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Review Article

Generation of smooth-pursuit eye movements: neuronal mechanisms and pathways

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SUMMARY

This article reviews the current state of knowledge of the primate smooth-pursuit system. The emphasis is on the neuronal mechanisms and pathways that control pursuit eye movements in the monkey. The review covers the neuronal structures believed to be involved in pursuit generation from striate cortex to the final premotoneuron structures in the brainstem. Information gathered from physiological and anatomical work is stressed.

INTRODUCTION

Smooth-pursuit eye movements have recently become an area of intense interest in systems and integrative neuroscience as a model for sensorimotor integration. In the past 5 years considerable progress has been made in the effort to clarify the neuronal pathways and mechanisms responsible for this specialized form of motor behavior. Two reviews that cover much of the behavioral and clinical material and some of the neural mechanisms exist [26,61]. The purpose of this review will be to focus on the more recent work done in this field in order to describe the functional importance of different regions of the brain in the generation of smooth pursuit and how sensory information is transformed into motor commands for the control of these eye movements. Space limitations require that we focus on neurophysiological and anatomical results in the monkey and largely ignore the parallel results being found in many excellent clinical studies in humans. Nevertheless, we assume that the results of the work in monkey have direct applicability to understanding the generation of pursuit eye movements in man.

Before we begin our summary of the neural results, it is useful to make several comments on the overall organization of the pursuit system, as well as to define several concepts that will be used extensively throughout the text. Pursuit eye movements are unusual because they are voluntary movements that require the presence of a concomitant sensory stimulus, in this case a moving visual stimulus that creates motion on some

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portion of the retina. There are exceptions to this rule under some special conditions (e.g., anticipatory pursuit and the pursuit of afterimages [54]), but there remains a clear difference between the ease with which voluntary saccades or limb movements are generated in the dark without any form of visual or other sensory stimulation and the general inability to make any smooth pursuit under similar conditions. This fact has led to the realization that the generation of pursuit eye movements is very tightly and inexorably linked to visual motion processing. Thus, it should come as no surprise that most of the work that we shall review here involves both the study of visual motion processing and pursuit eye movements.

Pursuit movements are also unusual because the predominant direction of cortical-generated pursuit is ipsilateral in contrast to the control over contralateral function usually associated with the cerebral cortex. This same preponderance of ipsilateral control over pursuit is also present in the pontine nuclei and, thus, it is unlikely to be due completely to cortical mechanisms.

There has been a general assumption that the smooth-pursuit system is organized hierarchically so that cells at input (upper) levels should possess signals related to visual motion processing while signals related to pursuit motor behavior are developed in subsequent neural structures. Finally it is posited that lower levels of the system should gradually carry signals related to the motor behavior. As we shall discuss below in our review, recent single-unit recording studies have partially supported this assumption, but surprisingly some structures that are commonly placed at a low level close to the final motor outflow (e.g., the cerebellum and the vestibular nuclei) still have many cells that carry both visual motion and eye movement signals. It is also clear that some extrastriate cortical areas which have been considered to be purely visual areas (e.g., the middle superior temporal visual area) reflect a possible motor signal related to pursuit. Thus it may be, as is so often the case, that we find that the brain confounds our simplistic expectations for schemes which attempt to specify the design of the system on the basis of distinctly separate functional blocks. Only recently have researchers realized that separating the components of this complicated linkage of the motion processing system and the pursuit generation system requires extremely sophisticated experimental design. Thus much of the early work which did not rigorously attempt to separate these two classes of signals can only provide suggestive inference about how and where the conversion from visual motion signals to motor command signals occurs.

Attempts to study the neural signals underlying pursuit generation have been aided by a type of stimulus pattern called the step/ramp paradigm [94]. In this paradigm the monkey fixates a stationary target which is suddenly extinguished following the appearance of a new target at an eccentric retinal location (the step) which simultaneously begins to move at a constant velocity (the ramp) [62] (Fig. 1). In response, the pursuit system initiates (after a latent period of about 80–100 ms) an eye acceleration in the same direction as target motion. This period (phase II) of rapid eye acceleration closely matches eye velocity to target velocity within about 200–300 ms. During this same phase the eye generally makes a saccadic eye movement which incorporates target velocity predictions that eliminate the remaining retinal position error [49]. This period of the response is called 'pursuit initiation' or the 'open-loop period', since the initial eye acceleration and the size of the saccade are based on retinal events that occurred in the previous time interval (phase I) before the eyes began to move due to visual processing delays. The step/ramp paradigm can also be used to vary the size and direction of the initial step and, hence, the retinal location of the initial motion stimulus (inset in Fig. 1). After the initiation period the eye continues to track the target in both position and velocity for the remainder of the

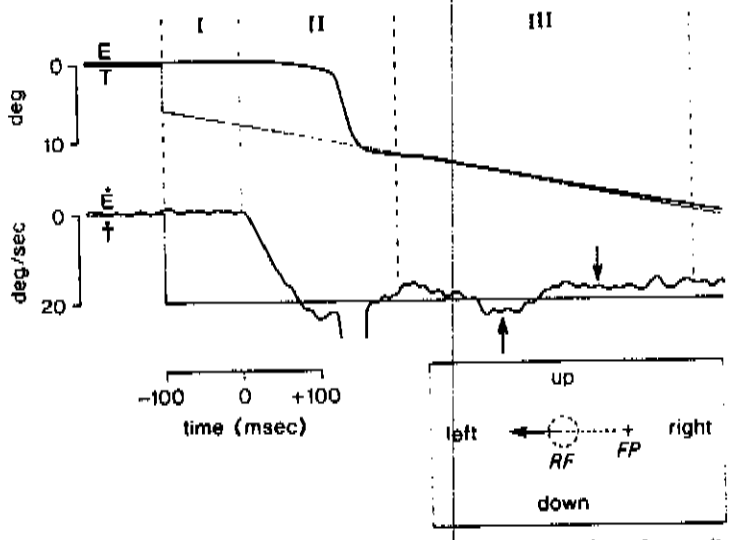

Fig. 1. Typical smooth-pursuit response in monkey to a step/ramp target motion of a small target spot in an otherwise dark room. Time is shown with respect to the onset of the eye tracking response (time 0). Shortly before this epoch, the target (T) steps to a new position in the visual field and begins to move at a constant speed ($\dot{T}$). The paradigm consists of three phases: a pure visual phase (I) where retinal position is determined by the step and retinal slip by the target ramp speed, since the eyes are still stationary; a pursuit initiation phase (II) during which the eye accelerates smoothly to approximately match target speed and saccades to place the fovea close to the moving position of the target; and a maintenance phase (III) with eyes closely tracking the target in speed and position but with interposed episodes of positive (upward arrow) and negative (downward arrow) retinal slip. The high velocity portion of the saccade is removed from the eye velocity record ($\dot{E}$). Inset at the lower right of the figure shows the events of phase I on a spatial map of the visual field. Target steps (dashed line) to a retinal position (RP) and starts moving with a constant velocity vector (solid line) while the eye remains at the fixation position (FP).

constant velocity portion of the target motion (phase III). During this period, which is called 'pursuit maintenance' or 'closed-loop operation', the target remains near the fovea and eye velocity and target velocity are closely matched. During maintenance, periods of tracking with eye speeds lower and even higher than target speed are observed. Nevertheless, retinal slip velocities during this phase remain low.

Two current classes of models exist which attempt to explain pursuit generation (Fig. 2). Efforts to apply either of these models to facilitate the interpretation of physiological data on the pursuit system illustrate the difficulties inherent in a functional analysis that attempts to place purported system neurons within a hierarchical structural scheme. Both classes of models receive their input from cells that solve the motion analysis problem of detecting a single moving target as distinct from the background and encoding its velocity in retinal coordinates (visual processing, in Fig. 2). After this common input level, the models diverge in their development at successive levels of pursuit organization.

In one class of models, shown at the top of Figure 2, a corollary discharge proportional to the outgoing pursuit command is fed back to upper, visual processing levels of the system and combined with the processed retinal motion signal to recreate a signal that represents target motion in space [84,95,122]. The advantage of this model is that it can maintain pursuit in the face of momentary loss of retinal slip input. This is accomplished by the presence of a leaky velocity storage element (an integrator) placed inside the positive feedback pathway. This model provides high system gain (eye speed can closely

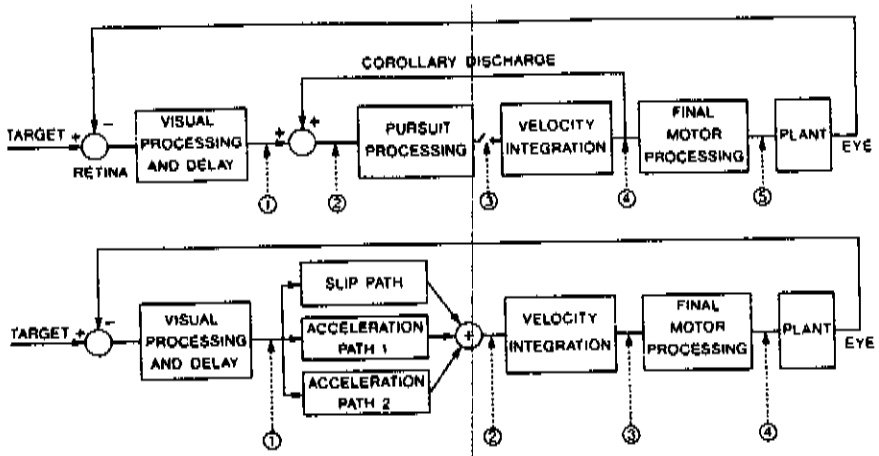

Fig. 2. Schematic diagrams of the two major classes of pursuit models. The upper diagram illustrates the corollary discharge feedback type of model and the lower shows the visual feed-forward type of model. The circled numerals on each indicate positions where the various types of neural signals discussed in the text would be expected to exist for these model systems. For the upper model: ① visual retinal slip velocity; ② a mixture of extraretinal (from the corollary discharge of eye velocity) and visual slip signals; ③ target velocity of target selected for pursuit (pursuit selection switch); ④ desired eye velocity command; ⑤ eye position command to the motoneurons. For the lower model: ① visual retinal slip velocity; ② mixture of highly processed visual signals including retinal slip and slip acceleration; ③ desired eye velocity command; ④ eye position command to the motoneurons.

match and even exceed target speed) and it overcomes the stability problem (growing oscillations) that is created by the long visual processing delay present on the sensory side of the system. One disadvantage of this model is that it requires that the extraretinal signal (corollary discharge in Fig. 2) be an unrealistically accurate representation of eye velocity, if this model is to recreate actual target velocity. Actual eye velocity signals have yet to be recorded, at least at the cortical level.

