Waitzman, David Myles

BURST NEURONS IN THE MESENCEPHALIC RETICULAR FORMATION (MRF) OF THE RHESUS MONKEY ASSOCIATED WITH SACCADIC EYE MOVEMENTS

City University of New York PH.D. 1982

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BURST NEURONS IN THE MESENCEPHALIC RETICULAR FORMATION (MRF) OF THE RHESUS MONKEY ASSOCIATED WITH SACCADIC EYE MOVEMENTS

by

David M. Waitzman

A dissertation submitted to the Graduate Faculty in Biomedical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

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by

David M. Waitzman

Advisor: Professor Bernard Cohen

Single neurons were recorded extracellularly in the mesencephalic reticular formation (MRF) of two rhesus monkeys trained to watch stationary and jumping spots of light on a TV screen. Eye movements were recorded using EOG. The area studied was about 2 mm in medial-lateral dimensions and about 1.5 mm in depth from dorsal to ventral. It is bordered medially by the oculomotor nuclei, laterally by the medial lemniscus, dorsally by the pretectum, and ventrally by the red nucleus. MRF burst neurons fired before and during spontaneous, visually-guided, and visually-targeted contralateral horizontal saccades. Increases in activity began as early as 120 msec prior to the onset of saccades and terminated in a burst of firing that preceded saccades by 20 to 30 msec. Peak activity of the burst was greater and occurred earlier when animals made visually-induced than spontaneous saccades. The number of spikes in a burst was related to the direction of the upcoming saccade, and was also roughly correlated with the amplitude of the horizontal component of movement. Most MRF neurons had

an irregular background rate of firing that was either enhanced or suppressed during active fixation of the target. This background firing was inhibited prior to ipsilateral saccadic eye movements. Inhibition was more profound when animals looked away from the target. Stimulation experiments have shown that small saccades are elicited from dorsal regions of the MRF and larger saccades from ventral regions. Combined stimulation/recording experiments indicate that there is a similar dorsal-ventral organization of neural activity in the MRF with respect to saccade amplitude. In some neurons peak firing in the burst occured earlier and had a higher frequency before small saccades. These neurons appeared to be located dorsally. Neurons which fired preferentially for large saccades appeared to be located more ventrally in the MRF. The distribution of MRF neural activity in relation to saccades of specific size in a dorsal-ventral fashion suggests a spatial coding of saccade amplitude in the MRF. Such activity could contribute to the generation of both spontaneous and visually-induced saccades. The burst of activity prior to saccades could contribute to the triggering of saccades, while the population of cells that is active could signal motor error in the horizontal plane.

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D.M. Waitzman

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DEDICATION

In memory of my father who would have wanted to edit this manuscript and see its completion.

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CHAPTER 1

RATIONALE AND GOALS

Early lesion and stimulation experiments have suggested that the mesencephalic reticular formation (MRF) plays an important role in the production of eye movements in the horizontal plane (Szentágothai, 1943; Bender and Shanzer, 1964). Following MRF lesions, monkeys had a gaze preference to the ipsilateral side although vestibular responses were unaffected (Komatsuzaki, Alpert, Harris and Cohen, 1972). Initially, the animals did not look at targets in the contralateral hemifield of movement. However, they were able to produce eye movements to the contralateral side in response to non-visual auditory stimuli. This suggested that MRF lesions may have impaired the ability of the animals to execute eye movements to the contralateral side in response to visual stimuli. The experiments presented here have been designed to test the hypothesis that neurons in the MRF participate in the control and production of visually induced eye movements. Single neurons were recorded extracellularly in the MRF of alert rhesus monkeys trained to fixate stationary targets and to follow jumping spots of light for a water reward. The goal of this research was to investigate the relationship between various parameters of the neural firing and the characteristics of the associated saccadic eye movements, e.g., direction, amplitude, and latency. This work may provide insights into

how the visual system codes neural information destined to initiate and guide saccadic eye movements. The literature review will briefly define the types of eye movements that have been studied. It will also describe the organization of the oculomotor system, the cortical and subcortical pathways which have been implicated in the control of visually induced eye movements, and how the MRF might participate in visual-oculomotor control.

REVIEW OF LITERATURE

Definitions of the Types of Eye Movements Studied

There are two major types of eye movements: fast and slow. Examples of rapid eye movements are spontaneous saccades, quick phases of nystagmus and microsaccades. Examples of slow eye movements are visual pursuit, slow phases of nystagmus, and vergence movements. This thesis has focused specifically on the control and the production of rapid eye movements. Slow eye movements will not be considered further.

The primary purpose of rapid eye movements is to acquire a new visual image on the retina, and to direct the eye so that the most sensitive portion of the retina, the fovea, is pointed at a target of interest. In this thesis three types of voluntary eye movements have been distinguished: spontaneous saccades, visually-guided saccades, and visually-targeted saccades. Spontaneous saccades are generated while a subject casually examines the visual world, or makes eye movements in

darkness while awake. Visually-guided saccadic eye movements occur when the eyes move toward a target which has jumped with unpredictable direction and amplitude. There is no prior knowledge of where the target will be and all processing to induce the eye movement takes place after the visual stimulus that generates the saccade has occured. Visually-targeted saccades are produced when a subject executes a saccade to a remembered target position that was initially established through the visual system. In this instance the information about the spatial coordinates of the target is known and only the decision and the final command signal that produce the saccade must be generated. All voluntary saccades which utilize visual information for their generation will be termed visually induced saccades.

Targeted saccades have been shown to be different from visually-guided movements (Hallet and Lightstone, 1976b; Mays and Sparks, 1980; Goldberg and Bushnell, 1981) particularly in their latency. This can be largely attributed to the prior knowledge of the spatial coordinates of the desired eye movement during targeted saccades. By distinguishing these two types of eye movements it has been possible to separate neural processing needed for calculation of the saccade vector from that needed for the decision in the visual system to execute a particular saccade. As will be shown subsequently there is little difference in activity responsible for these two types of saccades at the brainstem level. However, experiments on targeted saccades have shown that saccades in opposite directions may be processed in parallel (Becker and Jürgens, 1975; Hallet and Lightstone,

1976a; Mays and Sparks, 1980; Goldberg and Bushnell, 1981), and that saccade vectors (the amplitude and direction of a saccade) are stored in spatial, not retinotopic coordinates (Hallet and Lightstone, 1976a; Mays and Sparks, 1980). These experiments have also been of use in modelling of the oculomotor system. If the eyes can return to a position without the presence of a visual cue (i.e., using a targeted eye movement), then retinal error alone is not sufficient for guiding visually induced eye movements. More likely the brainstem must perform a comparison between desired eye position (the goal) in spatiotopic coordinates and absolute eye position (probably an efferent signal) (Robinson, 1975, Robinson, 1981; van Gisbergen, Robinson, and Gielen, 1981).

Organization of the Oculomotor System

Both the visual system and the vestibular system utilize the same ocular plant, i.e., the globe and muscles, to produce both rapid and slow eye movements. Robinson has shown that the ocular plant is an overdamped system (Robinson, 1964). To drive the eyes rapidly from one position of gaze to another he predicted that a pulse-step of activity would have to be generated in the oculomotor nuclei (Robinson, 1964). Extracellular recordings have shown that such a pulse-step in activity occurs in eye muscle motoneurons just prior to the execution of saccades (Robinson, 1970; Schiller, 1970; Fuchs and Luschei, 1970; Cohen and Komatsuzaki, 1972). The pulse causes the eyes to move rapidly from one position to another, and the step of activity holds the eyes in the new

position of fixation. The same motoneurons of the III, IV, and VI nerve nuclei carry activity to the eye muscles for the production of both rapid and slow eye movements. Moreover, it is clear that the concerted action of all twelve eye muscles is needed for production of any rapid horizontal eye movement (Henn and Cohen, 1973; Raphan and Cohen, 1978).

The immediate premotor supranuclear mechanism for the production of quick eye movements in the horizontal plane appears to be located in a region of the pons called the paramedian zone of the pontine reticular formation (PPRF) (Bender and Shanzer, 1964; Cohen, Komatsuzaki, and Bender, 1968; Cohen and Feldman, 1968; Goebel et al., 1971; Henn and Cohen, 1976). Lesions 1 to 2 mm in diameter in the rostral PPRF of monkeys caused a profound deficit in horizontal eye movements to the ipsilateral side (Bender and Shanzer, 1964; Goebel et al., 1971), although these animals were able to produce normal vertical eye movements in the hemifield opposite the lesion. Quick phases of OKN, OKAN, and vestibular nystagmus were also eliminated to the ipsilateral side (Cohen, Komatsuzaki, and Bender, 1968).

Single-unit studies demonstrated that the neural activity required to form the pulse-step and to drive the motoneurons was found in the PPRF (Luschei and Fuchs, 1972; Keller, 1974; Henn and Cohen, 1976). Neural activity for the generation of the pulse appears to be distinct from that needed to produce the step. Neurons in the rostral PPRF are typically phasic and burst with rapid eye movements (Cohen and Henn, 1972a; Cohen and Henn, 1972b; Lushei and Fuchs, 1972; Henn and Cohen, 1976). This activity was coded in a polar coordinate system with single

neurons generating activity for amplitude, duration and direction of movement (Henn and Cohen, 1976). The activity necessary for the step appeared to be produced around and caudal to the abducens nucleus (i.e., the periabducens region) and in the prepositus nucleus (Luschei and Fuchs, 1972; Keller, 1974). Thus the PPRF and periabducens regions are the premotor areas which are the targets for activity from the vestibular and visual systems for the production of quick eye movements in the horizontal plane.

Stimulation and lesion studies demonstrated that the pathways from various cortical areas converge in the internal capsule and descend into the reticular formation (Wagman, 1964; Bender and Shanzer, 1964). As stimulation was carried further caudal and ventral a physiologic decussation of oculomotor pathways appeared at the level of the oculomotor nuclei (Bender and Shanzer, 1964). Stimulation in the brainstem more rostral than the oculomotor nuclei produced contralateral saccades and stimulation more caudal than the oculomotor nuclei elicited ipsilateral saccades (Bender and Shanzer, 1964). Thus activity in oculomotor pathways above the decussation should be related to gaze movements to the contralateral side, while that below the decussation should be related to gaze movements to the ipsilateral side.

Organization Of Visual-Oculomotor Pathways

Voluntary, visually evoked saccadic eye movements are initiated in at least two and probably more areas of cortex. Ferrier (1875) and

Schäfer (1888) were the first to demonstrate in the monkey that stimulation of large areas of the cortex would elicit saccadic eye movements to the contralateral side. Portions of the frontal cortex and the parietal-occipital cortex are two areas where eye movements could be elicited at lowest threshold (Ferrier, 1875; Schäfer, 1888; see also Wagman, 1964 and Bender and Shanzer, 1964 for reviews).

Frontal Eye Fields (Area 8 of Brodman)

Electrical stimulation in and around the arcuate gyrus in alert monkeys disclosed a discrete region from which eye movements could be eilicted at low thresholds (Robinson and Fuchs, 1969). The eye movements were characteristically saccades to the contralateral side. Smooth, vergence and centering movements were never elicited from stimulation (Robinson and Fuchs, 1969). Variation in the stimulus parameters did not affect the size or velocity of the induced saccades. Rather saccade amplitude and direction were specifically related to stimulus location (Robinson and Fuchs, 1969). Simultaneous stimulation at two points in the FEF produced an eye movement whose amplitude and direction was between that produced by stimulation of either site alone (Robinson and Fuchs, 1969). These responses to electrical stimulation are characteristic of many portions of the visual supranuclear pathways as will be discussed below under the superior colliculus.

The results of electrical stimulation prompted early workers to investigate the relationship of single neurons to saccadic eye movements

(Bizzi, 1968). Cells in the arcuate gyrus (area 8 of Brodman) fired during and after all contralateral saccadic eye movements in both light and dark (Bizzi, 1968). Other FEF cells were found which discharged in association with either head or both head and eye movements (Bizzi and Schiller, 1970). The finding that cells associated with saccades fired after the onset of movement initially suggested that FEF cells might be associated with a signal indicating that an eye movement had occured (Bizzi, 1968; Bizzi and Schiller, 1970).

More recently these findings were extended using behaviorally trained animals (Goldberg and Bushnell, 1981; Bruce and Goldberg, 1981; Goldberg and Bruce, 1981). The response of FEF cells with visual receptive fields was enhanced as early as 150 msec before saccadic eye movements made to acquire targets of visual importance (Goldberg and Bushnell, 1981). These cells had visual receptive fields and were excited by spots of light within that field. However, their response was enhanced when a visual test stimulus was used as the target of a saccadic eye movement. The enhancement was spatially selective and was related specifically to saccadic eye movements, not to an increase in attention to a receptive field stimulus or to a stimulus which was the object of a hand movement.

Parietal-Occipital Cortex (Area 7 of Brodman)

Symmetrical bilateral lesions of parietal-occipital cortex in man produce deficits in oculomotor control and visuospatial perception

(Holmes, 1918). The associated oculomotor disorder was characterized by a slowness and instability in the fixation of stationary targets and an inability to break fixation once it was acheived (Hecaen and de Ajuriaguerra, 1954). Disorders of visuospatial perception following parietal lobe lesions included a distorted image of body form and very commonly a profound neglect of and inattention to the contralateral half of the body (Patterson and Zangwill, 1944; Oxbury, Campbell, and Oxbury, 1974). Such deficits in visuospatial tasks occurred more often following lesions of the right than of the left hemisphere (Hecaen, Gastaut, Bancaud and Rebufat-Deschamps, 1964).

Such a lateralization of function has not been demonstrated in monkeys with parietal lobe lesions. Rather such animals showed a symmetrical inattention to the contralateral side of the body and of space (Denny-Brown and Chambers, 1958; Heilman, Pandya, Geschwind, 1970). Deficits in spatial discrimination, and disorders in identification of shape, form and location followed parietal lobe lesions (Bates and Ettlinger, 1960; Ettlinger and Kalsbeck, 1962; Moffett and Ettlinger, 1970; Pohl, 1973). Hand reach tasks and visually guided behavior were also affected by these lesions (Mendoza and Thomas, 1975; Schwartzman, Gran, and Marcos, 1975). Although deficits in visual orientation and attention were noted, eye movements remained essentially intact following parietal lobe lesions. What appeared to be modified was the cortical drive to initiate eye movements which would direct the retina towards objects in contralateral space.

The complexity of the deficits following parietal lobe lesions seem

to be reflected in the variety of neurons which have been recorded here. Most neurons although responsive to visual stimuli could not be divided into simple, complex, or hypercomplex types. Rather, they have a variety of responses which are not specific for shape or form. A large group of neurons, termed "visuomotor neurons," were active before and during steady fixations as well as before eye movements which secured and maintained foveation of objects (Lynch, Mountcastle, Talbot and Yin, 1977; Yin and Mountcastle, 1978). Other neurons were related to visual tracking, hand manipulation and to saccades (Lynch et. al., 1977). A recent reinvestigation of these neurons showed that all of the parietal cortex neurons appeared to have visual recepive fields which could be driven passively by a spot of light (Bushnell, Goldberg and Robinson, 1981). The activity of these cells was enhanced if the animal used the spot of light as the target for a visually guided saccade (Bushnell et. al., 1981). Enhancement of the visual response was noted in other cells if the animal reached to touch the object or if the object was used as a visual cue for some other behavioral response (Bushnell et. al., 1981)

Implications of Neural Responses in Cortical Areas

The responses of parietal lobe cells would appear to provide a neural substrate for guidance of visual behavior in extrapersonal space (Lynch et. al., 1977; Yin et. al., 1978; Bushnell et. al., 1981). Enhancement of firing in FEF neurons prior to saccades appears to be more selective and occurs only before eye movements which will direct

the fovea towards an object of interest (Goldberg and Bushnell, 1981). However, in both cases the relationship of neural activity to visually guided saccades appears to be secondary to carrying out a visuospatial task. Thus both areas of cortex where electrical stimulation elicits saccades to the contralateral side have neurons with saccade related activity. Furthermore, the loss of either area alone does not impair the ability to generate saccades, even in response to visual stimuli. Seen in this context both cortical areas appear to direct movement towards objects in the visual world on the contralateral side of the body. In so doing, they utilize oculomotor pathways as well as other motor pathways to make behaviorally appropriate responses. Two brainstem areas, the superior colliculus and the MRF, which appear to subserve this function for the oculomotor system will be reviewed in the next two sections. The superior colliculus will be considered first since the experiments which have been used to study visually initiated eye movements in the SC were used as basis for developing the experiments in the MRF.

Superior Colliculus: Stimulation Studies

Adamük (1870) first demonstrated that the superior colliculus (SC) was important in the production of contralateral quick eye movements utilizing electrical stimulation. Apter (1946) constructed retinotopic sensory and motor maps for the superior colliculus by stimulation in the lightly anesthetized cat. More recently, by stimulating the superior

colliculus it has been possible to construct a retinotopic map for eliciting eye movements of specific size and direction regardless of the initial position of the eyes in the orbit (Robinson, 1972; Schiller and Stryker, 1972; Stryker and Schiller, 1975; Roucoux and Crommelinck, 1976; Harris, 1980). In the alert monkey, saccades of fixed amplitude and direction were elicited at a latency of 20 ms by electrical stimulation of the deep layers of the colliculus. Stimulation in lateral parts of the colliculus evoked saccades which had downward components and medial stimulation induced movements with upward components. Simultaneous stimulation of two points in the colliculus produced a single saccade whose amplitude and direction were the sum of the vectors of the two movements, dependent upon the relative intensity of stimulation at each site. Pure vertical or ipsilateral movements were never produced by collicular stimulation. Long trains of continuous stimulation produced a staircase pattern of saccades of fixed amplitude and direction. These were not, however, goal directed saccades; i.e., they did not bring the eyes to specific points in the orbit.

Superior Colliculus: Single-Unit Studies

The seven layered colliculus can be divided on both anatomical and physiologic grounds into two parts: superficial visual layers and deeper eye-head movement related layers. In the monkey, cells in the superficial layers have visual receptive fields organized with

on-centers and off-surrounds. Moving and stationary stimuli are equally effective in eliciting a response and firing rates of most cells are not affected by changes in the orientation, size, shape, velocity, or direction of the visual stimulus (Cyander and Berman, 1972; Goldberg and Wurtz, 1972a).

The deep layers of the superior colliculus contain single unit activity which precedes the occurrence of saccadic eye movements in both light and dark environments. These cells can begin firing as early as 300 msec before saccades but they usually have a burst of activity which precedes the saccade by about 20 to 50 msec (Wurtz and Goldberg, 1972a). Mays and Sparks (1980) found that 60% of these cells had visual receptive fields, especially those located in the intermediate layers of the colliculus. There was a background level of activity in cells in the intermediate layer, but this was uncommon in most cells located in the deep layers of the SC. The activity prior to visually-guided eye movements was much greater than that which preceded spontaneous eye movements. In the cat cells located in the caudal portions of the superior colliculus were related to head as well as to eye movements (Harris, 1980). During a coordinated head-eye movement to a visual target these cells responded to a retinal error signal.

In both cat and monkey most cells in the deep layers discharged before eye movements of specific size and direction. The group of eye movements for which the neuron was active defined a movement field for the cell (Goldberg and Wurtz, 1972a; Sparks, 1978; Mays and Sparks, 1980). In other words, these cells firied prior to eye movements which

would direct the fovea to a specific field of gaze. These movement fields were analogous to the visual receptive fields of the superficial cells and were normally in rough correspondence with the visual cells located just dorsal. That is, stimuli which would excite superficial visual cells would also cause the discharge of deep collicular cells directly below if the object was to be used as the target of a saccadic eye movement. One major distinguishing feature, however, was that with the exclusion of cells which had foveal movement fields, most collicular cells had movement fields which were both ipsilateral and contralateral. Movement fields were organized somatotopically: small medial movement fields anteriorly, larger lateral movement fields posteriorly, upward movement fields medially and downward movement fields laterally.

Although the characteristics of collicular activity have been well described, its exact function remains unclear. Most long-lead burst cells were loosely coupled to the metrics of the saccade and discharge did not always indicate that an eye movement was imminent. However, short-lead burst units were tightly coupled to the occurrence of eye movements and usually discharged 20 msec before the occurrence of all eye movements of specific size and direction. No relationship was found between the activity of tightly coupled cells and the metrics (velocity and duration) of the upcoming saccade (Sparks, 1978; Sparks and Mays, 1980). These cells have been postulated to provide a trigger signal for the PPRF indicating the onset of a saccade (Sparks, Mays, and Pollack, 1977; Sparks, 1978; Mays and Sparks, 1980; Sparks and Mays, 1980; Van Gisbergen et. al., 1981). Wurtz states that the cells of the deep

layers of the colliculus probably code a retinal error signal for the acquisition of a visual target (Wurtz, Goldberg, and Robinson, 1980). Both of these conclusions must be considered in light of the collicular anatomical connections as well as the deficits which result from superior colliculus ablation.

Superior Colliculus: Anatomical Connections and Lesion Studies

Anatomically the superior colliculus has connections which would seem to enable it to play an important role in eliciting and controlling visually-guided eye movements. The superficial layers receive input from both the retina and the visual cortex. There are relatively weak, but definite direct retinal afferents to the anteriomedial one-third of the superficial layers in and around where the fovea is represented in the colliculus (Hubel, LeVay, and Wiesel, 1975). These appear to be "patchy aggregates" with input alternating between the two eyes. More posteriormedially in collicular areas which represent more peripheral parts of the visual field the contralateral retinal input is much stronger. Even further posteriomedial there is a temporal "crescent" where only the contralateral eye input is present (Hubel, LeVay, and Wiesel, 1975). Indirect visual afferents come from ipsilateral striate and prestriate cortex layer V. In addition the ipsilateral colliculus receives a major cortical contribution from the frontal eye fields (area 8). The efferents from the superficial layers are to the lateral geniculate nucleus of the thalamus (both LGNv and LGNd), inferior

pulvinar, parabigeminal nucleus and the pretectum. The connections with the parabigeminal nuclei in the cat are reciprocal. The afferents to the pretectum have not been studied. The deep layers of the colliculus have connections with most parts of the neuraxis. Wurtz has summarized these in table form (see Table 1) (Wurtz and Albano, 1980). The major afferents to the deep layers from telencephalic levels are from striate, prestriate, parietal, prefrontal, and frontal cortex. At the mesencephalic level there are reciprocal connections with the cuneiform, subcuneiform, and parabigeminal nuclei. At metencephalic levels there are reciprocal connections with the nucleus reticularis tegmenti pontis. Nucleus pontis caudalis oralis projects to the deep layers and reticularis pontis oralis receives connections from the deep layers of the colliculus.

In view of the close relationship to the oculomotor system, it is surprising that superior colliculus ablation does not cause a gross deficit in visually-guided saccades. In an early study bilateral ablation of the colliculus produced no changes in spontaneous eye movements, OKN, OKAN, or vestibular nystagmus (Pasik, Pasik, and Bender, 1966). Wurtz and co-workers have done an exhaustive series of lesions in both trained and untrained animals (Wurtz and Goldberg, 1972b; Albano and Wurtz, 1978; Albano and Wurtz, 1981). They found that the latency between target movement and a resultant visually-guided saccadic eye movement was increased slightly after collicular lesions, but, the accuracy or duration of the subsequent saccades was not affected. They also noted a decrease in the number of spontaneous saccdes. In a

Table 1: Connections Of The Intermediate and Deep Layers Of The Superior Colliculus.

Afferent Connections

CORTEX
Striate & Prestriate cortex
Auditory, Somesthetic, Motor cortex
Regions of Parietal, Temporal cortex
Prefrontal cortex
Frontal eye fields

DIENCEPHALON
*Zona incerta
*Reticular n.
*Pregeniculate
(Ventral lateral geniculate)

PRETECTUM
*n. Posterior commissure
*Anterior, Posterior pretectal n.
*n. Optic tract

MIDBRAIN
*Cuneiform, Subcuneiform
*Substantia nigra (pars reticularis)
*Parabigeminal, peri-parabigeminal
*Paralemniscal
*n. Brachium inferior colliculus
*External n. inferior colliculus
*Pericentral n.
*n. Sagulum
*Locus coereleus
*Raphe dorsalis
*Lateral parabrachial n.

PONS & MEDULLA
*N. Pontis caudalis, oralis
*Reticularis tegmenti pontis
*Ventral n. lateral lemniscus
*Dorsomedial periolivary n.
*Medial n. trapezoid body (medial)
*Sensory, Spinal trigeminal
*Medial vestibular n.
*Perihypoglassa
*Cuneate, Gracile n.

CEREBELLUM
n* Gigantocellularis
*n.Paragigantocellularis lateralis

CERVICAL SPINAL CORD
Lateral cervical nucleus

Efferent Connections

ASCENDING
SUBTHALAMUS & THALAMUS
Zona incerta
Fields of forel
Reticular, Limitans n.
Reunions n.
Intralaminar n.
Parafascicular, Centromedian)
Mediodorsal n. (rim)
Supragenicuiate
Medial geniculate (magnocellular)
MIDBRAIN
Anterior, Posterior pretectal n.
n. Posterior commissure

DESCENDING IPSILATERAL
(Tectopontine/Tectobulbar)
MIDBRAIN
Parabigeminal, Peri-parabigeminal
Paralemniscal
Subcuneiform, Cuneiform
Inferior colliculus
External capsule
PONS
Reticularis tegmenti pontis
Reticularis pontis oralis
Dorsolateral pontine n.
Facial motor n.

DESCENDING CONTRALATERAL
(Tectospinal/Predorsal Bundle)
PONS
Reticularis tegmenti pontis
Reticularis pontis oralis, caudalis
Abducens, perioculomotor regions
Facial n.
MEDULLA
Submucleus B Medial accessory n.
inferior olive
Raphe
CERVICAL SPINAL CORD

COMMISSURAL PATHWAY

*=Not confirmed in monkey
From Wurtz and Albano, Ann. Rev. Neurosc., 3: 207, 1980.

related series of experiments Albano, Mishkin, Westbrook, and Wurtz (1980) found that collicular ablation caused a detection deficit that included both central and peripheral portions of the contralateral visual field. The deficit quickly recovered during the second post surgical week. This fit with previous data which showed a decrease in distractability during a fixation task as judged by a reduction in the number of saccades made to targets which appeared peripherally (Albano and Wurtz, 1978). These deficits were attributed to the inability of the animals to either select visual targets and/or to an inability to trigger visually-guided saccades. The relative ineffectiveness of SC lesions to cause a deficit in visually-guided saccades suggests that other structures may be involved in producing activity that initiates these movements. A likely possibility is the MRF.

Mesencephalic Reticular Formation (MRF): Lesion and Stimulation Studies

Szentágothai (1943) was the first to demonstrate that the MRF participates in the production of conjugate eye movements. Stimulation of the MRF in cats and dogs produced quick eye movements to the contralateral side. Lesions in the stimulated areas caused deficits in contralateral quick eye movements and abolished the quick phases of vestibular nystgmus. Bender and co-workers extended this work in the monkey (Bender and Shanzer, 1964). Stimulation of the MRF produced contralateral eye movements with occasional oblique components. Large lesions, 2 to 4 mm in diameter, caused impairments in saccades to the

contralateral side and transient changes in contralateral quick phases of vestibular (i.e. caloric) nystagmus. Both OKN and OKAN were permanently affected by MRF lesions.

The effects of MRF lesions were later repeated (Komatsuzaki, Alpert, Harris, and Cohen, 1972). These workers found that MRF lesions produced a profound gaze preference to the ipsilateral side which was distinct from the ipsilateral oculomotor paralysis found after PPRF lesions. The major changes which followed these MRF lesions included: 1) an inability to elicit contralateral OKN immediately after the lesions, 2) a decrease in the frequency of quick phases of contralateral OKN which persisted for over 10 months, 3) an inability to achieve slow phase velocities of OKN exceeding 35 degrees per second, 4) a striking decrease in the time constant of contralateral OKAN, and 5) a preservation of vestibular (i.e. caloric) nystagmus to both sides during the entire post-lesion period (Komatsuzaki et. al., 1972). It is important to emphasize that animals could still move their eyes into the contralateral hemifield in response to non-visual stimuli, e.g. auditory clicks. Thus, these MRF lesions had impaired some aspect of the visual input to the premotor areas located in the PPRF, but they did not affect pathways which mediated the vestibular ocular reflex (VOR).

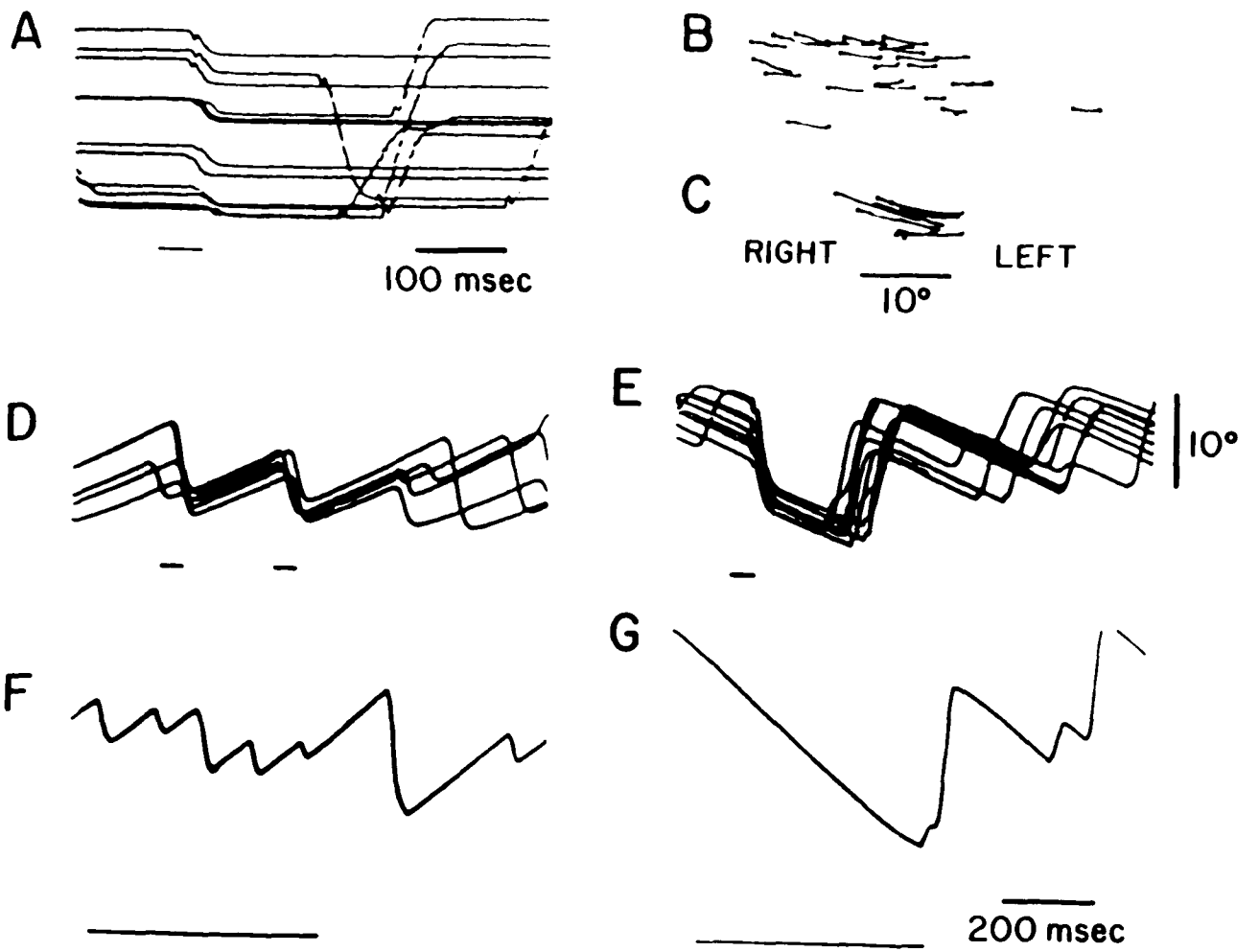
More recently stimulation in the MRF has provided a better insight into the function of the midbrain tegmentum. Cohen, Matsuo, Raphan, Waitzman and Fradin (1982), found that monopolar microstimulation in the dorsal regions of the MRF produced fixed amplitude contralateral saccades with latencies of 20 to 30 msec at stimulation currents of

about 20 to 30 microamp. These saccades could be induced from any position of the eyes in the orbit, and were followed by periods of fixation which lasted approximately 100 to 200 msec. The animal could not execute any saccades during the fixation period (Figure 1A). As the microelectrode was advanced more ventrally stimulation produced variable amplitude saccades that tended to carry the eyes to a portion of the contralateral movement field. These eye movements were characterized by larger saccades when the eye movement began in the ipsilateral hemifield and smaller saccades when the movement began in the contralateral hemifield of movement. Although the movements were predominently horizontal, oblique responses were produced which tended to bring the eyes back to a particular horizontal meridian.

