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MESENCEPHALIC REGULATION OF EVOKED INHIBITION IN THE CAT'S VISUAL CORTEX: AN EXTRACELLULAR STUDY

by

ISABELLE ALTER

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

1977

This manuscript has been read and accepted for the Graduate Faculty in Neuropsychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

6/20/77
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Abstract

MESENCEPHALIC REGULATION OF EVOKED INHIBITION
IN THE CAT'S VISUAL CORTEX:
An extracellular study

by
Isebelle Alter

Advisor: Professor William S. Battersby

Earlier microelectrode studies have shown both facilitatory and inhibitory effects on evoked responses in units of the visual cortex following activation of the mesencephalic reticular formation (MRF). Despite these observations, the conclusion drawn in the literature has been that the MRF's effect on the cortical neuron's responsiveness is in the main facilitatory. Those investigators who reported both facilitation and inhibition of the cortical unit's response generally observed the two effects in different units. Hence they ascribed the opposing MRF influences to the type of cortical unit encountered, or its locus, thus depriving the MRF of a causal role in the nature of the effect produced. Furthermore, since the presence of spike discharges is more conspicuous in the extracellular record than is their absence, the excitatory response to input has been the focal object of investigation. Yet it has been known for some time that inhibitory mechanisms are intimately involved in the neural coding of input. It is most unlikely that the MRF would influence the excitatory activity of the neuron without concomitantly influencing its inhibitory counterpart.

This study was designed to assess the effects - in the acute, flaxedilized cat - of MRF activation on the inhibitory portion of the

evoked response in units of the visual cortex. Through intracellular recording, Li et al. (1960) demonstrated that the periods of spike suppression observed in neurons of the visual cortex following a shock to the lateral geniculate body (LGB) were associated with membrane hyperpolarization. Hence an alteration of the duration of LGB-induced spike suppression would reflect the MRF's influence on inhibitory mechanisms in cortex.

Our results demonstrated that MRF activation will systematically curtail or prolong the duration of suppression in cortical units as a function of (1) the MRF-LGB interval; (2) the intensity of the MRF train; (3) the intensity of the LGB test shock. Short interstimulus intervals and high-intensity MRF trains contracted the inhibitory period, while the longer intervals and weaker MRF trains prolonged it. Prolongation of suppression by the MRF was much more pronounced with weak test shocks, while reduction of inhibition was the more marked effect at higher test-shock intensities. In several units, virtually identical results - when the interstimulus interval was varied - were obtained with conditioning in the superior colliculus (SC) when either a test shock to LGB or a photic test stimulus was administered.

The conclusion was drawn that the facilitatory effects observed at the short intervals and with intense MRF trains could very likely be explained by a superposition of the individual responses to the conditioning and test stimuli. On the other hand, the prolongation of inhibition at longer MRF-test stimulus delays and with weaker MRF trains could not readily be explained by a simple superposition. This datum ostensibly reveals an interaction of the two inputs at some point en route to cortex or within cortex itself - an interaction signalled by

a transitional interval where a high degree of response variability was noted.

In sum, the orderliness of our findings suggests that, in selecting evoked inhibition as our dependent variable, we have located the cortical mechanism most susceptible to MRF regulation. The MRF's signal contribution to cortical function may reside in its regulation of cortical inhibition.

Acknowledgements

First, I must express my genuine gratitude to my teacher and sponsor, Dr. W.S. Battersby, who, in the best spirit of modern midwifery, allowed me the luxury of a natural offspring: his patience during the prolonged gestation was exemplary; his guidance, much appreciated. I thank Larry Feldman, whose sustained kindness, good humour, and technical ingenuity, supported the continuance and made possible the termination of this project. At Larry's suggestion, I acknowledge Murphy, whose law states that if something can go wrong, it will. But then Larry was around to take care of Murphy. Then there's cousin Connie (Ezekiel Gloos) to thank - his considerable photographic talents made the data visible. And David Passikoff, for being David.

I am grateful to Sal Randazzo for his generous contribution of time, and also to Stan Bala, Steve Sabat, and Eugene Reiss, for theirs. Russell Speer's competence at the initiation of this study, and Marie Tucker's fine histology at its termination, have served me well.

I thank Larry Pinneo who made it possible for me to begin work in Dr. Battersby's laboratory, and Luis Marco who assured me that the cells would appear.

Others among my friends were invaluable, even Phineas (who may have thought otherwise), but, except for my mother and Bruno, I will extend my thanks to them personally or the list will be embarrassingly long.

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INTRODUCTION

The existence of inhibitory processes in cortex was deemed essential even prior to its substantiation. Given the high degree of interconnection in its networks, the cortex would undoubtedly go into oscillation without the intervention of some kind of dampening mechanism (see e.g. Fessard, 1961; Jung, 1961). As the contributions made by inhibitory mechanisms to cortical function were conceived and elaborated over the years - in receptive field organization and contrast enhancement, for example - a concurrent interest developed in the dynamic properties of cortical neurons. Investigations were conducted on neuronal behaviour in various brain states, during sleep and waking and the transition between these. Contrary to expectation, waking was often associated with a reduction in neuronal activity (e.g. Evarts, 1961). Despite the growing recognition that wakefulness and a preponderance of excitatory activity are not necessarily linked, the expectation has persisted that cortical activation is in fact accompanied by a heightened excitability in its neuronal elements. That persistence seems principally to be due to the results of numerous microelectrode investigations showing a predominantly facilitatory effect on cortical cells following mesencephalic reticular (MRF) activation. The MRF has long been known to govern electrocortical activation (Moruzzi and Magoun, 1949). These studies, however, have generally employed the extracellular recording technique. This has led to an inevitable emphasis on the excitatory aspect of the neuron's activity since what is directly visible in the extracellular record are neuronal spikes. Hence MRF activation was seen to enhance or attenuate the maintained or

evoked excitatory discharges in cortex while its influence on inhibitory processes as such - which are not readily discernible in the extracellular record - was disregarded or only tentatively inferred.

Once the existence of endogenous inhibitory mechanisms in cortex is granted, a heightened cortical excitability would either encompass all of its elements (including its inhibitory neurons) or, less likely, some selected subset (e.g. the excitatory neurons alone). While a number of studies employing MRF activation have demonstrated a decline in the maintained discharge frequency of a substantial proportion of cortical neurons, suggesting some inhibitory influence, the principal observation for evoked activity has been reported to be excitatory (see next section). It is in this very domain (regarding evoked activity), however, in the analysis of input or sensory coding, that inhibitory mechanisms are thought to play a crucial role - as in lateral inhibition. It is difficult to conceive that MRF activation would regulate the excitatory portion of the cortical unit's response without concomitantly modifying its inhibitory counterpart.

Intracellular recording for any length of time, particularly in the granular cortex of the unrestrained animal, has been singularly difficult to implement, thus hindering a detailed assessment of the dynamic properties of inhibitory function in the visual cortex. A means of circumventing some of the problems of intracellular recording has been available for some time, however, in the correlations established between spike suppression and inhibitory postsynaptic potentials (IPSPs) for some cortical responses. Tasaki et al. (1954) and later Li et al. (1960), for example, have demonstrated that the spike suppression elicited in visual cortex by electrical stimulation of visual

afferents is reliably correlated with membrane hyperpolarization. Any modification of the extracellularly monitored spike suppression would thus very likely reflect changes in the underlying polarization of the cell. It is thereby possible to evaluate the MRF's effectiveness in altering inhibitory activity in the visual cortex by monitoring its influence on an already present depression in spike discharge.

The vulnerability of inhibitory mechanisms to alterations associated with electrocortical arousal has hardly been explored. Non-sensory influences are known to affect sensory processing. To the extent that inhibition is thought to participate in mechanisms of sensory acuity, discriminative function, and the like, it must be subject to influences exerted by varying brain states. This study was designed to assess the effects of MRF activation on the evoked suppression of spike discharges in the visual cortex of the acute cat.

REVIEW OF THE LITERATURE

Analyses of MRF influence on both slow and micropotentials began concurrently in the late fifties and had similar aims: an exploration of the ways in which MRF activation altered cortical excitability. The initial unit studies had as an additional aim the demonstration of convergence of 'nonspecific' and 'specific' influences on the same cortical neuron. The investigations employing the gross potential technique provided the basis for Bremer's highly influential explanation of the MRF's effects on cortex. His view established the framework for the conclusions drawn from many of the unit studies conducted on the subject. A brief exposition, therefore, of the early results derived from gross potential studies, as well as of Bremer's explanation, will be presented prior to a description of the MRF's influence on single neurons in the visual cortex.

The MRF and Visual Macropotentials

For the visual system of the cat, it was early established that while MRF conditioning depressed the emplitude of cortical macropotentials elicited by photic ('peripheral') stimuli, it enhanced the amplitude of potentials evoked by electrical ('central') stimulation of the afferent pathways (Bremer and Stoupel, 1958; Dumont and Dell, 1960). Gauthier et al. (1956) had first reported this contrasting effect for the somatosensory evoked potential. Bremer regarded this finding as "An important advance in the understanding of reticulocortical arousal . . ." (1961a, pp. 34-35) because, given the potentiation of the electrically evoked response, he thought that the depression of the response to the

photic stimulus could also be explained in terms of facilitation - namely, by a process of occlusion of the facilitatory process:

> At the present stage of the problem, it is perhaps preferable to look for an explanation which would not require the postulate of two fundamentally opposed effects of reticular arousal on the operations of the brain cortex and, correlatively, of two antagonistic categories of reticulocortical fibres. We think that the suppressive effect on the responses to volleys of impulses emitted from peripheral receptors can be explained by the predominance, in this case, of a process of occlusion on the facilitatory process. Cortical interneurones weakly activated by the dispersed afferent impulses emitted from receptors would be blocked as a result of their supraliminal activation by the reticulocortical impulses. The denser (better synchronized) volleys evoked by "central" stimuli should overcome the relative refractoriness of these interneurones. Thus, the cortical units already responding in the control response should still be activated by the specific impulses. The addition of their contingent to the neurones recruited in the subliminal fringe should result in the overall potentiation of the response. (Bremer, 1961a, pp. 42-43.)