The other class of model also starts with a retinal image slip input but then contains several parallel sensory processing pathways including different branches related to position errors or the acceleration of image slip [55,61]. These pathways have essential non-linearities which together produce a combined signal that generates realistic initial pursuit waveforms as well ensuring stability during steady state. This model also accomplishes pursuit maintenance with the use of a lower-level neural velocity integrator that must have a long time constant. The parallel nature and the variety of predicted signals are the strong points of this model, but it fails to account for the corollary discharges that have been observed even at cortical levels of the system (e.g., in the middle superior temporal area).

Thus neither class of model can account satisfactorily for all of the neural signals that have been seen in areas related to pursuit. Another model has appeared that attempts to reconcile differences in the two classes of models while retaining the positive features of each [21]. Regardless of their individual shortcomings, these models are very useful in conceptualizing the organization of the variety of signals necessary for pursuit in terms of both their temporal characteristics and the level at which they are manifested. Therefore these models will be used to provide an organizational framework in the following review.

There has been considerable development in our understanding of the signals necessary to generate smooth-pursuit eye movements since neurons called 'pursuit cells' were first reported to exist in the inferior parietal lobule in monkey [41,81]. Although these authors

classified any neurons that responded as the monkey tracked a small target against a lighted background as pursuit cells, the responses that they studied may have been caused by the visual motion of the background on the retina (retinal slip) and not the pursuit movement itself. This possibility has since been confirmed for cells located on the dorsal convexity of inferior parietal lobule (area 7a) [96], where the previous authors had concentrated their studies.

A better condition to test whether a cell's response is actually related to pursuit and not background slip is to record its discharge during pursuit of a small target moving in total darkness. Using this type of paradigm, Sakata and collaborators found cells located in area 7a and in the depths of the closely adjacent superior temporal sulcus (STS) that responded during pursuit in the dark [100]. However, even this test is not sufficient to completely establish that a cell's response is related only to the act of pursuit because, as shown in Figure 1, pursuit eye movements do not exactly match eye speed to target speed, i.e. there remains some retinal slip even during optimal pursuit [61]. Unless one has studied the visual motion sensitivity of the cell for speeds down to this range of slip and shown that the cell is not sensitive to retinal slip with the eyes fixed, then the response of a cell during pursuit in the dark may actually be a visual response. Nevertheless, we will follow the established nomenclature in this review, i.e. we will call cells that respond well during small spot tracking in the dark 'pursuit cells' without necessarily meaning to imply that the response has been properly checked for other contaminations.

An additional problem concerns the extreme increase in visual sensitivity that accompanies dark adaptation. In most studies the animal is kept in a totally dark environment during neural testing for pursuit responses for periods of several hours. This allows the entire peripheral retina to become totally dark-adapted because the only visual inputs—the small pursuit targets—are kept very close to the fovea by the pursuit behavior. Under these conditions the peripheral retina becomes maximally sensitive, and scattered light (from the tracking target) or extremely dim and unfocused background illumination could activate visual cells during pursuit movements.

Newsome and collaborators have established several further refinements in testing paradigms that clarify the nature of the response of cells that respond during pursuit movements [84]. In all of these paradigms a background light is turned on during each intertrial interval to prevent increased sensitivity from dark adaptation. In order to determine whether the response occurring during pursuit in the dark originated from visual stimulation of the retina by the pursuit target or from a real pursuit response, they remove the visual motion stimulus transiently during pursuit either by blanking off the visual target briefly or by electronically stabilizing the target on the retina, thus preventing any further slip. If the pursuit response continues without interruption during these manipulations, the cell is said to contain an extraretinal component or signal. This choice of terms is judicious, since it indicates that the cell's response cannot be due entirely to visual motion signals (which are completely absent during blanking or stabilization), but does not prejudice the determination of the actual relationship of the cell to the pursuit movement, a step which requires further analysis including characterization of the latency of the response and its sensitivity to eye velocity.

HIERARCHICAL ORGANIZATION FOR PURSUIT EYE MOVEMENTS

Striate cortex

The geniculostriate pathways seem to be necessary for the normal production of pursuit eye movements. Monkeys with unilateral lesions of striate cortex cannot generate

pursuit when the moving target is maintained in the contralateral visual field and never regain this ability [102]. However, bilateral lesions which include this same cortex and initially result in the total loss of pursuit are followed by substantial recovery after a period of 8 weeks [123]. These apparently conflicting results could be explained if a rudimentary subcortical motion processing capability exists in the primate that can show substantial improvement when released from its normal dependence on remaining visual cortex. This raises the possibility that subcortical pursuit pathways may exist in the primate. Indeed, cells with pursuit-related discharge have been recorded in nuclei associated with the accessory optic system in the monkey [82]. Nevertheless, these units are relatively rare and the role they play in normal (pre-lesion) pursuit is unclear at this time. Therefore, this review will focus only on pursuit pathways that originate in the striate cortex.

Visual motion and pursuit areas in the region of the superior temporal sulcus

There are two distinct visual areas located in the caudal portion of the superior temporal sulcus (STS). The middle temporal area (MT) and the middle superior temporal area (MST) are normally distinguished on the basis of visual receptive field properties and anatomic connectivity, but in terms of function within the pursuit system it is now clear that a different division exists. Cells located in dorsal MT have visual fields which are eccentric and do not include the fovea; however, at its lateral edge, these fields become very small ($< 2°$ in diameter) and often do include the fovea. Based on this physiological distinction this part of MT has been called MTf [53]. When the response of MT neurons with eccentric visual fields are rigorously tested in the alert, behaving monkey, it has been shown that their properties may be explained as purely visual in origin [84]. Cells in MTf, on the other hand, often have a response related to the pursuit movement as well as a visual response. A similar extraretinal response is carried by cells in the lateral portion of MST which also represents the fovea as well as the periphery. We will discuss dorsal MT first and then turn to a consideration of MTf/MST.

Middle temporal area

The middle temporal area (MT) of extrastriate cortex, which lies on the posterior bank of the STS and receives a direct, heavily myelinated projection from area 17, is extensively involved in visual motion processing. A substantial percentage of its cells are directionally selective, i.e. they respond preferentially to the motion of small spots of light moving in a single direction [70]. These cells are also relatively insensitive to stimulus form or color [1,23,71].

Neurons in MT respond well to the motion of the stimulus spot while the eye remains stationary at the fixation point. They have retinotopically organized receptive fields which are relatively small in comparison to those reported in MST and area 7a (see below). The center of the visual fields of MT neurons are in the contralateral visual field and they do not include the fovea [53,99,113]. The directional tuning is broad with the average cell having a half-maximum, full-width bandwidth of about $80°$ i.e., there is a 50% reduction in the amplitude of the unit response to retinal image motion for stimuli moving in a direction $40°$ away from that yielding the best response [1,71]. Examples of the directional motion response of a typical MT unit and the average tuning response for a population of MT cells is shown in Figure 3. It is apparent from this figure that the slope of the population directional tuning curve is greater near the peak response, which suggests that neurons in MT have their greatest sensitivities to differences in stimulus direction near their best direction. All directions of motion preference, including both the ipsilateral and contralateral, are found in each MT although there were some departures from a uniform distribution [53,71].

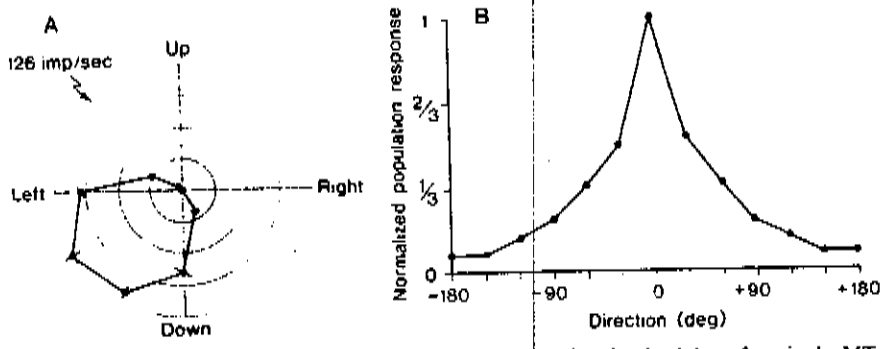

Fig. 3. Motion tuning directional responses in area MT. (A) Directional selectivity of a single MT neuron displayed as a polar plot of the average firing rate of the unit for 12 directions of small target motion. Bars indicate standard error of the mean for each point. (B) Average direction tuning curve for 163 units in MT. The tuning curve for each unit was first translated to bring the peak to zero degrees. Reconstructed from Maunsell and Van Essen [72].