During OKN to the contralateral side stimulation produced saccades which were similar to OKN quick phases (Fig. 1D). During ipsilateral OKN, stimulation produced forward saccades (Fig. 1E). In both cases the quick phases were followed by periods of slow phase of 100 to 200 msec in duration (Fig. 1D and E) during which quick phase generation was inhibited. Continuous MRF stimulation at frequencies too low to induce saccades, enhanced the generation of quick phases during contralateral OKN and caused a suppression of quick phases during ipsilateral OKN (Fig. 1F and G). This suggests that the effect of MRF lesions on slow phase velocity (Komatsuzaki et al., 1972) might have been secondary to the elimination of a visual trigger mechanism for quick phase production and not to a direct effect on slow phase eye movement generation.

The MRF has also been implicated in controlling eye movement

Fig. 1: Effects of stimulation of the right MRF in an alert monkey. The head was restrained. 0.5 msec pulses of 12-20uA were delivered through a microelectrode. A, D-G show traces of horizontal eye movement. Right is up. B & C are X-Y reconstructions of eye position on a storage oscilloscope. A. Stimulation from any point in the field induced a 2.5 degree saccade to the left. It was followed by a period of fixation of 150-200 msec before the eyes moved away. B & C. The Z axis of the scope was brightened just during the induced movement. Note the constant amplitude saccades in B and the variable amplitude saccades in C. Trains of pulses during OKN induced either quick phases (D) or forward saccades (E) on the slow phases. There was no interaction of the saccades and the slow phases other than each saccade was followed by 150-200 msec when a quick phase did not occur. F, G. Continuous MRF stimulation at frequencies too low to induce saccades induced enhancement of quick phase generation (F) or suppression (G) depending on the direction of the slow phases. The EOG cal shown beside E is the same for all traces.


A
100 msec
B
C
RIGHT
LEFT
10°
D
E
10°
F
G
200 msec

information which ascends in the reticular formation to reach thalamic and cortical levels, and in "gating" visual information coming from the retina enroute to occipital cortex. Pontine-geniculo-occipital (PGO) waves were originally described in the sleeping cat (Jouvet and Michel, 1959; Jouvet, Michel and Courjon, 1959). These were monophasic negative potentials which were associated with the occurrence of paradoxial or rapid eye movement (REM) sleep. It was later shown that these potentials were not associated specifically with the sleeping state, but were found in the alert preparation as well (Calvet, Calvet, and Langlois, 1965; Brooks, 1967; Brooks, 1968a; Brooks, 1968b; Cohen and Feldman, 1968; Feldman and Cohen, 1968). Stimulation in the reticular formation of the pons and mesencephalon produced monophasic negative potentials in the lateral geniculate nucleus (LGN) and occipital cortex (Brooks and Bizzi, 1963; Brooks, 1967; Cohen and Feldman, 1968; Feldman and Cohen, 1968) suggesting that activity for these PGO waves is carried through the MRF (Cohen and Feldman, 1968).

In a recent series of papers Singer proposed that the MRF stimulation produces both local and global disinhibition in the LGN and thus enhances cortical evoked potentials after optic chiasm stimulation (Singer and Bedworth, 1972, 1974; Singer, 1977). Such disinhibition would explain the early discovered phenomenon that MRF stimulation during behavorial states associated with high-voltage synchronized EEG, e.g., slow wave sleep and drowsiness, increased LGN transmission (For review see Cohen, Feldman, and Diamond, 1969 and Singer, 1977). One conclusion of these studies is that the MRF is important in directing

attention and in producing arousal. This will be considered further in light of the present studies.

Mesencephalic Reticular Formation (MRF): Anatomical Connections

A dual role has been postulated for the MRF on the basis of stimulation and lesion experiments. It has been implicated in producing descending activity to the pons related to quick phases and saccades, and in the generation of ascending activity to the thalamus and visual system indicating that an eye movement has occurred. These roles appear to be reflected in the types of neurons located in the midbrain tegmentum as well as the connections that they make. Ramón y Cajal (1911) showed that many of the reticular neurons were fusiform in shape and had axons that bifurcated sending one process caudally and a second rostrally. These roles of the MRF in controlling both ascending and descending information in the reticular core also appear to be reflected in the extent and distribution of the efferent and afferent connections which are made with other neural structures.

Efferents: Descending

Edwards has recently explored the efferent pathways of the MRF in the cat using injections of radioactive leucine (Edwards, 1975; Edwards and deOlmos, 1976). The injections into nucleus cuneiformis and subcuneiformis labelled only the cells within the injection site and not

fibers in passage. He divided descending fibers into ipsi- and contralateral components. The contralateral projection sweeps through nucleus linearis intermedius giving off many collaterals. Some fibers pass into the contralateral tegmentum, but most make a sharp caudal turn entering the brachium conjunctivum and descend to caudal levels in a ventromedial position. This fiber system has been called the "ventral tegmental bundle" (Edwards, 1975). During its course the bundle decreases in size giving off collaterals perpendicular to the direction of descent as it passes through the reticular formation. A major area of projection is to nucleus reticularis tegmenti pontis with additional label found in nucleus reticularis gigantocellularis and raphe magnus. Pause cells are known to be found in the region of the raphe nucleus. Some final terminations were observed in the dorsal cap of Kooey, but it was not apparent whether this was axonal or terminal. At the level of the superior olive numerous axons peeled off to pierce the abducens nucleus fibers and approach the facial nucleus ending in its dorsomedial and ventramedial portions (auricular and cervical portions in cat). Apparent in the drawings of transported label is a large termination of fibers in the periabducens region and PPRF (Fig. 3D, and E of Edwards, 1975).

Ipsilaterally descending fibers are more loosely organized. A large number of axons which remain dorsolateral as they course caudally, end in locus coeruleus and nucleus reticularis pontis oralis. Other fibers located more ventrally terminate in nucleus reticularis tegmentis pontis. There is also termination of fibers in the pons and especially

in the PPRF and periabducens region. Castiglioni et. al. (1978), using retrograde transport of HRP, have shown that there is a major contribution from nucleus cuneiformis in the rhesus monkey to the ipsilateral cervical spinal cord (C1 to C3).

Connections of the nucleus cuneiformis with structures within the midbrain are extensive and reciprocal. Fibers from the MRF terminate extensively within both the deep and superficial layers of ipsilateral superior colliculus. Additional fibers cross in the commissure of the superior colliculus to terminate solely in the contralateral stratum profundum. On both sides the collicular terminations appear to be axosomatic contacts. Both the parabigeminal and the Edinger-Westphal nuclei receive input from the nucleus cuneiformis as well (Edwards, 1977; Edwards et. al., 1979).

Efferents: Ascending

The majority of ascending efferent projections from nucleus cuneiformis in the cat are ipsilateral and form a diffuse radiation in the tegmentum. Medially the fibers form a more distinct bundle within the central gray. Ascending fibers terminate within the nucleus of the posterior commissure and the medial pretectal nucleus.
Fibers also innervate the nuclei of the posterior commissure on the contralateral side, the mediodorsal nucleus of the thalamus (MD), and the intralaminar nuclei. Specifically the parafascicularis and the central dorsal receive the heaviest amount of label (Edwards, 1975;

Edwards et. al., 1976). MD and intralaminar nuclei are also known to receive projections from the frontal cortex in the region of the frontal eye fields (DeVito and Smith, 1964; Kuypers and Lawrence, 1967; DeVito, 1969; Astruc, 1971; Orem and Schlag, 1971; Orem and Schlag, 1973; Kunzle and Akert, 1977; Kunzle, 1978; Hartman-vonMonakow, Akert and Kunzle, 1979). These structures do not project directly to the SC (Edwards, Ginsburgh, Henkel and Stein, 1979).

There is also a ventrally located "diffuse" radiation from the nucleus cuneiformis that passes through the fields of Forel and spreads into the zona incerta to terminate within the posterior and lateral hypothalamus. A portion of these ventral fibers separate and course within the zona incerta just ventral to the ventral basal complex and posterior nuclear group of the thalamus to terminate within both the stalk and the cap of LGNv which has been shown to project to SC (Edwards et al., 1979).

Afferents:

Whereas the efferent connections of the MRF have been delineated to some extent using the newest tracer techniques in the cat, the afferent connections have not been systematically studied. Ascending information may arise from the pontine tegmentum. Using the Golgi technique it has been shown that reticular neurons in the pons have bifurcating axons, one of which descends caudally and another which ascends and spreads collaterals throughout the midbrain tegmentum (Ramón y Cajal, 1911;

Scheibel and Scheibel, 1958). This pathway has been confirmed more recently using radioactive amino acid tracer techniques. Following injections of amino acids into the periabducens region and specifically in the PPRF, terminal fiber grains were found in the midbrain tegmentum primarily ipsilaterally, located just ventral and medial to the parabigeminal nucleus (Graybiel, 1977). It has been recently demonstrated that axons from Type II prepositus hypoglossi neurons can be antidromically activated by MRF stimulation (Hikosaka and Igusa, 1980).

At mesencephalic levels the major afferent pathway to the MRF arises from the deep layer of the superior colliculus thus completing reciprocal connections of the MRF with that structure (Benevento and Fallon, 1975; Harting, 1977; Cohen, Buettner-Ennever, Waitzman and Bender, 1981). Little is known of the descending projections to the MRF from diencephalic levels. Neurons in the intralaminar nuclei have been shown to have bifurcating axons which go both rostrally and caudally extending to the midbrain tegmentum (Scheibel and Scheibel, 1967). Axons from neurons in the reticular nucleus are known to project caudally but their termination site has not been precisely determined. There are no known connections from either the LGNd or LGNv to midbrain tegmentum.

The frontal and parietal cortex are the two main cortical areas which supply afferents to the MRF (Kuypers and Lawrence, 1967; Astruc, 1971; Künzle and Akert, 1977; Künzle, 1978). The frontal lobe supplies the more ventromedial parts and the parietal the dorsolateral portion.

The majority of projections from the frontal cortex to the midbrain tegmentum arise from Brodman area 6 especially the rostral and medial portions. The termination field of these axons are within the ventral medial portion of the MRF (Pearce, 1960; Künzle, 1978). The number of fibers arising from the "frontal eye fields," Brodman area 8, of the frontal cortex are modest and the number varies according to the technique used to demonstrate them, i.e. degeneration techniques show more than the amino acid tracer techniques (Astruc, 1971; Künzle and Akert, 1977; Künzle, 1978; Hartman-von Monakow et. al., 1979). Other major subcortical projections of the frontal eye fields are to the superior colliculus, medialis dorsalis of the thalamus and the intralaminar nuclei (Künzle and Akert, 1977; Künzle, 1978).

SUMMARY OF LITERATURE REIVEW AND IMPLICATIONS

The generation and control of visually induced eye movements in both cortical and subcortical areas of the brain have been reviewed. The precise mechanism for the generation of these rapid eye movements is still unclear. A clue to the function of these various areas has been provided by recent ablation studies. Collicular lesions must be paired with either striate cortex lesions (Schiller, Stryker, Cyander, and Berman, 1974; Mohler and Wurtz, 1977; Schiller, 1977) or with frontal eye field (FEF) lesions to produce a permanent deficit in visually evoked eye movements (Schiller, True and Conway, 1979, 1980). This suggests that these areas may form independent parallel pathways for the

control of visually induced saccadic eye movements and must have access to the premotor areas located in the PPRF, prepositus and periabducens regions.

Lesion and stimulation studies suggest that the MRF may be part of the parallel pathway carrying information from the cortex to premotor areas in the pons. Anatomic connections of this region are also appropriate for its playing an important role in the production of rapid eye movements. As yet, however, it is not known whether unit activity in the MRF is appropriate for participating in the generation of rapid eye movements. Investigation of this question was the goal of this study.

CHAPTER 2

METHODS:

I. Subjects:

The subjects for this study were 2 female rhesus monkeys (Macaca mulatta) ranging in weight from 2.5 to 3.8 kg. The first animal, Monkey #997, was trained and had 35 tracks on the right side and 22 on the left MRF. The second animal, Monkey #996, was also trained. It had 49 tracks in the right MRF and 3 tracks in the left MRF. This work is based on recordings made from 53 neurons related to contralateral eye movements.

II. Surgical Preparation:

Animals were surgically prepared for single unit recording under Nembutal anesthesia. The animal was placed into a stereotaxic frame (Kopf) and bone was removed over the MRF (Snider and Lee, 1961). A chamber for microelectrode recording (Trent Wells) was tilted laterally 15 deg off the stereotaxic vertical so that it was centered over A3.0, 2 mm lateral and 13 mm above the interaural line. It was secured with dental acrylic cement. In two animals a second chamber was implanted over the contralateral MRF. EOG silver-silver chloride electrodes for

recording horizontal and vertical EOG were placed in the bone at the lateral canthi of the eyes and above and below each eye (Bond and Ho, 1970). Three bolts were secured in dental acrylic for restraining the animal's head. Post-operatively animals were given antibiotics and analgesics to alleviate pain.

III. Behavioral Paradigm:

Animals were trained in a visual fixation/saccade task as described by Wurtz (1969). A schematic representation of the experimental training set-up is shown in Figure 2. At first the animal was trained to fixate a spot of light when it pressed a bar to receive a liquid reward. Animals were deprived of water for 24-36 hours prior to training sessions and hydrated with oranges during periods when not training. A 90% confidence limit was established as the level for "learning" the task (number of successes/number of trials). The EOG was also used for monitoring the animal's progression in training. Figure 3A is an illustration of an untrained animal just learning the task. Periods of fixation occurred rarely. Fig. 3B illustrates an animal who had acquired the task to the 90% level. The EOG was flat during the periods when the target was on. Once the animal's behavior was shaped it was transferred to a more challenging task.

The "sophisticated" task required the animal to press a bar and fixate a spot of light which appeared on a T.V. screen. The spot was

Fig. 2: Training and recording set-up. Animal sits on vestibular turntable under an optokinetic drum which can be lowered to provide full field visual stimulation. Animal sits facing T.V. monitor upon which spots of light are presented which are controlled by PDP8/E minicomputer. Water is supplied via a spigot and is controlled via a solenoid. Animal has one forelimb free to press on a bar. EOG and unit signals are sent to a Honeywell 7600 for recording on analog tape. Neural and EOG amplifiers can rotate with animal allowing vestibular and OKN testing while observing neurons.

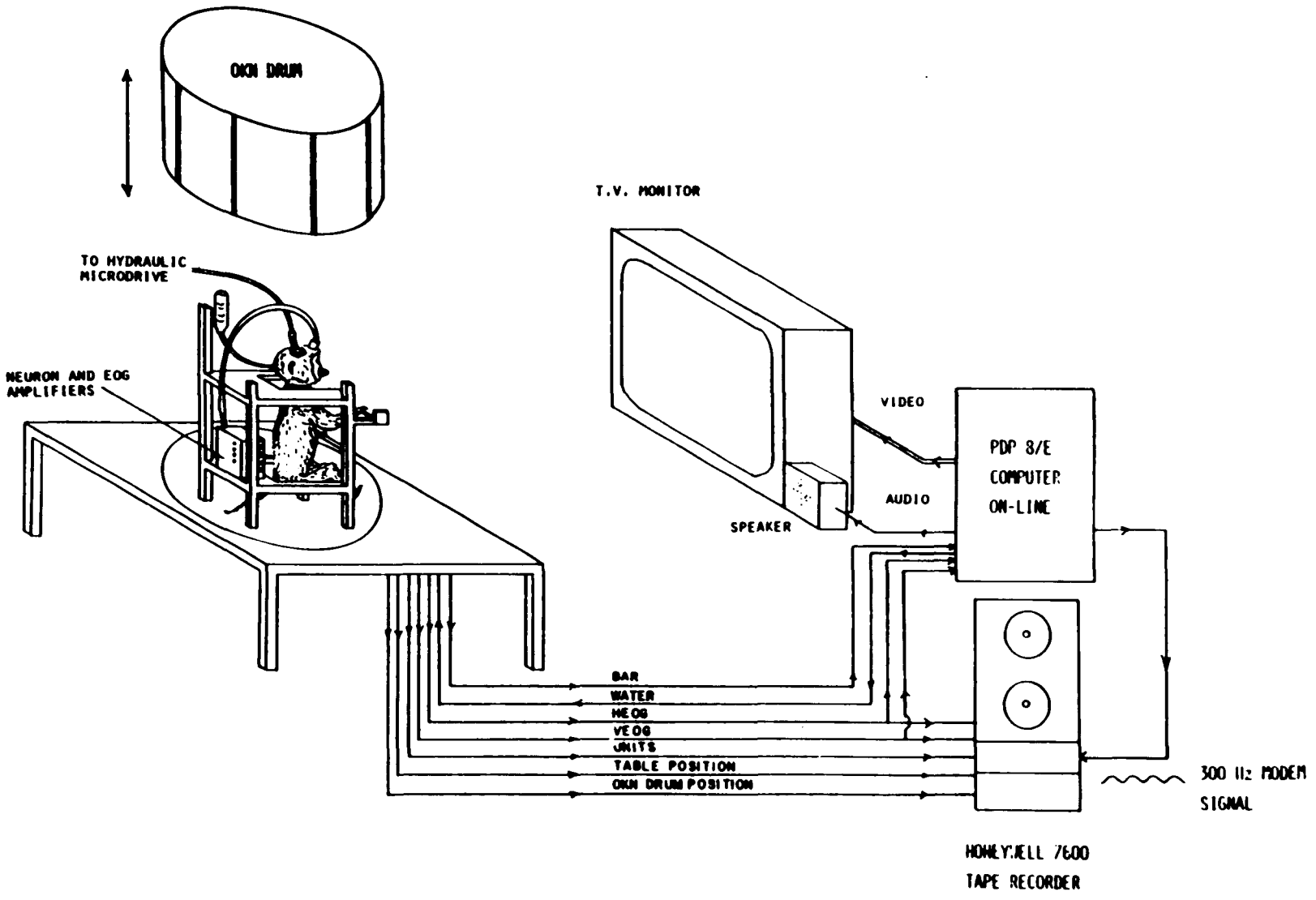
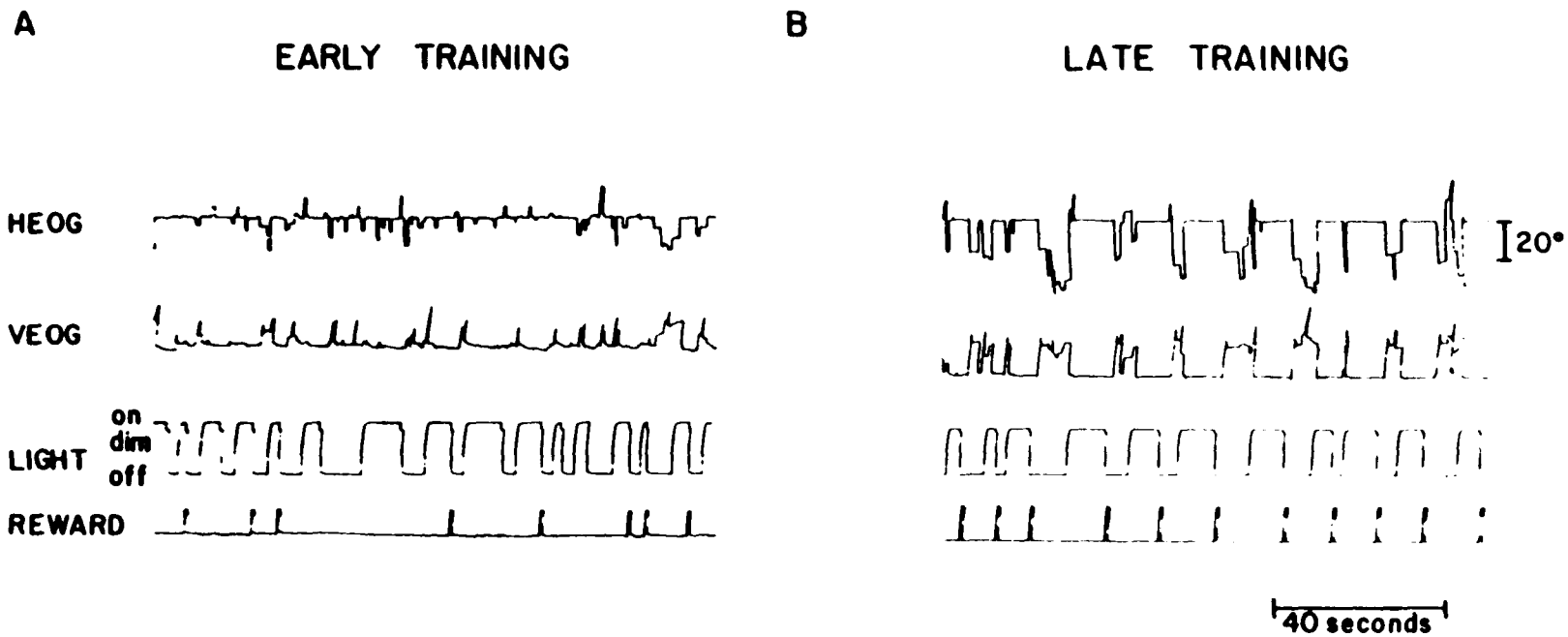

OKN DRUM
T.V. MONITOR
TO HYDRAULIC MICRODRIVE
NEURON AND EOG AMPLIFIERS
VIDEO
AUDIO
SPEAKER
PDP 8/E COMPUTER ON-LINE
BAR
WATER
HEOG
VEOG
UNITS
TABLE POSITION
OKN DRUM POSITION
300 Hz MODEM SIGNAL
HONEYWELL 7600 TAPE RECORDER

Fig. 3: Comparison of eye movements early and late in training. The traces from top to bottom, horizontal and vertical EOG, light on/off dim, and reward. In part A, early training, note a few periods of fixation during the time the light is on (trace up). In part B, late training, each time the light is on there is an associated period of fixation. All periods of fixation are rewarded. Calibration of 20 degrees is for both horizontal and vertical EOG.


A
EARLY TRAINING
HEOG
VEOG
LIGHT
on
dim
off
REWARD
B
LATE TRAINING
20°
40 seconds

under computer conrol and after a variable period of time (0.5 sec to 6 sec) the spot could jump to a new location in either the vertical, oblique, or horizontal directions. The animal now had to refixate the spot of light and wait until the spot dimmed before it released the bar. The animal had 500 msec after the light dimmed to release the bar, otherwise it received no reward. In 25% of the trials the light made a second jump to return to the original position on the screen. This type of trial was necessary to insure that the animals would fixate the spot at the preliminary position. (Otherwise they could choose to fixate the spot only after it had jumped). If the bar was released prior to the dimming of the target, animals were not punished, but rather a "dead zone" interval (.75-7.3 secs) was initiated during which bar presses did not cause the spot to reappear. The animals were rewarded for each trial with a drop of water whose size could be changed and with a 1000 Hz tone. The latter was useful in allowing the experimenters to monitor the progress of the experiment without watching the screen. On a number of occassions the tone was turned off to insure that there was no relationship of unit activity to it. Three specific types of eye movements were generated during these experiments.

The first is a saccade made to foveate the target after it had unpredictably changed position. This eye movement is called a visually-guided saccade (Wurtz, 1969).

Distinct from paradigms used by others, the trial in this set of experiments was not aborted if the animal broke fixation to look away from the target. Normally the animal would execute a second saccade

back onto target from 60 to 400 msec after the initial break in fixation. This sequence of movements is termed an off- and on-target saccade respectively. Occasionally the visual cue moved before the animal had had an opportunity to look back at the target. In this instance the amplitude and direction of the return (on-target) saccade were exactly that needed to direct the eye to the former location of the target. It then made a visually-guided saccade to the new target location.

IV. Experimental Conditions:

a. Single-unit recording set-up:

The trained animal sat on vestibular platform facing a 23" T.V. screen (Fig. 2). A bar was fixed for easy access by the right forelimb. The remaining 3 extremities were loosely restrained. A solenoid controlled liquid delivery system (BRS/LVE) was mounted on the chair and a tube with a small spigot was positioned near the animal's mouth. The nylon plug in the recording chamber was removed under sterile conditions, and an X-Y micropositioner (Trent-Wells) was inserted. After the appropriate coordinates for reaching the MRF had been selected a cannula (67 to 71 mm) and microelectrode attached to a hydraulic microdrive assembly (Trent-Wells) were then placed into the brain and fixed to the micropositioner. The vestibular turntable was situated underneath an optokinetic drum which could be lowered over the animal to

provide full field visual stimulation (Fig. 2). Horizontal and vertical EOG's were amplified and displayed on oscilloscopes showing both X-Y position of the eyes as well as eye position vs. time. Unit activity was amplified by a single-ended high input impedance amplifier (gain X1000) and displayed as either spike activity in time or as instantaneous frequency on a storage oscilloscope. Optokinetic drum and turntable velocities could be controlled independently. All signals plus the time code were fed to a Honeywell 7600 tape recorder and stored on 1" FM magnetic tape for off-line analysis. When the bar was pressed, a spot of light (5 minutes of arc) controlled by an on-line PDP8/E laboratory computer (Digital Equipment Corporation) appeared on the screen. The spot size could be changed to a larger size (30 minutes of arc) in order to relax the attention criteria for detecting the dimming of the fixation spot. The computer supplied a modem (300 Hz) signal which was recorded on analog tape. When there were changes in target position, bar pressing, target jumping, or other parameters of the task the computer put out a character to designate this event on the modem line, thus allowing the entire experiment to be recreated afterwards, off-line. The computer also supplied a DC voltage output indicating onset, dimming and offset of the light. This enabled the experimenter to display and trigger a storage oscilloscope during any trial of interest. When a unit was acquired the analog tape recorder was started and the unit activity and EOG's as well as the modem signal were stored for later off-line analysis. The visual responsiveness of the cells was tested using a hand held projector. While the animal was fixating the

target the light would be moved over each of the four quadrants of the field of vision. Cells were not formally tested for the extent of visual fields using test stimuli of specific size, shape or color. Tests were made for association of unit firing with ocular pursuit using a piece of apple or banana, with convergence, and with OKN, and optokinetic after-nystagmus (OKAN). Firing was tested in light and dark. Vestibular stimulation was induced using either pendular rotation or steps in the velocity of the platform. Trained animals became visibly angry if they were unable to bar press and work for water. Thus OKN and vestibular testing were usually reserved for units obtained at the end of a recording session.

b. Stimulation Set-Up:

During stimulation/recording experiments, unit recordings were done first. The tungsten microelectrode was left in place and connections switched to a WPI Stimulator. Ten to 13 pulses of 0.5 msec duration at a frequency of 333 Hz were passed every 0.25 mm along the track. Currents were constant and ranged from 20 to 40 uA. The depth of the microelectrode and the results of stimulation were noted.

c. Offline analysis

For off-line analysis the data recorded during the experiment was used to create a paper record. Horizontal and vertical eye position,

target position, reward, and frequency of firing were written out on a Beckman type R Dynograph (Fig. 4). The target position and reward were recreated by computer interpretation of the modem signal. The frequency of firing was "smoothed" using a hyperbolic approximation method implemented on the computer. The paper record was then used to decide which portions of the record should be digitized for further analysis.

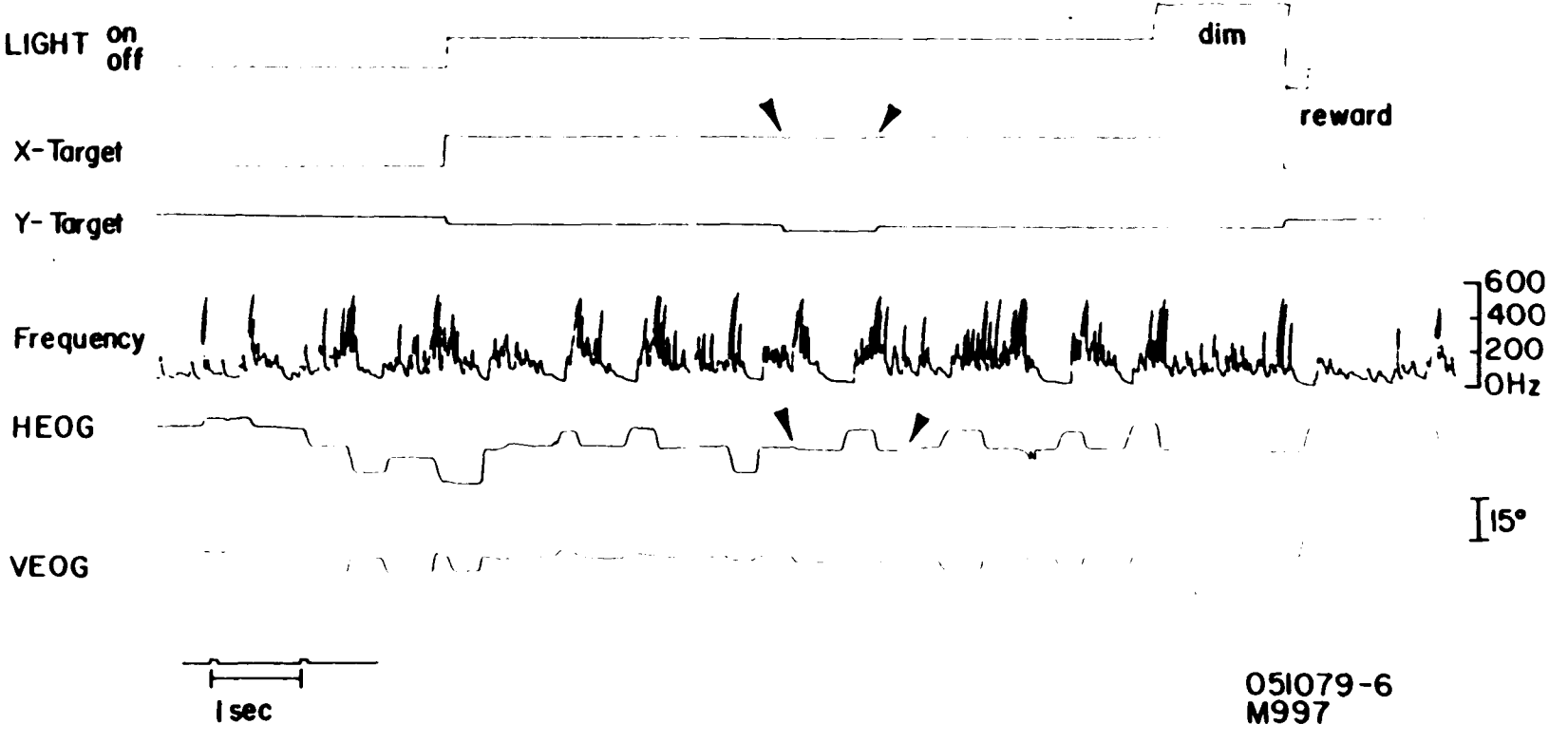
A data program was used for digitizing analog data at a sampling rate of 1.6 msec. Unit activity was digitized by feeding it to a window/pulse height discriminator which put out an acceptance pulse to the computer when a spike met specific criteria in time and amplitude (Bak and Schmidt, 1977). Simultaneously horizontal and vertical EOGs were sampled using a 10 bit Analog to Digital converter. Modem activity was monitored for any changes in the paradigm during the current sampling interval. Segments of data 3.1 minutes long could be digitized at one time. The resultant digital tapes were transferred to a high speed disk for further analysis in the computer.