Since Bremer's view did gain great currency, it must be understood that although he himself had stipulated that "An active inhibition mechanism at the cortical level cannot be excluded" (1961a, p. 42), his preference resided in other explanations. Sparse evidence for intracortical inhibitory processes existed at the time of Bremer's writing (but see Tasaki et al., 1954), and it did not satisfy him.

Bremer's view dictated an interpretation of alterations in evoked potential amplitudes which is not tenable once inhibitory processes are admitted into the picture. For if changes in excitatory processes are alone responsible for the amplitude shifts, then a unidimensional quantitative description is appropriate - namely, increased neuronal activity will generate a larger wave, and vice versa. But the introduction of inhibitory action will not brook such equations. The study of the amplitude of evoked potentials presents a host of serious problems for interpretation (e.g., see Creutzfeldt et al., 1969; MacKay, 1969; MacKay

and Jeffreys, 1973). Gross evoked potentials are thought largely to reflect the activity of graded neuronal potentials whose sign, however, is not readily ascertainable through surface recording. Thus a modification of the amplitudes of gross potentials reflects less about the properties of neuronal excitability and transmission than is often ascribed to it.

Although the interpretation of alterations in evoked potentials is complicated by the recognition of intracortical inhibitory activity, the need to postulate two antagonistic categories of reticulocortical influences is unwarranted. For a reticular activation of all cortical neurons would facilitate the activity of both excitatory and inhibitory units and hence an activating process can readily generate an inhibitory effect.

Bremer's formulation has tended to divert attention from a possibly crucial component of reticulocortical activation. For if inhibitory function is required for cortical information processing (a point hardly worth belabouring today) and also happens to have a higher excitability threshold, as it does (see below), then MRF activation may serve the primary function of bringing inhibitory processes into play. The next section elaborates on these points.

Cortical Inhibition and the MRF

While there is no question, by now, of inhibition occurring within the cortex, the existence of intracortical inhibitory neurons - that is, of inhibition generated by intrinsic as vs. extrinsic units - has been somewhat controversial, the weight of the evidence of the last few years tending to favour their presence. The evidence stems from both physio-

logical and anatomical sources.

The physiological argument emphasizes the latency differences for cortical excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) generated by input. The inhibitory processes are usually delayed, indicating the existence of an interpolated synapse (e.g., Creutzfeldt et al., 1969; Toyama et al., 1974; Watanabe et al., 1966). Furthermore, IPSPs have been recorded in an undercut cortex (Creutzfeldt et al., 1966) and therefore could only have been elicited intracortically.

The anatomical evidence rests largely on the assumption that different types of synaptic configurations subserve excitatory and inhibitory functions. The 'asymmetrical' variety of membrane thickenings at the synapse, for example, when associated with spherical vesicles, is thought to mediate excitatory function; while the other type of synaptic contact, the 'symmetrical' variety with flattened vesicles, is presumed to have inhibitory properties (Gray, 1959; Uchizono, 1965). If this assumption is correct, then all extrinsic influences upon the cortical receiving areas should be excitatory since all of the synaptic contacts formed by incoming fibers are apparently of the asymmetric variety (see Garey and Powell, 1971, for the visual system; and Jones and Powell, 1973). Inhibition would therefore have to be mediated by intracortical neurons. Furthermore, the existence in cortex of neurons of a particular morphological type (e.g. basket cells), whose inhibitory properties have been ascertained in other structures (in cerebellum and hippocampus, for example), suggests that they may perform the same function in cortex.

Inhibitory effects often appear to have higher thresholds than their excitatory counterparts (von Békésy, 1967). If this were so in cortex as well, any diffuse activating process

would then serve to maximize the expression of inhibitory action in cortex.

> The inhibitory mechanism [triggered by an electrical stimulus to cortex] could be evoked more readily in cortical neurones of increased excitability than in neurones of 'normal' excitability . . . It had a higher threshold and a longer latency than the excitatory mechanism; but once set in motion it was more powerful than the excitatory mechanism. (Li and Chou, 1962, p. 15)

That increased excitability is in fact necessary to initiate the expression of inhibitory mechanisms makes immediately evident that the activation of a structure such as the MRF, thought to be responsible for increased cortical excitability, would be most effective in accomplishing this function.

The MRF and Visual Micropotentials: Extracellular Recording

The experimental history of the MRF's influence on neurons in the visual cortex closely mirrors the theoretical predilections and the technical limitations of the times. The predominantly chronological survey which follows will show that the early studies emphasized the facilitatory effect of MRF activation. They were followed by a group of reports which demonstrated the MRF's dual capacity for inhibiting the activity of some units and facilitating it in others. An unusual report (Skrebitsky, 1969) revealed a predominantly inhibitory influence. Finally, the most recent investigations (Bartlett and Doty, 1974, for example) have come full circle in concluding that the MRF's influence on cortical units is largely facilitatory.

In a review of the work, Brooks and Jung (1973) thought the discrepancies could ". . . be explained either by species differences or by inclusion of geniculo-cortical fibres in the early work in the cat, since Skrebitsky found predominant facilitation after reticular stimulation in

LGB-neurones in the rabbit" (p. 405). They ignored differences in type of preparation used: Skrebitsky's animals were chronic while most of the earlier preparations had been acute. They also ignored possible differences in stimulus parameters as well as the particular dependent variable chosen for study. Both type of preparation and stimulus parameters are germane to the question of the animal's general condition, that is, to its brain state or 'level of arousal,' whose intimate relation to MRF function has been recognized for some time. Skrebitsky, for example, had used an MRF stimulus of low intensity, a parameter of some import as we shall demonstrate, one whose values were left unspecified in many of the studies at issue.

The dependent variables examined in these studies were either the maintained discharge of cortical units or the spike discharges elicited by electrical or photic input. For the latter, the effects on the excitatory response, that is, on the initial discharge to the stimulus (at whatever latency it occurred), were evaluated. (Narikashvili et al., 1965, were the exception - in having explored several aspects of the unit's response - see later). Little or no attention was consequently paid to the effects of MRF activation on cortical inhibition. This was possibly due to the scarcity of computers (as well as to the theoretical preconceptions noted): spike suppression is difficult to detect as such, particularly when the unit's maintained activity is low, without some means of data summation. This lack accounts at least in part for the emphasis on the MRF's influence on excitatory processes when recording is conducted with the extracellular method.

. . . . . .

The following exposition will be restricted to those studies in which the effects of MRF-induced arousal were investigated. Most studies

dealing with the related questions of 'sensory' and thalamically-induced arousal will not be included as they provide little additional clarification on the matter. Among the earliest demonstrations of MRF and sensory convergence on single neurons in the visual cortex of the cat (the animal most commonly used) were those of Jung and his collaborators in the 1950s (cited in Jung, 1961). . . It must be noted that the demonstration of convergence was functional, and that no conclusions about monosynaptic input from the MRF could be drawn from these findings.

Having identified several species of neurons in Area 17 of the cat on the basis of their responses to diffuse illumination, these investigators proceeded to categorize the effects of intralaminar thalamic and reticular stimulation on cortical neurons. They found that while activation of these 'non-specific' extra-visual structures did not alter the character of visual neuronal responses to light, it did facilitate the neurons' responsiveness to photic stimuli; that is, the neurons could be more strongly or easily driven by light (Creutzfeldt and Akimoto, 1957-8; Akimoto and Creutzfeldt, 1957-8; cited by Jung, 1961). While reticular stimulation was predominantly facilitatory, it could produce inhibitory effects, the main such effect being the disruption of the neuronal CFF (Jung, 1961). No further work on the subject was evidently carried out in Jung's laboratory since the early sixties as, in the overview co-authored with Brooks (1973), Jung relied heavily on the evidence furnished by Creutzfeldt and Akimoto which was published in, among other sources, the Freiburg symposium of 1961. The following are the key findings reported by these investigators:

Creutzfeldt et al.(1961) investigated the effects of MRF condi-

tioning on the response to optic tract stimuli in the visual cortex of encéphale isolé cats. They first noted that shocks to the optic tract produced several different response patterns in cortex, the majority of units responding with a short-latency and highly reliable spike discharge. MRF conditioning was followed by facilitation of this discharge. Variation of the MRF-optic tract stimulus intervals showed that the facilitation lasted as long as 300-500 msec after the end of the MRF train. The effect of MRF on the spontaneous discharge frequency of the cortical units varied: half of the units showed a transitory activation, that is, an increase in their spontaneous discharge frequency; one-third were unaffected altogether; and the remaining units (6/48) were inhibited during MRF stimulation.

At the same symposium in Freiburg, Akimoto et al. (1961) also reported on a number of similar investigations that they and their coworkers had conducted during the late fifties. Their studies had encompassed the effects of arousal - both 'natural' and MRF-induced - not only on the visual system but also on the somatosensory, auditory, and motor systems, as well as on the association cortex of the immobilized unanaesthetized cat. In the visual system, they investigated arousal effects on photically evoked unit activity in cortex. They also examined the responses elicited by single shocks in the optic radiation and the LGB.