Neurons in MT are also tuned with respect to speed. The half-maximum response width was two octaves above and below the best speed [71]. Preferred speeds ranged from 2 to 256°/s with a mean value near 32°/s. As was found for directional tuning, MT cells are maximally sensitive for differences in stimulus speed near their best speed. Three-dimensional plots of neural response as a function of speed and direction showed a rather sharp peak at the conjoint best speed and direction and fell off in response for deviations in either the speed or direction from this point [98]. Single MT cells thus code the retinal velocity of a target in an ambiguous manner because a decrease in response could signal a change in either the speed or direction of the stimulus. However, the population of MT neurons could code velocity without this uncertainty.

In terms of the visual signal sent by MT to downstream regions responsible for generating the command to the pursuit system, it is probably the summed activity of a population of MT neurons active for any given moving stimulus that encodes desired pursuit velocity. Not enough information on enough cells has been collected [98] to calculate the MT population response for velocity, but the population response has been determined as a function of retinal slip speed [71]. This response is shown in Figure 4 compared to the population response for dorsolateral pontine nucleus neurons (a brain-stem pursuit area to be discussed below) and the average initial eye acceleration during pursuit initiation. This figure shows that MT neurons could, as a population, provide a *visual* signal which codes an increase in slip speed monotonically from about 0.5–16°/s. Since eye acceleration continues to increase over a wider range of slip speeds, further processing is required to explain the generation of higher eye acceleration responses.

The latency of the typical MT neuron's response to the onset of a moving visual stimulus is about 94 ms [93]. However, some cells in this area have latencies as short as 40–60 ms [77,93]. Since the pursuit response of monkey to the sudden onset of target motion is about 100 ms [62], the response of most MT neurons only precedes the motor response by a few milliseconds which does not allow much additional time for further cortical and subcortical processing of the sensory outflow from MT.

Lesion studies in MT support the notion that the signal supplied to the pursuit system from this area is a visual one [86]. An ibotenic acid lesion placed in a region of MT where cells had receptive fields centered at 15° into the contralateral visual field led to a severe deficit in the initiation of pursuit in all directions when the moving stimulus appeared

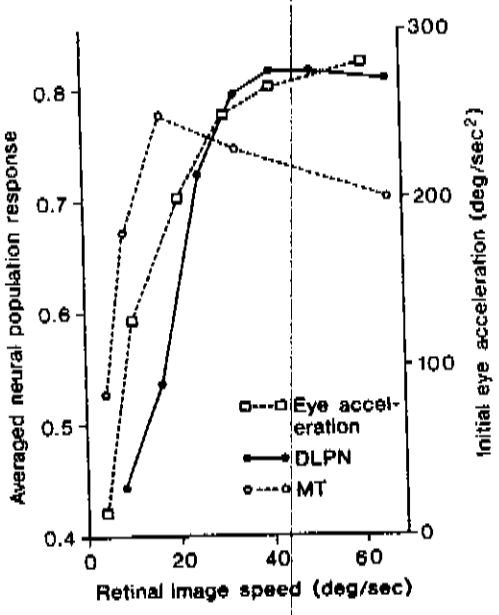

Fig. 4. Average speed tuning curves for a population of MT neurons (dashed curve) and DLPN neurons (solid curve) plotted on the same figure with the average initial eye acceleration in the first 100 ms of the response (dotted curve) to targets moving on the retina at speeds from 5–60°/s. Data on MT neurons replotted from Maunsell and Van Essen [72], data from DLPN neurons replotted from Suzuki et al. [110], data on eye acceleration average of 5 monkeys (Keller, unpublished data).

anywhere within this region. However, to compensate for this deficit, lesioned animals made a saccadic eye movement towards the moving target. At the completion of this saccade the retinotopic location of the target's image was no longer within the lesioned area and the eyes then showed a rapid acceleration in the direction of target motion and tracked the target with normal performance characteristics during pursuit maintenance. The initial saccade was also shown to be dysmetric and did not include the normal predictive component based on extrapolations from motion processing. In intact monkeys this initial 'catch-up' saccade in the combination pursuit/saccadic response to a moving target is very accurate and incorporates velocity prediction based on motion processing, as already discussed. Thus the inaccuracy of saccades to moving target in the MT-lesioned animals when the motion appears within the affected region of the visual field is also consistent with the notion that MT neurons do not supply motor commands to the pursuit system, but instead provide the sensory signals specifying the velocity of the moving target. This loss of the ability to process motion in a specified visual field locus following punctate ibotenic acid lesions in MT has been called a 'retinotopic deficit' [86]. The retinotopic deficits produced by these focal MT lesions recover rapidly and basically disappear after several days. The neurophysiological basis for this rapid recovery is still under investigation [120].

MT projects to a number of additional cortical areas, but undoubtedly the densest of these projections is to MST which is located on the anterior bank of the STS immediately adjacent to MT [72,116]. Other cortical projections of MT that might be significant for pursuit go to the fundus and deeper portion of the lateral bank of the interparietal sulcus (area VIP), to a visual area on the anterior bank of the parietal-occipital sulcus (area PO) [20] and possibly directly to the frontal eye fields (FEF) [116].

Medial superior temporal area / foveal MT

Physiological studies have shown that MST actually consists of at least two regions with different functional characteristics [53]. Pursuit cells (as defined above) were found in both areas but the visual properties of their responses differed. Those in MSTd (a dorsal-medial area in MST) preferred large moving stimuli like fields of random dots. In MSTl (a lateral-anterior area of MST) a mixture of response types was found, some like those in MSTd and others like those in MTf which preferred small moving spots. Visual fields in MSTl were very large and frequently included the fovea and a portion of the ipsilateral visual field [53]. Many cells in MST and MTf continued to discharge during target blanks and stabilization indicating that they receive an extraretinal input related to the pursuit eye movement [84]. Therefore it has been hypothesized that MST/MTf represents a downward transition in the pathway generating pursuit, since no cells in MT contained this signal.

Attempts have been made to relate this extraretinal signal more directly to the pursuit command; however this neural discharge began after the onset of the pursuit eye movement in a vast majority of, and perhaps all, MST/MTf neurons. Thus the activity of this class of cells cannot be responsible for the initiation of pursuit. It has been hypothesized that, instead, the discharge of these cells represents a corollary discharge from the pursuit command generated elsewhere. Such a signal is responsible for maintaining pursuit in the feedback model for pursuit generation [84] (see upper portion of Fig. 2). This hypothesis places MST in the feedback loop maintaining pursuit.

Electrical microstimulation experiments done in MTf or MST partially support this notion [52]. Short pulse trains of stimulation delivered when the eye was already pursuing a moving visual stimulus produced an eye acceleration towards the ipsilateral side after a latency of about 20 ms (Fig. 5). When the stimulation was left on, the acceleration gradually fell to zero and the new eye speed was approximately maintained for the duration of the stimulation period. Similar results were obtained when the target was stabilized on the retina at the time of stimulation, thus minimizing any possible effect from the visual slip evoked by the increased eye speed. When the stimulation was delivered with the eye fixing a stationary target, very little eye acceleration occurred. Komatsu and Wurtz claimed that this constellation of effects could be explained by supposing that the electrical stimulation 'substituted' for the normal visual signal and that it acted on the pursuit system at a point where the pursuit target had not yet been selected (prior to the selection switch in Fig. 2) [52]. The mixed distribution of cells with visual motion and pursuit signals recorded in MST is consistent with this result; however, computer stimulations of either model in Figure 2 (unpublished results) show that stimulations placed at any of the locations prior to the integrator lead to a maintained eye acceleration as long as the electrical stimulation is present.

The results of ibotenic acid lesions in MTf and MST support the idea that eye movement signals are first developed at this level of the system [24,25]. For ipsilaterally (towards the side of the lesion) moving targets, lesioned animals were unable to generate an eye speed that matched target speed even when the target was on or near the fovea. This deficit was present for a target step to any point in the visual field as long as the target motion was toward the lesioned side, i.e. a directional deficit. When the target stepped into the field contralateral to the lesion the animals showed, in addition, a retinotopic deficit for the initiation of pursuit. Saccades to moving targets in the ipsilateral field were normal for target motion in either direction, but saccades to moving targets in the contralateral field were dysmetric for both directions of target motion. This combination of pursuit and saccadic deficits suggests the impairment of a directional

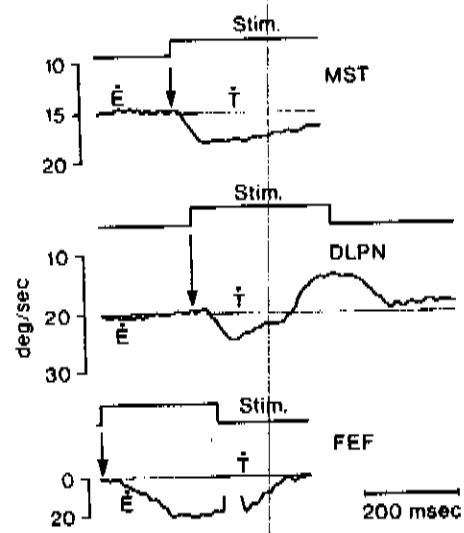

Fig. 5. Effect of electrical stimulation in three different regions of the brain. In each section the upper trace (Stim.) shows the onset (downward arrow) and the offset of electrical stimulation, if it goes off before the end of the trial. In the upper section stimulation is applied in the left MST with the eye already pursuing a target moving at 15°/s to the left (light horizontal line). Stimulation produces, after an extremely short latency, an eye acceleration to a speed of about 18°/s and this new speed is approximately maintained for the duration of the stimulation. Stimulation was 100 μA at 500 imp/s [52]. In the middle section stimulation was in the left DLPN with the eyes already pursuing a target moving at 20°/s. After a latency of about 18 ms the eyes accelerate to a new speed of 25°/s, but do not maintain this speed in the face of the oppositely directed retinal slip produced by the stimulation. Stimulation was 50 μA at 300 imp/s. In the lower section stimulation was in the left FEF with the eyes fixating a stationary target. After a somewhat longer latency (40 ms) the eyes accelerate to a speed of 20°/s and maintain this speed for the duration of the stimulation. Stimulation was 40 μA at 300 imp/s. Leftward direction is down in all sections.

pursuit motor mechanism and an additional general visual motion processing deficit for the contralateral field. The monkeys recovered rapidly from MST and MTf lesions just as they did for MT lesions so that pursuit and saccades to moving targets in all fields were normal within 1 week following small focal lesions in these cortical areas. Even large lesions that included most of MST and MT produced effects that were mostly ameliorated in about 3 months [120]. Although MT and MST may be in the normal pathway that produces pursuit eye movements, they are not essential for the production of this type of motor behavior.