V. Recording Methods:

a. EOG and calibration

The electro-oculograpm (EOG) was used to monitor the position of the eyes in the orbit. The horizontal EOG was derived bitemporally by recording the potential difference between the two lateral canthi electrodes. To obtain vertical eye position the two supraorbital

Fig. 4: Offline analysis of unit activity. Traces are from top to bottom: Light on/off/dim/reward, X target position, Y target position, frequency, horizontal and vertical EOG. The figure demonstrates activity from unit 051079-6 which fired with all contralateral (left) saccades. Firing was much higher prior to targeted saccades or visually guided sacccdes. Note that latency and peak firing were similar for these two types of saccades. Visually guided saccades to the left and to the right are indicated by arrows.


LIGHT on off
dim
reward
X-Target
Y-Target
Frequency
600
400
200
0Hz
HEOG
15°
VEOG
1 sec
051079-6
M997

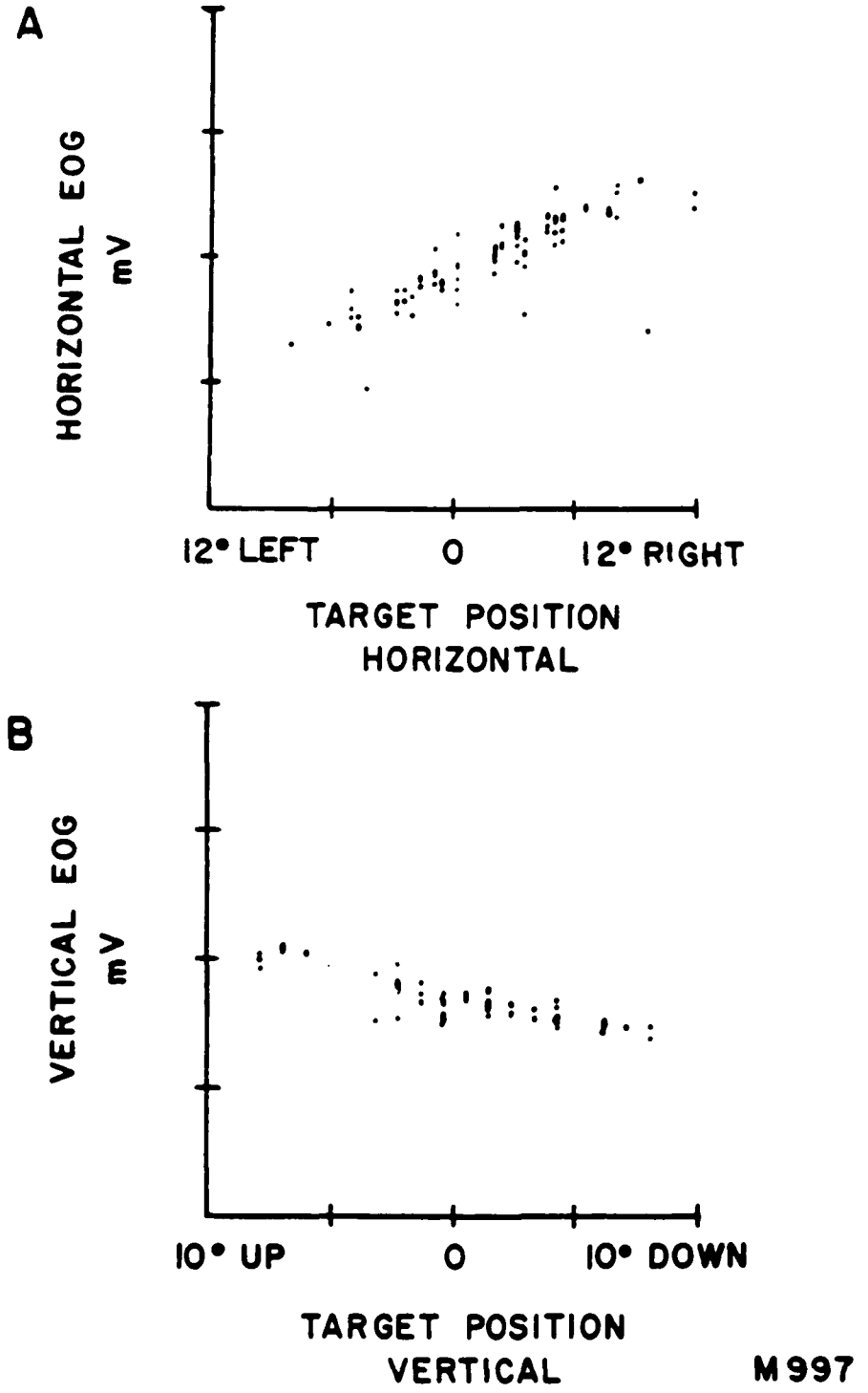
electrodes and the two infraorbital electrodes were tied together. The vertical signal was the potential difference between these two pairs of electrodes. By convention upward pen deflection indicates rightward and upward eye movements.

The trained animal fixated spots of light of known separation on the T.V. screen. The difference in the EOG record at each position of fixation provided a voltage change proportional to the angle (in degrees) the eye had moved in the orbit. The specific relationship between degrees of eye movement and EOG voltage change was calculated by the computer for each segment of recorded data. A typical example is shown in Fig. 5. The linearity of the EOG over $\pm$12 degrees is confirmed by this graph. The slope of the line of best fit through these data points provided the conversion factor from the A to D converter voltage to degrees of eye movement. The calibration allowed an estimate of eye position to within $\pm$1 degree of the true position.

b. Single-unit recording:

Chronic single-unit extracellular recordings were made using tungsten metal microelectrodes of 13-20 Megohms impedance (F. Haer). Electrodes were introduced into the brain through a stainless steel cannula 67 to 71 mm in length (21 gauge O.D.). The microelectrodes were advanced into the brain using a hydraulic microdrive (Trent-Wells) calibrated in microns. Criteria established by previous investigators were followed for separating recordings of neurons or neural processes

Fig. 5: EOG calibration, Monkey #997. Abscissa is target position in degrees, and ordinate is eye position in millivolts. Zero millivolts is at the midpoint of the ordinate. For each segment of data which was digitized the EOG was calibrated. Positions of fixation were found by the computer. Eye position was then plotted vs. target position during the time of fixation by a FOCAL program. A, plot for the horizontal and B, for the vertical EOG. The slope of a line of best fit was then used to calculate amplitude in degrees for the quantitative analysis.


A
HORIZONTAL EOG
mV
12° LEFT
0
12° RIGHT
TARGET POSITION
HORIZONTAL
B
VERTICAL EOG
mV
10° UP
0
10° DOWN
TARGET POSITION
VERTICAL
M997

from axons (Fatt, 1957; Bishop, Burke and Davis, 1962). First, the activity of a "supposed" single cell could be monitored over several hundred microns. Second, the cell discharged with a negative potential and if the electrode was close to the soma, this potential was made up of two parts separated by an inflection, the "A-B" break. The first component of the negative potential recorded extracellularly is derived from the cell body while the second component is the result of dendritic discharge (Fatt, 1957). Axons, on the other hand, normally discharge with a large positive potential sometimes followed by a smaller negative change. The initial positive potential is characterized by a smooth unbroken transition to maximum amplitude. Criteria to distinguish one cell from several utilized the measurement of the refractory period. A storage oscilloscope (Tektronix 564) was set to trigger on the rising edge of the negative potential. Many sweeps were superimposed and the time between the spike that triggered the scope and the next spike was measured. Single cell discharges should be separated by at least .8 msec.

VI. Analysis of Data:

a. Data Format

Data was digitized from analog magnetic tapes and stored on digital magnetic tape. The essential tasks of the data program are shown in

flowchart format in Fig. 6. The program acquired data in real-time. The format used for the analysis utilized four words of tape storage for each 1.6 msec sampling interval. The four words in the recorded order are 10 bits of horizontal and vertical EOG information, 11 bits of timing information and 8 bits of modem information. The computer clock placed the occurrence of the unit firing to within 100 microsec in the previous 1.6 msec interval. Thus, distance along the tape had a direct relationship to time into the record.

b. Further Processing After Data Acquisition

Once the 3.1 minutes segment of data was digitized, the tapes were then transferred to the disk where faster processing of the eye movements took place. The eye movements were detected and "marked" automatically to a 95% accuracy using a second program called FIND. A flowchart indicating the basic tasks of the FIND program is shown in Fig. 7. Once the eye movements were marked some corrections were normally needed. Such changes were accomplished using a variety of display/modify programs which allowed the data to be displayed on a T.V. monitor or to be written out on a pen writer. This allowed decisions to be made concerning the period of interest for examining spike activity. It could answer such questions as: what would be an appropriate interval for counting the number of spikes in relationship to the eye movements?

Once these various housekeeping tasks were accomplished this large segment of data was compressed to manageable system files. The GRIND

Fig. 6: DATA Program Flowchart. This assembly language program samples eye position every 1.6 msec. During this period the occurrence of spike is indicated by a Schmitt trigger which interrupts the program long enough to record the time in the interval when the spike occurred. Modem activity can also cause a program interrupt and the character is placed in the current 4 word block. The program was capable of digitizing spike frequencies to a maximum of 650 Hz. For neurons with higher spike frequencies the analog tape was played back at half-speed. Left side of chart shows inputs from analog tape. Output is 3.1 minutes of digital DECtape.

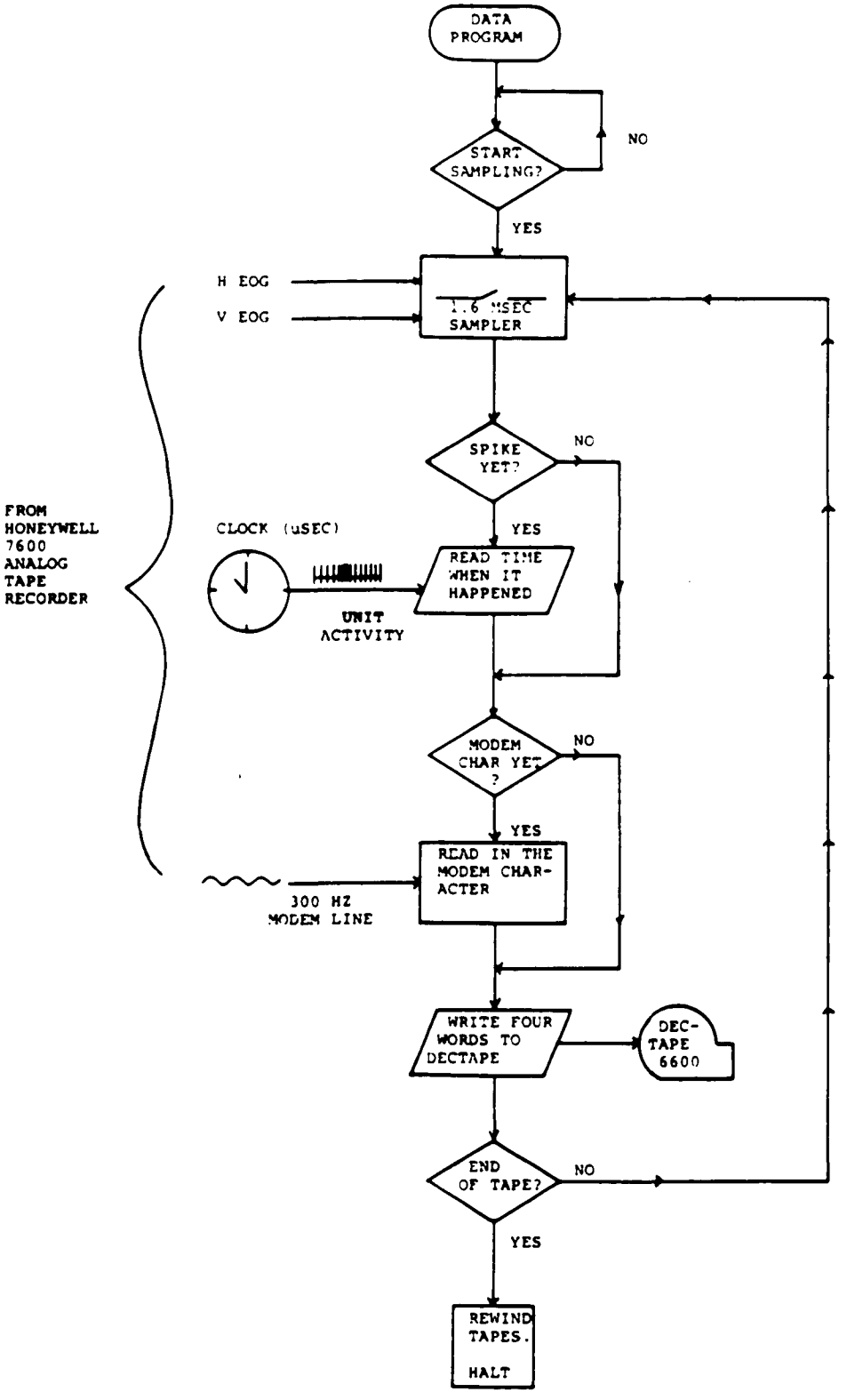
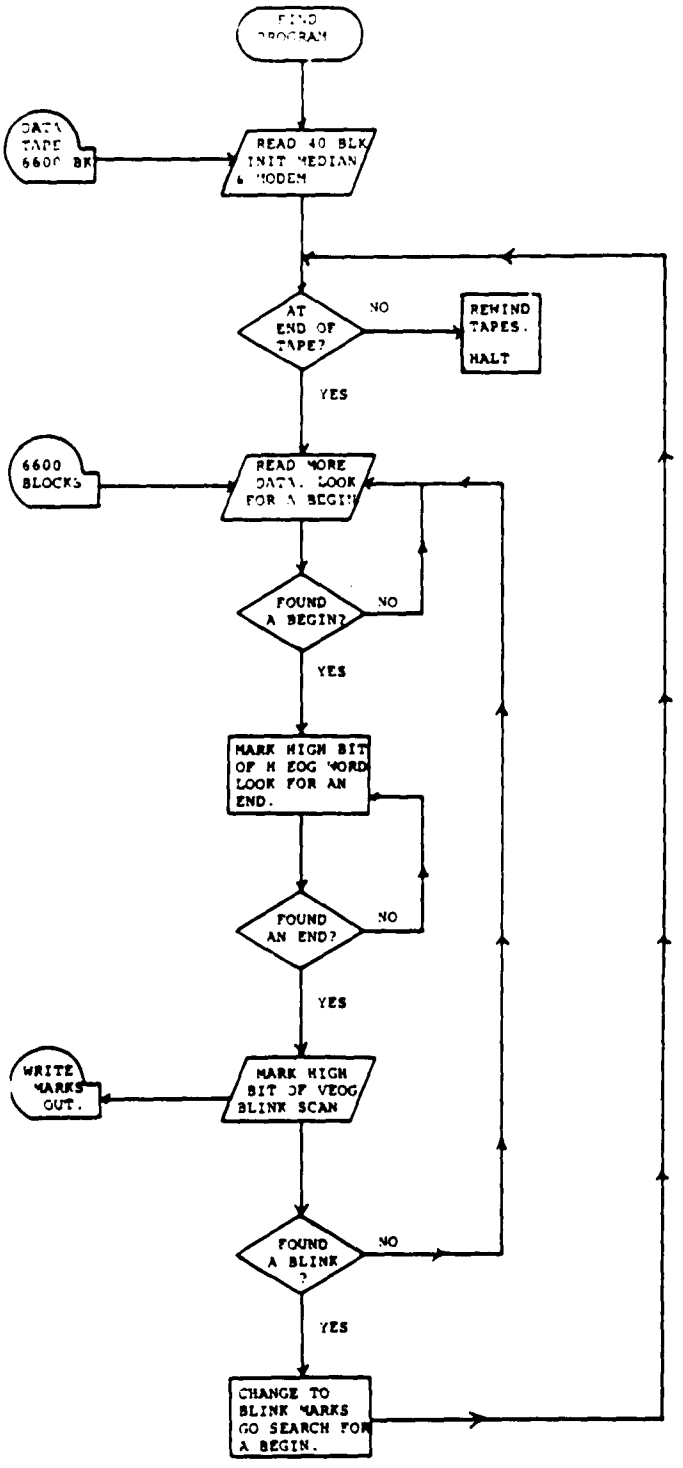

DATA PROGRAM
START SAMPLING?
NO
YES
H EOG
V EOG
1.6 MSEC SAMPLER
SPIKE YET?
NO
YES
FROM HONEYWELL 7600 ANALOG TAPE RECORDER
CLOCK (uSEC)
READ TIME WHEN IT HAPPENED
UNIT ACTIVITY
MODEM CHAR YET ?
NO
YES
READ IN THE MODEM CHARACTER
300 HZ MODEM LINE
WRITE FOUR WORDS TO DECTAPE
DEC-TAPE 6600
END OF TAPE?
NO
YES
REWIND TAPES.
HALT

Fig. 7: FIND Program Flowchart. The FIND program locates eye movements using a median technique. Using DECtape the H and V EOG are examined for changes from fixation. Specific parameters in the program set the sensitivity for eye movement search. When a beginning of eye movement is found, it is "marked" by turning on the high order bit of the H EOG word. The program then searches for an end. This is marked in the high order bit of the V EOG word. Spike occurrences have already been indicated by turning on the high order bit of the spike time word. Blinks are also recognized by the program and are marked by turning on the next to high order bit of the H EOG word.


END PROGRAM
DATA TAPE 6600 BK
READ 40 BLK INIT MEDIAN & MODEM
AT END OF TAPE?
NO
REWIND TAPES. HALT
YES
6600 BLOCKS
READ MORE DATA. LOOK FOR A BEGIN
FOUND A BEGIN?
NO
YES
MARK HIGH BIT OF H EOG WORD LOOK FOR AN END.
FOUND AN END?
NO
YES
WRITE MARKS OUT.
MARK HIGH BIT OF VEOG BLINK SCAN
FOUND A BLINK ?
NO
YES
CHANGE TO BLINK MARKS GO SEARCH FOR A BEGIN.

program was used to extract the relevant spike to eye movement relationships as well as the various eye movement parameters. This process destroyed the one-to-one correspondence between distance along the tape and time. Rather, all time relationships were oriented towards the eye movement. A flowchart indicating the various tasks of the GRIND program is shown in Fig. 8. The compression of the data into these "grind" files allowed a higher level language (FOCAL) to manipulate the data. A typical GRIND file is shown in Fig. 9. GRIND files can be stored for many 3.1 minute segments of data so that more than one segment can be utilized for analysis. Many FOCAL programs have been written to correlate the data and to graph various possible relationships. One sample program is shown in Fig. 10 which plotted the rasters and histograms in the following figures. FOCAL programs were used to bin the activity preceding eye movements of a particular size or other characteristics. This allowed the construction of histograms of spike activity and allowed the measurement of latency between spike activity and eye movements.

Fig. 8: GRIND Program Flowchart. This program condenses marked eye movement data into a file of numbers which can be read by a higher order language like FOCAL. The program is designed to calculate an absolute time scale for all events including spikes, eye movements and task parameters (modem). The eye movement oriented GRIND program which is charted here finds the beginning and end of an eye movement, calculates the duration of the saccade, whether the eye movement is a blink, and the specific characteristics of the neural burst. The results of these calculations are stored in decimal on a disk file which is compatible with the monitor (the operating system) and other higher level languages like FOCAL. This disk file can then be accessed by FOCAL to calculate various relationships between neural firing and saccades.

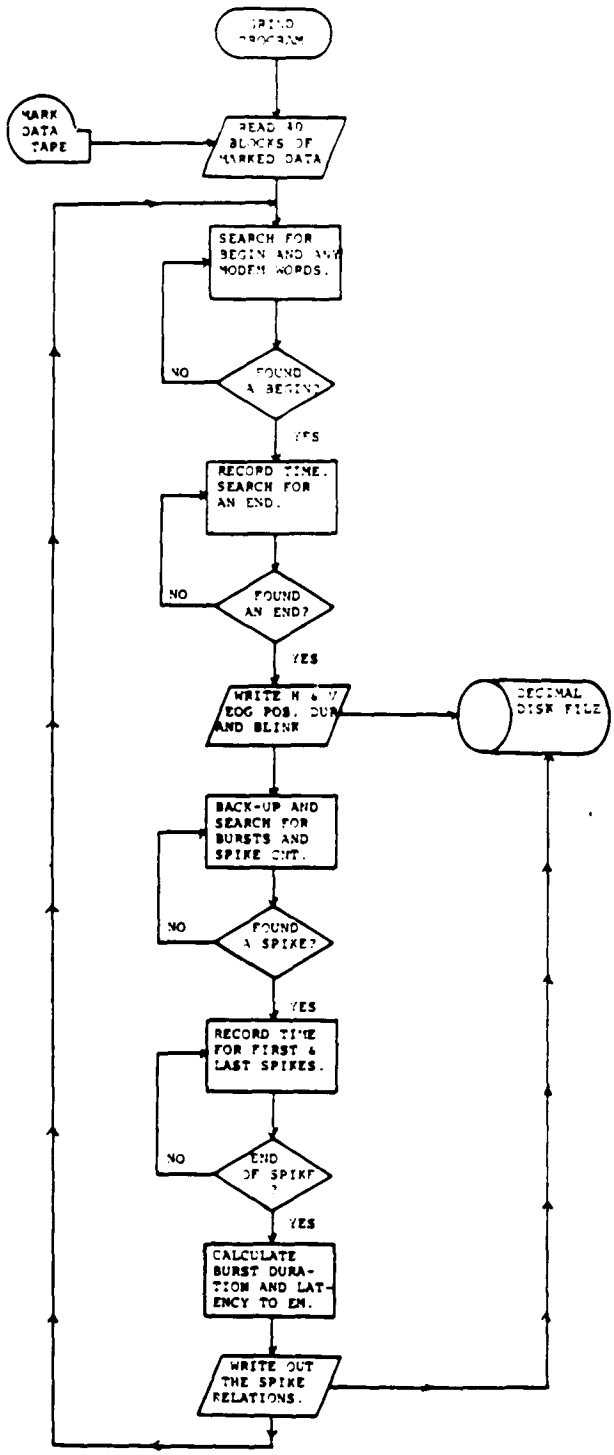

MARK DATA TAPE
READ 40 BLOCKS OF MARKED DATA
SEARCH FOR BEGIN AND ANY MODEM WORDS.
NO
FOUND A BEGIN?
YES
RECORD TIME. SEARCH FOR AN END.
NO
FOUND AN END?
YES
WRITE H & V EOG POS. DUR AND BLINK
DECIMAL DISK FILE
BACK-UP AND SEARCH FOR BURSTS AND SPIKE CNT.
NO
FOUND A SPIKE?
YES
RECORD TIME FOR FIRST & LAST SPIKES.
NO
END OF SPIKE?
YES
CALCULATE BURST DURATION AND LATENCY TO EM.
WRITE OUT THE SPIKE RELATIONS.

Fig. 9: GRIND File. Printout that illustrates the types of information produced by the output of the GRIND program. Each group of 3 lines show parameters of eye movement and unit data related to one eye movement. After the line number, the first four numbers represent the beginning (horizontal and vertical), and ending (horizontal and vertical) eye positions for the movement under consideration. The next number indicates the duration of the eye movement in milliseconds. The last number on the first line indicates whether there was a blink associated with the movement. On the next line, the five numbers show, in order, the parameters of the burst associated with the previous pause (duration and number of spikes), and the parameters of the burst related to the eye movement (duration, number of spikes, and time from the first spike of the burst to the beginning of the eye movement respectively). The third line has parameters of the paradigm including target position, jumped location, and light on/off or dim.

UA

100	98	-71	1	-91	38.4	129.6	0	
112	16.6	5	43.3	8	12.6			
120	-1	0	0	0	0	0	0	2
130	10	-79	117	-43	51.2	404.9	0	
140	288.5	32	0	1	-15.5			
150	79	-1	-1	-1	-1	0	0	2
160	117	-45	14	-77	41.6	108.8	0	
170	0	0	60.8	16	24.4			
180	79	-1	-1	-1	-1	0	0	2
190	11	-78	98	81	48.0	489.6	0	
200	370.3	43	31.1	3	-10.9			
210	79	-1	-1	-1	-1	0	0	2
220	96	57	20	-64	43.2	180.8	0	
230	61.9	11	61.4	14	30.5			
240	79	-1	-1	-1	-1	0	0	2
250	7	-74	166	81	144.0	352.0	1	
260	227.9	24	40.1	8	-99.0			
270	192	-1	-1	-1	-1	0	0	2
280	163	72	63	-41	46.4	96.0	0	
290	0	0	62.4	8	26.9			
300	192	-1	-1	-1	-1	0	0	2
310	58	-43	17	-73	25.6	142.4	0	
320	26.6	6	42.7	13	26.0			
330	192	-1	-1	-1	-1	0	0	2
340	13	-77	117	49	46.4	340.8	0	
350	215.1	36	60.4	5	26.5			
360	192	-1	-1	-1	-1	0	0	2
370	120	39	14	-81	43.2	110.4	0	
380	0	1	65.1	12	28.2			
390	192	-1	-1	-1	-1	0	0	2
400	10	-83	85	39	44.8	424.0	0	
410	301.9	51	39.6	4	25.2			
420	131	-1	-1	-1	-1	0	0	2
430	69	40	120	96	35.2	1593.6	0	
440	1426.4	42	0	0	32.0			
450	131	-1	-1	-1	-1	0	0	2
460	124	92	63	0	40.0	62.4	0	
470	0	0	61.4	12	31.6			
480	131	-1	-1	-1	-1	0	0	2
490	34	10	111	-36	32.0	422.4	0	
500	238.9	26	11.6	4	6.5			
510	131	-1	-1	-1	-1	0	0	2
520	115	-24	224	91	60.8	206.4	0	
530	92.7	11	0	0	32.0			
540	131	-1	-1	-1	-1	0	0	2
550	232	84	154	47	35.2	171.2	0	
560	33.6	4	54.3	13	25.9			
570	131	-1	-1	-1	-1	0	0	2
580	158	45	115	-7	32.0	164.8	0	
590	49.2	6	53.1	9	31.7			
600	131	-1	-1	-1	-1	0	0	2
610	104	-2	103	-2	43.2	756.9	0	
620	606.6	31	0	1	29.7			
630	131	-1	-1	-1	-1	0	0	2
640	118	9	47	-87	52.8	438.4	0	

Fig. 10: FOCAL Histogram Program. This program was designed to print out the rasters of neural activity and to construct histograms. The neural activty has been stored on the disk by the GRIND program. The FOCAL program reads the grind file and accepts only the kind of eye movement which is desired. In this case the program is set to display visually guided movements (H1 parameter equal to 1). Once a desired eye movement is found the program displays the raster on a storage oscilloscope and bins the activity for the eventual production of a histogram. After 30 movement rasters have been displayed, an appropriately scaled histogram is calculated and displayed. The program halts, waits for a picture of the storage scope screenface to be taken and will then continue to display further sets of unit activity. The program can be easily modified to display relationship to onset or jump of target instead of onset of movement.

```
HISTO

C FIT FOCAL SPIKE FACTOR/HISTOGRAM DISPLAY PROGRAM
C LAST EDIT: 1/8/81      22:30:02          DMS
C THIS PROGRAM USES A SPECIALLY CONSTRUCTED EPATCH TO RUN
C EPATCH CONTAINS FWRD, FELX, AND FIX OF EXIE TYPE!!!
C HISTOGRAMS OF UNIT DATA MUST EXIT ON ONE UNIT OF DISK
C EPATCH IS NOT USED, THIS IS UNBUFFERED OUTPUT TO 667
C MODIFIED TO DO LEFT VISUALLY GUIDED MOVEMENTS
C TO RUN: FOCAL;0/A/M 0PATCH;0 EPATCH;2 NOBUF;1 HISTO;1 LA;3 ZAP;1
C S DD=FDIS()
1.10 E
1.20 S SC=4;S ZE=2048;S MX=0;S Y=480*SC;S E.=4.82;S DD=819.2
C WHEN C1 IS SET TO .N, N GROUPS OF DESIRED BIN'S ARE SKIPPED
1.30 S CT=FITR(DD/E.);S HN=0;S C1=0;S CT=FITR(1220*SC/CT)
1.31 S LH=FITR(CT/2*SC)+1;S AL=0;S PS=512;S CA=(1024*SC/DD)*32
1.32 F A=0,CT;S SK=FWRD(A*512,0);S SK=FWRD(A+1024,0)
C FOR MK=40 FREQUENCY IS SET AT MAXIMUM OF 200 HZ ON ORDINATE
1.33 S BL=0;S MK=48
2.10 A BX;I (EX-3ZAP)2.20,2.98
C 2.20 A BY,EX,EY,T1,T1,EA,T2,N2,T3,D3,D4,D5,D6,VA,XT,YT,XJ
2.20 A BY,EX,EY,T1,T1,EA,T1,N1,T2,N2,T3,VA,XT,YT,XJ
2.30 A YJ,PJ,LT,ES,H1,H2,TX
2.40 I (H1)4.60,2.50;S EL=EL+4;S K2=K2+1
C 2.40 I (H1-1)2.50,2.70;S EL=EL+4;G 2.50
2.50 I (EK)2.65,2.65;S EL=EL+4;S K1=K1+1;G 2.10
C 2.50 I (EX)2.94,2.94;S EL=EL+4;S K1=K1+1;G 2.10
2.65 I (1-H2)2.94,2.94
2.70 S DX=EX-BX;S DY=EY-BY;I (EX)2.94,2.94
2.71 I (6495-EL)4.7,4.7;D 6
C 2.76 D 6
2.75 S KJ=KJ+1;I (HN-30)2.10;I (C1)2.8,2.8;S C1=C1-1;G 2.80
C 2.75 S KJ=KJ+1;I (HN-30)2.94
2.80 I (HD)2.89;D 5
2.88 D 11;D 10;D 12;D 3;S UF=FIX()
2.89 S HN=0;S KS=KS+KJ;F A=2,CT;S SK=FWRD(A*512,0)
2.90 S KJ=0;S MX=0;S Y=480*SC;I (EL)2.91,2.12,2.10
C 2.90 S KJ=0;S MX=0;S Y=480*SC;I (EL)2.91,2.94,2.94
2.91 S PS=512;S KJ=KS;F A=0,CT;S SK=FWRD(A*512,FWRD(A+1024))
2.92 D 9;D 11;D 10;D 12;D 3.5;D 3.51;D 4;G
2.94 S K4=KA+1;S BL=EL+4;G 2.10
2.98 S BL=-1;I (HN-1)2.89,2.80,2.30
3.30 T "PLOTTED MOVEMENTS:",KJ,!
C 3.30 T "PLOTTED TARGET ONSETS:",KJ,!
3.32 T "MODE IS",MX*32/KJ,"    SPIKES PER",EN," MSEC BIN",!
3.51 T "AT BIN #",HA,!
4.10 T "TOTAL MOVEMENTS IN COMPOSITE HISTO:",KS,!
C 4.10 T "TOTAL TARGET ONSETS IN COMPOSITE HISTO:",KS,!
C 4.15 T "REJECTED TARGET ONSETS:",K2,!
4.14 T "BLINKS:",K1,!
4.20 T "REJECTED MOVITS:",K4,!,"TOTAL MOVITS:",K1+KS+K4,!
4.22 T "TOTAL HISTOGRAMS GENERATED:",K1+K2+K4+KS,!
4.60 Q
4.70 T "BLOCK NUMBER OUT OF RANGE!!!";G
5.20 F A=0,CT;D 6
5.32 S TA=(KJ/30)*4A;S C1=FITR(.25*SC*PS)
5.40 F A=3,CT;D 9
6.10 S DD=FELX(EL);S EL=EL+4;S HN=HN+1
6.22 F I=0,511;D 7
6.30 S Y=Y-16*4;R
7.10 S SK=FWRD(I);I (SK)7.20,7.30
7.20 S A=FITR(I*1.6/EN);I (HL)7.22;I (-C1)7.22;S DP=FDIS(I*8-2748,Y)
7.22 S SK=FWRD(A*512,FWRD(A*512)+1);S SK=FWRD(A+1024,FWRD(A+1024)+1)
7.30 R
8.10 S SK=FWRD(A*512);I (MX-SK)8.30;R
8.30 S MX=SK;S MA=A;R
9.10 S XI=FITR(1220*SC*A/CT)-ZE;F X=XI,XI+LH;D 10
10.10 S SK=FWRD(A*512);S YX=FITR(SC*PS*SK/TA)-ZE
10.20 F Y=-512*SC,32,YX;S DD=FDIS(X,Y)
11.10 F I=-512*SC,CA,511+SC;F J=2,5;S DD=FDIS(I,J)+FDIS(I+1,J)
11.20 F I=-512*SC,C1,(PS*SC)-ZE;F J=0,5;S DD=FDIS(J-512*SC,I)
12.05 S GN=FITR(MX/4)
12.10 T !,!,"UNITS FOR ORDINATE:",GN,"  SPIKES PER BIN",!
12.20 T "UNITS FOR ABSCISSA:  32.00   MSEC",!
13.10 F Y=0,SC*12,SC*511;S DP=FDIS(2,Y)+FDIS(1,Y)
G
```

CHAPTER 3

RESULTS

DATA BASE

Single neuron extracellular recordings were obtained from 254 neurons in the brainstem of two rhesus monkeys. Eighty-eight (88) of these cells were located in the MRF using either histologic and/or electrical stimulation techniques.

