter of the saccade end points could be seen, but the latency remains normal, at least for those saccades made to a stationary target(Mohler and Wurtz, 1977; see also Segraves et al., 1987 for an effect on the latency of saccades to a moving stimulus).

Frontal eye field(FEF)

Frontal eye field is interconnected with area LIP, the supplementary eye field(SEF) and the dorsolateral prefrontal cortex(DLPFC), and it projects topographically to the intermediate and deep layers of the superior colliculus and the paramedian pontine reticular formation(PPRF) including omnipause cells in the brain stem(Huerta et al., 1987a and 1987b; see also Goldberg and Segraves, 1989, for a review). FEF neurons carry visual and visuomotor activities(Bruce and Goldberg, 1985a; Schall, 1991b). Electrical stimulation of this area evokes saccadic eye movement at low threshold and with a short latency(Robinson, 1969; Bruce et al., 1985b). Saccades evoked are of fixed vectors(Robinson, 1969; Bruce et al., 1985b; Russo and Bruce, 1993), the dimensions of which follow the topography of local neuronal activities.

Chronic lesion of the FEF generally produces neglect symptoms, which are demonstrated by the reduced frequency, and increased errors and latency of the saccades to localize objects in the contralesional field and a tendency to look to the ipsilesional field(Latto and Cowey, 1971; Crowne et al., 1981; Schiller et al., 1980; Van der Steen et al., 1986). Spontaneous head movements to the contralesional space are also rare, even though no tonic deviation of the eye or head is observed(Rizzolatti et al., 1983). It was shown in a head-free preparation that FEF lesion might disrupt eye-head coordination; animals were able to track objects in the contralesional space with combined eye and head movements after lesion, but failed to do so with eye alone. The finding that head movement with respect to the body was not affected suggested that the neglect phenomenon was not a simple visual field defect but an impairment in making contralesional eye movement(Van der Steen et al., 1986). Deng et al. showed that ablation of the FEF impaired learning of the memory saccade, but not visual saccade task. The memory saccades made into the contralesional field were slower in velocity and impaired in accuracy(Deng et al., 1985). In most of these studies, the behavioral deficits largely recovered within weeks.

A more recent reversible lesion study showed that, in contrast to chronic lesions, acute inactivation of the FEF produced severe effects on both the visual and memory saccades. After FEF lesions the monkey tended to look at the ipisilesional side of the fixation target, and both the accuracy and latency of visual and memory saccades were impaired(Dias et al., 1995).

On the other hand, even though isolated ablation of the superior colliculus or FEF did not lead to severe impairment of saccadic eye movements, combined lesions of these two structures resulted in dramatic deficits(Schiller et al., 1980; Keating and Gooley, 1988). Combined lesion of the SC and FEF greatly decreased the frequency of contralesional saccades, increased saccadic reaction times, reduced the range of eye movements and caused large and persistent targeting errors. And these deficits showed little recovery with time. These results suggest that there are two independent parallel pathways for oculomotor control (Schiller et al., 1980; Keating et al., 1983).

Dorsomedial frontal cortex(supplementary eye field)

The cortical and subcortical connections of the dorsomedial frontal cortex(DMFC) are similar to those of the FEF. The DMFC projects bilaterally to the superficial and intermediate layers of the superior colliculus and to the PPRF including the omnipause region(Huerta and Kaas, 1990; Huerta et al., 1987; Shook et al., 1990; Stanton et al., 1988b). The DMFC has reciprocal connections with other cortical oculomotor structures such as the FEF, DLPFC and area LIP(Huerta and Kaas, 1990). Unit recordings from the DMFC reveal presaccadic activities; it has been shown that DMFC neurons respond during self-initiated and task-related eye movements(Schlag and Schlag-Rey, 1987; Schall et al., 1991). A significant proportion of cells in this area also shows eye position activity; units increase their firing rate before the eyes move into their preferred position. The results are not consistent as to whether neurons in this area respond in a similar manner to spontaneous eye movements(Schlag and Schlag-Rey, 1985; Schall, 1991). Electrical microstimulation of this area evokes saccadic eye movements at low threshold but at a longer latency than in the FEF(Schlag and Schlag-Rey, 1987; Schall, 1991). In contrast to the FEF, saccades evoked from the SEF can converge to a relatively fixed zone of orbital position(Mitz and Goldschalk, 1989; Schall, 1991a; Schlag and Schlag-Rey, 1987) and it seems that such "convergence zones" are organized in topography and agree well with local eye position activities(Lee and Tehovnik, 1995). Furthermore, saccades are evoked even when the SC and the FEF are removed, suggesting a direct access of the DMFC to downstream oculomotor structures(Tehovnik et al., 1994). Other studies show that the DMFC is involved in oculomotor learning(Mann et al., 1988; Chen and Wise, 1995).

The literature regarding the effect of lesion of the DMFC on eye movements is relatively scanty. Clinical studies have not clearly demonstrated deficits in simple visual or memory saccades in patients with lesions in the supplementary motor area(SMA). However, these patients are impaired in making sequences of memory saccades(Gaymard et al., 1990, 1993). This finding is in agreement with other studies which show that the DMFC plays an important role in learning movment sequences(see Tehovnik, 1995, for a review; see also Tanji, 1994, for suggestion of a similar function for the supplementary motor area).

Dorsolateral prefrontal cortex

Anatomically the dorsolateral prefrontal cortex(DLPFC) is connected with the FEF, SEF, and area LIP (Huerta et al., 1987; Huerta and Kaas, 1990; Petrides and Pandya, 1984). The DLPFC projects directly to the intermediate and deep layers of the superior colliculus(Goldman and Nauta, 1976; Leichnetz et al., 1981). Single unit recordings from this area reveal cells that carry sustained activities in the delay period in the memory saccade tasks(Funahashi et al., 1989; Funahashi et al., 1991). It has been suggested that this delay activity reflects working memory of the spatial location of the target. This hypothesis is supported by the experiments using antisaccadic task, which demonstrate that the activity in the delay period is mostly coding for stimulus location(Funahashi et al., 1993).

Lesion by ablation of the DLPFC or depleting dopamine through injecting D1-antagonist in this area results in impairment of the accuracy of contralesional memory saccades, and the deficits seem to worsen when the delay period is increased (Sawaguchi and Goldman-Rakic, 1991; Funahashi et al., 1993). The latency and velocity of the memory saccades are not affected(Funahashi et al., 1993). Visually guided saccades usually remain intact after lesioning of the DLPFC(Sawaguchi and Goldman-Rakic, 1991; Funahashi et al., 1993). The result that the DLPFC is mainly involved in coding the stimulus location is also consistent with the finding that electrical microstimulation of this area fails to evoke any eye movement with current up to 150 microAmp(Boch and Goldberg, 1989).

basal ganglia

Saccade-related activities in the basal ganglia were found in the caudate nucleus and the substantia nigra pars reticulata(SNpr)(Hikosaka and Wurtz, 1983a; Hikosaka et al., 1989). Particularly prevalent in the caudate nucleus are the memory-contingent saccade-related activities. Caudate nucleus receives afferent projections from the DLPFC, FEF, SEF, and area LIP and in turns projects to the SNpr(Yeterian and Pandya, 1991 and 1993; Selemon and Goldman-Rakic, 1985; Selemon and Goldman-Rakic, 1988; Huerta et al., 1986; Huerta and Kaas, 1990; Hikosaka et al., 1993). The projection from caudate nucleus to SNpr is largely inhibitory(Hikosaka et al., 1993); the latter in turn inhibits the superior colliculus(Hikosaka and Wurtz, 1983b). Neurons in SNpr have high spontaneous discharge rate and invariably decrease their activity to a saccadic eye movement(Hikosaka and Wurtz, 1983a).

Lesion of the caudate nucleus impairs the metrics and dynamics of both visual and memory saccades(Kori et al., 1995). The latencies of contralesional memory saccades are consistently prolonged. And the amplitude and velocity decrease for contralesional visual and memory saccades. In contrast, inactivation of the SNpr results in irrepressible saccades to the contralesional visual field(Hikosaka and Wurtz, 1985b). It has been suggested that the basal ganglia contribute to the initiation of a saccade through a disinhibition mechanism(Hikosaka et al., 1989).

Aim of the Thesis Studies

The aim of this thesis is to further characterize the role of area LIP in processing saccadic eye movements. Specifically, I will show how oculomotor behaviors are impaired after inactivation of area LIP. Chapter 2 examines the effect on voluntary saccades(visual and memory saccades) and chapter 3 on spontaneous eye movement, fixation and visual extinction. The issue of how eye position signal is used to maintain spatial stability will be explored in chapter 4. And finally, evidence will be presented in chapter 5 to demonstrate that the fixation activity in the posterior parietal lobe subserves gaze holding.

CHAPTER TWO

The Effect of Area LIP Lesion on Visual and Memory Saccades

Summary

1. Previous studies from our laboratory identified a parietal eye field in the primate lateral intraparietal sulcus - the lateral intraparietal area or area LIP. Anatomically, area LIP is connected with other oculomotor structures such as the frontal eye field and superior colliculus, and physiological studies show that this area carries visual and saccade-related signals and is important for oculomotor planning. In this study we further explore the role of area LIP in processing saccadic eye movements by observing the effects of reversible inactivation of this area.

2. Muscimol, a GABAa agonist, shown in many other studies to be effective in inhibiting local neuronal activities, was used for the reversible inactivation. One to two μL's 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 to 30 minutes and disappeared after 5 to 6 hours in most cases and certainly when tested the next day.

3. 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.

4. 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 towards the upper space.

5. The peak velocities for memory saccades towards the contralesional space were decreased after muscimol injection. On the other hand, 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.

6. Varying the initial eye position does not significantly alter the effect on either the metrics or dynamics of visual and memory saccades. It thus appears that the impairment of single visual and memory saccades is best described in a retinotopic coordinate. These results, along with those obtained in a double saccade paradigm reported in a companion paper, lend further support to the hypothesis that, by combining retinal and extraretinal signals, area LIP contains both a retinotopic and a head-centered representation of the visual space.

7. Varying the delay period in the memory saccade task did not have an effect on the impairment of the saccade metrics, latency or velocity, in contrast to the observation following the lesion of the prefrontal areas that the oculomotor deficits were typically greater after a longer delay. In agreement with our previous recording results using the change of plan and double saccade tasks(Bracewell et al., In press, Mazzoni et al., In press), this result further suggests that the delayed-period activities observed in parietal

neurons probably does not reflect memory of the spatial location of the saccade target, as has been attributed for prefrontal activities.

8. Informal neurological examinations showed that the monkeys did not exhibit spatial neglect in either the far or near space. Nor did they have any motor weakness, impairment of prehension, or deficits in eye and hand tracking of hand-held objects moving in the space within reaching distance. Results of a systematic examination of visual extinction is reported in a companion paper.

9. Overall, these results demonstrated that we were able to selectively inactivate area LIP and observe its effect 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 that saccades toward the upper space were frequently involved is consistent with our unit recording data and a microstimulation study which suggested that there might exist a representational bias of the upper visual space in this area.

Introduction

It is well known that patients with lesions in the posterior parietal lobe have difficulty moving their gaze to the contralesional space(see Andersen, 1987; Lynch, 1980, for reviews). Reaction times are increased for saccades directed to the contralesional space and the velocities decreased(Braun et al., 1992; Nagel-Leiby et al., 1990; Sundqvist, 1979). Bilateral lesions of the posterior parietal lobe produced what classically is known as Balint's syndrome(Balint, 1909; Hecaen and Ajuriaguerra, 1954). In this case, the patients were not able to shift their gaze from one direction to another, a symptom which Balint 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 lesion of the posterior parietal or occipito-temporal 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 et al., 1991; Goodale and Milner, 1992). It was 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 have been observed in humans, lesions of the posterior parietal lobe in non-human primates oftentimes resulted in various attentional and visuomotor deficits(see Andersen, 1987; Lynch, 1980; Stein, 1989, for reviews). Saccades directed to the contralesional space had a longer latency and, in some cases, were transiently impaired in accuracy(Lynch and McLaren, 1989; Lynch, 1992). Other studies demonstrated deficits in reaching and grasping, that were reminiscent of what have been found in human parietal patients(Faugier-Grimaud et al., 1985; Faugier-Grimaud et al., 1978; Gallesse et al., 1994; Lamotte and Acuna, 1978; Quintana et al., 1989). These results suggested that the posterior parietal lobe might be important in integrating multiple modalities of sensory information and cognitive resources for movement planning(Andersen et al., In press).

Along with these advances in behavioral and clinical studies, neuronal recordings in behaving primates identified several distinctive areas in the posterior parietal lobe that might be important for visuomotor functions (Andersen et al, 1990a; Colby et al., 1993; Colby and Duhamel, 1991; 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; 1991b; Bracewell et al., In press; Mazzoni et al., in press; see also Andersen, 1995, for a review). It was shown in these studies that LIP neurons discharged prior to visual saccades and also to memory saccades where no visual stimulus was available. In a double saccade paradigm and a change of plan task that required oculomotor planning contingent upon instantaneous eye movements or visual cues, most LIP neurons displayed sustained memory activities only for the upcoming intended eye movements (Mazzoni et al., In press; Bracewell et al., in press). These results provide evidence that area LIP encodes motor intention for saccadic eye movements. Anatomical studies also showed that area LIP is connected with other oculomotor centers such as the frontal eye field and superior colliculus and thus constitutes an important node in the network of neural structures controling saccadic eye movements (Andersen et al., 1990a; Lynch et al., 1985).

In order to further explore how area LIP might play a role in processing saccadic eye movements, in this study we reversibly inactivated this area and examined how saccadic eye movements might be impaired. Emphasis was also placed on how the effects compared to those observed after lesions of the frontal eye field, superior colliculus and other oculomotor structures. Preliminary results of part of this work have been published in abstract form(Li et al., 1995).

Methods

Surgery and animal care

Two male rhesus monkeys weighing 3.5 to 6.5 kg were used in this study. During the period of training and experiments, the monkeys were restricted from water 5 days a week and worked for fluid until they were satisfied. The animals had unlimited access to water supply during the weekend and their water intake was carefully monitored during working days to make sure that the animals were not overly dehydrated. NIH guidelines for the care and use of animals were closely followed.

Prior to 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 Nembutal anaesthesia. Systemic antibiotics were administered before and after the surgery and the monkeys were allowed full rest for at least a week after surgery.

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 deg 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 msec in experimental sessions. Light spots were 0.5 deg in diameter and 45 cd/m^2 in luminance, 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 instead later on in the experiments.

In the visual saccade task, the monkey fixated on a light spot straight ahead for 1200 msec and was required to make a saccadic eye movement within a time window of 350 msec 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 msec within a space window of 8 deg 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 in three concentric circles of different radii(either 7, 12, 18 degrees or 10, 15, and 20 degrees) and in eight different directions(in spacings of 45 degrees), centered on the fixation point. Training for the fixation and visual saccade tasks was completed within a week, after which the monkeys generally performed at a 90% HIT rate with no more than a 15% MISS rate. See below for a definition of HIT and MISS trials.

The monkeys were next trained for the memory saccade task. In this task, while the monkey was fixating straight ahead, a light spot was flashed briefly (100 msec) at one of the 8 or 24 locations, and, when the fixation point went off after a delay of 950 msec, he was required to initiate a saccadic eye movement within 450 msec to the location where the target had appeared before. In a second version of this memory saccade task, 3 different delays(200, 600 and 1,200 msec) were used and randomized in the presentation. When a variable delay was introduced in the memory saccade task, the amplitude of saccade was fixed to 15 degrees. The spatial window for peripheral target is 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 is a circle of 8 degrees in diameter for 7-degree saccades; 10 for 10-degree saccades; 14 for 12-degree saccades; 18 for both 15- and 18-degree saccades; and 20 for 20-degree 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 to 4 weeks to complete. Both the training and experiments were carried out in otherwise total darkness in a room in which noise was significantly reduced. The room light was turned on periodically (typically every 5 minutes) to prevent the monkey from becoming dark adapted or drowsy.

We also varied the initial eye position for both the visual and memory saccade tasks in order to explore the reference framework of the behavioral impairment. Three different eye positions on the horizontal axis were tested, (-10, 0), (0,0), (10,0), and saccade amplitude was fixed at 15 degrees in this task.

Monkeys usually performed 1,000 to 1,500 trials in each session daily, in a period of 4 to 6 hours. They were generally given a short break of 5 to 10 minutes 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 at stimuli presented at nine different locations, typically 20 degrees 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 seconds and a trial was declared to start if he continued to fixate for another 300 msec. Failure to acquire the fixation point or to fulfill the initial stay at the fixation light for the criteria duration was regarded as a "MISS", and the trial was aborted and a new trial started over again. No data was collected in this case. When the monkey succeeded in acquiring fixation, if he 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, either because he broke fixation shortly after he acquired fixation, did not initiate a saccade within the preset time window, or failed to land on the target correctly. The data of the ERROR trials were collected up to the point the error occurred and the trial ended.

Recording and reversible lesion

Both glass-coated platinum-iridium and the commercial vinyl-coated tungsten electrodes, with impedence of 1-2 MegaOhm at 1K Hz, were used for the recordings. The electrodes were advanced through the dura with a guide tube with a resolution of 1 μM in depth. The electrode penetrations could be spaced with approximately a 1mm resolution on both the x and y axes for both microdrives. Electrical signals were fed into an amplifier and single units were isolated with a variable-delay window discriminator. Prior to the lesion experiments, recordings were carried out for a period of 2 to 6 months 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 stimuli in the medial bank of the intraparietal sulcus, and unit activities responding to motion stimuli deep in the sulcus(Johnson et al., 1993; Colby et al., 1993).

We used muscimol (Sigma, St. Louis, Missouri), a GABAa agonist, for the reversible lesion. The solution was made of 1 mg of muscimol in 125 μL's 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 μL of muscimol was used. The maximum amount of muscimol used at one time was 3 μL's and no more than 2 μL's 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 killed 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. Fifty-micron-thick sections of the brain were cut and stained with neurtral red for cytoarchitecture. Figure 1 shows a section of the brain that contains the intraparietal sulcus. 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. Performances during the days where no injection was made or normal saline was used served as controls. Data collected for muscimol experiments were compared with the control data pooled from those obtained one day before and after the lesion.

Trials with saccade latency shorter than 100 msec were most likely a result of anticipation and excluded from further analysis. The number of trials excluded comprised no more than 0.5% for monkey LBZ and 1% for monkey MRS of the total number of trials collected in each block.

The saccade amplitude was computed by subtracting the starting point from the end point of a saccade. The saccade beginning was defined as the time at which the velocity increased to more than 20 deg/sec and the saccade end when the velocity decreased to below 50 deg/sec. 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 using a two point differencing mechanism with a temporal spacing of 2 msec(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 of monkey LBZ and 6 lesions in one hemisphere of monkey MRS. Saccade amplitudes of 15 degrees and of a combination of 10, 15, and 20 degrees were routinely tested for both visual and memory saccade tasks. For several sessions, amplitudes of 7, 12 and 18 degrees were also tested. Since 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.

General performance

General performances of the two monkeys in terms of the MISS and ERROR rates for the visual saccade task were not different following the injection of muscimol compared to the controls. In the memory saccade tasks, however, 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 irreppressible 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. Data were taken from all lesion experiments with visual and memory saccades and their corresponding controls throughout the experiment.

In the following 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 to 30 minutes(85 minutes in one case with monkey LBZ) and disappeared within 5 to 6 hours in most 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 or directional dependence. In monkey MRS, ipsilateral saccades were also significantly hypermetric compared to the controls. In other words, the end points of memory saccades in all directions were shifted to the ipsilesional side, though to different degrees. The trajectories of the memory saccades otherwise appeared to be indistinguishable from those of the controls in most experiments. On the other hand, the metrics of the visual saccades were relatively intact. Figure 2 shows the eye traces for 15-deg visual and memory saccades taken from one typical set of experiment 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 scatter of the end points of the memory saccades were also larger after muscimol lesion. Figure 3 shows in x-y plots the average shift of the end points for 15-degree memory saccades across all lesion experiments for both monkey LBZ and MRS. Data were averaged from 14 lesions in monkey LBZ and 6 lesions in monkey MRS. Data for monkey LBZ were organized as if all lesions were done in the left hemisphere. Except for the saccade directed to the lower left in monkey LBZ, the change in amplitude for all other saccade directions is significant($p<0.01$ for all cases). For both monkeys, in many cases (6 out of 9 injection sites for monkey LBZ and 3 out of 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 denotes a 15% reduction in amplitude. The results were averaged across all sessions and 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. Even though 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 saccades directed to the upper space. A typical set of data of 15-deg visual and memory saccades from one control and lesion experiment with monkey LBZ is shown in Figure 4. 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 msec): ipsil. visual, 210 vs. 198 mec; contral. visual, 241 vs. 202 msec(ANOVA for interaction: $F(1, 859)=14.8$, $p<0.001$); ipsil. memory, 224 vs. 197 msec; contral. memory, 281 vs. 209 msec(ANOVA for interaction: $F(1, 634)=21.2$, $p<0.001$). Table 3 lists the average change of latency(lesion minus control) for contralesional and ipsilesional saccades for both monkeys. The latency change was computed for each experimental session and averaged across all experiments. Grouping of the data into upward and downward saccades(saccades with an upward and downward vertical component, respectively) showed that the latency of the upward saccades also significantly increased(average increase of latency: monkey LBZ, visual, 39 msec, and memory, 49 msec; monkey MRS, visual, 31 msec, and memory, 52 msec). In this analysis downward saccades also showed a significant increase in latency, but this was primarily due to the saccades with a contralesional horizontal component.

Velocity

Figure 5 shows the results of 6 experiments at different injection sites in the left hemispheres of monkey LBZ, in which the velocities for memory saccades toward the contralesional and upper space decreased. Similar results were obtained from monkey MRS. The reduction remained when velocities were compared between saccades with similar amplitudes. Figure 6(A, B) plots the main sequence 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. Note that the peak velocity of saccades increased with the amplitude and the velocities of saccades obtained in 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 sequence for visual saccades from one experiment with monkey LBZ was shown in C(contralesional) and D(ipsilesional). These data were obtained on the same day as those for memory saccades. We compared the velocities of both visual and memory saccades for three different amplitudes(7, 12, 18 degress) between the control and lesion data. Data were combined using horizontal saccades, whose amplitudes were approximately of these magnitudes(within 0.2 degrees), from all of the experiments. It was found that for all the three amplitudes, the velocity of memory saccades were significantly reduced after muscimol lesion. These results are shown in Table 4.

Duration

Figure 7 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 Figure 6 for saccade velocity above. Similarly, 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 degrees of amplitude) that was used for the comparison of velocity, and the results are shown in Table 5. It can be seen that, for both visual and memory saccades, the duration in general remained unchanged.

The effect of initial eye position

The results of varying the initial eye position in both the visual and memory saccade tasks are shown in Table 6 for both monkeys. Data were taken from 4 different lesions in monkey LBZ and 3 lesions in monkey MRS. Since results were only obtained using only one saccade amplitude, we were not able to determine the main sequence of peak velocity vs. amplitude. The gain of saccade amplitude compared to the control was calculated for each individual saccade direction in each lesion experiment and the results were averaged for contralesional and ipsilesional saccades in a given lesion experiment. The results shown are averages of gain change across all lesions for different eye positions. The saccade latencies are averages for contralesional and ipsilesional saccades from all lesion experiments. Note that the lesion was in the left hemisphere for monkey LBZ and in the right for monkey MRS. A one-factor ANOVA was performed for the amplitude data and a two-factor ANVOA(initial eye position x lesion vs. control) for the latency data. The results show that the initial eye position does not have an effect on the impairment either of saccade amplitude or latency.

The effect of varying the delay period in the memory saccade task

Figures 8 plots the effect of lesion on various saccade dimensions with respect to the duration of the delay in the memory saccade task. Data were taken from experiments of 15-degree memory saccades from both monkeys. Analysis of variance showed that varying the duration of the delay did not have an effect on the change of metrics , latency or velocity. For monkey LBZ, the average gain for contralesional saccades was 0.82 and did not vary with the duration of the delay(p=0.46). The average gain of the ipsilesional saccades was 1.0, which did not vary with the delay, either(p=0.75); for monkey MRS, the average gains for contralesional and ipsilesional saccades were 0.85 and 1.06, respectively, neither of which showed a significant variation with the delay(p=0.33 and 0.42, respectively). The latency of contralesional saccades for monkey LBZ increased from 222 to 269 msec, and the average latency of ipsilesional saccades increased from 217 to 230 msec. However, neither of these changes in latency varied significantly with the delay(p=0.29 and 0.55). For monkey MRS the latency changed from 228 to 287 msec for contralesional saccades and from 223 to 221 msec after lesion, and again did not depend on the delay(p=0.17 and 0.30, respectively). Finally, the velocity of the contralesional saccades decreased from 530 to 417 deg/sec, and the velocity of the ipsilesonal saccades decreased from 528 to 525 deg/sec, showing no interaction with the delay($p=0.14$ and 0.31), for monkey LBZ. For monkey MRS, the velocity decreased from 537 to 408 deg/sec for contralesional saccades and from 524 to 521 deg/sec for ipsilesional saccades; none of these effects varied with the duration of the delay($p=0.27$ and 0.61, respectively). Note that, since the saccades were hypometric after muscimol lesion, the velocities compared were not exactly from saccades of equal amplitudes.

Neurological testing for attention and other visuomotor functions

Spatial neglect was tested by bringing a piece of apple to the monkey from various directions. The monkey was stitting in a primate chair, secured only by a chest plate across and over his shoulders. No head restraint was imposed so that the monkey was free to turn his head to either side. No overt spatial neglect was observed; the monkeys were able to fixate on the apple, visually track it often using combined head and eye movement, and grasp the apple when it came into reaching distance. This was the case when the apple was presented in the contralesional space and moved in the ipsilesional direction and 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 peri-buccal space(both ipsilesional and contralesional side) evoked precise mouth grasping movements.

No motor 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 him by either hand. Their power grip was also normal as they could firmly grasp and pull the experimenter's finger. This was true even when the testing was done at the time when the impairment of saccadic eye movements was observed. On further examination, the monkeys did not show any impairment of prehension, either. They were able to preshape their hand by effectively opposing the fingers when they reached for an object, usually a 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 experimenter's hand smoothly across different parts of the space. And the monkeys were able to pursue the object no matter where the movement was initiated or in what direction it was moving. It was not clear, however, whether the impairment would be instantiated if the monkeys were tested for higher velocity pursuit. No abnormal bodily postures appeared to be present. Overall, other than the oculomotor deficits resulting from the muscimol lesion, the monkeys did not at any time during the experiment exhibit any signs of cerebrovascular accidents.

Discussion

In this study, by specifically inactivating area LIP, we were able to characterize in a controlled manner the resulting oculomotor deficits. In the following we will provide an overview of the results of recording studies in area LIP and the effects of area LIP lesion on saccadic eye movements that were obtained in this study. We will contrast these effects with those observed after the lesion of several different cortical and subcortical structures that are connected to area LIP. Reference to human studies will be made if relevant. Based on anatomical circuitry and the results from various lesion and recording experiments, we will emphasize the distinctive role of area LIP in processing saccadic eye movements.

Unit recordings of area LIP

Unit recordings from area LIP using a memory saccade task demonstrated that this extrastriate visual area contains both visual, memory and saccade-related activities(Andersen et al., 1990; Barash et al., 1991a; Barash et al., 1991b). Most of the saccade-related activities are pre-saccadic in nature, in contrast to area 7a, where these activities are mostly post-saccadic(Barash et al., 1991a). Spatial tuning of area LIP cells is typically broad, with a bandwidth of approximately 90 degrees(Barash et al., 1991b). The spatial tuning of visual, memory and saccade-related activities are for most cells very well aligned. The memory activities in the delay period, in which the monkey was instructed to withdraw his response, was shown in other studies to reflect the intended movement(Barash et al., 1991b; Bracewell et al., In press; Gnadt and Andersen, 1988; Mazzoni et al., In press). It was demonstrated in these studies that the visual receptive fields and motor fields of LIP neurons usually overlap, and, more importantly, most LIP neurons have little or no activity for the visual targets in their receptive fields if the task does not require eye movements into their motor fields(Andersen, 1995). Such activities for motor intention were later demonstrated for auditory saccades(Mazzoni et al., 1996), which lends further support to the view that the activity in the delayed period is most likely not sensory in nature.

Another line of research focused on the coordinate frame of the representation of space in area LIP(Andersen et al., 1985; Andersen et al., 1990; Zipser and Andersen, 1988; see also Andersen, 1995, for a review). These recording and simulation studies demonstrated that spatial locations are not represented explicitly at a single-cell level using a receptive field in space. The receptive fields of the neurons did not shift their retinal locations when eye position changed. Rather, the visual and eye position signals interact to form "gain fields" in which the amplitude of visual response was modulated by eye position. The location of a target in head-centered coordinate is then determined by the activity of a population of such cells. In other words, the representation of space can be considered to be distributed in this area over many neurons.

Overall, results from research along different lines support the view that area LIP is functionally situated between sensory and motor cortex. On the one hand, this area is involved in encoding spatial locations through distributed activities over a population of cells. On the other hand, the activities related to intended movements represent the lowest stage of the sensori-motor 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 to controls. Since these results were spatially selective and consistent across many individual lesion experiments in different monkeys, 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 which have been observed after chronic lesion of the posterior parietal lobe in humans and non-human primates(Braun et al., 1992; Lynch and McLaren, 1989; Nagel-Leiby et al., 1990). They are also similar to the results seen after the FEF or SC was inactivated, except that only latency was impaired for visually guided saccades after LIP lesion and this effect also seems to be less severe. 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 and Sparks, 1988), even though 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 lesion of area LIP. This finding is consistent with the recording data which showed that there was at best a rough topography in this area(Andersen et al., 1990). In many cases, the upper visual space was involved along with the contralesional field, in that the latency for the upward saccades was increased and the amplitude of the upward memory saccades was reduced. Consistent with this latter finding is our previous demonstration from unit recordings and a microstimulation study that there might exist a representational bias of the upper visual space in area LIP(Li and Andersen, 1994; Thier and Andersen, 1996). It was suggested that this finding might be related to the functional asymmetry of the different parts of the visual space(Li and Andersen, 1994; see also Previc, 1990).

That both the metrics and dynamics of saccadic eye movements were affected after lesion of area LIP is consistent with area LIP's role in integrating location information for movement planning. Since 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 disrupted metrics. On the other hand, it appears that the information about saccade metrics is probably also registered in other structures(most likely the SC), rendering the effect relatively small. 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., 1995). These studies demonstrated that eye movement dynamics could be altered by the cognitive or visuomotor strategies employed by subjects when performing a behavioral task. Since area LIP has been shown to be involved in movement planning(Bracewell et al., In press; Mazzoni et al., In press), it was consistent that lesioning of this area resulted in impaired dynamics of eye movements.

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 has been 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 lesion of area LIP lends further support to the view that area LIP is involved in the decision process of making a saccadic eye movement. On the other hand, the result that the amplitude and velocity of visual saccades remain intact observed after area LIP lesion suggests that this area does not play a crucial role in specifying the metrics and dynamics of visually guided saccades.

The results obtained from the reversible lesion of area LIP could also be examined in the context of a long-term debate as to whether the posterior parietal lobe is mainly involved in processing sensory information or in the generation of actions. Evidence supporting the role of the posterior parietal cortex in processing sensory information came from the findings that parietal neurons were activated by visual stimuli and such visual responses occurred when the monkey was engaged in tasks that did not require him to make any saccadic eye movements(Bushnell et al., 1981; Robinson et al., 1978; see also Andersen, 1987; Lynch, 1980, for reviews). It was further suggested that the enhancement of responses in parietal neurons prior to saccadic eye movements was mainly a result of attentional modulation. On the other hand, evidence favoring the posterior parietal cortex playing a role in commanding actions started with the studies of Mountcastle et al., which showed that there were many neurons in this area responding to active movements, such as saccades, hand manipulation, visual tracking and fixation(Hyvarinen and Poranen, 1974; Mountcastle et al., 1975;). The results obtained from the present 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 lesion of area LIP, the monkeys were still able to see the stimulus in the contralesional field and could successfully make saccadic eye movements to the targets, even though the saccades took longer to initiate and were slower in velocity(in the case of memory saccades).

On the other hand, the impairment of eye movement as a result of area LIP lesion did not seem to be as grave as those obtained from lesioning of the FEF or SC, which in general were believed to be the structures generating motor signals for saccadic eye movements. This distinction highlights the difference between area LIP and these oculomotor structures and further suggests a functional differentiation between different cortical and subcortical areas in the transformation of sensory information into movement commands.

That neuronal activities in area LIP do not reflect simple sensory or motor events has also recently been demonstrated(Shadlen and Newsome, 1996). Units were recorded from area LIP while the monkeys were performing a two-alternative forced choice task involving discrimination of motion direction. It was found that the activities of area LIP neurons in the delay period varied with the stimulus strength and, most importantly, evolved with time and appeared to predict the upcoming motor event. It was suggested that these signals reflect a neural decision for guiding movements. Further support for a role of the posterior parietal cortex in integrating visual information in preparation for movements also came from a functional imaging study(Deiber et al., 1996). In this study regional cerebral blood flow was measured while the subjects were performing a delayed cue-response task, with different cues varying in their predictive strength. It was found that the posterior parietal lobe was particularly activated under the partial cue condition compared to the full cue condition. This increased activation with restricted advance information suggests that this area is monitoring on-line visual information for motor actions.

Area LIP contrasted with other oculomotor areas

To be able to further illustrate the functional differences of these different areas in processing saccadic eye movements, we would need to consider the anatomy and physiology in some details. Based on the results obtained in this study, we will mainly concentrate on the differences between area LIP and other saccade centers, particularly the FEF. First, 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., 1987; Huerta et al., 1987a; Huerta et al., 1987b; Shook et al., 1990; Sparks and Hartwich-Young, 1989; Stanton et al., 1988b; Leichnetz et al., 1984a; 1984b). The projection from area LIP is mainly restricted to the lateral basilar pons, with little overlap with the terminals coming from the FEF, even though the two projections probably converge at the level of cerebellar vermis(Leichnetz et al., 1984a; 1984b; 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 and at longer latency compared to FEF or SC(Bruce et al., 1985b; Kurylo and Skavenski, 1991; Marrocco, 1978; Robinson, 1969; Shibutani et al., 1984; Thier and Andersen et al., In press), suggesting that area LIP might be a few more synapses away from the motor neurons than these other structures. Furthermore, lesioning of the SC with some efferents from FEF silenced the effects of stimulation of the posterior parietal lobe(Keating and Gooley, 1988). Therefore, it appears 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. After area LIP is lesioned, these other structures might still have access to signals required for initiating saccadic eye movements, rendering the effects of lesion smaller, compared to those observed when FEF and/or SC are directly lesioned.