ALTERNATIVE PATHWAY

There is mounting evidence that at least one and possibly several other pursuit pathways exist within the cortex. Cells which respond during smooth tracking movements have been found in the frontal eye fields (FEF) [15,36], and stimulation of this area can evoke smooth eye movements [15]. Posterior parietal cortex (area 7a) also contains cells which respond during smooth pursuit [44,67,81,96,100]. The anatomic results suggest that pursuit information could bypass MT/MST and reach the FEF by several different routes. Although not firmly established, there is some evidence that a direct V2 to FEF pathway exists [5]. Well-defined pathways are present, however, which could bring visual motion information to the FEF from V2 through the LIP/VIP complex [40,85]. This information could also be relayed to area 7a on its way to the FEF [2,6]. The FEF in turn sends projections to the DMPN, the DLPN, and the NRTP [103]. This notion of alternative

pursuit pathways is supported by the lesion data in studies of MT and MST which have already been mentioned [25,120]. Interestingly, lesions outside the STS to pontine pathways which destroy the FEF produce only a slight saccadic deficit, but severely degrade smooth tracking movements [63,68]. Thus it seems highly likely that pursuit information may flow through the parietal lobe and various interconnected frontal cortical areas to the pontine nuclei and NRTP, constituting a separate parallel path to the superior temporal sulcus/DLPN pathway. This section will discuss the neural processing related to smooth pursuit which occurs in these other areas outside of the classic pursuit pathway.

Posterior parietal cortex

The parietal lobe has been extensively studied with respect to the role it plays in cognitive functions. Probably the most notable disorder seen in patients with parietal lobe damage is the phenomenon of unilateral neglect, an inability to perceive objects in the contralateral hemifield. Human and animal studies have focused on the neural substrate of this and other related behaviors such as visual attention and spatial perception. Since eye movements are usually involved in attentional and spatial tasks, some early studies did attempt to describe neural signals correlated with oculomotor function, but unfortunately, not many studies have focused on the representation of smooth pursuit. Our knowledge of the specifics of how these eye movements are represented is further clouded by a lack of anatomical detail concerning the location of cells recorded with a pursuit component, as well as confusion about the different subregions of the parietal lobe. The majority of experiments which studied smooth pursuit were done in posterior parietal cortex (area 7a), but in many cases overlapped other more recently described anatomical areas including the lateral and ventral intraparietal sulci (LIP and VIP respectively), and areas in the superior temporal sulcus including MT and MST. Although lesion experiments in parietal cortex have rarely looked at smooth pursuit degradation, evidence of such a deficit has been documented in one study [66].

Two studies which directly investigated the nature of pursuit-related signals in area 7a have been done [44,100]. In both studies, neurons with directional preferences were found, with most neurons responding better for ipsilateral tracking. This is the first structure reported with such an unequal distribution of directional preferences. Kawano and collaborators also showed that, for a small sample of pursuit cells, there was evidence of speed tuning [44]. These units displayed maximal sensitivity for tracking speeds up to 10°/s, and seemed to saturate at 20°/s. Area 7a pursuit neurons in these studies also showed evidence of extraretinal signals.

Sakata and collaborators compared neural discharge during periods of visual tracking to brief periods of tracking where the target was blanked off [100]. They found that most cells maintained their activity during the blanking interval, evidence that these cells did have an extraretinal component to their activity. However, the large majority of neurons responding during pursuit were activated by small slits of light during a fixation task, indicating the presence of a strong visual signal in addition to the motor-related signal. Tracking in the light almost always produced a stronger response from cells, and the largest response was obtained when the animal tracked in the preferred direction of the neuron, thereby inducing oppositely directed background motion.

Kawano and collaborators, using an entirely different methodology, also found evidence of a motor response on area 7a pursuit cells, but it is not easy to conclude that this response is related to pursuit *per se* [44]. After determining that a cell responded during visual tracking, these investigators rotated the animal under several conditions to invoke the vestibulo-ocular reflex (VOR). Synchronous target and chair rotation (VOR suppres-

sion) produced activity similar to that found during tracking in the same direction, while chair rotation during fixation of an earth-fixed target resulted in activity similar to that found during oppositely directed tracking. About half of these cells did not respond during chair rotation in the dark, implying that neural signals during oppositely directed eye and head movements were canceled. These results suggest that signals related to motor activity are carried on these cells. However, much of this activity is probably vestibular in nature, while some of it may represent a motor command for pursuit which is present during combined eye and head (gaze) movements.

As previously mentioned, details concerning the exact anatomical location of pursuit cells within parietal cortex are scant in this literature, although most of these studies targeted area 7a, and it is probably safe to say that this region does contain cells responding during smooth pursuit. However, penetrations in several of these studies [67,81,96] extended into the intraparietal sulcus, and may have encountered areas LIP and VIP, and a few studies had penetrations which probably isolated cells in MT and MST[44,100]. This general area in the human has also been shown to have increased regional cerebral blood flow during smooth-pursuit tasks which was not as great during saccades [19]. Taken together, all of this work suggests that these areas may play a role in pursuit generation, which seems reasonable based on the anatomical connections of these parietal regions with other pursuit areas.

Frontal lobe

Most of the work regarding oculomotor function in the frontal lobe has targeted the neural processing for saccades. By far the most extensively studied area in this respect is a small region within the fundus and the anterior bank of the arcuate sulcus roughly corresponding to Brodmann's area 8, which is commonly referred to as the 'frontal eye field' (FEF). Quite surprisingly, however, lesions in this area do not affect saccade generation markedly, but have a drastic effect on smooth pursuit [65]. Lesion studies provide, at the moment, the best insight to neural processing for smooth pursuit generation in the FEF since single-unit and stimulation work in this area related to tracking eye movements is limited.

Several researchers have made discrete lesions in FEF and have shown a decrease in the gain of smooth eye movements using sinusoidal and constant velocity (ramp) target motion. Lynch studied both the initial effects and recovery of pursuit following large, bilateral lesions in the FEF which extended deep into the arcuate sulcus [65]. He found that pursuit gain was initially less than one-half of control values, and was still slightly depressed after 6 weeks of recovery. An interesting finding emerged in a later study which looked at the character of pursuit deficits produced by FEF lesions in more detail. Apparently, although pursuit gain is markedly reduced after such lesions, combined saccadic and smooth eye movements manage to keep the eyes on the position of the moving target [64]. This is not the case with MT lesions, implying that MT is necessary for calculation of target velocities, while the FEF may be more involved in the generation of the smooth movement.

The FEF may have yet another function regarding smooth pursuit generation. Experiments have shown that ablation of the FEF abolishes predictive smooth eye movements, i.e. tracking movements made which anticipate target motion. If animals are asked to track a target moving with a repetitive trajectory, they will make smooth eye movements which lead the target motion. Lesions to the FEF have been shown to remove this predictive capability [45,68].

Despite this evidence of FEF participation in smooth pursuit, only recently have cells

been found in this area which respond during these eye movements. These cells are tuned for pursuit direction, and begin firing 60–90 ms after target movement onset [68]. Moving visual stimuli during fixation also excite these neurons, and the response obtained in this condition is as strong as that during pursuit alone, despite the evidence that the pursuit movement drastically reduces the amount of retinal slip of the stimulus. Even though these cells were not tested explicitly during pursuit with retinally stabilized stimuli or with periods of target blanking, this finding suggests that signals on these cells may have an extraretinal component. Other research relating activity in the FEF to ongoing pursuit showed increased regional blood flow during tracking in a frontal area including the FEF [19].

Evidence of a predictive response has also been found on FEF neurons. In tasks involving pursuit of familiar sinusoidal motion, cells began firing before the target reversed to their preferred direction, and behaved in the same fashion even if the target was extinguished before this turnaround [68]. These neurons also exhibited firing related to anticipation of the continuation of predictable constant velocity ramp motion. In these trials, cell activity persisted for about 500 ms after stimulus motion terminated.

Electrical microstimulation of the FEF has been shown to evoke smooth movements even during fixation of a stationary visual target [15] in contrast to results in MT, MST and DLPN (see Fig. 5). It has been hypothesized that since stimulation in MT and MST during normal pursuit produces similar velocity changes to stimulation during periods when retinal slip is removed, the current affects the visual input to the system before extraretinal input is added [52] (see Fig. 2). The fact that no eye movements are evoked with MT/MST stimulation during fixation supports this view that eye-velocity-related information enters the system after these areas. Komatsu and Wurtz also suggest that FEF lies beyond the purely visual input circuitry since stimulation in these areas can initiate smooth eye movements even with the animal fixating a non-moving visual target [52].