In monkey M997 a total sample of 39 neurons were located in the MRF. Twenty-seven had a burst of activity which preceded all contralateral eye movements. Three MRF neurons were related to eye movements in all directions. Six neurons were related to the behavioral task, either by increasing their firing rate during fixation of the target (3 cells), by continuing to fire whenever the bar was depressed (2 cells related to attention), or by increasing their firing rate just prior to the dimming of the target (1 neuron). One MRF neuron in this animal had a burst of firing which preceded all ipsilateral saccades.

In monkey M996 49 MRF neurons were isolated. Twenty-six had bursts of activity which preceded all contralateral saccades. In this animal electrical microstimulation at the same locus where the cell was found produced a contralateral saccadic eye movement. Combined stimulation and recording experiments were undertaken to demonstrate the

relationship between neuron location in the MRF and preferred saccade size, and between electrode depth and the size of saccade produced by microstimulation. The size of the elicited saccade corresponded closely to that which occurred when the cell fired with earliest latency and highest peak frequency. Six neurons increased their firing during fixation of the target. Twelve neurons had a nonspecific relationship to eye movements, sometimes firing before contralateral eye movements, but at other times not. Other nonspecific neurons (n=4) were inhibited prior to contralateral saccades. Four neurons had a generally enhanced level of activity during the time the paradigm was performed. One neuron appeared to be related to the ambient light level in the room. One neuron appeared to be related to pursuit of targets (e.g., firing while the animal pursued the investigator's finger, or a piece of apple).

Other neurons in the sample were recorded from other locations in the brainstem. There were 38 neurons in the pretectum or pulvinar, 27 neurons in the superior colliculus and 12 cells in the oculomotor nucleus. Neurons which comprise the remainder of the sample were in other more distant regions of the brainstem.

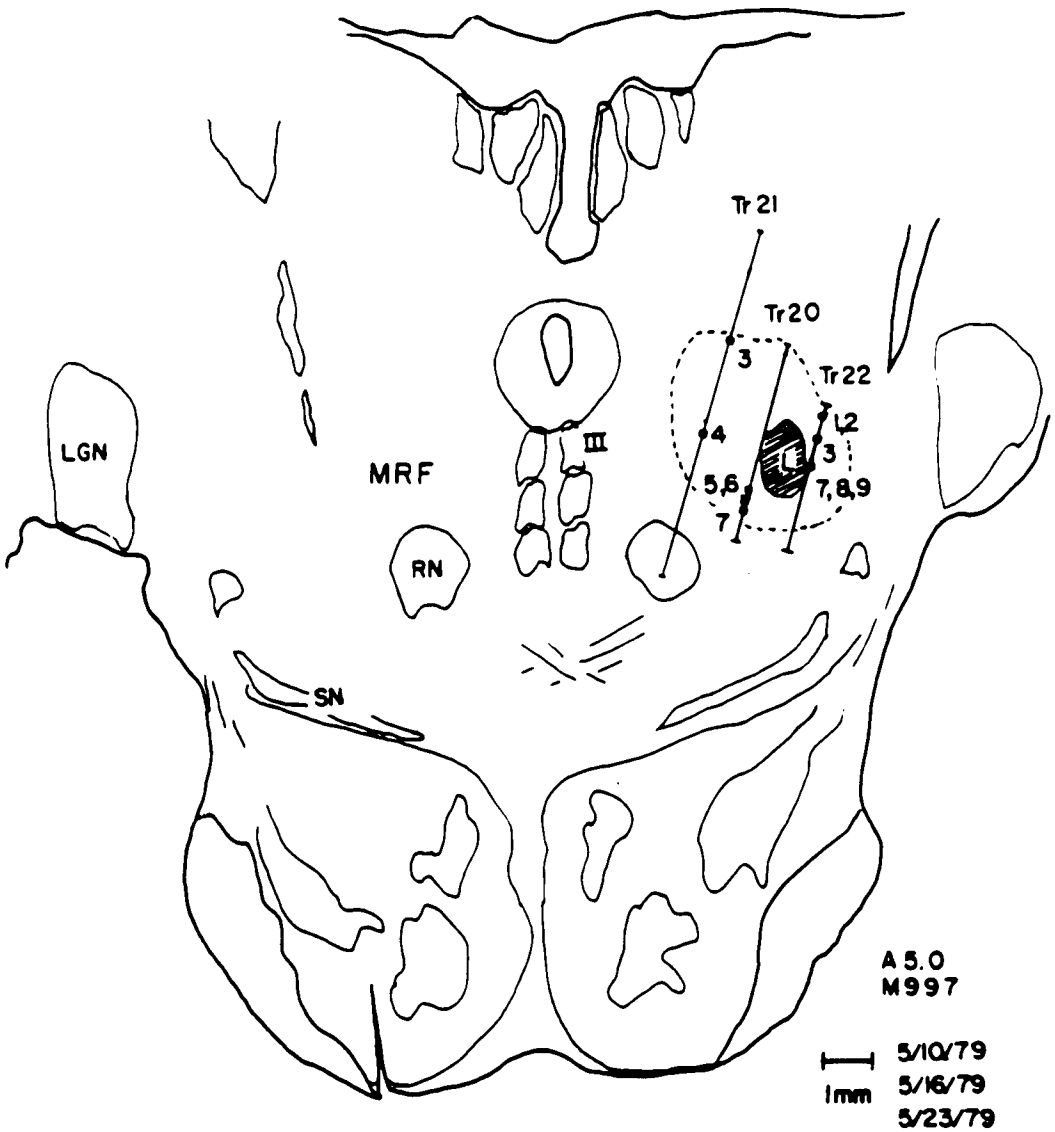
The results presented below are based on the total of 53 MRF neurons in the two animals which had bursts of activity that preceded contralateral eye movements. Background activity varied in these cells. Some MRF neurons had little or no spontaneous firing rate, others had a high spontaneous rate of firing. In some cells the spontaneous firing rate increased during the visual fixation task, in others it decreased

during the performance of the fixation task. In the qualitative results that follow two neurons have been selected which appear to be representative of low and high spontaneous activity cells. Whether these cells represent two different classes of neurons in the MRF or just the endpoints of a continuum with respect to the spontaneous level of background activity is not clear yet.

Most neurons encountered in the MRF that were associated with eye movements were similar in that they had bursts of activity that began before the onset of movement. Repeated examination of these cells using a hand-held projector while the animal fixated failed to show visual recepive fields as in cells of the superficial layers of the superior colliculus (Cyander and Berman, 1972; Goldberg and Wurtz, 1972a). Most cells were tested while the animal made spontaneous saccades in the light and the dark. The firing of the MRF neurons reported here did not seem to vary greatly under different ambient light conditions. There were still bursts of activity which preceded contralateral saccades by as much as 32 msec in the dark. No shift in latency was noted qualitatively during saccades in the dark, but this was not confirmed using raster displays.

All cells were verified to be in the MRF. A typical histologic section showing a number of tracks through the MRF is shown in Fig. 11. L indicates the area where an electrolytic marking lesion was made. Notice that the MRF is an area of the reticular formation bounded medially by the oculomotor nuclei, laterally by the medial lemniscus and LGN, dorsally by the pulvinar and ventrally by the red nucleus and

Fig. 11: Diagram of coronal section of M997 at A 5.0. Three tracks passed through the right MRF. Track #20 was located 1 mm medial to the center of the plug. 3 neurons (5, 6, and 7) were encountered in the MRF. All were related to contralateral eye movements. Neuron 051079-6 is #6 in this track. Two neurons, (3 and 4) were found in the MRF in Track #21. Both were related to contralateral on-target movements. Track #22 was recorded on 5/23/79. The 9 neurons located in this track were all in the right MRF. All of these cells fired in association with contralateral saccades during the attention task. The area marked by L and the shaded region around it was an electrolytic lesion which was placed at the bottom of track #22. Reconstruction and shrinkage factors may distort the area of the MRF slightly and show it larger than discerned by stimulation. Other abbreviations are LGN= lateral geniculate nucleus; RN = red nucleus; SN = substantia nigra; III = oculomotor nucleus. Cut (lower portion of figure) indicates left side of brain.


Tr21
Tr20
Tr22
3
4
1,2
3
5,6
7,8,9
7
III
LGN
MRF
RN
SN
A 5.0
M 9 9 7
1mm
5/10/79
5/16/79
5/23/79

substantia nigra.

MRF BURST NEURON WITH LOW BACKGROUND ACTIVITY

An MRF burst neuron with a low spontaneous level of activity is shown in Fig. 12. The firing was characterized by bursts of activity in association with contralateral spontaneous saccades, an increase in frequency of the burst during contralateral horizontal targeted movements, mild inhibition prior to spontaneous ipsilateral saccades, and profound inhibition prior to targeted ipsilateral saccades. With the onset of the task, (A, B, upward deflection of top trace) large bursts of firing accompanied each contralateral (left) on-target saccade. The latency of firing was approximately 50 msec before the onset of the movement (C,D) and the cell continued to fire for the duration of the movement. The activity often lasted for as long as 100 msec after the end of the movement.

The disparity between the firing of this cell during spontaneous and visually-targeted eye movements is demonstrated in Fig. 13. In association with left on-target movements (center), there was a broad burst of activity which began approximately 64 msec before the onset of the eye movement and continued for 100 msec after the start of the movements. For spontaneous saccades (left), the burst of activity was of shorter duration. It began approximately 32 msec before the onset of movement and continued for only 10 to 15 msec into the movement. There was an irregular low level of background activity. This activity was

Fig. 12: An MRF burst neuron with low background activity - U032079-5. A,B, From top to bottom traces are target light on/off, horizontal EOG, vertical EOG and instantaneous firing frequency. The time base for A and B is shown below B. Bursts of activity occured prior to contralateral saccades. Note the marked decrease in background activity and firing frequency during the bursts with the offset of the light (B). The neuron was inhibited prior to ipsilateral off-target saccades. The single on-target rightward saccade in (A) was not associated with inhibition of the firing. C, D, activity at faster sweep speeds. Activity began as early as 100 msec before an on-target movement and reached a peak of 500 spikes/sec. Activity persisted for as long as 150 msec after the end of the eye movement. 30 degree calibration beside D is for both horizontal and vertical EOGs.

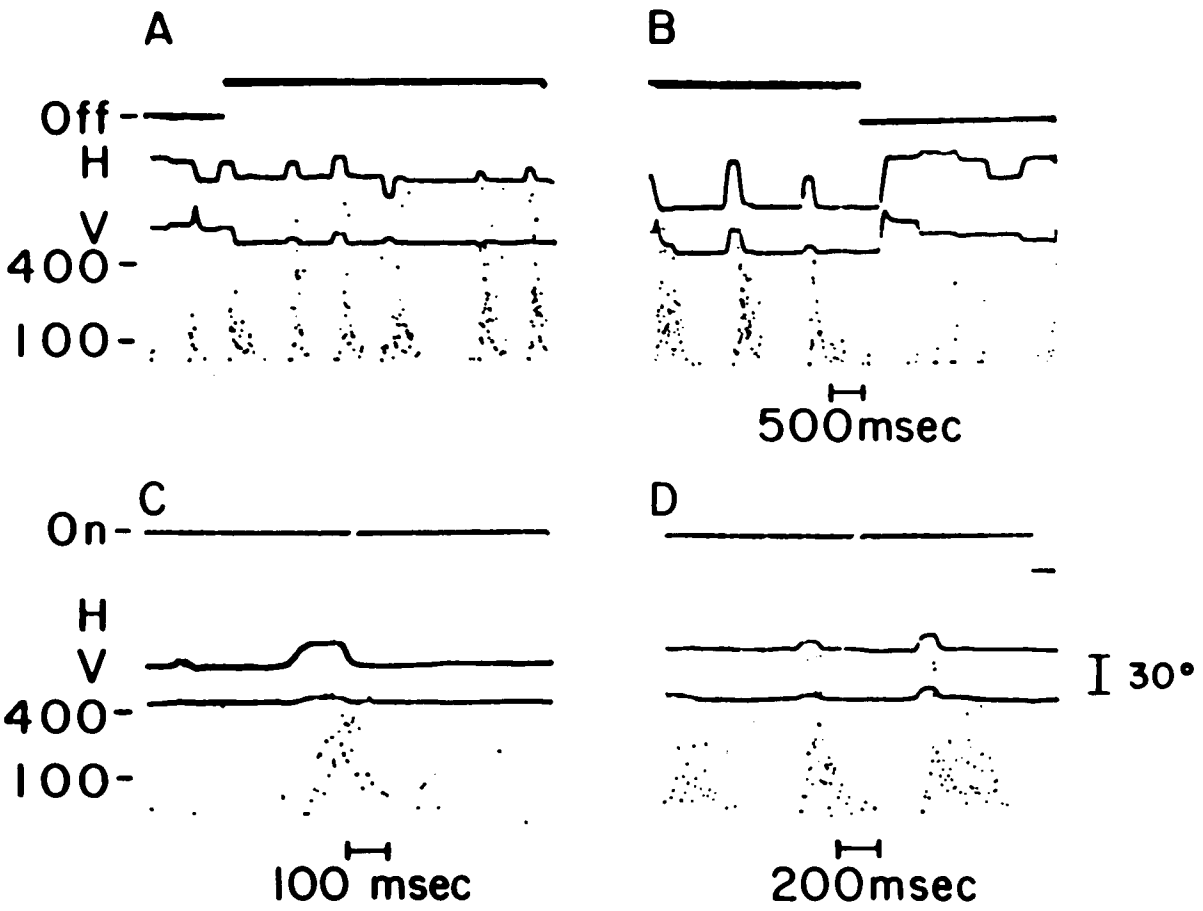
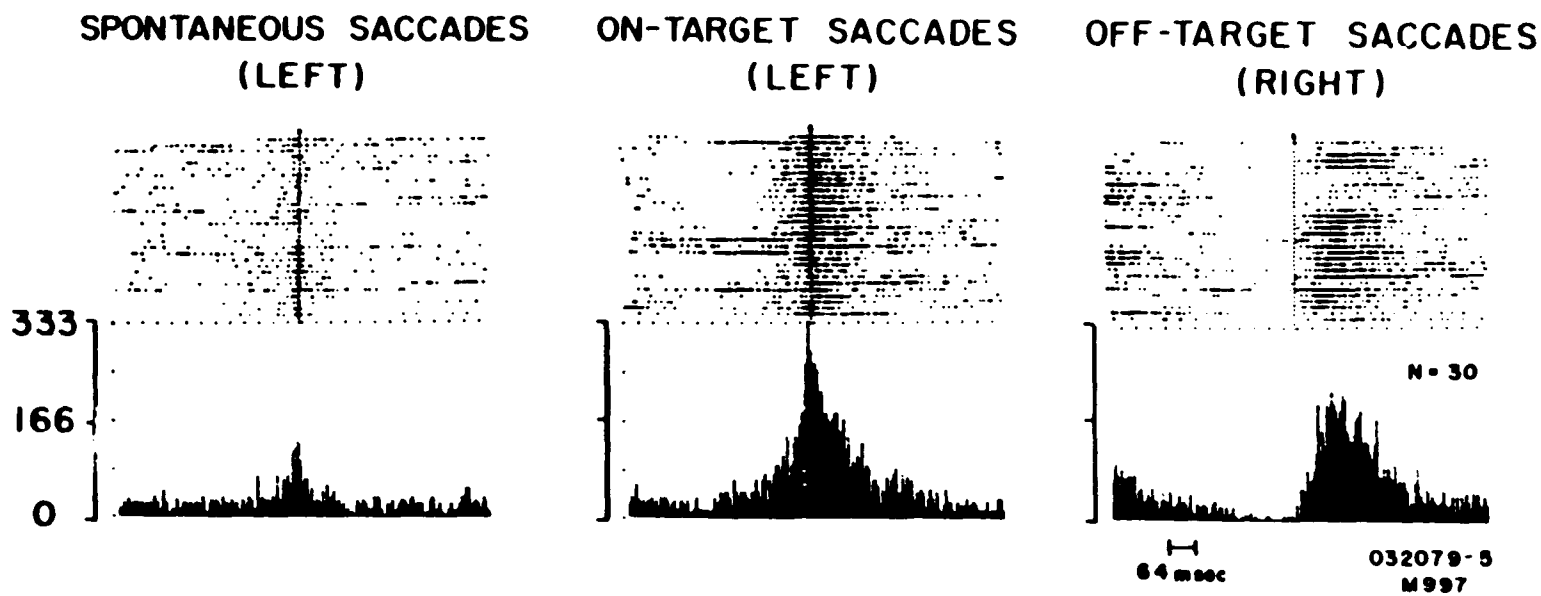

A
B
Off
H
V
400
100
500msec
C
D
On
H
V
400
100
I 30°
100 msec
200msec
U032079-5
M997

Fig. 13: MRF burst neuron 032079-5. Raster display of unit activity associated with 30 eye movements (above) and histogram of unit activity (below). Each dot on the raster represents a single neural discharge. The unit activity was synchronized on the beginning of the saccade. The onset of the eye movement is shown by the heavy black line through the center of the raster. The histogram below was constructed by collecting unit firing from each of the 30 eye movements into 4.8 msec bins. The average peak firing rate was approximately 100 spikes/sec in association with the the spontaneous contralateral (left) eye movements shown in the left column. Each line in the raster represents neural activity which started 409.5 msec before the eye movement and ended 409.5 msec after the beginning of the saccade. Not every spontaneous contralateral saccade was associated with a burst of firing. The middle column shows that activity associated with contralateral leftward on-target movements was more consistent. Right column. During 30 ipsilateral (rightward) off-target saccades there was inhibition of the spontaneous background level which began 120 msec before the saccade and continued for about 20 msec after the saccade had begun.


SPONTANEOUS SACCADES
(LEFT)
ON-TARGET SACCADES
(LEFT)
OFF-TARGET SACCADES
(RIGHT)
333
166
0
N = 30
64 msec
032079-5
M997

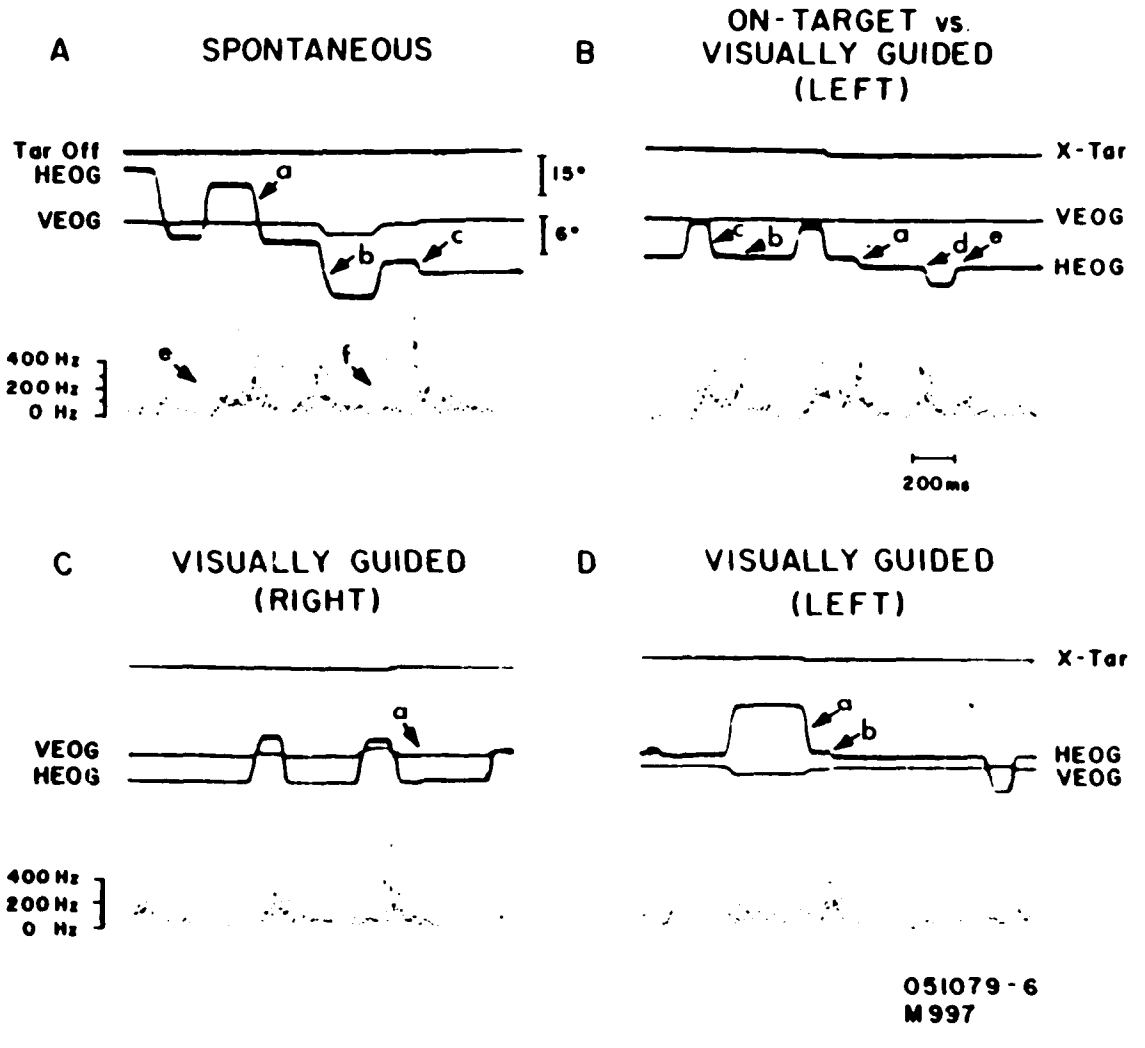
inhibited prior to the occurrence of spontaneous ipsilateral (rightward) movements (Fig. 13, right). During the target-on condition the background activity (intersaccadic activity) though still irregular was of slightly higher frequency, and the inhibition prior to off-target rightward (ipsilateral) movements was more profound (Fig. 13, right). In this case inhibition began 110 msec before the onset of movement, and the neuron remained silent for almost 32 msec into the movement. The intense firing shown in Fig. 13, right, which followed the inhibition was due to leftward (contralateral) on-target saccades which normally followed the off-target movements by 80 to 120 msec. An example of this off-target/on-target sequence is shown by Fig. 12C.

Summarizing, the firing of this MRF cell was related to all leftward (contralateral) movements but it was more intense prior to targeted movements. The most intense activity seemed to occur during smaller (1 to 7 degrees) saccades and the peak activity appeared to lead such eye movements by about 15 msec. The cell was inhibited before all rightward (ipsilateral) movements, but the inhibition was greater during off-target saccades. Lastly, there was a very low spontaneous level of activity.

MRF BURST NEURON WITH HIGH BACKGROUND ACTIVITY

The neuron shown in Fig. 14 demonstrates the characteristics of many of the cells located in the MRF. They had bursts of activity which began prior to eye movement and continued for as long as 200 msec after

Fig. 14: Activity of MRF burst neuron U051079-6 with high background activity. I. The relationship of neural firing to spontaneous eye movements is shown in A. Traces are from top to bottom: target off, horizontal and vertical EOG, and instantaneous rate of firing. There was a burst of firing prior to every contralateral saccade (arrows a, b, and c). In B, C and D the target was on. Only the x target position is shown. B. Firing associated with a contralateral visually guided movement (a) can be compared with firing associated with a contralateral targeted movement (b and c). A contralateral off-target movement is shown at d. The ipsilateral on-target movement (e) was not associated with the same inhibition seen for ipsilateral off-target movements. In C a similar lack of inhibition was seen for an ipsilateral visually-guided movement (a). D, Firing in association with medium sized saccade (a) and a visually-guided movement (b). Time base was 200 msec/cm for all traces. The gain for vertical EOG shown by the upper bar beside A was 15 deg for A, B, and D, and 6 deg for C. Horizontal EOG gain shown by the lower bar beside A was 6 deg for all parts.


A
SPONTANEOUS
B
ON-TARGET vs.
VISUALLY GUIDED
(LEFT)
Tar Off
HEOG
VEOG
15°
6°
a
b
c
X-Tar
VEOG
HEOG
400 Hz
200 Hz
0 Hz
e
f
200ms
C
VISUALLY GUIDED
(RIGHT)
D
VISUALLY GUIDED
(LEFT)
VEOG
HEOG
X-Tar
HEOG
VEOG
051079-6
M997

the end of the saccade. As shown by part A of this figure each spontaneous leftward (contralateral) eye movement was associated with a burst of firing with a latency which led the eye movement by about 30 msec (arrows a, b and c). The peak frequency of the cell appeared to be higher prior to smaller eye movements (compare arrows a and c). However, this was not always the case, and arrow b points to a large saccade which is associated with an intense burst of firing. The neuron displayed a background level of firing as the animal looked around the laboratory. There was mild inhibition of this activity prior to the execution of spontaneous (ipsilateral) rightward saccades (arrows e and f).

When the animal performed the visual attention task, firing was more intense before leftward (contralateral) on-target movements and started earlier, reaching peaks of 700 to 800 spike/sec (Fig. 14B, C and D). During the task the spontaneous level of activity appeared to increase and the inhibition prior to rightward (ipsilateral) off-target saccades was more profound. The peak firing and latency for a small contralateral visually-guided leftward movement (shown by a in Fig. 14B) was similar to the firing associated with small on-target leftward saccades (shown by b and c). Off-target leftward movements did not reach the same peaks of activity (d). Rightward on-target saccades were not associated with the typical inhibition seen for most ipsilateral eye movements (arrow e). Medium sized 6-8 degree saccades were associated with moderate bursts of firing (Fig. 14C). There was no inhibition of neuronal activity during a visually-guided rightward movement (a). Fig.

14D shows the difference in activity associated with large on-target and small visually-guided movements. Firing was weak during large movements (a) and intense during a small visually-guided movement to the left (b).

Fig. 15 demonstrates some of these relationships at a faster sweep speed (50 msec/cm). In A a large left on-target movement was followed by a small leftward on-target saccade. The burst associated with the large movement began approximately 50 msec before the saccade onset and reached a peak level of firing just after the start of the movement. The burst of activity associated with the smaller movement began approximately 20 msec before the movement and reached a high peak of firing 10 msec before the onset of the movement. Fig. 15B shows profound inhibition of the spontaneous activity, beginning 50 msec before the occurrence of the right off-target movement and continuing until approximately 20 msec after the end of the off-target movement. A build-up of activity then began which reached a peak level of firing approximately 10 msec before the onset of a 5 degree contralateral (leftward) saccade. Figure 15C demonstrates that firing prior to left off-target movements began only 10 to 15 msec before the saccade onset and regardless of amplitude appeared to reach its peak of activity during the saccade. Such activity was very similar to that seen for the spontaneous eye movement of somewhat larger size shown in Fig. 15D. The typical inhibition of firing prior to most ipsilateral (rightward) saccades was weaker for the rightward on-target movement shown by a in Fig. 15C.

The firing characteristics of this cell in raster form are shown in

Fig. 15: Activity of MRF burst neuron U051079-6 with high background activity. II. At a fast sweep speed the same unit as in Fig. 14. A, The latency of peak firing to onset of movement occurs 10 msec after the beginning of a large on-target saccade. The latency of peak firing for a smaller saccade occured 10 msec prior to the beginning of the eye movement. B, Inhibition and excitation associated with an ipsilateral off-target saccade and a contralateral 5 degree on-target saccade. C, D, Firing was similar during a contralateral off-target (C) and a spontaneous saccade (D) of larger amplitude. The timebase shown under A is 50 ms and was the same in all traces. Horizontal and vertical EOG gain is shown by the bar beside B. Frequency of firing is shown by the scale in A.

