Smooth-Pursuit Eye Movement Deficits With Chemical Lesions in the Dorsolateral Pontine Nucleus of the Monkey

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SUMMARY AND CONCLUSIONS

1. Anatomical and single-unit recording studies suggest that the dorsolateral pontine nucleus (DLPN) in monkey is a major link in the projection of descending visual motion information to the cerebellum. Such studies coupled with cortical and cerebellar lesion results suggest a major role for this basilar pontine region in the mediation of smooth-pursuit eye movements.

2. To provide more direct evidence that this pontine region is involved in the control of smooth-pursuit eye movements, focal chemical lesions were made in DLPN in the vicinity of previously recorded visual motion and pursuit-related neurons. Eye movement responses were subsequently recorded in these lesioned animals under several behavioral paradigms.

3. A major deficit in smooth-pursuit performance was produced after unilateral DLPN lesions generated either reversibly with lidocaine or more permanently with ibotenic acid. Pursuit impairments were observed during steady-state tracking of sinusoidal target motion as well as during the initiation of pursuit tracking to sudden ramp target motion. Through the use of the latter technique, initial eye acceleration was reduced to less than one-half of normal for animals with large lesions of the dorsolateral and lateral pontine nuclei.

4. The pursuit deficit in all animals was directional in nature and was not dependent on the visual hemifield in which the motion stimulus occurred. The largest effect for horizontal tracking occurred in all animals for pursuit directed ipsilateral to the lesion. Animals also showed major deficits in one or both directions of vertical pursuit, although the primary direction of the vertical impairment was variable from animal to animal.

5. Chemical lesions in the DLPN also produced comparable deficits in the initiation of optokinetic-induced smooth eye movements in the ipsilateral direction. In contrast to this effect on the initial optokinetic response, in the one lesioned animal studied during prolonged constant velocity optokinetic drum rotation, smooth eye speed increased slowly over a 10- to 15-s period to reach a level that closely matched drum speed. These results suggest that pathways outside the DLPN can generate the steady-state optokinetic response.

6. Saccades to stationary targets were normal after DLPN lesions, but corrective saccades made to targets moving in the direction ipsilateral to the lesion were much more hypometric than similar prelesion control saccades.

7. The pursuit deficits produced by lidocaine injections recovered within 30 min. The ibotenic acid deficits were maximal ~1 day after the injection and recovered rapidly thereafter over a time period of 3–7 days. Extensive cell loss was observed histologically in the DLPN (and in some cases in the lateral pontine nucleus) in all animals injected with ibotenate.

8. As has been previously reported, nor-
nal prelesion monkeys showed a lowered eye acceleration in response to target spot motion on a highly textured stationary background. After the ibotenate injections and the subsequent recovery of normal tracking for a target spot moving across a homogeneous background, a more persistent deficit for tracking against a textured background was found.

INTRODUCTION

Although previous studies have established the importance of various cortical and cerebellar structures in the genesis of smooth-pursuit eye movements (see Ref. 12 and 31 for recent reviews), very little is known about the organization of the pursuit-specific pathways connecting these two structures.

Among the multitude of cortical areas processing visual information, a preponderance of direction-selective visual activity of the type required for pursuit guidance has been observed in the striate cortex (11, 19), the superior temporal sulcus (1, 34, 38, 61, 68, 69), and the posterior parietal cortex (49, 50). The functional relationship of these cortical structures to smooth-pursuit control is indicated by the deficits in smooth-pursuit eye movements that are observed after lesions in one or more of these areas (10, 17, 32, 43, 67).

Anatomical results indicate that the dorsolateral pontine nucleus (DLPN) of the monkey is a major terminus for converging pathways from many of these vision- and visuomotor-related structures as well as a primary source of afferents to the flocculus and vermal lobules VI and VII (4, 25), two cerebellar regions involved with the regulation of eye movements (21, 29, 39, 44, 45, 54, 56, 60).

In addition to tectal (18, 41) and pretectal (65) afferents, the DLPN receives convergent inputs from a variety of parietooccipital cortical visual areas (2, 3, 15, 36, 66). Although some of this cortical input originates in a portion of the striate cortex representing the far periphery, the bulk of these visual cortical-pontine projections arise from those regions surrounding and including the inferior parietal lobule (16). Notable among these cortical regions are the floor and both the anterior and posterior banks of the caudal third of the superior temporal sulcus (including the areas MT and MST). These cortical regions are involved in visual motion processing and maintain relatively strong projections to the DLPN (13–15, 35, 62, 63).

Consistent with these pontine projections from visual cortical areas that process retinal motion information are the recent recordings of visual- and smooth-pursuit-related responses in DLPN (42, 55, 57). The visual responses recorded in DLPN were direction selective and were elicited by the movement of large background patterns and/or discrete spot movement during fixation (57). Notably, the responses to a moving discrete spot were often related to the speed of spot movement and were particularly prominent during smooth-pursuit eye movements when eye speed did not equal target speed, i.e., during periods of retinal image motion in the unit's preferred direction (57). Further evidence implicating the DLPN in the control of smooth-pursuit eye movement has emerged from recent microstimulation studies. Focal electrical stimulation applied in the region of the DLPN through a recording microelectrode led to a short-latency modification of the velocity of an ongoing pursuit eye movement (37).

Although the nature of the vision-related activity recorded in the DLPN was consistent with a DLPN role in smooth-pursuit control, the possibility remained that the observed visual responses were concerned with visually guided behavior other than smooth-pursuit eye movements. To provide behavioral support for the physiologically based conclusion that the DLPN is specifically involved with the regulation of smooth-pursuit eye movements, pharmacological lesions were placed in the DLPN, and the effects on pursuit were studied. After these lesions impairments in smooth-pursuit eye movements were consistently observed. These results implicate the DLPN in the processing of information that is utilized in the initiation and maintenance of smooth-pursuit eye movements.

A preliminary report of these observations has been presented (59).
MATERIALS AND METHODS

Preparation

Monkeys (Macaca fascicularis and M. radiata) were prepared by chronically implanting three devices under pentobarbital sodium anesthesia and aseptic conditions. 1) A coil of Teflon-covered, stainless steel wire was implanted over the recti muscle insertions of one eye (20). This coil, used in conjunction with alternating magnetic fields kept in spatial and temporal quadrature, provided eye movement measurements of high sensitivity and zero drift (47). 2) A stainless steel chamber was placed stereotaxically on the skull above the DLPN at AP +5 or +6. The chamber was tilted in the frontal plane by 20-24° and displaced 2-3 mm lateral such that the central axis of the chamber crossed the animal's midline from 2 to 6 mm below Horsley-Clark zero. 3) To immobilize the head, two transverse tubes were placed on the skull in the horizontal plane and embedded in dental acrylic cement. After recovery from these surgical procedures, the monkeys began daily behavioral training and recording sessions. Animals were placed in a primate chair, and their heads were fixed relative to the chair. Monkeys were returned to their home cages after each session.

Administration of pharmacological agents

Standard electrophysiological recording procedures were used to sample the visual and oculomotor-related response properties of neural units as tungsten microelectrodes were advanced through the brain stem toward the pons. Visual responses were assessed by having the animal fixate a stationary fixation target while a small 0.5° spot or full-field textured patterns were swept across the animal's visual field in various directions. Oculomotor-related responses were assessed by having the animal track a moving fixation target. Pharmacological agents were administered following the anatomical localization of the DLPN on the basis of characteristic visual and smooth-pursuit-related neuronal activity (57). No differences were observed in either the neuronal responses of D1P.0 or in the oculomotor behavior of Macaca fascicularis and M. radiata. Just before injection of a compound, unit activity was recorded with metal electrodes to determine the exact location of direction-selective visual units. The microelectrode was then withdrawn and replaced by an injecting cannula or micropipette. Lidocaine hydrochloride was employed to induce reversible functional lesions (33), whereas the excitotoxin ibotenic acid was used to destroy cell somata while sparing fibers passing through the region (52).