Their results generally conformed to those of Creutzfeldt et al. The most frequent observation with MRF activation was a facilitation of the cortical response to photic flashes. Furthermore, the responses to radiation and geniculate shocks were almost exclusively facilitated, an inhibitory effect having been observed in only one exceptional unit. When the MRF-test shock interval was varied (with single MRF conditioning

pulse), the responses to radiation or geniculate shocks were facilitated for interstimulus intervals ranging from 30 to 200 msec, with a peak augmentation between 40-80 msec. No inhibitory phase was seen. Yet in somatosensory cortex, single conditioning shocks to MRF produced not only the same interaction curves as in visual cortex but also curves with inhibitory phases at intervals of 50-120 msec. This was exceptional, however, as facilitation was characteristic of the effects in the auditory and motor cortices as well as of the response evoked by direct cortical stimulation. Thus, "The cortical facilitation as was seen in visual cortex is not a specific and areal phenomenon but a manifestation of more general feature of cortical arousal" (Akimoto et al., 1961, p. 371). In sum, although inhibition or suppression of transmission had in fact been observed, particularly in MRF-flash vs. MRF-shock interactions, facilitation was the more common and by far the more emphasized outcome of the interactions.

The value of the next three studies is limited in their having been confined to the evaluation of MRF's influence on the maintained discharge of cortical units. Nonetheless, Fuster (1961), using chronic preparations, found that high-frequency stimulation of the MRF in rabbits tended to enhance the firing of those striate units which were activated by diffuse light, while decreasing the discharge frequency of light-inhibited units. Sixty-one of his 100 units, however, were totally unaffected by brainstem stimulation. He concluded that the manner in which MRF affected the spontaneous activity of visual cortical units depended upon the type of unit monitored.

The larger number of units (81%) affected by the MRF in Velyka's (1966) rabbits may have been due to the preparation used, which was un-

specified. The maintained discharge was reduced in 64% of these units and facilitated in 32%, with a reciprocal relation observed for neighbouring neurons. Velyka also reported that MRF and photic stimulation had the same effect on the neuron's maintained discharge: for those units in which photic stimulation had produced suppression, MRF activation did so also, and vice versa. This held not so much for the 'on-response' to light as it did for the later changes in activity monitored during prolonged illumination - an important distinction to which we will return. The opposite effects of MRF activation on neighbouring neurons suggested to Velyka that the specific sensory or intracortical mechanisms are of major importance in determining the type of response obtained, a view somewhat similar to Fuster's.

In contrast to the above studies, Orem and Feeney (1971), whose observations were also restricted to the maintained discharge frequency, determined that whether facilitation or inhibition occurred depended upon the rostro-caudal locus of cortical recording in the immobilized cat. The majority of cells in rostral VC (visual cortex), tentatively identified by the authors as area 18 (on the basis of Otsuka and Hassler's criteria), were facilitated, while those in caudal VC (area 17) were inhibited. Thus locus of recording appears to be of some import - an observation serving to complicate an already muddled picture.

A distinction between the MRF's influence on the maintained as vs. the evoked discharge frequencies in cortical neurons was made explicitly by Narikashvili et al. (1965). While their results for the MRF's effects on the unit's maintained discharge accorded with those of Fuster and Velyka - in being correlated with the unit's response to photic stimulation - they pointed out that the MRF's effect on the neuron's

response to input was not so related. That is, whether a particular neuron's response to a photic stimulus was facilitated or inhibited did not depend upon the character of its response to the photic stimulus itself. Narikashvili et al. made several other valuable observations on their recordings from area 17 of the encéphale isolé cat. Briefly, they noted that the later components of the unit's response were more labile and more susceptible to reticular influence. Furthermore, both the frequency and the latency of these later spike discharges could be markedly reduced or augmented by MRF conditioning. The conditions under which such alterations were brought about were not specified. These authors postulated an MRF regulation of hypothetical inhibitory processes preceding the late activation - thus appearing to have been the first to note that the MRF may exercise its influence on cortex through its control of inhibitory function. A year later, Narikashvili et al. (1966) chose to examine in detail those units whose characteristic response to light had been altered by MRF conditioning (an unusual observation). Here they concluded that the facilitatory influence of MRF on cortical neurons is brought about by the removal of normally ongoing inhibitory mechanisms, again emphasizing the MRF's facilitatory effect.

Skrebitsky (1969) examined the effects of sensory or reticular arousal on neuronal responsiveness in the chronic rabbit's visual cortex and found that by far the more common effect was inhibitory. Among the units which had responded to light flashes, only 50% were affected by different arousing stimuli such as acoustic, electrocutaneous, and mesencephalic reticular stimulation; this lower percentage seems to have been a function of the unanaesthetized chronic preparation. The photically-evoked cortical discharge was inhibited in 75-80% of these units

and facilitated in the rest. "Different types of responses to light flash were inhibited by arousing non-visual stimuli, but predominantly it was the long-latency discharges which were often preceded by an inhibitory pause" (Skrebitsky, 1969, p. 274). Thus the discrepancy between Skrebitsky's report that inhibition of evoked discharge was the principal effect of arousing stimuli and the earlier emphasis on its facilitation may in part be explained by the aspect of the unit's response which he had chosen to observe.

Bartlett and Doty's (1974) investigation on the unanaesthetized squirrel monkey has again focussed attention on the MRF's facilitatory influence. Only a very small proportion of the striate cortical units (5/58) exhibited any significant inhibition of evoked discharges. The interval between conditioning and test stimuli (the latter having been either electrical or photic) was normally kept at 50 msec, although intervals of 25-100 msec were also explored. While the location of the mesencephalic electrodes was mostly dorsal to the MRF, in the superior colliculus (SC), a general similarity between the cortical effects of MRF and SC can be expected on the basis of gross potential data (e.g. Chalupa et al., 1973) and microelectrode recording (see Appendix A).

Despite intensive investigation of the problem, the factors governing mesencephalic alteration of evoked responses at visual cortex are still obscure. A clue may be provided, however, by both Narikashvili et al. (1965) and Skrebitsky (1969) who noted that it was the later components of the unit's response which were most affected by arousal or reticular input. It appears that an evaluation of this neglected aspect of the unit's response, the activity - or lack of it (spike suppression) - which succeeds the initial excitatory response to input, may

serve to clarify the nature of the mechanisms underlying reticulocortical regulation. Numerous studies using macropotential recording have shown that the later components of gross evoked potentials may be more sensitive to manipulations of MRF or arousal level than the primary evoked potential (e.g., Creutzfeldt and Kuhnt, 1973).

The Present Study

The primary aim of the present study was to evaluate the MRF's influence on spike suppression and, by inference, on inhibitory processes evoked in visual cortex by electrical or photic input. Few microelectrode studies have addressed themselves to this question as the intracellular method is difficult to implement while the extracellular technique may have been deemed inappropriate to the task. Evarts (1961) has shown, however, that useful inferences concerning inhibition may be drawn from extracellular monitoring of the duration of spike suppression in units of the visual cortex. Although his results demonstrated that suppression, evoked by a shock to the optic radiations, is lengthened during wakefulness in the intact cat, "The mechanism underlying this proposed increase of inhibitory activity remains to be determined" (1961, p. 173). Activation of the MRF, thought to produce facilitation of cortical units, would seem a logical starting point in the delineation of these mechanisms, especially in view of the conclusion drawn by Li and Chou (1962) that inhibitory processes have a higher threshold than their excitatory counterparts.

Evarts pointed out that the waking state which he had studied was different from the state of intense arousal which may follow novel stimu-

lation or strong electrical stimulation of the reticular formation. Although most of the reported studies provided no indication that MRF stimulus parameters may have had a bearing on the results, their manipulation seemed appropriate in view of the well-established behavioral and electrophysiological differences associated with different 'levels of arousal.'

In the present investigation, the duration of spike suppression following LGB shock was evaluated from extracellular records derived from the visual cortex of the flaxedilized cat. MRF-LGB intervals were varied, as was the intensity of conditioning and test stimuli. Conditioning in LGB was implemented as a control for locus of stimulation. In a few instances, MRF conditioning was replaced by conditioning in the superior colliculus (SC), and the LGB test shock by a photic stimulus (the latter, to improve upon the generality of the results). In order to satisfy the requirements of the intended analysis - that is, to test the sensitivity of the spike suppression measure in a variety of conditions - a large sample size was sacrificed for the purpose of as detailed an evaluation as practicable for each unit.

METHODS

Surgery, electrodes, and histology

Observations were made on a total of 23 adult cats (largely male) prepared as follows: A tracheostomy was performed after ether induction and a tracheal cannula was inserted. The animal was maintained on an ether bottle which was attached to the tracheal cannula until the cat was mounted and aligned in a stereotaxic apparatus (Kopf). The ether bottle was then removed and the animal's lungs were flushed with oxygen to reduce the remaining effects of ether. A mixture of Halothane (0.5-2%), nitrous oxide (N_2O: ca 55%), and oxygen (O_2: ca 45%), was administered at a total flow rate of 1.5L/min.

The left saphenous vein was cannulated for subsequent infusion of a 10% dilute solution (90% saline) of gallamine triethiodide (Flaxedil) and, occasionally, a solution of 5% dextrose in physiological saline to maintain hydration. A midline skin incision was made over the skull and the temporal muscles were reflected bilaterally to expose the calvarium. A trephine hole, made over the left cerebral hemisphere, was enlarged with rongeurs to produce a cranial opening extending rostro-caudally from approximately A13 to P3 over the left hemisphere, and from A6 to A0 over the midline above the right hemisphere; the exposure was extended to as much as 14 mm laterally over the left hemisphere and 6 mm over the right. The dura was resected in some cats, exposing portions of the marginal and suprasylvian gyri. When exposed, the cortex was kept moist with warm saline.

The cisterna magna was subsequently exposed and punctured. Bilateral thoracotomies were performed in several animals early in the inves-

tigation but were discontinued when they appeared to make no material difference to the development of brain pulsation. The cortex was stabilized (i.e. pulsation was controlled) by a variety of standard expedients, such as relative positioning of the head, occasional use of the surface recording electrode as 'pressure foot,' but mainly through careful cisternal drainage.