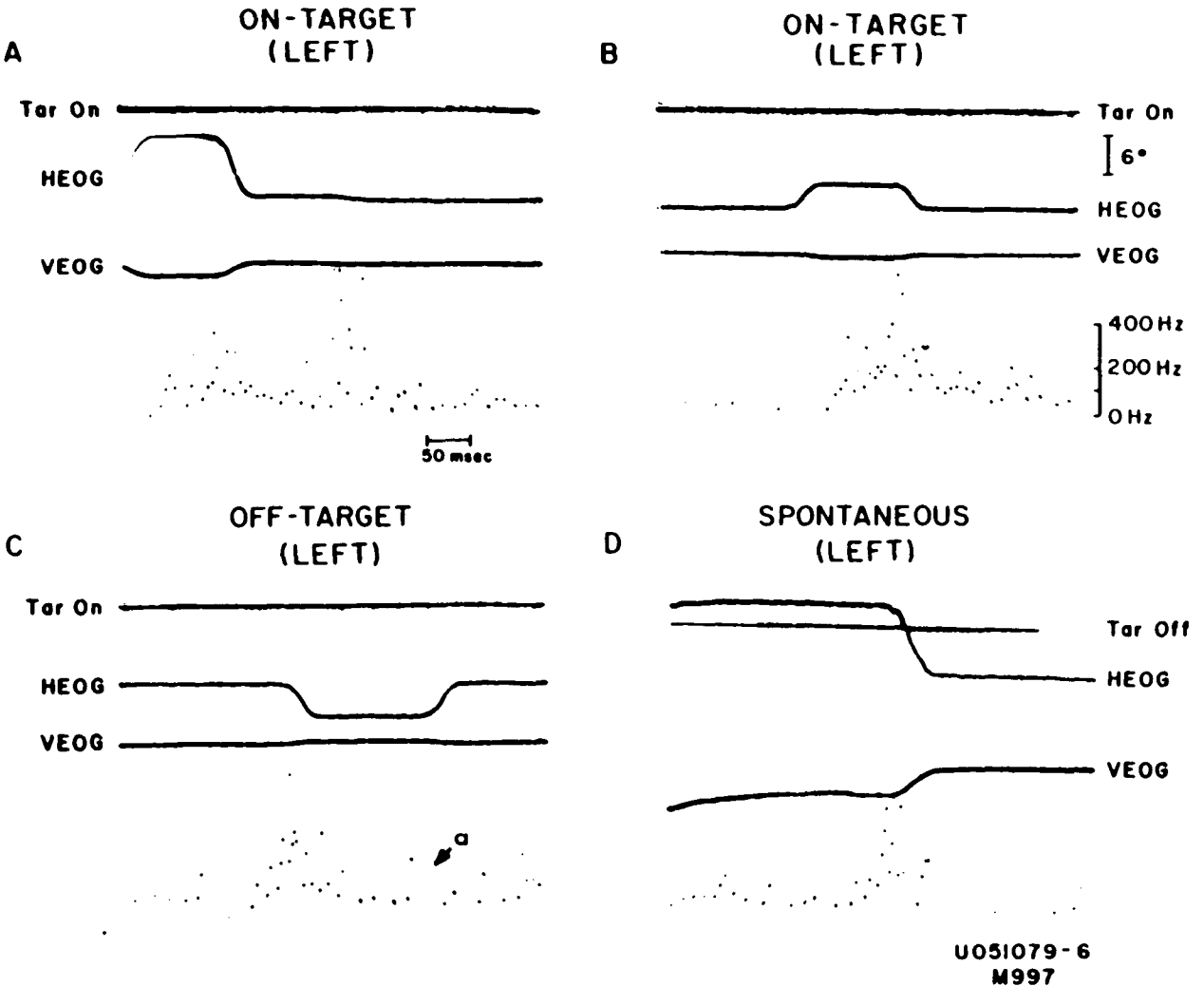
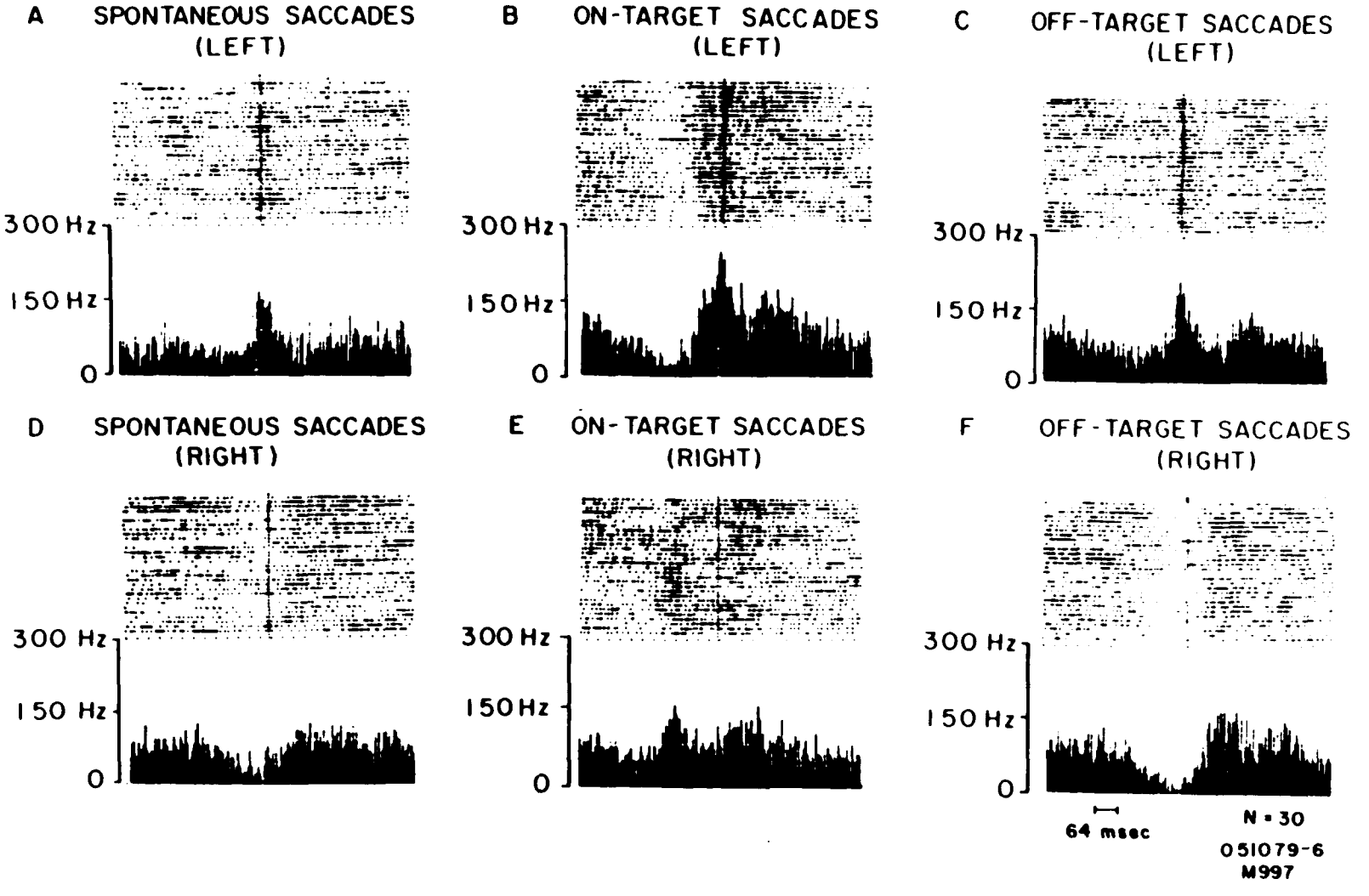

A
ON-TARGET
(LEFT)
Tar On
HEOG
VEOG
50 msec
B
ON-TARGET
(LEFT)
Tar On
6°
HEOG
VEOG
400 Hz
200 Hz
0 Hz
C
OFF-TARGET
(LEFT)
Tar On
HEOG
VEOG
a
D
SPONTANEOUS
(LEFT)
Tar Off
HEOG
VEOG
U051079-6
M997

Fig. 16. Movements of six types were separated and pooled. Fig. 16A shows a raster constructed from 30 spontaneous contralateral (leftward) movements. Most movements had a burst of activity which began from 10 to 32 msec before the movement and continued into the movement for about 10 to 20 msec. The peak activity occurred about 20 msec before the contralateral movement. The maximum averaged firing rate was approximately 175 spikes/sec. It should be noted that some of the contralateral movements had little associated unit activity. The background firing rate during the inersaccadic periods was approximately 75 spikes per second.

The leftward spontaneous movements are similar to the off-target saccades to the left (Fig. 16C). However, there are some differences between them. First, the background firing level was higher in the intersaccadic intervals when the animal was actively fixating than during spontaneous fixations. Second, the firing associated with the off-target saccades was more consistent. Every movement had an associated burst of firing. Third, there was some inhibition prior to the occurrence of off-target movements. Yet, despite these differences, the peak average activity associated with both the spontaneous (L) and off-target (L) eye movements was about the same at 175 spikes/sec.

The activity associated with leftward spontaneous eye movements is in marked contrast to that during leftward on-target movements (Fig. 16B). During on-target movements the activity began earlier, in some cases as much as 64 msec before eye movement onset, and continued throughout and after the movement for 50 to 100 msec. As shown by the

Fig. 16: Rasters of firing associated with saccades and histograms for neuron U051079-6 with high background activity. The neuron was in the right MRF and fired with contralateral (left) saccades. 30 movements were used to construct each raster and histogram. A, Relationship to spontaneous contralateral (left) saccades. The background level of firing was 75 spikes/sec, and the neuron reached an average peak of 150 spikes/sec during the movement. Some contralateral spontaneous saccades had no burst of firing associated with them. On-target movements to the contralateral side are shown in B. Firing began earlier during on-target than spontaneous contralateral saccades and the cell reached a higher peak firing rate of 275 spikes/sec (averaged). The background firing rate was 100 spikes/sec during periods of active fixation. Off-target saccades to the contralateral side (C) were associated with bursts of firing which began 30 msec before the eye movement. The average peak activity was 175 spikes/sec. Spontaneous ipsilateral (rightward) movements in D were associated with a period of inhibition of background firing level. Off-target movements to the ipsilateral side were associated with a stronger inhibition (F). There was no inhibition of firing during on-target movements to the ipsilateral side (E). The peak of firing that occurs 128 msec before the onset of eye movement in E is related to the preceding off-target contralateral saccade (as in C).


A SPONTANEOUS SACCADES (LEFT)
B ON-TARGET SACCADES (LEFT)
C OFF-TARGET SACCADES (LEFT)
D SPONTANEOUS SACCADES (RIGHT)
E ON-TARGET SACCADES (RIGHT)
F OFF-TARGET SACCADES (RIGHT)
300 Hz
150 Hz
0
64 msec
N = 30
051079-6
M997

histogram below B, the average peak activity of on-target movements (about 250 spikes/sec) occurred 15 msec before the eye movement began. The inhibition that was present about 100 to 200 msec before the leftward eye movement is due to the occurrence of a right off-target saccade. As shown in Fig. 16B there was an increase in the background activity of this neuron during active fixation of the target. Spontaneous intersaccadic fixations had about a 75 spikes/sec firing level while during the task the intersaccadic firing rate was about 100 spikes per second.

Ipsilateral saccadic movements are shown in Fig. 16D-F. Rightward movements were associated with a mild inhibition of the spontaneous firing rate which began 100 msec prior to the eye movement (Fig. 16D). The weak inhibition during spontaneous saccades was in contrast to the stronger inhibition of background activity associated with the right off-target saccades (Fig. 16F). This inhibition began 120 msec before the eye movement and continued for approximately 30 msec after the start of the movement. Excitation which followed the inhibition was related to left on-target saccades that normally occurred within 100 msec of the off-target movement (for example see Fig. 15B). On the other hand, rightward on-target saccades were not associated with inhibition (Fig. 16E). The burst of firing seen in advance of the on-target movements is the result of a leftward off-target movement that occurred from 60 to 200 msec before. This lack of inhibition for ipsilateral on-target movements was also seen during ipsilateral visually guided movements (see Fig. 14C).

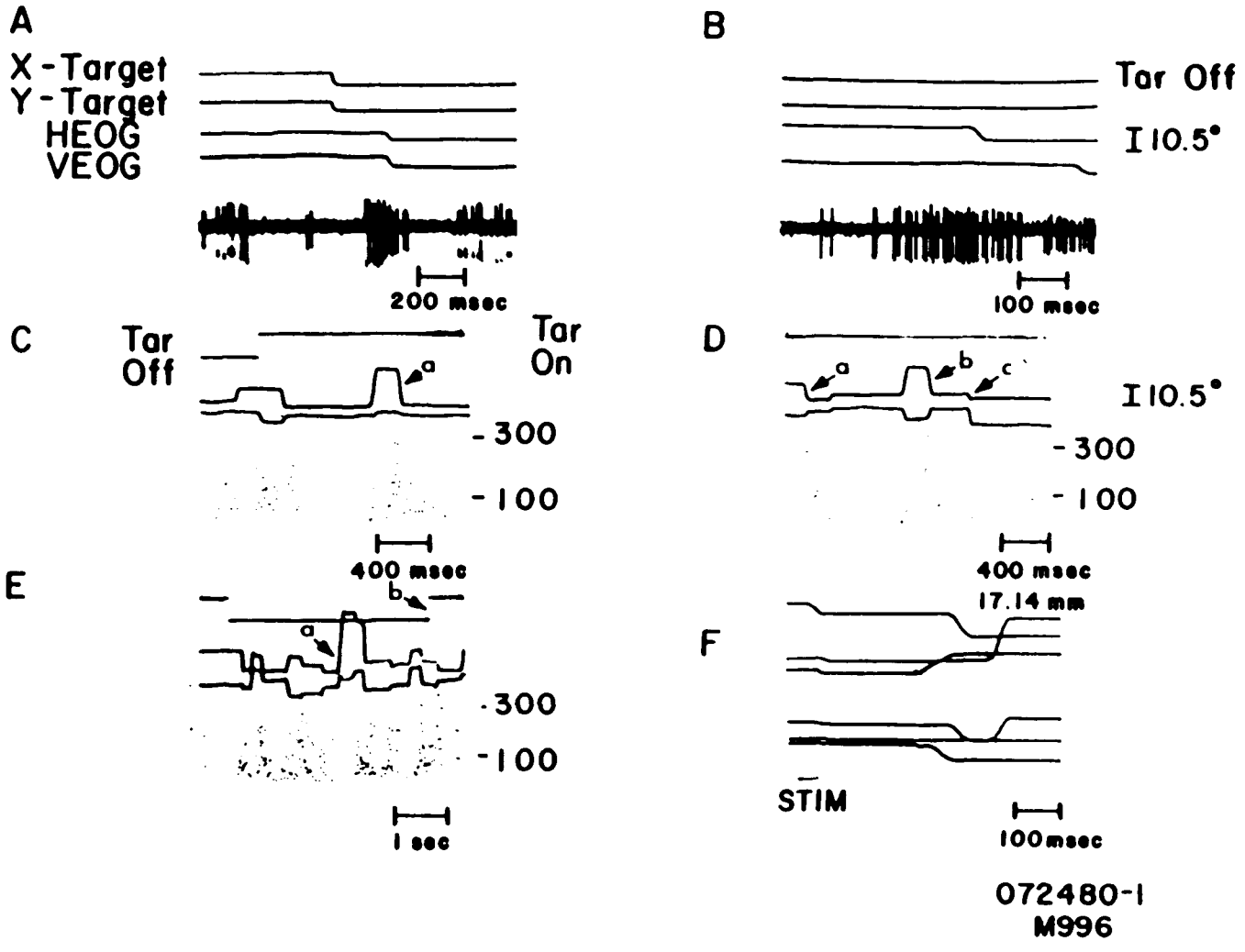
In summary, this cell began firing as early as 64 msec before the onset of on-target contralateral saccades and was inhibited as early as 100 msec before the occurrence of off-target rightward saccades. A burst of firing above this general increase in activity started 20 msec before the saccade onset regardless of saccade type. The burst of activity was greater both in peak frequency and in duration for on-target contralateral movements than for contralateral spontaneous movements. There is a suggestion that the peak activity of the cell occured earlier for saccades of medium amplitude. For rightward movements the cell was inhibited earlier and for longer duration for ipsilateral off-target movements than for spontaneous movements. However, ipsilateral (rightward) on-target movements were not associated with inhibition. Although interesting, the significance of this lack of inhibition is not clear. Lastly there was a difference between the intersaccadic firing rate for the on-target and off-target conditions. This suggests that the MRF neurons may be modulated by the general degree of arousal of the animal.

STIMULATION/RECORDING EXPERIMENTS

Previous stimulation experiments have suggested that different sized eye movements may be elicited from the MRF by varying the depth of a stimulating microelectrode (Matsuo et. al., 1980; Cohen et. al., 1982). These stimulation results prompted combined stimulation/recording experiments in one animal (M996) to correlate the

depth of the recording microelectrode and the amplitude of the horizontal component of eye movement. At each site where a neuron was isolated, electrical stimulation produced characteristic eye movements found during previous MRF stimulation studies. This type of correlation was made for 26 MRF neurons found in 10 different electrode penetrations. An example is shown in Fig. 17. Activity of this unit appeared to be related to medium (6 to 8 degree) saccades. In A the target was on at the beginning of the trace and jumped to a new location (to the left and down). Approximately 200 msec later the monkey executed a visually-guided eye movement onto the target. Associated with this 5 degree saccade there was an intense burst of firing which began about 40 msec before the onset of the eye movement to the contralateral side. The burst continued and ended approximately 40 msec after the end of the eye movement. Firing which occurred near the beginning of the trace was associated with a small off-target contralateral saccade. Fig. 17B shows activity of this neuron in relation to a spontaneous contralateral eye movement. The firing began 200 msec before the beginning of the movement with an increase in activity occurring 40 msec before the onset of the saccade. In Fig. 17C, approximately 200 msec after the target appeared on the screen, the animal executed an 8 degree saccade up and to the left to bring the eyes onto the target. This was associated with a burst of firing which exceeded 300 Hz. The burst began approximately 40 msec before and continued until about 20 msec after the end of the movement when the activity fell off quickly to zero. A larger on-target saccade (a) was

Fig. 17: Recording and stimulaion experiment. Track #35, U072480-1. In A the traces are from top to bottom X and Y target position horizontal and vertical EOG, and extracellular recording. In A, a visually guided saccadic eye movement occurs 200 msec after the target jumped to a new location. Firing in association with this guided movement began 40 msec before the eye movement and continued for 40 msec after the eye movement ended. B. Unit firing associated with a spontaneous contralateral saccade with approximately the same horizontal component of movement as the guided movement shown in A. In C, D and E the frequency of firing of the cell is the lowest trace and the target on/off condition is the top trace. C. Firing associated with a medium sized (8 degree) eye movement and a slightly larger 10-12 degree contralateral saccade (arrow a). Contralateral on-target saccades of 8-10 degrees in D were associated with high bursts of firing (a, b). A small contralateral saccade of 4-6 degrees (c) was associated with a much lower peak of firing. E, The spontaneous activity of the increased cell during the time when the target was off. Arrow a shows considerable inhbition of firing prior to an ipsilateral spontaneous movement. There was a marked decrease in the spontaneous firing level of this cell just after the appearance of the target (arrow b). F shows that stimulation at this same locus. The top 3 traces are the HEOG and the bottom 3 the VEOG. The calibration of 10.5 degrees shown beside B, applies to both horizontal and vertical EOG's in all parts of this figure.


A
X - Target
Y - Target
HEOG
VEOG
200 msec
B
Tar Off
I 10.5°
100 msec
C
Tar Off
Tar On
a
-300
-100
400 msec
D
a
b
c
I 10.5°
-300
-100
400 msec
17.14 mm
E
b
a
-300
-100
1 sec
F
STIM
100 msec
072480-1
M996

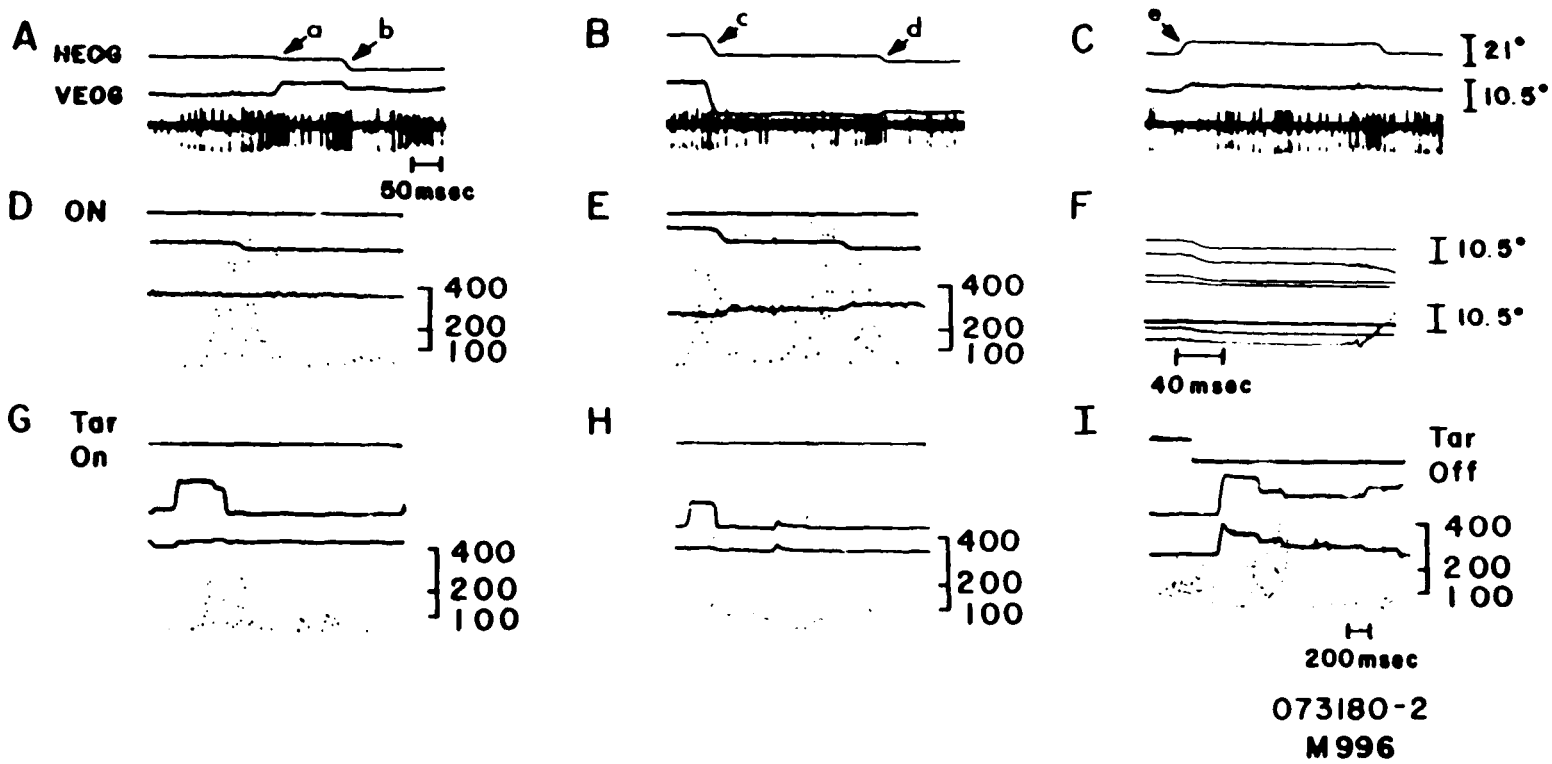
associated with a burst of firing that had similar temporal characteristics but a lower peak firing rate and the peak activity occurred during the saccade. This is also shown in D. The first movement of about 8 degrees (a) was associated with a high burst of firing which reached its peak frequency about 10 msec before the onset of movement. The second contralateral movement (b) was associated with a slightly lower peak frequency (450 Hz) and the peak firing came during the course of the saccade. The 2 degree contralateral saccade indicated by c is smaller than the first saccade of this trace (arrow a) and is not associated with a strong burst of activity. This suggested that this neuron fired most vigorously for saccades of the size (approximately 8 deg) indicated by arrow a. In this cell, the spontaneous level of firing increased when the target disappeared (Fig. 17E). Every spontaneous contralateral saccade was associated with a peak of firing which was about 200 to 400 Hz. The general increase in background firing may be related to the large amount of long-lead activity which preceded each spontaneous movement (Fig. 17B). However, when an ipsilateral rightward saccade occurred as at arrow a, there was a marked inhibition of the spontaneous level of firing which began as early as 100 msec before and continued for about 50 msec after the occurrence of the movement. The target reappeared at arrow b and within 150 msec the spontaneous background activity dropped to close to zero. Figure 17F shows the eye movements produced by microstimulation at the spot (17.14 mm) at which this cell was encountered. Stimulation with 40uA at a frequency of 333 Hz produced fixed amplitude saccades of about

8 degrees.

Recapitulating, this cell fired in conjunction with all contralateral saccades. There was long-lead activity which began 100 msec before contralateral spontaneous movements. During the target ON condition there was less long-lead activity before contralateral targeted saccades. On-target saccades with smaller or larger amplitudes were not associated with the same peak frequency as for medium sized saccades. Activity prior to medium sized saccades appeared to be greater and had an earlier latency for contralateral visually-guided or for on-target saccades. Microstimulation at the locus where this cell was recorded produced medium sized contralateral fixed amplitude saccades of 8 degrees.

The correspondence between the activity of the neurons and the size of the horizontal component of the eye movements elicited by electrical stimulation was striking. This phenomenon is demonstrated for the two neurons which appear to be related to 5 to 6 degree saccades shown in the next two figures. In Fig. 18 parts A through C are samples of spontaneous saccades. The neuron had a relatively high background level of firing during intersaccadic periods. A shows that the vertical component of movement did not affect the firing of the cell. Contralateral saccades up and to the left (arrow a) and down and to the left (arrow b) were both associated with a similar intensity of firing. The larger saccade shown in part B was associated with a moderate (but lower) burst of activity which began with the start of eye movement and continued just beyond the end of the saccade. During the medium sized

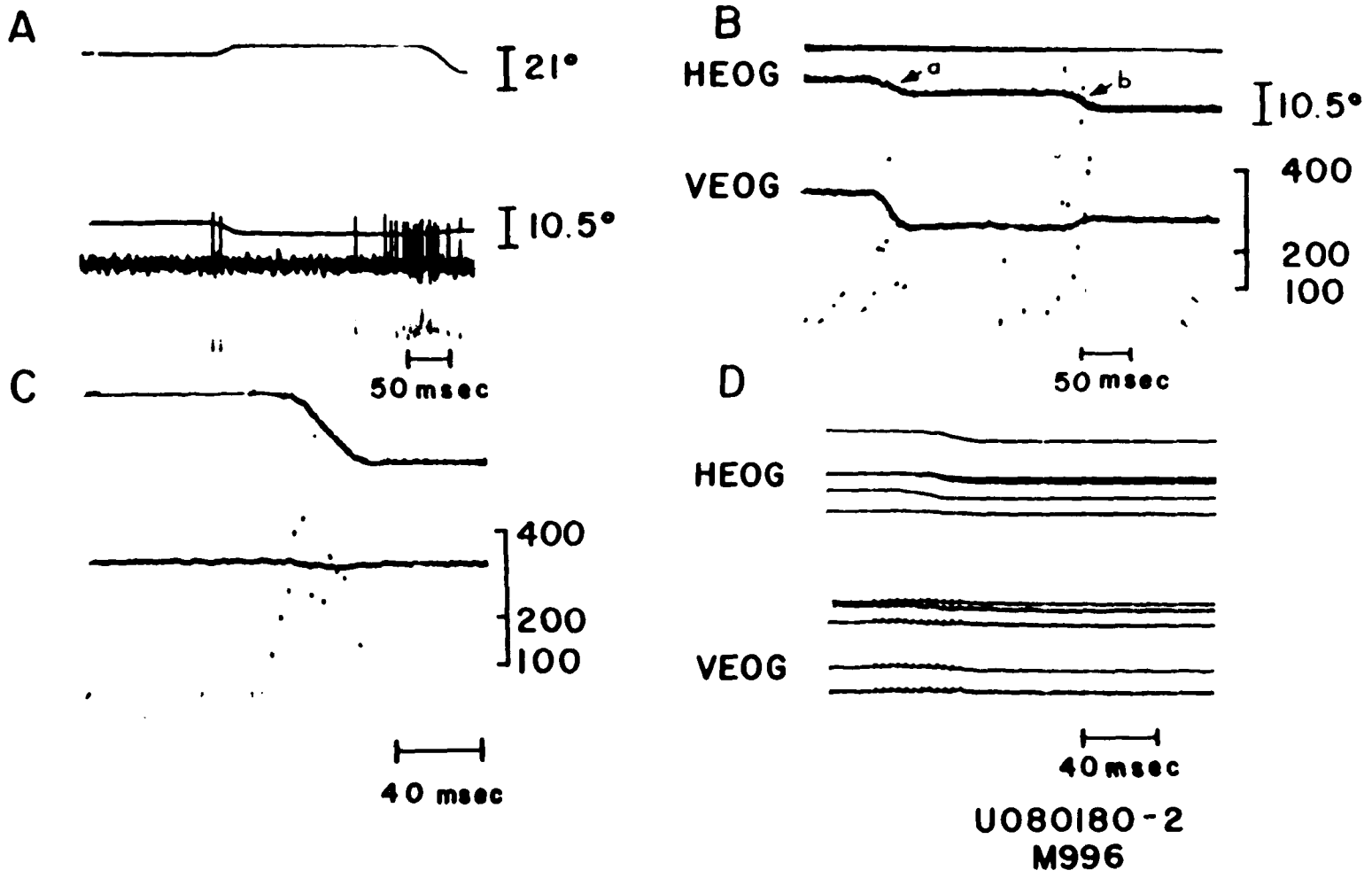
Fig. 18: Recording and stimulaion experiment for U073180-2, Track #40. All of the neural activity shown in this figure is from the same cell recorded in the right MRF. A-C, examples of neuronal activity associated with contralateral spontaneous eye movements. The direction of the vertical vector had little effect on the response of the cell (compare arrows b and d). Firing was associated with the horizontal vector to the left. The burst of activity began 20 msec before the onset of the leftward saccade and ended at the end of the movement (a,b,c,d). C, Saccades to the ipsilateral (right) side were associated with inhibition of neural firing (e). Peak frequency and relationship to various sized on-target saccades is shown in panels D, E and G-I. The cell reached a peak frequency of about 600 Hz in association with contralateral on-target saccade of 4-6 degrees. For example, the left on-target movement shown in E, was associated with a burst of firing which began 70 msec before the beginning of the saccade, reached its peak frequency 15 msec before and continued to fire for 40 msec after the end of the saccade. Larger on-target movements to the contralateral side are shown in panels G and H. There was less activity with larger saccades. Firing during spontaneous saccades is shown in I. Both background activity and and peak frequencies were somewhat lower than when the animal was performing the task. F, eye movemets which were produced by electrical stimulation at the locus of this recording in the right MRF. Fixed 4-6 degree (contralateral) saccades were generated by stimulation with a 333 Hz, 40 uA, 40 msec pulse train. EOG calibration for A-C shown by the bars beside C. Calibrations for D-I are the same and are shown by the vertical bars beside F.


A
HEOG
VEOG
a
b
50msec
B
c
d
C
21°
10.5°
D
ON
400
200
100
E
400
200
100
F
10.5°
10.5°
40msec
G
Tar
On
400
200
100
H
400
200
100
I
Tar
Off
400
200
100
200msec
073180-2
M996

saccade which followed (d), the burst began at least 10 to 20 msec before the eye movement and the activity reached a higher frequency. There was inhibition which began 30 msec before an ipsilateral (rightward) saccade (Fig. 18C, e), and the neuron returned to its spontaneous level approximately 50 msec after the end of the ipsilateral movement. Examples of instantaneous rates of firing while performing visually-guided and targeted saccades of various sizes are shown in D, E, and G-I. In E, for example, a contralateral on-target movement was associated with a burst of activity which began 70 msec before and reached a peak frequency of 600 Hz, 15 msec before the beginning of the movement. Larger (10 to 15 degree) contralateral saccades are shown in panels G and H. The neural firing associated with large contralateral on-target movements began at the same latency, but reached its peak firing during the execution of the saccade. I shows the effect of target fixation. The activity associated with spontaneous contralateral saccades rarely exceeeded 400 Hz, as opposed to similarly sized on-target saccades, where it often exceeded 600 Hz in peak frequency (compare I to panels D and E). The spontaneous background firing of this cell appeared to be approximately the same during active and spontaneous intersaccadic intervals (compare I to G and H). Stimulation at the locus where this cell was recorded produced contralateral eye movements of 5-6 degrees (F).

Another neuron which appeared to be related to 5 to 6 degreee saccades is shown in Fig. 19. The neural activity began 40 msec prior to contralateral (left) spontaneous saccades (A). There was little

Fig. 19: Neuron 080180-2 in M996 associated with medium sized (5-6 deg) saccades. Traces are from top to bottom: horizontal and vertical EOG, and units activity. EOG gains for A are shown by the bars beside A. The gain of the HEOG and VEOG was the same in B, C, and D and are shown by the bar beside B. A, neural activity associated with a contralateral saccade of about 15 degrees. This cell began to fire 20 msec before the onset of contralateral spontaneous saccades. In association with on-target eye movements to the contralateral side, (B), the cell began firing 20 to 30 msec earlier than for spontaneous saccades. The peak of firing appeared higher for 5 degree on-target saccades as opposed to 6-8 degree saccade (compare arrows a and b), and the peak firing preceded the eye movement (arrow b). In contrast, the 12 degree contralateral on-target movement shown in C was associated with a peak of firing which reached 500 Hz but occurred during the saccade. Stimulation at the site of recording with 40 uA at 333 Hz for 40 msec elicited a 5-6 degree saccade to the contralateral side.