Lidocaine (Elkins-Simms 4%) was injected in two monkeys (monkeys L and Z) by replacing the recording microelectrode with a 28-gauge stainless steel cannula. The tip of this injection cannula was placed just at the dorsal border of the DLPN based on the depth measurements of the prior extracellular pursuit-related unit recordings. The cannula was connected to a 10-μl syringe (Hamilton) with the syringe, connecting tubing, and cannula previously filled with lidocaine. Lidocaine delivery was controlled by advancing the syringe plunger with a micrometer head. Injection volumes varied from 5 to 10 μl.

Eye movement recordings were started immediately after lidocaine injections were made. In subsequent animals (monkeys S, F, M, O, and P), lidocaine and ibotenic acid injections were made using glass micropipettes and a precision-controlled pressure delivery system. Pressure connections were made through a WPI micropipette holder. Air pulses were delivered through an electronically controlled three-way solenoid valve (General Valve), whereas the meniscus level in the micropipette was monitored through a ×50 microscope. Delivery rate was controlled by adjustment of air pressure, pulse duration, and pulse rate.

Ibotenic acid was obtained either from Natural Products or from Sigma Chemical in powder form. The ibotenate was dissolved in either 0.9% saline or 0.1 M sodium phosphate buffer to yield a final concentration of 15–25 μg/μl. For both vehicles it was necessary to bring the pH of the mixture above 7.0 through the addition of small quantities of 1.0 N sodium hydroxide and to then sonicate it well before the ibotenate would go into solution. Ibotenic acid (volume usually 1.2 μl) was infused over a time period of ~0.5 h. The injecting micropipette was then left in place for an additional 15 min before it was slowly withdrawn and the animal returned to its cage. Eye movement recording sessions were then begun 24 h later in most animals. In monkey P, we attempted to lesion the whole rostral to caudal extent of the DLPN using several individual injections of ibotenic acid. The total amount of ibotenate injected was 64 μg (2.9 μl). In this animal large portions of the lateral pontine nucleus as well as parts of the DLPN were lesioned. A variety of somatic effects were noted over the following 12 h, including poor balance, paresis and paresthesia of the contralateral arm and leg, ipsilateral peripheral facial nerve palsy, and the deviation of the eyes into an extreme contralateral gaze position. Within 36 h of the injection, the animal had recovered from these neurological effects and the orbital position of the eyes appeared normal. Smooth-pursuit tests were initiated at this time in this monkey. Similar
but much milder effects such as circling away from the side of the lesion were seen in some animals during the first few hours after ibotenate injections though these other animals appeared normal the following day.

**Histological identification of lesion site**

The location of injection sites was determined through the histological reconstruction of electrode and micropipette penetration tracts, and in the case of the ibotenate injections by charting the extent of neuronal cell loss and reactive gliosis in the case of the ibotenate injections by charting the extent of neuronal cell loss and reactive gliosis in the case of ibotenate injections by charting the extent of neuronal cell loss and reactive gliosis. To aid in the reconstruction of the lidocaine injection sites, small electrolytic marking lesions were made near the site of injection after behavioral measurements were complete.

Animals that received injections of lidocaine were perfused with 10% neutral buffered Formalin. Animals receiving ibotenate injections were perfused with a 4% paraformaldehyde solution in a 0.1 M phosphate buffer (pH 7.4) followed by a series of 10, 20, and 30% buffered sucrose post-washes. Adjacent series of frozen sections were cut at both 20 and 40 μm with at least one set of 40-μm sections being stained with cresyl violet for each animal. Glial staining was enhanced by thoroughly defatting these sections in xylene before staining. An alternate set of sections from the ibotenate animals was stained using either luxol fast blue or a Wiel myelin stain to look for disruptions of passing fibers (23, 24).

Due to the unpredictable pattern of cell groups and intervening fiber fascicles within the pontine nuclei, it was not always clear which groups had disappeared on Nissl-stained sections. To aid in the localization of the lesioned region, additional sections were processed to demonstrate astrocytic processes, one component of the glial proliferation associated with neuronal degeneration (26). Astrocytes were visualized using either Cajal’s gold sublimate procedure or through the immunohistochemical demonstration of glial fibrillary acidic protein (GFAP) using the peroxidase-antiperoxidase method (53). Both procedures revealed areas of astrocytic proliferation within and surrounding the areas of cell loss and proliferating microglia observed on adjacent sections stained with cresyl violet.

**Behavioral paradigms and visual stimuli**

Monkeys were initially trained to fixate a small, target spot (0.5° in diam) that was backprojected by an oscilloscope projector system onto a 90 × 90° tangent screen placed 40 cm in front of the animals’ eyes. Animals were then trained to track the motion of this single target spot as it moved under computer control on the tangent screen. Liquid rewards were given contingent on the maintenance of gaze on the moving target. Deviations of gaze away from the target terminated the ongoing trial, thus imposing a mandatory intertrial delay before the task could be restarted and rewards could again be received. Daily adjustment of the eye movement system calibration was achieved by having the animal fixate a target spot as it was shifted to a series of known positions on the screen.

The oscilloscope projector was ideal for generating step-ramp movements of the target spot, since it could be stepped instantaneously to any position on the screen without the sweep limitations or oscillations inherent in many mirror galvanometer systems. It could also be turned on or off rapidly under computer control due to the quickly decaying P4 oscilloscope phosphor. In most of the experiments reported in this paper the target luminance was kept constant at 2.0 cd/m² against a very dim homogeneous screen (0.02 cd/m²).

Visual background stimuli were generated by a mirror galvanometer projection system that was equipped with a computer-controlled electronic shutter. In the present experiments the background generated by this system was a random check pattern that completely filled the tangent screen. Light and dark check size were each 1.2°/check, and the pattern contained on average one-half light and one-half dark checks. This highly textured background (average luminance level of 0.9 cd/m²; contrast = 0.74) either remained stationary or could be moved by applying a control signal to the mirror galvanometer.

To generate optokinetic eye movements with a field larger than that provided by the tangent screen, we employed a conventional striped drum (diam = 1.25 m), which could be lowered around the animal. The inside of the drum, including the top, was painted with a pattern of black and white stripes (vertical on the sides and radial on the top) of random width (1–8° of visual angle each), extending down 30° into the lower visual field. The inside of the drum was uniformly illuminated without shadows at a mean luminance of 5.0 cd/m² (contrast = 0.82). A mirror was also placed below the animal’s chin to reflect drum motion in the lower visual field. The drum was rotated by a servo-control system at constant rotation velocities of 40 or 60 deg/s in the present experiments. Step function inputs of constant velocity visual motion stimuli were generated with this system by turning the drum lights on or off after it had reached constant rotational velocity.

Smooth-pursuit eye movements were studied using two different types of target motion. Sinusoidal smooth eye movements were generated by varying target motion in a given plane (either horizontal or vertical) with a driving function of 0.4
FIG. 1. Single pursuit initiation trial illustrating the step-ramp paradigm and the experimental measurements of initial eye acceleration (made on a computer graphics scope). Top: eye position (E) just before and for ~500 ms after the onset of a constant velocity target (T) ramp at 20 deg/s shown at bottom. Middle: eye velocity response (E) for the same trial. In this case the target stepped instantaneously by 4° into the visual field opposite to the target ramp direction at the same time as ramp motion began. The occurrence, size, and direction of this step could be varied from trial to trial. An operator marked the time epochs of target motion onset (arrow 1), eye velocity response onset (arrow 2), and eye velocity magnitude at a point in time 100 ms after eye velocity onset (E100).

Hz ±10° (peak target velocity of 25 deg/s). The initiation of smooth pursuit was studied with the step-ramp paradigm first introduced by Rashbass (46). After a warning buzzer, a stationary target spot would appear, usually at primary position. The monkey was required to foveate this target and maintain steady fixation for a random interval of time (0.5–1 s). At the completion of this interval, the target began to ramp away at a constant velocity. On randomly ordered trials, the target would also step instantaneously to a selectable eccentric position while simultaneously starting its ramp motion (see Fig. 1, bottom). On these step/ramp trials the ramp motions could be directly toward or away from the fixation position (fovea). The step size, the plane of the ramp motion (horizontal or vertical), and the type of background condition were selected for a block of trials, whereas both ramp direction (e.g., left or right) and jump direction (e.g., no jump, left, or right) were randomized within this block of trials. Ramp velocities were selectable from 10 to 80 deg/s, but most data were collected at 20 deg/s.

