

Brain Research Reviews, 1 (1979) 69-105 ©
Elsevier/North-Holland Biomedical Press

BEHAVIORAL FUNCTIONS OF THE RETICULAR FORMATION

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(Accepted April 2nd, 1979)

Keywords: reticular formation — behavior — unit activity — raphe — locus
coeruleus

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1. INTRODUCTION

The behavioral correlates of activity in medial brain stem reticular formation (RF)* cells have been the subject of intensive investigation since the very first single unit recordings were performed. Early studies concentrated on the response of these cells to sensory stimuli. More recent investigations have focused on the behavioral correlates of RF unit discharge in unanesthetized animals. Many RF studies have been done by investigators interested in testing a variety of specific theories of RF function and, as a result, several independent bodies of literature on RF function have been developed. The conclusions drawn by these different groups of experiments have often been contradictory.

Most studies of RF cells have employed surgical or pharmacological paralysis, or head restraint. Only recently has it been possible to record from RF cells in unrestrained animals. These studies have shown that the majority of RF cells discharge in relation to specific head and body movements. The theme of this review will be that many of the apparent contradictions in the RF behavioral literature can be resolved if one considers the movement relations of these cells. I will not attempt to exhaustively review the enormous literature on RF activity, but will instead focus on selected behavioral investigations that have used unit recording techniques. Data relating specifically to the central gray and to monoaminergic nuclei such as the raphe and locus coeruleus, which are also commonly considered part of the brain stem reticular formation, will not be discussed, but rather the emphasis will be on the paramedial RF core. Studies in the cat will be emphasized, although when relevant, results in other species will be considered. I will first review the different kinds of behavioral studies that have been done on RF neurons and then attempt to show how the findings of these studies can be integrated.

2. BEHAVIORAL CORRELATES OF RF UNIT DISCHARGE 2.1.

Sensory

Most medial RF neurons respond to one or more sensory modalities. One of the most potent sensory inputs comes from the vestibular system. Stimulation of the vestibular nerve produced EPSPs or IPSPs in 75 % of medial reticular neurons¹⁶⁰. More than half of the medial pontomedullary reticular neurons received mono-

* Several terms are commonly used to describe portions of the medial brain stem reticular formation (RF). These include bulbar reticular formation (BRF), pontine reticular formation (PRF), paramedian pontine reticular formation (PPRF), nucleus gigantocellularis (NGC), nucleus reticularis parvocellularis, nucleus reticularis pontis caudalis (NRPC), nucleus reticularis pontis oralis (NRPO), midbrain reticular formation (MRF), and gigantocellular tegmental field (FTG). While some of these structures can be histologically distinguished¹²⁷, sharp divisions between nuclear fields cannot be made¹⁹⁵ and in common usage the anatomical locations they describe overlap. Thus, a location that one worker will describe as NRPC, is described as NRPO by a second, NGC by a third, and FTG by a fourth. This has impeded communication and contributed to a lack of integration in some of the RF literature. For this reason, in the following discussion I will attempt where possible to describe cat Horsley-Clarke (H.C.) coordinates, or anatomical landmarks, locating each of the areas studied.

synaptic input from the vestibular nuclei¹⁵⁸. Ten per cent of pontine reticular neurons were found to respond to lateral head tilt²²³.

Somatosensory responses are seen in neurons located throughout the medial RF. Seventy-seven per cent of medial reticular formation neurons responded to natural somatic stimuli²⁰¹. This study included medial reticular formation areas caudal to P8. Similar findings have been made in more anterior regions^{3,18,208}. Response latency to electrical stimulation of receptive fields ranges from 12 to 80 msec³. Spinal cord neurons responsive to a variety of somatic stimuli have been shown to project directly to medial RF areas⁶⁶. Specific responses to vaginal and other sexual stimuli have been demonstrated throughout the brain stem reticular formation^{90,183,185}. Unit responses to vaginal stimulation are increased during estrous^{183,186}. RF units responsive to bladder stimulation have been reported at the pontomesencephalic junction (APO)³³. Thermosensitive neurons have been seen in midbrain RF regions from APO to A4 in the cat⁵⁵ and also in the medulla oblongata^{114,115}. Seventy per cent of medullary neurons, 72 % of caudal midbrain units, and 18 % of rostral midbrain units are thermosensitive^{55,115}. At least 27 % of reticular formation units, recorded largely in the vicinity of the nucleus gigantocellularis in decerebrate cats, respond to proprioceptive input, as evidenced by their response to vibration of the gastrocnemius-soleus muscle¹⁷⁰.

Auditory responses in RF cells have been noted in several studies^{3,7,96}. Between 23 and 40% of RF cells responded to discrete auditory stimuli^{196,208}.

Visual responses in RF cells are most common in anterior regions, especially in the mesencephalic reticular formation^{18,65,82}. Faingold and Caspary⁶⁵ have shown that a convulsant drug can cause previously unresponsive RF units to respond to visual stimuli. Cells in the anterior pontine nuclei have been shown to have specific visual receptive fields⁷².

Motokizawa¹⁴⁰ has identified olfactory responses in 58% of the reticular formation neurons tested. His explorations were limited to the mesencephalic reticular formation.

Groves et al.⁸² have systematically mapped the anterior-posterior representation of sensory signals in the rat. Their work reveals differences in the anatomical distribution of different sensory modalities. However, there is considerable overlap between regions and even within neurons. As many as 57 % of RF neurons respond to more than one sensory modality²⁰⁸, but the convergence is clearly not unlimited^{31,111, 127,196,244} or random¹⁶⁰. The role of the RF in sensory integration is the subject of a recent review¹⁹².

2.2. Pain

Casey^{43,44} studied the discharge of NGC cells in cats trained to cross a barrier in order to escape painful electrical stimulation of the superficial radial nerve. He found that NGC unit discharge rates increased as stimulation intensities were raised to levels eliciting escape behavior. NGC cells respond to noxious stimuli applied to either spinal or trigeminal systems¹⁵³ and to injections of bradykinin which induced noci-

ceptive reactions²⁶. Most of these cells were also found to discharge in relation to natural noxious stimuli^{42,113}. Discharge in 57 % of the neurons in NGC of the cat was related to noxious skin stimuli or escape behavior⁴⁷. NGC neurons have also been reported to respond to presumably noxious gallbladder distension¹⁵². Similarly, units in the rostral mesencephalic reticular formation were found to respond to nociceptive stimuli^{12,183,245}, although other workers have contended that these cells respond primarily to non-noxious stimuli¹⁴⁵. Cells in the medial reticular formation of the caudal medulla oblongata also responded to nociceptive stimuli^{38,243}. Thus, cells responding to pain have been reported throughout the medial RF from A6.5 to PI and from P4 to P18.3 in the cat. The region between PI and P4 has not been systematically explored. Responses to painful stimuli were of long duration, often lasting several seconds, and including periods of silence and reciprocal discharge in neighboring neurons^{7,26,44,113,245}. Procedures which reduce pain responses, such as morphine administration and stimulation of the periaqueductal gray or of peripheral nerves, are effective in reducing both inhibitory and excitatory RF responses to noxious stimuli^{153,226,243}. The activation of RF neurons by painful stimuli has been interpreted as indicating that medial reticular formation cells were specifically concerned with the sensory and motivational aspects of pain^{3,43-47,245}. The criteria for identifying neurons involved in pain perception are carefully discussed in a recent review¹⁷⁶.

2.3. Conditioning and habituation

Several workers have recorded the activity of reticular formation neurons during conditioning. Buchwald et al.³⁷ systematically observed multiple unit activity in RF, sensory and motor systems during classical conditioning of a hindlimb flexion response. They conclude that 'activation of the conditioned stimulus and reticular systems are primary events in conditioning.' Yoshii and Ogura²⁴⁴ have studied classical conditioning of cells in the NRPC-NGC region. They find that 46% of cells are influenced by this procedure. Pragay et al.¹⁷⁴, working in monkeys, report that 67 % of the task-related RF units studied appeared to be involved in central processes underlying attention in visual discrimination tasks. Sparks and Travis^{216,218} studied RF unit activity in monkeys during a discriminative bar press task. They classified RF units into four different groups. Each group showed a distinctive pattern of changes in firing rate during the task. They mention in passing that a few RF units seemed to be related to head or eye movement. Most, but not all, of these units were described as being near the oculomotor nuclei. They note the need for careful observation and control of physiological variables, since in well-trained subjects consistent unit responses may be related to small undetected components of a stereotyped behavior pattern rather than to cognitive or psychological variables.'

Most RF neurons show a progressive decrease in their response to repeated stimuli. This 'habituation' process has been studied by several investigators^{18,81,82,147,161,194,200,201}. The Scheibels¹⁹⁴ report that 75% of bulbar and pontine cells show habituation to repeated sciatic nerve stimulation. Bell et al.¹⁸ report that the same

percentage of midbrain cells show habituation. After a 30-60 sec period without stimulation the habituated response returns, although subsequent habituation progresses more rapidly. Groves et al.⁸¹ have reported a progressive increase of response, or 'sensitization' in some reticular formation cells to certain stimuli. Peterson et al.¹⁶¹ have recently published a quantitative study of habituation in pontomedullary cells. They conclude that these cells display 'most of the parametric features of behavioral habituation' as defined by Thompson and Spencer²²⁸.