The other frontal areas which have been shown to be involved in saccadic processes have not been studied in detail for pursuit-related responses. However, the existence of smooth-pursuit-related responses as well as responses to moving visual stimuli have been described anecdotally in a study of saccadic activity in the dorsomedial frontal cortex (DMFC), or the 'supplementary frontal eye fields' [101]. This area is richly interconnected with other frontal regions including the FEF, and has its own inputs from MST, area 7a and LIP/VIP of the parietal lobe [39,40]. Regional blood flow has also been shown to increase during pursuit in frontal areas including the DMFC in humans [19]. Preliminary work done in our laboratory in the DMFC has found cells which seem to respond during smooth pursuit as well, but in which the response reflects a complex interaction between the eye movement and visual backgrounds and/or small spot slip (Heinen and Keller, unpublished data). Work still needs to be done in this area to sort out the relative contributions of visual and extraretinal information to the signals carried on these cells.

Since other prefrontal cortical areas have been found to be involved in saccadic and visual processes [9,31], and anatomical connections between these other regions and FEF are strong [39,40], recording from these areas for pursuit substrates still needs to be done to further characterize the role that the frontal lobes play in smooth-pursuit generation.

SUBCORTICAL PATHWAYS

Pontine nuclei

The descending control limb for pursuit eye movements from either of the cortical pathways discussed above appears to go mainly through the pontine nuclei (PN). This

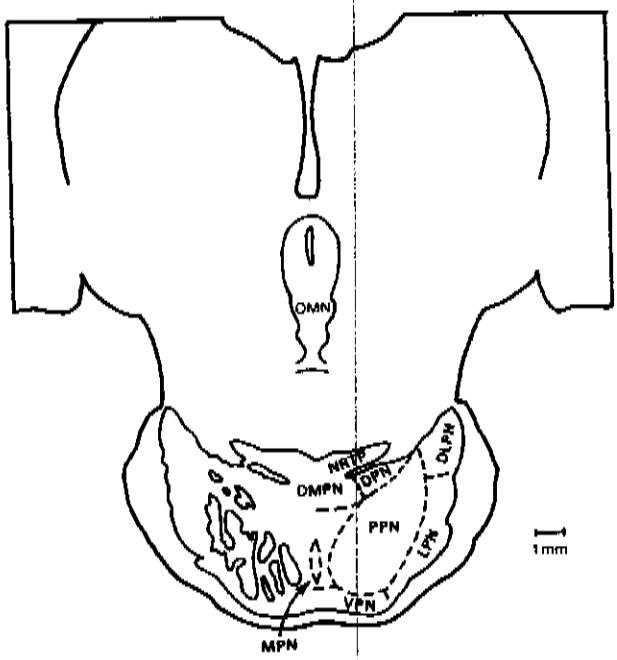

Fig. 6. Schematic division of the pontine nuclei of the monkey (modified from May and Andersen[73]). The figure shows a coronal section of the brainstem at a rostral level of the nuclei. DLPN = dorsolateral pontine nucleus; LPN = lateral pontine nucleus; VPN = ventral pontine nucleus; PPN = peduncular pontine nucleus; MPN = median pontine nucleus; DPN = dorsal pontine nucleus; DMPN = dorsomedial pontine nucleus; NRTP = nucleus reticularis tegmenti pontis. The boundary between the NRTP and the DMPN at this and more rostral levels is unclear and therefore is left out.

anatomically diffuse mass of neurons has expanded enormously in the evolution of the primate in parallel with the enlargement of the cortical mantel so that it occupies fully one-third of the brainstem at midpontine levels. Throughout this large region small clusters of cells are interspersed with descending and crossing fiber tracks so that it is difficult to clearly delimit any distinct nuclear subregions. Nevertheless, the pontine nuclei have been divided into several zones mainly on the basis of anatomic locations and some cytoarchitectonic features [91]. Figure 6 shows a schematic view of this somewhat arbitrary division of PN. The nomenclature of Nyby and Jansen [91] has been followed in this figure except for the rostral dorsomedial area of the nucleus which may form an important separate functional region [47]. This area, which has been labelled as part of the dorsal nucleus or the rostral extension of the nucleus reticularis tegmenti pontis (NRTP) will be called the 'dorsomedial pontine nucleus' (DMPN) in this review.

Glickstein and his colleagues, using retrograde anatomical tracing techniques (HRP), first established the detailed pattern of descending cortical connections to PN in the primate [33,34]. Their results indicate that the major components of this projection from visual structures of the cortex originate from a number of areas: MT, MST, area 7a of posterior parietal cortex, VIP and LIP, the rostral bank of the parietal-occipital sulcus (PO), the frontal eye fields (FEF), the supplementary eye fields, and the cingulate cortex. In addition, a small projection from VI and VII may exist, but only from those areas representing the most peripheral region of the visual field. More recent anterograde tracing studies from several of these cortical areas have confirmed these results and have shown that the projections go to a crescent-shaped region of the pontine grey that

includes the lateral, dorsolateral, dorsal and dorsomedial pontine nuclei as well as the NRTP [10,29,39,56,59,72,73,103,117].

These studies indicate that all of these cortical projections form small, locally dense, patches of terminations that are elongated along the rostral-caudal axis of the PN. No evidence of retinotopy has been reported in any of these projections. Almost all of the connections are ipsilateral; however, the projections to DMPN are an exception with bilateral terminations. It is difficult to rank these projections quantitatively because of the different techniques used in the various studies, but those to the DLPN and LPN appear most consistently. Projections from the FEF and the supplementary eye fields appear unique in projecting to DMPN and the NRTP as well as the DLPN.

The dorsolateral pontine nuclei

A number of single-unit recording studies have been made in the DLPN [83,108,110,114]. The cells recorded in here most closely resembled those reported in MT, MST, MSTf, area 7a and the FEF. Based on pursuit tracking trials in the dark, target blanking during such trials and on visual tests with small moving targets while the animal fixates, three major categories of cells have been reported in these studies.

One class responded to the motion of small punctate targets with most cells having receptive fields that include the fovea, although some are similar to MT neurons with localized, eccentric receptive fields [110]. These cells were directionally tuned with quantitatively similar properties to those in MT and MST (directional tuning bandwidths averaged 107°). Approximately equal numbers of cells with ipsilateral and contralateral directions of preferred motion were found in DLPN just as in MT and MST. Their visual responses led the onset of pursuit by about 20 ms. Visual neurons in DLPN were also speed tuned with preferred speeds ranging from 20 to 80°/s. The DLPN relationship between population response and retinal slip speed showed a linear increase in response up to about 40°/s and was very similar to the population response of MT neurons and to the actual initial eye acceleration produced at least for lower values of retinal slip (see Fig. 4).

There was one major difference in the organization of the visual fields for those DLPN visual cells which had large receptive fields that included the fovea when compared to foveal MST visual motion cells. The response to visual motion of the small test spot was not uniform over the receptive field but instead seemed to emphasize the fovea and parafoveal region. As a result of this effect, the discharge for motion in the preferred direction became greater as the target neared the fovea, although there was a directionally sensitive discharge for target motion anywhere in the cell's receptive field. Such a response type could be manufactured from weighted inputs from MTf cells (with small receptive fields centered on the fovea) and MST neurons with larger uniform receptive fields. Furthermore, these DLPN neurons with non-homogeneous receptive fields have the most sensitive speed tuning for the foveal component while the surround response is rather insensitive to changes in speed. Behaviorally, initial eye acceleration and retinal slip speed show this same type of field asymmetry [62].

In contrast to these visual cells other classes of DLPN neurons exist which contain both an extraretinal component of discharge related to pursuit eye movements and a visual signal, or just a motor-related component. Cells of these two latter classes form a distinct majority of the recorded cells in some studies of the DLPN [83,114]. These cells are similar to MT, visual MST and DLPN cells in that their responses have broad directional tuning for the pursuit movement (average half-maximum bandwidth was 129°) [83]. These two studies have concluded that most DLPN motor-related neurons show little variation

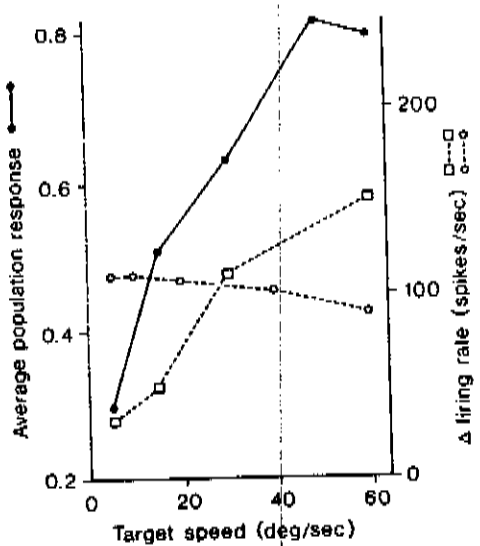

Fig. 7. The relationship between pursuit cell discharge in the DLPN and target speed. Since the data on discharge rate were obtained during pursuit tracking that closely matched target speed, the abscissa also approximately equals eye speed. The solid line shows the average population response for 22 cells (combined data from Thier et al. [114]; Mustari et al. [82]; Keller, unpublished data). All these cells continue to discharge during target blanks and, thus, this relationship most likely illustrates the behavior of an extraretinal component in the cell's discharge. The dashed curves show examples of two units from this population with opposite types of behavior. The unit illustrated with open circles shows no evidence of coding eye speed, at least over the range of speeds studied (5–60°/s). The unit shown with squares has a clear monotonic increase over this same range of speeds.

in discharge rate with respect to the speed of the pursuit movement although exceptional units exist [83,114]. We have also found examples of tuned and untuned types of behavior in motor-related DLPN cells (see Fig. 7). Nevertheless, for a sample of this type of DLPN neuron taken from all three studies, the population response plotted as a function of target speed during pursuit shows clear coding of eye speed up to a value of about 45°/s. Mustari et al. [83] have shown that the response of this type of DLPN cell begins after the onset of pursuit in step/ramp tracking trials, indicating that these cells cannot be responsible for pursuit initiation. Finally, the distribution of preferred directions of this class of DLPN unit includes all directions of pursuit or visual motion [83,114].