The reward window condition was relaxed at the time of target motion onset, but after a 350-ms interval the monkey was required to have reestablished an eye position within a selectable criterion distance of the new target position (i.e., within the adjustable reward window). The animal then had to track the target for a variable length of time (usually ~1 s) to receive a liquid reward. Coincident with reward delivery, the target light was extinguished and the system was reset for the initiation of another trial.

To permit reinforcement of the animal's impaired postlesion pursuit responses the reward window condition was selectively relaxed in the affected direction(s). When similar procedures were applied in the relatively unimpaired directions or with normal control animals, there was little observed effect on the animal's initial pursuit response.

In addition to the smooth-pursuit responses, saccadic eye movements were elicited in separate blocks of trials by using target steps without subsequent ramp movements of the target.

Experimental measurements and data analysis

Sinusoidal eye movements were recorded on a rectilinear polygraph together with target position, and retinal image motion velocity (target velocity-eye velocity) signals. The calculations of smooth-pursuit gain during sinusoidal tracking were based on handmade measurements taken directly from the polygraph records. Eye velocity
signals were obtained from the output of an analog differentiator circuit low-pass filtered at 180 Hz.

Data from the step-ramp paradigm were digitized in real time at 500 Hz (horizontal and vertical eye position, horizontal and vertical eye velocity, and horizontal and vertical target position) and stored on disk for subsequent off-line analysis. Event marks related to the start of target motion (step or ramp), light onset and offset, and reward delivery were stored in register with the eye movement records with a resolution of 2 ms. Each trial record consisted of an interval of steady fixation before target ramp as well as the period including the animal's tracking response up to the time of reward delivery or in some cases trial abortion.

Each record was analyzed with special software that allowed an operator to display selected portions of that trial on a graphics screen. On each trial, the operator indicated with a cursor (as shown in Fig. 1) the time of target motion onset (arrow 1), the time of pursuit eye movement initiation (arrow 2), and the instantaneous eye velocity at 100 ms after the initiation of pursuit (E_{100}). The program then computed average eye acceleration during the first 100 ms of pursuit initiation and stored this value in tabular form with the other measured values for each trial. The horizontal and vertical cursors generated by the program were long thin lines extending across the entire screen (crosshairs). The extended length allowed the operator to place the horizontal cursor on a subjectively estimated zero eye velocity for the purposes of defining the onset of pursuit. The operator placed the cursor for this measurement in the estimated middle of the noise seen on the eye velocity trace. The point in time of pursuit onset was normally very distinct even after ibotenic lesions because of the sharp inflection in eye velocity relative to the horizontal cursor (see Fig. 1). On selected data we had two operators independently average the same set of eye velocity responses. Both observers consistently obtained essentially equal values for the onset of pursuit initiation and of average eye acceleration over the first 100 ms.

We chose average initial eye acceleration as our quantitative measure of pursuit performance, since eye acceleration is generated by retinal image motion (28) and the acceleration observed during the first 100 ms of the pursuit response can be considered the open-loop response (22, 30) of the pursuit system to retinal image motion occurring during the previous 100 ms. Typically, six individual measurements (minimum of four) were averaged for each condition to obtain the quantitative values given in the following results. The relatively small number of trials used in the averages resulted from the need to gather data for all the various conditions described above within the short period of time that the animal would work in the face of frequently aborted trials due to the effects of the lesion.

Most quantitative measurements were made from trials using a step-ramp combination such that target motion occurred toward the fovea (illustrated in Fig. 1). Such trials typically produced pure pursuit tracking responses without saccadic components. These trials provided the best conditions for assumption-free measurements of E_{100}. For some conditions (e.g., step-ramp trials with large step components, pure ramp trials with no step and step-ramp trials away from the fovea) the initial tracking response often included a saccadic component. These saccades always occurred with a longer latency than the onset of pursuit, but sometimes intruded into the initial 100-ms measurement interval of this smooth-pursuit response. It was often possible to select only those records from a group of responses in which the saccade occurred just after this 100-ms epoch. When this selection procedure failed to yield the minimum four individual measurements, trials with saccades were included by having the operator make a linear interpolation on the eye velocity records between the velocity level before the saccade and to the initial level just after the saccade.

Although all quantitative measurements were made on individual records and the set of measurement values were averaged, it was also possible to align the set of eye velocity responses being considered on response onset and then have the computer average the ensemble point by point. These averaged responses are often used in the following RESULTS section to graphically illustrate the effects of ibotenate lesions on eye velocity. Before individual eye velocity responses were included in the ensemble to be averaged, an operator removed the high-velocity saccadic portions from each record by substituting a linear interpolation between the velocity levels just before and after the saccade.

RESULTS

The effects of pharmacological lesions in the DLPN on smooth-pursuit eye movements were investigated in seven monkeys. Of these seven animals, two were injected with lidocaine, four were lesioned with ibotenic acid, and in one monkey, both lidocaine and ibotenic acid were administered to the DLPN at different times. Injections in each monkey were always unilateral.

Impairments were observed in both the initiation and maintenance of smooth-pur-
suit eye movements as shown by the sample records presented in Figs. 2 and 3. Figure 2 shows the effect of a lidocaine injection in DLPN on the performance of sinusoidal pursuit eye movements, whereas Fig. 3 shows the effect of a similarly placed ibotenic acid lesion on the initiation of pursuit to the onset of sudden target ramp motion. As shown in these figures, the lesioned animals showed greater impairments for ipsilaterally directed horizontal pursuit than for tracking in the contralateral direction. Each animal also showed an impairment in at least one direction of vertical pursuit, although there was no definite trend in the direction of the vertical deficit over the six animals in which pursuit was studied in all four cardinal directions.

The effects of lidocaine on sinusoidal smooth pursuit are illustrated in Fig. 2. Figure 2, top illustrates the movement of a small target spot as it sweeps across the tangent screen in an otherwise dark environment. The upper set of traces illustrate normal tracking in animal L just before the lidocaine injection. The quality of tracking is most clearly appreciated by examining the lower trace in each set that depicts retinal slip velocity (constructed electronically from the difference between target velocity and eye velocity). Immediately following a 10-μl injection of 4% lidocaine into the left DLPN there was a dramatic increase in leftward (ipsilateral) retinal slip, although tracking to the right was also somewhat effected (Fig. 2, middle). Coupled with this lower smooth-pursuit gain this animal's tracking became more saccadic, particularly for the ipsilateral direction of target motion.

This impairment in smooth-pursuit tracking was quantified by calculating pursuit gain as the ratio of average peak eye velocity to the peak target velocity during tracking (see METHODS). For animal L, the smooth-pursuit gain for ipsilaterally directed tracking decreased from a control value of 0.92 (±0.05 SD) to 0.50 (±0.11) after the administration of lidocaine. This animal's postlesion performance was normalized (postinjection gain divided by preinjection gain) to yield a relative postlesion performance measure of 0.54. A partial recovery was observed 30 min after the injection as shown by the lower set of traces. Some slip still occurred during ipsilateral tracking, although ipsilateral gain had increased to 0.83 (±0.09).

Pursuit deficits were also obtained after the administration of ibotenic acid, a substance that is specifically toxic to cell soma (52). In the animal shown in Fig. 3A, the average eye acceleration over the first 100 ms of the response in the ipsilateral direction dropped from an average of 215 deg/s² (+21 SD) to an average of 95 deg/s² (±18) after the lesion, thereby yielding a relative postlesion performance measure (based on initial eye acceleration) of 0.45. The initial eye acceleration for contralaterally directed pursuit was also significantly lower than prelesion controls in this animal (relative postlesion performance of 0.79), although the impairment was less severe than in the ipsilateral direction. Although initial ipsilateral eye acceleration was markedly reduced in all five animals injected with ibotenate, impairments in initial contralateral eye acceleration were also statistically significant in two animals (Student's t test, P < 0.025) as shown in Table 1.