All wounds and pressure points were liberally infiltrated with prilocaine (Citanest) which was re-administered every 4 hours. Flaxedil was infused into the saphenous vein (with an initial dose of 3-4 mg/kg body weight) to immobilize the preparation and was supplemented (approximately 2 mg/kg) at 30-60 min interals (or as necessary). Artificial respiration was initiated at 22-26 rpm, with a volume of 30-35 ml/stroke. PCO_2 was not monitored but, after immobilization, stroke frequency was adjusted to simulate the animal's normal respiratory rate. A DC-powered heating pad was wrapped around the animal's abdomen to prevent any marked drop in body temperature.

When the dura was left intact, slits were made for the passage of two bipolar stimulating electrodes, flush-cut and insulated with formvar except at the tips. Each electrode was made of two pieces of .125 mm tungsten wire encased in a 20-gauge stainless steel tube which was also insulated with formvar. The tips of the stimulating electrodes extended approximately 2 mm beyond the edge of the tube and were horizontally separated by .5-1.0 mm. One electrode was directed at the lateral geniculate body (LGB), the other at either the mesencephalic reticular formation (MRF) or the superior colliculus (SC) according to the stereotaxic coordinates of the Jasper and Ajmone-Marsan (1954) cat atlas: the left LGB generally at A7.0, L9.5, and the right (contrala-

teral) MRF or SC at A2.5-3.0 and L2.0-3.0. For gross responses, a ball-tipped tungsten electrode was positioned over the left hemisphere at approximately A6.0 with the tip on mid-marginal gyrus. Cortical recording, done for the purpose of positioning the depth electrodes and monitoring the EEG, was always monopolar from the marginal gyrus, the referent being placed on the edge of a retracted temporal muscle.

A 15-23 megohm (at 1000 Hz) tungsten microelectrode (manufactured by Haer), insulated with a thermoplastic resin (Epoxylite), and with a tip diameter of less than 1 μm (and tip length of 5 μm), was then positioned within the compass of A1.0-4.5 and L1.0-5.0 over the left marginal gyrus and lowered, often without a prior incision in the dura.

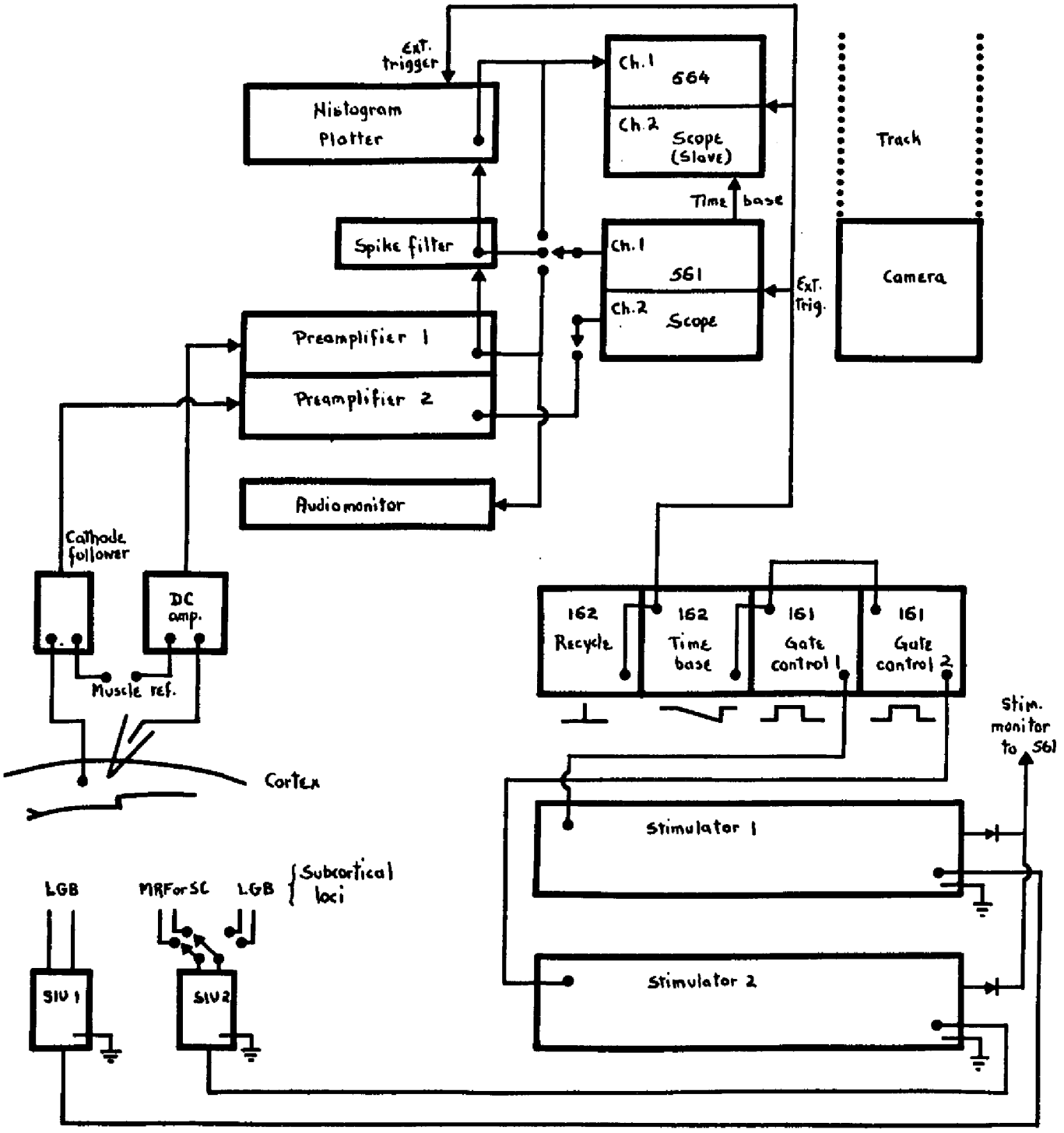
The brain was preserved for histology in 64% of the reported units. At the conclusion of the experiments, the level of anaesthesia was increased for these animals, and the subcortical stimulating sites were electrolytically marked by passing a DC current of .5 mamps between the electrode tip and the earbars of the stereotaxic instrument (cathode) for 25-30 secs. The animal was then killed with 8-10 cc of Nembutal injected intravenously, decapitated, its head rinsed and kept in a 10% formalin solution for several months. The brains were subsequently blocked and frozen coronal sections cut at a thickness of 50 μm. Every fifth section was then stained according to the Klüver-Barrera (1953) method. The stained sections were examined under a microscope to verify the location of the depth electrodes.

Control equipment: recording and stimulation

Cortical activity picked up by the surface electrode was fed through a Grass electrode follower and a Grass (P5) differential preamplifier with a band pass of 7 Hz to 2 kHz (-3 db). Unit activity monitored by the microelectrode was channelled through a DC-coupled preamplifier (Transidyne MPA-6), a Grass differential preamplifier (P5) with a band pass of 35 Hz to 10 kHz (-3 db), and a 60-cycle spike filter (Kopf, EFA-12). Both gross and unit derivations were then displayed on a split-beam oscilloscope (Tektronix 561). The filtered unit activity was fed into an audiomonitor and also into a histogram analyzer (Synax) with a 200 time-bin capacity and an adjustable threshold voltage. The output of the Synax unit was displayed in the form of histograms on a slave storage oscilloscope (Tektronix 564). Both samples of the single traces of unit activity on the 561 as well as the frequency distributions over 16-32 sweeps displayed on the 564 oscilloscopes were photographed for later data analysis on a Grass (C4) Kymograph camera (35 mm).

Overall timing control for stimulation of the subcortical loci and for recording the surface as well as the unit responses was accomplished by a Tektronix waveform generator (Model 162). Every 4-6.3 secs, it triggered another identical waveform generator which served as a time base for two pulse generators (Model 161). Each pulse generator gated a Grass (S-4) stimulator for activation of the LGB and the MRF (or SC) with square-wave pulses (see below for parameters) delivered by two stimulus isolation units. Fig. 1 presents a flow chart of the stimulating and recording equipment.

Fig. 1. Flow diagram of electrophysiological stimulating and recording system.


Ext. trigger
Histogram Platter
Ch.1 664
Ch.2 Scope (Slave)
Track
Time base
Spike filter
Ch.1 561
Ch.2 Scope
Ext. trig.
Camera
Preamplifier 1
Preamplifier 2
Audiomonitor
Cathode follower
DC amp.
Muscle ref.
162 Recycle
162 Time base
161 Gate control 1
161 Gate control 2
Stim. monitor to 561
Cortex
Stimulator 1
Stimulator 2
LGB
MRF or SC
LGB
Subcortical loci
SIU 1
SIU 2

In those few animals (cats 287, 290, and 292) where photic stimulation was used, the above-mentioned Tektronix units regulated the optic stimulator as well, while a photocell record of the stimulus duration was displayed on one channel of the oscilloscope. The beam from a glow modulator tube was projected through a 10X30 mm rectangular aperture which, at a distance of approximately 385 mm from the nodal point of the eye, formed a target of $1\frac{1}{2}^{o}$X$4\frac{1}{2}^{o}$ of visual angle. The duration of the photic stimulus varied between 400-600 msec. Its intensity (filtered) and that of the background illumination (dim) were not calibrated. The target was directed at that portion of the retina subserved by the estimated locus of projection in contralateral cortex where the unit recording was taking place. Lacril was applied to prevent corneal dehydration. The contralateral eye was occluded by suturing the eyelids.

Atropine sulfate was administered topically for 2 of these animals to produce mydriasis. Its administration also served to demonstrate that the effects to be described did not depend upon a reacting pupil. Furthermore, pupillary dilation proved to be minimal if not unobservable at our chosen stimulating loci in MRF (at least during the administration of Halothane).

Procedure

Most of the experiments were conducted in a dimly illuminated, shielded room, with several of the early experiments carried out in total darkness. The subcortical electrodes were lowered toward their respective stimulating sites, their terminal loci being determined both by calculated stereotaxic coordinates as well as by the response characteristics monitored by the cortical surface electrode.