A
21°
10.5°
50 msec
B
HEOG
a
b
10.5°
VEOG
400
200
100
50 msec
C
400
200
100
40 msec
D
HEOG
VEOG
40 msec
U080180-2
M996

intersaccadic background activity. B shows the firing in association with two contralateral on-target saccades of 7 (arrow a) and 5 (arrow b) degrees in amplitude. The neural activity started about 70 msec before the saccades. This was 30 msec earlier than the latency seen for spontaneous contralateral saccades. The peak firing was higher for the 5 degree than for the 7 degree saccade (arrow a vs. b). Furthermore, the peak activity appeared to precede the 5 degree movement and occured during the execution of the 7 degree saccade. The peak of firing also occured during the execution of the 12 degree saccade shown in C. Stimulation at the locus where this neuron was found produced the contralateral 5 to 6 degree saccades shown in D. The latency was about 20 msec between the onset of stimulus and the onset of eye movement.

Two neurons recorded in the same track and related to larger (8 to 12 degree) saccades are shown in Fig. 20. The neuron shown in A fired with both on-target and spontaneous saccades of about 8 to 10 degrees in amplitude. Though it fired in association with smaller contralateral movements the firing did not reach the same peak frequency as during the medium sized movements. This cell was also inhibited prior to rightward movements. The neuron shown in part B was the more ventral of the 2 MRF neurons shown. It fired with highest peak frequencies in association with 10 to 15 degree spontaneous and targeted saccades. The firing reached higher peak frequencies during on-target movements. This neuron was inhibited prior to ipsilateral rightward movements.

Stimulation every 0.25 mm along this track is shown in Fig. 21. Stimulation parameters were 40 uA, 333 Hz and 40 msec pulse train.

Fig. 20: Two neurons related to larger amplitude contralateral saccades recorded in Track #36: 072580-4 and 5. A, B, neurons recorded in the ventral portions of the right MRF. A, A neuron associated with medium sized saccades of 6 to 10 degrees. Peak firing was less for the smaller contralateral saccade that occurred later in the trace. B, High peak frequency in association with a large 12-14 degree on-target saccade to the contralateral side. This eye movement was followed by a number of smaller contralateral on-target movements that were not associated with similar changes in firing. The EOG gain was 10.5 degrees/cm for both horizontal and vertical EOG.

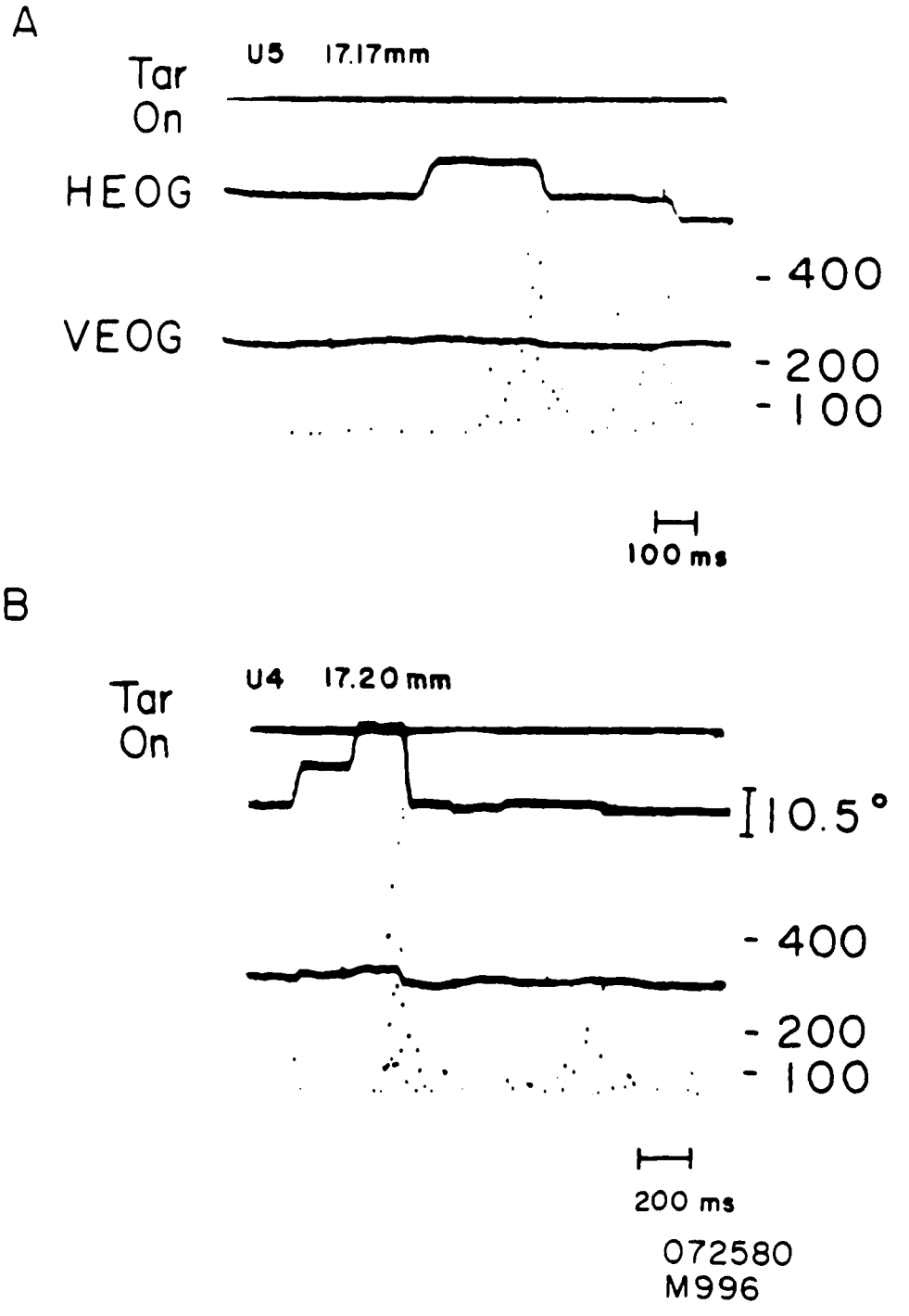
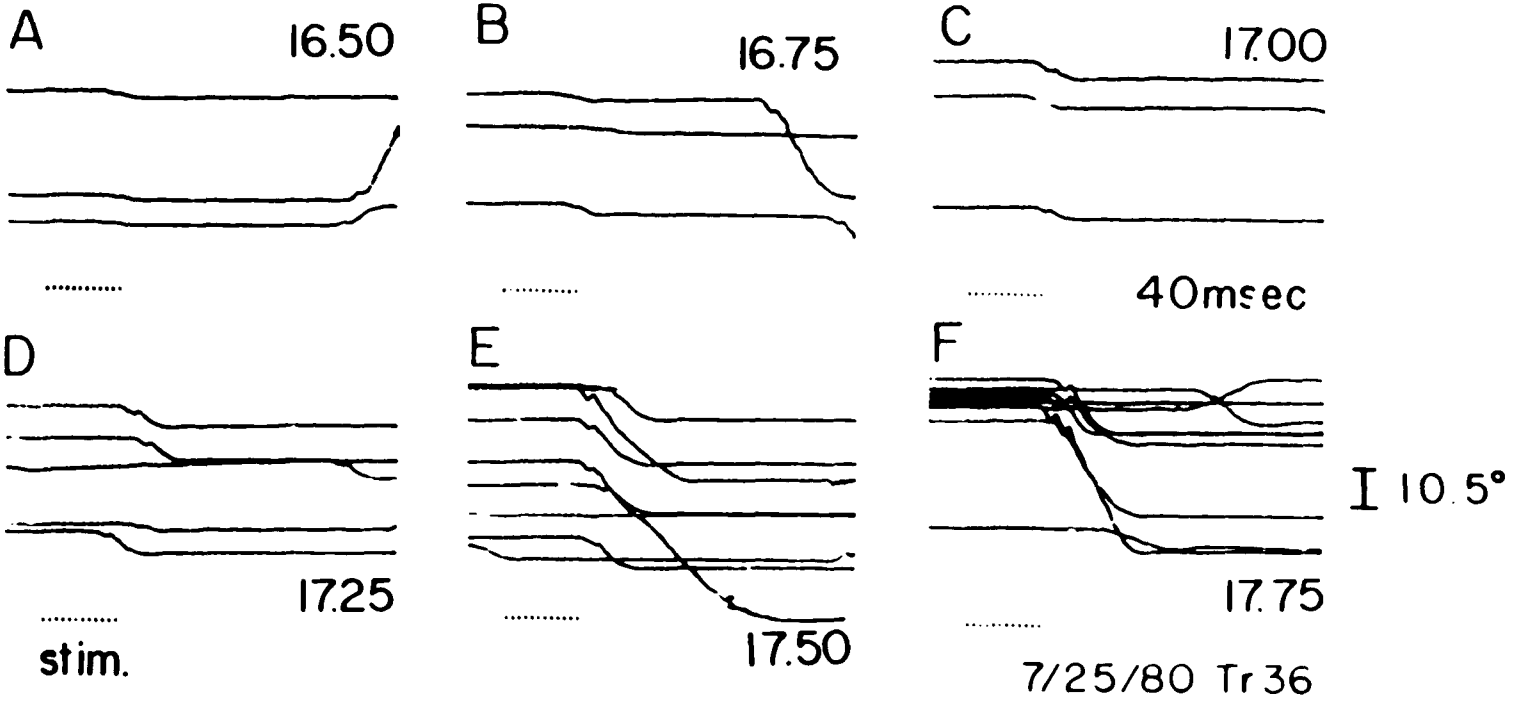

A
U5 17.17mm
Tar
On
HEOG
VEOG
-400
-200
-100
100 ms
B
U4 17.20 mm
Tar
On
10.5°
-400
-200
-100
200 ms
072580
M996

Fig. 21: Stimulation along Track #36 of 07/25/79. Microstimulation at 0.25 mm intervals along the track from which the neurons presented in the previous figure were recorded. A, Stimulating currents of 40uA, 333 HZ, for 40 msec produced 1-2 degree contralateral (left) saccades at latency of 10 msec. B, Saccades were slightly larger as the electrode was advanced from dorsal to ventral. C and D show eye movements produced from stimulation above and below the recording sites for neurons 4 and 5 in track #36 (see Fig. 20A and B). Electrical stimulation produced 8-10 degree (C) and 10-12 degree (D) saccades to the contralateral side at short latency. Stimulation at more ventral sites (E and F) produced larger saccades. Time scale is shown by the duration of the stimulating pulse train which was 40 msec. Only the horizontal EOG is shown. The gain is 10.5 degrees shown beside F.


A
16.50
B
16.75
C
17.00
40msec
D
17.25
stim.
E
17.50
F
17.75
I 10.5°
7/25/80 Tr 36

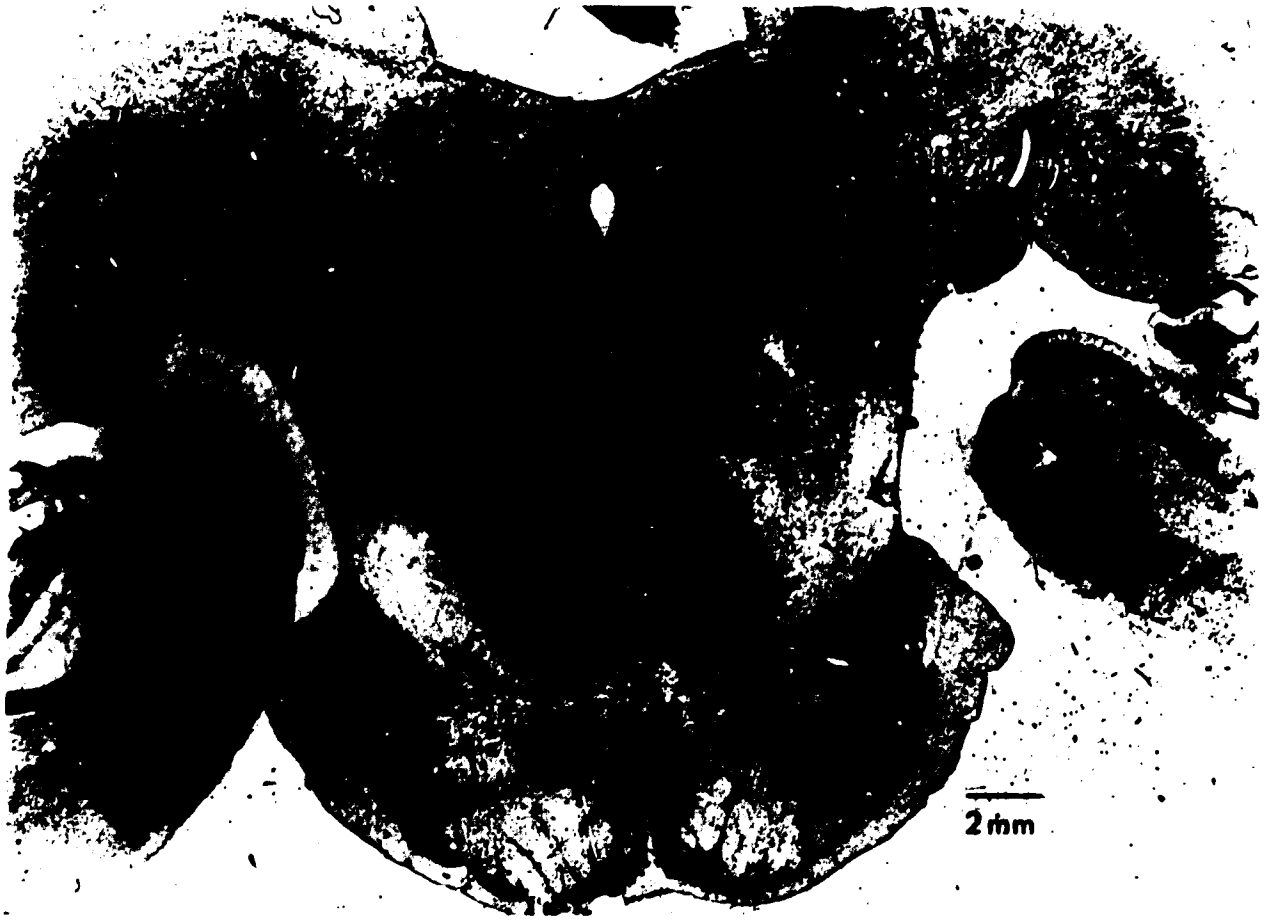
Small contralateral saccades were produced by stimulation in the dorsal MRF (Fig. 21A, B). Deeper (more ventral) the saccades became larger (C-E). Below this the effect of stimulation was more variable, but stimulation tended to carry the eyes to the contralateral side (F). There was a close correspondence between the preferred saccade size of the single neurons shown in Fig. 20A, B and the amplitude of the saccades elicited by microstimulation at that site. The recording sites of units 4 and 5 were between the stimulation records in Fig. 21C and D. Stimulation near the site of U072580-5 (shown in Fig. 20A) produced fixed amplitude saccades of about 8 degrees (Fig. 21A). Stimulation near the site of U072580-4 (shown in Fig. 20B) produced 12 degree fixed amplitude saccades (Fig. 21D). The loci of these neurons in the MRF and of the stimulation track are shown in Fig. 22. An electrolytic lesion labelled by an open arrow was produced at the bottom of the track at the end of the stimulation/recording experiment. The upper filled arrow shows the location of unit recording.

The results of the stimulation/recording experiments suggest a size specific anatomical and physiologic relationship in the MRF. Pathways and cells controlling small saccades appear to be localized dorsally and pathways and cells involved in the generation of larger saccades appear to be more ventral.

QUANTITATIVE ANALYSIS OF UNIT ACTIVITY

Two questions were posed to relate metrics of the eye movements to the unit activity: Can visually-targeted movements be separated from

Fig. 22: Histologic section of M996 showing Track #36. This is a coronal section through the brainstem at a level of A 3.5. The oculomotor nuclei are prominent. The lesion at the bottom of one of the tracks was placed made by passing 100 microamperes for 45 secs (marked by open arrow). It was 5.75 mm below the site in the MRF at which the 2 units of Track #36 (Fig. 20A,B) were recorded (marked by upper of two filled arrows).

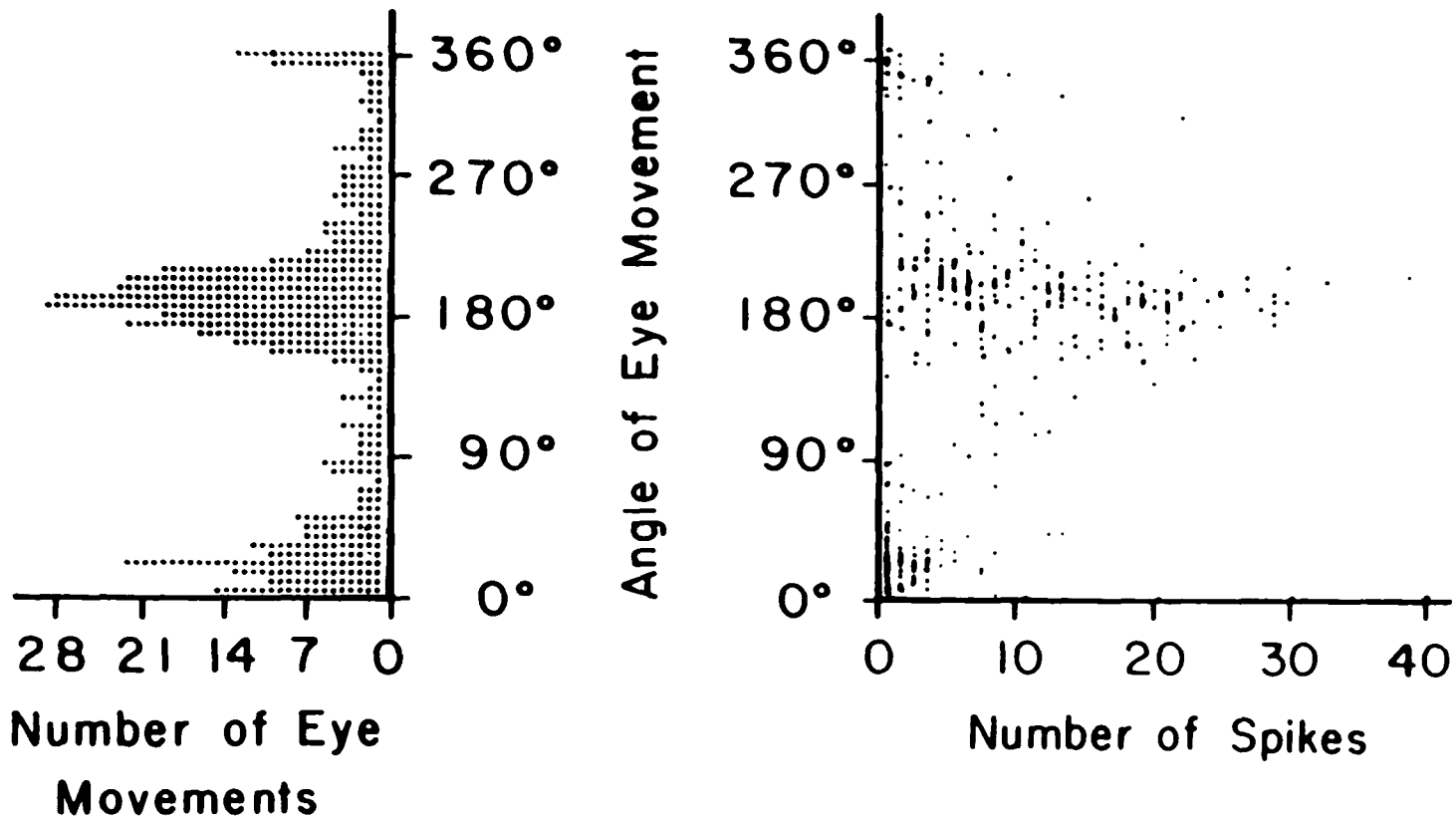

2 mm

spontaneous movements on the basis of the unit activity? What information might be contained in the neuronal firing patterns? Two parameters of neuronal firing were used: the number of spikes in a specified interval (N) and the mean peak frequency of firing (Fmax). N was chosen because neurons in the MRF might project to the PPRF where a delta N/ delta position relationship is known to be associated with production of saccades (Henn and Cohen, 1976). Microstimulation of the MRF has shown that a minimum number of pulses are necessary to elicit a contralateral saccade (Matsuo et al., 1980; Cohen et. al., 1982). Frequency of the stimulating pulses had little effect in changing the size of the induced movement, but was important in decreasing the latency to the beginning of the saccade. In addition, stimulation studies suggested that because of the anatomic organization of the MRF, higher peak frequencies occurring before a movement in certain regions might play an important role in generating saccades of particular sizes. The initial part of the analysis was to determine if N was related to the direction and amplitude of contralateral saccades.

To test the hypothesis that these neurons might contain directional information in their firing rates, the relationship between number of spikes and angle of movement was examined for the neuron with low background activity (see Figs. 12 and 13) in the right MRF (Fig. 23). The greatest number of spikes occurred in association with contralateral (leftward) movements. As the number of spikes in the burst increased it was more likely that the direction of movement would be to the left (180 deg). The distribution of the movements according to angle is shown on

Fig. 23: Direction of eye movement versus number of spikes for U032079-5. The ordinate for the left histogram is the direction of the eye movement in polar coordinates. 0 degrees is an eye movement to the right, 90 degrees up, 180 degrees to the left, and 270 degrees down. The bin width was 6 degrees. There was a predominance of right and left saccades. The right histogram has the same ordinate. The number of spikes in the the interval 32 msec before to 4.8 msec before the end of the saccade interval is graphed on the abscissa for the same set of 396 on-target and spontaneous eye movements seen on the left. Movements with more than 6 spikes in the associated burst were to the left or the contralateral side (180 degrees).

SPONTANEOUS AND ON-TARGET SACCADES



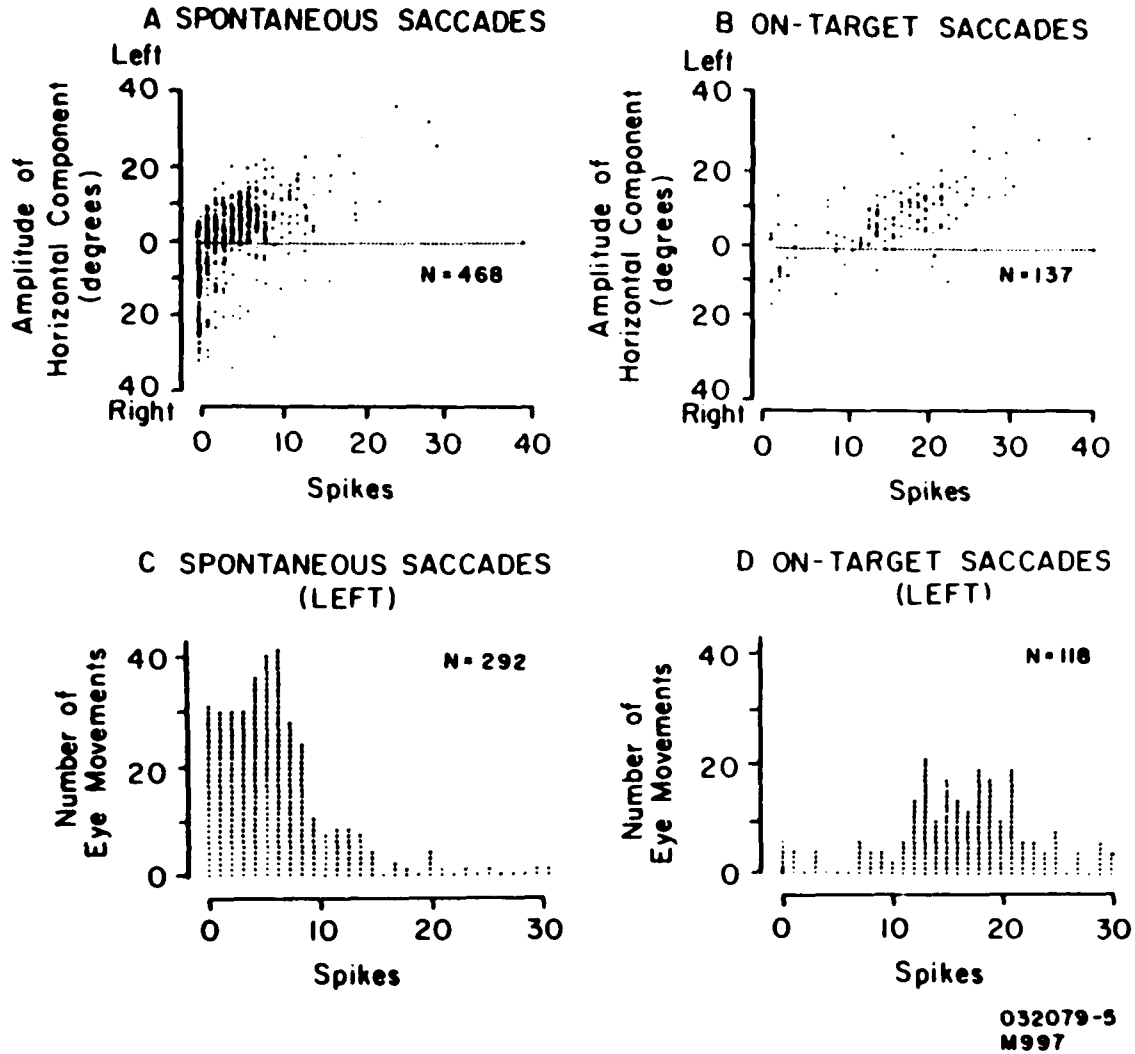
032079-5
M997 N=396

the left side of Fig. 23. There were more horizontal than vertical movements. However, movements to the right (0 and 360 degrees) were not associated with increases in firing (Fig. 23, right), and there was a gradual buildup in activity as the direction of the movement approached 180 degrees. There was no apparent difference between the distribution of angles for the spontaneous and the on-target movements (not shown).

Fig. 24 shows the amplitude of the horizontal component of movement plotted against N for spontaneous (A) and on-target movements (B). The period of analysis was from 32 msec before the onset of movement to 4.8 msec before the end of movement. In both cases there was an increase in the number of spikes as the amplitude of the 180 deg (left) component increased. C and D are histograms showing the number of leftward movements associated with various N's. The targeted movements (D) were associated with a larger number of spikes than the spontaneous movements (C). The modes for the two distributions were 6 and 14 spikes for the spontaneous and the on-target movements, respectively.

Possible relationships between neuronal activity and the metrics of the upcoming movement in MRF burst neurons with high background activity were also examined (see Figs. 14, 15, and 16). Two intervals were considered. The first was a period that began 32 msec before the eye movement and ended with its onset. The second interval encompassed activity from 32 msec before the onset of movement to 4.8 msec before the end of the movement. The first period was chosen to coincide with many of the high bursts of activity associated with left movements and periods of maximal inhibition for rightward movements. Activity in this

Fig. 24: Amplitude vs. number of spikes in the burst for U032079-5, M997 (See also Figs. 12 and 13). The period of analysis began 32 msec before the saccade began and ended 4.8 msec before saccade ended. A, Spontaneous eye movements. There was a rough association between the number of spikes in the period of analysis and the horizontal component of movement to the contralateral side shown on the ordinate. The relationship appeared to be stronger for on-target saccades shown in B. The histograms in C and D show the distribution of the contralateral (left) eye movements. Most contralateral spontaneous saccades had 12 or less spikes in the analysis interval (C). Contralateral on-target movements in D, however, had 12 or more spikes in this interval.


A SPONTANEOUS SACCADES
Left
Right
Amplitude of Horizontal Component (degrees)
40
20
0
20
40
N = 468
0
10
20
30
40
Spikes
B ON-TARGET SACCADES
Left
Right
Amplitude of Horizontal Component (degrees)
40
20
0
20
40
N = 137
0
10
20
30
40
Spikes
C SPONTANEOUS SACCADES (LEFT)
Number of Eye Movements
40
20
0
N = 292
0
10
20
30
Spikes
D ON-TARGET SACCADES (LEFT)
Number of Eye Movements
40
20
0
N = 118
0
10
20
30
Spikes
032079-5
M997

period had the appropriate latency to influence the generation of the upcoming saccade. The second period was chosen because as noted above the highest peak of activity often did not occur until after the eye movement had already begun.

The relationship to direction in the 32 msec period preceding eye movement is demonstrated in Fig. 25. The highest N's were associated with movements to the left (i.e. 180 degrees) for both spontaneous and on-target movements. This is similar to findings for the more phasic neuron analyzed in Fig. 23 (Unit 5, 032079). Figure 25C demonstrates that the distribution was relatively uniform for movements of all directions in this sample. This suggests that information about saccade direction, not saccade size was present in the number of spikes that occurred in the interval that just preceded the eye movement in burst neurons with high background activity.

Analysis of eye movements for neuron 051079-6 using the period from 32 msec before to the onset of the movement is shown in Fig. 26. The amplitude of the component of movement in the horizontal plane (0-180 degrees) is shown on the ordinate and the number of spikes in the specified 32 msec interval on the abscissa. Spontaneous movements are shown in A and on-target movements in B. When this neuron fired more than 4 spikes the horizontal component of the impending eye movement was leftward. However, the number of spikes in this interval was not correlated with the size of the horizontal component. Contralateral on-target but not spontaneous movements were almost always associated with neural activity. This is shown more clearly by the histograms in

Fig. 25: Direction of eye movement versus number of spikes in burst and amplitude histogram for U051079-6 eye movements. A, B, Angle of movement vs. number of spikes for unit U051079-6. The number of spikes in the 32 msec period just preceding the saccade is shown along the abscissa in A and B, and the angle of movement on the ordinate. There were more spikes prior to leftward on-target saccades than rightward on-target movements (B). This relationship of neural activity to saccade direction to the contralateral side was also present for spontaneous saccades (A). The distribution of angles of movement of both on-target and spontaneous movements is shown in C. The number of eye movements in each 6 degree bin is shown on the ordinate. There was a relatively even distribution across direction. The distribution of amplitudes for the same set of 1001 eye movements is shown in D. Most eye movements averaged 6-8 degrees in size.