Studies in human patients provided other evidences that oculomotor functions of frontal and parietal eye fields might be essentially different. It was found in Guitton et al. that patients with frontal lobe lesions(presumably involving prefrontal cortex, FEF, and, in some cases, the SEF) were impaired in a antisaccade task(saccade to a location opposite that of the cue), but not in a prosaccade task(saccade to a cue)(Guitton et al., 1985). A particular prominent deficit in these frontal patients was that they could not suppress reflexive saccades to the peripheral cue in the antisaccade task. These disallowed visual saccades were of very short latency(80-140 msec). It was suggested that the FEF might be involved in inhibiting reflex-like oculomotor activities and in triggering appropriate volitional movements. Other studies documented in humans with FEF lesions a similar impairment in generating self-initiated saccades(Pierrot-Deseilligny et al., 1993; Rivaud et al., 1994). In a more controlled study in which patients with prefrontal lesions involving the FEF were compared with those sparing the FEF and normal controls, it was found that FEF lesions delayed voluntary saccades to the contralesional field and reflexive saccades to the ipsilesional field. Furthermore, contrary to what has generally been reported in primate experiments, reflexive contralesional saccades were decreased in latency(Henik et al., 1994). In other words, these experiments suggested the existence of some controlled inhibitory activities in the FEF that regulate saccade generation and that lesion of the FEF might release the cross-collicular inhibition, resulting in delayed initiation of ipsilesional reflexive movements(Henik et al., 1994). It is interesting at this point to note that, even though most studies documented saccades evoked from electrical stimulation of the FEF, there is also evidence that stimulation of the lateral prearcuate cortex could suppress visually triggered saccades(Azuma et al., 1994). Furthermore, removal of the FEF was shown to lower the current threshold of evoking saccades from stimulating the superior colliculus(Azuma et al., 1991). Lesion of the posterior parietal cortex either in humans or non-human primates, on the other hand, invariably lead to an increase in the latency of contralesional saccades(Braun et al., 1992; Lynch and McLaren, 1989; Nagel-Leiby, 1992; Sundqvist, 1979). Overall, the results of these studies seem to suggest that FEF(and perhaps also other frontal oculomotor structures) might play some as yet not well-explored roles in oculomotor control, ones that are disctinct from the functions of visuomotor integration in area LIP.

Another important line of evidence supporting a distinctive role of area LIP in processing saccadic eye movements came from studies addressing the issue of the reference framework of coding of target locations. In contrast to neurons in FEF, whose movement field is organized in a retinotopic coordinate(Bruce and Goldberg, 1985), neurons in area LIP encode target locations through eye position modulation in a distributed head-centered scheme(Andersen et al., 1990). Further evidence supporting such a difference came from unit recordings in monkeys perfoming auditory saccades. Even though the sound locations were mainly encoded in a craniotopic coordinate, neuronal responses in the FEF and SC to auditory saccades appeared to be mainly related to the amplitude and direction of the saccades, and not to the spatial location of the auditory targets(Jay and Sparks, 1984; Russo and Bruce, 1994). In contrast, a significant portion of the auditory memory activities in area LIP was anchored in a head-centered coordinate or an intermediate frame-of-reference other than the eye-centered coding scheme(Stricanne et al., In press). Furthermore, microstimulation studies showed that the saccades evoked from FEF and SC were fixed vectors, the dimensions of which were largely independent of the orbital position(Bruce and Goldberg, 1985; Russo and Bruce, 1993; Schiller and Stryker, 1972), whereas those evoked from stimulating area LIP were modulated by eye position(Thier and Andersen, 1996). Finally, the results on the impairment of eye position signal obtained in a companion study further supports that area LIP contains a head-centered representation of the visual space, and, more specifically, that eye position signal is used to construct such a representation(Li and Andersen,). Since saccadic eye movements ultimately involve a change of orbital position(a displacement of eyes), these results suggest that FEF and SC are closer to the motor output, whereas area LIP plays an important role in the intermediate coding of target location and sensorimotor integration, so that such information can be correctly transformed and relayed to FEF and SC for oculomotor outputs.

Visuospatial signals from area LIP might also be relayed to the SEF for oculomotor learning, planning of movement sequences and integration of egocentric and allocentric spatial information(Chen and Wise, 1995; Olson and Gettner, 1995). Lesion of the SEF in general did not result in defective simple visual or memory saccades; however, these patients were impaired in making sequences of saccades. It is interesting to note that visuospatial signals in SEF might also be elaborated in a craniotopic framework, since neurons in this area were shown to be active before the eyes settle into the cell's preferred orbital position. It is important in future studies to explore how visuomotor singals are processed differently in these cortical oculomotor areas.

Finally, in contrast to the dorsolateral prefrontal cortex(DLPFC)(Funahashi et al., 1993), the results obtained in this study showed that the duration of the memory delay did not have an effect on the disruption of the memory saccade. This is consistent with the results of studies in which transcranial magnetic stimulation was applied to the prefrontal and parietal areas while the subjects were performing the memory saccade task. It was found that the stimulation over the parietal area disrupted the saccadic eye movements when applied early after cue presentation , but the stimulation was effective later during the memorization phase of the task when applied over the prefrontal cortex(Muri et al., 1995; Brandt et al., 1995). Other experiments showed that lesion of the area 7 of the posterior parietal lobe did not impair visuospatial short-term memory(Pu et al., 1993), and the impairment in a visuomotor delayed response task after parietal lesion did not vary with the delay, in contrast to that of the prefrontal lesion(Quintana and Fuster, 1993). Furthermore, even though cooling of the posterior parietal cortex resulted in slower reaching and inaccurate eye movements, it did not seem to impair the monkey's basic ability to perform correctly in a spatial delay task(Quintana et al., 1989). These results overall suggested that, even though the delayed oculomotor activities are both observed in area LIP and the DLPFC, they probably have different functional roles in the upcoming actions. Whereas the prefrontal cortex is keeping the spatial location of the target in short-term memory(Goldman-Rakic, 1995), the posterior parietal cortex is involved in planning for the intended movement(Andersen, 1995; Bracewell et al., In press; Mazzoni et al., In press).

FIGURE LEGENDS

FIGURE1

A section of the brain of monkey LBZ, showing area LIP and the lesion marks created by muscimol injections. The two white lines mark approximately the location of the lateral intraparietal area.

FIGURE 2

The metrics of the memory and visual saccade in an experiment with monkey LBZ. The saccades were made to targets 15 degrees away from the fixation point and in eight directions. Six trials each are plotted for visual saccades and eight to ten trials for memory 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. Besides, the amplitude 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.

FIGURE 3

The effect of area LIP lesion on the metrics of memory saccades, averaged from all lesion experiments using saccades of 15-degree amplitude. For both monkeys, the contralesional saccades are consistently hypometric. For monkey MRS, the end point of ipsilesional saccades are also shifted to the ipsilesional side, even though to a lesser degree. Moreover, the amplitudes of upward saccades are reduced in both monkeys. The center of the boxes are the average end points of the saccades and the width and height of each box was the standard deviation of the x and y components of the end points. Arrows show the change of the metrics as a result of the lesion. See text for further explanation.

FIGURE 4

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, B) and memory(C, D) saccades after muscimol injection, but the effects on the contralesional saccades were much greater. Open and filled squares were control and lesion data, respectively. See text for statistics of the difference between the lesion and control data.

FIGURE 5

The effect on saccade 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 one experiment were of 15-degree saccades. The velocities of the saccades in 8 different directions are organized in a polar plot, with their values represented by the the distance from the center. Control data were blank and lesion data were stippled. It can be seen that the contralesional and upward saccades are affected in most cases. *, $p<0.01$; **, $p<0.001$.

FIGURE 6

The main sequences of the relationship of peak velocity versus amplitude for both visual and memory saccades from an experiment with monkey LBZ. The open and filled symbols were control and lesion data, respectively. Memory saccades(A, B) were represented by circles, and visual saccades(C, D) by diamonds. 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. Note that the vertical scales are different for visual and memory saccades.

FIGURE 7

The main sequence of the relationship of saccade duration versus amplitude. Data were taken from the same set of data as shown in Figure 4. The saccade duration increases with the amplitude, but the scatter is greater than that of peak velocity versus amplitude. This relationship appears to remain intact for both visual and memory saccades after muscimol lesions. Convention for the symbols are the same as in Figure 4. See text for statistics and further explanation.

FIGURE 8

The effect of the duration of the delay period in the memory saccade task on the impairment of the saccade metrics and dynamics. Data on the left and right panels are for monkey LBZ and MRS, respectively. The upper row shows the effect on the amplitude change, expressed as a gain(lesion/control), the middle row shows the data of saccade latency and the third row shows the effect on velocity. Note that the scales of gain change for the two monkeys are not the same. Data for contralesional saccades were marked "C" underneath the histograms and those for ipsilesional saccades marked "I." The black bars are lesion data and white bars controls. Data for saccade amplitude were shown as ratios of the post-injection amplitude/pre-injection amplitude, so only one historgram is available for each contralesional and ipsilesional data set.

TABLE LEGENDS

TABLE 1

The effect of muscimol lesion on the MISS and ERROR rates of visual and memory saccades. The results were averages(standard deviations in brackets) of all lesion experiments, and data of monkey LBZ were shown on the left and those of MRS on the right. Both the MISS and ERROR rates were increased after muscimol lesion for both monkeys. See text for further explanation.

TABLE 2

The change of saccade metrics was shown as a ratio of post-injection amplitude/pre-injection amplitude. The numbers in the brackets are standard deviations. The results were averages of all lesion experiments and listed according to saccade amplitude. The total numbers of lesions are different for different saccade amplitudes because the frequencies of the experiments in which saccades of different amplitudes were tested are not the same. 15-degree saccades were most frequenctly tested. Data of monkey LBZ were shown on the left and those of MRS on the right. See text for further explanation.

TABLE 3

The increase of saccade latency for both visual(lower panel) and memory(upper panel) saccades. The results were averages of all lesion experiments and listed according to saccade amplitude. The data are orgazined as in Table 2.

TABLE 4

The decrease of velocity after muscimol lesion shown for visual and memory saccades of 7-, 12-, and 18-degree amplitudes. The results were averages of velocities of the saccades of comparable amplitudes. For both monkeys the velocities of contralesional memroy saccades were reduced. See text for further explanation.

TABLE 5

The saccade durations remained unchanged after muscimol injection for both visual and memory saccades. These results were from the same saccades the velocities of which were listed in Table 4. The data are also organized in the same way.

TABLE 6

The effect on initial eye position(iep) on the impairment of saccade amplitude and latency after muscimol lesion. Results are shown for memory(upper panel) and visual(lower panel) saccades for monkey LBZ(left) and MRS(right). Neither the reduction of saccade amplitude(memory saccade) nor the increase of latency(visual and memory saccade) varies with the initial eye position. See text for further explanation.

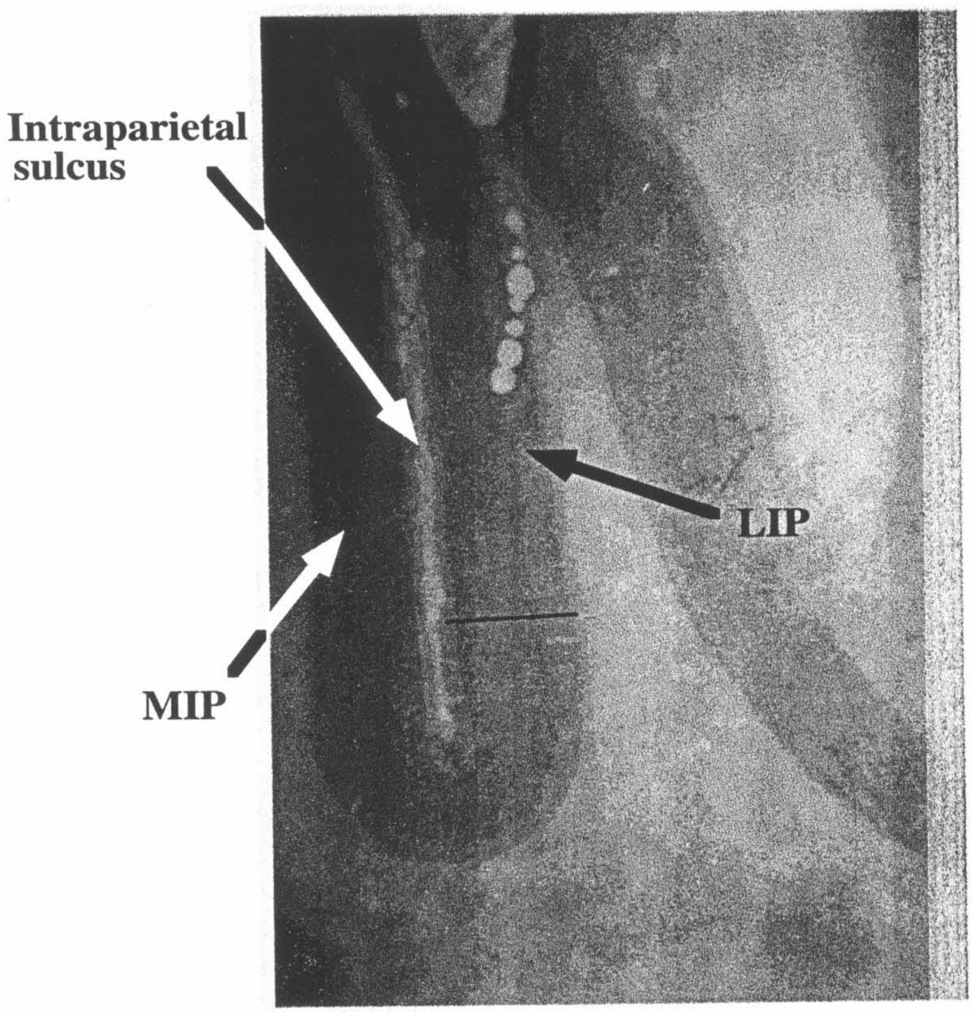


Figure 1

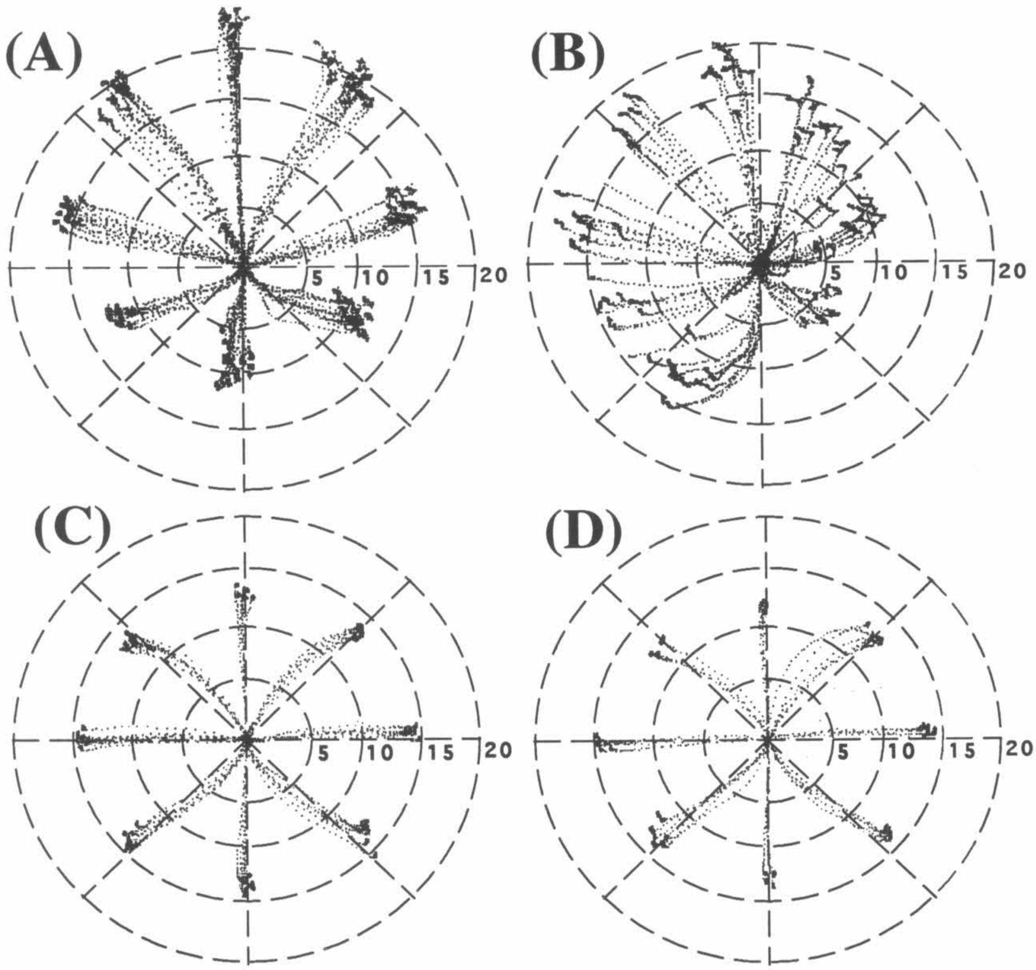


Figure 2

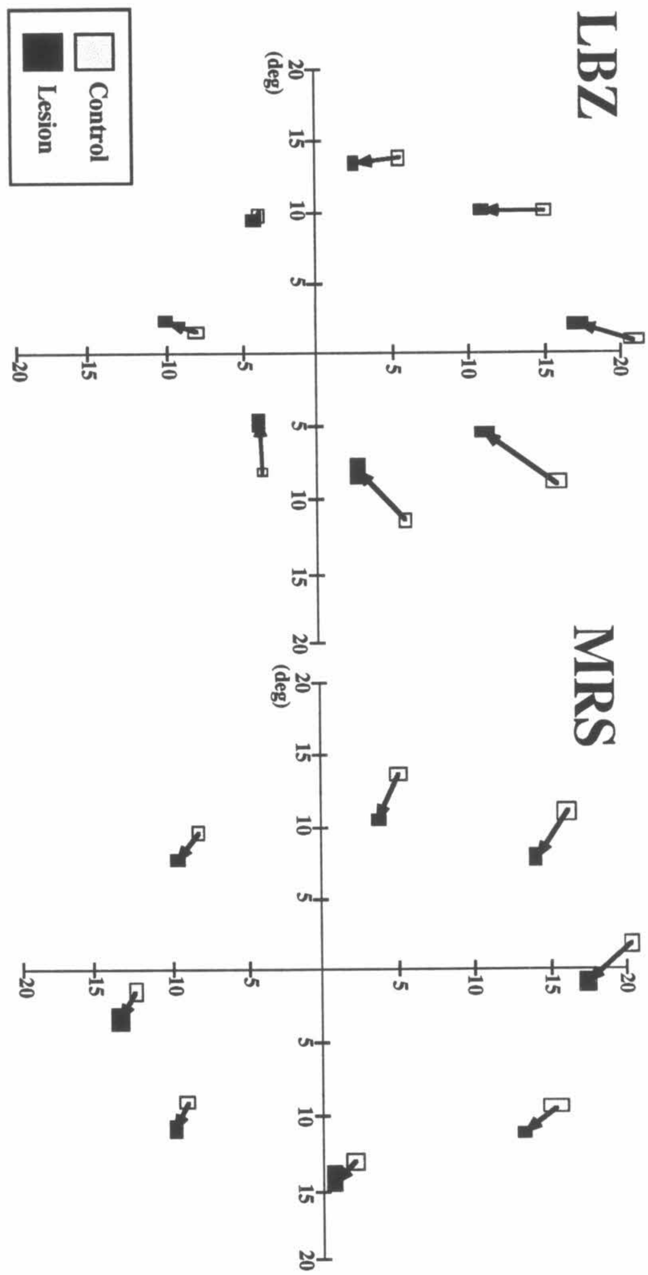


figure 3

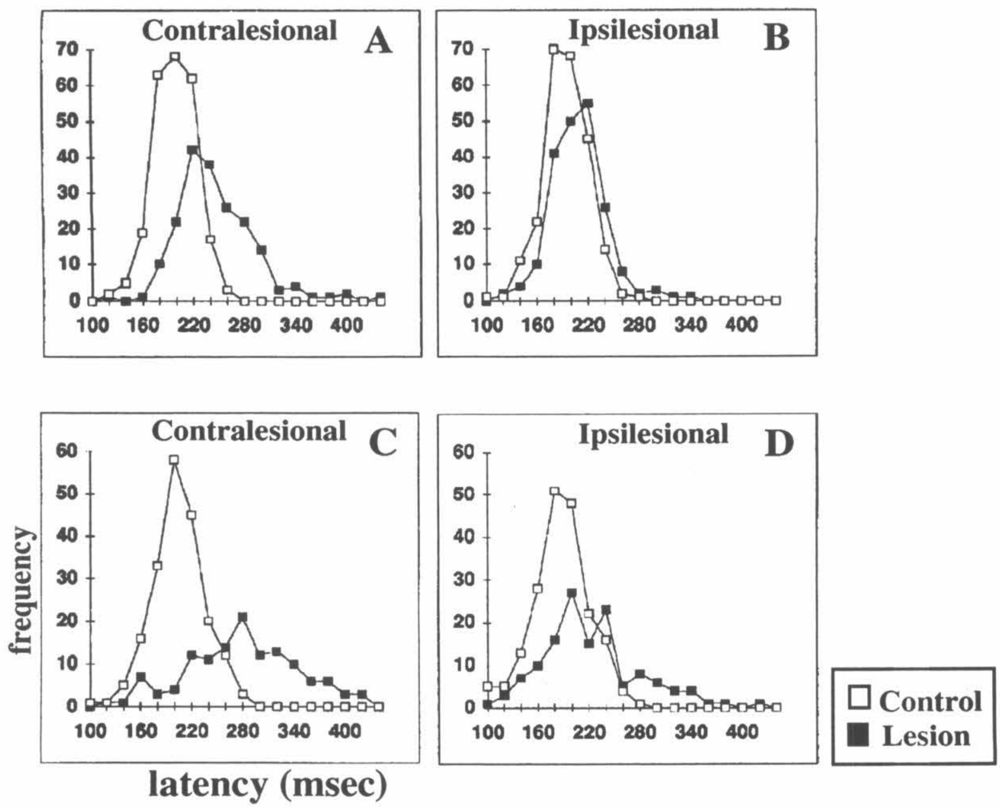

Contralesional
A
Ipsilesional
B
Contralesional
C
Ipsilesional
D
frequency
latency (msec)
Control
Lesion
100 160 220 280 340 400

figure 4

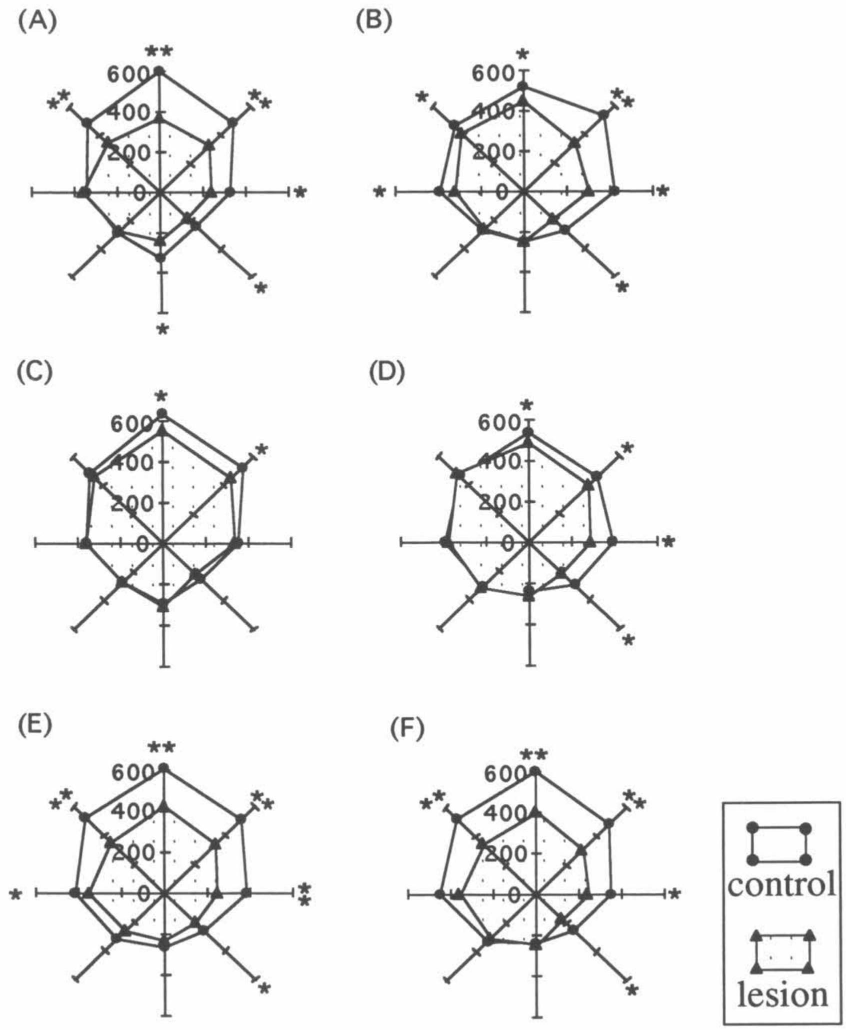


Figure 5

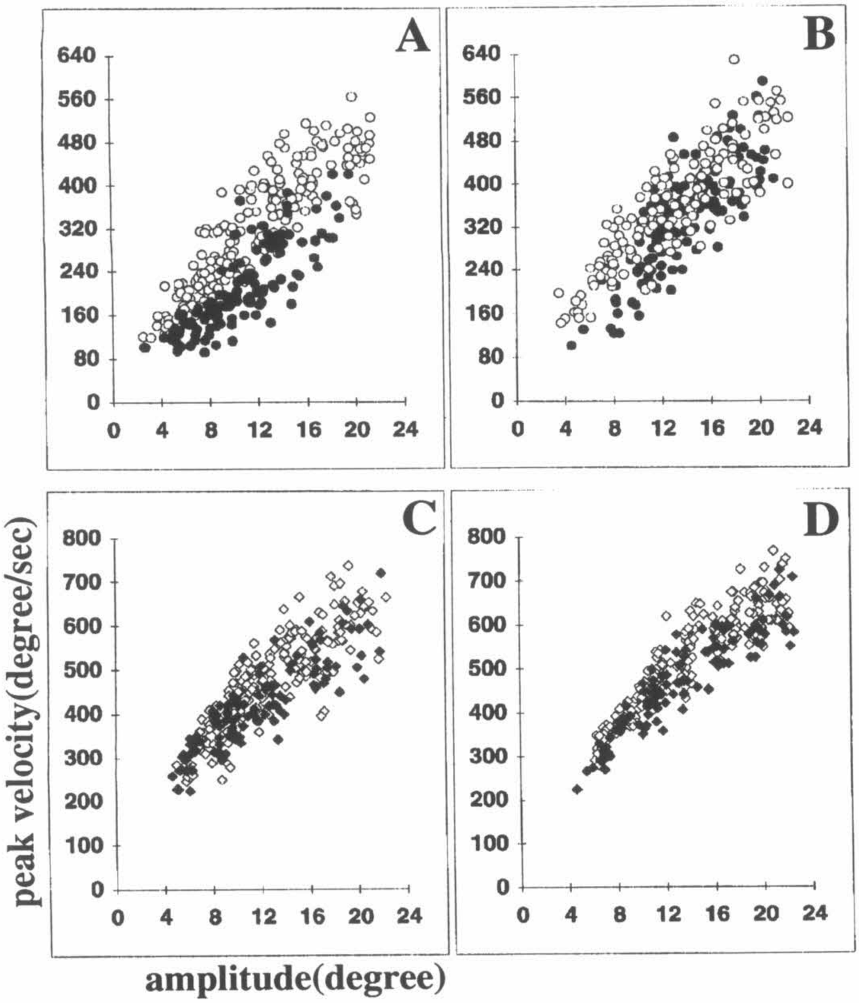

A
B
C
D
640
560
480
400
320
240
160
80
0
800
700
600
500
400
300
200
100
0 4 8 12 16 20 24
peak velocity(degree/sec)
amplitude(degree)

Figure 6

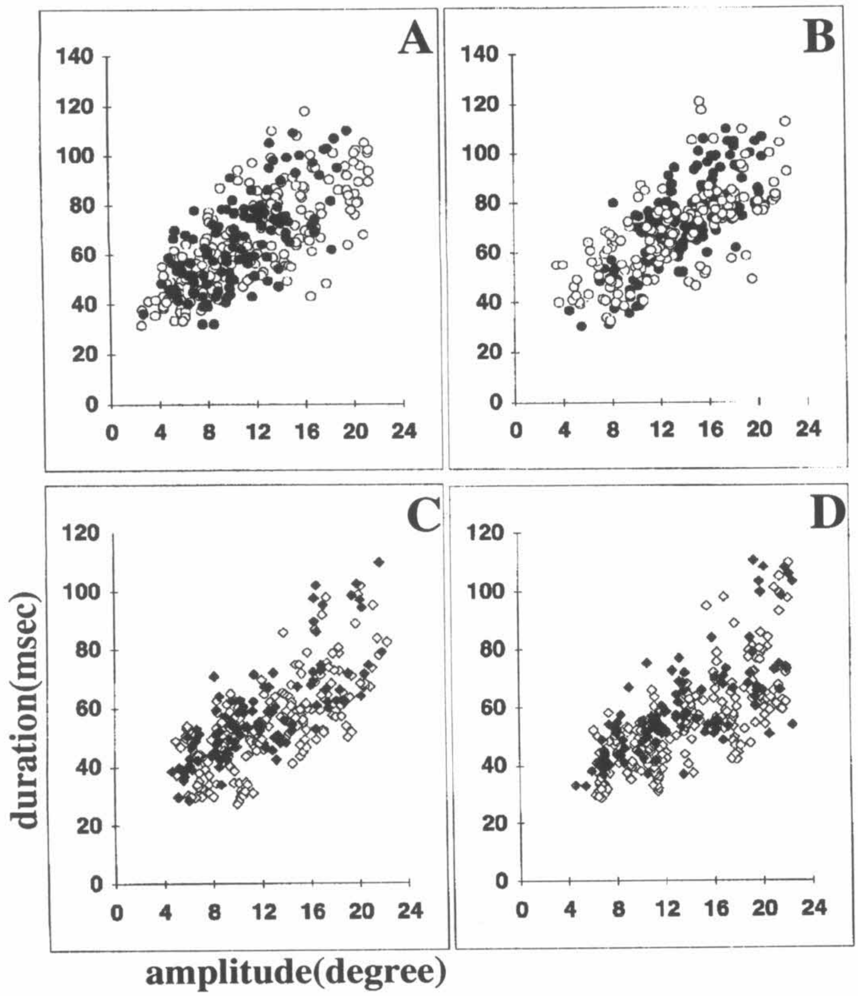

A
B
C
D
140
120
100
80
60
40
20
0
0 4 8 12 16 20 24
duration(msec)
amplitude(degree)

Figure 7

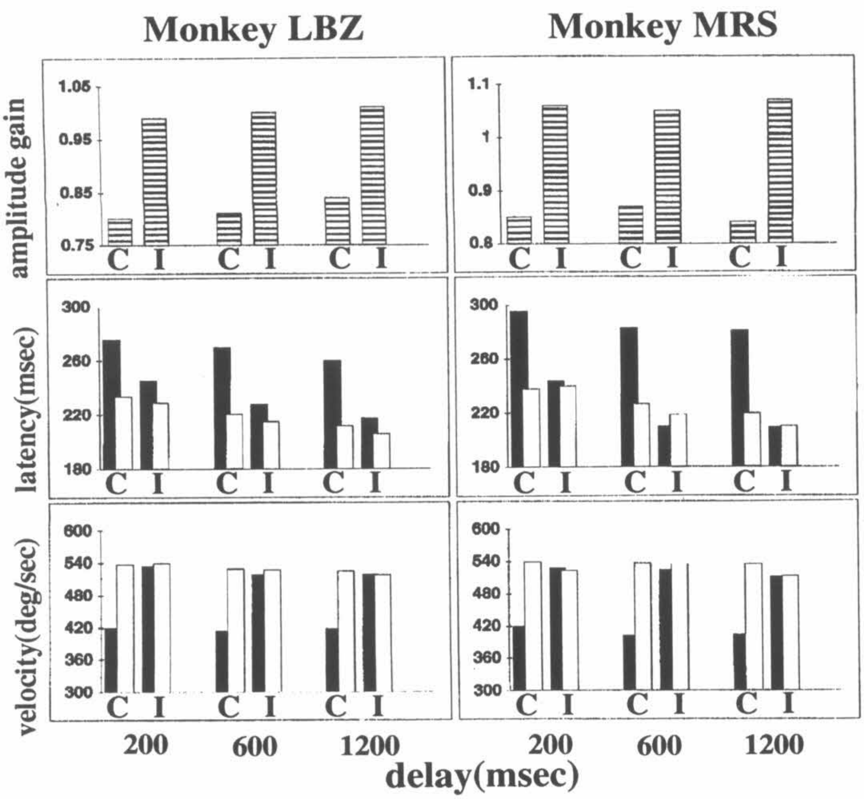

Monkey LBZ
Monkey MRS
amplitude gain
latency(msec)
velocity(deg/sec)
C I C I C I
200 600 1200
delay(msec)

Figure 8

		Monkey LBZ			Monkey MRS		
visual saccade		# of lesions	MISS rate(%)	ERROR rate(%)	# of lesions	MISS rate(%)	ERROR rate(%)
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)

*p<0.01; **p<0.001

Table 1

	memory saccade			memory saccade		
	contral.	*ipsil.*	*# of lesion*	*contral.*	*ipsil.*	*# of lesion*
ampl						
7	0.84(.07)	1.00(.08)	7	0.83(.12)	1.03(.08)	4
10	0.82(.05)	1.02(.03)	10	0.89(.04)	1.09(.08)	6
12	0.76(.09)	0.94(.05)	7	0.84(.07)	1.10(.09)	4
15	0.68(.11)	0.92(.06)	14	0.86(.05)	1.05(.07)	6
18	0.70(.10)	0.92(.06)	7	0.82(.09)	1.06(.11)	4
20	0.71(.08)	0.95(.05)	10	0.84(.05)	1.05(.04)	6
average	0.75(.08)	0.96(.05)		0.85(.07)	1.06(.08)	
	visual saccade			visual saccade		
7	1.04(.06)	0.97(.04)	4	1.03(.04)	0.97(.03)	4
10	1.00(.02)	0.95(.05)	7	1.04(.05)	0.95(.06)	4
12	1.01(.04)	1.02(.05)	4	0.99(.05)	1.02(.06)	4
15	0.97(.04)	0.99(.03)	9	1.06(.09)	0.99(.04)	4
18	0.98(.04)	1.01(.07)	4	0.98(.04)	1.01(.05)	4
20	1.01(.06)	1.01(.03)	7	1.01(.04)	1.01(.06)	4
average	0.99(.04)	0.99(.04)		1.02(.05)	1.00(.05)	