The results of electrical stimulation in the DLPN were somewhat similar to those already discussed for cortical area MST [75]. When the stimulation was delivered with the monkey fixating a stationary target, no eye movement was evoked, but stimulation delivered during ongoing pursuit produced a short-latency eye acceleration which was usually in the ipsilateral direction (Fig. 5). These results imply that DLPN is, like MST, upstream of the pursuit selection switch (see Fig. 2). However, unlike the situation in MST, the evoked increase in eye speed was not sustained for the duration of DLPN stimulation. When the stimulus was stabilized on the retina, a steady eye acceleration was produced for the duration of the stimulation (May and Keller, unpublished data). This result suggests that DLPN is located at a visual motion processing level of the pursuit system, a conclusion which is consistent with the existence of the visual single-units discussed above.

Probably the most compelling evidence that the pontine nuclei are involved in the generation of pursuit eye movements comes from studies in which focal chemical lesions

have been made in these nuclei [74,76]. Lesions in the DLPN resulted in decrements in pursuit performance of more than 50% when measured as the initial eye acceleration in response to step/ramp target motion. The deficit in initial pursuit acceleration was on average about 6 times larger in the ipsilateral direction than in the contralateral direction, although there was often a significant deficit in the contralateral direction as well. Steady-state pursuit performance was also lowered. The deficit during pursuit initiation was about the same when motion occurred in the ipsilateral or contralateral visual field or in the region of the fovea; therefore, the deficit cannot be considered a retinotopic one. The consistently larger effect of DLPN lesions on the ipsilateral direction of pursuit is difficult to explain on the basis of the rather uniform distribution of preferred directions of units found in the area. These lesions produced the same direction of asymmetry found following cortical lesions in MST and MSTf [24,25]. It was hypothesized on the basis of these cortical studies that the asymmetry might be produced by an unequal projection of cortical units with different preferred directions to the pons. Since the vast majority of corticopontine projections are ipsilateral, this hypothesis implies that only STS units with ipsilateral preferred directions project to the pons and units with contralateral preferred directions project elsewhere, perhaps to the opposite cortex. The fact that the DLPN contained a uniform distribution of preferred directions makes this explanation unlikely, as do the asymmetric direction of the pontine deficits following lesions there. It now seems more likely that the asymmetry comes about due to unequal projections of units with different preferred directions to the cerebellum or to asymmetric processing within the cerebellar cortex itself.

Animals with ibotenic acid lesions in the DLPN regain almost normal values of initial pursuit acceleration within 2–12 days following the injection of the toxin. In an attempt to determine if this recovery in function was accomplished by the remaining DLPN, both one-stage and two-stage bilateral lesions were made with ibotenic acid [74]. In both cases animals regained most of their pursuit performance, although the time course of recovery was lengthened to more then 2 weeks.

In summary, although there is evidence of considerable convergence of visual motion processing and pursuit-related inputs onto DLPN from a variety of cortical areas, the effects of lesions of this nucleus on pursuit performance are no larger and longer lasting than those placed in either frontal or parietal sources of corticopontine input. The fact that inputs from each cortical motion processing or pursuit area project in a very patchy manner to several pontine nuclei suggests that these corticopontine pathways may comprise a highly parallel system for the processing of pursuit-related information [73,91]. This idea is supported by the results of an ibotenic acid lesion study in one animal which affected several subdivisions of this nucleus [76]. In this experiment the injection of ibotenate, which was aimed at the DLPN, actually was centered in the LPN and only impinged on a very tiny portion of DLPN. This lesion created a transient pursuit deficit as large as that seen with DLPN lesions.

DMPN and NRTP

In a single-unit recording study Keller and Crandall [47] found that a majority of the cells in a small region in the rostral dorsomedial pontine nucleus (DMPN) and the closely adjacent part of the nucleus reticularis tegmenti pontis (NRTP) responded to the motion of large-field moving stimuli. The responses of these neurons were directionally selective and somewhat selective for speed over a narrow range (0.5–10°/s) of target speeds. A minority of these cells were also pursuit cells (37%). These cells were located in a region in the rostral pons that appears to receive a distinct projection from the FEF and from the

supplementary eye fields [39,59,103]. Very recently it has been confirmed that DMPN/NRTP contains visual motion cells that respond to small moving targets in a similar fashion to those in DLPN and that chemical lesions in this region cause a smooth-pursuit deficit [112]. Thus it may be that this area, which includes parts of two nuclei, forms the descending link from the frontal cortex in the alternative smooth-pursuit pathway.

To definitely demonstrate that two major pathways for the generation of pursuit eye movements exist through the pontine nuclei, it is important to know what the next links in both pathways are. Older anatomic studies utilizing degeneration techniques have shown that most, if not all, of the outgoing projection of the pontine nuclei goes exclusively to the cerebellum where the projecting fibers terminate as mossy fibers [11]. More recent studies have made HRP injections in various subdivisions of the cerebellum and have traced the origins of the pontocerebellar connections by retrograde techniques. A number of clear projections have been identified with this technique. Lobules VI and VII of the vermis receive a very prominent projection from both the DLPN and the DMPN [14]. These vermal projections appear to originate from exactly those regions of the PN where visual motion and pursuit neurons are found in DLPN and DMPN [47,112]. The uvular lobule of the vermis (lobule IX) receives an equally heavy pontine projection, most prominently from the DLPN, but also from a small region of the DMPN [58]. The flocculus receives a weak projection from a number of areas of the PN, but consistent input is seen from the lateral pontine nucleus and the NRTP [13,58], and occasionally from the DLPN and the DMPN [58]. The flocculus receives a weak projection from a number of areas of the PN, but input is consistently seen from the lateral pontine nucleus and the NRTP [13,58]. It is well to point out that the rostral most portion (folia 6–10) of the monkey flocculus is more correctly considered to be part of the ventral paraflocculus on the basis of the origin of its climbing fiber and mossy fiber inputs [32]. This fact presents us with a difficult problem in this review because most of the literature on the flocculus, both anatomical and physiological, has not made this distinction. Therefore, we will use the term 'flocculus' to refer to the entire 10 folia of the structure as is commonly now done. The reader is cautioned that this choice will not then distinguish between anatomical locations within the flocculus. A study in the cat utilizing anterograde tracing techniques following massive injections in the PN [97] forms a valuable supplement to the work using retrograde tracers in the monkey, although the pontine nuclei in this animal are known to be organized differently than in the primate [33]. In this study large medial or dorsolateral injections of anterograde tracers produced heavy projections to the uvula and to vermal lobule VII. The most consistent projection, however, went to the paraflocculus, a pathway not emphasized in the monkey. However, work in the monkey cited above [58] also shows that the extent of labelling in the pontine nuclei, and especially in the DLPN, was more intense from those floccular-targeted injections in the cerebellum which also included a portion of the paraflocculus.

Cerebellum

The cerebellum has been demonstrated to be extensively involved in, if not necessary for, the generation of pursuit eye movements. It is likely that all pursuit signals pass through the cerebellum before they form the final pre-oculomotor command to move the eyes, since total cerebellectomy abolishes smooth pursuit [118]. In spite of this finding, probably more emphasis has been placed on studying cerebellar involvement in saccadic eye movements than in pursuit, but recent studies have begun to expand our knowledge of neural processing for pursuit in this structure. Most research has looked at the role that the flocculus plays in this processing, but the paraflocculus, vermal lobules VI and VII

(the oculomotor vermis) and IX (the uvula), have also been shown to contain neural correlates of smooth tracking in single-unit recording studies.

The stereotypic cytoarchitecture of the cerebellum makes it an attractive structure for study since measures of neural activity at both its input and output can be made, which allows the formation of hypotheses about its internal signal processing. Most cellular recordings are made from the Purkinje cells (P-cells), the only output elements of the cerebellum, which are physiologically easy to identify from their characteristic discharge. However, some researchers have also recorded from either mossy fibers or climbing fibers (accessory optic system) inputs to gain insight about the nature of the processing which occurs in this structure. (For a complete summary of the functional architecture of the cerebellum see Ito [42].)

Flocculus

Bilateral ablation of the flocculus (and portions of the paraflocculus) result in major deficits in smooth pursuit control [124]. Following these lesions, smooth pursuit gain was reduced to about 0.64, and only partially recovered to a value of 0.78 after 6–12 weeks. This severe and lasting deficit suggests a major role for the flocculus in the control of smooth tracking eye movements. Electrical stimulation in this area has also been shown to elicit smooth eye movements, providing further evidence for such involvement [8]. The evoked slow eye movements, like those seen following FEF stimulation and in contrast to the situation in MST or DLPN, occurred even if the animal was attempting to fixate a stationary target. These results suggest that the flocculus lies beyond the gate for pursuit selection.

The flocculus, as just discussed, has access to visual information via the LPN and DMPN/NRTP, and probably the DLPN [13,58]. Oculomotor information could also be conveyed through these pontine structures [83,114] or from the NPH/VN [12,58], to the flocculus. Anatomical projections have been demonstrated from the flocculus back to the vestibular nuclei (VN) as well [4,57]. This rich set of interconnections establishes the anatomical basis for the notion that the flocculus is a center for smooth-pursuit control.