A deficit in the maintenance of steady-state pursuit can also be seen in the set of records presented in Fig. 3A. Before the lesion the animal achieved an eye velocity that closely approximated the target velocity (20 deg/s) within a 200-ms period after pursuit onset. After the lesion, ipsilateral pursuit velocity plateaued near 15 deg/s. Although not seen in this animal, these steady-state pursuit impairments were usually accompanied by a series of small corrective saccades in the direction of target motion to keep the target near the fovea. As seen in Fig. 3B, steady-state tracking in the contralateral direction was very similar to prelesion controls.

The latency from the onset of target motion increased very slightly in each of the ibotenate-lesioned animals. The mean pursuit latency in the five monkeys tested with the ramp tracking paradigm was 107 ms (range = 93–117). After DLPN lesions, this mean value increased to 115 ms (range = 108–125), although this increase was not statistically significant.

**Histological observations of pontine lesions**

Single injections of ibotenic acid (1.3 μl; 19 μg) produced regions of cell loss extending
FIG. 2. Deficits in sinusoidal smooth-pursuit eye movement tracking in monkey with unilateral dorsolateral pontine nucleus (DLPN) lesions. The eye movement responses show a monkey lesioned in the left DLPN with a lidocaine injection. Each set of records, except the uppermost group, show horizontal eye position (E) in the upper trace and retinal slip velocity (S) in the lower during smooth-pursuit tracking of a target moving sinusoidally in the horizontal plane. Target motion (T) (a 0.4 Hz ± 10° sinusoid) was identical for each episode of tracking shown in the figure and is only included in the upper set of records. S records were desaccaded to remove the high-velocity incursions present during some corrective saccades. Top: an episode of tracking with injecting electrode located in the DLPN just before lidocaine injection. Middle: similar records taken from the same animal 10 min after a 10-μl injection of lidocaine. Bottom: the same animal, but now 30 min after lidocaine injection. Rightward direction and velocity are shown as up on all records. The vertical calibration adjacent to T is in degrees for eye position (E) and target (T) and deg/s for S and applies to all traces. Records are shown from animal L.
FIG. 3. Smooth-pursuit eye movement deficits during constant velocity ramp tracking. Each set of records show a representative collection of eye position responses (E) just before toxin injection (pre), 1 day after a 1.5-μl injection of ibotenate in the left DLPN (post), the averaged eye velocity (E) response before the lesion (pre) and 1 day after the injection (post). A: the eye movement response in the leeward (ipsilateral) direction. B: similar responses in the rightward direction. The pre- and post-eye velocity responses were constructed by averaging the individual trial velocity responses that were desaccaded before averaging as explained in METHODS. The averaged traces (pre and post) are shown superimposed for ease of comparison. Position traces are shown aligned on target (T) movement onset. Velocity traces are shown aligned on response onset (vertical line). The vertical dashed line to the right on the velocity averages shows the time epoch of eye velocity measurements (100 ms after response onset) used to quantify the responses in the present study. The vertical bars on the averaged eye velocity responses show the standard deviations of the mean eye velocity values at the 100-ms measurement point. The time, velocity, and position calibrations shown in A apply to traces in B as well. Records shown are from animal P for 20 deg/s ramp target velocity.

from 0.8 to 1.5 mm in diam. These lesioned regions were also characterized by the proliferation of microglia and astrocytic processes. An example of an ibotenate lesion is shown in Fig. 4 for monkey M, the animal that sustained the most extensive DLPN lesion. This animal received two ibotenate injections in the left DLPN followed 1 wk later by two additional injections centered within the same region. The extent of the lesion as judged by neuronal cell loss and the proliferation of microglia is indicated on the representative section outlined in Fig. 4C (⋯⋯). The photomicrograph in Fig. 4d depicts the extensive cell loss and reactive gliosis seen throughout the effected DLPN (section stained with cresyl violet). A distinct border can be seen in the lower right-hand corner between the neuron-rich intact area and the lesioned region containing a high density of glial nuclei and a conspicuous lack of large neuron cell bodies. There were often a few small surviving neurons within the lesioned area, which appeared as pale ghostly outlines due to their poor staining with the Nissl stain. These were seen primarily in the cases receiving only one injection. It is not clear if these surviving neurons are functionally intact or if they may mediate any of the recovery seen after these lesions.

Reactive gliosis was restricted to the actual nuclear zones containing degenerating neurons, since intervening regions of white matter within injection zones showed only low levels of gliosis. Regions of astrocytic proliferation, however, as seen on sections processed with GFAP immunohistochemistry or with Cajal's gold sublimate procedure, were somewhat more extensive than the regions of cell loss and microglial reaction observed in the cresyl violet material (see Fig. 4B). This astrocytic response may provide a
TABLE 1. Pursuit performance before and after DLPN lesions

<table>
<thead>
<tr>
<th>Animal</th>
<th>Direction</th>
<th>Sinusoidal Gain</th>
<th>Initial Acceleration, deg/s²</th>
<th>Normalized Performance</th>
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<tr>
<td></td>
<td></td>
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<td>Post</td>
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<tr>
<td></td>
<td></td>
<td>Normalized</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>L</strong></td>
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<td>0.85 ± 0.15</td>
<td>0.66 ± 0.14</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>F(Lido)†</strong></td>
<td>I</td>
<td>232 ± 26</td>
<td>166 ± 21</td>
<td>0.71*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>188 ± 18</td>
<td>201 ± 23</td>
<td>1.07</td>
</tr>
<tr>
<td><strong>F(Ibo)†</strong></td>
<td>I</td>
<td>222 ± 20</td>
<td>150 ± 11</td>
<td>0.68*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>221 ± 29</td>
<td>230 ± 18</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>I</td>
<td>0.97 ± 0.07</td>
<td>0.84 ± 0.09</td>
<td>147 ± 20</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.96 ± 0.09</td>
<td>0.98 ± 0.08</td>
<td>119 ± 23</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>0.81 ± 0.08</td>
<td>0.67 ± 0.07</td>
<td>122 ± 30</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.89 ± 0.15</td>
<td>0.63 ± 0.09</td>
<td>115 ± 20</td>
</tr>
<tr>
<td><strong>P†</strong></td>
<td>I</td>
<td>215 ± 15</td>
<td>95 ± 18</td>
<td>0.45*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>190 ± 19</td>
<td>150 ± 21</td>
<td>0.79*</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>211 ± 38</td>
<td>64 ± 5.2</td>
<td>0.30*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>266 ± 30</td>
<td>124 ± 17</td>
<td>0.47*</td>
</tr>
<tr>
<td><strong>O†</strong></td>
<td>I</td>
<td>150 ± 20</td>
<td>66 ± 5</td>
<td>0.44*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>126 ± 5</td>
<td>91 ± 10</td>
<td>0.77*</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>160 ± 12</td>
<td>92 ± 7</td>
<td>0.58*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>230 ± 10</td>
<td>115 ± 11</td>
<td>0.50*</td>
</tr>
<tr>
<td><strong>M†</strong></td>
<td>I</td>
<td>226 ± 39</td>
<td>115 ± 16</td>
<td>0.51*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>223 ± 31</td>
<td>222 ± 21</td>
<td>1.00</td>
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<tr>
<td></td>
<td>U</td>
<td>177 ± 22</td>
<td>67 ± 22</td>
<td>0.38*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>169 ± 23</td>
<td>115 ± 11</td>
<td>0.68*</td>
</tr>
</tbody>
</table>

Values are means ± SD. I, ipsilateral to dorsolateral pontine nucleus (DLPN) lesion; C, contralateral; U, up; D, down; Lido, lidocaine; Ibo, ibotenic acid. Sinusoidal gain is calculated as the ratio peak eye velocity to peak target velocity. Initial acceleration is the average eye acceleration in the first 100-ms period of pursuit to a ramp stimulus. Normalized performance is prelesion value divided by postlesion value, either sinusoidal (sin) or ramp tracking (ramp). * Significant differences (P < 0.025, t test); † significantly different effect of the lesion on ipsilateral vs. contralateral pursuit (P < 0.01, two-way analysis of variance). Asymmetry tested on the ramp tracking experiments only.

better indication of the spatial extent of the ibotenate-affected region during the first few days than that delimited by the cell loss on Nissl-stained tissue. Not only would the overall dendritic zone of the missing neurons be greater than the area indicated by the Nissl stain but the astrocytic reaction extends further into regions where the concentration of ibotenate was not high enough to cause significant cell loss but may still have been effective in temporarily suppressing neuronal processing. These observations provide some anatomical support for the hypothesis that much of the recovery seen after these injections may have been due to the transient suppression of areas surrounding the smaller lethal zone apparent in Nissl-stained material.