Table 2

	Monkey LBZ			Monkey MRS		
	memory saccade			memory saccade		
	contral.	ipsil.	# of lesion	contral.	ipsil.	# of lesion
ampl						
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			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)	

Table 3

Monkey LBZ	Memory saccade			
	contralesional		ipsilesional	
ampl	control	lesion	control	lesion
7	212(40)	156(24)*	234(48)	219(33)
12	371(62)	296(48)*	390(67)	405(60)
18	550(84)	411(67)*	581(53)	590(82)
	Visual saccade			
7	240(39)	229(54)	245(45)	251(47)
12	382(56)	375(27)	393(51)	387(66)
18	606(73)	583(96)	620(49)	609(78)

Monkey MRS	Memory saccade			
	contralesional		ipsilesional	
ampl	control	lesion	control	lesion
7	222(42)	176(33)*	216(40)	222(61)
12	384(52)	315(78)*	378(81)	379(72)
18	562(57)	436(79)*	560(76)	556(53)
	Visual saccade			
7	248(43)	231(77)	250(51)	239(73)
12	389(53)	379(67)	380(44)	388(69)
18	610(69)	606(64)	621(68)	630(68)

Table 4

Monkey LBZ	Memory saccade			
	contralesional		ipsilesional	
ampl	*control*	*lesion*	*control*	*lesion*
7	44(11)	49(14)	42(14)	44(18)
12	61(20)	66(17)	55(15)	62(13)
18	78(29)	85(33)	78(28)	85(34)
	Visual saccade			
7	40(12)	42(11)	42(9)	39(10)
12	58(16)	57(17)	55(12)	54(13)
18	76(20)	79(21)	78(19)	74(22)

Monkey MRS	Memory saccade			
	contralesional		ipsilesional	
ampl	*control*	*lesion*	*control*	*lesion*
7	42(17)	46(12)	45(13)	49(10)
12	63(22)	62(23)	59(18)	65(25)
18	78(18)	82(26)	76(24)	84(36)
	Visual saccade			
7	39(8)	43(15)	40(14)	41(13)
12	59(20)	61(18)	58(27)	62(22)
18	80(31)	79(33)	81(34)	86(37)

Table 5

		(Monkey LBZ) Memory saccade				(Monkey MRS) Memory saccade			
		contralesional		ipsilesional		contralesional		ipsilesional	
	iep	lesion/control		lesion/control		lesion/control		lesion/control	
amplitude (gain)	(-10,0)	0.80(0.09)		0.97(0.07)		0.86(0.10)		1.01(0.05)	
	(0,0)	0.82(0.07)		0.98(0.07)		0.84(0.05)		1.03(0.09)	
	(10,0)	0.82(0.10)		1.01(0.08)		0.87(0.08)		1.06(0.10)	
	ANOVA	p=0.86		p=0.73		p=0.66		p=0.69	
		control	lesion	control	lesion	control	lesion	control	lesion
latency	(-10,0)	202(33)	237(35)	234(37)	244(25)	249(30)	284(45)	208(29)	202(32)
	(0,0)	210(27)	244(30)	206(30)	218(38)	227(26)	259(36)	215(34)	212(26)
	(10,0)	230(36)	277(49)	198(32)	208(24)	216(22)	245(38)	235(40)	247(37)
	ANOVA	p=0.89		p=0.87		p=0.72		p=0.25	

		Visual saccade				Visual saccade			
		contralesional		ipsilesional		contralesional		ipsilesional	
	iep	lesion/control		lesion/control		lesion/control		lesion/control	
amplitude (gain)	(-10,0)	0.97(0.04)		0.97(0.05)		0.97(0.03)		0.99(0.05)	
	(0,0)	1.01(0.07)		0.98(0.05)		0.98(0.04)		0.98(0.04)	
	(10,0)	0.99(0.04)		1.01(0.06)		0.99(0.04)		0.99(0.05)	
	ANOVA	p=0.54		p=0.69		p=0.82		p=0.91	
		control	lesion	control	lesion	control	lesion	control	lesion
latency	(-10,0)	191(22)	220(29)	207(21)	222(31)	221(27)	246(41)	198(19)	205(32)
	(0,0)	197(27)	235(21)	200(25)	206(30)	210(26)	239(36)	206(30)	216(28)
	(10,0)	216(30)	248(44)	189(29)	191(29)	201(35)	229(29)	214(39)	219(42)
	ANOVA	p=0.47		p=0.33		p=0.85		p=0.86	

Table 6

CHAPTER THREE

The Effect of Area LIP Lesion on Spontaneous Eye Movements, Fixation and Visual Extinction

Summary

1. The primate lateral intraparietal area(area LIP) contains visual and saccade-related activities. These activities are retinotopically organized but their overall response magnitudes are modulated by eye position. It was proposed that area LIP plays an important role in encoding the location of stimuli in a head-centered space and is involved in transforming sensory information for intended eye movements. This area is also characterized by active eye position-dependent fixation activities, in addition to visual and saccade-related responses . These neurons generally increase their firing rate when the monkey maintains his gaze in the contralateral space. In this, the second part of a study examining the effects of the lesioning of area LIP on oculomotor behaviors, we describe our results concerning spontaneous eye movement, fixation, and visual extinction.

2. Three μL's of muscimol(8 mg/mL) were used for reversible inactivation in each lesion experiment. Injections were performed at locations where saccade-related and fixation activities were recorded in two hemispheres of two macaque monkeys.

3. To explore the effects on spontaneous eye movements, we recorded the eye movements both in light and in darkness. The results showed that lesioning of area LIP slightly but significantly decreased the number of contralesional saccades when the animals were tested in light, but the dynamic characteristic of saccades in terms of peak velocity versus amplitude remained unchanged. The distribution of the sizes of the saccades made in the light or in darkness also did not consistently differ from that of the control

experiment. However, the monkeys tended to confine their gaze to the ipsilesional space whether in light or in darkness after area LIP lesion.

4. Parietal lesions in humans are frequently implicated in visual extinction, a failure in processing a contralesional stimulus in the presence of ipsilesional stimulus. Since area LIP neurons have been shown in recording studies to encode stimulus locations in a head-centered coordinate, it is interesting to see whether the inactivation of this area would result in visual extinction and in which frame-of-reference this would occur. We first demonstrated the existence of visual extinction after lesioning area LIP and we then explored the coordinate frame in which it occurred.

5. The monkeys were trained in a task where regular trials of visual saccades were interleaved with extinction trials, in which the targets appeared on both sides of the fixation point simultaneously. Each monkey had a distinct pattern of eye movement in the extinction trials and the saccade latency in these trials was invariably longer than in the regular visual saccade trials. After lesioning area LIP, the monkeys consistently made many more saccades to the ipsilesional target and ignored the contralesional one in the extinction trials. Besides the altered frequency of ipsilesional and contralesional saccades, the existence of visual extinction was also demonstrated by the disappearance of the latency increase in ipsilesional saccades in the extinction trials. To explore the coordinate frame of visual extinction, we varied the starting eye position so that in some conditions the light stimuli which fell on different retinal hemifields would be located in the same head-centered hemispace. The results showed that when the eyes started at an ipsilesional position so that both targets appeared in the ipsilesional hemifield with respect to the head, the frequency of ipsilesional

and contralesional saccades in the extinction trials was similar to that obtained in the control experiment. This result suggests that the severity of extinction of the contralesional stimulus is modulated by eye position and can best be described in a head-centered framework.

6. In a second paradigm used to examine visual extinction, the monkeys were trained in a cued visual saccade task, in which a cue preceded the target at the same location. In the extinction trials, targets were presented on both sides of the fixation following cue presentation. The monkeys were required to make a saccade to the target at the cued location in both the regular and extinction trials. The results showed that, after muscimol lesioning of area LIP, the monkeys made many more errors when cued to make contralesional saccades and the latency of contralesional saccades was also much longer compared to that of the control. Varying the location of the initial fixation point on the horizontal axis demonstrated an eye position effect. When the monkeys started out fixating to the right or left, so that the targets on both retinal hemifields appeared in the same head-centered hemispace, the effect on both the error rate and latency of the contralesional saccades was decreased.

7. The results from these extinction experiments provide further evidence supporting the role of area LIP in encoding visual stimuli in a head-centered coordinate. Also, consistent with previous recording studies, area LIP does not seem to play a preempting role in the control of spontaneous eye movements. Finally, the altered fixation pattern recorded in task-free conditions suggests a disrupted representation of the contralesional space.

Introduction

It is well documented in the clinical literature that parietal patients oftentimes have difficulty moving their eyes to and holding their gaze in the contralesional space(Gainotti, 1993; Tijssen et al., 1991). For example, when asked to search for a target in darkness or a particular item among an array of distractors, parietal patients generally confine their gaze to the ipsilesional hemifield(Chedru et al., 1973; Hornak, 1992; Karnath and Fetter, 1995). A similar spatial limitation of eye movements is found during ocular exploration of a simple stimulus(Ishiai et al., 1987; Ishiai et al., 1989; Karnath, 1994b). It is worth noting that this ipsilesional bias is not simply a result of some difficulty in making contralesional saccades, since saccades in both directions are relatively normal in the ipsilesional field(Doricchi et al., 1991; Ishiai et al., 1989). Nor is it a deficit associated with hemianopia, since not all parietal patients demonstrate hemianopia, and hemianopic patients generally adopt a very different strategy when they visually explore the environment(Hornak, 1992; Ishiai et al., 1987; Meienberg et al., 1981; Meienberg et al., 1986; Zihl, 1995).

Besides having these oculomotor abnormalities, parietal patients also encounter difficulty directing their attention to the contralesional space, which can easily be demonstrated in the classical line bisection and letter cancellation tasks(see Andersen, 1987; Bisiach and Vallar, 1988; Lynch, 1980, for reviews). In everyday life they ignore objects on the left and miss the left side of a page while they are reading. It is generally accepted that the problem of spatial neglect is not a result of a primary sensory deficit, but rather a failure in allocating attention to the contralesional space, such that information represented in the neglected space is not properly accessed and processed. Evidence for this view includes the finding that neglect could occur across several sensory modalities(Bisiach et al., 1984; De Renzi et al., 1989a; Farah et al., 1989), in tasks of manual exploration without visual guidance(Chedru, 1976; De Renzi et al., 1970, Gentilini et al., 1989), in an imagined or recalled representational space(Bisiach and Luzzatti, 1978; Bisiach et al., 1979; Meador et al., 1987), and in a conceptual space involving speech and language(Baxter and Warrington, 1983; Barbut and Gazzaniga, 1987). The neglect in the olfactory system, in which the pathway from the sensory periphery to the central nervous system is uncrossed, occurs in the contralesional space as well(Bellas et al., 1988; Bellas et al., 1989). Furthermore, neglect can happen to the rightmost item even when all stimuli are presented in the intact field(De Renzi et al., 1989b; Ladavas et al., 1990). Finally, unilateral neglect also occurs in a object-centered coordinate(Behrmann and Moscovitch, 1994).

Other studies suggest an oculomotor mechanism underlying spatial neglect(see Gainotti, 1993, for a review). This hypothesis views unilateral neglect as a result of disrupted oculomotor functions. Evidence supporting this hypothesis comes from experiments demonstrating a close functional linkage between eye movements and the orienting of attention(Hoffman and Subramaniam, 1995; Honore et al., 1989; Kowler et al., 1995; Meador et al., 1987; Sheliga et al., 1994, 1995; Shepard et al., 1986). It is also supported by studies showing that the alteration of gaze patterns by vestibular or optokinetic stimulation changes the severity of unilateral neglect(Cappa et al., 1987; Pizzamiglio et al., 1990; Rubens, 1985; Vallar et al., 1990) and that leftward rapid eye movements diminish during sleep in subjects with unilateral neglect(Doricchi et al., 1991). Furthermore, even though attention can be covertly shifted without eye movement, eye movement necessarily entails movement of attention(Shepherd et al., 1986). It seems that shifting of gaze is the primary carrier that moves attention from one place to another in most circumstances and that impaired eye movements disrupt the reorienting of attention.

Another related behavioral abnormality frequently implicated in parietal lesions is visual extinction. When two objects are presented simultaneously, the parietal patients tend to ignore the one closer to the contralesional side, even though they can correctly localize a contralesional stimulus when it is presented alone. An important finding in the studies of the extinction phenomenon is that it occurs in a spatially defined frame-of-reference and does not depend on a sensory coordinate frame(Moscovitch and Behrmann, 1994). Moscovitch and Behrmann presented simultaneous tactile stimulation to parietal patients at two different points on a single wrist(usually the ipsilesional hand). Testing was conducted in two different conditions: palm up and palm down, so that the somatotopic and spatial frames of reference could be decoupled. The rationale is: if extinction is defined in a somatosensory frame-of-reference, then the stimulus on a fixed location(say, the one near the thumb) would be extinguished, whether tested palm up or palm down. On the other hand, if extinction occurs in a spatial coordinate, then the stimulus on the environmentally defined contralesional side would be ignored in either case. Their results supported the spatial framework hypothesis. This experiment provided important evidence that, similar to overt spatial neglect, extinction is also anchored in a higher-order spatial frame of reference.

Recent physiological and anatomical studies have identified several different areas in the posterior parietal lobe(Andersen et al., 1990a; Colby and Duhamel, 1991; Colby et al., 1994; Galletti et al., 1995; Sakata et al., 1995; Taira et al., 1990), and among these the lateral intraparietal area(area LIP) was shown to be important for encoding target locations and transforming sensory signals into motor commands(see Andersen, 1995, for a review). More specifically, it was proposed that area LIP neurons combine retinal and extraretinal information, including eye and head position signals, to encode target locations in head- and body- centered coordinates(Andersen et al., 1985; Andersen et al., 1990b; Brotchie et al., 1995). This intermediate representation of head- or body-centered space is then instrumental in facilitating spatially directed actions in an egocentric space(see Jeannerod, 1988, for a review). Other than having visual and saccade-related responses, area LIP also contains active fixation activities. These fixation neurons increase their firing rate when the monkey directs his gaze to the contralateral space. As the second part of a study examining the effects of the lesioning of area LIP on oculomotor behaviors, we report the results regarding spontaneous eye movements, fixation, and visual extinction.

Methods

Surgery, animal care, eye position monitoring and muscimol injection

Two male macaque monkeys were used in this experiment. The details of the surgery, as well as the instrumentation, unit recording and muscimol injection are described in the previous paper(Li et al.,). NIH guidelines were closely followed for the care and use of animals. Eye position was recorded with the scleral search coil technique(Judge et al., 1980) with calibration performed daily before the experiments. Three µL's of muscimol(8 mg/mL) were used for each lesion experiment in this study.

Behavioral tasks

Two different tasks were used to test visual extinction. In the first task, VEXT_1.1, the monkeys were trained to do visual saccades. The monkey started out fixating straight ahead, and after a period of 800 msec, the fixation light went off and the peripheral target came on. The monkey had a time window of 350 msec to saccade to the target and stay there for another 400 msec, within a space window of 4 degrees in diameter, to receive a juice reward. The saccade target could appear at one of 6 different locations; namely, (-11,11), (11,11), (-15,0), (15,0), (-11,-11), or (11, -11) relative to the fixation point, (0,0). However, in one fifth of the trials, unlike in the regular visual saccade task, two light stimuli appeared at opposite sides of the fixation point at the same time. Targets were presented at symmetric locations relative to the vertical meridian, that is, (-11,11) & (11,11), (-15,0) & (15,0), and (-11,-11) & (11,-11). In these "extinction trials," the monkeys were rewarded 100% of the time, whether they chose to stay at the fixation point or to make a saccade to either one of the targets. Given that the visually guided saccades are generally automatic and that the frequency of presentation of these extinction trials was relatively low, we expected the monkeys to make a saccadic eye movement to one of the targets most of the time. An intertrial interval of 2 to 2.5 seconds was used. Typically 600 to 800 trials were collected in each session, one fifth of which were extinction trials. Data were collected using this task during 3 lesion sessions each with monkey LBZ and monkey NWT.

In a second version of this task, VEXT_1.2, we varied the position of the fixation point, so that the saccade would start at seven different locations: (-15,0), (-10,0), (-5,0), (0,0), (5,0), (10,0), (15,0). Target locations were 10 degrees to the left and right of the fixation point. Therefore, in the conditions where the fixation point was at (-15,0) and (15,0), targets on the two sides of the fixation were in opposite retinal hemifields but in the same hemispace relative to the head. Similarly, for the two cases where the fixation point was (-10, 0) and (10,0), target locations were also confined to a head-centered hemispace including the midline. Such arrangements dissociated the locations of the targets in retinal and spatial coordinates and allowed us to explore the reference framework of visual extinction. Again, typically 600 to 800 trials were collected in each experimental session, of which one fifth were extinction trials. Data were collected using this task during 2 lesion sessions with monkey LBZ and 3 lesion sessions with monkey NWT.

The second task (VEXT2) for testing visual extinction was a cued visual saccade task. In this task, a cue(50 msec) preceded the target by 600 msec and the monkey was required to make a visual saccade to the target appearing at the cued location. In one third of the trials(extinction trials), two targets appeared on opposite sides of the fixation point. The criteria for correct responses were the same for both trial conditions. The locations of the fixation points and targets were the same as in VEXT_1.2. Data were collected using this task in 4 lesion experiments with monkey NWT.

To explore the effects on spontaneous eye movement and fixation, the monkeys' eye position was recorded in a task-free condition. Each experimental block consisted of 60 trials in the light and 40 trials in the dark, each lasting 5 seconds. Fewer trials were collected when the animals were tested in the dark, because they tended to become drowsy in prolonged darkness. Extreme care was used to make sure that the visual scene remained the same during both the control and the lesion sessions and that the noise in the environment was minimal during these experiments. The juice reward was also turned off to avoid any effect that might result from an attentional bias. The recordings taken in light and in darkness were alternated and typically data from 2 sessions each were collected in each experiment.

Data analysis

VEXT_1.1 To quantify the behaviors of visual extinction, the frequency of rightward and leftward saccades made in the extinction trials was calculated and a Chi-square test was performed to see if there was any significant change after muscimol lesion.

Since the visual saccades made after the simultaneous presentation of the targets on both sides(extinction trials) invariably increased in latency compared to those made to a single target(Findlay, 1983; Levy-Schoen and Blanc-Garin, 1974; Marzi et al., 1995; Walker et al., 1995), we also compared the increase in saccade latency after the simultaneous double target presentation in both the control and the lesion conditions. An analysis of variance was used to examine if the latency increase in the extinction trials was different between the control and the lesion sessions. In some extinction trials, the monkey did not initiate a saccade until towards the end of the trial. Since data were only collected up to the point the trial ended, the data containing the saccade trajectory for these trials were incomplete, rendering it impossible to analyze saccade amplitude and peak velocity. However, for these trials, the initial excursion of the movement allowed us to tell in which direction the saccades were intended.

VEXT_1.2 For quite a few of the extinction trials in this task, the monkeys did not make any eye movements to either of the targets. We took this into account and considered this non-saccade as one of the response modes. The frequency of the different responses(rightward saccade, leftward saccade, stay put) was then calculated for each eye position and the results were pooled from individual sessions for both the control and the lesion experiments. To characterize the severity of the extinction for different starting positions, an analysis of variance was performed on the frequency data(Sokal and Rohlf, 1981), with the lesion vs. control and the eye position as two independent variables. Specifically, we looked at whether the distributions of the responses were different between the control and the lesion experiments, and if they were, whether such a difference would depend on eye position.

VEXT_2 For this behavioral task, we computed the error rate for each different starting eye position in extinction trials, and compared the results between the lesion and control data. The error rates were calculated separately for rightward and leftward saccades in each lesion experiment. A repeated measures ANOVA was then performed to determine, for rightward and leftward saccades respectively, if there was any difference in the error rates between the lesion and control experiments and whether such a difference varied with the starting eye position. Likewise, we computed for each saccade direction the latency increase due to simultaneous presentation of the targets in the extinction trials in both the control and the lesion experiments. The data were then subjected to a repeated measures ANOVA to see whether such a latency increase differed between the lesion and the control experiments and whether such a difference varied with eye position.

SPONTANEOUS EYE MOVEMENT AND FIXATION To quantify the spontaneous eye movements, we computed the total number of contralesional and ipsilesional saccades made in each experiment. The amplitude and velocity of individual saccades were also computed, using velocity criteria to define the beginning and the end of a saccade(Li et al.,). The intersaccadic intervals were calculated by subtracting from the time when a saccade began the time when the previous saccade ended. The data obtained from saccades in midflight were excluded from analysis.

Results

Spontaneous eye movement and fixation

The eye traces for the saccade and fixation patterns of monkey LBZ and NWT are plotted in Figures 1 and 2 for experiments in the light and in darkness, respectively. The data were taken from one control and one lesion experiment and will be used to illustrate the effect of muscimol lesioning. The time in which the data were collected was approximately 10 minutes in the light and 6.7 minutes in the dark. The data showed that the monkeys made fewer saccades in darkness and that the spatial range of eye movements was also smaller compared to the spatial range in light. In particular, fixation in the dark was mostly restricted to the upper hemifield. After area LIP was inactivated, the monkeys tended to confine their gaze to the ipsilesional space, and this ipsilesional bias was greater when the animals were tested in light. In some cases, this deficit was more restricted to a particular quadrant of the space, as is illustrated for monkey LBZ in Figure 1.

The durations of the intersaccadic intervals are shown in Figures 3 and 4 for this experiment in light and in darkness, respectively. The intersaccadic intervals are plotted with respect to the x and y position where the preceding saccades ended. The ipsilesional fixation bias following muscimol lesion is clearly visible in these plots. It is also notable that, when monkey NWT was tested in the light, the few fixations in the contralesional field were of short duration following muscimol lesioning. The average intersaccadic intervals of the data from all the control and lesion experiments are shown in Table 1. The results show that, for both monkeys, the intersaccadic intervals were longer when the animals were tested in darkness: 0.80 second(in darkness, all control data) vs. 0.46 second(in light, all control data) for monkey LBZ($p<0.001$) and 0.78 second vs. 0.44 second for monkey NWT($p<0.001$). For monkey NWT, the average intersaccadic interval in the ipsilesional hemifield was also longer following area LIP lesioning, when compared to the average intersaccadic interval in the contralesional hemifield, both in light($p<0.02$, ANOVA) and in darkness($p<0.05$, ANOVA). This change in the intersaccadic intervals was consistently observed, even though the significance of the change varied to some degree across experiments. For instance, the results from monkey LBZ did not appear to show a consistent pattern of change across experiments. Following muscimol lesioning, the average intersaccadic interval did not vary with the location of the fixation points, either in the light($p=0.27$, ANOVA) or in darkness($p=0.31$, ANOVA). Because of the ipsilesional fixation bias, the total duration of all the intersaccadic intervals in a given experimental session was much longer in the ipsilesional field for both monkeys.

After muscimol lesion, the average number of saccades made in the contralesional direction significantly decreased for monkey NWT($p<0.005$, χ^2 test), when tested in the light. The average number of contralesional saccades also decreased in monkey LBZ, even though this change did not reach statistical significance($p>0.1$, χ^2 test). On the other hand, the frequency of ipsilesional and contralesional saccades remained similar following muscimol lesion when the monkeys were tested in the dark($p>0.5$ for both monkeys, χ^2 test). The average numbers of all the saccades made in different conditions, together with the average amplitudes of the saccades, are shown in Table 2.

Figure 5 shows the average distribution of the sizes of the contralesional and ipsilesional saccades made in the lesion and control experiments. It shows that, in agreement with a previous parametric study(Bahill et al., 1975), the distribution of the amplitudes of the saccades made in a natural setting is skewed towards small ampliudes. Across all the data collected in the light in control experiments, 68% of the saccades were 15.2 deg or less (monkey LBZ) and 15.5 deg or less (monkey NWT) in amplitude. For the data collected in the dark, 68% were 18.1 deg or less(monkey LBZ) and 16.9 deg or less(monkey NWT) in amplitude. The average amplitudes of all the saccades collected in different conditions are shown in Table 2. The results show that the average amplitude of the saccades made in the dark is significantly larger than that in the light for monkey LBZ($p<0.01$, t-test): 16.8(dark, all control data) vs. 12.7 deg(light, all control data). For monkey NWT, the average amplitude of the saccades made in darkness was also larger compared to that obtained in the light(15.3 vs. 13.0 deg), even though the difference did not reach statistical significance(p=0.22, t-test). After muscimol lesioning, there was not a consistent pattern of change in the average saccade amplitude across experiments. For the data collected in all the experiments, the average amplitude of the contralesional vs. ipsilesional saccades did not show a significant change in monkey LBZ, either when tested in the light(p=0.77, ANOVA) or in darkness(p=0.37, ANOVA). Similarly, for monkey NWT, the average amplitude of the contralesional vs. ipsilesional saccades also did not change after muscimol lesion, either in the light(p=0.80, ANOVA) or in darkness(p=0.09, ANOVA).

Finally, to characterize the dynamic characteristics of the saccades, the main sequence of the relationship between peak velocity and amplitude is plotted in Figures 7 and 8. It can be seen that the main sequences remain relatively intact following muscimol lesion. We then compared the saccade velocity for three different amplitudes and the results are listed in Table 3. Data were taken from saccades with magnitudes of approximately 6 +/- 0.2 deg, 18 +/- 0.5 deg, and 30 +/- 2 deg, collected from all of the experiments. The results show that the saccade velocities decreased in some cases for monkey LBZ, but that this effect did not differ between contralesional and ipsilesional saccades. In other words, it was not spatially selective. For monkey NWT, the saccade velocities remained unchanged for all three of the amplitudes tested, whether in light or in darkness.

Visual extinction

VEXT_1.1 The average HIT rates for task VEXT_1.1 were 94.2%(control) and 96.6%(lesion) for monkey LBZ, and 95.1%(control) and 92.7%(lesion) for monkey NWT. The average MISS rates were 3.1%(control) and 5.5%(lesion), and 4.4%(control) and 8.7%(lesion) for monkey LBZ and NWT, respectively. In very few cases did the monkeys not make a saccade to either one of the targets in the extinction trials, even though some saccades were delayed such that they were not completed before the end of the trials. Trials where no saccades were made were not included for further analysis.

As a first test for any effects of muscimol lesioning, we examined the data to see if we could replicate the results obtained in the previous study(Li et al.,). For this behavioral task, we checked whether the latency of contralesional saccades(averaged across the three directions) increased in the regular saccade trials. The results showed that, for contralesional saccades, the latency increased from 211 msec to 260 msec for monkey LBZ($p<0.001$), and from 217 msec to 244 msec for monkey NWT($p<0.01$). For ipsilesional saccades, the latency remained relatively the same; 212 msec vs. 217 msec(lesion vs. control) for monkey LBZ($p=0.75$), and 236 msec vs. 230 msec for monkey NWT($p=0.87$).

The pattern of the saccades made in the extinction trials of one control and one lesion experiment for both monkeys is shown in Figure 9. For monkey NWT, an approximately equal number of rightward and leftward saccades were made in the control condition, but after the muscimol injection in the left hemisphere, the monkey predominantly made leftward saccades in the extinction trials. The distribution of leftward vs. rightward saccades is 54% vs. 46% in the control condition. After the muscimol injection in the left hemisphere, the frequency became 93% leftward vs. 7% rightward(χ^2 test, $p<0.0001$). For monkey LBZ, the frequency of leftward vs. rightward saccades was 92% vs. 8% for control(possibly as a result of chronic recording from the left hemisphere for up to two years prior to this lesion experiment). After muscimol injection into the right area LIP, the frequency became 6% leftward vs. 94%, rightward(χ^2 test, $p<0.0001$).

We then examined the effects on saccade latency. Since the monkeys made very few contralesional saccades in the extinction trials, we only performed the analysis on ipsilesional saccades. An analysis of variance showed that the increase of latency which occurred in the ipsilesional saccades in the extinction trials(as a result of bilateral presentation of the targets) is significantly smaller after muscimol lesioning. For monkey LBZ, the latencies of ipsilesional saccades were (regular saccades vs. extinction trials) 211 vs. 255 msec and 260 vs. 286 msec, for the control and lesion experiments, respectively(ANOVA, $p<0.001$). For monkey NWT, the results were (regular vs. extinction trials) 236 vs. 288 msec for the control, and 230 v. 244 msec for the lesion(ANOVA, $p<0.001$). In other words, for both monkeys, the increase of latency seen for ipsilesional saccades in extinction trials of the control experiment greatly diminished after muscimol lesion of area LIP.

VEXT_1.2 As in VEXT_1.1, we first documented the effect of muscimol lesioning by comparing the latency of the contralesional and ipsilesional saccades in the regular visual saccade trials. The results showed that the contralesional saccades were consistently increased in latency(averaged across different fixation positions) for both monkeys(lesion vs. control): 277 vs. 235 msec(contralesional, $p<0.005$) and 232 vs. 233 msec(ipsilesional, $p=0.96$) for monkey LBZ; 280 vs. 241 msec(contralesional, $p<0.002$) and 243 vs. 232 msec(ipsilesional, $p=0.32$) for monkey NWT.

An analysis of variance showed that the distribution of response modes in extinction trials was also different after area LIP lesion: 23%, 14%, 63%(leftward saccades, stay puts, rightward saccades) for control, and 58%, 8%, 34% after lesion for monkey NWT($p<0.001$, χ^2 test). Similar results were obtained for monkey LBZ: 63%, 13%, 24%(leftward saccades, stay puts, rightward saccades) for control, and 14%, 12%, 74% after lesion($p<0.001$, χ^2 test). Note that the lesion was in the left hemisphere for monkey NWT and in the right hemisphere for monkey LBZ. Furthermore, this change of the distribution of the response patterns varied with eye position($p<0.001$ for monkey NWT; $p<0.03$ for monkey LBZ). Let us take monkey NWT as an example to describe in some detail the change in behaviors in the extinction trials as a result of muscimol lesioning. The histograms of the number of rightward and leftward saccades in the extinction trials, collected from all the experiments, are shown for different eye positions in Figure 10. The distribution of rightward vs. leftward saccades in the extinction trials was fairly even when fixation point was straight ahead in the control condition. As the fixation point moved to either side, the monkey made more saccades towards the midline than to the periphery. Eventually, when the starting point was at (-15,0) or (15,0), almost all saccades made were centripetal. After the muscimol injection(in the left hemisphere), the distribution of leftward vs. rightward saccades in the extinction trials changed; overall, more ipsilesional saccades were made, and this altered frequency of ipsilesional vs. contralesional saccades varied with the starting eye position. When the monkey started out fixating straight ahead, nearly all of the saccades made were in the ipsilesional direction. When the fixation point moved 5 or 10 degrees to the right, again most of the saccades made in the extinction trials were to the left, not unlike those observed in the control condition. The critical observation occurred when the fixation point moved to locations 5, 10 and 15 degrees to the left(the ipsilesional field). When the fixation point was 5 deg to the left, in which case the targets on the two retinal hemifields were also located in opposite hemispaces relative to the midline of the head/body, the monkey made many more ipsilesional(leftward) than contralesional(rightward) saccades. This differed greatly from the control condition where the saccades made were mostly to the right(i.e., toward the midline). At 10 deg to the left, the monkey was still inclined to make more leftward saccades than he did in the control condition, but the difference was not as dramatic as when the fixation point was straight ahead or 5 deg to the left. Finally, when he started out fixating 15 deg to the left, in which case targets were on opposite retinal hemifields but in the same head-centered hemispace, the monkey behaved similarly as he did in the control condition; most of the saccades he made were towards the midline, in the contralesional direction(rightward). In other words, the severity of visual extinction greatly decreased when the targets were located in the same head-centered hemispace. A similar behavioral pattern was observed for monkey LBZ.

VEXT_2 The performance of monkey NWT in the regular saccade trials for both the control and lesion experiments(average HIT rates: 98.4 and 96.1%, respectively) in this behavioral task was nearly perfect. Figure 11(A) shows the error rate in the extinction trials for different initial eye positions in both the lesion and control experiments. In the control experiments, when the monkey started out at 15 deg to the right or left, he made a few errors when cued to make a saccade further away from the midline. His performance with the fixation point at less eccentric locations was quite good. After musicmol lesioning, overall, he made more errors in the extinction trials when the cued target was in the contralesional field. The average error rates were: 15.9% vs.

34.6%(control vs. lesion, $p<0.001$, ANOVA). Furthermore, the error rates also depended on the initial fixation positions($p<0.01$, ANOVA). When the fixation point was at the straight ahead or 5 deg to its right or left, the monkey made many more errors when the cued location was on the contralesional side. Instead of making a contralesional saccade, the monkey would made a saccade toward the ipsilesional target. In these cases, targets on opposite retinal hemifields were also located in opposite head-centered hemispaces. However, as the fixation point moved further to the periphery, so that both targets were confined to the same head-centered hemispace(even though they were still in opposite retinal hemifields), the error rates in the extinction trials dropped and eventually mimicked the pattern seen in the control condition. Therefore, the error rate in the extinction trials varied with the initial eye position and increased when the monkey was cued to make a saccade towards a target in the head-centered contralesional hemispace. On the other hand, no significant differences in error rate were found for ipsilesional saccades(control vs. lesion): 8.8% vs. 9.8%($p=0.78$, ANOVA), nor were there any effects of initial eye positions($p=0.14$, ANOVA).

The second part of the analysis for this behavioral task focuses on the latency increase in the extinction trials(Figure 11B). The average increase in latency(lesion minus control) in the extinction trials as a result of bilateral presentation of targets was computed, separately for rightward and leftward saccades. These values were then compared between the lesion and control experiments, using the starting position as another variable, and with a repeated measures ANOVA. The results showed that, for rightward(contralesional) saccades, the latency increase in the extinction trials was greater in the control than in the lesion experiment: The latency was increased from 251 msec to 304 msec in the control and from 260 msec to 271 msec in the lesion experiment($p<0.01$). Furthermore, such difference was significantly modulated by eye position($p<0.001$). For leftward(ipsilesional) saccades, the latency increase was not significantly different between lesion and control: The latency increased from 237 msec to 254 msec in the control and from 243 to 258 msec in the lesion experiment($p=0.29$), and this difference did not vary with eye position($p>0.5$).