Analysis of the properties of habituation manifested in RF cells suggests that the habituation process does not result from postsynaptic inhibition of RF neurons themselves but rather from alterations in the pathway between sensory receptors and RF neurons. The evidence supporting this conclusion includes: (1) a PRF neuron habituated to one stimulus will respond normally to a different stimulus^{81,161,194}. In some cases a neuron may even show habituation to one stimulus and sensitization to another; (2) there is no evidence of IPSPs in reticular formation neurons during habituation²⁰⁰; and (3) there is no decrease in the spontaneous activity of RF neurons during habituation¹⁶¹.

Changes in unit activity during conditioning and habituation have been reported for virtually all medial RF areas from A4 to PI2.

2.4. Arousal and complex behavioral states

In 1949 Moruzzi and Magoun¹³⁹ reported that MRF stimulation in intact cats produced a long-lasting cortical desynchrony. This classic observation has been repeatedly confirmed. Further work developed and refined the concept of an ascending reticular activating system contributing to both behavioral and electroencephalographic arousal. Arousal came to be viewed as a separate dimension of behavior that energized the organism's interaction with the environment¹²⁵. The advent of unit recording techniques allowed investigators to explore the RF for the neural substrate of these phenomena.

An early study by Machne et al.¹²¹ reported a marked increase in the activity of most MRF units in response to arousal caused by either sciatic nerve or brain stem stimulation. They also reported that arousal disrupts temporal correlations between the discharge of adjacent neurons thus 'desynchronizing' them. Schlag¹⁹⁷ and Schlag and Balvin¹⁹⁸ reported similar correlations between RF activity and cortical EEG. Podvoll and Goodman¹⁶⁸ and Bambridge and Gijbers¹⁰ reported a strong positive correlation between behavioral arousal and the level of MRF and PRF multiple unit activity (MUA) in the unrestrained cat. Beyer et al.²⁸ extended these observations by reporting decreased MRF multiple unit activity during 'relaxation behavior' induced by petting, feeding, grooming and similar activities. Single unit studies in unrestrained cats have reported correlations between arousal and level of MRF activity^{94,103,128}. A subclass of 'attention' units responding only to novel stimuli was also reported. The proportion of such units is unknown⁹⁴.

More detailed behavioral analyses have been directed at further defining the motivational variables responsible for relations between RF activity and arousal. A

study by Phillips and Olds¹⁶⁵ manipulated drive states in rats by food or water deprivation and observed unit activity in rats that were trained to remain still. They found that MRF activity was greatest when rats were signalled to expect the reinforcement for which they were most strongly motivated. A similar paradigm was used by Olds et al.¹⁴⁶. They found a marked acceleration in activity in every MRF unit as reinforcement became imminent. They conclude that the MRF activity increase is specifically related to *anticipation of reward*. This conclusion can be contrasted with the findings of Vertes and Miller²³⁴ and Best et al.²⁷ (in rats), and Umemoto et al.²³¹ (in cats). These workers studied the activity of pontine and mesencephalic units during the conditioned emotional response (CER), using a procedure similar to the one used by Olds et al. In this behavioral paradigm, a previously neutral stimulus signals an unavoidable shock. These studies reported an increased firing rate in RF units during anticipation of the shock. The increased RF activity was hypothesized to relate to *fear of the shock*. Umemoto et al. reported that 68 % of encountered neurons discharged *specifically in relation to the CER*. Best et al. reported that 85 % of recorded cells increased their discharge rate in relation to the CER.

Another behavioral approach to the study of RF neurons has been the study of elicited fighting behavior. In these experiments midbrain RF and central gray units were recorded while cats or rats were induced to fight^{1,2,173}. In the cat, 80% of midbrain cells increased their discharge during fighting behavior. Ten per cent of midbrain cells were found to fire almost exclusively during fighting behavior and therefore 'had the characteristics expected for cells mediating affective defense behavior'¹. Most of these cells were located in the central gray, the area most thoroughly explored. However, a few were located in adjacent regions of the MRF. A more recent study done on rats¹⁷³ did not report cells discharging only during affective behavior, but did find that 19 % of all midbrain cells studied and 4 of 32 cells (12.5 %) in midbrain RF regions adjacent to central gray, discharged predominantly during fighting. The careful behavioral observation procedures employed led the authors to conclude that these cells participate in the integration of fighting behavior. However, it was also noted that the data do not compel this conclusion and that 'some subtle aspect of the sensory stimulus presented by the opponent rat or some subtle aspect of the motor response of the subject conceivably could account for the maximal firing during the fight sequence'¹⁷³.

Several recent studies have pointed out that traditional concepts of arousal level can not adequately explain changes in RF activity. Goodman and Mann⁷⁴ studied MRF MUA during natural sleep, waking and anesthesia. Their goal was to determine if the loss of consciousness and pain response in anesthesia could be explained by a parallel decrease of MRF MUA. They found that different anesthetics could produce anesthesia of similar depth even though MRF MUA differed significantly. Even more striking was their observation that surgical anesthesia could be achieved even though MRF MUA was no lower than that seen in normal slow wave sleep. They conclude that 'the characteristics of spontaneous unit firing at reticular ... sites cannot be used to differentiate between wakefulness, sleep and anesthesia'. Similar results were found using single unit techniques¹⁹⁷.

Other studies, while reporting RF cells related to arousal, have also noted that some MRF cells show correlations with more specific behavioral patterns. Thus, Komisaruk and Olds¹⁰⁸ reported on a cell that fired rapidly during any form of locomotion but not when the alert rat was standing still. Malmö and Malmö¹²⁶ reported a significant correlation between midbrain MUA and body movement. Vertes²³³ reports a significant increase in pontine unit activity during movement detected by an unshielded 'free wire' attached to the headplug.

Schwartzbaum¹⁹⁹ studied MRF MUA in rats during a variety of behavioral situations. He found that midbrain MUA covaried with behavioral state, progressively increasing as the rat shifted from slow wave sleep to stationary waking, to 'face-washing' and lapping behavior, to more vigorous movement categories. He found that MUA activity during sensory stimulation and conditioned emotional response remained correlated with the movement category elicited by the stimulus." He concludes that MRF activity relates to the 'extensive and intensive properties of movement, although the data would not rule out other more specific relationships'. These findings are compatible with either MRF modulation by the sensory feedback from movements or MRF participation in the facilitation of movement.

It is worth noting that a few recent studies have also detected general relations between movement and MUA activity in forebrain areas^{71,126,199}. Thus, many of the considerations discussed here in connection with RF activity may apply to more rostral regions.

Studies of correlations between RF activity and arousal have explored rat midbrain regions most thoroughly. Cat studies have extended from approximately A4 to P5. The relations reported have generally not been found to be localized to specific portions of the area investigated.

2.5. REM sleep

Decerebrate cats show both rapid eye movement (REM) sleep and slow wave sleep (SWS)^{88,100,236}. Lesions within the brain stem RF can disrupt REM sleep^{14,15,40,41,84,100,101,129,188}. Therefore, many studies have recorded from RF units to determine if any particular subgroup of cells showed activity changes consistent with a role in the generation of REM sleep.

Hobson and McCarley and their co-workers have reported, in a series of studies, that cells in the pontine FTG field discharge at much higher rates in REM sleep than in either waking or SWS. During waking and SWS 'most FTG neurons either showed very low discharge rates (< 1 impulse per second) or were silent' while during REM sleep they discharged in rapid bursts¹³⁰. Therefore, the ratio of REM sleep rates to waking and slow wave sleep rates or 'selectivity' was very high. It was concluded that because of this high selectivity 'FTG units are at present the best candidates' for REM sleep generator neurons⁸⁹.

Pompeiano and Hoshino have conducted a series of studies that parallel the studies of Hobson and McCarley^{91-93,171,172}. They investigated unit discharge in the PRF of decerebrated cats during the cataplectic state induced by the anticholinester-

ase, eserine sulfate. The loss of motor tone and the eye movement bursts of this state are reminiscent of REM sleep, although there are important differences in eye movement pattern and level of consciousness between the cataplectic state and REM sleep^{92,93,135}. Their results are similar to those of Hobson and McCarley in finding that the discharge of cells in the FTG region is highly selective for the cataplectic state.

The Hobson and McCarley studies were performed in cats adapted to head restraint. The Hoshino and Pompeiano studies were done on the acute decerebrate preparation, which does not show spontaneous movements. Therefore, it appeared possible that the apparent selectivity of these cells for REM sleep was a function of the abnormal waking immobility of these preparations, a possibility discussed in early studies⁸⁹.