Single-unit studies have attempted to define the precise nature of the oculomotor-related neural processing in the flocculus. One of the earlier studies along these lines documented this structure as carrying signals which primarily conveyed retinal slip information [79]. Other studies have found activation of floccular P-cells by patterned visual stimuli which were moved sinusoidally during fixation [89] or during periods of eye velocity reversals during tracking of triangle waves [63]. These latter researchers attributed these discharges either to eye acceleration at stimulus turnaround or to increased visual slip when the target changed directions, but did not perform the critical experiment to differentiate between these alternative hypotheses.

However, current thinking about the role of the flocculus in smooth pursuit centers more on its involvement in coding gaze velocity, i.e. eye velocity in the head plus head velocity in space. The gaze velocity signal from floccular P-cells could be used in a positive feedback loop with a brainstem structure generating eye velocity commands to form the velocity integrator [61] shown in either model in Figure 2. The eye velocity components of this signal presumably originate in the brainstem premotor circuits [61,69] or even the periabducens region [58] as an efference copy signal. The purpose of this loop would be to sustain neural activity and thus eye velocity during steady-state tracking or stabilization with no further input of retinal slip [61].

Evidence that the flocculus generates a gaze velocity signal comes from tests involving various combinations of eye and head rotations. Floccular P-cells recorded during both

sinusoidal and step-ramp tracking show discharge which is related to eye position, but which is also strongly related to eye velocity [16,63,80,88,90,104]. Most of these cells respond best for pursuit directed towards the side being recorded from (ipsilateral) or vertically in the down-direction. Pursuit opposite to the preferred direction usually produces inhibitory activity on the cell. When tested during head rotation with the eyes fixating a spot which moves with the head (VOR suppression), the cell shows a similar modulation of firing rate as that seen during pursuit in the same direction [63,80]. This implies that both head and eye velocity are represented in a similar fashion on the neuron, and could be added together to obtain a neural correlate of gaze velocity.

Lisberger and Fuchs performed the critical experiment which showed this to be the case, and also described the nature of the summation [63]. These researchers monitored P-cell activity while monkeys tracked sinusoidal targets which moved at speeds which were different from and in and out of phase with head velocity. They found that the discharge of floccular P-cells in these conditions could be predicted reliably by a linear vector summation of cell activity which occurred during head or eye rotation alone. These results predicted that rotation in the dark, which produced almost equal and opposite head and eye rotations (the VOR), should result in a cancellation of these signals at the P-cell level. In confirmation, very little modulation of these cells occurred in this condition.

For these tests to exclusively define a signal related to gaze velocity, it is important that the signal be uncontaminated by visual information. Unfortunately, transient activations are seen on floccular P-cells during pursuit initiation to step-ramp targets, as well as at target reversal points during triangle-wave tracking. These are intervals associated with considerable eye acceleration as well as retinal slip. Stone and Lisberger attempted to determine which of these inputs (eye acceleration or visual slip) dominated this transient response [104]. To achieve this, they rotated the head in the dark in a trapezoidal fashion, thereby creating eye accelerations (through the VOR) which were comparable to those seen during their step-ramp smooth pursuit trials. These accelerations failed to yield a transient response on floccular P-cells, implying that the responses related to onset of smooth tracking were visual. However, it is possible that these cells respond to both eye and head acceleration, and these signals are canceled in a like fashion to the eye and head velocity signals during VOR. These authors also tested for visual responses on P-cells during steady-state tracking by electronically stabilizing the target for brief intervals, thereby eliminating retinal slip. Little or no change in the response was seen during these periods. These results suggest that floccular P-cells carry information about retinal slip only during pursuit initiation. These cells probably utilize largely non-visual inputs from the brainstem after the eye has reached steady-state pursuit tracking, and are therefore carrying a signal related to eye velocity under these conditions. It is clear that this signal cannot directly drive motoneurons because they have a signal more nearly in phase with eye position during steady-state tracking [46].

Paraflocculus

Since the floccular lesions which affected smooth-pursuit gain included portions of the paraflocculus [124], this area may be suspected of participating in pursuit generation as well. This suspicion is strengthened since, as discussed in the section on the pontine nuclei, the paraflocculus receives a stronger input from visual pontine nuclei than does the flocculus. Only one study has been done which investigated smooth pursuit and visual signals on paraflocular P-cells in the primate [87]. These researchers found some evidence of neural modulation during visual motion, but a greater proportion of cells responded during

tracking of a sinusoidal target. Cellular activity showed a similar phase relationship and sensitivity to pursuit velocity as that seen on floccular P-cells. No tests were performed to determine a head velocity component on the paraflocculer neurons; however, the similarities of these cells to floccular neurons in other respects suggest that these two areas may perform the same functions in pursuit generation.

Vermis

Lesions of the flocculus (and portions of the paraflocculus) can only partially account for the total loss of smooth pursuit following complete cerebellectomy. Therefore it is reasonable to suspect that other cerebellar regions may be involved in the generation of pursuit eye movements as well. One area that had been extensively studied with respect to saccadic control, but which has only recently been targeted for smooth tracking correlates, encompasses vermal lobules VI and VII (hereafter called the 'vermis'). Although anecdotal reports from early studies involving discrete vermal lesions to this area suggested that smooth pursuit looked normal [92], a more recent study reported a gain reduction of 60–70% in vermal-lesioned animals [109]. The magnitude of this reduction is similar to that found after flocculectomy [124], suggesting that the vermis may play a role in pursuit generation at least as strong as that of the flocculus. In addition to its extensive visual pontine input, the vermis also receives projections from visual and pursuit related areas of the NRTP [14]. The vestibular nuclei also project to this structure, although connections from VN are not as strong to the vermis as to the flocculus [13,14,58]. Vermal P-cells send their axons to the mediocaudal aspect of the fastigial nucleus [119], which in turn projects largely back to NRTP and DLPN [7,105].

The question, then, that single-unit studies in the vermis have set out to address, is whether or not the flocculus and the vermis form parallel paths for the processing of smooth-pursuit signals, or whether their functions are somehow complementary. The earliest studies which explored the vermis for non-saccadic activity did find one very different property on P-cells there in comparison to those in the flocculus. Vermal cells seemed to respond much better to the slip of visual stimuli on the retina [43,111]. These cells were tested both with sinusoidal small spot and textured background motion while the animals fixated. It was found that vermal neurons encoded retinal slip velocity for small spot motion quite well, but only yielded directional information (no speed sensitivity) for the textured background.

Tests were also done in these studies to assess smooth-pursuit-related components of these neurons. Tracking of sinusoidal target motion revealed responses very much like those recorded in the flocculus, in that they were nearly in phase with target velocity, and increased with target velocity.

These cells responded best for the same direction of pursuit as for retinal slip, which suggests that they may represent target velocity with respect to head position. However, according to the corollary discharge class of pursuit models, it is important that the target velocity be reconstructed with respect to the world [121]. The neural reconstruction of such a signal requires information about target slip with respect to the retina, eye velocity with respect to the head and also head velocity with respect to the world.

A recent series of papers has demonstrated the existence of vermal P-cells which carry a target-velocity signal [106,107]. These researchers first used standard sinusoidal tracking and visual stimuli to verify the existence of retinal slip and eye movement signals on vermal P-cells. As in previous studies, they found that both of these signals were related to velocity, and increased with greater slip or tracking speeds. They also tested some cells during tracking across a textured background, and found that the response of these

neurons could be predicted by algebraic summation of the activity occurring during tracking in the dark and background motion during fixation. These cells were also tested during VOR suppression to document a head-velocity component in the response. Like floccular cells, these vermal P-cells were modulated nearly in phase with head velocity during this paradigm and increased their firing rate in a linear fashion as head velocity was increased. Again, as in the flocculus, it was found that an algebraic summation of this head-velocity response and the eye velocity response predicted the neural modulation obtained during combined head and eye movement out of phase and/or at different velocities. An example of a unit that carries the three component signals of target velocity is shown in Figure 8.

The vermis and flocculus therefore process information for smooth pursuit in a similar fashion, but with some important differences. Most notable is the fact that while floccular P-cells only code gaze velocity during steady-state tracking, vermal cells also have a retinal slip component which allows a reconstruction of target velocity in space. On average, neurons in the vermis do not have as high a sensitivity to eye velocity (0.62 sp/s/deg/s) [106] as those in the flocculus (0.92 sp/s/deg/s) [63]. Taken together these two facts suggest that the flocculus is more involved in the motor aspects of maintaining ongoing pursuit, whereas the vermis may exert its influence on the pursuit system when retinal slip is high, i.e. during rapid changes in target velocity.

Uvula

The uvula (lobule IX of the vermal cerebellum) receives visual projections from the pontine nuclei which are as strong as, if not stronger than, those going to the flocculus and vermis [13,97]. Output from the uvula either goes directly to the vestibular nuclei [3] or courses through the fastigial nucleus to the VN/NPH premotor structures [7,105]. Surprisingly, the uvula has not been studied until very recently to determine its role in visual or smooth-pursuit processing. Punctate chemical lesions made in the uvula in two monkeys yielded a marked asymmetry in smooth pursuit (Heinen and Keller, unpublished data). In these animals gain was lower in steady-state pursuit directed contralateral to the lesion than it was for ipsilateral pursuit. However, most uvular P-cells were only activated by long-duration optokinetic stimulation, and not by pursuit eye movements or small spot motion. A small percentage (7%) of uvular cells did show evidence of a signal related to tracking or retinal slip of the target during active pursuit [36]. Therefore, the uvula may play a role in smooth pursuit, but a minor one compared to other cerebellar structures. The importance of large-field moving stimuli in the response of uvular P-cells suggests that this structure may be important in pursuit generation which requires that a distinction be made between target and background [51].