Discussion

The results obtained in this study show that, in agreement with a previous chronic ablation study(Lynch and McLaren, 1989), even though lesion in the posterior parietal lobe in monkeys does not produce an overt spatial neglect, it does result in the extinction of the contralesional visual stimulus. By varying the initial fixation position, so that the retinal and spatial locations of the targets are dissociated, we further demonstrate that the extinction of the contralesional stimulus is best described in a head-centered framework. On the other hand, area LIP lesioning does not appear to severely affect spontaneous eye movements, other than slightly decreasing the number of contralesional saccades made when the animals are tested in the light. However, inactivation of this area consistently results in a relative restriction of gaze to the ipsilesional space. We will discuss these findings in the following.

Spontaneous eye movement and visual fixation

Studies in behaving primates have identified several cortical and subcortical areas that contain saccade-related activities. Neurons in the frontal eye field(FEF), the dorsolateral prefrontal cortex and the posterior parietal cortex increase their firing rate to task-related saccadic eye movements, but do not seem to discharge at an equally high rate for spontaneous saccades in the intertrial intervals or other task-unrelated conditions(Bruce and Goldberg, 1985; Funahashi et al., 1991; Goldberg and Bushnell, 1981; Mountcastle et al., 1975; Lynch et al., 1977; Schall, 1991b; Segraves and Goldberg, 1987). It is notable that in Bizzi's original experiment, in which the monkeys were not engaged in controlled saccade tasks, only 4% of neurons were found to be saccade-related and very rarely pre-saccadic(Bizzi, 1968). It seems that the enhanced motivation in task-related conditions increases saccade-related neuronal discharges in these cortical areas.

One documented exception appears to be the supplementary eye field(SEF), where Schlag and Schlag-Rey found that neurons responding before self-initiated and visually guided saccades discharged equally well before spontaneous eye movements(Schlag and Schlag-Rey, 1985; Schlag and Schlag-Rey, 1987). In fact, some cells were found to respond exclusively before spontaneous saccades(Schlag and Schlag-Rey, 1987). It was suggested that the SEF is specialized for processing saccades based on internal cues. One important piece of evidence supporting this hypothesis is the prelude activities in the SEF, which gradually increase 300 msec before a saccade is initiated(Schalg and Schlag-Rey, 1987). However, Schall presented some evidence seemingly to the contrary(Schall, 1991). In this study he found that neurons in the SEF did not appear to discharge in task-unrelated conditions. It was suggested that this discrepancy between the two separate findings likely reflected the differences between the two experimental paradigms and reward contingencies. Unlike most other studies, in Schlag and Schlag-Rey's experiments, there was no clear distinction between the trial and intertrial intervals, necessitating that the monkey be alert all the time. This hightened motivation could presumably lead to a higher neuronal discharge rate.

This view could presumably explain the lack of spontaneous activities found in the FEF and other cortical areas in earlier studies(Bizzi, 1968; Bruce and Goldberg, 1985). However, in Goldberg and Bushnell's experiment, FEF neurons activated before task-related saccades were found not to repsond to spontaneous eye movements even when the monkeys were rewarded(Goldberg and Bushnell, 1981). This latter result and the finding that some SEF cells respond exclusively to spontaneous saccades(Schlag and Schlag-Rey, 1987) could not easily be explained by the "motivation" hypothesis. Further studies are required to determine how much of this variation of saccade-related activities in task-related and task-free conditions result from different states of motivation of the monkey, and whether a disctinction can be made among the different cortical areas involved in the generation of task-related and spontaneous eye movements.

Finally, the activities before spontaneous saccades are less ambiguous in the superior colliculus(SC). Other than the "visually triggered movement cells," most eye movement-related cells in the SC discharge before spontaneous saccades(Mohler and Wurtz, 1976; Schiller and Koerner, 1972; Schiller and Stryker, 1972; Wurtz and Goldberg, 1972) and the quick phase of the nystagmus(Schiller and Stryker, 1972; Wurtz and Goldberg, 1972). It is interesting to note that prelude activities similar to those observed in the SEF were also found in the SC(Mays and Sparks, 1980).

Similar to most of the aforementioned recording studies, most lesion experiments were carried out with the animals engaged in controlled behavioral tasks. Except for one study in which chemical lesioning of the caudate nucleus was shown to result in reduced amplitude and peak velocity, and prolonged duration of the contralesional saccades(Kato et al., 1995), most of these experiments did not systematically examine the effect of lesioning on spontaneous eye movements. As was discussed in the previous paper(Li et al.,), lesioning of the FEF and the SC seems to affect the metrics and dynamics of both visual and memory saccades(Dias et al., 1995; Hikosaka and Wurtz, 1985). However, other than briefly describing that contralesional saccades were slower(Hikosaka and Wurtz, 1985), they did not address whether these effects on saccadic eye movements would be replicated if the monkeys were tested under no-task conditions. On the other hand, unilateral decortication appears to have less of an effect on spontaneous eye movements than on predictive and visually guided saccades(Tusa et al., 1986). It was shown in this study that the removal of one cortical hemisphere resulted in severe impairment of voluntary saccades but not in the initiation of spontaneous eye movements even during the initial post-operative period.

Most of the chronic ablation and reversible inactivation experiments reported a reduced frequency of eye movements to the contralesional field after FEF or SC lesions(Rizzolatti et al., 1993; Albano et al., 1982a; Latto and Cowey, 1971). In the case of FEF lesion, the lesioned animal kept his gaze at the ipsilesional field most of the time and rarely explored the environment in the contralesional space. The tracking of an object which initiated in the ipsilesional field and moved in the contralesional direction often stopped at the midline(Rizzolatti et al., 1993; Latto and Cowey, 1971). A similar disorder in visual fixation was observed after the ablation of the SC(Albano et al., 1982; ; Schiller et al., 1980). Combined lesioning of the FEF and SC further reduced the range of eye movement and the total number of saccades made also drastically decreased(Keating et al., 1988; Schiller et al., 1980). When different orbital positions were tested, it was found that targeting errors for saccades to visual targets increased with the eccentricity of the targets(Albano and Wurtz, 1982b). It was suggested that this finding indicated that the oculomotor deficits observed after lesioning the SC and neighboring pretectal structures(presumably involving the descending pathway from the FEF to the brain stem) were related to the position of the eye in the orbit. Likewise, studies in which local dopamine was depleted in the caudate nucleus showed that spontaneous saccades became less frequent, and the range of saccadic eye movements became narrower and shifted to the ipsilesional field(Kato et al., 1995; Miyashita et al., 1995). Similar deficits related to eye position were found after unilateral hemi-decortication(Tusa et al., 1986). It was shown that the quick phases of nystagmus and spontaneous saccades could be initiated immediately after the operation, although those initiated away from the side of the lesion were reduced in amplitude and rarely moved the eyes into the contralateral craniotopic space. This study suggests that the cerebral cortical structures provide the information which specifies the desired eye position in eye movements.

In our experiments, there was a clear separation between trials and intertrial intervals. The results showed that, following area LIP lesioning, the frequency of the contralesional saccades decreased slightly. The eye movements recorded either in light or in darkness did not differ in velocity or consistently in amplitude. Lesioning of area LIP, therefore, did not appear to have a severe effect on the saccadic eye movements in task-free conditions. On the other hand, the inactivation of this area resulted in a consistent pattern of altered fixation - the monkeys tended to confine their gaze to the ipsilesional field, either when tested in light or in darkness. This result is consistent with the findings of the clinical studies of parietal patients, which showed that the exploratory eye movements of these patients were normal in both directions even though they were mostly engaged in the ipsilesional field (Chedru et al., 1973; Doricchi et al., 1991; Ishiai et al., 1989). Overall, these results seem to suggest that area LIP does not play a preempting role in processing the metrics and dynamics of saccades carried out in no-task conditions. Along with the results obtained in the previous experiments on visual and memory saccades, it further supports the idea that area LIP is specifically involved in transforming sensory information for movement planning.

As was discussed in the previous section, similar observations of an ipsilesional fixation bias were made in lesion studies of the FEF, SC and the caudate nucleus. Thus, it seems that the shift of gaze to the ipsilesional field is one among the most common findings obtained after lesioning of these cortical and subcortical oculomotor areas. One possible explanation for the abnormal fixation behaviors observed after lesioning of these oculomotor structures is that the lesioned animals suffer attentional deficits and are unable to direct their attention to the contralesional space. In other words, their access to the representation of the contralesional space is impaired, rendering a biased shifting of gaze to the ipsilesional space. The representation of the visual space itself is probably still intact, as evidenced by the finding that the monkeys could still make a visually guided saccade to a target in the contralesional field. On the other hand, since eye movements are likely to be the primary mechanism in orienting attention, it is plausible that the failure to access the representation of the contralesional space is a result of defective eye movements. Such a pathophysiological mechanism could explain the ipsilesional shift of gaze observed following lesioning of the SC, given that lesioning of this structure appeared to affect spontaneous saccades(Hikosaka and Wurtz, 1985a). Moreover, it has been shown that inactivation of the substantia nigra pars reticulata(SNpr) results in an ipsilesional shift of eye position(Hikosaka and Wurtz, 1985b). Presumably the removal of tonic inhibition of the SNpr on the SC leads to continual saccades towards the ipsilesional side, resulting in the change of eye position. However, in the case of area LIP lesioning, since we did not observe a severe effect on the spontaneous eye movements per se, the ipsilesional shift of gaze is probably not simply a result of failing oculomotor functions. On the other hand, it has been shown that area LIP is involved in encoding the contralesional space(see Andersen, 1995, for a review); it appears that the eye position deficits observed in this study are more due to defects at a representational rather than at a motor level unlike those obtained in the SC or FEF lesion studies. Overall, these different studies seem to suggest that the disruption of either the oculomotor mechanisms or the neural representation of space could result in similar impairments of ocular fixation.

Visual extinction

It has long been known that parietal patients tend to neglect the contralesional space. The spatial domain of neglect can include the patient's own body, the peripersonal and the far extrapersonal space(see Grüsser, 1983, for a review). Many studies further demonstrate that the unilateral neglect of the extrapersonal space occurs in an egocentric framework with reference to the midline of the body(Karnath, 1994a; Karnath et al., 1991; Karnath et al., 1994c). A related behavioral problem frequently encountered in parietal patients is visual extinction. This behavioral deficit appears to be the result of a failure to encode a contralesional stimulus in the presence of competing ipsilesional sensory stimuli (Bisiach, 1991). Visual extinction could occur as a result of the lesioning of neural structures at many different levels throughout the nervous system, and it is frequently encountered in parietal patients(Bisiach, 1991). Even though its exact pathophysiological mechanism is yet to be clarified, many studies suggest that, as has been demonstrated for unilateral neglect, visual extinction is not caused by primary sensory deficits(Bellas et al., 1988; Moscovitch and Behrmann, 1994). Studies in parietal patients with extinction have generally implicated a failure in the early orienting of attention as a mechanism of extinction, such that information in the contralesional space is not properly encoded when faced with stimuli competing for registration from the intact hemifield(Bisiach et al., 1989; Di Pellegrino and De Renzi, 1995; Ladavas, 1990). Such an attentional-representational account of extinction in parietal patients is also supported by studies showing that visual extinction can be induced by transcranial magnetic stimulation of the parietal, but not the occipital or temporal lobe(Pascual-Leone et al., 1994).

The reference frame of visual extinction has not been as systematically investigated as it has been in spatial neglect. There are several studies, however, suggesting that the severity of visual extinction varies according to both the spatial and retinal locations of the stimuli. By manipulating the locations of the visual stimuli, Di Pellegrino and De Renzi demonstrated in parietal patients that when both stimuli were in the left(contralesional) hemifield, extinction still occured but at a frequency(86%) lower than that(100%) which occurred when stimuli were presented at opposite sides of the fixation point. Furthermore, the patients invariably perceived both stimuli when they were presented in the right(ipsilesional) hemifield(De Pellegrino and De Renzi, 1995). Similar results were obtained in another study(Rapcsak et al., 1987), in which it was shown that both the retinal and spatial locations of the target contributed to the severity of visual extinction.

The phenomenon of extinction has also been demonstrated in parietal monkeys, both in tactile(Eidelberg and Schwartz, 1971; Schwartz and Eidelberg, 1968) and in visual modalities(Lynch and McLaren, 1989). In the latter sudy, it was found that ablation of the parietooccipital area resulted in the extinction of the contralesional stimulus when targets were presented on both sides of the fixation point in a visual saccade paradigm. No overt spatial neglect was observed after such lesions, as the monkeys could make saccadic eye movements to a contralesional target. It was suggested that the altered performance in the two-target task was not produced by visual or oculomotor deficits but rather by a change in the monkey's ability to attend to a stimulus in one situation but not in another. In other words, the results in this study confirmed that lesion of the parietooccipital area is sufficient to alter the monkeys' ability to attend to events in their visual environment, even though these alterations were mild compared to the contralesional neglect observed following posterior parietal lesions in humans.

In this study we confined our lesion to a relatively well defined area in the posterior bank of the lateral intraparietal sulcus and replicated the results concerning visual extinction obtained by Lynch and McLaren. Besides finding an altered frequency of rightward versus leftward saccades, we were also able to demonstrate visual extinction by observing the effects on saccade latency in extinction trials after muscimol lesioning. The results showed that the latency increase that was seen in extinction trials(as a result of bilateral presentation of targets) disappeared after area LIP was inactivated.

Furthermore, in order to explore the coordinate frame of visual extinction, we systematically varied the location of the initial fixation position while keeping the visual targets at the same retinal locations. We showed that the altered frequency between contralesional and ipsilesional saccades varied with the initial eye position. These results suggest that visual extinction is best described in a head-centered coordinate frame. Such extraretinal modulation of the extinction of the contralesional stimulus is further confirmed in the experiment using paradigm VEXT_2, in which both the number of error and the change of saccade latency in extinction trials were shown to vary with initial eye position. These results are consistent with unit recordings from area LIP, which show that this area is engaged in encoding stimulus location in a head-centered space(see Andersen, 1995, for a review). Together with the experiments in a companion paper(Li and Andersen, in preparation), which demonstrated a deficit in eye position signal, the results obtained on visual extinction in this study lend futher support to the existence of a representation of a head-centered space in the posterior parietal cortex.

FIGURE LEGENDS

FIGURE 1

Eye traces of monkey LBZ in one control(A) and lesion(B) experiment, and monkey NWT in one control(C) and lesion(D) experiment. These data were collected when the animals were tested in the light. Each dot represents an instantaneous eye position sampled every 2 msec. For both monkeys, the eye positions were nearly symmetrically distributed across the vertical meridian in the control condition. Following muscimol lesioning(in the right hemisphere of monkey LBZ and left hemisphere of monkey NWT), their fixations were relatively restricted to the ipsilesional field. In the case of monkey LBZ, this effect was primarily seen in the lower quadrant.

FIGURE 2

Eye traces of monkey LBZ in one control(A) and one lesion(B) experiment, and monkey NWT in one control(C) and one lesion(D) experiment carried out in darkness. In contrast to those data obtained in the light, the fixations in darkness were biased toward the upper hemifield. The number of saccades made decreased and the range of eye movement narrowed compared to the behavior in the light. After muscimol lesioning, there was a tendency for the monkeys to shift their gaze towards the ipsilesional field, even though this ipilesional bias did not appear to be as great as that seen in the light.

FIGURE 3

The intersaccadic intervals of the data shown in Figure 1. Data were collected in one control and one lesion experiment in the light for both monkeys. The control data(pre-L) are shown in the upper row and the lesion data(post-L) in the lower row. The left four panels are data from monkey LBZ and the right four from monkey NWT. The intersaccadic intervals are plotted with respect to the x and y positions where the antecedent saccades ended. The arrow heads mark the zero points of the x and y axes. See the text for further explanation.

FIGURE 4

The intersaccadic intervals of the data shown in Figure 2. These data were collected in the dark and organized as in Figure 3. See the text for further explanation.

FIGURE 5

The distribution of the saccade amplitudes for all data from both monkeys collected in the light. Each bar in the histogram represents the average number of saccades of a specified amplitude made in a 10 min period. The data are shown separately for contralateral(c) and ipsilateral(i) saccades. The control data(pre-L) are shown in the upper row and the lesion data(post-L) in the lower row. For the saccades collected in the light, the distributions skew towards small amplitudes. See the text for statistics and further explanation.

FIGURE 6

The distribution of the saccade amplitudes for all data from both monkeys collected in the dark. Each bar in the histogram represents the average number of saccades of a specified amplitude made in a 6.7 min period.The data are organized as in Figure 5. The average amplitudes of these saccades are larger than those made in the light. See the text for statistics and further explanation.

FIGURE 7

The main sequences of the saccade's peak velocity vs. amplitude for the data collected in the light and shown in Figure 1. The data are organized as in Figure 5. The velocities of the saccades increase with amplitude and this relationship remains intact after muscimol lesioning. See the text for further explanation.

FIGURE 8

The main sequences of the saccade's peak velocity vs. amplitude for the data collected in the dark and shown in Figure 2. The velocities of saccades do not differ between the lesion and control experiments either for ipsilesional or contralesional saccades. Note that the scales of the x and y axes are proportional to those in Figure 7. See the text for further explanation.

FIGURE 9

Eye traces of monkey NWT in the extinction trials from one experiment using paradigm VEXT_1.1. In the control condition(pre-L), an approximately equal number of rightward and leftward saccades were made. Following muscimol lesion(post-L), the saccades made were predominantly in the ipsilesional direction. The lesion was in the left hemisphere.

FIGURE 10

The distribution of different responses(leftward saccades, stay puts, rightward saccades in the extinction trials using the paradigm VEXT_1.2. The data are plotted for different initial eye positions(iep). The control and lesion data from monkey LBZ are presented in the upper two rows and those from monkey NWT in the lower two rows. See the text for statistics and further explanation.

FIGURE 11

The number of errors(upper row) and the latency increase(lower row) in the extinction trials using paradigm VEXT_2. The data are plotted for different initial eye positions(iep). For each panel, the two bars on the left contain data from ipsilesional saccades and those on the right contain data from contralesional saccades. See the text for statistics and further explanation.

TABLE LEGENDS

TABLE 1

The average duration of the intersaccadic intervals(standard deviations in brackets) for all data. The data collected in the light and in the dark are shown separately for both the contralesional and ipsilesional saccades. See the text for statistics and further explanation.

TABLE 2

The average number and amplitude of the saccades(standard deviations in brackets) for all control and lesion sessions. The data collected in the light and in the dark are shown separately for both the contralesional and ipsilesional saccades. See the text for statistics and further explanation.

TABLE 3

The average velocity of the saccades for three different amplitudes(standard deviations in brackets). The differences in velocity were tested for each amplitude of saccade using ANOVA; the first p value stands for the difference between the lesion and control data and the second p value for the interaction between the test condition(lesion vs. control) and the saccade direction(contral. vs. ipsil.). See the text for further explanation.

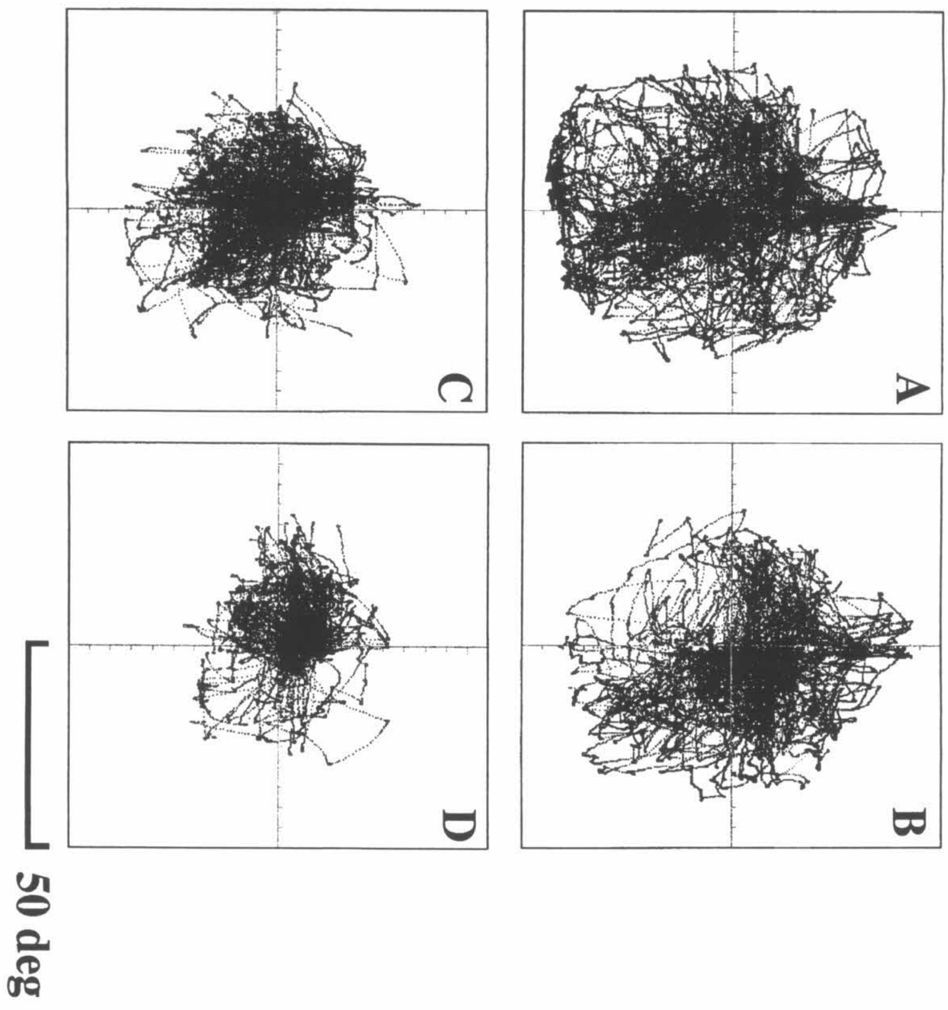


Figure 1

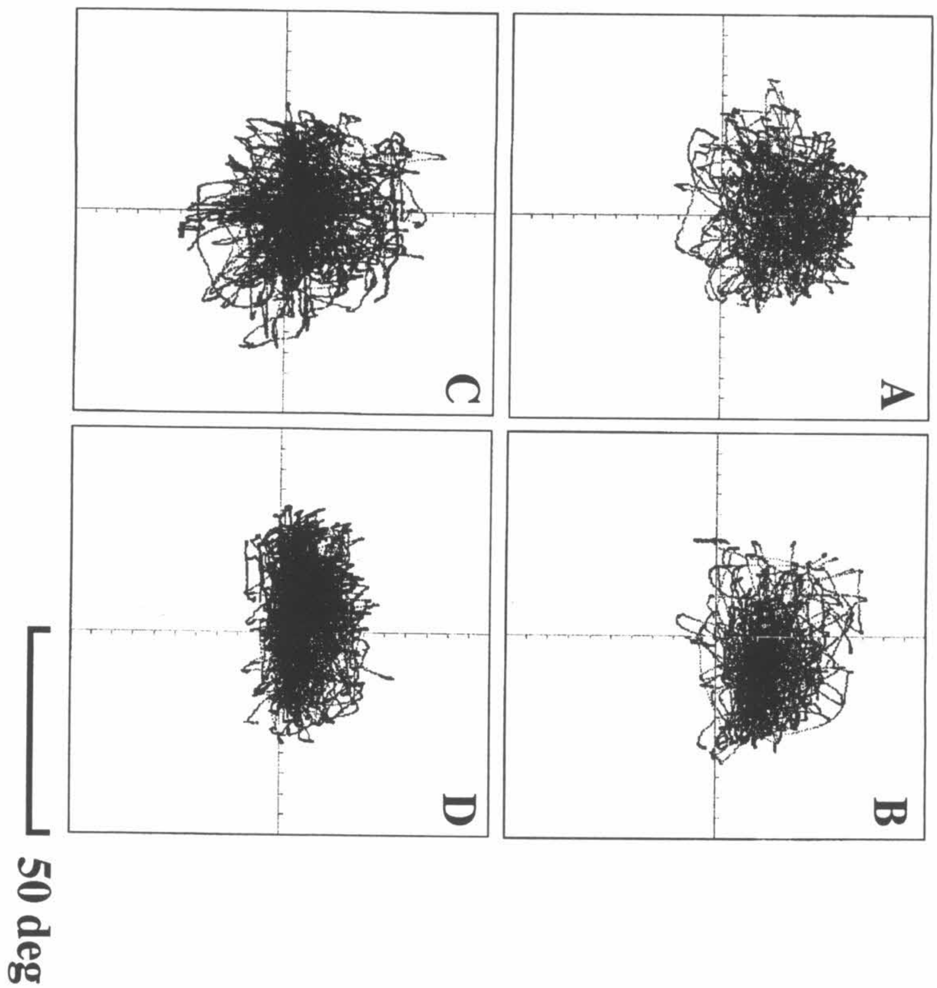
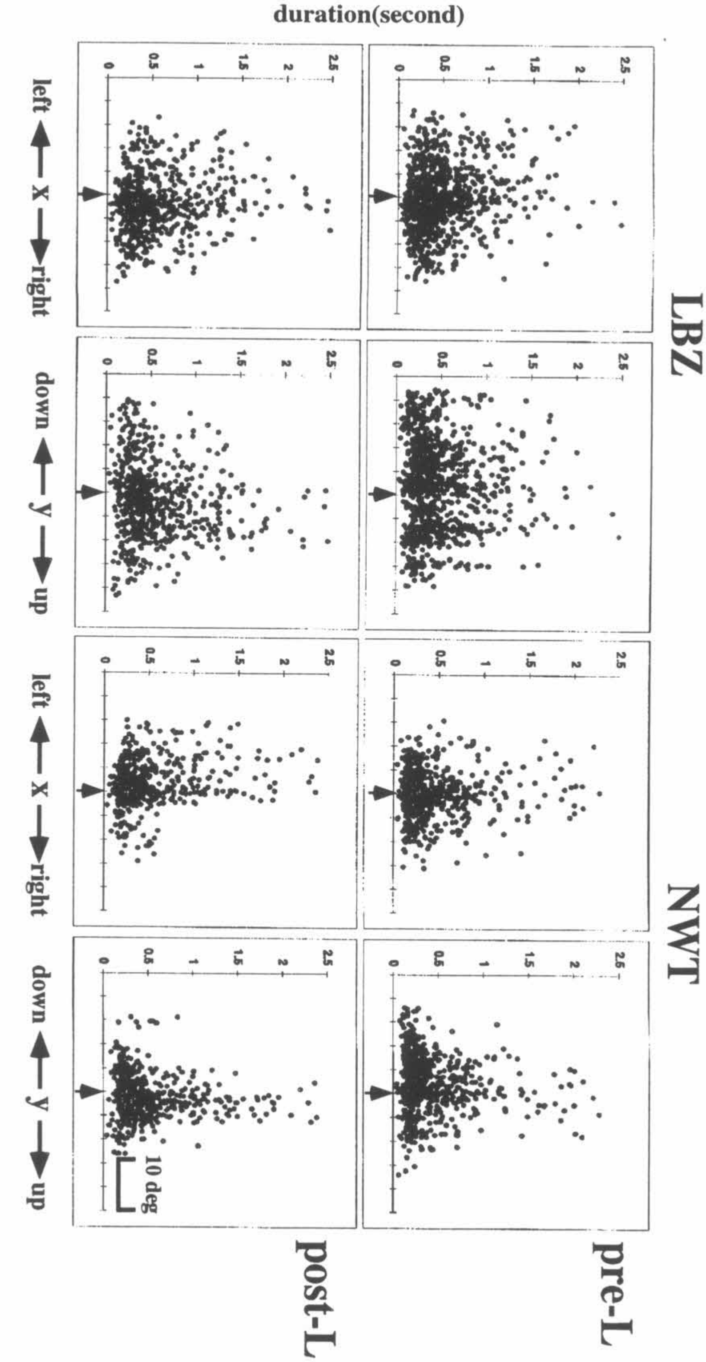


Figure 2



duration(second)
LBZ
NWT
pre-L
post-L
left ← x → right
down ← y → up
10 deg
0
0.5
1
1.5
2
2.5

Figure 3

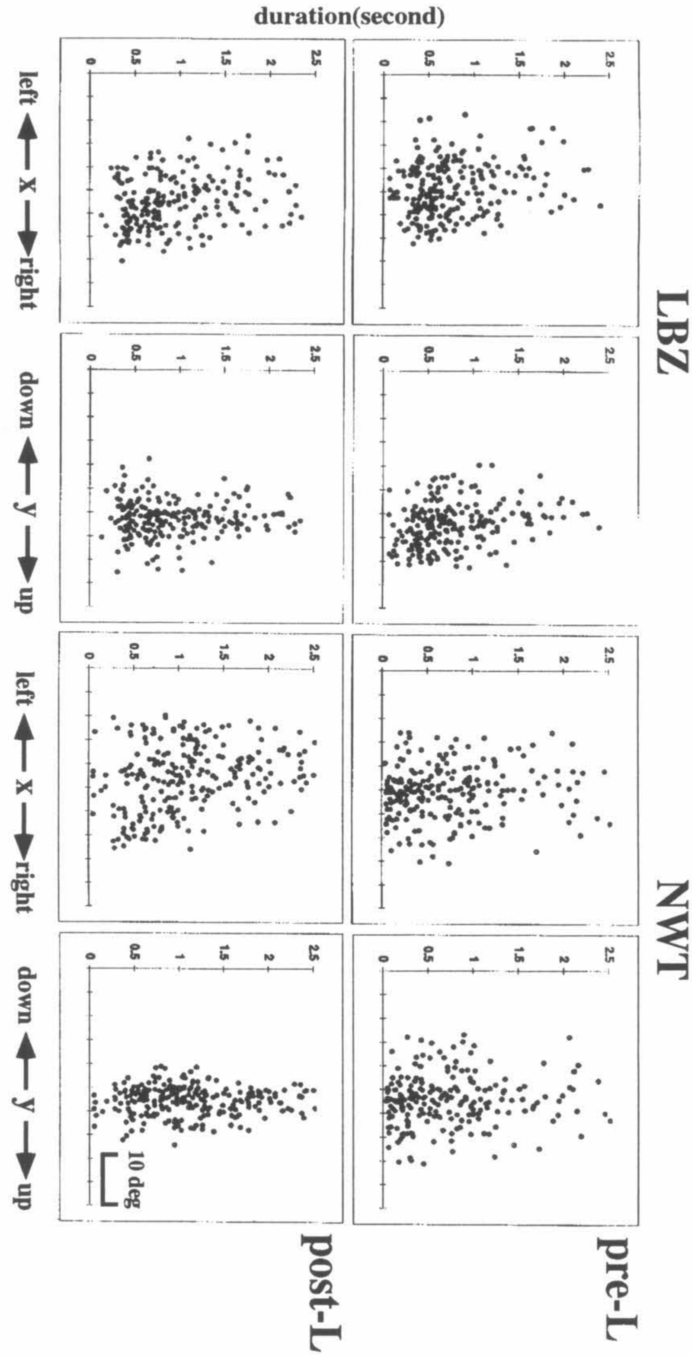

duration(second)
LBZ
NWT
pre-L
post-L
left ← x → right
down ← y → up
10 deg
0
0.5
1
1.5
2
2.5

Figure 4

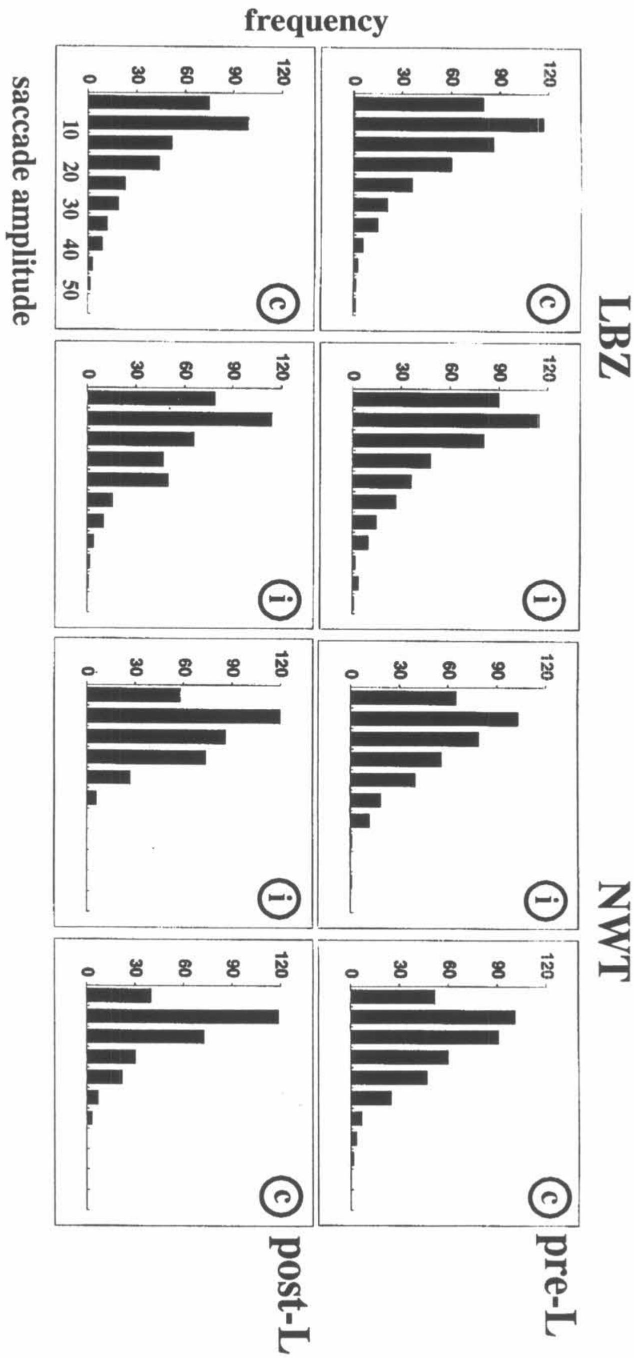
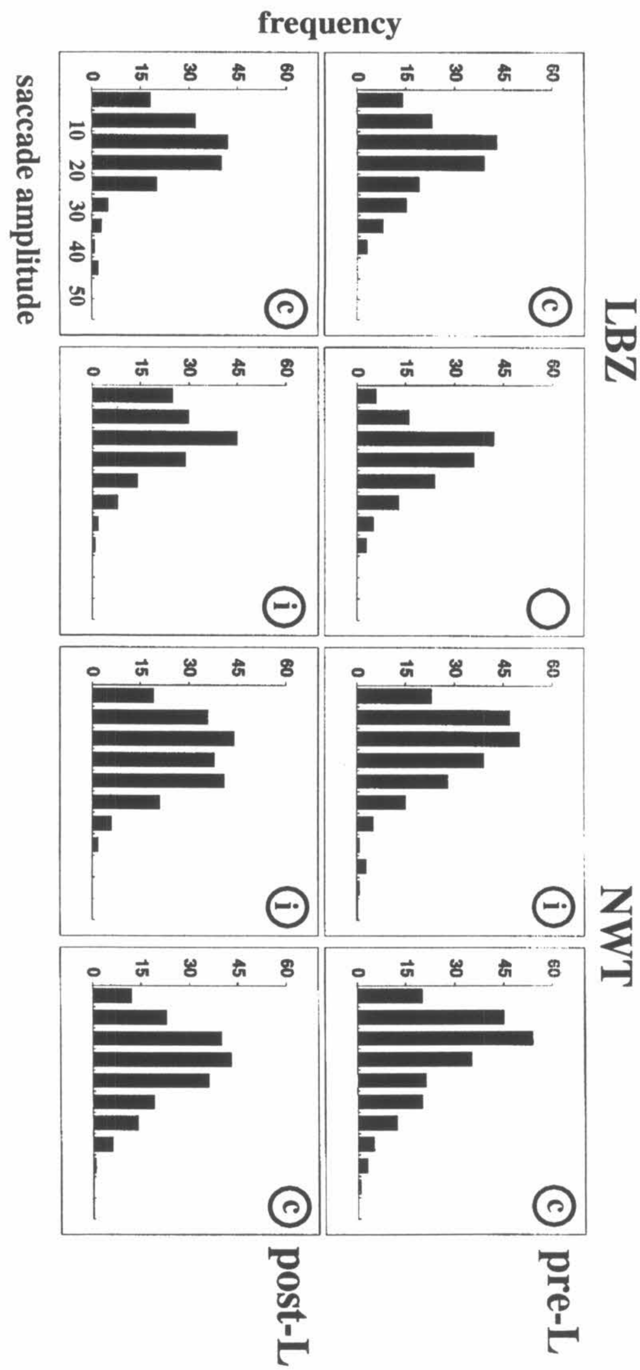