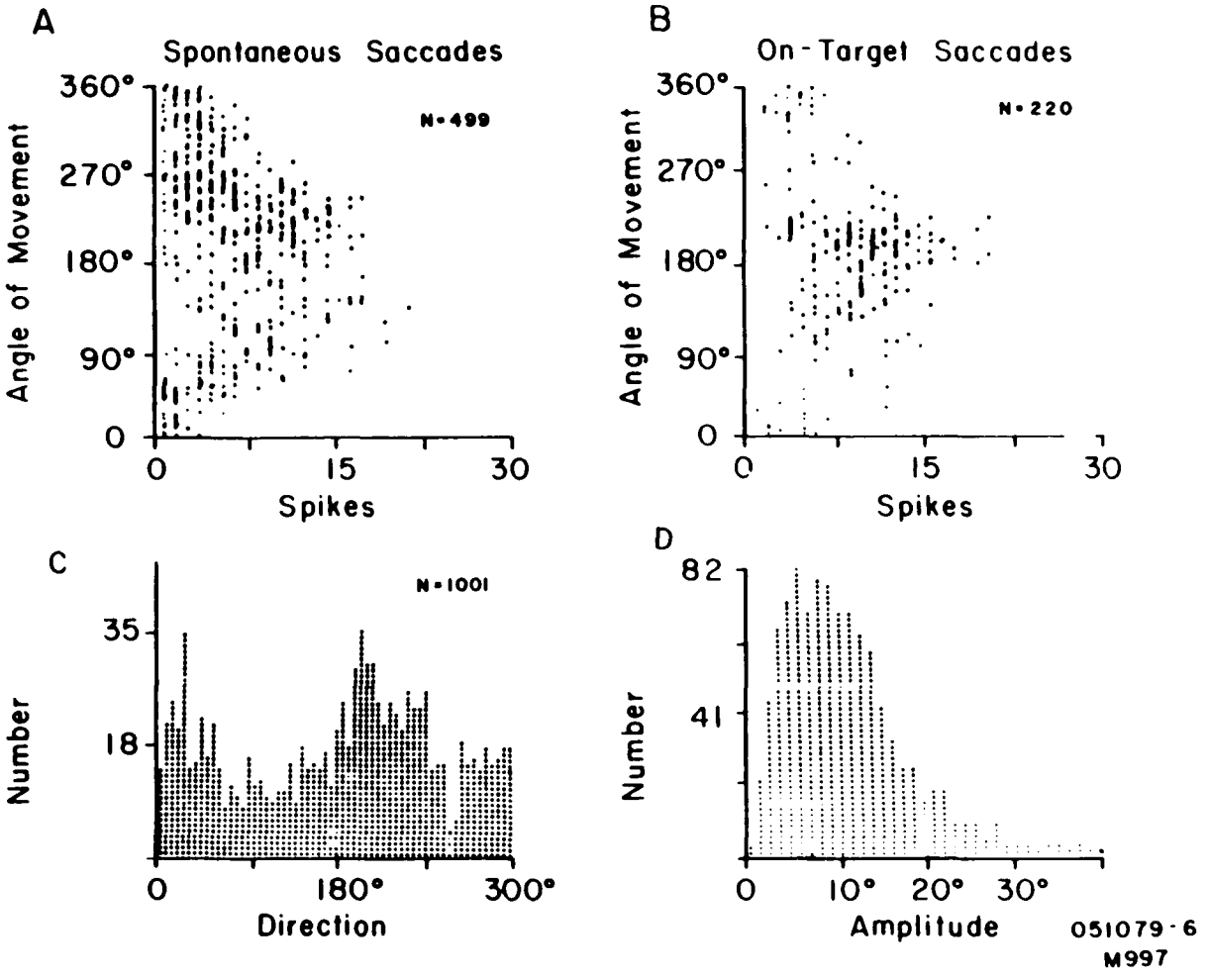
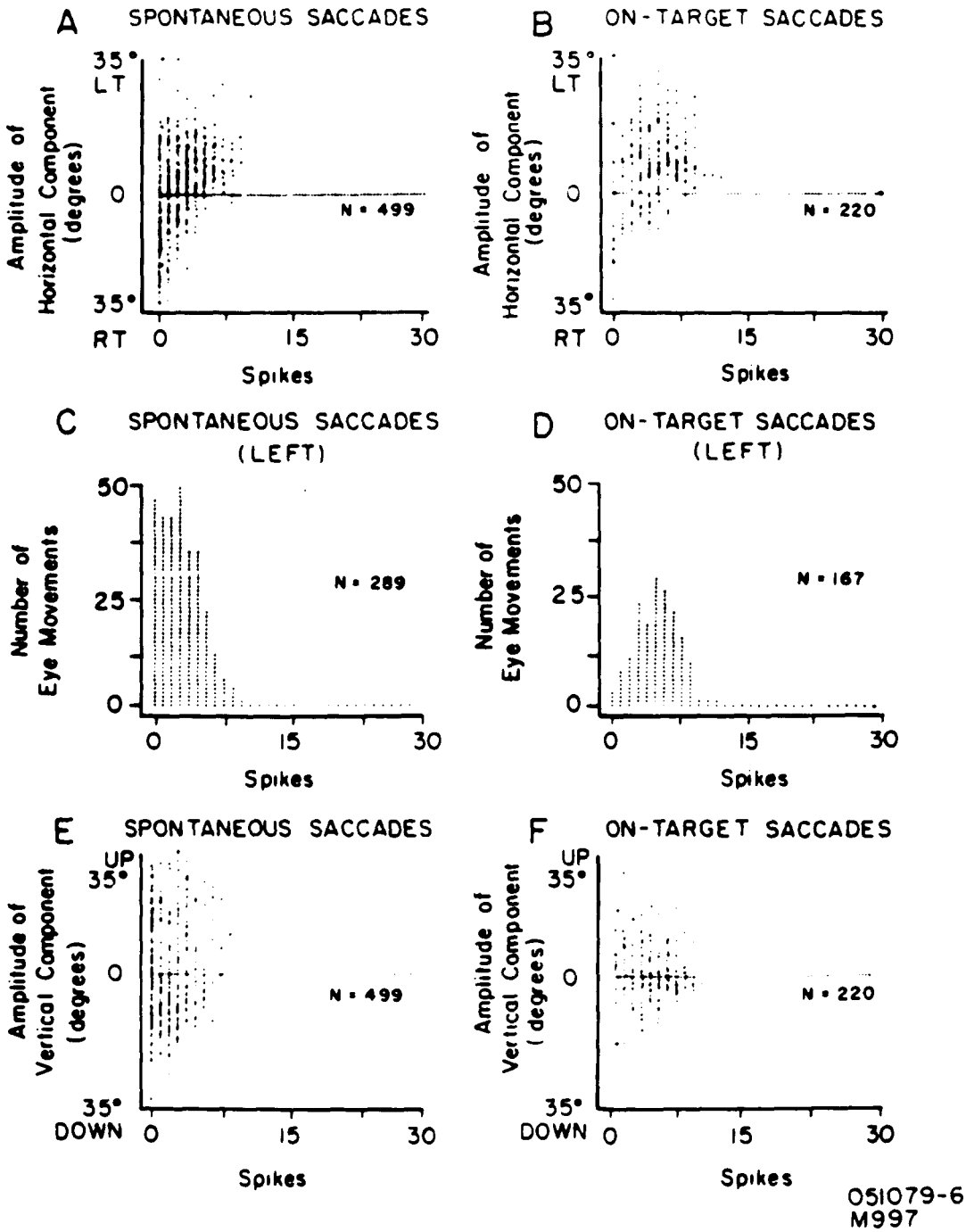

A
Spontaneous Saccades
N=499
360°
270°
180°
90°
0
Angle of Movement
0
15
30
Spikes
B
On-Target Saccades
N=220
360°
270°
180°
90°
0
Angle of Movement
0
15
30
Spikes
C
N=1001
35
18
Number
0
180°
300°
Direction
D
82
41
Number
0
10°
20°
30°
Amplitude
051079-6
M997

Fig. 26: Amplitude vs. number of spikes before saccades for unit U051079-6. The abscissa in each graph shows the number of spikes in the 32 msec interval which preceded the saccade. In A and B the amplitude of the horizontal component of movement (in degrees) is plotted on the ordinate. Eye movements with no horizontal component are at zero. Increasing amplitude to the left is indicated above and increasing amplitude to the right is shown below the zero line. A, When spontaneous saccades had a horizontal component to the left there was a greater number of spikes than for movements to the right. This was also true for on-target saccade (B). The histograms in C and D indicate the number of leftward eye movements (on the ordinate) associated with different numbers of spikes in the specified interval. Firing tended to be higher in association with leftward on-target saccades. The modes are 50 movements at bin 3 for C and 29 movements at bin 5 for D. The vertical component of movement is plotted against number of spikes in E and F. No relationship was found for either the spontaneous (E) or on-target (F) saccades.

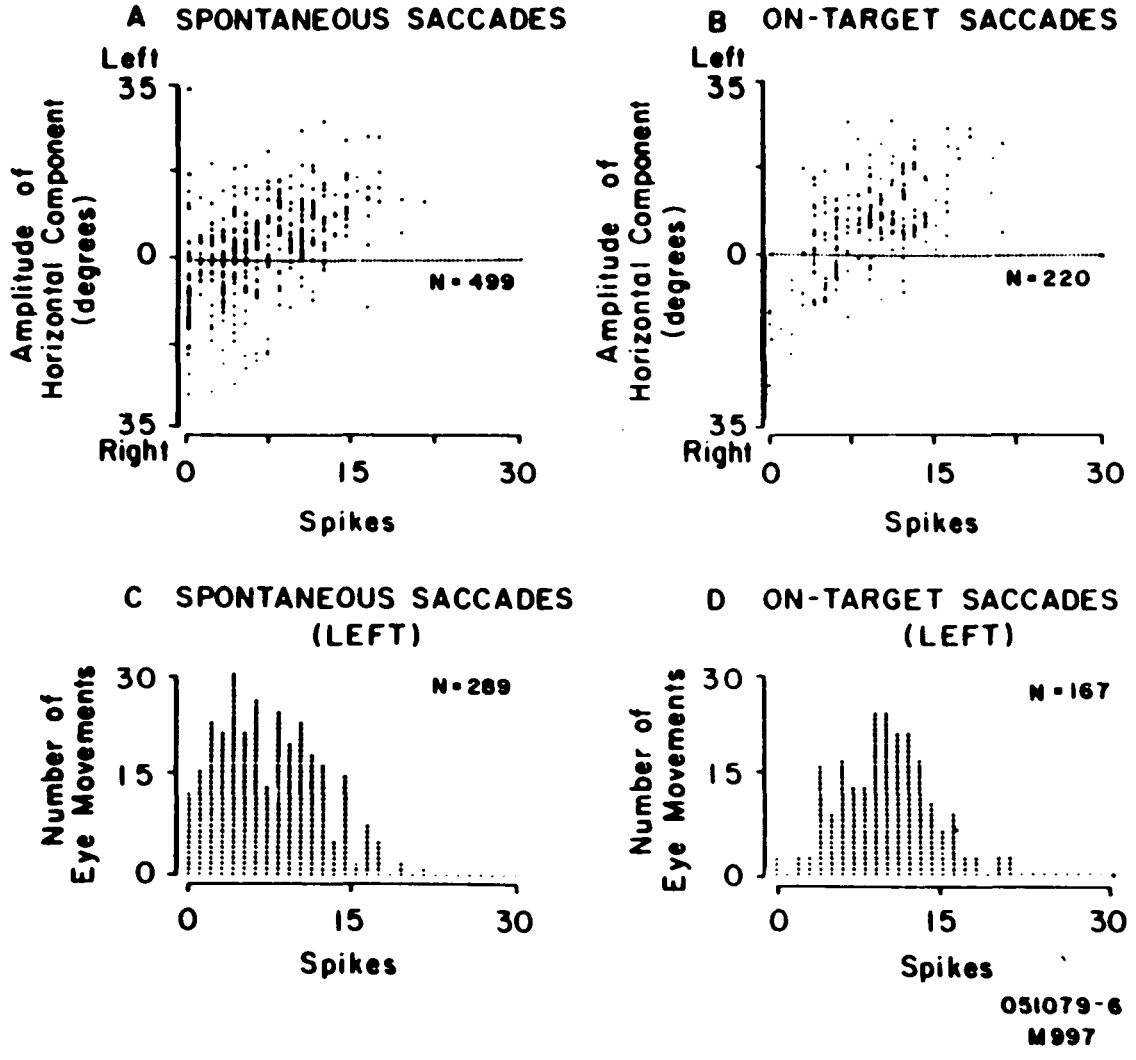

A
SPONTANEOUS SACCADES
Amplitude of Horizontal Component (degrees)
35° LT
0
35° RT
N = 499
0
15
30
Spikes
B
ON-TARGET SACCADES
Amplitude of Horizontal Component (degrees)
35° LT
0
35° RT
N = 220
0
15
30
Spikes
C
SPONTANEOUS SACCADES (LEFT)
Number of Eye Movements
50
25
0
N = 289
0
15
30
Spikes
D
ON-TARGET SACCADES (LEFT)
Number of Eye Movements
50
25
0
N = 167
0
15
30
Spikes
E
SPONTANEOUS SACCADES
Amplitude of Vertical Component (degrees)
UP 35°
0
35° DOWN
N = 499
0
15
30
Spikes
F
ON-TARGET SACCADES
Amplitude of Vertical Component (degrees)
UP 35°
0
35° DOWN
N = 220
0
15
30
Spikes
051079-6
M997

parts C and D. Even though the modes for the two sets of leftward movements were separated by just 2 spikes/interval, the concentration of on-target movements in the range of 3 to 8 spikes was much higher for on-target than for the spontaneous movements which were clustered into the 0 to 5 range. There were no correlations between the number of spikes in the burst (N) and the component of movement in the vertical plane (parts E and F).

When the period of analysis was extended to include 32 msec before the movement to 4.8 msec before the end of the movement, the entire burst of firing was encompassed for almost all movements. For many of the burst neurons the high background activity during periods of fixation was irregular and was not related to eye position. This made it unnecessary to correct for the number of spikes that occurred in the different time intervals associated with eye movements of varying amplitudes. Furthermore, these cells typically continued to fire for some time (up to 100 msec) after the end of many on-target leftward movements. This activity was not considered in the present analysis.

Analysis of the period encompassing the entire eye movement is shown in Fig. 27. Large sized movements were associated with a greater number of spikes in the analysis interval than smaller saccades. This positive association was present for both the spontaneous and on-target movements. Very few of the two degree leftward saccades were associated with more than 7 spikes whereas most 12 degree leftward movements contained more than 4 to 5 spikes. Restated: the burst associated with most 2 degree saccades contained from 0 to 7 spikes, while the burst

Fig. 27: Amplitude vs. number of spikes in the burst for unit U051079-6. The analysis period began 32 msec before the eye movement and extended to 4.8 msec before the end of the movement. These graphs should be compared to those in A-D of Fig. 26 where the period of analysis went just to the onset of movement. A, There was an increase in amplitude to the left as spike number increased. B, This relationship was also present during on-target movements. Below each of these graphs is a histogram of the leftward movements. On-target movements (D) were associated with more spikes than spontaneous saccades (C). The modes for C and D were 30 movements at bin 4 for spontaneous saccades (C) and 27 movements at bin 9 for the on-target saccades (D).

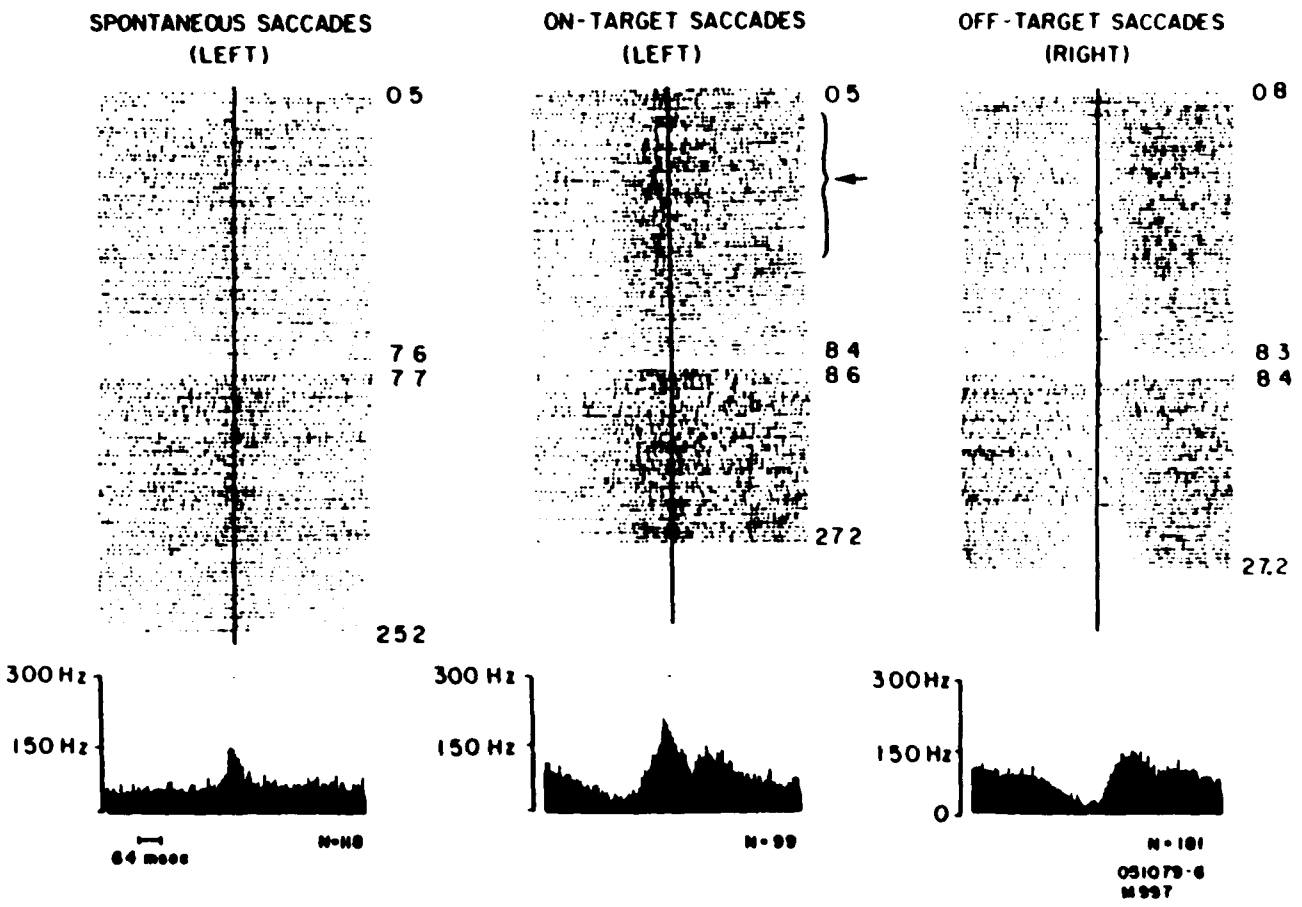

A SPONTANEOUS SACCADES
Left
35
0
35
Right
Amplitude of Horizontal Component (degrees)
N = 499
0
15
30
Spikes
B ON-TARGET SACCADES
Left
35
0
35
Right
Amplitude of Horizontal Component (degrees)
N = 220
0
15
30
Spikes
C SPONTANEOUS SACCADES (LEFT)
Number of Eye Movements
30
15
0
N = 289
0
15
30
Spikes
D ON-TARGET SACCADES (LEFT)
Number of Eye Movements
30
15
0
N = 167
0
15
30
Spikes
051079-6
M997

associated with most 12 degree saccades contained from 4 to 12 spikes.

Histograms of this data demonstrate that left visually targeted movements could be separated from the spontaneous movements on the basis of the number of spikes contained in the period of analysis (Fig. 27C and D). There were more spontaneous movements than on-target movements that had no spikes associated with the movement. The modes were 4 and 9 spikes/interval, respectively. There was no relationship between number of spikes and saccade direction or size in the vertical plane (not shown).

The relatively loose relationship between saccade size and number of spikes in the associated burst was puzzling in light of the close association of neural firing with amplitude which was demonstrated in the stimulation/recording experiments. This suggested that other parameters might be related to saccade amplitude. This was pursued by constructing ordered rasters of spike activity using the horizontal component of movement as the ordering variable. Rasters for contralateral spontaneous on-target movements and ipsilateral off-target movements are shown in Fig. 28. The rasters span a range from 0.5 to 27 degrees of amplitude with the smaller movements shown at the top and the larger movements at the bottom. There was no striking difference in firing associated with different sized spontaneous saccades (Fig. 28, left). For on-target movements, however, there was a general increase in burst duration with increased horizontal amplitude of the movement. Since the duration of large movements is longer than for small movements this provides an explanation for the rough positive relationship between

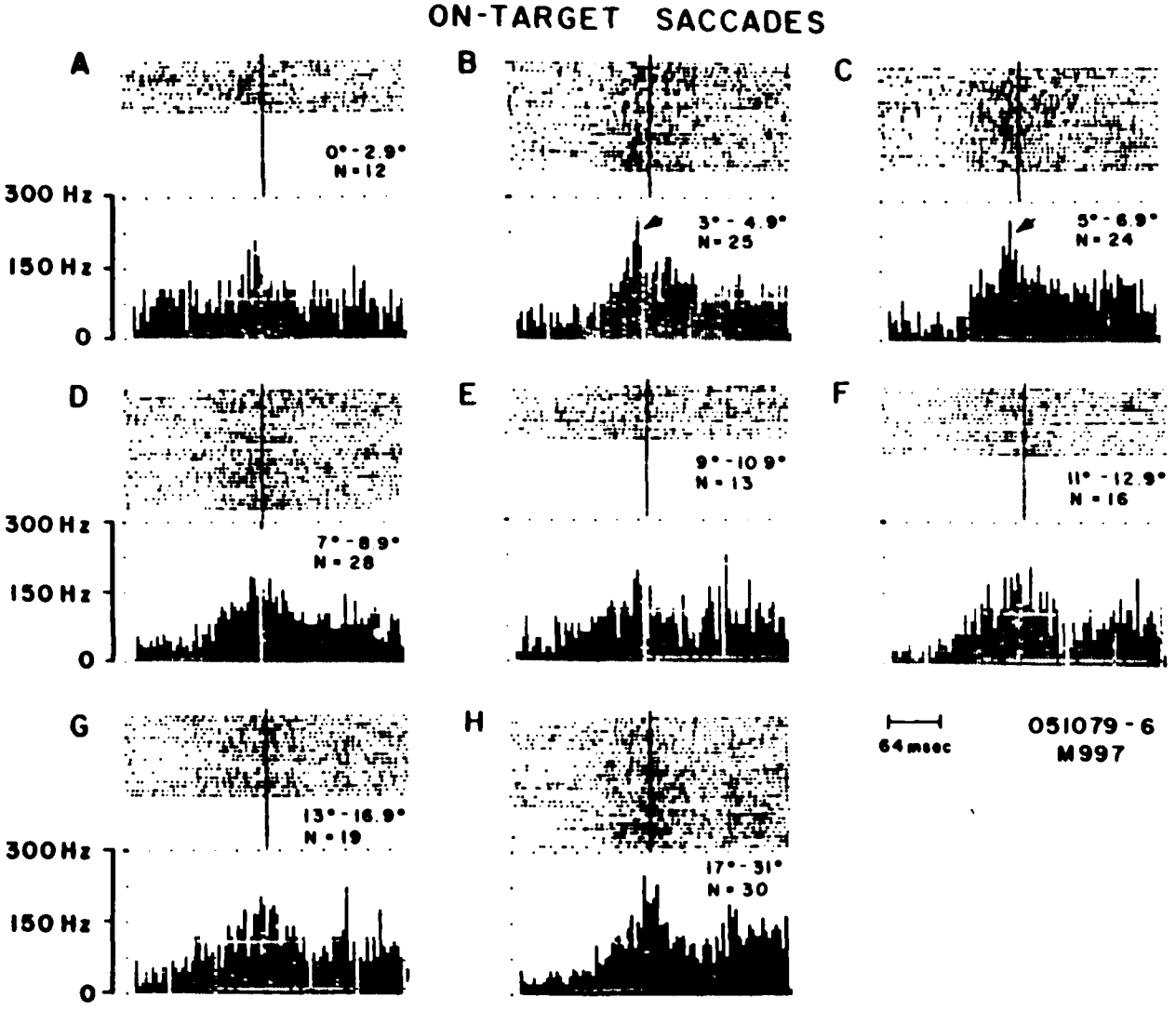
Fig. 28: Raster ordered for amplitude of movement for unit activity of neuron U051079-6. Small saccades were associated with firing shown on the top and large saccades with activity on the bottom. The vertical scale is not linear but reflects occurrence of the various sized eye movements. Several amplitudes are marked. These were related to the beginning and end of computer files used to generate the rasters. Spontaneous saccades are shown on the left. There was an increase in firing during the movements as shown in the histogram below but there were no striking changes in unit activity associated with differences in amplitude. Activity in the histogram below was collected into 4.8 msec bins. Averaged peak activity over 118 movements was 150 spikes/sec. The middle column shows on-target movements to the left. The peak of activity shown by the clustering of black dots began earlier for saccades in the range of 3-6 degrees (bracket and arrow). It came after or at the beginning of saccade of other sizes. The peak activity averaged over 99 movements was 275 spikes/sec shown in the histogram below. Note the increased background level of firing and the decrease in firing before the burst related to the prior off-target saccade. The third column shows ipsilateral off-target movements which were associated with inhibition of firing. Although the inhibition did not appear to be amplitude specific, it tended to be longer before saccades of larger amplitude. The period of inhibition extended past the end of the saccades. 104 movements were used to form the ordered raster in the third column; the histogram contains data from 181 movements. The increase in firing which followed the inhibition was secondary to contralateral on-target saccades which occurred 60 to 200 msec after the off-target saccades.


SPONTANEOUS SACCADES
(LEFT)
ON-TARGET SACCADES
(LEFT)
OFF-TARGET SACCADES
(RIGHT)
05
76
77
252
05
84
86
272
08
83
84
27.2
300 Hz
150 Hz
64 msec
N=48
300 Hz
150 Hz
N=99
300Hz
150 Hz
0
N=181
051079-6
M997

saccade amplitude and number of spikes found in Figs. 26 and 27. An unexpected result of this analysis was that the most intense bursts of activity began before eye movements of particular sizes and occurred at or after the beginning of other eye movements. Specifically, the highest density of points before the onset of eye movements was in the range of 2 to 6 degrees (Fig. 28, center, bracket). The approximate center of this region is shown by the arrow. The high density of neural firing in association with other saccades of 0.5 to 2 degrees and 6 to 12 degrees came at the start of the movement. The high cluster of points came after the beginning of on-target contralateral saccades of greater than 12 degrees. This occurred despite the fact that long-lead activity tended to begin earlier for saccades of larger sizes. The period of inhibition of neural activity associated with right off-target movements also tended to increase as saccade size became larger (Fig. 28, right).

To demonstrate the earlier occurrence for peak activity during movements of certain amplitudes, movements were separated into groups of different sizes (0.5 - 1.99 degreees, 2.0 - 3.99 degrees, 4.00 - 5.99 degrees, etc.) and rasters and histograms of the number of spikes were plotted (Fig. 29A to H). Peak frequencies occurred earliest for saccades of 2 - 6 degrees, and preceded eye movements by 10 to 30 msec (Fig. 29B and C, arrows). Though the cell fired actively for larger saccades, peak frequencies did not reach the same level as during smaller saccades. Thus, although the burst associated with larger on-target eye movements had more spikes than the burst associated with

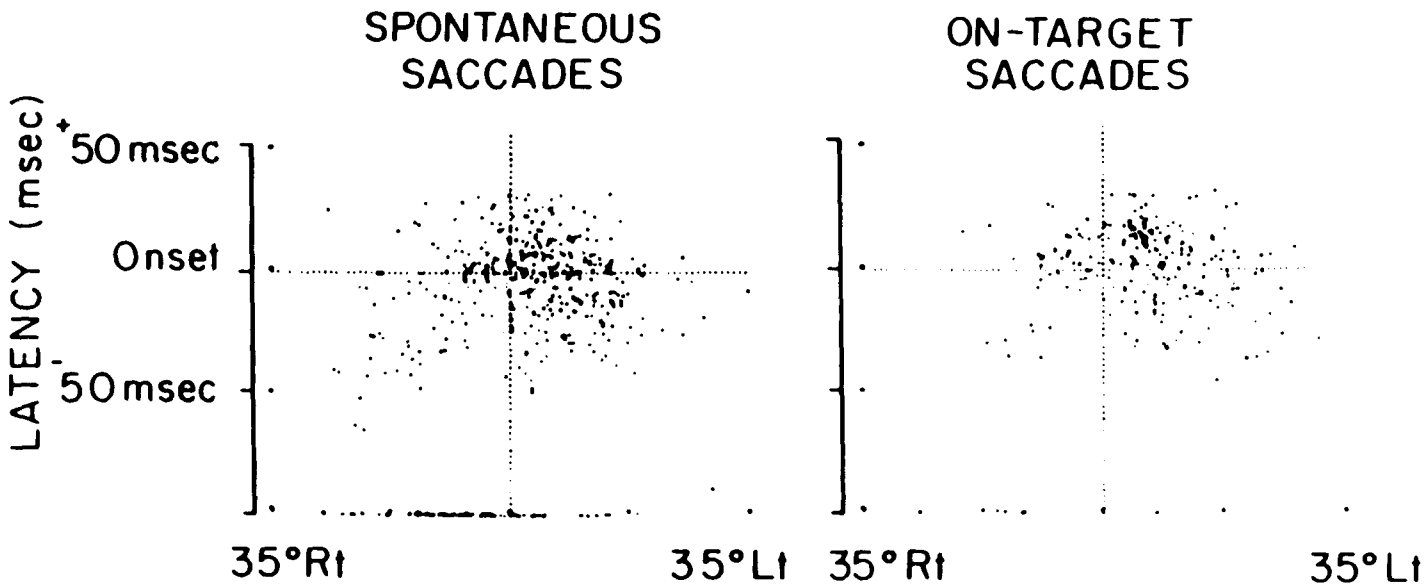
Fig. 29: Rasters and histograms of unit activity associated with on-target saccades of different sizes for U051079-6. The data from Fig. 28, center, was used to generate this figure. A to H show rasters collected into groups containing on-target eye movements of specific amplitudes. The histograms immediately below the rasters were scaled for N=30 and a peak of 300 spikes/sec. Peak activity had the highest frequency and occurred earliest in B and C in association with on-target movements of 3 to 7 degrees, where it led the onset of the saccade by about 20 to 25 msec.


ON-TARGET SACCADES
A
0° - 2.9°
N = 12
300 Hz
150 Hz
0
B
3° - 4.9°
N = 25
C
5° - 6.9°
N = 24
D
7° - 8.9°
N = 28
E
9° - 10.9°
N = 13
F
11° - 12.9°
N = 16
G
13° - 16.9°
N = 19
H
17° - 31°
N = 30
64 msec
051079 - 6
M997

smaller targeted eye movements, it occurred over a longer interval and the point at which the peak firing occurred was delayed until after the start of the movement (Fig. 29G). The second peak shown in the histogram constructed from large saccades in Fig. 29H is probably related to the occurrence of a small refixation or corrective saccade that was made after the initial large on-target movement.

In order to analyze the time of occurrence of peak activity of firing in relation to size and onset of movement, a program was written which would find the shortest interspike interval (i.e. highest frequency) during the interval from 32 msec before eye movement to 4.8 msec before the end. The interspike intervals immediately preceding and following the shortest interval were also determined. The reciprocal of the average of these three periods was called the mean peak frequency (Fmax). The latency from the beginning of the shortest interspike interval to the beginning of spontaneous and on-target saccades is shown in Fig. 30. The peak firing either preceded or came after the onset of, or was not found for spontaneous movements. The peak firing for saccades with horizontal components of amplitude from 5 degrees right to 7 degrees left preceded the movement by about 0 to 10 msec (Fig. 30 left). For spontaneous saccades whose amplitudes fell outside of this range of amplitudes (5 deg R to 7 deg L) the peak activity occurred after the beginning of the movement (negative latency). Many spontaneous eye movements had no associated peak frequency (points at the bottom of the graph) in the interval studied (from 32 msec before the beginning until 4.8 msec before the end of the movement). During

Fig. 30: Latency of peak firing vs. saccade amplitude for U051079-6. The peak frequency for this and the following figure was determined by finding the shortest interspike interval in a period which began 32 msec before a contralateral spontaneous or on-target saccade and ended 4.8 msec before the saccade end. Each frequency was then calculated as described in text. The time of peak firing is positive if before and negative if after the beginning of the saccade and is shown on the ordinate. The amplitude of the saccade in the horizontal plane is shown on the abscissa. Peak firing of spontaneous saccades (N=499), shown on the left-side, were clustered at and around the onset of movement. The dots along the bottom of the graph indicate movements which were not associated with spikes or which had their peak frequency occur more than 100 msec after the beginning of the saccade. The on-target saccades (N=220) shown by the graph on the right had peak firing which occurred 20 msec before saccade onset. The heavy cluster of points with large positive latency were for contralateral (left) on-target saccades of 4-6 degrees.