Brainstem

In order to exert its profound influence in smooth pursuit generation the cerebellum must carry out this control function through its connections to brainstem pre-motor circuits. Most likely, cerebellar pursuit control is mediated by connections to the vestibular nuclei (VN). Cells in the medial and superior vestibular nuclei [30,38,50,78] and in the y-group of the vestibular nucleus [18] have been shown to discharge during pursuit eye movements. The signal carried by these cells is proportional to eye velocity and there is no evidence of any visual sensitivity to the motion of small spots, although this was not carefully checked in these studies.

The nucleus prepositus hypoglossi (NPH), which is anatomically closely connected with the vestibular nuclei, has also been shown to contain pursuit cells with properties

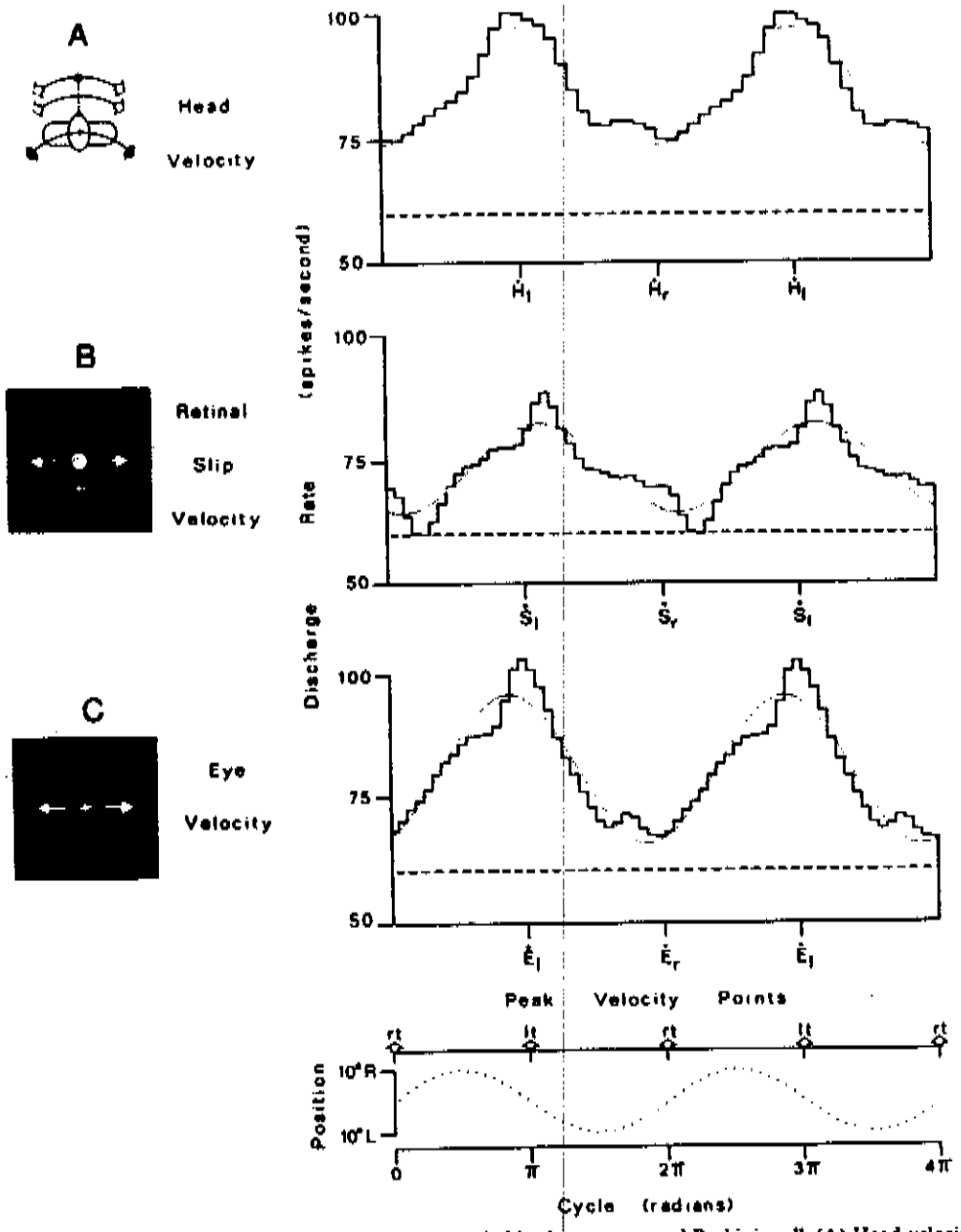

Fig. 8. The three, target-velocity component signals recorded in the same vermal Purkinje cell. (A) Head-velocity component during suppression of the vestibulo-ocular reflex. (B) Retinal slip-velocity component during ocular fixation and small visual target movement. (C) Eye-velocity component during pursuit tracking in the dark. Dotted curves show best fitting fundamental sinusoids; dashed lines are the spontaneous discharge rate of the cell; bottom curve shows the stimulus profile (either head or target motion or both). All movements were at 0.4 Hz ± 10°. From Suzuki and Keller [107].

very similar to those reported for VN neurons [69]. Thus it is possible that these two nuclei together make up the final pre-motor substrate for pursuit. It is possibly significant that the FEF has been reported to project directly to the NPH, thus bypassing the pontocere-

bellar pathways already discussed [60,103], as it might thereby form another parallel pursuit pathway [26].

Most VN cells have a sensitivity to the visual motion of large-field textured backgrounds, but this response only develops very slowly and is probably related to the slow build-up of optokinetic following eye movements, another function that VN neurons may control [38]. Many VN cells also carry a variety of other signals in addition to an eye velocity command including eye position, head velocity and saccadic eye movement velocity. The construction of a proper pursuit command to the oculomotor neurons from this diverse group of single-unit responses requires population arguments or additional processing at the level of the motoneurons [115].

Most of the studies at this level of the system have been carried out with steady-state sinusoidal responses. Thus, it is not possible to say anything about the time leads or lags of these cells with respect to the eye velocity as could be done with the step/ramp response. However, it is clear from quantitative studies of the discharge of oculomotor neurons (see Ref. 46 for a review) that the signal required to produce this discharge in motoneurons should lead eye position and not eye velocity by about 30° at 0.5 Hz (a typical frequency used in these studies). Consideration of these data from motoneurons implies that one clear signal-processing step has occurred in the vestibular nuclei upon the cerebellar pursuit signal. The cerebellar signal, as outlined above, is in phase with eye velocity during pursuit in the flocculus, paraflocculus and the oculomotor vermis. This post-cerebellar processing may be described in a systems theoretic sense as an integration and is depicted in both types of systems models (Fig. 2) as final motor processing. On the basis of chemical lesions made in the VN/NPH complex there is good evidence that these nuclei form the substrate for this processing [17]. The results of these lesions are quite different than those already discussed for other areas in the pursuit system, in that they totally remove the necessary neural integration needed for the generation of all types of eye movements as well as for pursuit. The effects cannot be accounted for as a loss of

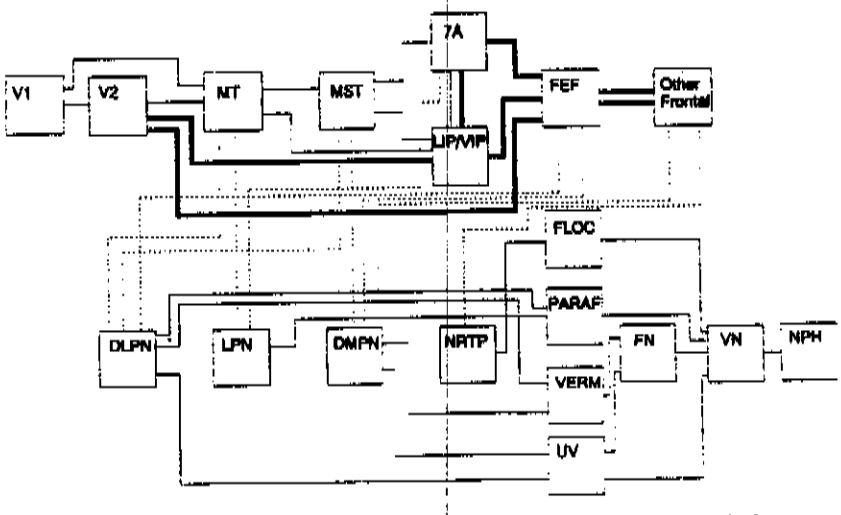

Fig. 9. Pursuit pathways in the brain. Shown are main and alternative (heavy lines) cortical routes, corticopontine projections (dotted lines), and cerebellar and premotor outputs. Possible accessory optic system pathways have been left out (see text). Double lines between structures indicate reciprocal connections which have possible functional significance for pursuit. FLOC = flocculus; PARAF = paraflocculus; VERM = vermis; UV = uvula; for other abbreviations, see text.

either the visual slip signal or the pursuit eye velocity command. Instead, the deficits following chemical lesions in the VN/NPH involve a loss in the ability to convert the velocity command into an eye position signal as required by motoneurons.

The cerebellum might also mediate its pursuit control through its connections to the brainstem reticular formation [7,105]. A group of cells located in the reticular formation near the abducens nucleus were reported to discharge in relation to horizontal pursuit eye movements [27]. Like VN neurons these cells exhibited a broad range of phase leads with respect to eye position during pursuit eye movements. However, ibotenic acid lesions of large extent in the reticular formation that included this region did not produce deficits in pursuit movements [37]. Therefore it seems likely that the cerebellum controls pursuit through its abundant connections to the VN.

Figure 9 shows a summary of the pathways for the control of pursuit that we have discussed in this review. On it we have tried to show the major flows of organization. We are hopeful that it forms a useful representation of the extent of our knowledge of this system at this time.

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