The electrode intended for stimulation of the LGB was lowered in .5 mm steps beginning at 2 mm above its calculated surface. With each advance of the electrode, the occurrence and characteristics of the cortical response evoked at the marginal gyrus by a .5 msec, 7-8 V, shock were evaluated. When the 'classical' shock-elicited four- or five-component response was reliably produced, that position of the electrode which produced it was selected for use throughout the experiment. The electrode destined for the MRF was then positioned in a similar fashion, using one 30-msec train of .1 msec pulses at 300 Hz and 4-6 V. The final location of the MRF electrode depended upon its effecting a reliable enhancement of the amplitude of the LGB-elicited cortical response (see Review of the Literature). The MRF-LGB interval was set at 20 msec or longer since such enhancement was reliably observed only at these longer intervals. In some experiments, the MRF electrode was either initially or subsequently positioned in the predetermined locus for the SC.

Following placement of the subcortical stimulating electrodes (and adjustment of the optic stimulator when photic stimulation was employed), Halothane was withdrawn for some animals. With 2 exceptions (see cats 316 and 333 in Table I, Appendix B), when Halothane was withdrawn, it was for the duration of the experiment. For cat 316, different units were monitored with and without Halothane. For one unit in cat 333, however, Halothane was withdrawn and readministered iteratively (see Results).

The microelectrode was then positioned over the left marginal gyrus and lowered until auditory contact was made with either the dura (when not resected) or the pia mater. The point of contact of the

electrode with the pial (or dural) surface, as measured on the micro-drive vernier, was taken as the zero reference (H-0). Its rostro-caudal (A-P) and lateral (L) locations were established by measuring its distance from the stereotaxically positioned MRF electrode and the sagittal sinus. A 1-megohm shunt resistor which had been switched across the input to the DC probe head (in order to prevent high current densities from damaging the electrode tip) was then switched out. The electrode was subsequently advanced in 25-50μ turns within a 2-3 mm range and usually left in situ for a few minutes initially to permit cortical stabilization following the dimpling ordinarily caused by the microelectrode penetration.

Biased sampling of neurons when recording with microelectrodes often arises because those neurons which generate a notable degree of spontaneous activity are most likely to be picked up for recording. In order to avoid that bias, several kinds of stimuli were administered concurrently during the search for units in cortex, the purpose being to drive those units that were not spontaneously, or frequently, active. The assortment of stimuli used were the following: periodic shocks to the LGB; photic stimulation with a moving flashlight; occasionally, MRF tetanization, changes in ambient illumination and levels of Halothane.

When a sizeable and relatively clean unit was located - as determined by auditory signals and oscilloscope tracings - and held for longer than a few seconds, the histogram plotter was set to cumulate the results of 16-32 sweeps, with 200 time bins at .5 msec/bin (to coincide with the total sweep duration on the oscilloscope of 1 sec). If several neurons were registered simultaneously, the threshold voltage was used in an attempt to filter out all but the largest unit (the spike amplitudes ranged from several hundred microvolts to several millivolts). When

good unit resolution was not obtainable, unit clusters were sometimes recorded as they were found to generate the same effects. Such characteristics of the unit's activity as its waveform, duration, spontaneous firing frequency, response to photic stimuli, receptive field location, were roughly assessed and included in the experimental protocols. The depth of the microelectrode placement was noted following the experimental treatments. When recording in cortex was precluded by uncontrollable brain pulsation, the microelectrode was advanced to monitor the responses of presumed radiation fibers and units in midbrain regions.

With the histogram plotter operative, the frequency distribution generated by a single pulse to LGB was roughly compared to that produced by the spontaneous activity of the unit; that is, the unit was assessed as being either responsive or not to LGB stimulation. If it showed any time-locked activity, as many of the following treatments were implemented as was made possible by the length of time the unit was held. Histograms were plotted for (1) the background or spontaneous level of unit firing; (2) response to LGB (or photic stimulus) alone; (3) variation of LGB intensity; (4) the effects of LGB conditioning; conditioning pulses delivered to LGB itself prior to the LGB test shock, at interstimulus intervals ranging from 0 through 400 msec; (5) MRF (or SC) alone; (6) MRF (or SC) conditioning, at interstimulus intervals ranging from 0 through 300 msec (calculated from the end of the conditioning train); (7) variation of MRF intensity, for a fixed MRF-LGB interval; (8) variation of LGB intensity with MRF conditioning. A quasi-random sampling strategy was used for the various conditions since each unit was to have been monitored for an indeterminate length of time (ranging from a few minutes to several hours).

The conditioning stimulus to LGB was generally identical to the test shock to LGB (.5 msec pulse) and was delivered via the same electrode. In the two instances where conditioning in LGB consisted of a train of pulses, these were still delivered through the same electrode by connecting the stimulus isolation units in series. The stimulus parameters for the LGB train were identical to those set for the MRF (or SC) trains: a 30-msec train of .1 msec pulses at 300 Hz. Current flow in the stimulating circuit was estimated as falling in the range of 30-200 μamps (at 50 kohms*) for the more common voltage settings of 1.5-10V.

The influence of several other variables, such as Halothane level and background illumination, were briefly evaluated as well. Faster sweeps (2-20 msec/cm) than the standard 100 msec/cm were photographed in 20% of the units to permit an assessment of the influence of the experimental treatments on the initial spike discharges to LGB shock. Notes were recorded in several experiments' protocols on the changes occurring in spike frequencies which were beyond the purview of the 1-sec oscilloscope tracings.

Given the administration of Flaxedil, the animal's level of alertness or arousal was assessed by sporadically monitoring its cortical EEG as well as the extent of its pupillary dilation. The EEG pattern seen most commonly with Halothane was one containing high-amplitude, low-frequency waves interrupted by periods of desynchronization. Such periods were more frequently observed after Halothane had been

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* In this particular series of experiments, electrode impedances, as measured in normal saline, varied between 25 and 65 kohms, values of 50 kohms being most representative. Electrode impedances of similar values were established in vivo in earlier experiments in this laboratory; on-line measurements with a Tektronix induction-coupled probe have indicated that our current values were within the range cited above.

withdrawn. The most common pupillary status, during Halothane in particular, was a high degree of constriction (usually associated with sleep or drowsiness). Various degrees of pupillary dilation were often noted, however, after Halothane had been withdrawn. A fair range of arousal levels seems to have been in effect over the course of this study.

Analysis of Data

The completion of a histogram plot (PSH) of the recorded unit's spike distribution following a single electrical shock to LGB was the minimal condition for inclusion in Table I of Appendix B. Units that exhibited no time-locked response to the test stimuli were discarded. Among such, however, were a few units which had responded with a total cessation of firing for protrated periods - that is, for longer than 1 sec (the longest sweep duration used); and others which had failed to give rise to suppression after the initial traces (possibly as a result of habituation), were discarded as well, any ostensible response having been obliterated after the first few traces in the histogram.

The units sampled in this study were assigned to three general locations: those in cortex, its adjacent white matter, and in the midbrain. The cortical units included (1) those recorded at any laterality when the depth of the microelectrode tip did not exceed 2 mm below the pia mater (and 2-2.5 mm below the dura); and (2) units at any depth (up to 6 mm) whose laterality did not exceed 2 mm from the midline (for reasons evident in Fig. 2b). Fig. 2a shows that most of our microelectrode penetrations centered around the border of areas 17 and 18 (according to Otsuka and Hassler, 1962) and in Hubel's VII cortex (but see Woolsey, 1971).

The units in the second category - white matter adjacent to cortex - were allocated by exclusion since their coordinates did not meet the above criteria for cortical units and yet were too shallow for location elsewhere. Because of the occurrence of cortical 'dimpling,' however, many units in the second category no doubt belonged to the first. The loci of the midbrain units, few in number and of minor interest in this study, were roughly estimated from their stereotaxic coordinates and the atlas of Jasper and Ajmone-Marsan (1954).

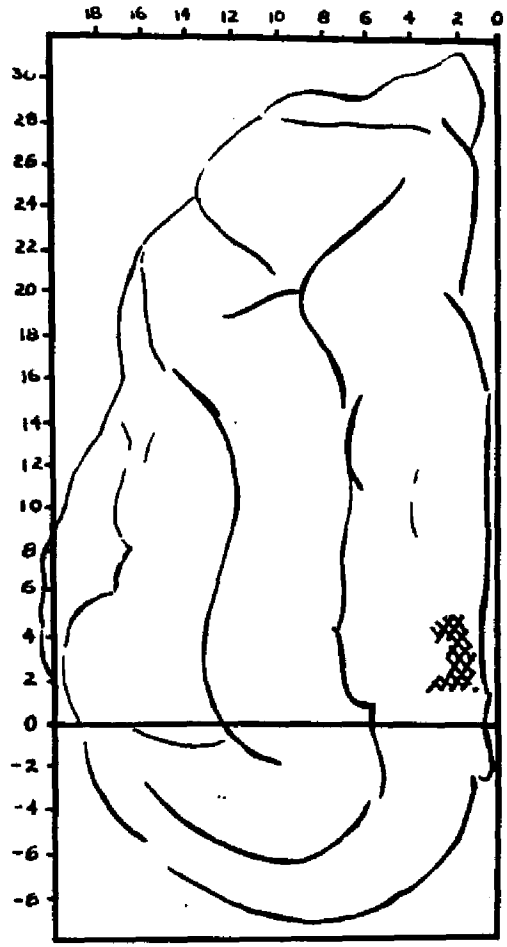
The histograms for each unit filmed at 100 msec/cm sweep speed were evaluated primarily for alterations in the duration of suppression of spike discharge following the LGB test shock (or photic stimulus). The occurrence of suppression was ascertained by a decrease in discharge frequency as compared to that preceding the stimuli (see Fig. 3a). Its duration, measured with the aid of a microfilm reader, was then expressed in msec. The 'control' value used to assess the effects of experimental treatments was established by averaging the suppression measurements for all available frequency distributions (when more than one was obtained) generated by a shock to LGB alone (or by a photic stimulus). The values for suppression duration were then expressed in terms of the percent of the control condition.