We have investigated these cells in unrestrained cats during both waking and sleep^{131,132,207,208,212}. We found three cell types in the FTG region. Type 1 had no spontaneous activity during quiet waking and sleep, discharging only during movements. Type 2 had high rates of tonic activity during both quiet waking and slow wave sleep which further increased during waking movement and REM sleep. Type 3 had low activity rates during quiet waking and slow wave sleep, but discharged in bursts during both waking movements and REM sleep. Units with augmented discharge restricted to REM sleep were not observed. All FTG cells discharged rapidly during specific waking movements at rates exceeding mean REM sleep rates. FTG units' REM sleep discharge rates were significantly, and positively, correlated with their rates during waking movement, i.e. cells that discharged at high rates in REM sleep tended to have relatively high rates during active waking²¹². We also studied these same cell types while cats adapted to head restraint. This procedure greatly reduced motor activity and correlated FTG unit discharge. We concluded that the restraint, by reducing waking discharge rates, would make these cells appear to be selective for REM sleep. Our results are consistent with a role for FTG units in the motor activation common to waking and REM sleep, but not with an 'executive' role in REM sleep generation. Vertes²³³ has reported congruent results in the rat. These findings, and their relationship to theories of sleep control, have been discussed in detail elsewhere²⁰⁶.

Single and multiple unit studies have also been made in anterior midbrain areas AI-AS^{9,5794,103,109,116,128,134,240} and in the nucleus reticularis pontis oralis-caudalis (RPO-RPC) region A1-P4^{208,213}. This latter area has been described as the RF area crucial for REM sleep^{41,100}. Virtually all medial RF cells within this region (A2-P4) showed a marked increase in discharge rate as the animal shifted from non-REM sleep into REM sleep. This rate enhancement, similar to that seen in pontine regions, is largely due to discharge bursts correlated with the eye movements and muscle twitches of REM sleep. A similar unit activity increase was observed during active waking periods. The same three cell types described in the pontine FTG field are seen in the RPO-RPC region²⁰⁶.

A recent study by Netick et al.¹⁴² has reported the observation of 4 cells which concentrated their discharge in REM sleep. These cells were located in the medullary RF at about P9.5, LI.6. However, these cells were recorded in head-restrained

preparations and may therefore appear to be selective for REM sleep by virtue of the reduction in waking rate caused by head restraint, as was the case in the PRF units. Therefore, we recorded from this region in unrestrained cats^{206,211}. We saw the same 3 cell types in this area that we found in RPO-RPC and in the pontine gigantocellular area. Waking discharge related to motor activity, as was the case in the more anterior regions. Several cells in this area discharged at high rates when the cat held particular postures. If the cat shifted into a different position, the discharge rate was greatly reduced.

We saw no cells which discharged selectively in REM sleep, as Netick et al.¹⁴² reported. However, two of the posture-related cells discharged at a low rate in quiet waking and SWS, showed a tonic rate increase during the SWS-REM sleep transition and maintained this rate throughout REM sleep. Therefore, the sleep and quiet waking behavior of these cells is strikingly similar to that of the cells seen by Netick et al. Since these workers were recording from cats which were adapted to head restraint, they would not have been able to observe unit activity in a variety of postures. Therefore, it appears likely that the REM sleep-selective cells they observed are similar to the posture-related cells which we have seen. If this is the case, then the REM sleep-related acceleration can be understood as reflecting the motor activation of REM sleep. Just as cells which are phasically active in waking show phasic activity in REM sleep, these cells, which discharge tonically while postures are maintained in waking, also show tonic REM sleep activity. It is also possible that medullary RF cells with discharge selective for REM sleep are rare and have not yet been encountered in the unrestrained cat.

The region explored in these studies lies from 0.3 to 3.0 mm lateral to the midline and between A2 and PI3. More than 72 % of the cells in this area discharge in REM sleep and virtually all discharge at high rates during waking movements^{206,208,212}.

2.6. *Eye movement*

Studies in the head-restrained monkey have demonstrated relationships between the discharge of medial RF cells and eye movement. In these experiments, the animals are typically trained to track a visual target or are allowed to spontaneously explore their environment while RF unit activity is recorded and correlated with EOG activity. A variety of cell types, including pause units which stop discharging during eye movements, long and medium lead burst units which begin discharging up to 20 msec before eye movements, and tonic units, which discharge in relation to eye position, have been reported in both midbrain and pontine regions^{39,52,68,85,106,120}. Intermediate cell types also occur and other cell type classification systems have been developed²¹⁷. It has been reported that 'almost every unit' encountered in the medial pontine region relates to eye movement^{52,53}. The relationship of brain stem neuronal activity and eye movements was the subject of a recent symposium⁸.

Anatomical studies in the monkey have shown that eye movement cells are widespread but are not homogeneously distributed throughout the reticular formation, being concentrated in dorsomedial regions¹²⁰. The distribution of types of eye

movement cells from the midline to 3 mm lateral to the midline has been mapped¹⁰⁶. In the anterior-posterior plane, these cells extend from at least 3.75 mm anterior to 3.75 mm posterior to the center of the abducens nucleus. Since the monkey brain stem is oriented at a more acute angle to the stereotaxic vertical plane than the cat brain stem, this would correspond to an area beginning several mm posterior to the cat's abducens nucleus in ventral RF regions. Eye movement cell types similar to those seen in the monkey have been found in dorsomedial positions of the cat RF between P3.5 and P9.5. The RF region around the abducens nucleus was the most intensively studied. Quantitative data on the percentage of cells with eye movement relations was not presented⁸⁶. Cat RF activity has also been shown to precede the eye movements of REM sleep¹⁶⁷. A variety of cell types related to eye movements have been seen in the vicinity of the cat abducens nucleus^{73,175,177,178}. Cells related to nystagmus-induced eye movements have been observed in the pons of the rabbit^{50,58} and guinea pig⁶. It has been concluded that discharge in pontine reticular formation cells is 'predominantly related to eye movement'⁵¹.

2.7. *Respiration*

The relationship of RF unit activity to respiration has been extensively studied in acute preparations. Typically, respiratory related units are sought in cats that are paralyzed with Flaxedil and artificially ventilated. Units related to respiration are detected by visual observation of periodicities in discharge rate, or more frequently, by computer analysis of temporal relations in unit firing. Units related to respiration have been found throughout the RF. The proportion of units that are related to respiration ranges from 21 % in the MRF to 36% in the PRF of the cat²⁵. Inspiratory and expiratory units are concentrated in distinct anatomical areas. Although many units related to respiration are in lateral RF regions, there are also large numbers in medial areas²³⁵. RF units related to respiration can be found from P2.5 to P11^{24,235}.

2.8. *Locomotion*

The neural circuitry underlying locomotion has been extensively studied in the cat (see reviews by Grillner⁷⁶; Shik and Orlovskii²⁰⁴; Wetzel and Stuart²³⁸). It has been found that stimulation of a circumscribed midbrain region produced rhythmic stepping behavior in a decerebrate cat placed on a treadmill⁷⁹ and speeds locomotion in the intact cat²²⁵. This midbrain locomotor region (MLR) has been localized to the area ventral to the inferior colliculus and predominantly dorsal to the brachium conjunctivum, in the vicinity of the nucleus cuneiformis⁷⁹⁻²²⁴.

Since there are no direct connections between the MLR and the spinal cord, and since spinal cord areas containing reticular projections show a marked activity increase during locomotion, it was hypothesized that reticulospinal pathways might form part of the system producing both spontaneous and MLR-induced locomotion¹⁴⁸. Orlovskii has, therefore, studied the activity of reticulospinal neurons during locomotion. In his preparation, the head and spinal cord of the cat are fixed to a

stereotaxic frame and the limbs rest on a treadmill. In this way he has been able to record intracellularly during MLR-induced locomotion. High and low decerebrate cats are used. Reticulospinal neurons were identified by antidromic stimulation from the L1 level of the spinal cord.

Orlovskii found that there are monosynaptic projections from the MLR to reticulospinal neurons. Furthermore, it was shown that 69 % of reticulospinal neurons were activated during MLR-induced locomotion and that half of the activated neurons showed rhythmic rate modulation related to the limb movements of locomotion^{148,149}. In high decerebrate cats it was possible to observe the same relationships during spontaneous treadmill locomotion¹⁴⁹. It was concluded that the 'transfer phase' of locomotor movement was the most active point for reticulospinal cells, but that individual cells varied widely in their relation to movement. Orlovskii also observed reticulospinal neurons during locomotion induced after cerebellar removal. Under these conditions 62 % of the neurons were activated during locomotion but only 8 % of these activated cells showed frequency modulation in step with locomotion¹⁵⁰. Both cerebellar removal and decerebration lower the spontaneous discharge rates of RF neurons.

Orlovskii recorded from neurons in the area bounded by H.C. planes *PS* to *PIS* and L0.5 to L1.5¹⁴⁹. This includes mainly medial regions of the nucleus gigantocellularis and the nucleus paramedianus. Sixty-nine per cent of reticulospinal neurons were found to be activated by locomotion. Similar modulation with locomotion has been observed in most cells in the nucleus reticularis tegmenti ppntis²⁴⁶. It has been hypothesized that the RF's role in locomotion is to facilitate and readjust locomotor activity whose basic rhythm is generated in the spinal cord⁷⁶.