Representative anatomical sections depicting the location and extent of the pontine ibotenate-induced lesions are presented in Fig. 5 for three animals. The darkened areas represent regions of almost complete neuronal cell loss as determined from cresyl violet-stained sections. Animal O sustained the smallest lesion of the series and exhibited the...
FIG. 4. Histological features of ibotenate lesion in animal M. The line drawing in C presents a view of the left pontine nuclei taken from a coronal brain stem section. The borders of the dorsolateral (DLPN) and lateral (LPN) pontine nuclei are indicated (---). The small solid rectangle encloses the area corresponding to the photomicrograph presented in A (cresyl violet-stained section). A clear border can be seen in the lower right-hand corner between the neuron-rich "intact" area and the lesioned region containing a high density of microglial nuclei but a lack of neuron cell bodies. The perimeter of the lesioned region is depicted in C (•••). The photomicrograph in B is taken from a nearby section stained for astrocytes with Cajal's gold sublimate procedure. Note the pronounced astrocytic reaction includes the region of cell loss (as seen in A) as well as a larger area extending into the surrounding regions. This astrocyte response provides anatomical evidence suggesting that areas outside the primary zone of cell loss may be effected by ibotenate injections. The calibration bars on the photomicrographs represent 300 µm.
fastest recovery. The region of cell loss was quite small (0.8 mm) and was centered near the border of the dorsolateral and dorsal peduncular nuclei. The lesion in animal S was similar in size but centered within the rostral DLPN (not shown). The largest lesions were seen for animals M and P, both of which received two injections. As described above, animal M received repeated injections 1 wk later and represents the most complete DLPN lesion of the series. The lesion in animal P involved a large portion of the lateral pontine nucleus with only minimal damage to the caudal portions of DLPN. Because all injections were guided by electrophysiological recordings and this animal exhibited a pronounced pursuit impairment, this portion of the pontine nuclei is likely to work in conjunction with the DLPN in smooth-pursuit control. The lesion in animal F was intermediate in size between cases O and P and involved portions of both the dorsolateral and lateral pontine nuclei (not shown).

The injections of lidocaine in animals Z and L were both centered within the DLPN as judged by the location of electrolytic marking lesions made through a tungsten microelectrode, which was placed at the same coordinates as the injection micropipette after the animals had recovered from the lidocaine injections.
Down S P M MC

FIG. 6. Normalized smooth-pursuit performance in 6 monkeys with dorsolateral pontine nucleus (DLPN) lesions. In each case the control performance is represented as the corners of a square for the 4 directions and with numerical values of 1.0. The pursuit performance after the lesion is normalized by dividing postlesion measurements by control values from the same animal and is represented by the internal white rectangle in each case. Case L shows results in the same animal as case M, but for an earlier ibotenate control injection dorsal to the DLPN in the region of the substantia nigra.

Directional deficits

Figure 6 summarizes the directional effects of DLPN lesions for the six monkeys where the pursuit response was measured in all four cardinal directions. The data used to construct this figure were obtained from step-ramp trials with a ramp velocity of 20 deg/s, a step size of 2 or 4°, and an initial ramp motion directed toward the fovea. The results in this figure are presented such that normalized prelesion pursuit performance is represented by the perimeter of the outer diamond; the relative postlesion performance is depicted by the internal white rectangle; and the relative postlesion impairment is represented by the intervening shaded area. All animals exhibited asymmetrical horizontal impairments (greater in the ipsilateral direction) as well as deficits in at least one of the vertical directions. This was seen after lidocaine injections (cases L and Z) where sinusoidal pursuit was examined as well as after ibotenate injections (cases O, S, P, and M) where pursuit initiation to sudden target-ramp motion was measured. The pattern and severity of impairments were similar for both sinusoidal and step-ramp tracking in the ibotenic animal (case S), which was tested with both paradigms. Case M shows the results for an earlier injection of ibotenic acid placed dorsal to the DLPN in the same animal presented as case M. This control injection resulted in an extensive loss of cell somata in the substantia nigra, but no loss in pursuit performance was noted.

Table 1 summarizes the numerical directional data for all seven animals, including raw as well as the normalized measures of pursuit performance. Sinusoidal data presented in this table was obtained at 0.4 Hz ± 10° of target motion (animals L, Z, and S). All the ramp tracking data presented were obtained with step-ramp motion stimuli that jumped 2° out from the fovea and then subsequently moved toward the fovea at 20 deg/s. Asymmetric horizontal effects were obtained for both lidocaine (animals L and Z) and ibotenate (animals O, S, P, and M) injections, and in animal F, which received both types of lesions. In every case there was
a larger effect on ipsilateral compared with contralateral pursuit initiation. In animals O and P, the contralateral acceleration values were also significantly smaller than prelesion control values.

A two-way analysis of variance was conducted on each of the five cases of ramp tracking data to determine which of these animals showed a significant asymmetric effect of the lesion on horizontal tracking. The larger effects on ipsilaterally directed pursuit were significant in all cases except monkey S. Even animals P and O, which had significant differences in pre- and postlesion behavior in all directions of pursuit, showed a highly significant horizontal asymmetry in the effect of the lesions on horizontal pursuit.

**Effect of retinal position of the motion stimulus**

There appeared to be little dependence of the retinal location of target image motion on the magnitude of the pursuit impairments observed after DLPN ibotenate injections. Figure 7 summarizes these results from the four cases in which the most extensive data relating to this question were collected. By using the step-ramp paradigm we could control the retinal locus of the target image motion that generated the initial 100-ms pursuit response. This initial eye acceleration was our quantitative measure. Thus this paradigm allowed us to compare the effects of foveal, ipsilateral, and contralateral retinal image motion on the initial pursuit response. All the results in Fig. 7 were obtained for ipsilaterally directed ramp motion, the direction of horizontal pursuit most affected by the lesions and are presented as normalized postlesion performance measures. The pursuit impairments observed in three of these animals were nearly equal for ipsilateral target motion presented either on the fovea or in the ipsilateral or contralateral visual field. Similar results were seen in some animals using larger 10° target steps (not shown). In one animal (monkey S), the impairment was much greater in the case of foveal target motion but the deficits observed for motion in the ipsilateral or contralateral fields were almost equal.

We conclude that pursuit deficits created by unilateral DLPN injections are related to the direction of visual motion and are not dependent on the hemifield in which the visual motion stimulus occurs. Foveal or parafoveal motion results in similar directional deficits in most cases. The reasons for the more severe foveally centered deficit in case S is not known. This was the case with the mildest overall deficit and one of the smallest regions of cell loss. We have not systematically checked the effect of motion in the far eccentric retina, and therefore add the cautionary note that our results are only suggestive with respect to this region of the retina.

**Ibotenate effects on optokinetic eye movements**

We conducted two types of additional experiments to examine the effects of ibotenate injections on the slow eye movements induced by visual motion of a large textured field (often called optokinetic following). In the first paradigm the monkey initially maintained fixation on a small stationary target spot that was superimposed on a 90° x 90° background field of random checks. On most trials, after a random fixation interval, the target spot began to move at a constant velocity and the monkey was required to track the image of the target to receive a reward. These trials were identical to the tracking trials described previously except the monkey was tracking the target across a random check background. On a few trials, inserted at random in the sequence, the target was turned off as the background began to move simultaneously at constant velocity in either the ipsilateral or contralateral direction. Because there was no longer a stationary visual feature in the field of view, the animals' eyes moved reflexively in the direction of background motion. The monkey was not rewarded on trials of this type, since there was no defined target. By inserting a few of these optokinetic trials within more frequently occurring tracking trials, we were able to obtain a set of optokinetic responses with the animal at the same level of alertness and motivation as on the tracking trials.