LBZ
NWT
pre-L
post-L
frequency
saccade amplitude
c
i
i
c
c
i
i
c
0
30
60
90
120
10
20
30
40
50

Figure 5



LBZ
NWT
pre-L
post-L
frequency
saccade amplitude
0
15
30
45
60
10
20
30
40
50
c
i

Figure 6

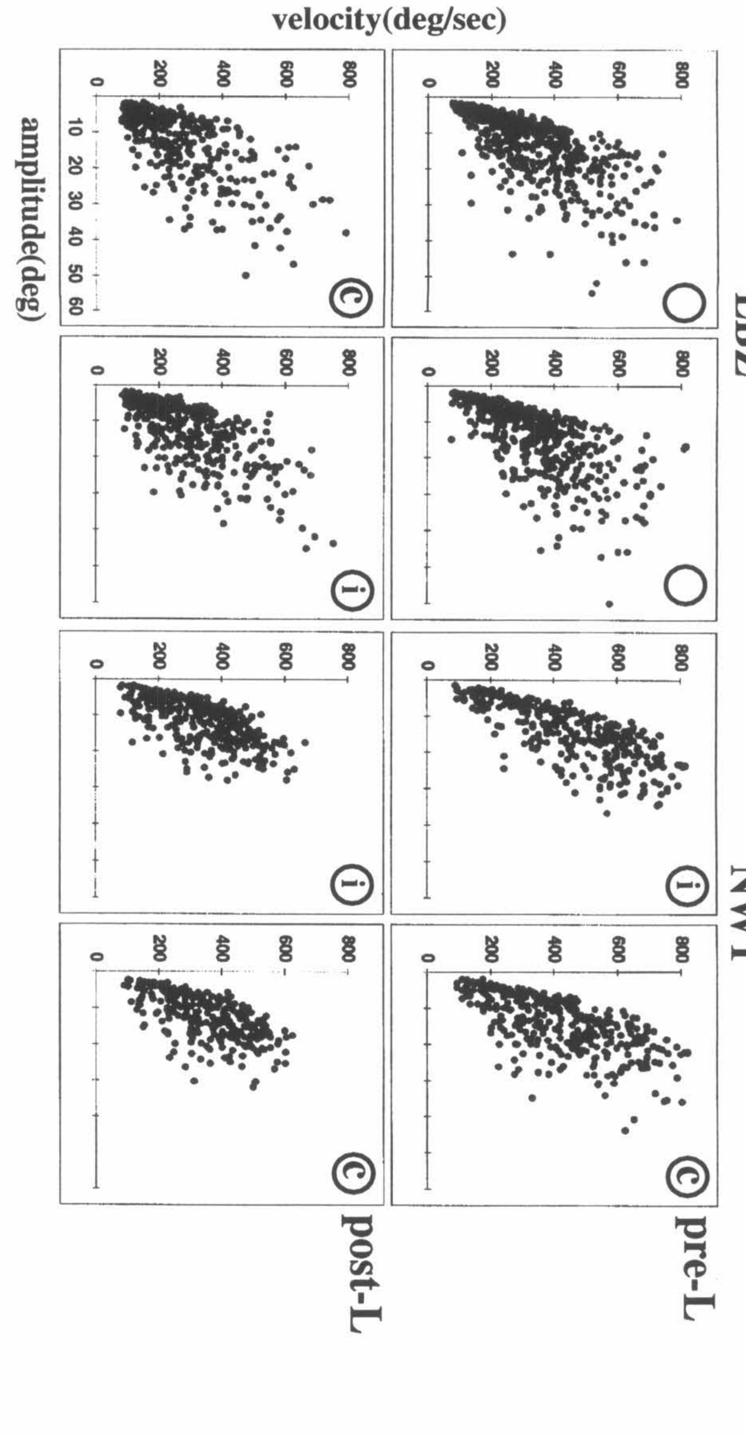

LBZ
NWT
pre-L
post-L
velocity(deg/sec)
amplitude(deg)
0
200
400
600
800
10 20 30 40 50 60
c
i
i
c

Figure 7

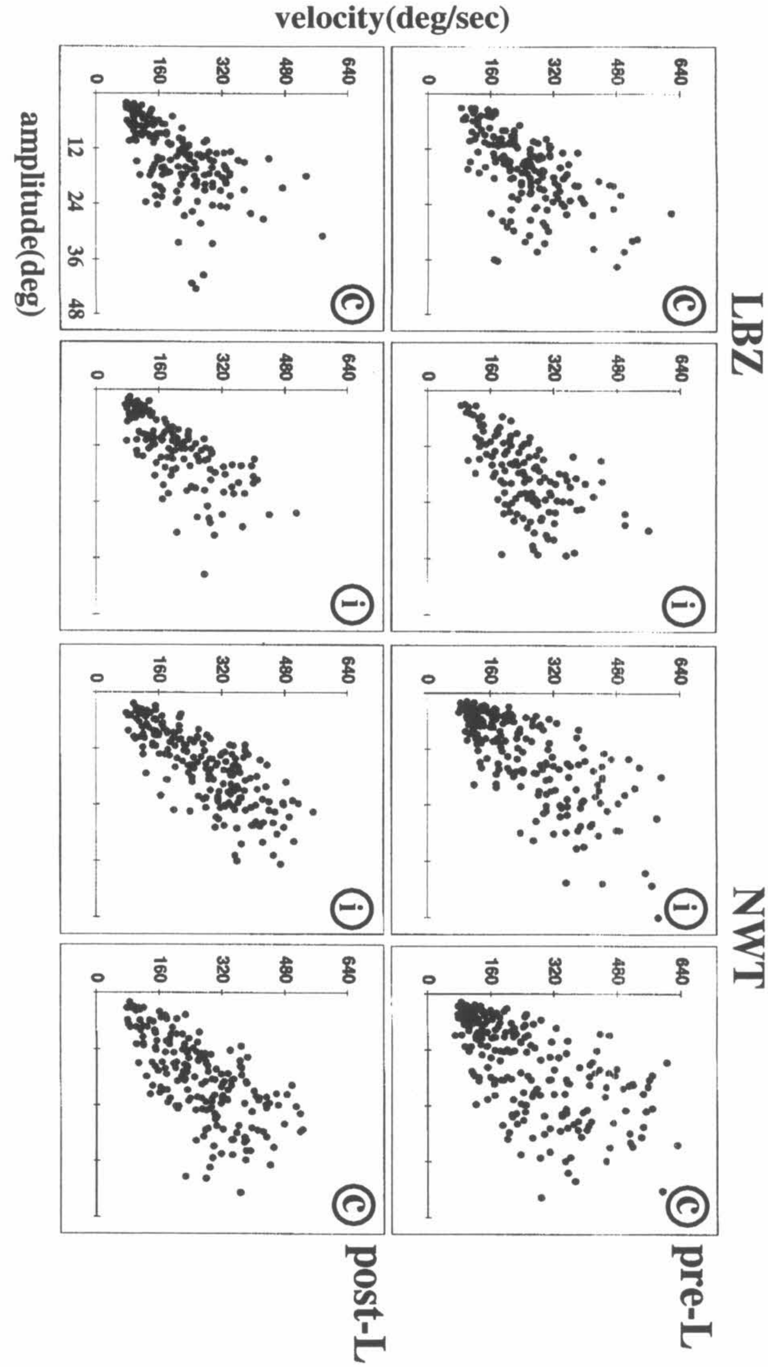

velocity(deg/sec)
amplitude(deg)
LBZ
NWT
pre-L
post-L
c
i
i
c
c
i
i
c
0
160
320
480
640
12
24
36
48

Figure 8

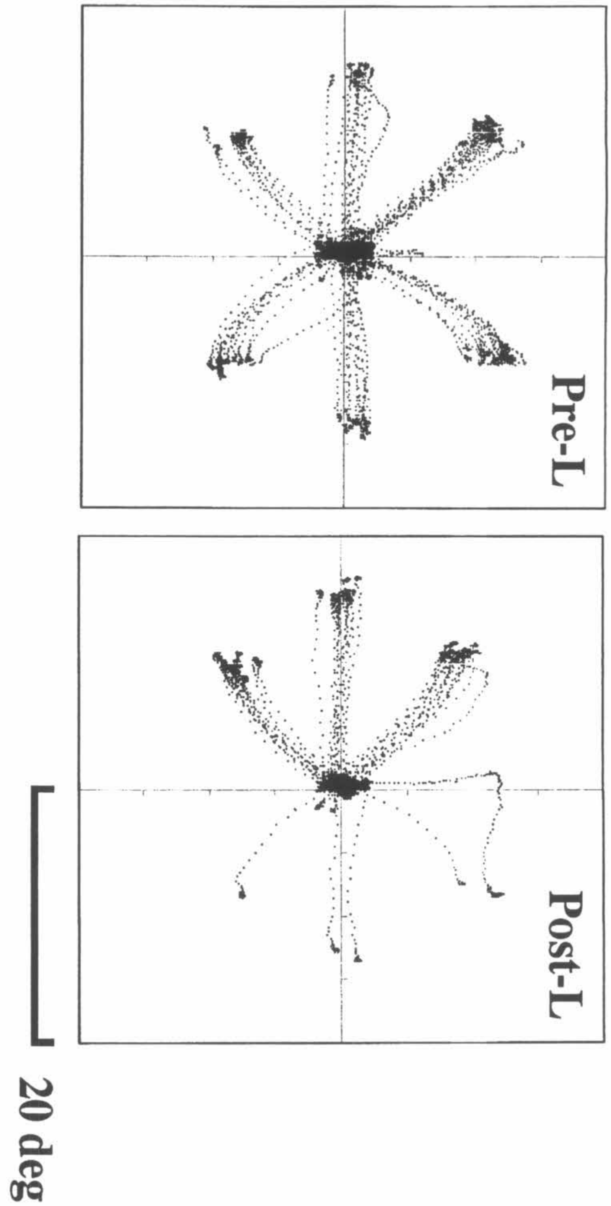


Figure 9

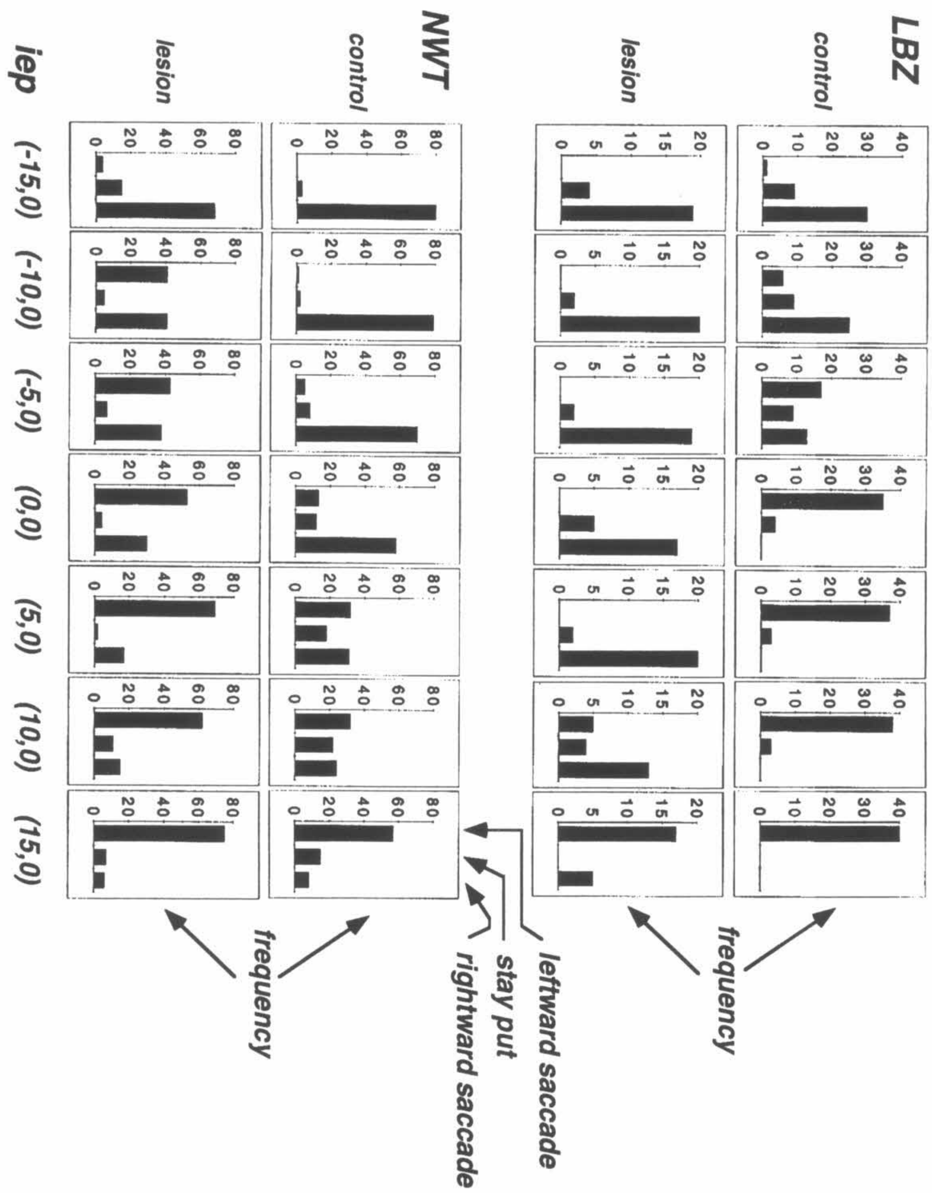

LBZ
control
lesion
NWT
control
lesion
iep
(-15,0)
(-10,0)
(-5,0)
(0,0)
(5,0)
(10,0)
(15,0)
frequency
leftward saccade
stay put
rightward saccade
frequency

Figure 10

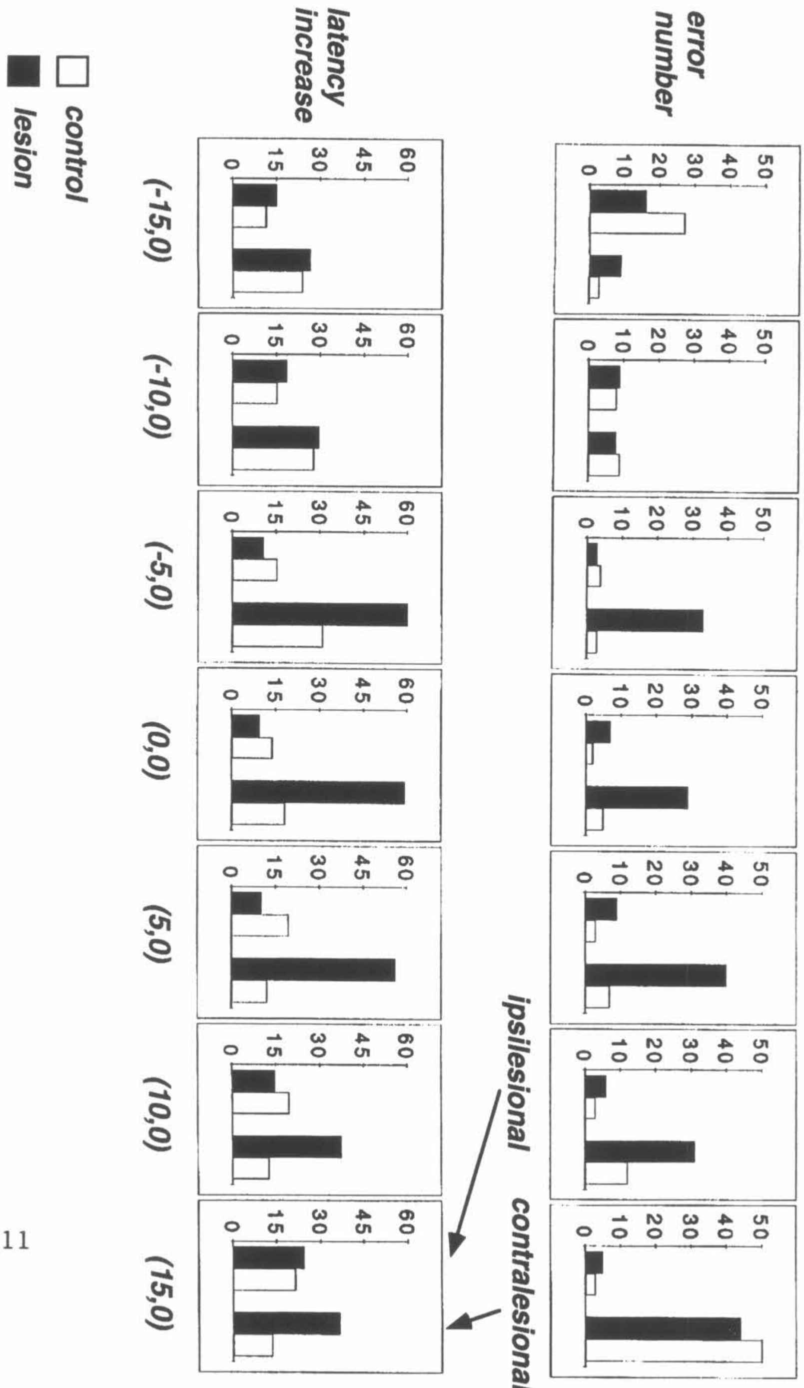

error number
latency increase
control
lesion
(-15,0)
(-10,0)
(-5,0)
(0,0)
(5,0)
(10,0)
(15,0)
ipsilesional
contralesional

Figure 11

		control		*lesion*	
		contral.	*ipsil.*	*contral.*	*ipsil.*
LBZ	*in Light*	0.49(0.13)	0.43(0.20)	0.67(0.17)	0.53(0.18)
	in Dark	0.90(0.28)	0.70(0.31)	1.01(0.33)	0.89(0.33)
NWT	*in Light*	0.46(0.12)	0.42(0.15)	0.44(0.15)	0.59(0.21)
	in Dark	0.69(0.31)	0.86(0.35)	0.96(0.44)	1.34(0.54)

Table 1

			control		lesion	
			contral.	*ipsil.*	*contral.*	*ipsil.*
LBZ	*in Light*	*# of saccade*	427(82)	426(97)	338(74)	389(63)
		av. ampl.	12.5(9.1)	13.0(9.4)	12.0(9.6)	12.6(8.5)
	in Dark	*# of saccade*	164(46)	145(53)	163(62)	154(41)
		av. ampl.	16.2(7.5)	17.3(8.1)	14.7(7.7)	15.2(7.3)
NWT	*in Light*	*# of saccade*	395(66)	381(70)	297(59)	390(106)
		av. ampl.	13.4(6.6)	12.6(6.7)	12.3(6.3)	11.7(6.0)
	in Dark	*# of saccade*	216(67)	212(59)	194(41)	207(60)
		av. ampl.	14.9(9.2)	15.6(7.1)	17.1(9.3)	16.4(8.0)

Table 2

		in Light				in Dark			
		control		lesion		control		lesion	
		contral.	*ipsil.*	*contral.*	*ipsil.*	*contral.*	*ipsil.*	*contral.*	*ipsil.*
LBZ	*ampl*	5.98(0.02)	6.01(0.04)	5.99(0.04)	6.00(0.04)	5.97(0.03)	6.01(0.02)	6.03(0.05)	5.97(0.06)
	vel	235(31)	229(39)	245(35)	248(29)	145(22)	144(27)	136(28)	135(26)
	ANOVA	p=0.26, p=0.47				p=0.29, p=0.91			
	ampl	18.1(0.1)	18.0(0.1)	18.0(0.2)	17.9(0.2)	17.9(0.4)	17.9(0.3)	17.8(0.6)	17.8(0.5)
	vel	396(50)	429(62)	347(62)	352(56)	270(24)	259(33)	256(40)	257(47)
	ANOVA	p<0.01, p=0.29				p=0.56, p=0.30			
	ampl	30.3(0.6)	29.9(0.9)	29.8(0.8)	29.9(0.8)	29.9(0.5)	29.8(0.6)	29.5(0.9)	29.8(1.1)
	vel	448(69)	474(67)	464(70)	457(66)	310(60)	314(68)	318(66)	329(61)
	ANOVA	p=0.75, p=0.06				p=0.68, p=0.47			
NWT	*ampl*	5.99(0.02)	6.00(0.03)	6.01(0.04)	5.98(0.03)	6.01(0.04)	6.00(0.03)	6.00(0.03)	6.01(0.02)
	vel	240(31)	245(36)	247(25)	265(30)	171(26)	166(25)	170(28)	159(29)
	ANOVA	p=0.23, p=0.28				p=0.81, p=0.65			
	ampl	17.9(0.1)	17.9(0.1)	18.0(0.2)	18.0(0.2)	17.9(0.2)	18.0(0.2)	17.9(0.2)	17.9(0.2)
	vel	514(46)	529(39)	475(52)	498(54)	310(49)	298(50)	300(55)	304(57)
	ANOVA	p=0.07, p=0.50				p=0.90, p=0.16			
	ampl	29.8(1.0)	29.9(0.7)	29.7(1.2)	29.8(0.9)	29.8(0.8)	30.0(0.9)	29.7(1.2)	29.7(1.0)
	vel	597(58)	615(62)	558(70)	579(69)	372(60)	366(71)	377(86)	358(78)
	ANOVA	p<0.05, p=0.63				p=0.68, p=0.19			

Table 3

CHAPTER FOUR

The Effect of Area LIP Lesion on the Use of Eye Position Signals for Saccadic Localization

Summary

1. Neurons in the primate lateral intraparietal area (area LIP) carry visual, saccade-related and eye position activities. The visual and saccade activities are anchored in a retinotopic framework and are modulated by eye position(gain field). It was proposed that the modulation by eye position might be the basis of a distributed coding of the target location in a head-centered visual space. Such a head-centered coding scheme offers a solution for maintaining a stable visual environment despite eye movements. An alternative hypothesis suggested by other studies holds that area LIP neurons update their visual receptive field with saccadic eye movements, thus maintaining visual stability exclusively in a retinotopic coordinate frame. These two hypotheses offer different mechanisms for spatial localization. In the distributed head-centered scheme, eye position information is crucial in registering target location, whereas in the retinotopic scheme, saccadic localization can be achieved by a displacement model(a vector subtraction mechanism) carried out in a retinotopic coordinate. Thus, in the double saccade task widely used for psychophysical and physiological experiments(Hallet and Lightstone, 1976), eye position would be used to recompute the second saccade in the distributed head-centered scheme and eye displacement signal would be used in the vector subtraction scheme.

2. The principal aim of this study was to distinguish between these two different hypotheses by employing a double saccade task, which required the monkey to use extraretinal information to localize a remembered target. In this behavioral task, a target was briefly presented while the monkey was

fixating. When the fixation light went off, another target was presented, and the monkey had to make a visual saccade to this target and stay for a criterion duration. After this period the light went off, signalling him to make another saccade to the remembered location of the first target. By varying the direction and the end point of the first saccade and selectively lesioning area LIP in one hemisphere with muscimol injection, we were able to distinguish between the two mechanisms by observing how the second saccade was impaired in this task. The vector coding scheme predicts that if the first saccade was in the contralesional direction, the second saccade would be impaired, and the end point of the first saccade would not be important. On the other hand, the distributed spatial scheme predicts that if the first saccade ends in the contralesional space, the second saccade would be impaired, no matter in which direction the first saccade was made.

3. Results showed that after area LIP lesion, when the first saccade stepped into the contralesional field, the error rate of the second saccade became higher and the latency longer. Moreover, when the end point of the first saccade was controlled for, it showed that the direction of the first saccade largely did not have an effect on the impairment of the second saccade. These results are consistent with area LIP in combining retinal and eye position information to implicitly encode target location in a distributed head-centered framework.

4. Overall, this study provides further evidence for a head-centered representation of target location in space in the posterior parietal cortex and, more specifically, that eye position information plays a crucial role in constructing such a distributed representation.

Introduction

It has long been a focus of intense interest in the studies of spatial vision to understand how the brain encodes target location in visual space and maintains visual stability despite constant eye, head and body movements. A possible neural algorithm has neurons with visual receptive fields anchored in an absolute egocentric framework, in head- and body-centered coordinates; namely, neurons encode the spatial location of a target relative to the head and/or body. A cell with a head-centered receptive field, for example, would fire whenever a target falls into its receptive field with respect to the head, no matter where the eye is in the orbit. Other than a few reports (Gentilucci et al., 1983; Schlag and Schlag-Rey, 1977, 1983; Galletti et al., 1993), however, physiological studies in the past twenty years have largely failed to find cells with such receptive field properties. Instead, neurons have only been found to have retinotopic visual receptive fields.

Galletti et al. reported the existence in area PO of "real position" cells, which have head-centered visual receptive fields(Galletti et al., 1993). But the proportion of cells with such receptive fields was relatively small in their sample and most of these cells had their receptive fields in the visual periphery. These findings agree with some earlier studies which showed that area PO is mainly subserving vision in the peripheral visual space (Covey et al., 1982; Colby et al., 1988), but did not seem to provide strong evidence for a topography of headcentric space in this area. Actually a more recent study from the same group found that most of the neurons in this area have retinotopic visual receptive fields but their overall magnitudes of response are modulated by eye position(Galletti et al., 1995). Gentilucci et al. recorded from premotor area 6 and found cells with their receptive fields anchored to a particular part of the space with respect to the head (Gentilucci et al., 1983) . Similar observations were made later by Graziano and Gross in area 6, area 7b and putamen(Graziano and Gross, 1992; Graziano and Gross, 1993; Graziano et al., 1994). It was found that such cells usually have congruent visual and somatosensory receptive fields centered around some body part. It was claimed that a somatotopically organized map of the visual space exist in these areas. However, since most of these cells prefer stimuli in the near space and some even move their receptive fields with a particular body part, it is likely that such neurons subserve some particular modular functions in the immediate extrapersonal space, as suggested in these studies, to facilitate movement under visual guidance, and are less likely to be important for coding the space in general. That monkeys with lesion of area 6 suffered neglect in the near but not in the far space provided further evidence for this argument(Rizzolatti et al., 1983).

An alternative way of encoding correct target location in spite of ever-changing retinal information was through the use of extraretinal signals. Following von Holst and Mittelstaedt, many people explored both in theory and experiments how this might be achieved(Grossberg and Kuperstein, 1986; Matin, 1972; Sparks, 1989; see also Grüsser, 1986, for a review of the history). Although many behavioral experiments supported the existence of extraretinal signal, how it is integrated with retinal information physiologically remained elusive only until recently. One possible way of how this mechanism might be achieved neurally was suggested by Andersen and colleagues, whose experiments showed that visual information, and eye and head signals converge onto individual parietal neurons(Andersen and

Mountcastle, 1983; Andersen et al., 1985, Andersen et al., 1990; Brotchie et al., 1995). Individual parietal neurons, recorded from area 7a and the lateral intraparietal area(area LIP), maintain a retinotopic visual receptive field but their overall response magnitude is modulated by eye and head positions. It was proposed that object location in a head- or body- centered space could be encoded through a distributedly population of such parietal neurons. Schlag and co-workers were the first to report such gaze modulation of visual and movement-related activities in the intralaminar nucleus of the thalamus and the superior colliculus of the cat(Schlag et al., 1980; Peck et al., 1980). Many later studies found similar results in several other brain areas (Weyand and Malpeli, 1993; Trotter et al., 1992; Galletti et al., 1989; Van Opstal, et al., 1995). How such activity patterns could form the basis of a spatial coding mechanism was suggested by subsequent modeling studies, which showed that visual and eye position activities could indeed be combined in a multiplicative manner to encode target location in a distributed framework(Zipser and Andersen, 1988; Goodman and Andersen, 1990). Further exploration of the network model revealed properties similar to those observed in physiological experiments (Goodman and Andersen, 1989; Thier and Andersen, 1996). Such a distributed head-centered scheme implicitly encodes target location through a population of cells. In contrast to the explicit coding hypothesis, it suggests important mechanisms in which neural signals in several different coordinate frames can be integrated and transformed for visuomotor behaviors.

How such a distributed coding scheme could be used to maintain spatial stability across eye movements was illustrated by the neuronal behaviors in the posterior parietal cortex. In a double saccade task, in which the monkey was trained to make a saccadic eye movement to a remembered target location and then back to the fixation point, it was found that parietal neurons are active only for the upcoming eye movement if this movement is in the cell's preferred direction(Gnadt and Andersen, 1988; see also Mazzoni et al., in press, for a more elaborate investigation of this issue). Since the second eye movement did not appear to be preplanned, it was suggested that the eye position at the end of the first saccade was used to calculate the trajectory of the second movement.

Another possibility of how visual stability might be maintained across eye movements using extraretinal signals was suggested by Goldberg et al., drawing on recording results from the frontal eye field(Goldberg and Bruce, 1990). It was suggested that saccadic localization can be achieved through a vector subtraction model. Similar rationales were later extended to studies in the posterior parietal lobe, in which it was found that parietal neurons predictively update their receptive field with each saccadic jump, thus maintaining a retinotopic representation of the visual space (Duhamel et al., 1992; Colby et al., 1993; Colby et al., 1995). It was claimed that such a predictive updating mechanism helped to facilitate the programming of a saccadic eye movement to an upcoming target in downstream oculomotor structures in a retinotopic coordinate. In other words, the extraretinal signal used to maintain visual stability is an efference copy of the saccade command associated with each eye movement and such a mechanism does not entail the presence of a head-centered representation of space.

The present study aimed to distinguish these two different hypotheses by using a double saccade task, modified from the one used by Hallet and Lightstone and other people in psychophysical and physiological experiments(Hallet and Lightstone, 1976; Goldberg and Bruce, 1990; Mays and Sparks, 1980; Mazzoni et al., In press). This task required the monkey to use the information associated with the first saccade to be able to make the second sacccade correctly. Since both the saccade-related and eye position activities in area LIP show a contralateral bias(Andersen et al., 1990; Li et al., ; Lynch et al., 1977; Barash et al., 1991), by selectively lesioning this area in one hemisphere, we disrupted contralateral eye position and saccade-related activities. We then systematically varied the direction and end point of the first saccade, and tried to determine how the impairment of the saccade and eye position activities might affect the second saccade in this task. A predominantly directional effect would favor the retinotopic model whereas an eye position effect would support the distributed head-centered scheme. A preliminary report of part of this study was presented in abstract form (Li et al., 1995).

Methods

Surgery, animal care, unit recording , eye position monitoring and muscimol injections

Two macaque monkeys, LBZ and NWT, were used in this experiment. Surgical procedures and animal care were described in detail in a previous paper(Li et al.,). Eye position was monitored by the scleral search coil technique(Fuchs and Robinson, 1966; Judge et al., 1980), and calibration was preformed daily before experiments started. After behavioral training was completed, recordings and lesions were performed in area LIP in three hemispheres of the two monkeys. Two to three microLiters of muscimol(8 mg/mL, Sigma, St. Louis, Missouri) were used in each lesion in this experiment. In one given experiment, injections were usually done at two different locations where saccade-related and eye position activities were recorded. On two separate occasions, saline injections were used for controls. A total of 6 lesions were performed in 2 different hemispheres of the first monkey and 4 lesions in one hemisphere of the second monkey.

Behavioral tasks and training

The monkeys were trained in this experiment to do a behavioral task requiring two sequential saccades. In this task, after the monkey acquired a fixation point(total duration of fixation, 1200 msec), a light target T2 was briefly flashed(100 msec). The fixation light was turned off 800 msec after the presentation of T2, and, at the same time, another light target T1 was presented. The monkeys were trained to make a visually guided saccade to T1 within a time window of 400 msec and stay there for a criterion duration (600 msec for one monkey and 400 msec for the second), after which, T1 was turned off. The monkey then had to make another saccade to the remembered location of T2 within a time window of 500 msec. There are therefore two saccades involved in this task; the first one is a visual saccade and the second one a memory saccade. The spatial windows were typically 4 and 12 degrees in diameter, respectively, for the visual and memory saccades.

The location of the fixation light and saccade targets were arranged so that the fixation light could appear at one of four different locations on the horizontal axis: (-15,0), (-5,0), (5,0), and (15,0), respectively, relative to straight ahead, (0,0). Target T1 was also always positioned on the horizontal axis, so that the first saccade either went right or left, and was always 10 degrees in amplitude. Target T2 was located on one of the two diagonals centered at the end point of the first saccade, so that the second saccade was also 10 degrees in amplitude, and directed either up left, up right, down left or down right. The direction and amplitude of the two saccades were chosen such that the oculomotor behaviors were within a reasonable range of motion. A distinct combination of each first and second saccade was called a "class." This behavioral paradigm is schematically illustrated for several different classes in Figure 1.