2.9. Specific movements

With only a few exceptions, the studies mentioned above have employed animals whose heads and bodies were restrained. Siegel and McGinty²⁰⁸ studied PRF activity (P4-P8) in unrestrained cats. We reported that, of 35 cells studied, we were able to identify consistent, individually distinctive motor correlates of discharge in 32 cells (91 %). These included head and neck (n=21), ear (n=3), forepaw (n=1), scapula (n=2), tongue (n=2) and facial (n=3) movements. Each cell responded only during a single kind of movement. For example, cells related to ear movements did not increase discharge during head movements and vice versa. Furthermore, a given cell did *not* discharge in relation to *all* head movements or *all* tongue movements; each cell related to directionally specific movements. For example, cellular discharge was found to be related to turning the head right, or moving the tongue out and to the left.

While natural stimuli could repeatedly elicit unit activity in the unrestrained unanesthetized cat, the duration and intensity of unit discharge was not closely related to the eliciting stimulus. For example, stimulation applied by lightly placing a cotton swab in the concha of one of the ears produced intense discharge in the three PRF 'ear movement' cells. However, the discharge normally continued with undiminished rate for 1-10 sec after the swab was removed from the ear, ending abruptly with a change in

the ear's position. Rhythmic movement of the stimulus did not produce rhythmic discharge in the unit. Furthermore, in most PRF units we observed discharges at rates equal to or exceeding those induced by our most effective stimuli during small, spontaneous movements.

Obviously, spontaneous behaviors produce a variety of sensory stimuli. In order to determine whether or not stimuli generated by motor activity were responsible for observed unit activity, randomly selected cells responding to vestibular, auditory, visual, or localized somatic stimuli were subjected to a procedure designed to eliminate or reduce all identified sensory inputs. Vestibular stimuli were eliminated by an atraumatic head restraint system. The receptive fields of somatic cells were locally anesthetized with injections of lidocaine supplemented by topical application of lidocaine jelly. Visual input was eliminated by placing the cat in a light-tight box. Auditory input was attenuated in responsive cells by blocking the ear canals with wax. Unit rates were not reduced by these procedures. Phasic unit discharge continued to be correlated with motor activity visible in the EMG. We concluded that PRF unit activity is more closely related to motor output than to sensory input²⁰⁸. Studies in curarized cats demonstrate that proprioceptive input can be eliminated without preventing high rates of PRF discharge^{17,113}. Thus, modulation of muscle spindle, tendon and joint receptor input does not appear to be required for PRF activation. Further, work in our laboratory has shown that cats rewarded for increasing discharge in PRF units rapidly learn to make repetitive directionally specific movements in order to gain more reinforcements³⁴. Photographic analysis of the relationship between movements and unit discharge has enabled us to describe the specific movement vectors related to unit activity (Siegel et al., in press). This analysis has demonstrated that body movement onset occurs within 50 msec of the onset of PRF unit discharge. Recent studies have found similar movement relations in cells in the NRPO and NRPC (A1-P3) and in caudal medullary regions (P8-P14)²⁰⁸.

3. OVERVIEW OF RF BEHAVIORAL RELATIONS 3.1.

Anatomical considerations

How can one integrate the various behavioral relations reviewed above into a coherent picture of the functional role of RF neurons? The most obvious approach is to acknowledge the complexity and heterogeneity of RF behavioral relations and conclude that many disparate cell types occur within it, being concentrated in distinct anatomical regions. However, as one can readily see in Fig. 1, the different cell types are not segregated at different A-P levels. There is a nearly complete anatomical overlap of all functional groupings. Lateralities (0.5-2.5 mm from midline) and horizontal levels (0-10 mm ventral to stereotaxic zero) are also similar. This overlap is even more striking when one realizes that the limits of the distributions sketched do not, in most cases, represent points beyond which cells in a particular functional grouping could not be found. Rather they represent the limits of exploration, i.e. there is no reason to think that relations between RF cells and locomotion could not be

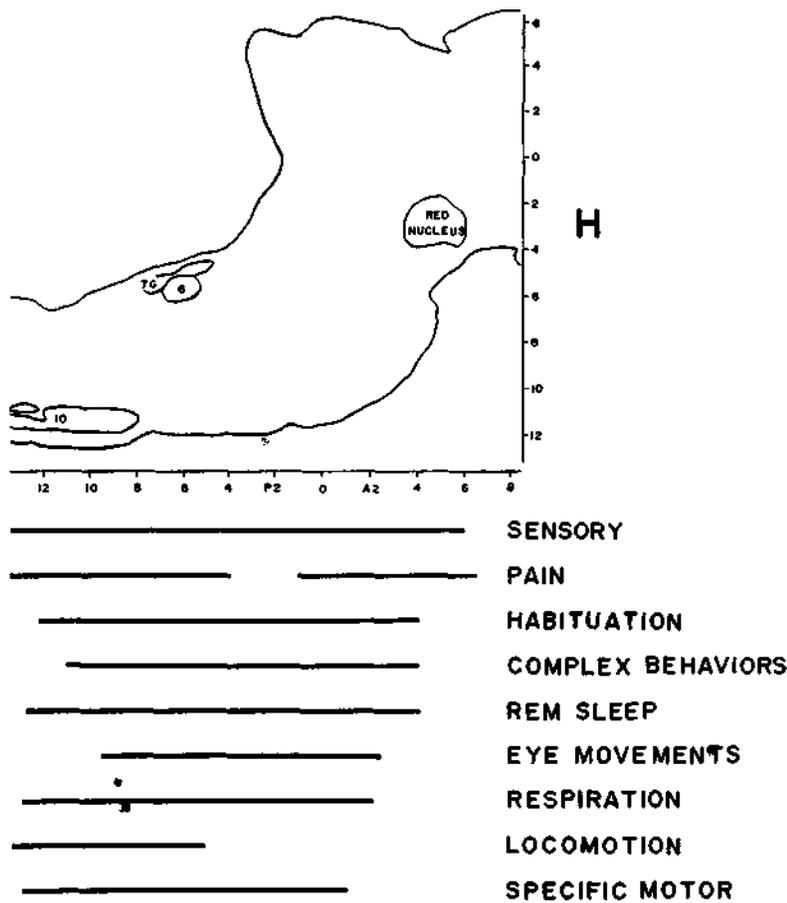


Fig. 1. Anatomical distribution of cell types within the reticular formation. Figure shows sagittal view of the brain stem of the cat. Bars at bottom indicate the anterior-posterior distribution of cells identified as having specific behavioral functions. Cells with different behavioral properties are not localized in different RF areas. G, abducens nucleus; 7G, genu of the facial nerve; I.O., inferior olive.

found rostral to P5, or that relations between RF cells and pain could not be found between P4 and P1.

3.2. Cell selection procedures

A way of dealing with the anatomical overlap of cell types is to postulate that each group of investigators has selected cells with particular behavioral correlates while ignoring the other cell types in the same area. Clearly this could be the case in Adams' study¹ where the cells of interest were found by eliciting fighting behavior. Since these cells were relatively inactive at other times, other investigators might never have noticed them. Similarly, Hobson et al.⁸⁹ searched for REM sleep-selective cells in

REM sleep, and one might wonder if the failure of others^{131,132,208,212,233} to observe such cells resulted from these experimenters searching for cells during waking. However, the cells that Hobson et al. report on, unlike Adams' cells, were not silent in waking. Their mean waking rates equalled or exceeded those found by these other investigators during quiet waking. For example, Hobson et al.⁸⁹ report a mean waking rate of 6 spikes/sec while Siegel et al.²¹² report mean waking FTG rates ranging from a minimum of 0 spikes/sec to a maximum of 49 spikes depending on the cell type and the activity level of the cat. The average REM sleep rate of 17.8 spikes/sec reported in unrestrained cats²¹² is also close to Hobson et al.'s⁸⁹ mean of 17.4 spikes/sec. Therefore there is no reason to believe that REM sleep-selective cells were missed when units were located in the waking animal. RF cells without spontaneous activity in waking *and* sleep have recently been described²⁰⁷. However these cells do not appear to have qualitatively different behavioral relationships from cells with higher spontaneous activity rates. The vast majority of RF cells recorded in the studies reviewed above were not found during specific behaviors. Normally cells were first detected by observing their spontaneous activity and *then* studied in relation to behavior. Therefore the behavioral techniques used to locate cells are not a major factor causing discrepant results.

3.3. Microelectrode techniques

Another approach to integrating these findings is to attribute the varying results to differences in microelectrode techniques. However, a careful study of this issue did not reveal any difference in unit discharge correlates when one switched from 1 μm glass electrodes to 10 μm steel electrodes¹²⁷. Multiple unit electrodes have reported the same behavioral relations as single unit electrodes^{168,199}. Most findings have been replicated with several different unit recording techniques. For example, response habituation, with a similar time course, has been seen with glass intracellular electrodes of tip diameter less than 1 μm ²⁰⁰, metal electrodes with tip diameter 2-4 μm ¹⁹⁴ and with microwire electrodes with 32 μm tip diameter²⁰⁸. Conversely, similar unit recording techniques have been used in reports finding a variety of behavioral relations in the same reticular areas. For example, tungsten electrodes less than 7 μm at the tip have been used in studies linking reticular activity to pain^{17,38}, REM sleep⁹¹, respiration²⁵, sexual behavior¹⁸⁵, polysensory responses, habituation⁸¹, and olfactory responses¹⁴⁰.