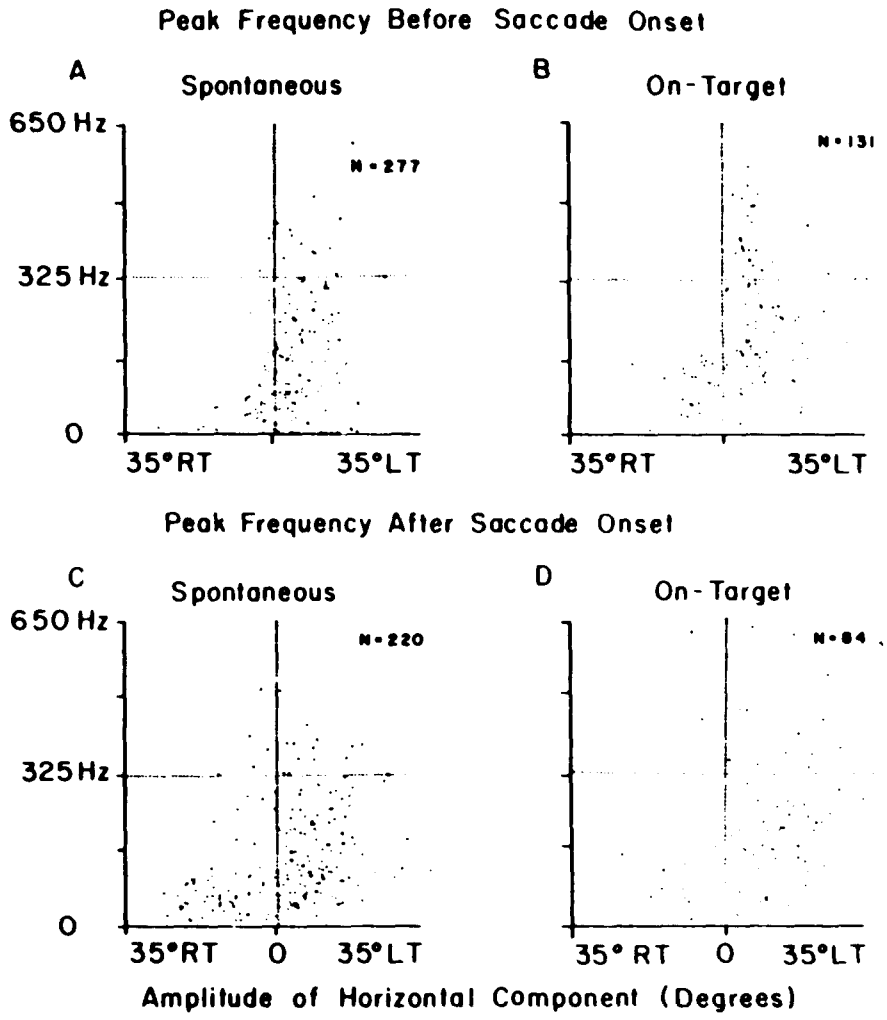


051079-6
M 997

performance of the task (Fig. 30, right), there were many 4-5 deg leftward saccades that were preceded by peaks of firing at an early latency. Larger movements were generally associated with smaller positive latencies or negative latencies. There were fewer on-target than spontaneous movements whose peak frequency occurred after the beginning of the movement. This suggests that the effect of attention and visual guidance on this cell was to cause peak firing to occur earlier and to inhibit the cell from firing in association with saccades to the ipsilateral (right) side.

The positive shift in latency for on-target saccades shown in Fig. 30, right, was also associated with an increase in the peak frequency (Fig. 31). The eye movements were divided into two groups: those whose peak frequency occurred prior to the eye movement (A and B) and those whose peak frequency came at or after the start of the saccade (C and D). The majority of spontaneous eye movements had peak frequencies that fell in the range of 100 to 325 Hz. Peak frequencies before spontaneous movements (A) rarely exceeded 400 to 500 Hz and were associated almost exclusively with leftward eye movements in the range of 3 to 15 degrees. During on-target movements, on the other hand, there was a precise clustering of peak frequencies in the 325 to 625 Hz range in association with saccades of 4 to 6 degrees. Peak frequencies were lower for saccades that fell outside this range. The clustering of movements with high peak frequencies in the amplitude range of 4 to 6 degrees corresponds to the movements shown in Fig. 30, right, which had the longest positive latency.

Fig. 31: Peak frequency before and after saccade onset vs. saccade amplitude for U051079-6. Same unit as in previous figure. Ordinate indicates peak frequency of firing and amplitude of horizontal component is shown on the abscissa. Spontaneous saccades whose peak frequency occurred before the eye movement are shown in A. Most bursts did not exceed 450 Hz and only a few were higher than 325 Hz. On-target movements shown in B had higher peak frequencies and the maximum peak frequency occurred before contralateral saccades with horizontal components of 4-6 degree amplitude. This maximum corresponded to the dense clustering of movements seen in Fig. 30 (right) for on-target saccades. Peak frequencies which occurred after the beginning of the saccade are shown in C and D. Few spontaneous saccades (C) had peak frequencies above 325 spikes/sec. There were many fewer movements which occurred after the onset of on-target saccades (D), and the firing was generally associated with larger 17 to 35 degree saccades.


Peak Frequency Before Saccade Onset
A
Spontaneous
650 Hz
325 Hz
0
N = 277
35°RT
35°LT
B
On-Target
N = 131
35°RT
35°LT
Peak Frequency After Saccade Onset
C
Spontaneous
650 Hz
325 Hz
0
N = 220
35°RT
0
35°LT
D
On-Target
N = 84
35° RT
0
35°LT
Amplitude of Horizontal Component (Degrees)

The two lower graphs of Fig. 31 (C and D) show eye movements whose peak frequencies fell after the beginning of the movement. Such bursts rarely exceeded 500 Hz. For the spontaneous movements (C) there was a general increase in peak firing associated with leftward eye movements, but it was not possible to differentiate either the direction or the size of the associated movement from the parameters of the burst. The separation of saccades into positive and negative latency also separated eye movements of different amplitudes. Peak frequencies of larger movements generally occurred after the eye movement had begun (Fig. 31C and D). Small spontaneous leftward movements were associated with either a positive or negative latency (Fig. 31A and C). Small on-target saccades, however, usually were associated with peak frequencies that occurred before the onset of eye movement (Fig. 31B). The sharp peak of activity which preceded small on-target movements, Fig. 31B, indicates that both saccade size and direction were associated with latency and magnitude of the peak frequency in this unit. Moreover, these figures demonstrate that the positive latency of peak firing was most closely associated with the size of the upcoming saccade.

CHAPTER 4

DISCUSSION

This study has characterized neural activity in the MRF, a region that appears to be important for producing or controlling spontaneous and visually evoked saccadic eye movements (Szentágothai, 1943; Bender and Shanzer, 1964; Komatsuzaki et. al., 1972). The major findings are that there are neurons in the MRF which fire preferentially before saccades whose horizontal component of movement is to the contralateral side and that these neurons begin firing earlier and reach higher peak frequencies before visually guided or visually targeted saccades. There is also a suggestion that the activity of MRF neurons is of earliest latency and highest peak frequency prior to specific sized contralateral rapid eye movements. Moreover, there is a suggestion that this relationship to saccade size may be organized in a dorsal-ventral manner in the MRF. Neurons which were maximally excited prior to small saccades appeared to be located in the dorsal regions of the MRF. Neurons associated with larger rapid eye movements were in ventral regions. The following sections will consider each of these points in terms of a possible role of the MRF in visual-oculomotor processing.

RELATIONSHIP OF MRF BURST NEURONS TO THE DIRECTION OF SACCADES

The results indicate that the MRF is likely to be an area

associated with the generation of visually induced eye movements to the contralateral side. The firing of MRF neurons was highest prior to saccades which had a component of movement in the horizontal plane, and there was no relationship to either vertical or oblique eye movements. Moreover, the tuning of MRF neurons for the contralateral direction was related to behavioral state. The firing was more consistent and the relationship to contralateral saccades was stronger prior to visually induced eye movements than to spontaneous movements.

Clinical and experimental observations have suggested that information for the generation of the horizontal and vertical components of rapid eye movements is processed in separate areas of the brainstem (Goebel et. al., 1971; Cohen et. al., 1968; Kömpf, Pasik, Pasik, and Bender, 1979; Bender, 1980; Bender, Pasik, Pasik, and Rudolph, 1980; Büttner-Ennever, Büttner, Cohen and Baumgartner, 1982). The PPRF appears to be the premotor region responsible for the production of horizontal eye movements. Rostral portions of the MRF and the interstitial nucleus of the MLF appear to be the premotor areas for the production of vertical gaze (Büttner, Büttner-Ennever, and Henn, 1977; Büttner-Ennever and Büttner, 1978; Büttner-Ennever et. al., 1982). How these vectors are separated anatomically and physiologically in supranuclear pathways from the cerebrum is not clear (Bender, 1980). However, it is of interest to compare directionally-specific activity in the MRF with that in the PPRF.

There are two types of neurons in the PPRF whose firing rates appear to be have a relationship to direction. The most specific are

the units in which the firing rate varies by the cosine of the angle between the horizontal plane and a vector representation of saccade amplitude and direction in a polar coordinate system (Henn and Cohen, 1976). The amplitude of saccades does not appear to be represented in the firing pattern of these neurons. These types of neurons were not encountered in the MRF. A second type of PPRF neuron has a relationship between number of spikes in a period before the onset of eye movement and amplitude. The relationship between number of spikes and amplitude was weak in MRF neurons, although there was a clear relationship between direction and number of spikes. Thus, while there is directionally-specific information that is temporally related to the onset of eye movement in the MRF, it is not similar to that found in the PPRF. If the MRF is located in descending visual-oculomotor pathways, the MRF burst neurons are situated at a point where horizontal and vertical components of movement are separated. However, the lack of similarity with PPRF burst neurons indicates that the MRF must be above the region where horizontal saccades are actually generated.

DORSAL-VENTRAL ORGANIZATION OF MRF MOVEMENT FIELDS

Relationship to Saccade Amplitude

The stimulation results suggest that the MRF is arranged in a specific topographic fashion with respect to saccade amplitude. The

region from which small movements were elicited in this and another study (Cohen, Matsuo, Raphan, Waitzman, and Fradin, 1982) was dorsal in the MRF. Large saccades were always elicited from ventral portions of the MRF. This suggests that the response to stimulation can be used to indicate the dorsal or ventral position of the microelectrode.

In various tracks cells were encountered which fired primarily in relation to small or large eye movements. Stimulation at loci where cells were related to small saccades elicited small saccades. These sites appeared to lie more dorsal in the MRF. Neurons whose peak activity was greatest and occurred earliest for saccades with large amplitudes (10 to 15 degrees) appeared to be located more ventral in the MRF. This suggests that there is also a topographic organization of cells whose activity is related to saccades of different sizes in the MRF as well.

This anatomic organization is similar to the spatial-motor maps seen in other supranuclear visual areas like the superior colliculus and the frontal eye fields execept that only the horizontal component of movement is represented in the MRF. In this regard it is of interest that there is a differential projection from the superior colliculus into nucleus cuneiformis (Cohen, Buttner-Ennever, Waitzman, and Bender, 1981). The caudal colliculus where large saccades can be elicited by microstimulation and where cells with large movement fields have been recorded, projects to the ventral (large saccade) area of the MRF. The rostral colliculus where cells have foveal and para-foveal movement fields projects to the dorsal (small saccade) portion of the MRF (Cohen et. al., 1981). The physiologic and anatomic correspondence with the

superior colliculus may situate the MRF close to the SC in supranuclear visual-oculomotor pathways. The apparent separation of the horizontal vector in the MRF suggests that the neural processing in the MRF is either independent of or after that occuring in the superior colliculus where both horizontal and vertical components of the saccade are represented.

Relationship of the MRF to Gaze

It has recently been suggested that the SC in the cat has a relationship to gaze. Stimulation of the SC anteriorly produces retinotopically oriented eye movements (Guitton, Crommelinck and Roucoux, 1980; Roucoux, Guitton and Crommelinck, 1980). Stimulation of intermediate collicular areas elicits both a head saccade and eye saccade. The VOR adjusts the size of the eye saccade, terminating it so that gaze remains fixed in space during the head movement. Stimulating more posteriorly causes the production of gaze shifts of up to 60 degrees in which both head movements and forward eye movements are elicited (Guitton et al., 1980; Roucoux et al., 1980). The VOR appears to be inactivated during these large gaze shifts. The specific interconnections of posterior colliculus with the ventral MRF (Cohen et. al., 1981), and the similarity in the size of eye movements elicited by stimulation of both of these areas suggests that the MRF may also play a role in large shifts in gaze. (This assumes that functionally the superior colliculus is similar in the monkey and the cat.) Older

evidence supports the possibility that the MRF may participate in gaze shifts. Stimulation in the MRF in freely moving monkeys produced a combined head and eye movement to the contralateral side (Wagman, 1964; Bender and Shanzer, 1964). Lesions in the same area caused an ipsilateral gaze preference and a head tilt (Bender and Shanzer, 1964). More recently an efferent pathway from the MRF to the cervical spinal cord has been demonstrated in the monkey using HRP (Castiglioni et. al., 1978).

If the activity of MRF neurons was related to shifts in gaze (i.e. to movements of the eyes and head) then some of the imprecision in the analysis of neural activity in the MRF might be accounted for by a relationship of activity in some neurons to intended head movement during gaze shifts. The initial pulse of activity of MRF burst neurons might then be directed to the PPRF and the prolonged activity to either spinal cord or vestibular system. This remains an area for further investigation.

OCULOMOTOR SYSTEM MODELS AND MRF BURST ACTIVITY

The experiments characterizing MRF neurons provide clues that both timing (latency) of peak firing and the activation of specific anatomic channels are important variables for the triggering of visually evoked saccades. These variables may assist in determining the direction and amplitude of visually initiated saccades. Models of the oculomotor system suggest that the input to the medium lead burst neurons is a

motor error signal (Robinson, 1975; Robinson, 1981; Van Gisbergen et. al., 1981). This signal is derived by taking the difference between desired eye position and an internal feedback of instantaneous eye position. In Robinson's model a saccade is initiated by a trigger signal which inhibits omnipause neurons. This trigger momentarily releases the medium lead burst neurons from inhibition allowing them to generate a saccade based on the current motor error (Van Gisbergen et. al., 1981). The activation of the medium lead burst neurons closes a switch (i.e., the latch) which continues to inhibit the omnipause neurons until motor error is zero (i.e., the medium lead burst neurons stop firing). MRF burst neurons could participate in such a scheme by mediating both a trigger signal from the visual system and a motor error signal. The firing patterns of the MRF neurons do not appear to be appropriate for mediating a signal related to desired eye positon.

Several pieces of evidence suggest that MRF burst neurons might process a trigger signal for the production of saccadic eye movements. Pathways from nucleus cuneiformis to the omnipause region (pontine raphe nucleus) have been demonstrated in both cat and monkey using radioactive tracers techniques (Edwards, 1975; Edwards and deOlmos, 1976; Harting, 1977; Harting et. al., 1980; Cohen et. al., 1981). Electrical stimulation of the MRF at subthreshold levels enhances the production of contralateral quick phases during OKN (Matsuo et. al., 1980; Cohen et. al., 1982). The peak of activity in MRF burst neurons prior to visually guided saccades (peak frequency to saccade onset of 15 msec) is temporally linked to onset of inhibition in omnipause neurons (Keller,

1974; Keller, 1977).

The apparent dorsal-ventral distribution of MRF activity may, in addition, represent an anatomical map of motor error for visually evoked saccades to the contralateral side. This would account for the association with direction to the contralateral side. The latency of MRF discharge (15 msec) prior to visually evoked saccades of the specified size is appropriate for driving medium lead burst neurons and the MRF projects to portions of rostral PPRF and nucleus reticularis tegmenti pontis where saccades may be generated (Edwards, 1975; Edwards et. al., 1976; Harting, 1977; Cohen et. al., 1981). Ascending efferent connections from pontine levels which appear to project to the MRF (Graybiel, 1977; Hikosaka and Igusa, 1980) might supply an efference copy of eye position from the neural integrator (prepositus and periabducens regions) that could be used in formulating motor error.

Short lead, tightly coupled superior colliculus cells have been hypothesized to supply a trigger signal for saccades (Mays and Sparks, 1980; Sparks and Mays, 1980). Alternatively, the SC could supply both a trigger and a MRF motor error signal in the horizontal plane that work in concert to produce visually evoked saccades. A hypothetical scheme utilizing the discharge of both SC and MRF burst neurons to trigger and generate visually evoked saccades could occur via two pathways (Schiller et. al., 1979, 1980). One could utilize connections which travel via the superior colliculus. A second pathway might utilize connections in the reticular formation (Schiller, True and Conway, 1980). The timing and distribution of neural discharges in both the SC and the MRF would

be appropriate for inhibiting omnipause neurons and supplying motor error to medium lead burst neurons. Probably an ensemble average of activity from a number of different neurons in different anatomical locations within the brainstem is responsible for triggering (or gating) saccades of different sizes. It would be more parsimonious if the trigger and the motor error signal were one and the same but, further details of this spatial-temporal transformation between SC or MRF and the PPRF are as yet unclear.

MRF BURST NEURONS AND ENHANCEMENT

The results suggest that there are two types of enhancement of neural firing which occurs in the MRF i.e., specific activation related to production of visually induced eye movements and general enhancement related to behavioral state. Increased peak activity and early latency prior to both on-target and guided, but not off-target or spontaneous saccades appears to be a specific augmentation of the burst before eye movements. The enhanced firing prior to the visually induced eye movements was not due to an increase in the background activity since there was also enhancement of the peak activity prior to visually induced saccades even in MRF neurons whose background activity decreased during target fixation. This enhancement appears to be the same for both on-target and visually guided movements suggesting that at the level of the MRF there was no difference in the firing associated with on-target and visually guided saccades (vide infra).

There was also general enhancement of the background activity during intersaccadic target fixations. For a number of MRF neurons the background activity increased as the animal pressed the bar and began searching for the target. This increase continued until the animal detected the dimming of the light and released the bar.

Other studies have suggested that there is a relationship between MRF neural activity and visual attention as well as to general arousal of the animal. Bakay-Pragay et. al. (1978) recorded activity in the mesopontine reticular formation (MPRF) of the monkey during a visual attention task. Activity of phasic cells was enhanced in relation to "go" (motor) trials. There was also a tonic increase in other neurons that was thought to reflect an availability of reinforcement or an increase in long-term arousal. There was some difficulty in interpreting the results because eye movements were not measured, neurons were recorded from many areas of the brainstem and an analysis on a trial-by-trial basis was not attempted. However, the study did indicate that attention to visual phenomena and arousal are important factors for enhanced activity in the reticular formation.

Lesion and stimulation results have also provided clues that the MRF may play a role in mediating both specific and general attentional responses. Trimodal (visual, tactile, and auditory) neglect was produced by discrete lesions in the MRF of stump-tailed monkeys (Watson, Heilman, Miller, and King, 1974). Unilateral stimulation in the MRF seems to impair attention in a selective visual discrimination task (Bakay-Pakay et. al., 1975). Bilateral stimulation in the dorsal MRF

causes the eyes to be "pinned" to one location as soon as the stimulus is applied (Cohen and Matsuo, unpublished observations). These experiments have suggested that the bilateral increases in background activity seen in intersaccadic periods may be a part of a fixation mechanism to hold the eyes on target by inhibiting saccade generation in the pons. Alternatively, this enhancement of the background level may be representative of a general increase in the state of alertness or arousal.

Over what pathways the enhancement seen in the MRF is generated is not known. Several studies indicate that there may be a convergence of inputs from various areas of the cortex where enhancement of neural responses to visual stimuli are occuring. The more general enhancement of background activity of MRF cells could arise from inferior parietal lobule and superior temporal gyrus in the cortex. Neglect or inattention has been produced by discrete lesions in the inferior parietal lobule-superior temporal gyrus (Welch and Stuteville, 1958; Heilman, Pandya, and Geschwind, 1970). Single unit studies in the inferior parietal lobule have shown that these cells have enhanced activity prior to a variety of attention tasks (Lynch et. al., 1977; Yin and Mountcastle, 1978; Bushnell et. al., 1981). The parietal cortex projects to the cingulate gyrus which has been shown to project to the MRF (Crosby, Humphrey, and Laver, 1962; Pandya and Kuypers, 1969). Cingulectomy itself has been shown to produce neglect in primates (Watson, Heilman, and Cauthen, 1973).

Eye movement specific enhancement seen in the MRF could come from the superior colliculus and the frontal cortex. Frontal arcuate lesions

have been shown to produce neglect (Welch and Stuteville, 1958; Eidelberg and Schwartz, 1971). Units in the frontal eye fields and the superor colliculus have specific enhancement of firing rates prior to saccades which foveate targets (Goldberg and Wurtz, 1972b; Wurtz and Goldberg, 1972c; Wurtz and Mohler, 1976a; Wurtz and Mohler, 1976b; Wurtz, Goldberg and Robinson, 1980; Goldberg and Bushnell, 1981). The frontal cortex projects to both SC and cingulate gyrus, areas with efferents to the MRF. However, the number and significance of direct projections between FEF and the MRF are not clear. Degeneration methods show a substantial number of fibers arising in the FEF (Brodman area 8) while amino acid tracer techniques show a much smaller projection to the MRF (Kuypers and Lawerence, 1967; Astruc, 1971; Künzle and Akert, 1977; Künzle, 1978; Hartman-von Monakow et. al., 1979). Further investigation is necessary to clarify whether neural enhancement found in the MRF might also be correlated with visually guided hand movements, head movements, or other more general sensory-evoked responses.

COMPARISON OF VISUALLY TARGETED AND VISUALLY GUIDED SACCADES

The majority of the eye movements whose analysis form the basis for this thesis have been termed visually targeted saccades. Our paradigm required the trained monkey to maintain fixation, but distinct from earlier experiments the trial was not aborted when the monkey made extraneous eye movements.

Activity preceding contralateral on-target movements of specific sizes was not different from activity which preceded visually guided movements. Both the step in activity above background 120 msec before and the high burst of activity which preceded on-target movements were both present prior to and during visually guided saccades. These responses were seen in the qualitative data (see Fig. 14B). Although there are undoubtedly differences in how these saccades are initiated, there appears to be no difference in what type of visually induced saccade is produced in the activity of MRF burst neurons.

COMPARISON OF MRF BURST NEURONS TO NEURONS IN FRONTAL EYE FIELDS AND SUPERIOR COLLICULUS

Neurons in the MRF, the deep layers of the superior colliculus (SC) and the frontal eye fields (FEF) have been implicated in the control of visually induced eye movements, but there are differences between them. First, the cells in the MRF do not appear to have the responses to visual stimuli that are present in cells of the superificial layers of the SC. Second, the MRF cells fire specifically for horizontal movements, and they do not have movement fields localized to either vertical meridian. Third, the spontaneous activity of MRF cells is higher than either FEF or SC neurons.

The MRF cells begin firing as early as 120 msec before all contralateral saccades regardless of saccade type: spontaneous or targeted. This activity is similar to that seen in pure saccade cells

in the superior colliculus. However, the MRF cells were also inhibited prior to saccades to the ipsilateral side. Inhibition of a spontaneous firing level prior to ipsilateral saccades was not seen in SC or FEF cells. Superior colliculus cells do not have a shift in peak activity as was demonstrated in MRF neurons prior to saccades of specific amplitude. Rather the movement fields of SC cells show graded responses, i.e. there is a large amount of firing for a 10 degree saccade and proportionately lower amount of firing for a 12 degree saccade. Graded responses were not found in the MRF neurons that were analyzed. For peak activities which preceded saccades (+ latency) there was a narrow range of amplitudes associated with high peak frequencies. For example, U051079-6 fired at high rates in advance of saccades of 3 to 6 degrees. Saccades to the ipsilateral side or of other amplitude ranges were associated with significantly lower and much delayed peak firing rates.

The prolonged after-discharge of many MRF neurons was similar to the quasi-visual cells of Mays and Sparks (1980) which fired for 200 msec or more after the occurrence of the appropriate saccade. They suggest that this after-discharge may be related to the absolute position of targets in space. We did not test the MRF burst neurons in the "eye-position" paradigm used by these and other authors (Mays and Sparks, 1980; Schlag, Schlag-Rey, Peck, Joseph, 1980), but their discharge patterns do not appear to be appropriate (i.e., they do not have tonic firing) to mediate such a signal.

ASCENDING ACTIVITY: MRF BURST NEURONS AND COROLLARY DISCHARGE

The presence of a corollary discharge or efference copy was originally proposed by Helmholtz to account for the stability of the visual world as we move our eyes (Helmholtz, 1859). He envisioned this as a signal distributed in the central nervous system by the neurons that were generating or controlling the upcoming movement. There is now considerable evidence that an ascending corollary discharge from the oculomotor system does not represent the major factor in eliminating saccadic blur (Matin and Matin, 1972; Matin, 1974; MacKay, 1970; MacKay, 1971; Creutzfeld, Noda and Freeman, 1972; Judge, Wurtz and Richmond, 1980). A large part of this stabilization of the visual world is probably due to a rapid displacement of an image across the retina with resulting foward and backward masking in the visual cortex (MacKay, 1970; MacKay, 1971; Jung, 1972; Creutzfeld et. al., 1972; Campell and Wurtz, 1978; Judge et. al., 1980). A number of models of the oculomotor system have suggested that a signal corresponding to absolute eye position (i.e., corollary discharge) should exist for the calculation of motor error (Robinson, 1973; Robinson, 1975; Robinson and Wurtz, 1976; Richmond and Wurtz, 1980; Wurtz, Richmond and Judge, 1980; Robinson, 1981; Van Gisberger et. al., 1981). The firing by MRF neurons during and after saccades is such that it would also be appropriate as a corollary discharge which would assist in the calculation of motor error. Further investigation will be needed to determine the role of such post-saccadic neural firing.

CHAPTER 5

SUMMARY AND CONCLUSIONS:

1. Neurons were recorded in the mesencephalic reticular formation (MRF) of the rhesus monkey that have activity which is related to spontaneous, visually-targeted, and visually-guided saccadic eye movements. The area of the MRF that was studied approximately corresponds to nucleus cuneiformis in the human (Olszewski and Baxter, 1954). In the rhesus monkey its medial border is located 1-2 mm lateral to the oculomotor nuclei. It is about 2 mm in diameter from medial to lateral and 1.5 mm in depth from dorsal to ventral. It extends from A 3.0 to A 6.0 in the rhesus monkey (Snider and Lee, 1961). Its center is located 13 mm above the intra-aural line. In the review of the literature it was shown that this area receives projections from the frontal and parietal cortex and the superior colliculus and projects to the superior colliculus and to regions of the pontine reticular formation which are related to generation of saccadic eye movements.

2. MRF burst neurons fired prior to both targeted and spontaneous contralateral horizontal saccades. There was no relationship to slow eye movements. Increases in frequency above background began as early as 120 msecs before the onset of contralateral saccades and continued for up to 200 msec after the end of movement. Bursts of firing normally occured 20-30 msec before saccade onset. Background activity was

enhanced or suppressed when animals actively fixated a visual target.

3. Burst activity was significantly higher before contralateral visually-guided or targeted movements than before contralateral spontaneous eye movements. There was no apparent difference in burst activity associated with visually-guided and visually-targeted eye movements. Firing of these cells was inhibited prior to ipsilateral saccades. Inhibition before ipsilateral saccades was stronger when the eyes moved off-target than during spontaneous ipsilateral saccades. There was no inhibition in some neurons when the eyes made an ipsilateral on-target saccade.

4. Firing of MRF burst neurons occurred in association with contralateral saccades, and there was no association with the vertical component of movement. There was a rough relationship between the amplitude of the horizontal component and the number of spikes in an interval which began 32 msec before the movement and ended 4.8 msec before the end of movement. Most cells fired in association with saccades over a wide range of amplitudes but it appeared that there was some selectivity for amplitude. Increases in peak frequency and latency of the peak frequency before eye movements appeared related to movements of certain sizes. Neurons were encountered that fired preferentially before small, medium, and large contralateral saccadic movements. No relationship was found to other parameters of saccadic eye movements such as velocity or duration.

5. Other studies have shown that small contralateral saccades are elicited by stimulation in the dorsal MRF and large contralateral

saccades by stimulation in the ventral MRF. Combined stimulation/recording experiments were done to determine the organization of cells related to eye movements of different sizes in the MRF. All cells fired in association with saccades over a wide range of amplitudes. The peak of the firing occurred either before or during contralateral eye movement. However for cells in the dorsal region the peak firing occurred earlier and was higher when it preceded small and medium sized saccades (2 to 4 and 6 to 8 degrees). Small and medium sized saccades were induced by stimulation at these locations. In ventral regions where the earliest and highest peak frequencies occured before larger saccades (e.g. 10-12 degrees), larger saccades were elicited by stimulation. From this it seems likely that there is a dorsal-ventral organization of cells related to eye movements of various sizes in the MRF. This dorsal-ventral organization of the MRF appears to correspond to the rostral-caudal movement field map in the intermediate and deep layers of the colliculus except that only the horizontal component is represented in the MRF. Topographic projections from the superior colliculus to the MRF could provide important input for activating cells related to eye movements of different sizes.

6. Firing of MRF burst neurons was compared to that of cells in the superior colliculus. The MRF neurons that were studied did not have visual receptive fields as do cells in the superficial layers of the superior colliculus. The firing of MRF cells was specifically tuned for horizontal movements to the contralateral side. This was in contrast to activity in the superior colliculus which is associated with vertical

components of movements as well. The spontaneous activity of some MRF neurons is higher than that of superior cclliculus cells. Both MRF and collicular cells increase their activity before contralateral saccades, reach high peak frequencies and have firing that is most intense prior to targeted movements of specific amplitudes and directions. Neuronal discharge after the end of movements is seen in neurons in both structures. However, an increase in the positive latency of peak firing of SC cells prior to visually induced saccades of specific sizes has not been noted.

7. The MRF could make several contributions to the generation of horizontal saccades that presumably takes place in the pons. The temporal sequence and latency of peak activity of MRF neurons before contralateral horizontal saccades could contribute to triggering of visually-induced movements. The increased frequency of MRF nerons in association with saccades of specific sizes suggests that the cells have movement fields. The organization of cells with movement fields in a dorsal-ventral fashion suggests that motor error may be distributed anatomically in the MRF (i.e. by a spatial code).

8. Two types of enhancement have been demonstrated in the firing of MRF neurons, i.e., both specific and general. The specific enhancement associated with visually induced saccades was present regardless of increases or decreases in the background firing. Such activity may be relayed to the MRF via other supranuclear structures like the superior colliculus and frontal eye fields. Specific eye movement related enhancement has been recorded in both these areas. The general enhancement (or suppression) of background activity during intersaccadic

periods may reflect the increased attention required to fixate the target. Such activity could be transmitted to the MRF from parietal cortex where similar responses have been recorded.

9. MRF unit activity could also play a role in fixation via the enhancement (or suppression) of firing which occured during intersaccadic intervals. Activity, especially in ventral areas of the MRF, may be important for producing head movements that might occur in association with eye movements during gaze shifts. Finally, the prolonged discharge after the occurence of a contralateral saccade might be a corollary discharge to the visual system signalling that a rapid eye movement has occured.

10. Considered together with the lesion and stimulation results the MRF neural activity appears to participate actively in the generation of contralateral horizontal saccadic eye movements. This activity may be important in linking the visual and oculomotor systems for the production of visually induced saccades or shifts in gaze.

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