Figure 8 (top) shows an example of the pre- and postlesion optokinetic tracking induced in one animal by this type of large field motion in the ipsilateral direction. It is apparent from even a cursory comparison of these records that there is a severe deficit in the initial optokinetic following of this animal after the DLPN lesion. For comparison, Fig. 8, middle, shows the smooth-pursuit deficit (for
spot tracking) in the same animal on the same day. Pursuit was initiated in this case by motion of the small target on a dim homogeneous background, yet a comparable deficit was apparent. Under these optokinetic stimulation conditions (sudden target extinguishment and simultaneous background motion) all of our prelesion monkeys showed a lower initial eye acceleration than they did for pursuit tracking of the target spot motion of the same velocity. This is shown in Fig. 8, bottom, where the prelesion optokinetic following response (from Fig. 8, top) and the prelesion pursuit response (from Fig. 8, middle) are superimposed for better comparison. A lower initial acceleration is readily seen for the optokinetic-induced response compared with the pursuit response in the prelesion animal. It can also be seen that by 200–300 ms after the responses began, both types of tracking responses have reached about the same level of speed, a speed very close to that of the target or background. The latency of the optokinetic responses were not statistically different from the latency of the pursuit responses. The mean optokinetic latency for the three animals was 109 ms (range = 103–114).

The quantitative deficits in initial eye acceleration during optokinetic stimulation are given in Table 2 for three monkeys with DLPN lesions. Only deficits for the ipsilat-
FIG. 8. Effects of dorsolateral pontine nucleus (DLPN) lesions on the initiation of optokinetic (large field)-induced pursuit. All traces are averaged eye velocity responses for 6 individual trials. Constant speed (20 deg/s) background or spot target motion is shown by the dashed curve in set of traces. Top: comparison of pre- and postlesion optokinetic (OK) responses in the same animal. Middle: comparison of pre- and postlesion smooth-pursuit (SP) responses in this animal. Bottom: comparison of initial SP and OK responses in this animal before DLPN lesion. The upward direction is to the right (ipsilateral to the lesion). All data shown are from case M.

In each animal the deficit, as seen in the normalized performance figures, was approximately equal for optokinetic and pursuit initiation. It can also be seen in this data that the normal (prelesion) initial accelerations for this type of optokinetic stimulation are only \( \sim 50-60\% \) of those for small target spot pursuit.

Ocular following was also studied in one animal using a more conventional optokinetic stimulus, that provided by an evenly illuminated large rotating drum with irregular width vertical stripes. Figure 9A shows the prelesion smooth eye velocity responses in this animal for steps in drum speed to the right and to the left. Drum motion induced an optokinetic nystagmus of which only the slow phases are shown in Fig. 8 with the quick phases removed. After the onset of drum motion in either direction eye velocity accelerated rapidly (in <500 ms) to a speed closely matching drum speed for both values of drum speed tested (40 and 60 deg/s). Results are shown only for the lower speed in Fig. 9. This level of optokinetic following was then maintained (except for randomly occurring fluctuations), throughout the 30-s period of drum rotation.

The short random periods of lowered smooth eye velocity seen in this figure were commonly observed in all of our animals during prolonged drum-induced optokinetic nystagmus. They may have been caused by attempts of the monkey to fixate the edges of the mirror under its chin or the edges of the

<table>
<thead>
<tr>
<th>Animal</th>
<th>Initial Acceleration, deg/s²</th>
<th>Normalized Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>135 (215)</td>
<td>0.54 (0.45)</td>
</tr>
<tr>
<td>O</td>
<td>80 (150)</td>
<td>0.45 (0.44)</td>
</tr>
<tr>
<td>M</td>
<td>141 (226)</td>
<td>0.57 (0.51)</td>
</tr>
</tbody>
</table>

Values of initial acceleration are means of 6 trials for the ipsilateral direction. Values given below in parentheses are for pursuit initiation to the small spot as in Table 1. Normalized performance values are acceleration postlesion divided by acceleration prelesion.
A 40R-0 seconds 10

FIG. 9. Optokinetic responses to sustained drum rotation. Top: the time course of rotating optokinetic drum stimulation (D) for all the eye speed records shown below. Drum is accelerated to constant speed (not shown) in total darkness. At the upstroke of the D trace the drum is illuminated providing a step stimulus in visual surround speed. Drum rotates at constant speed for 30 s and then its illumination is turned off at the downstroke of the D trace placing the monkey in the dark. A 10-s period of time is eliminated from all the records (oblique dashes) to focus on the events at the onset and offset of visual motion stimulation. A: eye velocity responses to the right and left before a lesion in the left dorsolateral pontine nucleus. Records are individual eye velocity (E) responses aligned on the onset of optokinetic stimulation. All saccades have been removed from the smooth E traces for clarity. B: eye velocity responses after the DLPN lesion. The ipsilateral (left) slow-phase component of optokinetic afternystagmus shown on the right in the lowest trace persisted for over 2 min (not shown). All data shown is from case P.

magnetic field coils which extended into the visual field at about ±60°.

At the end of the 30-s period of rotation, the drum lights were turned out (at the downstroke of the drum speed trace), and the animal was then maintained in total darkness. Eye speed dropped rapidly to a lower level (~40–50% of the 40 deg/s perrotational speed), and a short period of optokinetic afternystagmus (OKAN) ensued. Figure 9B shows the results of optokinetic stimulation in this same animal after a lesion in the left DLPN. This experiment was conducted on the 2nd day after the ibotenate injection
when the animal's initial smooth-pursuit performance to target spot motion in the leftward direction was 0.4 of prelesion values (as determined by the initial eye acceleration method). Its rightward pursuit performance (0.7) was also affected but to a lesser extent. At the onset of drum motion to the right, the eye accelerated rapidly and reached a speed nearly matching drum speed within a few hundred milliseconds. This speed was maintained throughout the 30-s period of drum rotation. When the drum light was extinguished there was a rapid drop in speed followed by a normal period of OKAN. This sequence closely resembled the prelesion response (compare the upper E traces in Fig. 9, A and B). In contrast, the leftward direction of drum motion (at 40 deg/s) elicited only a very small initial eye acceleration in the direction of drum motion. This was followed by a prolonged build up of slow eye velocity until eye speed finally reached a level close to drum speed after ~15 s. This speed was then maintained until the drum lights were turned off (downward stroke of the drum velocity trace). At this point a small transient oscillation in eye speed occurred, but there was no rapid drop of a lower level. Instead a prolonged period of OKAN ensued that persisted for over 2 min in duration.

Impairments in saccadic eye movements

We tested three of the lesioned animals (cases P, O, and M) for saccadic eye movement deficits in response to stationary target jumps of 2, 5, and 10° in all four cardinal directions. There was no difference in saccadic accuracy to these fixed targets after ibotenic lesions for any of these animals tested. There were obvious abnormalities, however, when saccades were made by these animals to targets moving in the direction ipsilateral to the lesion during step-ramp trials.

Typical examples of these saccadic responses to step-ramp targets are shown in Fig. 10 for one animal (case O). These examples show that prelesion saccades made during pursuit in both horizontal directions were quite accurate so that the eye landed very close to actual target position at the end of the corrective movement. After DLPN lesions, saccades became hypometric and more scattered in time when target motion was directed toward the side of the lesion.

We lacked sufficient data to be able to determine whether this asymmetric effect on saccadic eye movement was dependent on position in the visual field or whether it was caused by the inability of the lesioned animal to process target motion information per se. Such an analysis would require saccadic error information at a variety of target speeds and for a variety of initial step sizes.
Recovery from the effects of DLPN lesions

Each of the animals showed complete, or near complete, recovery of pursuit performance as measured by the initial eye acceleration method. The greatest deficit was always observed on the day following ibotenic acid injections. A rapid recovery ensued thereafter such that most animals regained eye accelerations close to prelesion levels within 6–7 days following the lesion. Recovery data for three animals are plotted in Fig. 11. Monkey P (■) received the largest injection of ibotenic acid and exhibited extensive cell loss within much of the lateral pontine nucleus as well as in portions of the caudal DLPN (see Fig. 4). This animal showed the greatest reduction in initial pursuit performance with a small deficit still apparent at day 12, the last day on which measurements were made in this animal. Monkey M received a second repeat injection of ibotenate in the same region of DLPN in which an initial injection had been placed (○). The second injection (made after motion-sensitive single units had been recorded in the area of the first lesion) caused an immediate return of the pursuit deficit with a similar magnitude. Recovery from this second lesion was less rapid, with a small residual deficit still remaining at day 11 following the second injection. No functional direction-selective or pursuit-related units could be recorded in the region surrounding the injection site after the second lesion, although several electrode penetrations into the region were made.