This double saccade paradigm is different from the one introduced by Hallet and Lightstone(Hallet and Lightstone, 1976) and later refined by Mays and Sparks for physiological experiments(Mays and Sparks, 1980). This new paradigm was used in this study based on two reasons. First, since we have shown in a previous study that lesioning of area LIP disrupts the metrics of memory saccades, employment of the traditional double saccade paradigm, in which two memory saccades were executed, would make it difficult to evaluate the impairment of eye position signal in this behavioral task. Any deterioration of performace would have to take into account the impairment of the first memory saccade per se. Second, by making the first saccade visually guided and imposing a criteriron stay at the end of this first eye movement, we could have a precise measurement of the latency of the second saccade, which would be difficult to obtain in the Hallet and Lightstone paradigm.

As a control experiment, data from monkey LBZ making two successive visually guided saccades were also collected. In this task, instead of presenting target T2 for the monkey to memorize while fixating, T2 was presented immediately after the criterion stay at T1, and he was required to make a second visual saccade within the same time window to acquire the target. The spatial window for acquiring each target was a circle 6 degrees in diameter.

Different classes were presented in a pseudorandom manner during the experiment. To ensure an even sampling of all classes, those classes which have occurred on fewer occasions have a higher priority of being presented until the same number of HIT trials is achieved for all classes. However, to avoid oversampling a particular class which the monkey had missed or failed repeatedly, if the monkey failed a class for a successive five trials, the class was temporarily switched off. It was switched on again after the monkey successfully performed trials in at least two other classes. This procedure avoided falsely increasing the error rate and any possible effects on saccade accuracy and latency for that particular class. Other than in one initial experiment with monkey LBZ, the sampling of different classes was fairly even. A total of 10 or 12 HIT trials was usually collected for each class in each block of the experiment. A detailed description of the definition of MISS, HIT, and ERROR trials is provided in a companion paper(Li et al.,).

Training and experiments were conducted in otherwise total darkness, so the monkeys had no access to any other visual information in any phases of these experiments. The room light was turned on every 5 to 10 minutes to prevent the monkey from becoming dark-adapted or falling asleep. Training for both monkeys in this experiment started with the double visual saccade task, which showed them that there would be two saccades involved in the task. Training for the sequential visual and memory saccades started with a short criteria stay at the end of the first saccade, which was gradually increased through training. After approximately one month of training, one monkey was able to stay at target T1 for a duration of 600 msec and the other monkey 400 msec successfully completing the task over 80% of the time. The size of the spatial window for the memory saccade for both training and experiments was typically 12 degrees in diameter.

Data analysis

The amplitude, latency and velocity of the first saccade were first computed to document the effect of lesion on visual saccades, as was described in the previous paper(Li et al.,). A preliminary analysis of variance showed that, either for ipsilesional or contralesional saccades, these parameters did not vary significantly with different second saccades, so the same first saccades were pooled in their individual groups for further analyses. There are 3 groups of rightward saccades, starting at (-15,0), (-5,0), and (5,0) and 3 other groups of leftward saccades, starting at (-5,0), (5,0), and (15,0). Analyses of variances for amplitude, velocity and latency were performed on the rightward and leftward saccades for the lesion and control data with respect to different starting positions. The computation of saccade latency, velocity and metrics was described in detail in the previous paper(Li et al.,). The control data used for comparison were usually collected the day before or after the lesion experiments.

The main part of the data in the first experiment were analyzed to see whether, after muscimol injection into area LIP, the execution of the second(memory) saccade was impaired after the first(visual) saccade was made. It was then determined how the impairment differed according to the directions and/or end points of the first saccade. To characterize the performance of the second saccade, we looked at the error rate, latency and metrics in each condition. Analysis of variance showed that the error rate, latency and scatter of the end points did not vary significantly among the four different second saccades which could follow a common first saccade in most experiments; therefore, the following analyses of error rate, latency and scatter of the end points were applied to data in which the second saccades were pooled according to the direction and end point of the first saccade. On the other hand, since the four different second saccades differed in amplitude, analysis of the saccade accuracy in terms of amplitude change was performed separately for each of the four second saccades. Finally, there were six different groups of such second saccades for both control and lesion data; three of them with the first saccades going right and ending at (-5,0), (5,0) and (15,0) and the other three with the first saccade going left and ending at (-15,0), (-5,0) and (5,0), respectively.

There were two variables in this experiment that might differentially contribute to the impairment of the second saccade in the lesion condition. The first one was the direction of the first saccade - whether it was in the contralesional or ipsilesional direction. The second variable was the end position of the first saccade - whether it was on the contralesional or ipsilesional side, relative to the midline. A schematic is shown in Figure 2 to demonstrate the predictions about how the first saccades would affect the performance of the second saccades according to the two different hypotheses. In the first analysis, we looked at how the impairment of the second saccade varied with the end point of the first saccade. Analysis of variance was applied to the data using general linear models(Zar, 1984). In essence, a linear model composed of terms of independent variables and of interaction of these variables was used to fit the data. It was tested whether the fit would be significantly different when one of these independent variables or interaction terms is left out from the model. In the first analysis, there were two independent variables; namely, lesion vs. control and the three different end points of the first saccade. This analysis was done separately for the two different directions, rightward and leftward, of the first saccade to see how the impairments of the second saccade might vary depending on the end points of the first saccade. Using the same set of data, we then looked at the instances in which the end points of the first saccade were the same. There are two such cases, one with two different groups of rightward and leftward saccades ending at (-5,0) and the other one with those ending at (5,0). Therefore, in the second analysis, the two independent variables were lesion vs. control and the two different directions of the first saccade. In other words, we controlled the end point of the first saccade, and examined whether the impairment of the second saccade depended on the direction of the first saccade.

These analyses were applied to the error rate, latency and metrics of the second saccade. Only trials that the monkeys successfully completed were included for the analysis of latency and metrics. The latency of the second saccade was defined as the time it took for the second saccade to be initiated(to reach a velocity criterion of 20 deg/sec) after the offset of target T1. For the metrics of the second saccade, we computed both the amplitude, the direction and the scatter of the end points of the second saccades. The direction of the second saccade was calculated as the *arctangent*(in degrees) of the ratio of the y component over the x component of the saccade. Those saccades directed towards the upper left and lower right, therefore, have a negative value and those of the other two directions a positive one. The absolute values of saccade direction were used in this analysis for simplicity. The magnitude of scatter was computed as the average distance between the end points of individual saccades and the target location. Finally, we computed the number of the error trials in each block of experiment, in which 10 to 12 HIT trials collected for each class. Since only one error measurement is available for each of the six different groups of data in a given lesion experiment, an ANOVA with repeated measures was used for this analysis. The combination of error rate and metrics jointly determined the accuracy of the second saccades.

Results

General performance

Example eye traces from a control experiment with monkey LBZ is shown in Figure 3. Different classes composed of 10 trials each were shown and the second saccades were grouped and plotted in the same panel according to the first saccade. In general, the first(visual) saccade is fairly precise and the second(memory) saccade is not as precise. Some of these saccades showed a characteristic up-shift of end points, such that the upward saccades were hypermetric and the downward hypometric. Saccades made toward the orbital periphery from an already peripheral position also tended to be hypometric. Although lesions were perfomed in both hemispheres for monkey LBZ, unless noted otherwise, data from this monkey were organized as though the lesions were all in the right hemisphere for the following analyses.

We first examined the effect of lesioning on the first(visual) saccades(see Table 1). The results showed that the latency of the contralesional saccades increased after muscimol injection. An analysis of variance showed that the latency increase did not vary with starting position of the saccade: ANOVA, $F(2,954)=1.28$, $p>0.5$, for monkey NWT; $F(2,1081)=0.78$, $p>0.5$, for monkey LBZ. The metrics and velocity of the first saccade were also not significantly different from those of the control data. Similar results were obtained for both monkeys.

To document the impairment of the second saccade, data from all of the conditions(different directions and end points of the first saccades) were combined according to the direction of the second saccade. Table 2 shows the data from these two monkeys for both saccade amplitude, latency and velocity. Except for the saccades in the upper right direction in monkey NWT, the mean amplitude of the second saccade did not seem to be different from the controls, but the latency of the second saccade increased and the velocity became slower for both monkeys after area LIP lesion. Given that the memory saccades in this task were of one fixed amplitude, we were not able to deduce the relationship between the peak velocity and amplitude. However, since the saccade amplitudes were not significantly reduced in most cases, the reduction in velocity was probably a result of altered processing of saccade dynamics due to the lesion. These results reproduce the effects on memory saccades described in a previous paper(Li et al.,)

Impairment of eye position signal

Figure 4 shows the results of the ANOVA for the error data for monkey LBZ and NWT, respectively. Note that the lesion was in the right hemisphere for monkey LBZ and in the left for monkey NWT. Overall the number of errors in the second saccade increased after muscimol lesion($p<0.001$ for both monkeys). The left panel(A) shows the dependence of error rate on the end point of the first saccade. The left half of figure (A) shows the data in which the first saccades are all towards the right but end in different positions while in the right half the first saccades are all towards the left. It can be seen that, in both monkeys, the dependence on end points was significant for both saccade directions. The right panel(B) shows the results of an analysis which takes the same set of data and examines how the direction of the first saccade might affect the impairment of the second saccade. The end point of saccades were fixed in both cases, at (-5,0) on the left and (5,0) on the right. It can be seen that except for one case in monkey LBZ, the direction of the first saccade did not contribute to an increase in the error rate of the second saccade.

Figure 5 shows the results of an ANOVA for the latency data. The data are organized in the same format as in Figure 4. The latency of the second saccade increased significantly after muscimol lesion($p<0.001$ for both monkeys). The left panel(A) shows the effect of varying the end points of the first saccade on the latency of the second saccade, whereas the right panel(B) shows the effect of varying the directions of the first saccade. For both monkeys the increase in latency differed significantly with respect to the end point of the first saccade(A). When the end point of the first saccade was controlled(B), the latency increase was not significantly different between the two different directions of the first saccade.

The same analyses were applied to the scatter of the end points of the second saccades. The results show that the scatter was not significantly different between the lesion and control cases(p=0.36 for monkey LBZ; p=0.17 for monkey NWT). Furthermore, neither the direction nor the end position of the first saccade contributed to a difference in the scatter between lesion and control. Results of the scatter are listed in Table 3(A). The effects of end position led to p-values of p=0.36 and 0.11, for monkey NWT, and p=0.21 and 0.19 for monkey LBZ, for rightward and leftward first saccades, respectively. The effects of saccade direction led to p-values of p=0.88 and 0.61, for monkey NWT, and p=0.42 and 0.25 for monkey LBZ, for end points of (-5,0) and (5,0), respectively.

Finally, ANOVAs were performed on the amplitude and direction of the second saccades. Since the four second saccades were of different directions and amplitudes(upward saccades tended to be hypermetric and downward saccades hypometric), this analysis was done for each of the four different classes of the second saccade. The results(see Table 3 (B) and (C)) show that neither the position nor the direction contributed to an amplitude difference between the lesion and control experiments, and this was true for all four directions of the second saccade. For saccades toward the upper left: effect of end position, p=0.51 and 0.17(money LBZ, rightward and leftward first saccade, respectively) and p=0.81 and 0.36(monkey NWT); effect of saccade direction, p=0.20 and 0.24(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.37 and 0.41(monkey NWT). For saccades toward the upper right: effect of end position, p=0.36 and 0.18(money LBZ, rightward and leftward first saccade, respectively) and p=0.37 and 0.42(monkey NWT); effect of saccade direction, p=0.11 and 0.14(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.86 and 0.83(monkey NWT). For saccades towards the lower left: effect of end position, p=0.29 and 0.59(money LBZ, rightward and leftward first saccade, respectively) and p=0.49 and 0.18(monkey NWT); effect of saccade direction, p=0.67 and 0.70(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.54 and 0.65(monkey NWT). For saccades towards the lower right: effect of end position, p=0.85 and 0.38(money LBZ, rightward and leftward first saccade, respectively) and p=0.22 and 0.17(monkey NWT); effect of saccade direction, p=0.63 and 0.51(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.64 and 0.44(monkey NWT).

The lesion also did not affect the direction of the second saccade: For saccades towards the upper left: effect of end position, p=46 and 0.27(money LBZ, rightward and leftward first saccade, respectively) and p=0.58 and 0.18(monkey NWT); effect of saccade direction, p=0.71 and 0.17(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.90 and 0.28(monkey NWT). For saccades towards the upper right: effect of end position, p=0.85 and 0.30(money LBZ, rightward and leftward first saccade, respectively) and p=0.61 and 0.61(monkey NWT); effect of saccade direction, p=0.31 and 0.86(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.37 and 0.09(monkey NWT). For saccades towards the lower left: effect of end position, p=0.29 and 0.34(money LBZ, rightward and leftward first saccade, respectively) and p=0.38 and 0.06(monkey NWT); effect of saccade direction, p=0.90 and 0.28(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.07 and 0.11(monkey NWT). For saccades toward the lower right: effect of end position, p=0.11and 0.09(money LBZ, rightward and leftward first saccade, respectively) and p=0.15 and 0.22(monkey NWT); effect of saccade direction, p=0.07 and 0.88(monkey LBZ, end point of first saccade at (-5,0) and (5,0), respectively) and p=0.18 and 0.28(monkey NWT).

Figure 6 shows an example of the eye traces for the error trials in one control and lesion experiment from monkey LBZ, in which muscimol lesion was done in the right hemisphere. Only error trials in which the second saccades were in the upper right direction were shown. Note that these second saccades were in the ipsilesional direction and the monkey would not be impaired in making these saccades in the single memory saccade task. Comparing the lesion with the control data showed that after the muscimol injections the monkey made many more errors in the second saccades when the first saccades ended in the contralesional(right) field. Similar patterns of errors occurred for the trials in which the second saccades were in the other directions.

Other than an increased number of error trials, examination of the error trials across experiments also revealed important differences between the errors made in the control and lesion experiments. Figure 7 shows these error trials in x(y)-t plots. The few errors mostly made in the control experiments were the trials in which the monkey could not stay at the first target location long enough to meet the criterion stay or in those trials where their upward saccades overshot the target. However, the lesion data show a very different pattern of errors. These usually consisted of the trials in which the monkey made his first saccade toward the remembered location of the second saccade target, sometimes before the offset of the fixation, or in which he made an erroneous second saccade after the criterion stay at the first target location, or in which he stayed put after the first saccade until the time window for making the second saccade was past. In this last case, it was as though the monkey did not know what to do after the first saccade. These errors were seldom seen in the control data. Similar error patterns were seen for both monkeys.

Finally, results from monkey LBZ in the control task of double visual saccades showed that there was an increase of latency of the second saccade after muscimol lesion. However, this latency increase did not depend on either the end point($p=0.33$ and $p=0.54$, for rightward and leftward first saccades, respectively) or the direction($p=0.16$ and $p=0.14$ for (-5,0) and (5,0), respectively) of the first saccade. Posthoc analysis showed that the latency increase of the second saccade occurred primarily in the saccades in the contralesional direction. The metrics of the second saccade in this task, both in terms of the amplitude and scatter of end points, were not significantly different from the control, and no variation was found among different end points($p=0.82$ and 0.86 for amplitude, and $p=0.85$ and 0.41 for scatter, for rightward and leftward saccades respectively) and directions($p=0.95$ and 0.90 for amplitude and $p=0.89$ and 0.24 for scatter, for (-5,0) and (5,0), respectively) of the first saccade. Finally, the overall average error rates were both very low, 4.2%(control) and 4.6%(lesion), and did not vary with either the end position($p=0.67$ and $p=0.59$, for rightward and leftward first saccades, respectively) or the direction($p=0.87$ and $p=0.91$ for (-5,0) and (5,0), respectively) of the first saccade. These results are listed in Table 4. Overall, these results show that other than an increase of the latency of contralesional saccades, the performance of the second saccade in the double visual saccade task was the same after muscimol lesion.

Discussion

We will first address the issue of visual stability across saccadic eye movements in general, then discuss two neural algorithms of combining retinal information and extraretinal signals to maintain visual stability and how the present study provides evidence favoring a head-centered scheme. Finally, other possible functions of a head-centered representation of space and uses of extraretinal signals in spatial orientation and actions will be described.

Spatial localization and visual stability across saccadic eye movements

As we move our eyes from one point to the next or move our heads from one side to the other, the retinal images of objects become smeared and differ from one moment to another. We nevertheless perceive the objects around us to be stationary. Such constancy of the locations of objects in space facilitates visually guided actions. We are able to look or reach towards an object of interest, even if it is projected on different parts of the retina at different times or even when such retinal information is no longer available. How such perceptual and oculomotor localization is possible given the constraint of limited retinal information has been an intriguing problem in psychology and neuroscience for several decades(Grüsser, 1986).

Studies on this issue have long recognized the importance of extra-retinal signals for accurate spatial localization and maintaining space constancy across saccadic eye movements(Bridgeman et al., 1995; Grossberg and Kuperstein, 1986; Howard, 1982; Matin, 1972). But different studies did not agree on the precision and nature of the extraretinal signals for spatial localization. Hallett and Lightstone, for example, reported that people could make an accurate second saccade to the position of a light spot briefly flashed in darkness during a preceding saccade (Hallett and Lightstone, 1976). Since the retinal location of the saccade target is spatially dissociated from the saccade required for its acquisition, the second saccade has to be reprogrammed and it is contingent upon the direction and amplitude of the first saccade. The fact that subjects were able to make a correct second saccade has frequently been cited as evidence that instantaneous eye position information is available for spatial localization. Other experiments using similar paradigms also showed that the extraretinal signals provided precise information to enable pointing to a perisaccadic flash(see Skavenski, 1990, for a review).

However, Matin and his colleagues in earlier experiments, in which subjects were asked to report the location of a 1-msec flashed target, presented at various times during a saccade, found the apparent headcentric direction of the target began to move in the direction of the saccade 100 msec before the saccade and continued to move until several hundred msecs after the saccade(Matin and Pearce, 1965; Matin et al., 1969, 1970). Similar results were obtained for both perceptual and oculomotor localization tasks in other experiments(Mateeff, 1978; Honda, 1989; Honda, 1991). In another study, Dassonville et al. systematically varied the timing of the peri-saccadic flash and found that the eye position information used for saccadic localization is a damped version of the veridical eye position signal(Dassonville et al., 1992). Overall, these other experiments demonstrated a systematic bias in perceptual and oculomotor localization, and suggested that moment-to-moment eye position information is not closely monitored by the nervous system.

As pointed out by several investigators, this apparent discrepancy concerning the use of extraretinal signals for spatial localization probably occurred as a result of differences in the design and procedures of the experiments. In the Hallet and Lightstone experiment, the prior saccade was of constant amplitude, the flash always occurred at the same time and the position of the flash was revealed to the subjects after they made the second saccade(Howard, 1982; Honda, 1989). In this setting, the subjects could have learned to perform accurately by registering the relative retinotopic locations of the flashed target and the preceding fixation point. When similar experiments were performed later which introduced uncertainty both about the time and location of the flash and did not inform the subjects of the results(Honda, 1989,1991; Dassonville et al., 1992), the saccadic inaccuracy was consistent with the results of Matin et al. In other words, flashes occurring just before or early in the saccade were mislocalized in the direction of the saccade whereas those occurring late in the saccade or just after it were mislocalized in the opposite direction(Honda, 1989,1991; Dassonville et al., 1992). Similarly, experiments on open-loop reaching to a perisaccadic target generally demonstrated localization errors consistent with those of the experiments discussed above(Miller, 1996).

Other observations provided further evidence that visual stability is not fully achieved *during* eye movements. When the eyes move back and forth, the visual world appears to move from side to side, a phenomenon known as oscillopsia. Some people can voluntarily produce oscillopsia (Nagle et al., 1980; Enright, 1995). Oscillopsia occurs because there is little or no compensation for image motion during saccades. It seems, therefore, in situations where there is a rapid succession of eye movements, an efference copy of the oculomotor command would fail to compensate for the sensory consequences of the eye movements, and we would cease to experience a stable visual world. On the other hand, the reason that we perceive a stable visual world in everyday life may be because we seldom execute a series of saccades within a short period of time. Rather, most oculomotor events in a natural setting include individual saccades intermixed with pauses of relatively long durations. Grüsser et al. performed an ingenious experiment to document the failure of efference compensation during high frequency eye movements(Grüsser et al., 1987). Subjects were asked to follow side-to-side auditory signals with eye movements, after a foveal afterimage was created in the dark. They reported seeing the afterimage following the eye movement during saccades with frequencies below one Hz. When the frequency of saccades was increased, the apparent movement of the afterimage became smaller until, at frequencies above approximately 3 Hz, the afterimage appeared to remain still at one location. Similar results were reported by Ohmi and Howard; while subjects made side-to-side saccades to the beat of a metronome a stroboscopically illuminated display of dots was shown for a few milliseconds, either during the saccades or in the intervals between them. Subjects reported seeing a stable visual scene only when the display was illuminated within the intersaccadic intervals and when it was more than 100 msec away from the start or end of a saccade (Ohmi and Howard, 1988). Likewise, the gain of the efference copy for pursuit eye movment decreased from 0.82 to 0.4 when the oscillation frequency of the pursuit target was increased from 0.5 to 2 Hz(Pola and Wyatt, 1989).

Overall the results of these studies seem to support the argument that eye position is not closely monitored during saccadic eye movements. With a rapid succession of saccades, the eye position signals during the intersaccadic intervals are too brief to allow headcentric information to be updated and are thus unlikely to be the mainstays of visual stability. On the other hand, results from many psychophysical experiments suggest that the problem of visual stability during eye movements is greatly alleviated by saccadic suppression (Bridgeman et al., 1975; Stark et al., 1976; Campbell and Wurtz, 1978; see Volkmann, 1986, for a review). Mack et al., 1970 and Bridgeman and Stark, 1979 showed that smearing of retinal images during saccadic eye movements was visually masked by the retinal information both preceding and following the eye movements. They also found that the threshold of detecting image displacement during eye movement was elevated, regardless of the relative direction of eye and target movement. They saw that saccadic suppression began for stimuli delivered prior to the onset of saccades and continued until several tens of milliseconds after the end of the saccades. This suggests that, even though correct eye position information is not available *during* saccadic eye movements, we nevertheless are able to maintain the percept of a stable visual environment.

The question remaining is that, with the retinal image of objects constantly changing across successive fixations, why doesn't it cause perceptual instability? How is the information about object locations integrated across saccades to avoid perceptual instability and to enable spatial actions? A possible answer to this question was suggested by psychophysical studies, which showed that subjects could use exocentric cues to maintain a stable percept of the visual world(Irwin et al., 1988; Irwin et al., 1990). In the exocentric scheme of coding object location, the relative positions of objects with respect to each other are encoded during individual eye fixations. Since these relative positions do not usually change from one fixation to the next, they provide important cues that would lead to a stable percept of the environment. Karn et al. investigated how the saccadic localization of a remembered target might be disrupted by intervening saccades, and found that even though the performance in general decreased when the number of intervening saccades increased, the presence of an exocentric cue greatly improved the precision of localization(Karn et al., 1993). Similarly, Dassonville et al. explored the relative roles of exocentric and egocentric references for saccadic localization, and found that, in the presence of exocentric cues, the error of localization was greatly decreased(Dassonville et al., 1995). Finally, the finding that an afterimage of a complex scene did not shift(as a small afterimage did) with eye movement(Pelz and Hayhoe, 1995) further supports the hypothesis that there is a perceptual disposition to see the visual world as stationary despite changes in eye position.

Other experiments indicated cognitive factors as an important source of information for perceiving a stable visual environment. Bridgeman presented to naive subjects sets of Escher prints in which a series of interlocking figures filled the whole picture. Subjects assigned one set of forms to be "figure" and the other set "ground," and could reverse the two at will. They were then tested in a displacement detection task, in which the displacement of the picture was timed to voluntary eye movements. It was found that when a near threshold displacement was introduced, the subjects saw parts of the picture that were conceived to be "figure" move but not the "ground"(Bridgeman,1981). In other words, what was perceived to move or to remain stationary depended on cognitive "designation."

The perception of a stable visual world, however, cannot be explained solely in terms of relative position information or cognitive resources. It has long been known that passively displacing the eye causes the world to move in a direction opposite to that of the displacement. Stark and Bridgeman showed that this was true even when the subject was fixating on a earth-fixed location, which suggested that it is the oculomotor command countering the external force which keeps the eye still that causes the world to appear to move(Stark and Bridgeman, 1983). Other studies showed that when the extraocular muscles were paralyzed, any attempt to move the eyes would cause the world to move and change the perceived location of object in the dark(Stevens et al., 1976; Matin et al., 1982). Furthermore, many studies demonstrated that subjects maintain some ability to localize a visual sitmulus across changes in eye position even when such a stimulus was briefly presented in total darkness. (Schlag et al., 1990; Viviani and Velay, 1987; see also Skavenski, 1990, for a review). These results indicate that spatial locations can be represented even when relational visual cues are absent and that extraretinal signals are important for the registration of object locations in such a representation.

Mechanisms to achieve visual stability using extraretinal signals

Along with the psychophysical experiments discussed in the previous section, studies in behaving primates demonstrated similar use of efference copy signals to achieve saccadic localization in space. Mays and Sparks trained monkeys to localize a briefly flashed target with an eye movement(Mays and Sparks, 1980; 1983). The target was turned off before the saccade started. In some trials a given locus in the superior colliculus was electrically stimulated after the target went off but before the saccade was initiated. It was found that the monkeys could compensate for the electrical perturbation of eye position and localize the target correctly. These studies came to the conclusion that saccades are programmed to reach the target in a fixed orbital position and, furthermore, that this localization is achieved by combining retinal error with an extraretinal eye position signal. Such a computation scheme was supported by the finding of an anatomical projection from the perihypoglossal complex in the brain stem to the superior colliculus(Hartwich-Young et al., 1990). In a subsequent study, in which the proprioceptive inputs from the extraocular muscles were disrupted by transection of the ophthalmic nerves, it was found that the monkey could still compensate for the perturbation(Guthrie et al., 1983). This study provided crucial evidence that the extraretinal signal was active in nature; namely, an efference copy(or corollary discharge) of the oculomotor command provided the extraretinal information that was required for correct saccadic localization in this task. These experiments did not, however, address an important aspect about the nature of the efference copy, that is, whether it is an efference copy of the saccade command(eye displacement signal) or of the eye position signal.

With all these studies demonstrating the importance of extraretinal signals for spatial localization, evidence about how the combination of retinal and extraretinal signals is implemented in the nervous system came from the recording studies of parietal areas 7a and LIP(Andersen and Mountcastle, 1983; Andersen et al., 1985; Andersen et al., 1990). It was found that the visual and saccade-related activities of these parietal neurons were retinotopic but their overall magnitudes of response were modulated by eye position. This suggested that the saccade-related signals could provide eye displacement information. Furthermore, it was proposed that a population of cells with such eye position effect(gain field) might serve to encode target locations in a headcentric coordinate(Zipser and Andersen, 1988). Subsequent studies extended these findings to auditory inputs(Stricanne et al., In press). Other studies found that extraretinal modulation might also occur with head position signals, and thus parietal neurons might be coding object location in a body-centered coordinate(Brotchie et al., 1995; ; Xing et al., 1994).

How does such a headcentiric mechanism allow the monkey to perform the double saccade task in this experiment or similar paradigms in other experiments? The mechanism could be as follows: when the target is presented while the monkey fixates, information about the retinal location of the target is combined with the current eye position signal in a distributed way to form a headcentric representation of the target location in space. Then with the first saccade, new eye position information comes in and is subtracted from the headcentric signal which is then used to compute the corrrect second saccade. Such a neural algorithm requires the use of eye position information to form an intermediate coding of a head-centered space. We demonstrated in a simulation study that a push-pull mechanism together with the use of eye position signal was indeed sufficient to allow the network to perform the double saccade task successfully(Xing et al., 1995). After the network was trained to do the double saccade task, excitatory connections were developed among units with similar directional tuning and inhibitory ones among those with dissimilar tuning. Such a pattern of neuronal connections lock in the ongoing activity in the network for the first saccade until the movement is made, at which point, with the new eye position integrated, a new population of units becomes active for the second eye movement. Together with the results obtained in previous modelling studies(Xing et al., 1994; Zipser and Andersen, 1988), this study demonstrated that, in addition to forming a distributed head-centered space, eye position signals could also be used dynamically to maintain spatial stability.

On the other hand, drawing on recording results from primate frontal eye field(FEF), Goldberg and Bruce suggested a different mechanism in which the computation for the second saccade in the double saccade task could be done(Goldberg and Bruce, 1990, see also Moschovakis and Highstein, 1994, for a brief discussion of this issue and evidence supporting this alternative mechanism). In this coding scheme, the efference copy from the first saccadic eye movement is a displacement vector, which, as suggested, was reflected in the post-saccadic activities observed in some FEF neurons. This displacement vector is then subtracted from the retinotopic memory of the target for the second saccade to derive the correct amplitude and direction of the second saccade. In other words, the entire computation is done through a vector subtraction mechanism in a retinotopic framework and thus a head-centered representation would not be necessary. Additional evidence supporting such a mechanism was gathered subsequently from recordings in the posterior parietal cortex and the superior colliculus, which receives a direct projection from both the FEF and area LIP (Duhamel et al., 1992; Walker et al., 1995). It was shown that a proportion of neurons in both of these areas would predictively update their visual receptive fields such that a neuron would increase its firing rate anticipating the appearance of a target or even its memory trace in its receptive field following a saccadic eye movement. As a result of this predictive remapping mechanism, spatial localization in the double saccade task could be correctly achieved entirely in a retinotopic coordinate without the need for the representation of a head-centered space. These studies were subject to the criticism about the critieria they used to define predicitive activities(Mazzoni et al., In press). In essence, many neurons which increased their firing rate only after the first eye movement was completed would fall into their "predictive" category.

However, additional evidence in favor of this mechanism was proffered from some clinical studies, in which parietal patients were asked to perform the same double saccade task(Duhamel et al., 1992; Heide et al, 1995). It was found that if the first saccade stepped into the contralesional field, the patient made more errors in making the second saccade. It was interpreted that the parietal patients failed to use the efference copy associated with the first saccadic eye movement to be able to perform the second saccade. Because in these studies, whenever the patient made a saccade in the contralesional direction, the eye position also stepped into the contralesional field, any information concerning eye displacement and eye position was essentially confounded. Therefore, although these studies were instrumental in documenting the failure of the parietal patients to use extraretinal signals, they did not address the nature of this extraretinal information. (On the other hand, since the eye position information could derive from the neural integration of the displacement signal, failures in the subjects' performance could actually be a result of failure to use the eye position rather than the displacement signal.)

Our experiments in this study were specifically designed to test which one of these two hypotheses is correct. In other words, it is clear that efference copy information is required for accurate performance in the double saccade task, but what is the nature of the efference copy: is it based on a displacement vector or an eye position signal? Previous studies indicated that neurons in area LIP contained both saccade-related and eye position activities, which both showed a contralateral bias(Lynch et al., 1977; Andersen et al.1990; Shabtai et al., 1991). We know that saccade-related neurons become active when the monkey makes and prepares to make a saccade into the contralateral field. Similarly, cells with eye position activities raise their activities when the monkey moves his eyes to the contralateral space and decrease firing when he looks to the ipsilateral side. Therefore, if area LIP is lesioned by muscimol and contralesional saccade-related and eye position activities are impaired, the two hypotheses predict different results for the experiments: If the vector subtraction hypotheses is correct, and since muscimol injection would inactivate neurons subserving saccades in the contralesional direction, whenever the first saccade goes in the contralesional direction, the second saccade would be impaired. On the other hand, if the distributed head-centered scheme is correct, as long as the first saccade ends in the contralesional space, the utilization of eye position information would be impaired and the monkey would not be able to perform the second saccade correctly. In this latter case, it would not matter whether the first saccade is in the ipsilesional or contralesional direction. Finally, given that the receptive and motor fields of LIP neurons are retinotopic but, on the other hand, their activities are modulated by eye position to form a distributed coding of spatial locations, it is not inconceivable that both representations could be used and be affected by muscimol lesioning.

Results in this study show that it is mainly the end point of the first saccade that determines the performance of the second saccade. Whenever the first saccade ended in the contralesional space, the latency of initiating the second saccade increased and the number of errors in making such second saccades also increased. This was true even when the second saccade was in the ipsilesional direction. Therefore, the results overall favor the distributed head-centered scheme and provide evidence that the efference copy information used in the double saccade task in this study depends on eye position. When considering the accuracy of the second saccade, we took into account both the error rate and the metrics of the second saccades performed. The increased error rate implies a decreased accuracy in perfoming the second saccade. The fact that the accuracy of the second saccades for those trials the monkeys successfully performed did not seem to be impaired might be because some other oculomotor structures was able to take over the task when parietal neurons were not properly functioning. Since the initiation of these saccades were delayed, it seems that these other structures carried out the computation correctly but with longer latency. Alternatively, the lesioning may not have affected the whole area. Neurons in the area not affected by muscimol computed for the second movement. On the other hand, there is some evidence in the error rates that a displacement signal might be used for the computation as well. For both monkeys, when the end position of the first saccade was in the healthy field, the direction of the first saccades seemed to affect the number of errors the monkeys made in doing the second saccade(even though the results did not reach statistical significance in one monkey). That is, when the first saccade is in the contralesional direction, the monkeys' performances were worse. It thus appears that a displacement signal might also be used to compute the second saccade although to a much lesser extent. This result is not inconsistent with the hypothesis that multiple representations of space exist in the posterior parietal cortex.

Further evidence supporting the eye position-based head-centered scheme came from some psychophysical experiments(Karn et al., 1993). In these experiments subjects were asked to localize a remembered location of a briefly flashed target with or without some intervening saccades. In the former case, the subject was required to make a saccade to the remembered target location after the last intervening saccade. Another variable in these experiments is whether an exocentric cue was presented at the same time along with the target. In the presence of the exocentric cue, the subject was required to make a saccade to this cue first before executing a saccade to the remembered target at the end of the trial. It was found that the subjects' performance overall was much better when the exocentric cue was present, and that their performance deteriorated with increasing numbers of intervening saccades. Furthermore, the deterioration of performance in the presence of intervening saccades did not seem to be different whether or not an exocentric cue was present. This latter result suggests that the decreased performance is most likely a result of deterioration of the short term memory of the target location, rather than of an accumulation of the updating error associated with intervening eye movements, as would be predicted by the displacement model. These experiments thus provided behavioral evidence against the vector coding hypotheses.