The RF area has a great number of large cells³⁶ and a common observation in RF studies is that a large percentage of the cells have 'giant' spikes and large signal-to-noise ratios. Many cells can be recorded while microelectrodes are moved over a distance of greater than 100 μm and some can be recorded for as much as 500 μm ²⁴¹. The preponderance of large cells, which can be recorded with all unit techniques, minimizes the effect of sampling bias. While one would expect small cells to be under-represented, this would be true in virtually all of the studies reviewed above.

3.4. Conclusion: Different RF studies are observing the same cell populations

Another explanation is that all of the cell subtypes co-exist in the same areas. However, if one calculates the percentage of encountered cells that have been reported to have each behavioral function (Table I), it is clear that this is an arithmetic impossibility. The different cell type percentages add up to far more than 100%. For example, some studies^{89,130} report that virtually all pontomedullary cells discharge specifically in REM sleep while others^{39,120} report that between 70 % and 90 % of these cells relate specifically to eye movements and others^{12,38,47} report that 57-88% of these cells relate specifically to the sensory and motivational aspects of pain. Therefore, we are forced to conclude that different RF studies are investigating the same populations. *The same cells* that one group of studies are describing as sensory integrators are being described by another group of studies as specifically concerned

TABLE I

A partial list of the behavioral functions attributed to RF cells

Cat stereotaxic coordinates were estimated from figures or taken from the authors' description. General anatomical terms were used in rat and monkey studies and in cat studies where precise AP levels were not available. Third column

<i>Function or stimulus</i>	<i>Cat AP stereotaxic coordinate or anatomical designation</i>	<i>Percentage of encountered cells</i>	<i>Reference</i>
Vestibular	P15-AO	75	Peterson et al., 1975
Somatosensorv	P18.5-P8.5	77	Segundo et al., 1967
	P8-P3	71	Siegel and McGinty, 1977
Auditory	A2-A4	68	Bell et al., 1964
	P8-P3	40	Siegel and McGinty, 1977
Olfactory	BRF, MRF	23	Scheibel et al., 1955
	APO-A6	58	Motokizawa, 1974
Pain	P18.3-P12.1	82	Burton, 1968
	P11-P6	57	Casey et al., 1974
Habituation	AO-A3	88	Bames, 1976
	BRF	75	Scheibel and Scheibel, 1965
Reinforcement	A2-A4	75	Bell et al., 1964
	MRFt	100	Olds et al., 1969
Fear	MRFt	85	Best et al., 1973
	MRF	68	Umemoto et al., 1970
REM sleep	P7-AO	100	Hobson et al., 1974
	P9-P3	72	Siegel et al., 1977
Eye movements	MRF*	70	Buttner et al., 1977
	PRF*	92	Luschei and Fuchs, 1972
Locomotion	P15-P5	69	Orlovskii, 1970 (ref. 149)
Respiration	PRF	36	Bertrand et al., 1973
	MRF	21	Bertrand et al., 1973
Specific movements	P8-P3	91	Siegel and McGinty, 1977

* Monkey studies.

t Rat studies.

with the sensory and motivational aspects of pain, by a third group as being primarily related to the conditioning and habituation process, by a fourth group as relating primarily to reward, by a fifth group as relating primarily to fear, by a sixth group as being candidates for the role of the executive neurons of REM sleep, by a seventh group as predominantly related to eye movements, by an eighth group as being respiratory neurons, by a ninth group as being related to the transfer phase of locomotion, and by a tenth group as being related to arousal.

One might hypothesize that individual RF cells can have several of these often contradictory functions. This hypothesis would require a mechanism that would somehow change the function of most RF cells in different behavioral situations, and simultaneously mask their other functional modes of operation. Since most studies have employed the same behavioral situation (i.e. an intact immobilized cat or rat presented with stimuli) it is difficult to imagine what cues control this switching mechanism and why most investigators only see one cell type (e.g. fear cells or reward cells, or REM sleep cells, etc.). Such an hypothesis is non-reductionistic and does not readily lend itself to scientific test. The alternative is to seek some underlying relationship that can explain the participation of these cells in so many different behaviors.

3.5. *A behavioral hypothesis explaining RF unit discharge relations*

Is there a model of RF unit function that can encompass the findings reviewed above? I propose the following hypothesis: *that discharge in most RF cells is primarily related to the excitation of specific muscle groups*. It is hypothesized that individual cells would have their own distinctive muscle relations. For example, one cell might relate to extending the tongue (genioglossus muscle), another to turning the head (e.g. cleidomastoideus, biventer cervicis, complexus), another to fixating the back (e.g. thoracic and lumbar interspinales). More complex relations are possible. For example, a single unit might function to facilitate muscles involved in head turning *and* forelimb muscles supporting the head in its new position. RF control would be mediated by excitation or inhibition of motor neurons innervating each muscle in the group. The relationship of RF cells to simple movements would be responsible for the variety of complex behavioral relations attributed to RF cells. This hypothesis provides a framework in which to integrate previous results without the necessity of attributing complex or multiple behavioral properties to RF units.

The ascending projections of RF cells might serve to relay a 'collateral discharge' for skeletal muscles to forebrain areas. This discharge would be similar to that which has been thought to accompany eye movements. The collateral discharge would: (1) allow perceptual constancy by compensating for sensory changes induced by body movements, (2) facilitate sensory channels to speed the acquisition of information needed to guide the movement, and (3) allow higher neuronal mechanisms to interact with movement patterns.

The RF has long been thought to be involved in motor control. In their pioneering stimulation studies, Magoun and Rhines¹²⁴⁻¹⁸² demonstrated motor facilitation and inhibition from RF stimulation. Related studies, briefly discussed below,

have developed this concept. The emphasis in these studies was on the generality of the motor effects mediated by the RF. Thus, for example, it was shown that both flexors and extensors at all levels of the body were inhibited by stimulation applied to a wide area in the medullary RF⁹⁹⁻¹²⁴. The present concept differs from these previous formulations by hypothesizing a highly specific RF relation of individual RF cells to movements in particular muscles or muscle groups.

This hypothesis is aimed at integrating the behavioral findings surveyed above. As will be reviewed in the next section there are a variety of established synaptic mechanisms that can mediate this relationship. RF cells receive inputs from many 'higher' motor areas and send axons to ventral spinal cord areas. RF cells can exert mono- and disynaptic influence on motoneurons. Critical tests of the hypothesis proposed here would require precise behavioral experiments to determine the strength and stability of RF-movement linkage in a variety of situations, and coordinated physiological studies to clarify the central and peripheral mechanisms underlying observed relationships.

4. RELATED FINDINGS

4.1. *Anatomical and physiological data*

The hypothesis that RF units relate to the excitation of specific muscle groups is consistent with a variety of anatomical and physiological findings. Ingram et al.⁹⁷, in one of the early studies making use of the Horsley-Clarke stereotaxic apparatus, beautifully demonstrated what they described as the 'tegmental response'. This response could be elicited in the cat by electrical stimulation of the reticular formation from midbrain to caudal pontine levels, and consisted of 'a curving of the head, neck and trunk toward the side stimulated, flexion of the ipsilateral forelimb and extension of the contralateral forelimb, with varying movements of the hind limbs'. Stimulation of these areas in anesthetized or decerebrated cats produced non-reciprocal inhibition or excitation in a wide range of muscles and widespread changes in reflex excitability²²². According to the present hypothesis these non-specific effects may be a consequence of the anatomical proximity of groups of neurons with a variety of behavioral correlates. This proximity would cause suprathreshold electrical 'macro-stimulation' to recruit groups of adjacent units, thereby producing more generalized spinal cord effects. Sprague and Chambers²²⁰ used finely graded electrical stimulation of both anesthetized and unanesthetized cats to further define the motor properties of the RF. They did not find pure excitatory and inhibitory effects when using liminal stimulation. Instead they emphasized that stimulation at all levels of the RF produced reciprocal changes in flexor and extensor muscles. Stimulation of the mesencephalic RF has been shown to affect gamma motoneurons⁵ and alter reflex excitability¹⁴¹.