Persistent impairments for tracking against a textured background

All of the results reported so far involve the tracking of a small target spot on a dim homogeneous background. When we required the lesioned animals to track a target spot moving across a textured stationary background, we observed significant reductions in initial eye acceleration as expected. When the animal had recovered to near normal pursuit performance, as judged by tracking on the homogeneous background, we re-
tested each animal for tracking on the textured background. The results of these experiments are shown in Fig. 12 for the same three animals shown in Fig. 11. Each animal's relative postlesion pursuit performance for the homogeneous background condition is shown (□). All data were collected for ipsilaterally directed pursuit for target speeds of 20 deg/s. Each of the animals had recovered to a level of 90% or better for tracking against a homogeneous background at the time these measurements were made (the number of days of recovery after the lesion are shown below the abscissa). Results of tests made on the same day for each animal when the tracking was initiated on the textured background are also shown (■). The results in Fig. 12 show that when the tracking task is made more difficult by adding the background, the animals that had shown considerable recovery for the easier tracking task still showed a prominent pursuit deficit several days after the ibotenate injection.

DISCUSSION

The major conclusion supported by the current experiments is that the DLPN comprises at least part of the neural machinery normally involved in the generation of smooth-pursuit eye movements. Focal chemical lesions of cell somata within this structure and the adjacent region of the lateral pontine nucleus produced profound, but transient, deficits in both the initiation and the maintenance of ocular pursuit. Impairments were seen for both constant velocity ramp tracking and sinusoidal pursuit. These results are consistent with the findings of anatomical studies (4, 5, 13, 15, 25, 36) and single-unit recording and electrical microstimulation investigations in DLPN (37, 42, 57).

Two chemical agents were used in the current experiments. Lidocaine hydrochloride was employed as a functional probe in the early experiments because of its immediate and reversible effects. The excitotoxin ibotenate was used in later experiments to produce permanent damage specific to neuronal somata within the pontine nuclear region. The use of ibotenic acid also permitted the more extensive step-ramp analysis that was precluded in the lidocaine studies due to the short time window of its effect.

The lidocaine injections produced an immediate decrement in ipsilateral tracking performance, but the effect required the injection of relatively large volumes of fluid. Almost complete recovery of pursuit performance occurred within 30 min of lidocaine injections, which indicates that the longer-lasting deficits produced by the injection of ibotenate were not due to nonspecific pressure effects imposed on the surrounding neural tissue. On the other hand, the pursuit impairments seen after ibotenate injections provide evidence that the lidocaine effects were not due solely to the suppression of activity in fibers of passage. In addition the site and extent of neuronal loss induced by ibotenate injections could be observed histologically.

The measure of pursuit performance we chose for the most extensive analysis was the initial eye acceleration in response to the onset of constant velocity target ramp motion. Initial eye acceleration was defined as the average acceleration over the first 100-ms period of the pursuit response. This period of time was chosen because it represents, for the monkey, the open-loop response of the pursuit system to retinal slip velocity occurring during the latent period (80–100 ms) before the eye begins pursuit tracking (22, 30). Measurements made during this open-loop response period should be more sensitive indicators of pathology in the neural circuits generating pursuit eye movements than similar measurements made later when the system is operating in the normal closed-loop mode of operation and visual feedback has had time to improve system performance. Similar arguments and methods were used in measuring pursuit performance following chemical lesions made in the superior temporal sulcus (9, 10, 43), thus allowing direct comparisons to be made between the magnitude of the deficit produced by cortical lesions and by our pontine lesions.

Relation to cortical ibotenate lesions

Wurtz and colleagues (9, 10, 43) have described two types of pursuit impairment following ibotenic acid lesions involving the visual cortical regions within the superior temporal sulcus that process visual motion information. Lesions that involve extrafoveal portions of area MT result in retinotopic deficits of pursuit initiation to targets whose
initial motion originates in the affected portion of the visual field. This deficit is omnidirectional and appears to result from a specific but spatially confined impairment in the processing of visual motion information. These monkeys can track normally once the target moves out of the affected region, either due to its own motion or as the result of a corrective saccade, which brings the target onto the foveal region.

A second type of pursuit deficit is seen after injections of ibotenic acid into the foveal portions of MT and portions of MST. After such injections, animals display normal pursuit initiation on step-ramp trials when the initial target motion originates in the extrafoveal visual field but exhibit a pronounced directional deficit in the maintenance of pursuit for target motion directed toward the side of the lesion (ipsilateral pursuit).

Injections of ibotenate into area MST can produce either retinotopic, directional, or both types of impairment depending on the locus of damage. Thus animals sustaining lesions within area MST tend to exhibit patterns of pursuit impairment that can be explained as combinations of these two basic categories of deficits (9).

Unlike lesions in MT, the effects of dorsolateral pontine lesions do not appear to be related to impairments in motion processing or pursuit generation that are specific to circumscribed regions of the visual field. Our DLPN lesions produced deficits in pursuit initiation to stimuli originating in the fovea as well as in all of the ipsilateral and contralateral locations of the visual field tested (limited to the central 10°). Another salient difference between the effects of cortical and pontine lesions on pursuit initiation is the directional asymmetry seen after pontine lesions. Although most animals exhibited both horizontal and vertical deficits the degree of impairment was clearly asymmetrical. Even though pursuit initiation was significantly impaired for targets moving contralateral to the lesion in two animals, ipsilaterally directed pursuit was significantly impaired in all five ibotenic monkeys and the deficit was always greater than for contralateral pursuit.

This pattern of nonretinotopic impairments is not too surprising given the large receptive-field size typical of visual pontine units and the lack of any apparent retinotopic organization of the pontine nuclei (unpublished observations). Lesions in this area are likely to corrupt visual motion information originating from widespread cortical regions, areas that, taken together, represent large portions of the visual field. This type of mechanism might be responsible for the large field, nonretinotopic character of the pursuit initiation deficit seen after the pontine lesions.

These pontine lesions would also be expected to compromise incoming information from the foveal representation of areas MT and MST. Like foveal MT and MST lesions we often saw directional deficits in maintained pursuit for ipsilaterally directed target motion (cases O, P, and M). Although these directional steady-state deficits are consistent with the effects produced by foveal MT, MST, and large occipitoparietal lesions (9, 10, and 32), the mechanism producing this asymmetry is not clear. Electrophysiological observations reveal a relatively balanced representation of directional selectivity within visual units in MT (34) as well as in the pontine nuclei (58). Dursteller et al. (9) suggest that this directional effect may reflect an asymmetric distribution of directionally selective pursuit-related neurons within MST but data adequate to support this hypothesis are not available.

The similarity in the degree of impairment seen after both cortical and pontine lesions is consistent with anatomical observations, which suggest that visual motion information is conveyed from area M1, both directly and indirectly via other cortical areas such as MST and area 7a, through the DLPN to the cerebellum.

Recovery of smooth-pursuit performance

The rapid recovery of pursuit performance was rather surprising in light of anatomical evidence suggesting DLPN to be a major terminus funneling visual motion and pursuit-related information from several parallel cortical pathways into the cerebellum. The recovery following pontine injections of ibotenic acid followed a time course very similar to that observed in monkeys with M1 lesions (43). In the three animals where extensive recovery measurements were made after the initial injection of ibotenate, the deficit was always worst on the day after the injection yet showed complete recovery by the end of
the 1st wk. Subsequent injections in animal M produced somewhat greater impairments over a slightly longer period of time. Several explanations may be proposed to account for this recovery: 1) recovery of transiently impaired neurons spared by the injections, 2) functional compensation by units in the contralateral pontine nuclei, and 3) mediation of pursuit by alternate nonpontine pathways.