Another experiment provided results that were difficult to reconcile with the displacement model or the vector subtraction hypotheses. In this experiment, the monkey was trained to localize using a saccadic eye movement a target that was flashed while he was pursuing another target. It was demonstrated that the monkey could to some extent localize the correct spatial location of the flashed target(Schlag et al., 1990). Similar results were obtained in other studies(Gaymard et al., 1994; Ohtsuka, 1994). In other words, the monkeys could compensate for the eye position change as a result of the pursuit before a saccade was made to the remembered target. Since the nature of the neural signals commanding smooth pursuit is essentially different from that of saccadic eye movement, it is not easy to conceive how to incorporate such signals in the vector subtraction model. On the other hand, the head-centered scheme would have no problem accommodating the eye position change essential for correct spatial localization. This head-centered mechanism gains further support from another experiment, in which the double saccade paradigm was extended to explore the version-vergence system(Krommenhoek and Van Gisbergen, 1994). By using a double saccade task similar to Hallet and Lightstone's but with targets presented at different depths, they found that the change of eye position in depth could be accounted for in the programming of the final eye movement. Furthermore, even the slow post-saccadic eye drift was taken into account in the computation of sequential saccades. As pointed out in the study, such results are difficult to explain in terms of the displacement model.

The results obtained in this study overall support the use of eye position signal for computing the second saccade in a double saccade task. In a separate experiment reported in a companion paper(Li et al.,), we showed that single visual and memory saccades were impaired after lesion of area LIP. Moreover, varying the initial eye position did not have an effect on the severity of these impairments.

Altogether these results support the existence of multiple representations of space in the posterior parietal cortex. The computation may be carried out in a retinotopic framework for tasks that only require a simple eye displacement, as in visual and memory saccade tasks. However, in the double saccade task, in which the programming of the second saccade would require the use of eye position signals, the computation may then be performed in a head-centered coordinate.

Other functions of the representation of a head-centered space

Other than maintaining visual stability across saccadic eye movements, the representation of a head-centered space might serve other biological ends. Reaching towards visual targets, for example, requires a series of coordinate transformations so that the visual information of the object, initially acquired in a retinal coordinate, can eventually be transformed to a set of proper muscular activities to mediate the reaching movement. Since a proper reaching movement would require knowledge of the eye, head and limb position before the movement is initiated, a head-centered representation could very well be an important intermediate stage in such a transformation. Many experiments provided evidence for the existence of such a supra-retinal representation of the visual space for spatial orientation and actions(see Jeannerod, 1988, for a review). It was shown, for example, that the vibration of the extraocular and/or neck muscles would result in an illusory movement of the target in an open-loop pointing task(Roll and Roll, 1991). Thus both extraretinal signals were taken into account in processing the goal-directed movements. Enright also demonstrated, in a task involving manual pointing to a remembered target location, that gaze position affected both the bias and scatter of the indicated target direction(Enright, 1995).

Anatomically such a functional linkage could be realized through the intrinsic connections within the parietal lobe and the corticocortical connections between the posterior parietal and the frontal premotor areas(Pandya and Seltzer, 1982; Boussaoud, 1996; Cavada and Goldman-Rakic, 1993). The existence of such functional connections was further supported by the findings that neuronal activities in the premotor areas were modulated by eye position(Boussouad et al., 1993; Boussouad, 1995). Finally, since saccadic eye movements were made not only to visual but also to auditory and somatosensory targets, to integrate multiple modalities of sensory information for movement planning requires a representation of the space that goes beyond a retinocentric coordinate.

Passive or active eye position signal?

The present study does not investigate whether the eye position signal is the efference copy of an active fixation command or the result of modulation by proprioceptive inputs from the extraocular muscles. In one of the experiments disccussed above, Guthrie et al. suggested that it was the corollary discharge of the oculomotor command that provided the extraretinal signal in the spatial localization task in which retinal registration of the target location and the movement command were spatially dissociated(Guthrie et al., 1983). Consistent with this finding, such an active eye position signal was indeed what has been characterized of the fixation neurons in the posterior parietal lobe. It was demonstrated in several recording studies that the parietal fixation neurons raise their activities only when they were engaged in a state of active fixation(Mountcastle et al., 1975; Lynch et al., 1977). The activities of these neurons greatly decreased when the monkey was in a state of relaxation, even when the eyes wandered into the preferred positions of the neurons. We here also made some interesting additional observations from monkeys whose parietal lobe had been chronically recorded from(presumably with some damage) which might suggest that the eye position signal does indeed come from active fixation and gaze-holding activities(Li and Andersen,). In this observation, these "parietal" monkeys were tested in a task where they were required to hold their gaze for an extended period of time at the end of a memory saccade. It was found that when tested in the dark, their eyes consistently drifted in the ipsilesional direction at the end of the saccade, no matter in which direction the saccade was made. This result suggested that damage of the parietal fixation neurons might compromize gaze holding, and, at the same time, provided further evidence for the existence of active eye position activities in the posterior parietal lobe.

FIGURE LEGENDS

FIGURE 1

The sequential saccade paradigm. While the monkey fixates, a target **Tmemory** appears briefly. At the end of the fixation, another light target **Tvisual** appears. The monkey was required to make a saccade to **Tvisual**, stay there for a criteria duration, after which **Tvisual** was turned off, signaling him to make another saccade to the location where **Tmemory** has appeared before. The targets were arranged so that the first saccades were all on the horizontal axis and the second saccades were on one of the two diagonals centered at the end point of the first saccades. Both saccades were 10 degrees in amplitude. The latency of the second saccade was measured as the time it takes for the monkey to initiate the saccade after the offset of **Tvisual**. **Tvisual** and **Tmemory** are represented as **T1** and **T2**, respectively, in the text.

FIGURE 2

A schematic showing the predictions of the two models as to the performance of the second saccades(dashed arrows) as a function of the end point and direction of the first saccade(solid arrows). According to the retinotopic hypothesis, as long as the first saccade is in the contralesional direction, the second saccade would be impaired; in other words, it predicts no difference in the performance of the second saccade for the two conditions in A, in which the first saccades both go left. On the other hand, it predicts a difference for the two conditions in B, since the first saccades are not of the same direction. The distributed spatial coding hypothesis predicts the opposite result. In B, where the end point of the first saccades are the same for the two conditions, the impairment of the second saccade would not be different. In A, where the first saccades are of different directions but ending at different locations, this model predicts that the performance of the second saccade would be worse for the condition where the end point of the first saccade is in the contralesional field. The thin dashed lines are the horizontal and vertical axes of the screen.

FIGURE 3

Example eye traces from experiment 1. A, B, and C showed the trials where the first saccades were all directed to the right and ended at (-5,0), (5,0), (15,0), respectively, and D, E and F those to the left and ending at (-15,0), (-5,0), (5,0), respectively. Trials with different second saccades were grouped and plotted in the same panel according to the same first saccades. It can be seen that the scatter of the end points of second(memory) saccades is much greater, and some of the second saccades showed the characteristic up-shift of the end points. And the saccades made further into the orbital periphery are hypometric.

FIGURE 4

The data of error rate for both monkeys in the sequential visual and memory saccade task. All the histograms were drawn to the same scale. The horizontal bar represents the standard deviation of the number of errors across experiments. The schematics at the bottom of this histograms illustrate the direction and end point of the first saccade in screen coordinate. The contralesional field is shaded. The panel on the left and right compared the effect of the end points and directions, respectively, of the first saccade on the error rate of the second saccade. Data from monkey LBZ were shown in the upper row and those from monkey NWT were shown in the lower row. The lesion of monkey LBZ was in the right hemisphere, and that of monkey NWT was in the left. It can be seen that, for both monkeys, the error rate of the second saccade varies significantly with the end point of the first saccade. Furthermore, except for one case in monkey LBZ, the direction of the second saccade did not significantly contribute to the increase of error rate after muscimol injection.

FIGURE 5

The latency of the second saccade for both monkeys in the sequential visual and memory saccade task. The arrangement of the data is the same as in Figure 4. The left panel tested the effect of the end point and the right panel the direction of the first saccade on the increase of the latency of the second saccade after muscimol injection. The results showed that the latency increase varies significantly with the end point, but not with the direction, of the first saccade. Similar results were obtained for both monkeys. See text for further explanation.

FIGURE 6

X-y plots of the eye traces for the error trials for one control and lesion experiment from monkey LBZ. The lesion was in the right hemisphere. The data were organized as in Figure 3, except that only those trials in which the second saccades were in the upper right direction were shown here. For both control and lesion data, the upper panels(A, B, C) show the eye traces with the first saccade goint rightward, and the lower panels(D, E, F) those with the first saccade going leftward. The end points of the first saccades are different in different panels. It is clear that when the first saccades ended in the left(contralesional) field, many more errors were made in the second saccade. See text for further explanation.

FIGURE 7

Typical error patterns in the sequential visual and memory saccade task(A, B, C, D). Eye traces were shown for two HIT trials in (E). The schematic at the bottom of panel (E) illustrates the duration of the fixation(fix) and the timing of targets T2 and T1 in this task. The appearance of target T2 and the offset of the fixation point was represented by the first two dashed lines and the last dash line, respectively, in the panels. The errors in control experiment(A) mostly consisted of trials in which the monkey failed to stay at target T1 for the criteria time before he broke fixation, and those where the upward saccades overshoot the target. On the other hand, the errors in lesion experiments comprised those trials where the monkey made a completely erroneous saccade(D), failed to initiate a second saccade until he passed the preset time window(B), and made a saccade to target T2 immediately after its presentation or did not initiate the first saccade(C). See text for further explanation.

TABLE LEGENDS

TABLE 1

The latency, amplitude and velocity of the first sacade. Results were shown for contralesional and ipsilesional saccades starting at different eye positions(standard deviations in brackets). Data of monkey LBZ is listed in the upper panel and those of monkey NWT in the lower. See text for further explanation.

TABLE 2

The latency, amplitude and velocity of the second saccades. Results were pooled for lesion and control condition from all experiments according to the four different classes of the second saccade. It shows that on average the latency is increased and velocity decreased after muscimol lesion. These and the results on visual saccade shown in Table 1 replicate the effects of muscimol lesion obtained in a previous study. See text for further explanation.

TABLE 3

The scatter of the end points(A), amplitude(B), and direction(C) of the second saccades in the sequential visual and memory saccade task(standard deviation in bracket). The results are organized according to the direction and end position of the first saccade and listed both for control and lesion condition. These saccade parameters are not significantly affected by muscimol lesion. See text for details of statistics and further explanation.

TABLE 4

The error rate, latency, amplitude and scatter of the end points of the second saccade in the double visual saccade task. The results are organized according to the direction and end position of the first saccade. It shows that other than the saccade latency, these dimensions of second saccade are not affected by muscimol lesion. See text for statistics and further explanation.

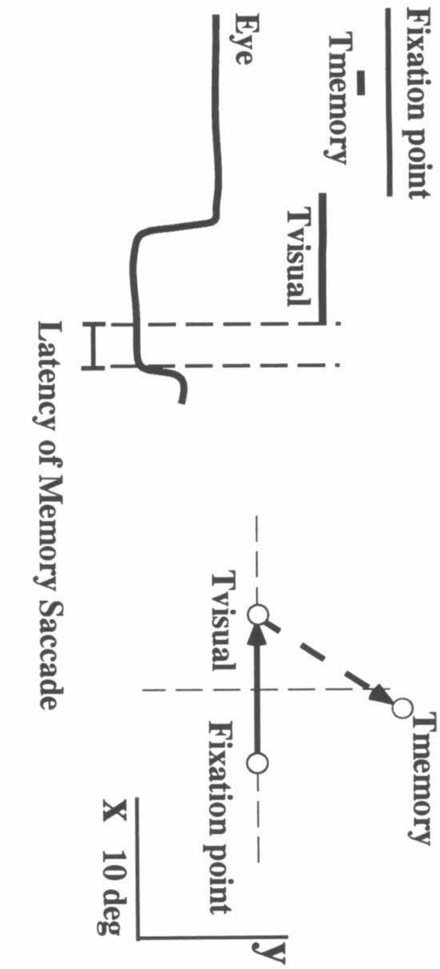

Fixation point
Tmemory
Tvisual
Eye
Latency of Memory Saccade
Tmemory
Tvisual
Fixation point
y
X 10 deg

Figure 1

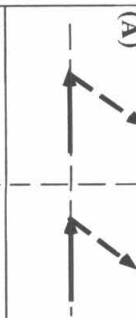
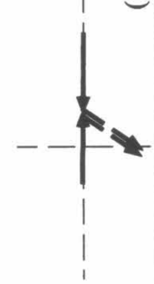
	(I) Retinotopic Coding	(II) Distributed Spatial Coding
(A) 	No Difference	Difference
(B) 	Difference	No Difference

Figure 2

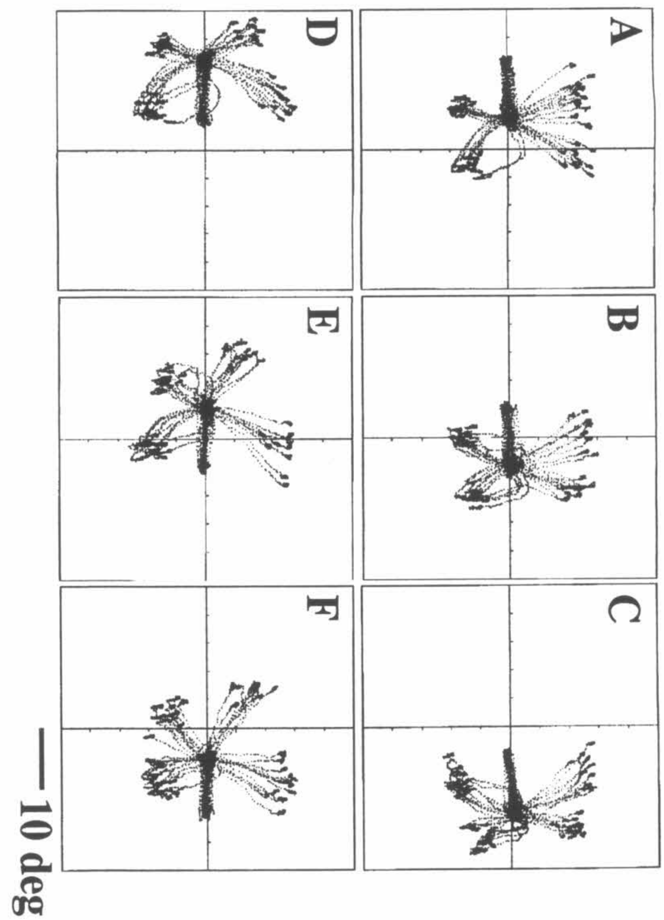


Figure 3

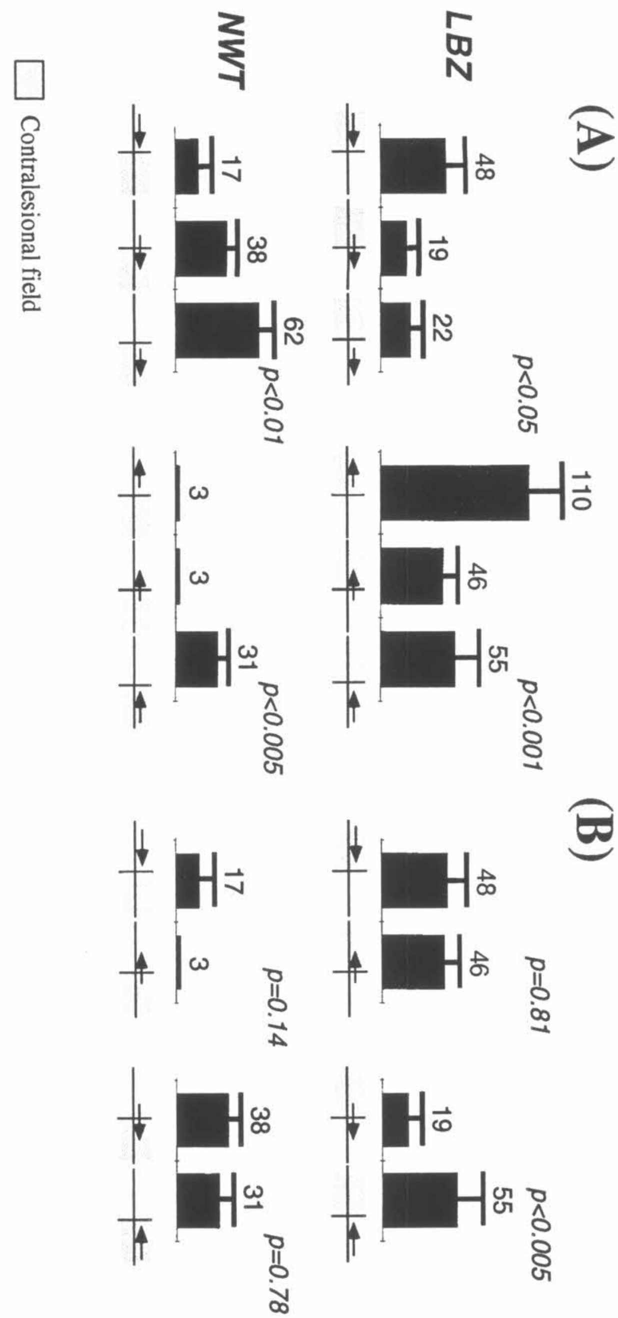

(A)
(B)
LBZ
NWT
48
19
22
p<0.05
110
46
55
p<0.001
17
38
62
p<0.01
3
3
31
p<0.005
48
46
p=0.81
19
55
p<0.005
17
3
p=0.14
38
31
p=0.78
Contralesional field

Figure 4

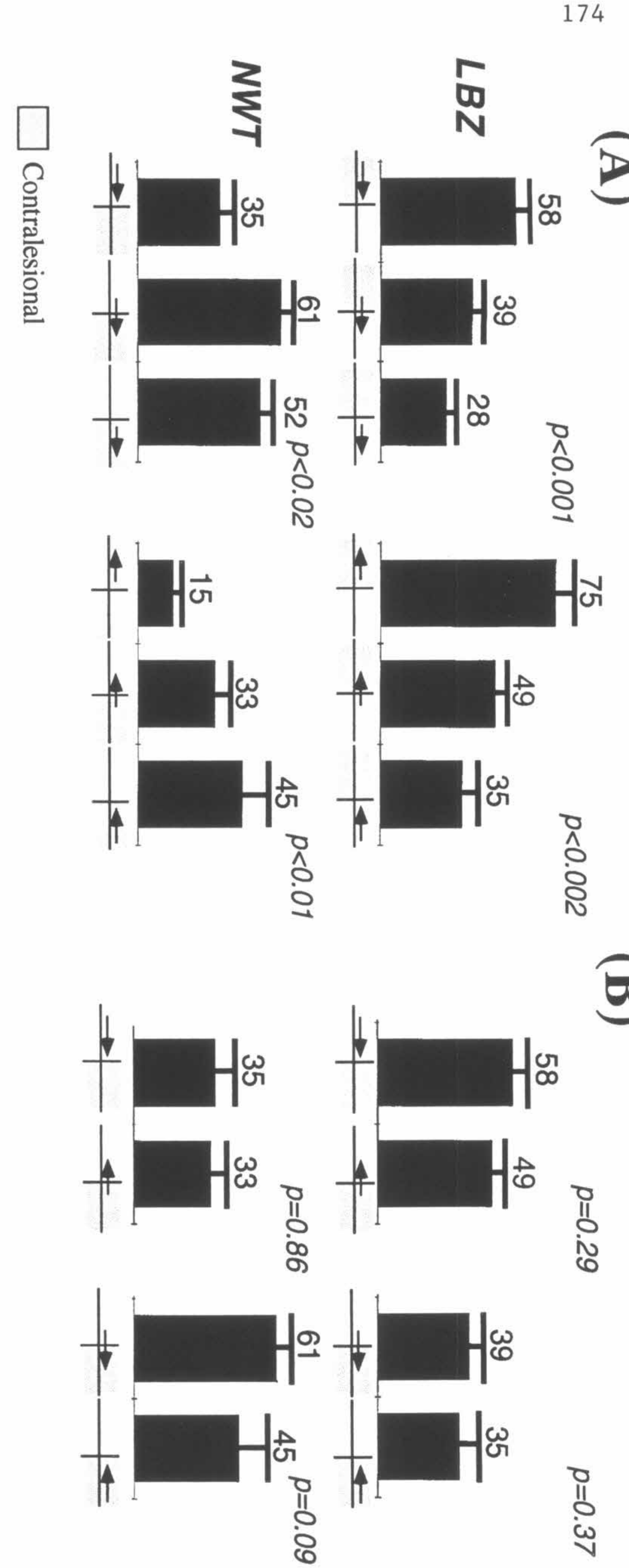

(A)
LBZ
NWT
58
39
28
p<0.001
75
49
35
p<0.002
35
61
52
p<0.02
15
33
45
p<0.01
Contralesional
(B)
58
49
p=0.29
39
35
p=0.37
35
33
p=0.86
61
45
p=0.09

Figure 5

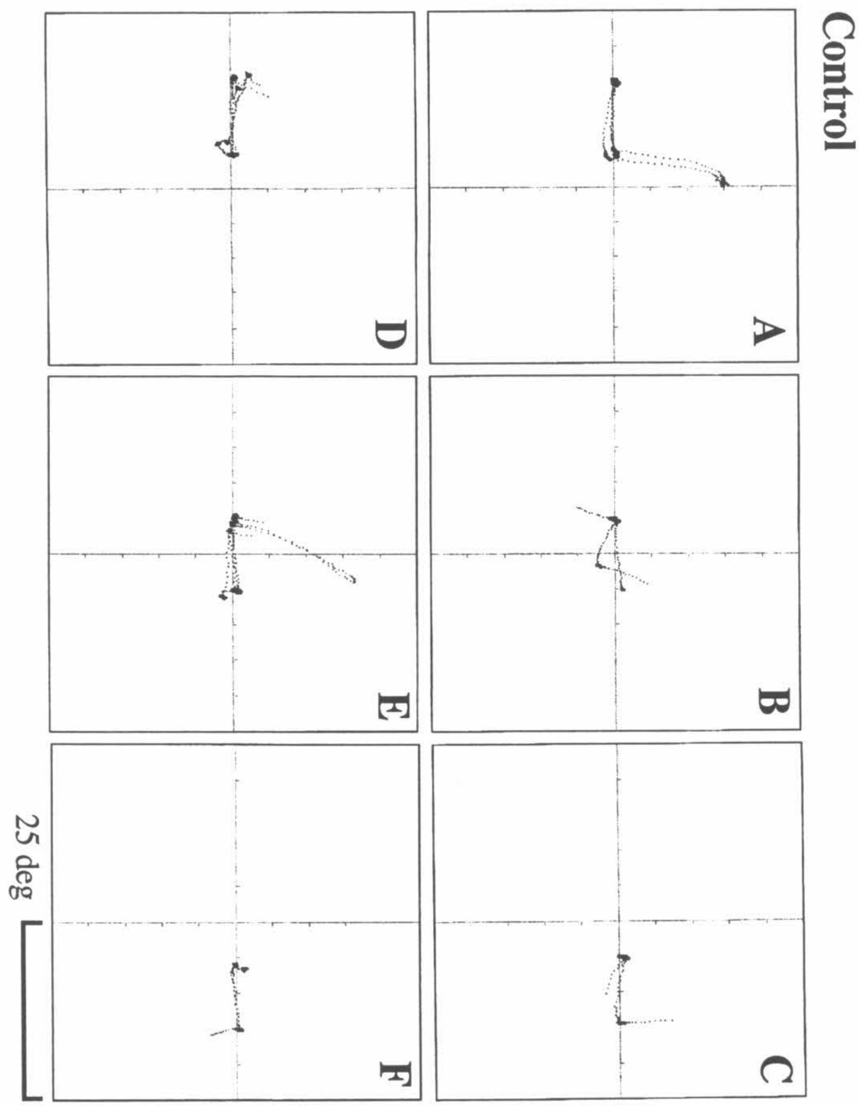


Figure 6

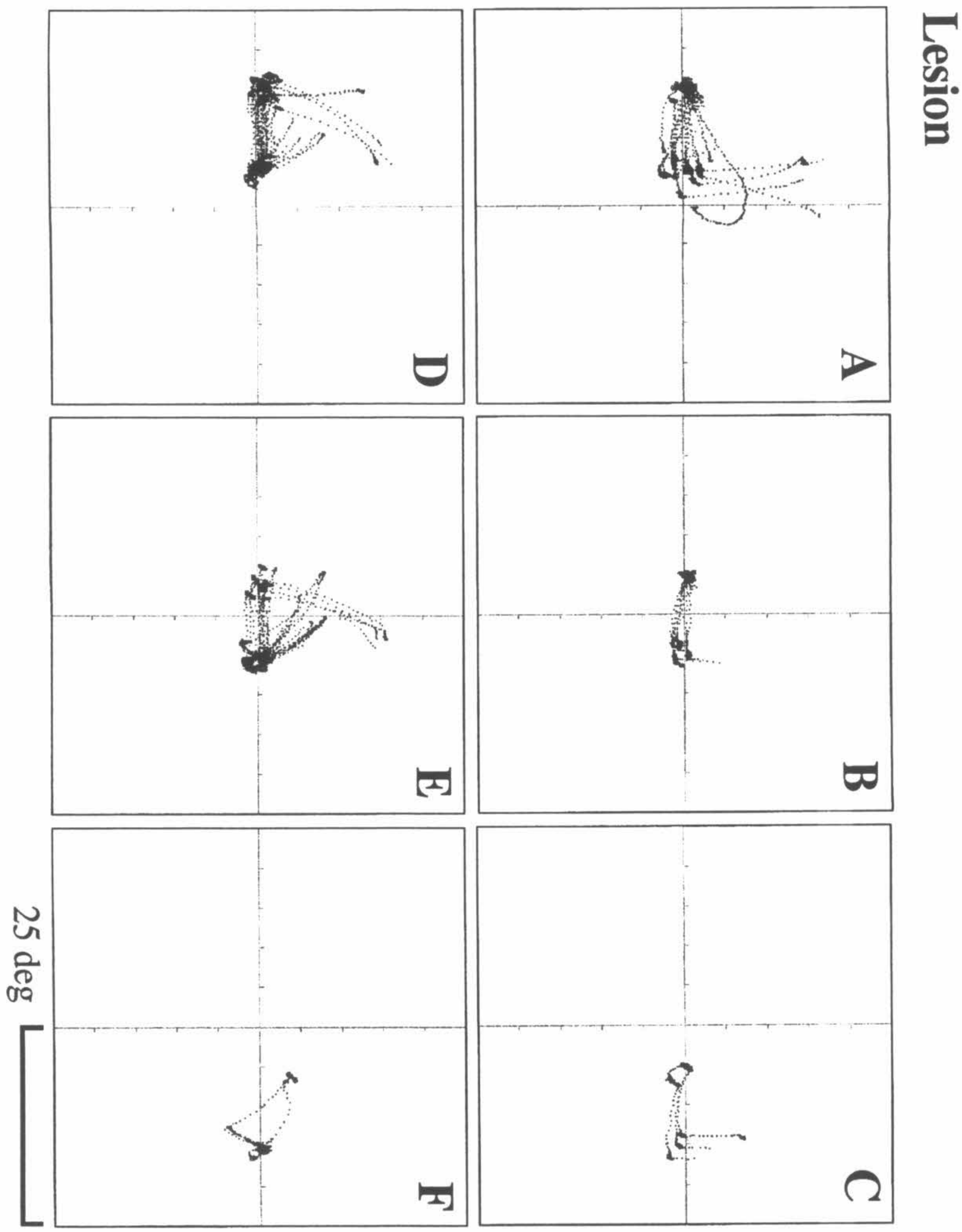


Figure 7

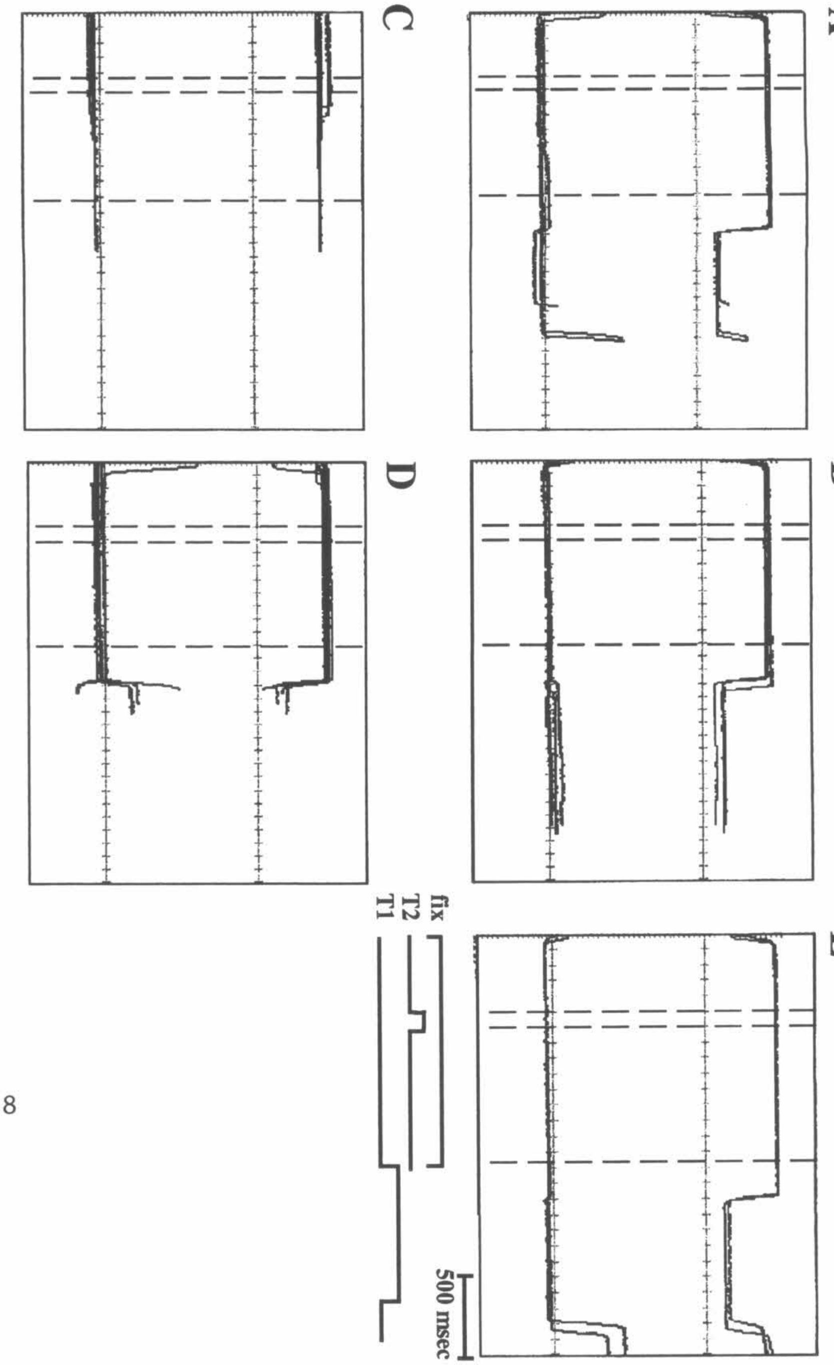


Figure 8

saccade direction		up left	up right	down left	down right
latency	control	232(34)	224(29)	245(33)	238(34)
	lesion	268(27)**	231(30)	287(49)**	237(42)
amplitude	control	12.0(2.6)	11.7(1.9)	10.7(2.0)	11.0(2.5)
	lesion	11.8(2.9)	11.8(2.5)	10.5(2.2)	10.7(2.8)
velocity	control	278(36)	289(40)	198(37)	211(31)
	lesion	224(51)**	288(56)	142(64)**	190(35)

Monkey NWT

saccade direction		up left	up right	down left	down right
latency	control	212(24)	209(30)	220(34)	215(39)
	lesion	220(33)	267(48)**	230(28)	276(51)**
amplitude	control	11.7(2.4)	12.5(1.6)	10.5(2.6)	11.0(2.2)
	lesion	11.5(2.3)	11.4(1.4)*	10.4(2.1)	10.7(2.4)
velocity	control	301(39)	287(42)	224(49)	239(39)
	lesion	298(47)	247(34)**	228(50)	189(27)**

*, $p<0.01$; **, $p<0.001$

Table 1

Monkey LBZ

		ipsilesional(rightward)			contralesional(leftward)		
	starting position	(-15,0)	(-5,0)	(5,0)	(-5,0)	(5,0)	(15,0)
latency	control	201(21)	210(19)	226(24)	217(22)	206(18)	189(19)
	lesion	207(29)	210(26)	221(30)	250(31)*	234(20)*	238(25)*
amplitude	control	9.8(.2)	9.6(.1)	9.2(.2)	9.4(.2)	9.5(.1)	9.5(.1)
	lesion	9.8(.1)	9.4(.1)	9.2(.2)	9.3(.2)	9.6(.1)	9.7(.2)
velocity	control	370(40)	375(36)	340(41)	329(34)	368(39)	379(30)
	lesion	367(35)	352(45)	334(44)	340(37)	355(45)	377(43)

Monkey NWT

		contralesional(rightward)			ipsilesional(leftward)		
	starting position	(-15,0)	(-5,0)	(5,0)	(-5,0)	(5,0)	(15,0)
latency	control	193(31)	204(32)	214(40)	219(42)	196(28)	195(33)
	lesion	237(29)*	241(38)*	266(37)*	222(37)	201(35)	201(34)
amplitude	control	9.4(.1)	9.4(.1)	9.1(.2)	9.3(.2)	9.5(.1)	9.6(.2)
	lesion	9.3(.1)	9.4(.1)	9.2(.1)	9.2(.1)	9.4(.1)	9.3(.3)
velocity	control	358(29)	355(40)	326(31)	323(33)	358(35)	374(39)
	lesion	366(41)	352(35)	324(28)	330(27)	359(41)	367(44)