Torvik and Brodal²²⁹, investigating retrograde changes in cats after spinal cord lesion, found that more than half of the pontine and medullary cells send projections into the ventral, motor regions of the spinal cord. All pontine fibers descend homolaterally, while some medullary fibers also descend contralaterally. Nyberg-

Hansen¹⁴⁴, using silver impregnation methods, noted that pontine and medullary reticulospinal fibers descend in the ventral part of the lateral funiculus and end in laminae 7, 8 and 9 of the ventral spinal cord. Similar results were reported by Petras¹⁶⁴ who emphasized the contributions of the NGC to the spinal cord. Direct spinal projections from midbrain RF tegmental regions have been demonstrated in primates⁴⁸, but not in the cat. Brodal³⁵ reported extensive reticular projections to the cerebellum. Anatomically localized RF projections to the oculomotor nuclei have been defined using horseradish peroxidase, autoradiographic and electrophysiological techniques^{75,122,180}. Basbaum et al.¹³ have mapped the projections of rostral medullary RF cells using [³H]leucine injections. They conclude that NGC 'projects primarily to 'motor' related sites' including cranial nerve nuclei and ventral spinal cord areas. Spinal cord terminals were predominantly ipsilateral with major projections to Rexed's lamina VII and smaller projections to VIII and IX. Horseradish peroxidase studies have shown similar reticulospinal projection patterns in the primate¹⁰⁷. Golgi preparations in the cat have shown RF fiber terminations on internuncials and on motoneuron dendrites¹⁹⁵. The terminations of the cat's reticulospinal system contrast with the more dorsal termination of corticospinal fibers from motor cortex, which end in layers 5, 6 and 7 chiefly or exclusively on internuncials³⁶.

Recent studies have used electrophysiological techniques to investigate the connections of RF units. Magni and Willis¹²³ extended the caudal limits of reticulospinal projections beyond those described using anatomical techniques by antidromically exciting reticular neurons from sacral levels of the cord. Individual RF neurons branch extensively in the ventral horn, often innervating both sides of the cord and extending over several levels¹⁶². The number of RF neurons projecting caudally is far greater than the number projecting rostrally, the ratio being approximately four to one⁶⁰. Grillner and Lund^{77,78} conclude that a pathway producing monosynaptic EPSPs on flexor motoneurons in lumbar spinal cord regions originates from medullary and pontine reticulospinal cells, which send their axons through the medial longitudinal fasciculus (mlf). A disynaptic RF pathway mediated by propriospinal neurons and ending on hindlimb alpha motoneurons has been demonstrated electrophysiologically²⁰³. Disynaptic IPSPs mediated by a ventral reticulospinal pathway have been reported in decerebrate cats". Stimulation of the pontomedullary reticular formation can produce monosynaptic EPSPs and IPSPs in neck motoneurons¹⁶³. Back motoneurons receive monosynaptic EPSPs and polysynaptic IPSPs from pontomedullary RF regions while limb motoneurons receive EPSP's from PRF stimulation but do not respond to medullary RF stimulation¹⁶⁶. Orlovskii¹⁴⁸ found that pontine and medullary reticulospinal neurons receive monosynaptic projections from the mesencephalic tegmentum. Thus, MRF neurons have disynaptic access to spinal cord motor areas⁴.

Inputs into the RF are also suggestive of motor functions. RF neurons receive monosynaptic projections from the cerebellum. The synaptic relations between RF neurons and spinal cord and cerebellum have been the subject of several detailed studies^{32,60,62,70,79,98,117,118,230}. The RF also receives extensive projections from the tectum^{96,105}. Magni and Willis¹²³ and Peterson et al.¹³⁹ all report that the precruciate, or motor, cortex is the most effective cortical site for evoking EPSPs in RF neurons.

RF unit response to repetitive precruciate stimulation does not habituate, as does RF response to peripheral sensory stimuli¹⁶¹. They conclude that reticulospinal neurons are not well suited to function as relays for repetitive sensory inputs, but may serve as a motor relay. Direct projections to RF areas from motor cortex and from orbital cortex, which has specific motor inhibitory properties, have been demonstrated with anatomical and physiological techniques^{136,143,187,191}.

Physiological investigations of the RF have left many fundamental questions regarding its motor role unanswered. These include: (1) do individual RF cells exert bilaterally symmetrical, relatively non-specific effects on motoneuron pools; (2) are RF cells activated synchronously during movements; (3) do RF units discharge in relation to specific movements, and (4) is the relationship of a given RF cell to movement dependent on the means by which the movement is elicited? For example, do some RF cells mediate only movements in response to painful stimuli, while others mediate movements during either exploration or REM sleep, or conditioning or sexual behavior? Our behavioral findings and hypothesis suggest an affirmative answer to question 3 and negative answers to the remaining questions, at least for the majority of RF cells. Further work is needed to explain the synaptic mechanisms mediating the observed behavioral relations and to determine the frequency and anatomical distribution of cells related to various specific movements.

4.2. Phylogenetic data

functional role of mammalian RF cells, it is instructive to consider findings on the RF of other vertebrate classes. The medial RF of the most primitive vertebrates, the cyclostomes, contains a number of giant cells, the Muller and Mauthner cells. These are the principal source of descending control, running the whole length of the spinal cord¹⁵⁵. Like mammalian reticulospinal cells, these neurons receive convergent sensory inputs and make monosynaptic connection with motoneurons²⁰². Rovainen¹⁸⁹ defined Muller cells in the sea lamprey (*Petromyzon marinus*) as the cells of origin of 8 pairs of large uncrossed axons in the medial longitudinal fasciculus of the spinal cord. Two pairs of Mauthner cells were defined by their location near the eighth nerve and by their decussating axons extending into the cord. Other large reticulospinal elements were also identified. High frequency stimulation of individual Muller or Mauthner axons produced stimulation bound movements of the neck, posterior body, dorsal fins and tail. Rovainen concludes that these cells form a descending system producing the withdrawal, swimming and coiling movements of the lamprey.

The medial RF of teleost fish contains a pair of giant Mauthner cells. The neurobiology of the Mauthner cell is the subject of a recent book⁶⁴. Discharge in these cells, produced by electrical or natural stimuli, has been shown to produce non-graded tail flips in the lungfish²³⁹. These cells are thought to carry the motor output of a startle response system⁵⁶. In other respects, the reticular formation of fish resembles that of cyclostomes, although fish have more reticulospinal cells²⁰². Stimulation of the medial midbrain tegmentum in the carp (*Cyprinus carpio*) produces stimulus-bound

* In evaluating the

swimming movements¹⁰⁴ and lesions of this region produce abnormalities in swimming behavior in the goldfish¹⁵⁷.

Elasmobranchs do not have Muller and Mauthner cells, but have other large medial reticular cells. Restieaux and Satchell¹⁸¹ have described reticular cells up to 250 μ m in length in the dogfish (*Squalus lebruni*). Like large reticular cells in other vertebrate orders, they receive a variety of sensory inputs and project to the spinal cord. Restieaux and Satchell conclude that these cells are 'well suited to mediate turning movements towards or away from biologically meaningful stimuli'.

Mauthner cells are absent from the brains of adult tetrapods with the exception of urodeles (salamanders and newts). Other amphibia, such as the frog, while lacking specialized Muller and Mauthner cells, have well developed reticulospinal systems¹⁵⁵. The frog's reticulospinal cells are the largest neurons in its brain and make monosynaptic connections with spinal cord motoneurons. These connections are concentrated in cervical segments. Vestibule- and tectospinal tracts play only a secondary role in motor control in amphibia²⁰².

The medial medullary RF of reptiles is more highly differentiated than the amphibian RF and 'can be regarded as the homologue of the gigantocellular pontomedullary RF in mammals'. RF neurons in turtles have excitatory, monosynaptic projections to motoneurons at lumbar levels of the cord. Stimulation of rubro- and vestibulospinal tracts produces smaller effects on motoneuron firing probability than reticular stimulation²⁰².

Thus the brain stem RF of more primitive vertebrate orders contains large or giant medially located cells as does the mammalian RF. Like their mammalian counterparts, many of these cells respond to a variety of sensory stimuli, project monosynaptically to spinal cord motoneurons and have generally low levels of spontaneous activity. In advanced vertebrate classes there is a trend towards somewhat smaller and more numerous reticular cells although even in mammals there are only 5000-6000 giant RF neurons²²⁹. Synaptic inputs and outputs of RF cells are similar in all classes. Physiological and behavioral evidence suggests that RF activity in primitive vertebrates is closely coupled to movements, and in the most primitive vertebrate classes they are clearly the predominant source of motor control. These findings complement the hypothesized relationship of mammalian RF cells to motor function.

4.3. Summary

While the anatomical, physiological and phylogenetic findings are consistent with our hypothesis, they do not in and of themselves compel one to view the RF as a motor control system in mammals. RF cells with bifurcating axons and ascending projections reaching cortical levels^{19,69,123,193,232} and innervating sensory nuclei^{214,215} have been described. The widely ramifying RF projections can support a large number of functional hypotheses. However, the anatomical and physiological data, considered in the context of the behavioral studies reviewed here, make the motor hypothesis a plausible one. The discussion that follows shows the utility of our hypothesis in integrating previous behavioral findings on RF units.

5. RECONSIDERATION OF BEHAVIORAL CORRELATES OF RF UNIT DISCHARGE FROM STANDPOINT OF OUR BEHAVIORAL HYPOTHESIS

5.1. *Sensory stimuli and pain*

In the unrestrained behaving cat, only a small proportion of RF unit activity was related to identified sensory stimuli; small spontaneous movements produce far more intense discharge than even the most effective stimuli²⁰⁸. The brief, short latency response to discrete sensory stimuli parallels the motor startle response to such stimuli. Sensory inputs such as somatic stimulation on a particular side of the body or auditory stimulation from a particular point in space might be expected to bring the same groups of muscles into play in orientation responses, thereby resulting in polysensory receptive fields. RF unit responses to thermal stimuli may reflect thermoregulatory motor responses such as postural adjustments and changes in motor tone.