It must be noted that these suppression values were obtained from histograms accumulated from 16 (or 32) individual traces. A PSH, which

Fig. 2. (a) Tracing from the atlas of Jasper and Ajmone-Marsan (1954) illustrating the superior surface of one hemisphere of the cat's brain and the area of microelectrode penetration in this study (cross-hatched). (b) Xerograph of a coronal section (at A3) of one cerebral hemisphere from the cat atlas of Fifková and Maršala (1967).

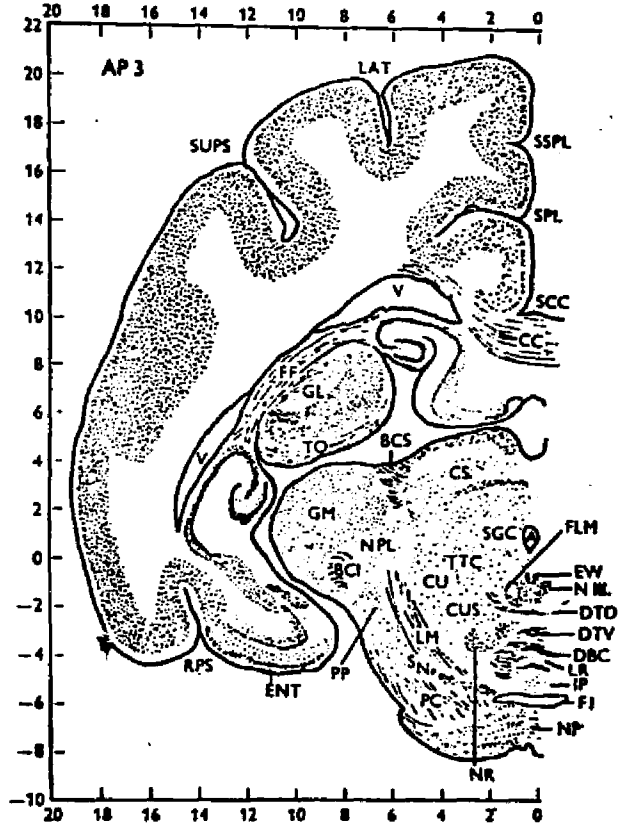
a

Superior surface



b

Coronal section at A3



displays the number of neuronal discharges occurring at various times after each of a series of identical stimuli, indicates the distribution of probability of unit discharge following LGB (or photic) excitation (Burns, 1968). When the 'spontaneous' or maintained activity preceding the stimulus was low - thus providing no reliable estimate of the 'sampling error' - and the nature of the spike distribution following the suppression period tended towards the normal as in Fig. 3b, the suppression values are representative of a minimal rather than an average duration per histogram. For only that interval which was entirely free of recorded events could be adjudged as 'suppressed.'

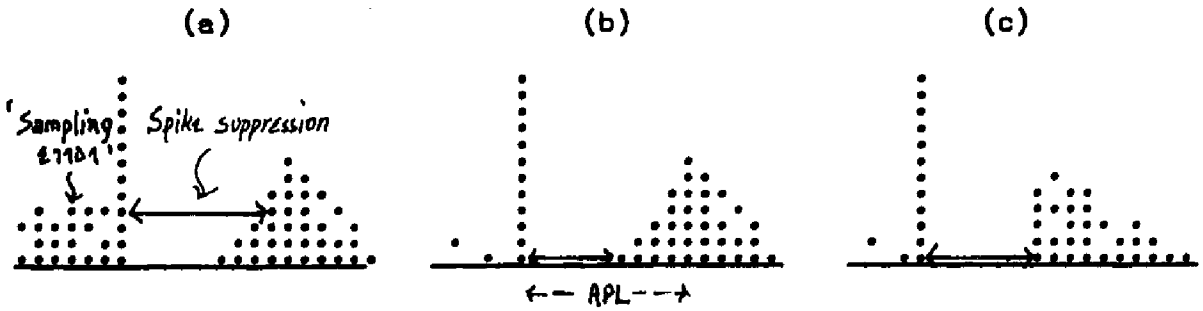


Fig. 3. Schemata of PSHs generated by a shock to LGB illustrating the three components of the cortical unit's response (for details, see Results): (a) PSH with 'sampling error preceding the response; (b) measurement of minimal suppression duration due to lack of sampling error; (c) PSH with skewed afterdischarge distribution.

Even when the spike distribution was very skewed, as in Fig. 3c, the error tended to be one of underestimation of the duration of suppression. This was shown by a number of comparisons between the duration of spike suppression in single traces and in the associated histograms (e.g. Unit 294/1 in Fig. 4) where it was evident that suppression was of far longer duration in the individual sweeps.

For some units, the latency to the peak of the spike distribution following suppression (APL, as in Fig. 3b, for 'afterdischarge' peak latency) was measured as well. Furthermore, the overall size of these distributions was roughly estimated as being either augmented or diminished in relation to the afterdischarge produced by the test shock to LGB. A similar assessment of the effects on the distribution of the initial spike discharges was made when a faster sweep was employed. But the characteristics of the discharges which immediately succeeded the stimulus often had the earmarks of field potentials; that is, their waveform and particularly the variability in their amplitudes indicated that they could have been recorded with a macroelectrode. Since an accurate assessment of alterations in the initial spike discharges seemed precluded thereby, these data were discarded and the reported results were confined to the slower sweep speeds necessary to monitor spike suppression in this study.

RESULTS

General Characteristics of the Unit Response in the Visual Cortex to LGB Shock

Several response patterns were observed from the 72 units of the visual cortex and its adjacent white matter following a single electrical shock to LGB. The most common and conspicuous pattern (for 75% of these units) at slow sweep speeds (100 msec/cm) was a sequence comprising a brief high-frequency cluster of spikes*, followed by a period of discharge suppression of variable duration, followed in turn by another variable period of often increased firing frequency (the 'afterdischarge'). Samples of individual traces which were accumulated to produce the accompanying histograms are illustrated in Fig. 4 for two different units.

The major differences observed among units monitored at slow sweep speeds resided in their being truly single units (as in Unit 294/1 in Fig. 4) or unit clusters (as in Unit(s) 333/1), in the level of their spontaneous discharge frequencies, and in the degree of their afterdischarge. Although the differences in spontaneous activity and afterdischarge are evident in the two histograms, the latter are distinctly similar in the marked period of suppression following the LGB test shock. For the individual traces, however, the term suppression is an inappropriate characterization for the silent period following

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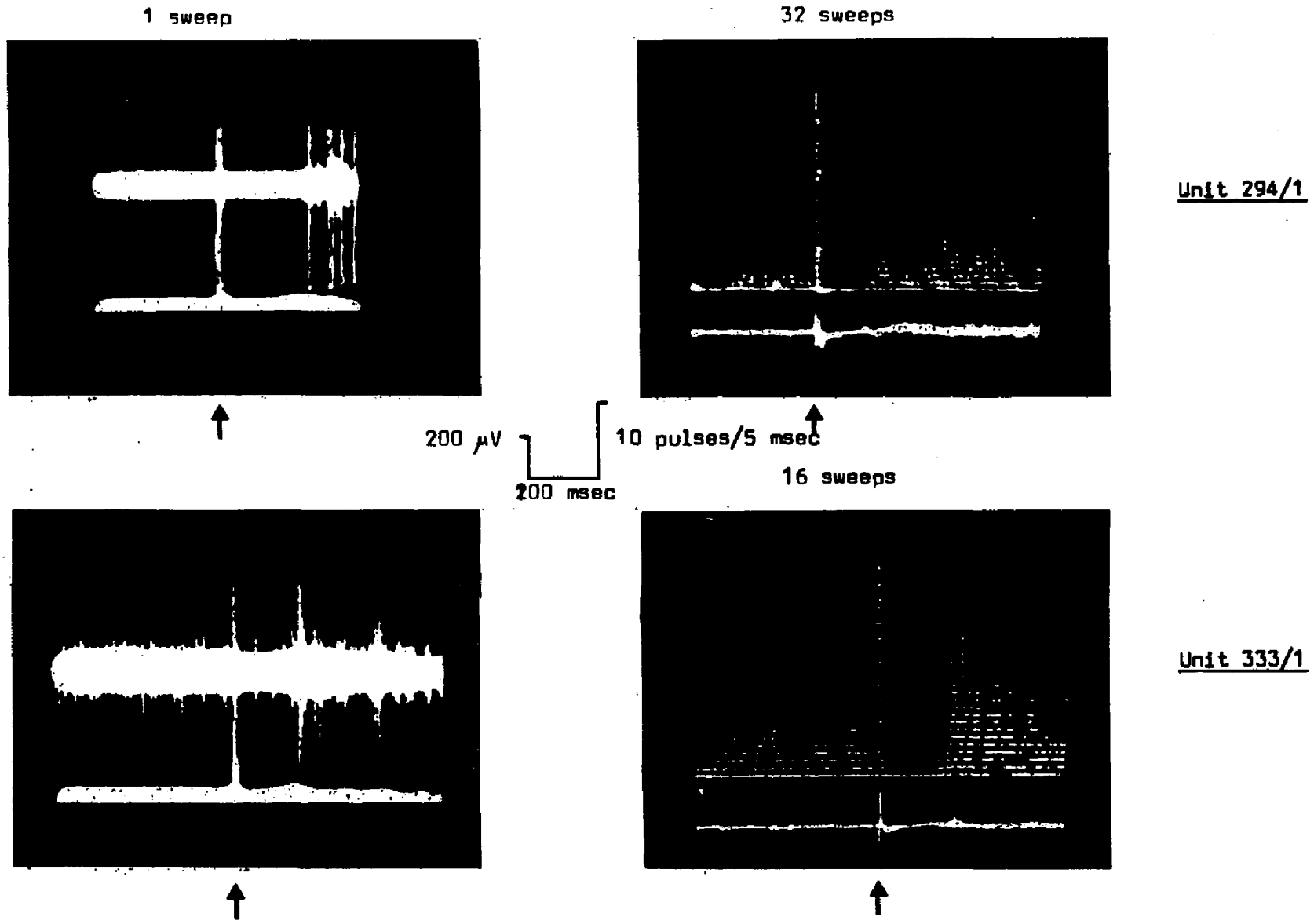
* At faster sweeps, these resolved into a burst of 3-5 spikes, all of which were cotemporal with the positive-components phase of the evoked potential recorded epicortically. The number of spikes preceding the discharge suppression was sometimes seen to vary as a function of the several experimental treatments administered. As earlier noted, however, the meaning of such observations is rendered moot by the questionable nature of the initial spike burst in this study. As a consequence, little additional mention will be made of this aspect of the unit's response.