*, $p<0.001$

Table 2

				first saccade rightward			first saccade leftward		
				end position			end position		
		second saccade		(-5,0)	(5,0)	(15,0)	(-15,0)	(-5,0)	(5,0)
(A)	scatter	monkey LBZ	control	3.5(2.3)	4.1(2.0)	4.3(1.7)	4.4(2.0)	4.1(1.7)	3.9(1.7)
			lesion	4.4(1.9)	4.5(2.8)	4.8(2.4)	4.8(2.3)	4.6(2.1)	5.3(1.9)
		monkey NWT	control	4.0(2.0)	4.2(2.7)	4.1(2.8)	4.5(2.3)	4.9(2.7)	4.0(1.6)
			lesion	4.1(2.1)	4.7(2.3)	4.4(2.7)	4.2(2.4)	4.8(2.2)	4.7(2.2)

				first saccade rightward			first saccade leftward		
				end position			end position		
		second saccade		(-5,0)	(5,0)	(15,0)	(-15,0)	(-5,0)	(5,0)
(B)	amplitude (up left)	monkey LBZ	control	12.4(2.4)	12.2(2.1)	12.8(2.0)	10.2(2.0)	11.0(2.4)	13.5(3.0)
			lesion	12.0(2.9)	12.1(2.7)	12.9(2.6)	9.7(1.8)	11.8(2.9)	12.6(3.3)
		monkey NWT	control	11.9(3.1)	12.1(2.5)	12.3(2.8)	9.4(2.0)	11.4(2.1)	13.2(2.7)
			lesion	11.5(2.7)	12.0(2.6)	12.0(3.4)	9.6(1.8)	11.5(2.3)	12.6(2.8)
	(up right)	monkey LBZ	control	12.4(2.0)	11.8(2.5)	9.4(2.2)	12.5(2.7)	12.0(2.1)	12.1(2.9)
			lesion	12.0(2.1)	12.1(1.7)	9.6(2.7)	13.0(2.4)	12.8(2.5)	11.6(2.9)
		monkey NWT	control	13.1(2.6)	12.3(3.0)	10.3(2.0)	12.7(2.6)	13.0(2.0)	12.8(2.5)
			lesion	11.9(2.6)	11.6(2.5)	9.4(1.5)	11.5(2.1)	11.8(2.2)	12.2(2.4)
	(down left)	monkey LBZ	control	9.5(2.2)	11.0(1.8)	12.5(2.4)	8.5(1.9)	10.6(2.5)	11.7(2.8)
			lesion	9.2(2.1)	10.8(1.9)	12.7(2.6)	8.4(2.0)	10.5(2.5)	11.2(2.6)
		monkey NWT	control	9.4(1.9)	11.2(2.3)	12.2(2.4)	8.4(1.4)	9.6(2.3)	12.0(3.1)
			lesion	9.5(2.4)	10.9(2.5)	12.2(2.0)	8.6(1.5)	9.1(2.1)	11.9(2.7)
	(down right)	monkey LBZ	control	12.9(2.7)	10.6(2.4)	8.0(2.1)	12.5(2.8)	11.9(2.6)	10.2(2.0)
			lesion	12.8(2.8)	10.4(2.7)	7.7(1.9)	12.6(3.4)	11.5(2.4)	9.5(2.1)
		monkey NWT	control	13.3(2.6)	11.0(2.4)	8.1(2.0)	13.0(2.7)	10.7(2.6)	9.8(2.3)
			lesion	12.7(2.0)	11.0(2.1)	7.4(2.3)	12.9(2.9)	10.4(2.5)	10.1(2.5)

Table 3

			first saccade rightward			first saccade leftward		
			end position			end position		
	second saccade		(-5,0)	(5,0)	(15,0)	(-15,0)	(-5,0)	(5,0)
(C) direction (up left)	monkey LBZ	control	61(14)	57(10)	52(9)	64(13)	52(8)	49(11)
		lesion	62(9)	60(14)	51(10)	59(10)	51(12)	44(9)
	monkey NWT	control	66(13)	61(12)	53(10)	62(14)	44(10)	33(11)
		lesion	58(10)	57(12)	50(11)	54(11)	36(9)	34(9)
(up right)	monkey LBZ	control	59(10)	64(13)	70(10)	59(10)	62(11)	69(14)
		lesion	59(12)	65(12)	69(14)	57(9)	65(9)	71(12)
	monkey NWT	control	62(12)	70(13)	76(13)	55(12)	61(11)	67(12)
		lesion	58(11)	67(14)	76(12)	57(10)	61(12)	71(11)
(down left)	monkey LBZ	control	70(10)	62(9)	60(14)	69(12)	64(12)	53(9)
		lesion	68(11)	63(9)	55(9)	68(9)	62(8)	50(10)
	monkey NWT	control	77(9)	67(10)	62(12)	75(11)	62(9)	55(10)
		lesion	74(11)	69(9)	63(10)	75(10)	62(13)	55(11)
(down right)	monkey LBZ	control	44(6)	52(11)	65(10)	46(9)	60(11)	65(9)
		lesion	49(10)	50(9)	62(10)	48(9)	55(9)	64(13)
	monkey NWT	control	55(13)	58(12)	66(11)	50(10)	57(12)	64(10)
		lesion	53(9)	64(11)	67(9)	51(9)	61(12)	69(13)

Table 3(continued)

		first saccade leftward end position			first saccade rightward end position		
second saccade		*(-15,0)*	*(-5,0)*	*(5,0)*	*(-5,0)*	*(5,0)*	*(15,0)*
error	*control*	4.4(2.8)%	5.2(3.3)%	4.9(2.7)%	2.2(1.2)%	4.1(2.3)%	4.8(2.8)%
	lesion	3.6(1.5)%	6.1(2.9)%	5.3(2.1)%	3.4(1.5)%	4.5(2.5)%	4.5(1.9)%
latency	*control*	226(34)	217(25)	221(31)	213(35)	209(35)	217(34)
	lesion	239(40)	228(36)	243(37)	240(37)	235(38)	232(44)
scatter	*control*	0.77(0.19)	0.76(0.25)	0.65(0.14)	0.82(0.28)	0.77(0.13)	0.76(0.22)
	lesion	0.71(0.11)	0.69(0.11)	0.56(0.23)	0.74(0.12)	0.83(0.19)	0.79(0.20)
*amplitud*ι	*control*	9.8(0.4)	9.5(0.5)	9.6(0.4)	9.6(0.4)	9.7(0.3)	9.8(0.6)
	lesion	9.5(0.3)	9.7(0.5)	9.7(0.4)	9.6(0.4)	9.5(0.5)	9.5(0.5)

Table 4

CHAPTER FIVE

Disruption of Gaze Holding in Parietal Monkeys

Summary

1. Neurons in the primate posterior parietal lobe are active during sustained visual fixation. Furthermore, this fixation activity varies with eye position. This eye position effect could either be a result of proprioceptive modulation or reflect the central neural command to hold the eyes at a desired position. The existence of both of these neural signals has been supported to a variable extent by physiological and psychophysical experiments. Here we report the oculomotor behaviors of parietal monkeys, which suggest that the eye position activities in the posterior parietal cortex might subserve gaze holding.

2. We tested parietal monkeys with a memory saccade paradigm in which they were required to hold their gaze at the end of a saccade for up to 1.2 seconds in complete darkness. Compared to normal monkeys, the eye of the parietal monkeys consistently drifted toward the ipsilesional side at the end of the saccade. The direction of the drift was the same no matter in which direction the saccade was made. The velocity of the drift was typically 2 to 3 deg/sec and remained fairly constant throughout the period of fixation. In one monkey tested, the magnitude of the drift was found to depend on the duration of the delay in the memory saccade paradigm. The longer the delay period, the larger the drift. No such drift was seen when the monkeys performed a visual saccade task or the memory saccade task in the presence of a visual background.

3. These oculomotor abnormalities were unlike the gaze-holding problem observed after lesion of the neural integrators in the brain stem or saccadic

dysmetria as a result of lesion of some cerebellar structures. We attribute the eye position drift to the damage of the gaze-holding capacities of the fixation neurons in the posterior parietal lobe.

Introduction

Eye movements in a natural setting consist of sequences of saccades and fixation of variable duration in the intersaccadic intervals. We make saccadic eye movements to a target of interest and foveation in the intersaccadic intervals allows us to observe its details. During these periods of foveation we need to hold our gaze actively so that a constant eye position can be maintained and the target remains within the region of maximal visual acuity.

The neuronal substrate mediating gaze-holding has generally been thought to reside in the brain stem. The activities of neurons in the nucleus prepossitus hypoglossi(NPH) and the medial vestibular nucleus(MVN) are modulated by eye velocity and in a linear manner by eye position. It has been proposed that the reverberating activities through the connection of these neural integrators and cerebellar structures serve to sustain gaze-holding(Leigh and Zee, 1991).

Other than these neuronal substrates in the brain stem to subserve gaze holding consequent to a saccade, it is plausible that there is also a cortical component to this function, given the highly cognitive nature of eye movements in most natural settings. In visual search for a target in a crowded environment, for example, we must not only be able to decide where to move our eyes from moment to moment but also where to stay and for how long. Holding our gaze at a given spatial location is a cognitive operation and presumably requires cortical mechanisms to facilitate its integration with other cognitive capacities.

Besides saccade-related activities, the posterior parietal cortex(PPC) has been shown to contain neurons that discharge during active fixation(Lynch et al., 1977; Sakata et al., 1980; 1985). Even though the firing of many fixation neurons was shown to decrease without a light stimulus, the activity of the majority was sustained in darkness as long as the monkey continued to fixate(Lynch et al., 1977; Sakata et al., 1985). In other words, the activity of visual fixation neurons in the PPC clearly reflects extraretinal signals and are not simply visual in nature. This fixation activity has been shown to be modulated by eye position both in the horizontal and vertical axes, and in depth(Lynch et al., 1977; Mountcastle et al., 1975; Sakata et al., 1980; 1985). This extraretinal signal could potentially come from two different origins, firstly, from proprioception from the muscle spindles of the extraocular muscles, or, secondly, efference copy of the neural command to maintain fixation on the target of interest. In the latter case, the activity seems to subserve the function of holding the gaze at a desired position, in contrast to the passive, sensory nature of the proprioceptive signals. The aim of this study is to describe some experimental results which might help to distinguish between these two hypotheses.

Methods

Subjects and experimental setup

Three macaque monkeys(LBZ, MRS, and BCR) were used in this experiment. These monkeys were examined before and after extensive recording studies characterizing the role of the lateral intraparietal area(area LIP) in processing saccadic eye movements. Chronic recording from this area over a period of several years resulted in some deficits in oculomotor behavior, such as hypometric and slower saccades to the contralesional field. Informal neurological examination also revealed that these animals had difficulty in persistently fixating at contralesional locations, particularly lower locations. Another evidence for the damage to the posterior parietal cortex as a result of extensive chronic recording was the demonstration in some of these animals of the extinction of the contralesional stimulus(Lynch and McLaren, 1989).These behavioral abnormalities are not seen in monkeys free from any extensive recording or lesion experiments. The monkeys were otherwise normal in their behaviors. No motor deficits or overt spatial neglect were observed throughout these experiments. Finally, histological examination of the brain sections of monkey LBZ revealed extensive penetration marks and gliosis in the posterior parietal cortex. General experimental procedures and setups were described in detail in another study(Li et al.,). N.I.H. guidelines were closely followed for the care and use of these animals.

The monkeys were trained to fixate different locations on the screen, to make visually guided and memory saccades. See Li et al., for a detailed description of these paradigms. For the purpose of this experiment, the monkeys were trained for a particular version of the memory saccade task in which the "hold" period at the end of the saccade was increased to up to 1,200 msec. In one monkey(LBZ) we also varied the duration of the delay period in some experimental sessions. Three different durations were used: 200, 600 and 1,200 msec. Saccade amplitude was typically fixed at 10 or 15 degrees when a variable delay period was used in the experiment. The memory saccade task was tested both in darkness and in the light to see if the presence of a visual context might have an effect on the gaze-holding behavior. A different version of the fixation task, termed the "gap fixation" task, was also employed to examine the gaze-holding behavior. In this task, the monkeys were trained to hold their gaze at different target locations throughout the fixation(typically 1,800 or 2,400 msec), including a gap period in which the light stimulus was turned off. The duration of the gap period was typically either 600 or 1,000 msec. Regular fixation and visual saccade tasks were also carried out for comparison.

To characterize the eye position drift at the end of the saccade in the memory saccade task, the total distance of the drift was taken by subtracting the eye position at the end of the saccade(which is defined as the point when the eye velocity declined to 50 deg/sec) from the eye position at the end of the trial(when the critical duration of gaze holding is fulfilled). Dividing this result by the "hold" duration yields the average velocity of the drift. In rare instances(no more than 1% of the trials for both monkey LBZ and MRS, and nil for monkey BCR), the monkey would make a second small saccade in the hold period. Such saccades appeared to be random in direction and ranged from 0.5 to 2.3 degrees in amplitude. If such saccades occurred, the trials were excluded from analysis. Similarly, in the gap fixation task, the difference between the eye positions at the end and the beginning of the gap period was taken to derive the magnitude of the drift and the velocity of the drift was calculated by dividing it by the gap duration.

Finally, analysis of variance was performed to examine if the variable delay had an effect on the eye position drift in the memory saccade task.

Results

Figure 1 showed the example traces of the eye drift of monkey LBZ(A) and MRS(B) and of monkey MRS(C) prior to any recording experiment as control. These eye traces were collected in the memory saccade task in darkness. The saccades were made in eight different directions to targets 15 degrees away from the fixation point and the monkey was required to hold his gaze for 1,200 msec at the end of the saccade. The lesion was in the left hemisphere of monkey LBZ and in the right hemisphere of monkey MRS. It can be seen that, for both monkeys, the eye drifted in the ipsilesional direction at the end of the saccades. The results were similar for saccades in all directions, even though the drift toward the primary position consistenly had a larger magnitude than those going in the other directions. Downward saccades tended to have a larger upward drift. Eye traces for the same task from a normal monkey(in this case, monkey MRS prior to any recording) were shown on the right(C) and typically the eyes drifted upward at the end of the saccade. This latter finding seems to be typical of the eye position change in darkness(Becker and Klein, 1973).

No eye drift was observed in the visual saccade task or the same memory saccade task performed in light, even when the monkeys were required to hold his gaze at the end of the saccade for a comparable duration.

The drift velocity averaged across all saccade directions was 2.7, 2.8, and 2.1 deg/sec for monkey LBZ, MRS, and BCR, respectively, and significantly different from that obtained in the memory saccade task in control condition ($p<0.001$ for all three monkeys). The velocity of the drift remained fairly constant throughout the entire "hold" duration such that the longer the monkeys were required to hold their gaze, the larger the eye drift became.

The drift velocity(and magnitutde) also varied with the saccade direction($p<0.001$, for monkey LBZ and MRS, and $p<0.01$ for BCR, ANOVA). Centripetal drift tend to have a higher average velocity(and magnitude) than centrifugal drift.

Figure 2 showed the similar drift of eye position during the gap period in the gap fixation task from monkey LBZ. Data were taken from one session, in which the monkey was required to fixate at 9 different locations: straight ahead, (0,0), and eight other locations 15 degrees away from (0,0). The velocity and magnitude of the drift was comparable to that observed in the memory saccade task. The average drift velocity was 2.5 deg/sec, which is significantly different from that(0.04 deg/sec) observed in the regular fixation task($p<0.001$). Such eye drift was observed repeatedly at different times for monkey LBZ throughout an experimental period of 8 months.

Results from monkey LBZ in the memory saccade task in which the duration of delay was varied showed that the magnitude of the drift varied with the duration of the delay($p<0.001$, ANOVA). The longer the delay, the larger the drift. These results are the same for saccades in all directions.

No spontaneous nystagmus was observed either in light or in darkness.

Discussion

Gaze-holding failure after lesion of neural integrators and the cerebellum

Failure of gaze-holding has commonly been attributed to the lesion of the neural integrators in the brain stem or other related structures such as flocculus and paraflocculus in the cerebellum(Cheron et al., 1986; Cannon and

Robinson, 1987). In these experiments in which either chemical or electrolytic lesion was placed in the area of the nucleus prepossitus hypoglossi(NPH) and/or the medial vestibular nucleus(MVN), the eye drifted rapidly back to the null position following saccadic eye movements, with a time constant approximately determined by the mechanical properties of the orbital tissue. After lesion of NPH and/or MVN on one side, the centripetal drift followed both ipsilesional and contralesional saccades and were present even when the saccades were made in the light(Cannon and Robinson, 1987; Anastasio and Robinson, 1991; Straube et al., 1991; Mettens et al., 1994). Similar gaze-holding failure was found for vertical eye movement after lesion of the interstitial nucleus of Cajal or the posterior commissure(Fukushima et al., 1992; Partsalis et al., 1994). After ablation of one cerebellar hemisphere, the animals were unable to maintain steady fixation on targets on the side of the lesion, and ipsilesional saccades were followed by centripetal drift(Westheimer and Blair, 1974). Likewise, after lesion of flocculus and paraflocculus, post-saccadic drift occurred, the direction of which seemed to vary with saccade direction and eye position and also showed some individual variation. The drift followed an exponential time course and appeared to be a result of pulse-step mismatch of the saccade command. Gaze-paretic nystagmus was oftentimes associated with such post-saccadic eye drift (Zee et al., 1981).

The post-saccadic eye drift shown in this study is very different from those observed following the lesion of the neural integrators in the brain stem or cerebellar structures. The direction of the drift was always directed to the ipsilesional side, no matter in which direction the saccade was made. Furthermore, it manifested itself in the gap fixation task, in which no saccade was performed, and the eye drift was not present in the visual saccade task or when the memory saccade task was performed in the presence of a visual background. These oculomotor behaviors could not be explained by extraocular muscle palsy, either. Other than being slightly slower and hypometric, the monkeys were able to saccade to a contralesional target in one rapid movement. Staircase eye movements were never observed. Moreover, they looked well into the periphery of the contralesional and ipsilesional visual field. Finally, no gaze-paretic or spontaneous nystagmus was ever observed throughout the experiment. These results overall suggest that the eye drift observed following parietal lesion is different from those resulting from lesion of the cerebellum or the neural integrators in the brain stem and deserves new explanation.

Fixation activity in the oculomotor system

Fixation activities have been described in several cortical and subcortical structures. Of the cortical areas that are reported to be involved in processing saccadic eye movements in primates, many are also shown to be involved in active visual fixation. In the frontal eye field(FEF), for example, besides the well-known saccade-related activities, Bizzi and Schiller reported the existence of "type II" cells, that showed chronic sustained activities when the monkey is statically fixating on or pursuing a light spot. Moreover, these neuronal activities were modulated by the changes of eye position(Bizzi, 1968; Bizzi and Schiller, 1970; Bruce and Goldberg, 1985). They postulated that this activity might play a role in the control of muscle contraction during visual fixation(Bizzi and Schiller, 1970). In other words, these neurons might be involved in holding gaze at a desired position. Segraves et al. reported that, besides movement related signals, there is a relative preponderance of foveal excitability in the population of neurons projecting to the superior colliculus. It was not clear whether the activities of these neurons were modulated by eye position, but it was suggested that the FEF neurons active during attentive fixation would have a suppressive effect upon collicular movement neuorns and thereby assist in the maintenance of fixation(Segraves and Goldberg, 1987).

Further evidence that the FEF might be part of an ocular fixation system comes from studies which showed that microstimulation of the lateral prearcuate cortex could suppress or delay visually triggered saccades(Azuma et al., 1994; Burman and Bruce, 1990). Removal of the FEF was shown to lower the current threshold of evoking saccades from stimulating the superior colliculus(Azuma et al., 1991). Furthermore, anatomical studies have demonstrated that the lateral part of the FEF(where saccades of small amplitudes are represented) project directly to the omnipause area in the brain stem(Büttner-Ennever et al., 1988; Stanton et al., 1988). Overall these results suggest that the FEF is not just involved in generating saccades, but rather in an intricate functional network of generating saccades and maintaining fixation.

Fixation neurons with their activities modulated by eye position were also found in the dorsomedial frontal cortex(DMFC, the supplementary eye field)(Bon and Lucchetti, 1992; Lee and Tehovnik, 1995; Schlag et al., 1992). Since these neurons did not show similar modulation by eye position in the intertrial intervals or other "non-task" conditions, it was argued that these eye position-dependent fixation activity did not unconditionally reflect an eye position signal, as has been observed in the brain stem or in the thalamus(Schlag et al., 1992; Bon and Lucchetti, 1992; Luschei and Fuchs, 1972; Schlag-Rey and Schlag, 1984). Furthermore, the DMFC neurons become active before the eyes move into the preferred position of the cell(Lee and Tehovnik, 1995; Schlag and Schlag-Rey, 1987). It was suggested that these neuronal activities might specify the goal of a saccadic eye movement. Such suggestion is consistent with the results from studies in which microstimulation of the DMFC evoked saccades that converge to a relatively fixed zone of orbital position(Mitz and Goldschalk, 1989; Schall, 1991; Schlag and Schlag-Rey, 1987) and that such "convergence zones" were organized in a topography in good agreement with local eye position activities(Lee and Tehovnik, 1995).

Another cortical area where neurons were identified to be active during sustained fixation is the dorsolateral prefrontal cortex(DLPFC). The fixation activity observed in the inferior part of the DLPFC is likely more related to the motivation state of the monkey. Moreover, the fixation activity in this area did not seem to be modulated by eye position (Suzuki and Azuma, 1977; Suzuki et al., 1979; Joseph and Barone, 1987).

Neurons in the rostral pole of the mammalian superior colliculus increased their tonic discharge when the monkey actively fixated a target or pursued a moving target, and this sustained activity persisted without a light stimulus as long as the monkey continued to fixate(Munoz and Wurtz, 1993a). Activation of the fixation zone by electrical stimulation delayed the initation of saccades and arrested saccades in midflight, whereas inactivation of this strucure with a GABA agonist decreased the latency of visual saccades and rendered fixation difficult(Munoz and Wurtz, 1993b; Pare and Guitton, 1994). These findings suggest that the rostral pole of the superior colliculus inhibits the generation of saccades and is part of the oculomotor fixation system. Such a function of the collicular fixation zone is further supported by the demonstration of a direct projection of this area to the omnipause neurons(OPN's) in the brain stem(Pare and Guitton, 1994). Neurons in the omnipause area display similar behaviors as the cells in the collicular fixation zone(Delgado-Garcia et al., 1989; Evinger et al., 1982; Keller, 1974). OPN's discharge at a steady tonic rate and exhibit a complete cessation of activity before saccades in any direction. Microstimulation at the sites of OPN's prevents the occurrence of saccade and interrupts it in midflight for the duration of the stimulation. Neither the collicular or omnipausal fixation activities seem to be modulated by eye position(Keller, 1974; Munoz and Wurtz, 1993a). However, there appear to be a separate group of neurons in the pontine reticular formation, whose activities showed a direction and eye position dependency(Keller, 1974). Unlike OPN's, these "pausing" neurons paused only for saccades in the ipsilateral direction and their tonic discharge rate was also modulated in a linear manner by eye position.

Finally, neurons in the basal ganglia discharge in relation to visual fixation and their activities appear to be highly dependent on the presence of a visual stimulus(Hikosaka and Wurtz, 1983; Matsumura et al., 1992) or the expectation of a reward(Hikosaka et al., 1989). Inactivation of the subtantia nigra pars reticulata(SNpr) resulted in fixation difficulty and irrepressible saccades to the contralesional visual field(Hikosaka and Wurtz, 1985b). It was suggested that the basal ganglia contribute to the initiation of a saccade through a disinhibition mechanism(Hikosaka et al., 1989). In other words, it appears the tonic fixation activity in the basal ganglia has to be turned off before a saccade can be initiated.

Anatomically it has been shown that the injection of tracers in the fixation zone of the SC labelled the lateral part of the FEF and the SNpr(Aizawa et al., 1995). Given that both the FEF and SC project to the omnipause area in the brain stem(Büttner-Ennever et al., 1988; Pare and Guitton, 1994; Stanton et al., 1988), it appears that there is a network of cortical and subcortical areas subserving ocular fixation. This fixation system would work in a reciprocal manner with the saccade-generating systems. The ncrease of activity in the latter and decrease in activation of the former triggers a saccade whereas a dominant signal from the the fixation system immobilizes the eye in between saccades. Evidence for such interaction could be found in studies which demonstrate that the fixation of a visual stimulus elevates the current threshold of eliciting a saccade from electrically stimulating either the SC, FEF or the posterior parietal cortex, compared to that in complete darkness(Goldberg et al., 1986; Schiller and Sandell, 1983; Shibutani et al., 1984; Sparks and Mays, 1983).

The existence of a fixation system is also supported by a recent psychophysical study of vergence-associated saccadic eye movements(Enright, 1992). It was found that the saccades that occur near the onset of asymmetrical change in vergence differ from ordinary saccades in that the excursions of the two eyes are typically unequal and that the post-saccadic behaviors of the two eyes are very different. These results indicated, it was suggested, that the pulse and step components of a saccadic eye movement may be generated through entirely independent processes. In other words, it appears that to hold the eyes at a desired position at the end of a saccade, the system does not simply rely on the integration of saccade velocity, but, rather, an independent signal specifying the final eye position.

A possible gaze-holding mechanism in the posterior parietal lobe

Fixation activities in the posterior parietal cortex(PPC) were first identified by Mountcastle and colleagues(Mountcastle et al., 1975; Lynch et al., 1977). It was shown that the visual fixation neurons increase their discharge when the animals attentively fixate a target, as when he was expecting a reward. These neurons are relatively inactive when the animals casually inspect the surrounding environment. Most fixation neurons have a gaze field; that is, these neurons increase their discharge when the eyes move into their prefered orbital position. Most of these gaze fields are fairly large and could subtend up to a whole hemifield. The gaze field of most parietal neurons weighs toward the contralateral field(Li et al., in preparation; Lynch et al., 1977). Fixation neurons also increase their activity during smooth pursuit movement as long as the eyes stay within the cells' prefered position. One interesting finding is that the activity of the fixation cells in posterior parietal lobe was suppressed prior to or synchronous with saccadic eye movements, either those induced by stimuli or spontaneous saccades occurring in the absence of sensory events(Lynch et al., 1977). Such behavior is not inconsistent with a role of gaze holding for these fixation neurons. The parietal neurons differ from the collicular cells, however, in that their fixation activities are typically modulated by eye position and that they do not appear to pause for all saccades in all directions.

In this study we demonstrated that chronic lesion of the posterior parietal lobe resulted in gaze holding deficits. The magnitude of the eye drift either in the memory saccade task or in the gap fixation task increased with the duration he was required to hold his gaze in darkness. No similar drift was seen when the monkey held his gaze at an eccentric position for a comaprable duration in the visual saccade task or when the memory saccade was performed in the presence of a visual background. It seemed, therefore, that in parietal monkeys, the reafference of the visual stimulus provides a sufficient input to acitivate other cortical or subcortical mechanism for gaze holding. In the memory saccade task where the duration of the delay was varied, we showed that the magnitude of the drift increased with the duration of the delay period. It appears that the memory activity of the target location acitivates the visual fixation system and such activity helps keeping the eye at a desired location. It is interesting to note that the fixation neurons in the basal ganglia are generally sensitive to the presence of a light stimulus(Hikosaka and Wurtz, 1983; Matsumura et al., 1992).

We have shown in other studies that the eye position activities in the PPC might provide the extraretinal signals for saccadic localization in a double saccade task(Li and Andersen,). It was reported in other studies that transection of the ophthalmic nerve(thus disrupting the proprioceptive inputs from the extraocular muscles) did not impair the monkey's ability in compensating for the change of eye position to correctly localize a remembered target location(Guthrie et al., 1983). In other words, it is the efference copy of the oculomotor signal that is used in the computation of the second movement in such a double saccade task. The results in this study provided further evidence that this eye position activity is indeed active in nature, serving to hold the eye at a desired position.

Clinical studies documented in patients with extensive cortical lesions disorders in gaze holding(Chedru et al., 1973; Tijssen et al., 1991). These patients oftentimes have problem holding their gaze in the contralesional space. Lesion experiments in behaving primates also showed that after unilateral decortication the monkeys were unable to move their gaze into the contralesional hemifield either during spontaneous eye movement or the quick phase of nystagmus(Latto and Cowey, 1971; Tusa et al., 1986). In cases where the monkeys did make a saccade to a target in the contralesional space, it was difficult for them to maintain fixation at this new location and they quickly made saccades back to the midline. This difficulty of maintaining fixation progressively increased with eccentricity from the midline(Tusa et al., 1986). It thus appears that extensive damage to the whole cortical network of ocular fixation would severely disrupt the monkeys' ability to hold their gaze in the contralesional space. The results shown in this study suggested that the PPC is an important node in this visual fixation system. Lesion of the PPC as a result of chronic recording did not result in full-blown failure in gaze holding; nevertheless, it disrupted the fixation at the end of a saccadic eye movement. Further studies are required to understand how these cortical and subcortical areas connect with each other and interact to subserve fixation. Of prime importance is the question of how the fixation activities are integrated with the saccade-generating mechanisms.

FIGURE LEGENDS

FIGURE 1

Eye traces in the memory saccade task in which the monkeys were required to hold their gaze for 1,200 msec at the end of the saccade. Five to six trials were shown for each saccade direction. Each dot represents the instantaneous eye position sampled at every 2 msec. (A) and (B) show the result from a typical session from monkey LBZ and MRS, respectively, after they have been extensively used for chronic recording. Data from a session of monkey MRS prior to any recording experiment is shown in (C) as control. See text for further explanation.

FIGURE 2

Eye traces during the gap period one trial each for a different starting position were shown from monkey LBZ in the gap fixation task. The duration of the gap was 1,000 msec. The circles mark the eye position when the gap period started. The lesion of monkey LBZ was in the left hemisphere. The eye consistently drifted upward and toward the ipsilesional side. See text for further explanation.

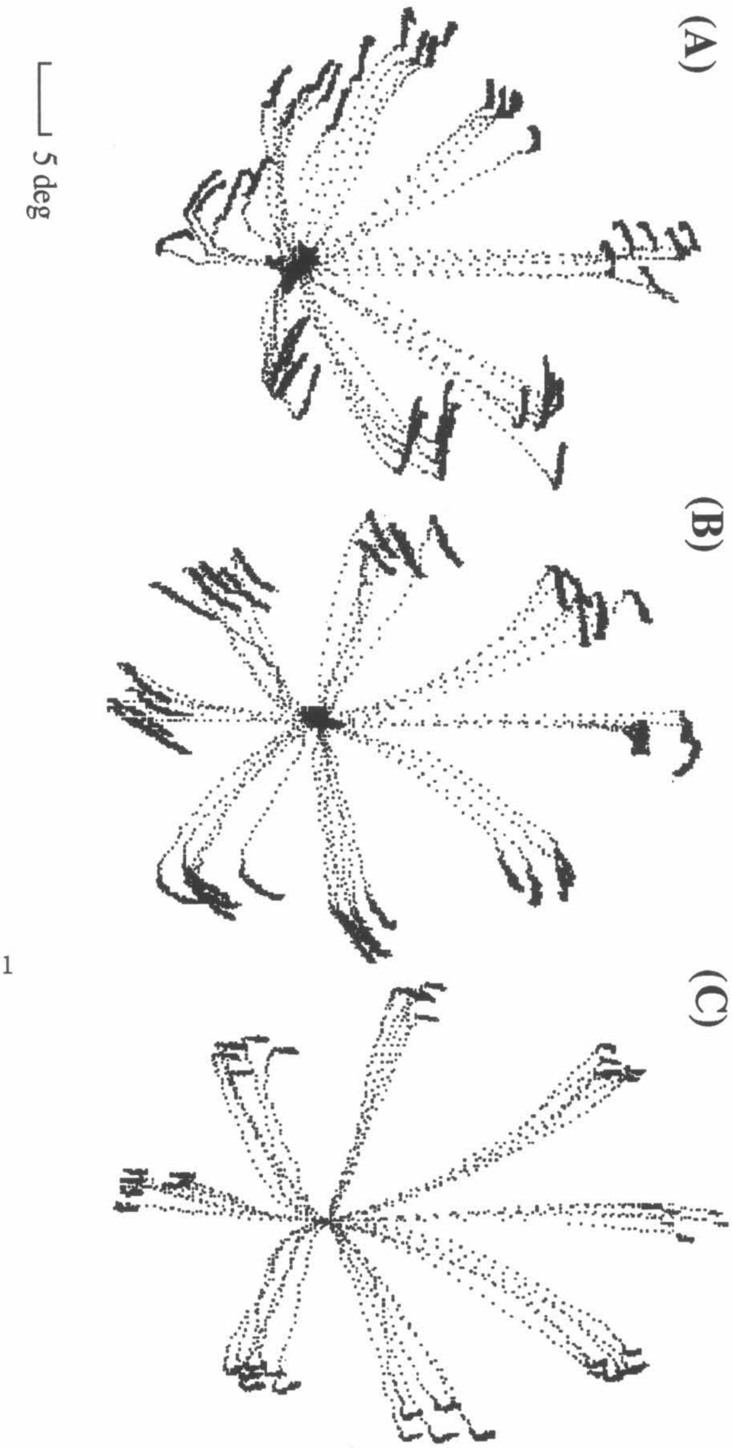


Figure 1

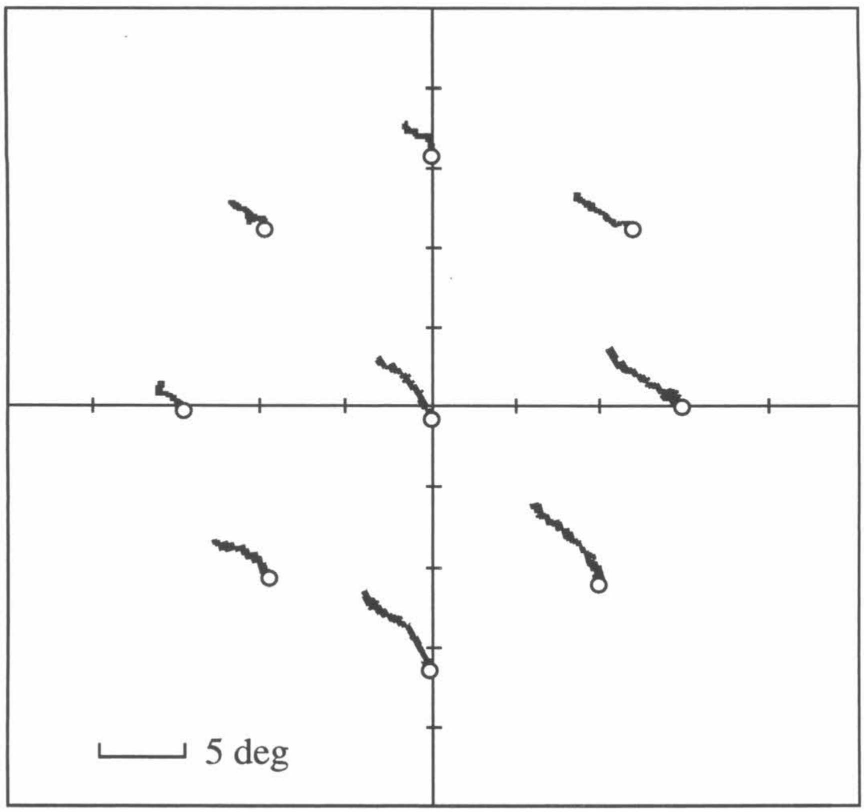


Figure 2

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