Noxious stimuli and such stimuli as vaginal probing would be expected to elicit vigorous movement (including lordosis responses¹⁸⁵) and escape attempts. The temporal relations to the stimulus and the often prolonged discharges are consistent with this explanation. Changes in unit activity lasting for 20 sec after noxious stimuli and 'wind-up' phenomenon, which are characterized by progressive increases in the intensity of neuronal response that are not temporarily related to individual presentation of the stimulus, have a time course similar to the expected motor responses to noxious stimuli. Similarly, unit response latencies of up to 3 sec (ref. 7) are difficult to explain as sensory responses but might well relate to a portion of the motor response to the stimulus, such as attempted escape. Since many of these studies were performed in animals in which muscle activity was prevented by Flaxedil, the motor correlates of unit responses could not be observed. However, it is reasonable to assume that a flaxedilized animal would attempt to withdraw a part of the body to which noxious stimulation had been applied and that cells related to such movements would discharge during the attempt. Conversely, procedures that are known to have analgesic effects, such as morphine administration, would be expected to reduce motor response to pain. Therefore, our hypothesis is consistent with findings that RF responses to noxious stimuli are reduced by such procedures. Finally, our observation that all PRF cells fired at their highest rates during spontaneous behaviors²⁰⁸ is inconsistent with a PRF role in pain mechanisms since, by definition, an animal will not voluntarily inflict noxious stimulation on itself. Discharge rates during small movements greatly exceeded discharge in response to strong electric shock.

5.2. *Conditioning and habituation*

Bell et al.¹⁸ have cautioned that although RF units do show phenomena resembling habituation 'even if one were to record the discharges of a neuron whose responsiveness changes corresponded to those in a behavioral act or EEG, shift one might still know little more concerning the genesis of the latter since the recorded unit might simply be in the motor pathway of the event in question'. A similar view has

been presented by Groves and Lynch⁸⁰. Consistent with this idea are findings from an analysis of the time course of RF activity during the learning of an appetitive classically conditioned task¹¹⁰. This study demonstrated that RF unit activity tended to be temporally related to orientation responses.

In our studies²⁰⁸ we report a close relationship between specific movements resulting from a stimulus and the changes in PRF unit activity during repetitive stimulation. For example, two PRF 'neck dorsoflexion' cells increased discharge when any object was rapidly brought toward the cat's eyes. This stimulus elicited a behavioral flinch response. When after 3 or 4 repetitions of the stimulus the flinch response stopped, the unit acceleration also stopped, despite the fact that the cat continued to observe the approaching object. Three of the 19 FTG cells tested showed no response decrement with stimulus repetition. Two of these discharged during tongue extensions which could be induced by pushing the tongue to the rear of the oral cavity. (These 'tongue cells' were in the pontine RF, several mm away from the hypoglossal nucleus.) Another unit fired during head shaking which could be triggered by placing a foreign object in either ear. In these three cases the behavioral response to the stimuli also showed no decrement with stimulus repetition. All units which exhibited response decrement with repeated sensory stimulation failed to show rate decrement during repetitive motor activities such as 'grooming'. The 'habituation' seen in PRF cells can be likened to the habituation of response that one can record in a peripheral muscle unit. Existing data on RF activity during conditioning and habituation processes are consistent with the hypothesis that discharge in individual RF cells relates to activity in specific muscle groups.

-5.3. *Arousal and complex behavioral states*

As outlined above, a variety of relations between RF unit activity and complex behavior have been reported. Several of these relationships seem contradictory, such as RF unit relations to both fear and anticipation of reward. The hypothesis of a relationship of RF unit discharge to activity in specific muscle groups is able to reconcile these contradictions. Emotional states in animals are closely correlated with motor activity. It is difficult to imagine fearful or reward anticipation situations that would not correlate with changes in muscle tone, or overt movements.

RF cells related to certain muscle groups might be expected to show better correlations with some complex behavioral states simply because certain muscle groups show better correlations with these states. For example, RF units related to ear flattening or back arching might show somewhat specific relations with fear states, while paw muscle tone might correlate with preparation for operant responses and consummatory behavior. Activity in postural muscles might be expected to correlate with 'arousal' but be relatively difficult to correlate with specific movements if only visual observation was employed. However, it would be expected that most muscle groups would show some activity with most active behavioral states. Therefore, one would predict that discharge in most RF cells would correlate with arousal *and* relaxation *and* anticipation of reward *and* fear *and* fighting behavior, as has been reported.

Multiunit techniques have been used in most studies relating RF activity to arousal. By averaging the activity of several motor units, and by integrating this averaged data, these techniques obscure specific movement relations. While some studies have related integrated MUA to arousal, others have emphasized relations between RF activity and the intensity of movement. In many cases movement relations have been detected with a 'free wire' which responds non-specifically to any cable movement, thus making it difficult to detect directionally specific movement relations. The general relations between RF activity and movement are consistent with the hypothesis that discharge in individual RF cells is related to the activation of muscle groups. The hypothesized relation of RF discharge to activity in specific muscle groups provides a framework for encompassing previous results without the necessity for attributing complex properties to these cells.

5.4. REM sleep

RF discharge in REM sleep may be a correlate of the motor activation of this state. Other motor centers also have increased discharge in both REM sleep and waking movement^{63,112-156}. REM sleep motor activation can be seen most dramatically after lesions of the pontomesencephalic tegmentum. These lesions disrupt the peripheral atonia of REM sleep producing an animal which engages in intense motor behavior during a state otherwise resembling REM sleep⁸⁴⁻¹⁰¹. The motor behavior of these animals during REM sleep is episodic with quiet periods separating intense movement bursts. In intact animals, periodic twitching of facial and distal limb musculature and eyes are the hallmark of REM sleep, although the full expression of this motor activation is prevented by the postsynaptic inhibition of motor neurons¹⁶⁹. In younger animals the contractions are so intense that this state is often labeled active sleep. RF units show burst-pause discharge patterns that are similar in time course to the episodic motor activation of REM sleep. This is clearly seen when one compares the mean 10 sec maximum rate for PRF cells during REM sleep of 63.8 spikes/sec, with their mean 10 sec minimum REM sleep rate of 0.8 spikes/sec. REM sleep discharge rates were positively correlated with rates during waking movement²¹².

High rates of firing are readily observed in RF cells recorded in unrestrained animals. PRF cells *on the average* reach 250% of their mean sleep rates during waking²¹². Thus, high rates of firing in RF cells are not linked uniquely to the REM sleep state and are not sufficient for its triggering. The activity pattern of RF cells across the sleep cycle is not consistent with an executive role for these cells in the triggering of REM sleep but is consistent with the hypothesis of RF relation to the contraction of specific muscle groups.

5.5. Eye movement

The hypothesis that RF activity relates to muscle activity is of course consistent with the findings discussed above that RF activity relates to eye movements. Most eye movement cells have been found to be related to eye movement in specific directions

and hence to activity in specific extraocular muscles. A smaller percentage of RF eye movement-related cells do not relate to directionally specific movements. For example, 'pauser' cells that cease firing before eye movements in any direction and burster cells that fire before saccades in several directions have been reported¹²⁰. An important challenge is to determine whether the relation of discharge in such cells is specific to eye movements, and if cells can be found with similar relation to activity in other groups of somatic muscles.

The only substantive difference of interpretation regarding eye movement cells concerns whether or not they are the 'predominant' cell type in the feline PRF. In our explorations we found that only a small percentage of RF cells were specifically related to eye movements^{208,210}, although we systematically tested for eye movement relations in every cell we encountered. Most of the eye movement-related cells we found were at the border between the PRF and abducens nuclei. The gigantocellular tegmental field (FTG) units that we identified as head movement cells, the most common cell type, all showed intense discharge without any eye movement. Conversely, rapid eye movements and maintained eye positions in both the horizontal and vertical planes without accompanying unit discharge were observed in each of these cells. Since head movements tend to be associated with eye movements these cells do show a general correlation with eye movements. Cells specifically related to eye movement may exist in the PRF⁸⁶, but clearly they are not the predominant cell type in the FTG area, which comprises most of the PRF.

Several other findings illustrate the lack of relationship between unit activity in most FTG cells and eye movement, (a) During adaptation to head restraint, FTG unit firing decrement correlated closely with decrease in neck electromyogram^{208,212}, not electrooculogram (EOG). (b) Most cells habituated to rapid head acceleration in conjunction with changes in neck muscle tone. However, EOG response to such stimulation does not habituate, (c) Operant conditioning of increased firing rate in those FTG cells which appeared to discharge in relation to head movement was accompanied by repetitive head movements. In no case did we observe a conditioned increase in unit firing correlated only with increased eye movements, (d) During REM sleep many of these cells discharge in long intense bursts. This firing does not result from increased numbers of eye movements^{89,207}. (e) Many FTG cells were found to be entirely unrelated to head or eye movement. We have observed cells which discharge in close relationship to directionally specific tongue movements. Other cells exhibited activity related to facial musculature and to specific postures²⁰⁷⁻²⁰⁸. It would be difficult to reconcile such findings with the claim that FTG cells relate predominantly to eye movement.