Fig. 4. Samples of the cortical response to LGB shock for 2 units (294/1 and 333/1) at 100 msec/cm. Individual traces are seen on the left (negative up). Histograms accumulated from 32 (for 294/1) and 16 (for 333/1 and all units hereafter) such traces are on the right. The bin width for all histograms was 5 msec. The arrow below each photograph indicates the onset of the cortical response - both the unit response (top channel) and the gross potential (bottom channel: seen clearly only in the lower right-hand trace). The 2 upper traces were retouched.


1 sweep
32 sweeps
Unit 294/1
200 μV
10 pulses/5 msec
200 msec
16 sweeps
Unit 333/1

the LGB shock since the spontaneous activity was often not high enough to warrant it. But both the accumulated activity in the histograms, as well as the membrane hyperpolarization known to accompany these silent periods, justify its use.

Responses consisting solely of an increased discharge frequency were more unusual (25%), the frequency increment occurring at long latencies and probably corresponding to the above-mentioned afterdischarge. Minor variations of these two patterns were also seen; the most notable involved a delay in the onset of discharge suppression (illustrated in Fig. 10). Except for these units, the latency of the suppression period usually consisted of the time taken for the occurrence of the initial spike burst which, at the slower sweep speeds (100 msec/cm) used to evaluate alterations in the suppression period throughout our experiments, was inseparable in the histogram plots from the stimulus artifact (the bin width being 5 msec).

When an LGB shock elicited any suppression at all in the cortical (and adjacent) units, its average duration was 155 msec (range: 20-300+ msec), a value compatible with the reported duration (100-200 msec or more) of intracellular polarizing potentials initiated in cortex by stimulation of the optic tract or radiations (e.g. Watanabe et al., 1966).

The foregoing summary was drawn in large part from Table I of Appendix B. Table I also provides information on the location and levels of anaesthesia for all units included in this report. All tables referred to hereafter will be found in Appendix B.

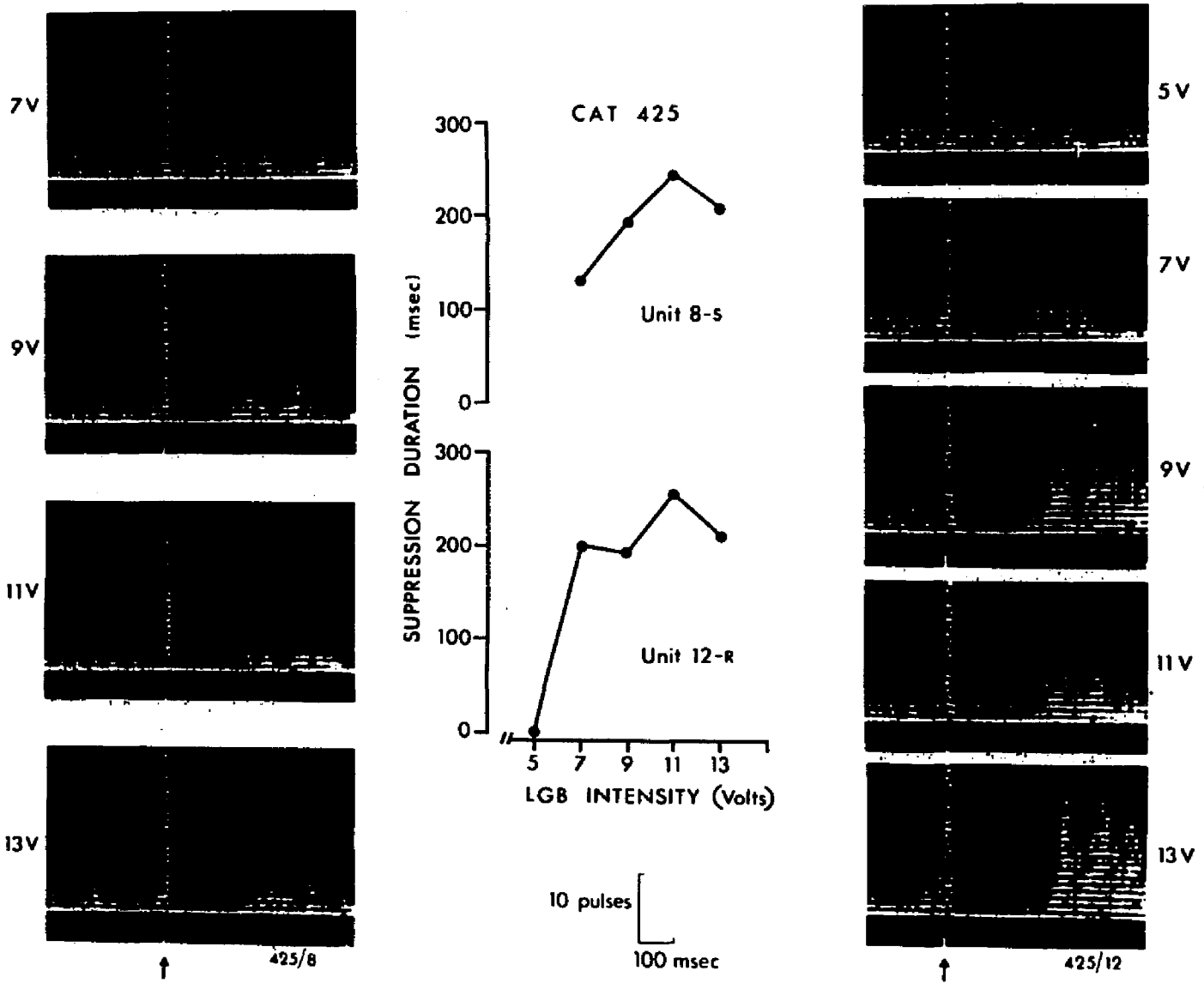
Effects of Varying Shock Intensity to LGB

In 11 units (10 in cortex and one in its adjacent white matter), the responses elicited by increasing intensities of LGB shock showed that the duration of spike suppression varied directly with the intensity of LGB stimulation (Table II). Fig. 5 demonstrates that at relatively low shock intensities there may be little or no suppression (see graph and oscilloscope tracing at 5V for Unit 425/12), while increasing shock intensities generated progressively longer periods of discharge arrest. This suggests that increasing LGB intensity may have revealed suppression in those units where none was actually observed (the 25% of the units referred to in the last section). The order of stimulus presentation, whether sequential (S), that is, presented in order of increasing intensity, or quasi-random (R), was clearly inconsequential (see same Fig.). Only one negative instance (where the LGB shock had not elicited the classical surface potential) and one questionable sequence were observed, the latter for a midbrain unit.

The effective range of shock intensities on varying the duration of discharge arrest appeared equal to or greater than the range affecting the amplitudes of the gross cortical surface potential. Since the LGB-shock intensity employed for most of the experiments in the following sections was one which produced a just submaximal surface potential (in order to secure its reliability), this observation suggests that the duration of discharge suppression used as criterion ('control') was below its maximal value.

The effect of increasing the intensity of the LGB shock on the

Fig. 5. Effects of increasing LGB shock intensity on the LGB-elicited spike suppression for 2 units in the visual cortex of the same cat. The stimuli were presented in increasing intensities (S) for 425/8 and in quasi-random order (R) for 425/12. The ordinate scale for the histograms on the oscilloscope tracings refers to 10 pulses/5 msec taken over 16 trials (as will all such scales hereafter).