We do not know the actual functional extent of the inactivated region produced by the ibotenic acid injections. Although we observed an extensive loss of cells within the pontine region in each animal (plotted in Figs. 4 and 5), we suspect that a much larger region of cells was suppressed by the toxin in the days immediately after the injection. The recovery of these cells could therefore account for behavioral recovery. This is similar to a suggestion put forward by Newsome et al. (43) to explain recovery in their cortically lesioned animals.

Even within the region of extensive cellular loss and gliosis, occasional neurons were found, although these neurons often had rather pale-staining cytoplasm and were relatively small. It is possible that recovery of these cells, although initially rendered nonfunctional by the toxin, was sufficient to provide the observed amelioration in pursuit performance.

Observations following repeated injections in monkey A lend some support to the notion that the recovery of a surrounding halo of cells, initially depressed by the action of the toxin but not killed, is responsible for much of the observed recovery in pursuit function. No motion-sensitive cells were observed in recordings made after the second injection, and there were almost no surviving neurons within central DLPN, yet pursuit function recovered almost as well as after the first injection. The fact that the second ibotenate injection, made after the full recovery of the first injection, created a pursuit deficit of almost identical severity to that produced by the first injection at the same site also weighs against the suggestion that recovery is mediated through functional compensation by units in the contralateral DLPN. If this were the major mechanism for recovery, the second injection into the ipsilateral DLPN would not be expected to have much effect. Instead the data is consistent with the idea that a wider region of the pontine nuclei may be concerned with smooth-pursuit eye movements than just the dorsolateral portion. This fringe hypothesis is supported by the fact that the ibotenic lesion in monkey P, which produced the largest magnitude of pursuit deficit, involved large parts of the lateral pontine nucleus and only minimal damage to the caudal DLPN. Likewise, in case O, the area of the lesion was centered within the border zone between DLPN and the dorsal peduncular nucleus. Thus a wide crescent of pontine cells including the lateral, dorsal, and dorsolateral regions may all be involved in the mediation of pursuit. This notion would correspond closely to the emerging anatomical picture in which all these pontine regions receive patchy projections from multiple cortical visual areas (36). It may be that the diffuse distribution of visual information across a wide crescent of the pontine nuclei is related to the need to provide reliable visual information to a variety of cerebellar regions mediating various types of visuomotor guidance (for example, visually guided locomotion and reaching).

Finally, an alternative explanation is that an additional nonpontine pathway from cortex to the brainstem is used to provide the compensation. Because most of the prestripate and parietal cortex outflow that might be linked to pursuit eye movements goes through the broad crescent of dorsal and/or lateral pontine nuclei (3, 8, 36, 66), one candidate for this nonpontine pathway is the recently demonstrated projections from the frontal eye fields to the paramedian pontine reticular formation (52) or to the nucleus prepositus hypoglossi (27). Both these latter regions have well-demonstrated oculomotor function but have not been specifically linked to the smooth-pursuit system. Likewise it remains to be shown that the frontal eye fields have a major role in mediating smooth-pursuit eye movements, although a few units recorded in this structure that respond during pursuit have been noted parenthetically in the study of saccade-related frontal eye field activity (6).

More persistent impairments for tracking against textured backgrounds

Recent experiments in monkey have shown that the initiation of pursuit on a textured background is a more difficult pursuit task than initiation on a homogeneous back-
ground (22). This difficulty is manifested in considerably lower initial eye acceleration in ramp tracking trials even though final steady-state eye velocity is only slightly lowered. Due to the inadequately low initial eye acceleration, tracking responses become more saccadic and animals tended to abort or quit trials more often. These difficulties presumably reflect additional demands placed on the neural processing of target motion caused by the highly textured background.

All three of the animals extensively tested on this paradigm showed large postlesion impairments in initial eye acceleration when tracking against a textured background was required. This effect persisted even when the animals' pursuit response against the homogeneous background had fully recovered. This more persistent impairment seen for pursuit initiation in the presence of a background may reflect a special role of the DLPN pathways in facilitating tracking across a background. Indeed, a large number of units in DLPN discharge more vigorously during pursuit across a textured rather than a homogeneous background, and often show an oppositely directed visual response to the motion of a large field (58).

Saccadic deficits

The pattern of saccadic deficits produced by MT and DLPN lesions resembled the respective effects these lesions had on pursuit initiation. Lesions of extrafoveal MT produced retinotopic, omnidirectional impairments in the monkeys' ability to use velocity information in programming corrective saccades to moving targets. Although saccades to stationary targets were normal, these animals exhibited specific impairments in their ability to compensate for the effects of target motion when programming corrective saccades to moving targets that originated in the effected portion of the visual field. In contrast, lesions of DLPN can produce a directional impairment in the programming of corrective saccades to targets moving in the direction ipsilateral to the lesion.

Both the saccadic and the pursuit deficits seen in MT-lesioned animals appear to result from a common underlying impairment in the processing of velocity information within a portion of the visual field. In contrast to this correspondence, there was no directionally selective motion-related impairment in saccadic programming after foveal MT or MST lesions. This observation implies that the directional deficits seen in these animals during pursuit maintenance were specific to the pursuit-related connections of these areas.

The asymmetric directional nature of the saccadic deficit produced by DLPN lesion cannot be explained simply by conjoint projections from MT and MST to the pontine nuclei. Further studies are needed to clarify the degree of asymmetry and functional character of these saccadic deficits after pontine lesions.

Effects on optokinetic eye movements

We found that the effects of DLPN lesions on the initial phase of optokinetic-induced eye movements were qualitatively similar to the effects produced on pursuit initiation. Initiation of optokinetic following, under the conditions utilized in our experiments, has been hypothesized to utilize neural mechanisms similar, if not identical, to those employed by the smooth-pursuit system (48). Impairments in our monkeys' initial eye acceleration responses to both optokinetic and pursuit targets after DLPN lesions partially support this notion. After the onset of large-field visual motion the eyes showed a sudden onset of eye acceleration in the direction of the motion stimulus with a latency identical to the onset of pursuit accelerations in response to single-spot target motion. There were some quantitative differences in the initial open-loop response to the two types of motion stimuli. The average eye acceleration over the first 100-ms period of the response was always lower for the optokinetic motion stimulus and the initial eye velocity overshoot and oscillation frequently present in the smooth-pursuit response (see Fig. 8) was absent in the optokinetic-induced responses. After a DLPN lesion, constant-velocity optokinetic drum stimulation produced an initially low eye velocity response that showed a steady buildup [commonly called charging of the velocity storage mechanism (7)] until eye velocity reached normal levels. Further evidence that this slow charging mechanism was not affected by DLPN lesions was the fact that a slow decay of eye velocity (OKAN) persisted, although the initial drop in eye velocity after cessation of the optokinetic drum
lights seen in the prelesion animals was missing. The initial drop has been hypothesized to represent that portion of the steady-state optokinetic eye velocity carried by the pursuit system, whereas the much more slowly decaying phase of eye velocity represents that portion carried by the velocity storage mechanism (7).

The optokinetic responses in our lesion animal closely resembles that reported for monkeys with bilateral occipital lobe lesions (67) and for monkeys with bilateral lesions of the cerebellar floccular lobe (64). Cortical or floccular lesioned animals also showed a poor or missing initial response to velocity steps of drum rotation, but could slowly increase this response over a period of time until eye velocity closely matched drum velocity. Taken together all three studies support the idea of a corticopontocerebellar mechanism, which has evolved in foveate animals to carry out rapid-pursuit movement. An older perhaps subcortical mechanism may mediate velocity storage for optokinetic nystagmus. The present work suggests that this latter mechanism does not involve the DLPN.

We never observed the extremely short-latency (~50 ms) ocular following responses reported by Miles et al. (40) even though the visual parameters of our experiment were very similar to theirs. However, our monkeys were required to avoid saccades and fixate a stationary target before the onset of background motion. Because these short-latency responses are very small, are only enhanced after saccades, and decay away with a post-saccadic time constant of ~50 ms, then, if present, they may be smaller than the velocity noise encountered in our experiments.

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