Eye and head movements are normally coordinated and therefore it should not be surprising that eye movement relations have been found in cells related to head and other movements. Indeed, as Bizzi et al.³⁰ have pointed out, neck muscles are activated prior to eye muscles in coordinated movements. Neck muscle activation can also be detected in head-restrained animals. Most studies of eye movement relations in PRF cells have been performed in head-restrained animals. Therefore, correlations between activity in head movement cells and EOG in these preparations might speciously

suggest that these cells were triggering eye movements²¹⁰ (copyright 1978, AAAS).

It is likely that there are substantial species differences in the proportion of RF cells related to eye movement. Monkeys and man, which explore their visual world with frequent eye movements, would be expected to devote a higher proportion of their RF to this function than cats, which are inclined to use their more mobile heads in visual exploration.

Although they do not appear to be the predominant cell type, eye movement cells clearly do exist in the feline RF. According to our hypothesis we can see the eye movement-related RF cells as a subpopulation of the RF's muscle-related cells. They appear to be generally localized to dorsomedial RF regions. The precise documentation of RF eye movement relations can serve as a model for the future quantitative study, in unrestrained animals, of motor relations in other RF areas.

5.6. *Respiration*

Respiration involves not only the use of the diaphragm and intercostal muscles, but also a variety of 'accessory' muscles. Accessory musculature can include not only facial, jaw and tongue musculature, but also skeletal musculature moving the head, neck, chest and back. Indeed, many proximal muscle groups are involved in intense respiration. Sophisticated computer techniques for detecting respiratory-related units, applied to flaxedilized animals, allow one to detect respiratory-related units that would be missed by casual visual observations in behaving animals. Thus, the high percentage of respiratory related units in flaxedilized cats is not inconsistent with the absence of reports of such cells in the vast majority of RF unit recordings in behaving animals. RF respiratory related units can be seen as relating to the facilitation of groups of skeletal muscles with primary and accessory respiratory function.

5.7. *Locomotion*

The discharge of RF cells during locomotion is entirely consistent with what is known about the behavioral relations of these cells in unrestrained cats. Thus one would expect that the large numbers of head movement cells that have been described would discharge rhythmically during the rhythmic activation of muscles facilitating vertical head movements during locomotion. RF cells related to static postural mechanisms²⁰⁶ would be expected to show a non-rhythmic enhancement of discharge during induced locomotion. The reduction in the number of rhythmically activated cells in preparations with cerebellar removal¹⁶⁰ could be related to the poorer modulation of locomotion in these ataxic preparations.

6. DISCUSSION

By hypothesizing that most RF cells have the relatively simple functional role of controlling small groups of muscles, I do not mean to imply that they do not have roles in complex behavioral functions. Several investigations have shown that chronically

maintained cats and rats with brain stem transections at mesencephalic and even pontine levels exhibit a wide range of behaviors^{11,16,49-119,242}. Chronically maintained decerebrate rats²⁴², and cats decerebrated at a young age²⁹ are able to eat solid foods, lap milk, show auditory reflexes, proprioceptive hopping responses, effective defense reactions with appropriate vocalizations, climbing, and prey pursuit behavior. They showed a high level of spontaneous activity and have nearly normal righting reflexes and locomotion. Clearly the brain stem contains the basic machinery for the control of behavior.

Lesion and stimulation studies support the findings of the transection studies in finding a wide variety of complex behavioral effects as a result of manipulations of the RF. For example, lesions have been reported to produce loss of REM sleep and arousal functions^{41-100,102}, paralysis of eye movement⁵⁴, analgesia⁸³, deficits in lordosis behavior¹³⁷, hypokinesia and changes in emotionality²²¹. Conversely, reticular formation stimulation has been reported to enhance REM sleep⁶⁷⁻¹³⁸, and produce eye movements⁹⁵, escape behavior and EEG arousal⁴⁵⁻¹⁹⁰, postural and motor reflex changes^{77-97,220}, changes in speed of locomotion²²⁵, and increases in specific complex behaviors^{21,23,133,237}. While it is beyond the scope of this paper to review the histological differences between the various lesion and recording sites, it can be said that, as was the case with the unit recording studies, there is a considerable anatomical overlap of the RF areas producing these effects. The main determinant of the experimental outcome seems to be the techniques used and the experimenters' observational emphasis.

How can we reconcile our hypothesis that individual RF units are related to excitation of small groups of muscles, with the complexity of the behaviors mediated by the brain stem? There are several possible explanations for this "apparent paradox.

(1) *Complex behaviors are mediated by other brain stem structures.* Lateral reticular structures, the central gray, monoaminergic reticular nuclei such as the raphe and locus coeruleus, cranial nerve nuclei, pontine nuclei and tectal structures have not been discussed. These areas might have more important roles in organizing higher order behavioral functions than medial reticular cells. Another possibility is that RF cells related to 'complex' behaviors are located in the medial RF but are rare or are in areas that have not yet been explored.

(2) *Complex behaviors are mediated by smaller cells within the RF.* As pointed out above, unit studies of the RF have focused on the larger cells in this region. While large cells are well suited for rapid conduction of neural outputs, smaller cells might be effective in the organization of long behavioral sequences. Electrical stimulation and lesions would affect the activity of these cells while single unit recording studies would tend to miss them. While the sampling problem is perhaps more severe in studies using fine wire techniques, conventional microelectrodes also are subject to sampling bias. The behavioral and physiological correlates of these small cells, and especially any differences between small and large cells, may hold the key to many of the mysteries of RF function. Intracellular staining techniques that allow one to correlate neuronal size and morphology with other measures would be useful in exploring this possibility.

(3) *Complex behaviors are emergent properties of nerve nets.* While it is tempting

to explain complex behaviors by looking for cells correlated with specific behaviors, this anthropomorphic approach does not necessarily 'explain' anything. The extension of the concept of neural 'centers' to the single cell, stretches an already tenuous concept beyond the breaking point. In order to understand the neural mechanisms underlying complex behavior, reductionistic principles must be applied.

In 1952 Sperry²¹⁹ presented a model of complex behavioral control utilizing such principles. His thesis was that the understanding of the neural control of complex behavior could best be achieved if one views the brain as "a mechanism for governing motor activity... overt behavior, upon analysis, we find to be constituted almost entirely of patterns of muscular contraction. It follows that the principal function of the nervous system is the coordinated innervation of the musculature. Its fundamental anatomical plan and working principles are understandable only on these terms. .. If any scheme or plan at all is evident in the complicated fiber association and nuclear interconnections of the brain, it is a design patterned throughout for governing excitation of the 'final common (motor) pathways'."

When one considers the views of Sperry and other behaviorists, that motor activity is not merely the output of the brain, but is also integrally involved in neural processing, our hypothesis of reticular relation to specific movement patterns no longer seems inconsistent with the behavioral roles of the RF. Neural control need not be mediated by single cells relating primarily to complex behaviors or behavioral states. Instead, it may be seen to be coded in patterns of excitation within the neural networks interconnecting cells, each of which has specific motor correlates. The behaviors that result are emergent properties of the network not manifest in the activity of any of its constituent neurons. This behaviorist view may or may not apply to fore-brain areas, but the available evidence does suggest such an interpretation of medial RF functioning.

We hope that our hypothesis, by providing an explicit experimental challenge for RF researchers to meet in distinguishing movement-related unit discharge from more complex behavioral relations, will help stimulate research in this area. The further understanding of the RF will help reveal the operational principals of the brain stem regions which contain the basic mechanisms controlling behavior.

7. GENERAL SUMMARY

Studies of the behavioral correlates of activity in reticular formation cells, usually performed in restrained animals, have found units whose discharge relates to sensory stimuli, pain and escape behavior, conditioning and habituation, arousal, complex motivational states, REM sleep, eye movements, respiration and locomotion. Units with these different behavioral correlates were found in the same anatomical areas. Most studies report that a large proportion of encountered cells related to the behavior being studied. If one adds up the reported percentages, the total far exceeds 100%. Therefore it appears that many investigators are looking at the same cells and reaching very different conclusions about their behavioral roles. On the basis of observations in unrestrained cats, it is hypothesized that discharge in most RF cells is

primarily related to the excitation of small groups of muscles. This hypothesis can parsimoniously explain many previous observations on the behavioral correlates of these cells, and is consistent with anatomical, physiological and phylogenetic studies of the reticular formation. The hypothesized simplicity of reticular formation unit function is contrasted with the complexity of the behavioral functions mediated by the RF, and the implications of this contrast discussed.

ACKNOWLEDGEMENTS

I thank Dr. Dennis McGinty for advice, encouragement and many valuable discussions. This work was supported by the Medical Research Service of the Veterans Administration and National Institutes of Health Research Grant NS14610.

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