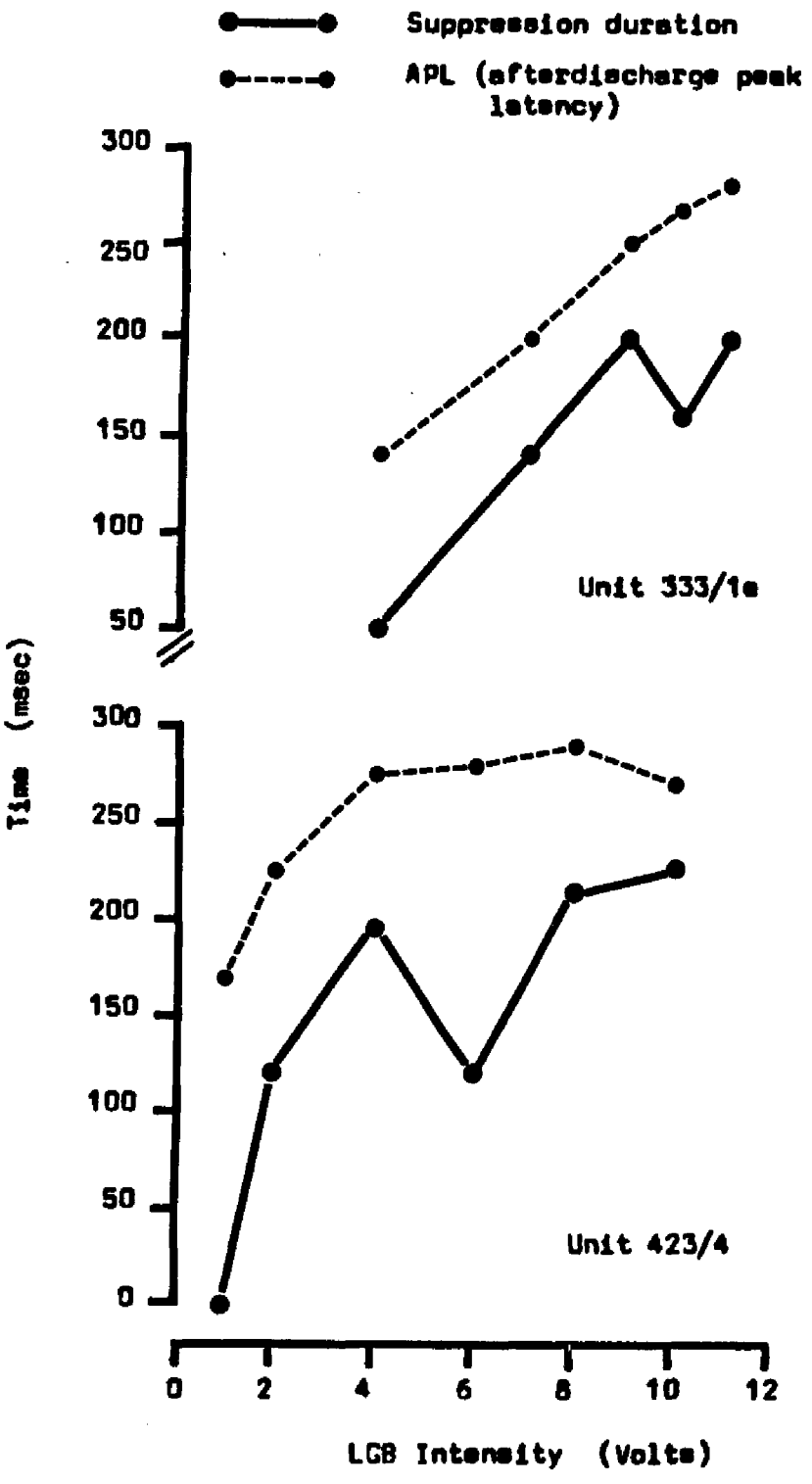

7V
9V
11V
13V
425/8
CAT 425
300
200
100
0
SUPPRESSION DURATION (msec)
Unit 8-s
Unit 12-R
5 7 9 11 13
LGB INTENSITY (Volts)
10 pulses
100 msec
5V
7V
9V
11V
13V
425/12

unit's afterdischarge was clearcut in some units and imperceptible in others. Increasingly long suppression was accompanied by increased afterdischarge in Unit 425/12 (Fig. 5), but the two were not correlated for Unit 8 in the same cat (same Fig.). When altered, the degree of afterdischarge appears here to have been directly related to the extent of prior discharge suppression. As will be seen later, however, the two - duration of discharge suppression and degree of afterdischarge - were not always related in this manner.

The histograms for Unit 425/12, which exhibit a relatively high degree of afterdischarge, suggest that the duration of the alterations in spike discharge frequency induced by an intense LGB shock exceeds the compass of our photographed observations (1 sec). Since this last was often the case, and also because the density of afterdischarge was often not great enough for reliable quantification, a measurement of the latency to the peak of the afterdischarge distribution (APL) was introduced. Riggs (1971) has pointed out, furthermore, that ". . . it is often true, in the electrical recording of visual responses, that latency measurements are more reliable than measurements of amplitudes of response potential waves or frequencies of nerve impulses." (p.309).

The histograms in Fig. 5 indicate that as the LGB shock intensity was increased, and as the duration of spike suppression increased concomitantly, so did the APL, an observation quantified and presented for two different units in Fig. 6. Although the APL and the duration of spike suppression are here shown to be closely related, the utility of these independent measures may lie in their differential susceptibility to random deviation (as will be seen later).

Fig. 6. Effects of increasing LGB shock intensity on two independent measures: on suppression duration and on the afterdischarge peak latency (APL) in two different units.


Suppression duration
APL (afterdischarge peak latency)
300
250
200
150
100
50
Unit 333/1a
300
250
200
150
100
50
0
Unit 423/4
Time (msec)
0
2
4
6
8
10
12
LGB Intensity (Volts)

Influence of LGB Conditioning on the Response to LGB Test-Shock

When the LGB test shock was preceded by an identical conditioning stimulus to LGB - delivered via the same electrode and with the same stimulus parameters (.5 msec pulse at 8V in the forthcoming instance) - the curve seen in Fig. 7 was obtained as a function of the interstimulus interval. At the shorter conditioning-test intervals (less than 50 msec), the duration of suppression was extended, when expressed in terms of percent of the control level (which was the duration of suppression elicited by the LGB test shock by itself); while at the longer interstimulus intervals (100 msec and longer), suppression was abbreviated . It is evident that when the second shock is administered early within the suppression period generated by the first shock (before it has run its course), then the suppression following the second stimulus might be expected to combine with that from the first to produce a more prolonged period of suppression. This is, in fact, what occurred. On the other hand, when the interstimulus interval is increased, the suppression generated by the second shock would coincide with the afterdischarge elicited by the first stimulus, and the two opposing effects might be expected partially to cancel one another out in an algebraic summation, as it were. As is demonstrable in the same Fig., less suppression was indeed observed at these longer intervals, while the afterdischarge elicited by the first shock was partially obliterated.

Fig. 8 provides another illustration of the dual-LGB effect on discharge suppression. It also shows that when multiple conditioning shocks (6 shocks at 300 Hz) were administered to the LGB instead of a

Fig. 7. Effects of a conditioning shock to LGB on the spike suppression elicited by an identical LGB test shock (S_t). The duration of suppression is expressed as a percent of the control value (S_t) - that duration of suppression (shown in msec on the graph) elicited by S_t alone. The oscilloscope tracings demonstrate, as does the graph, that the duration of spike suppression declines as a function of the length of the interstimulus interval.

LGB + LGB(S_t)

Unit 315/3

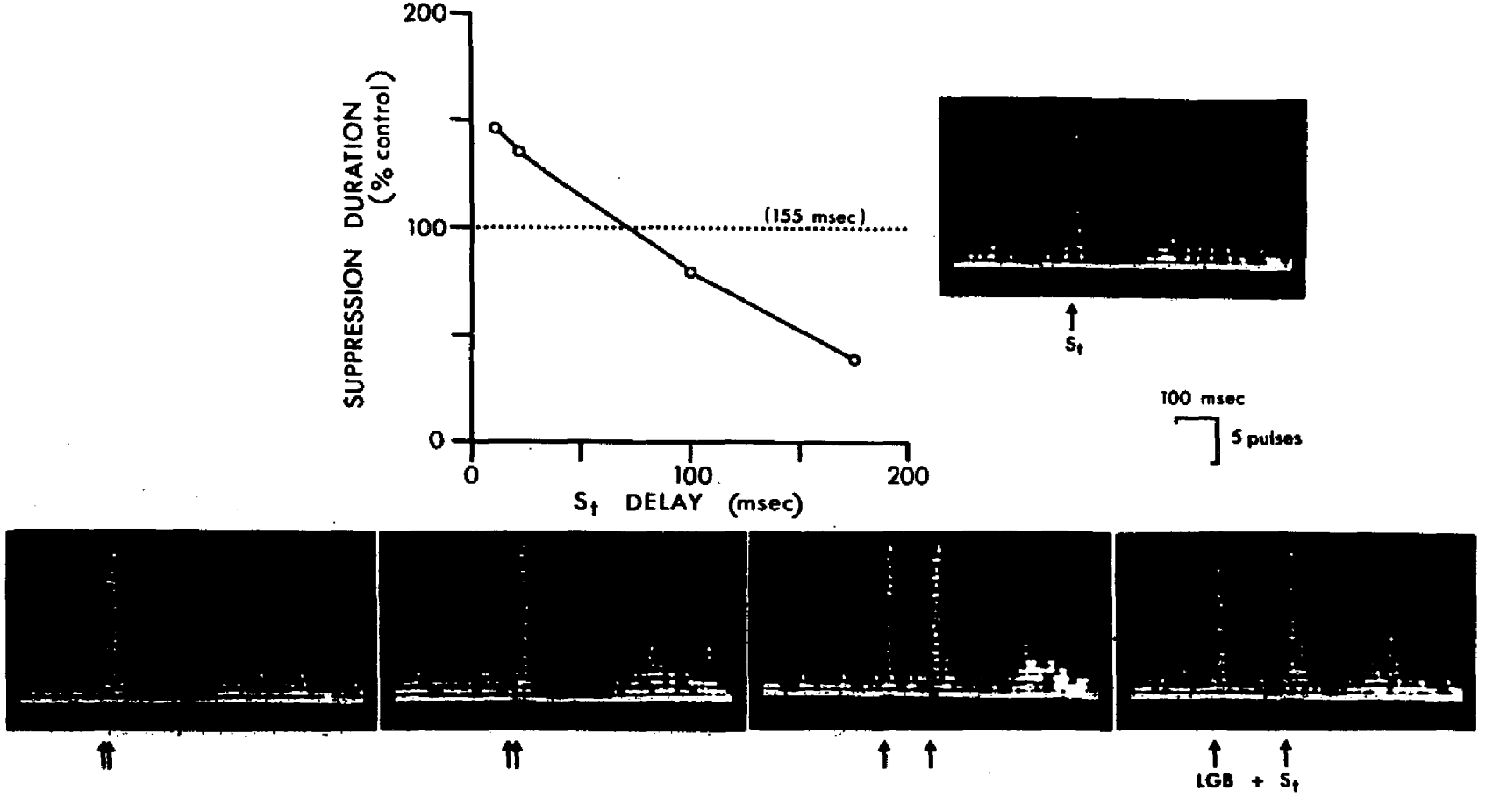
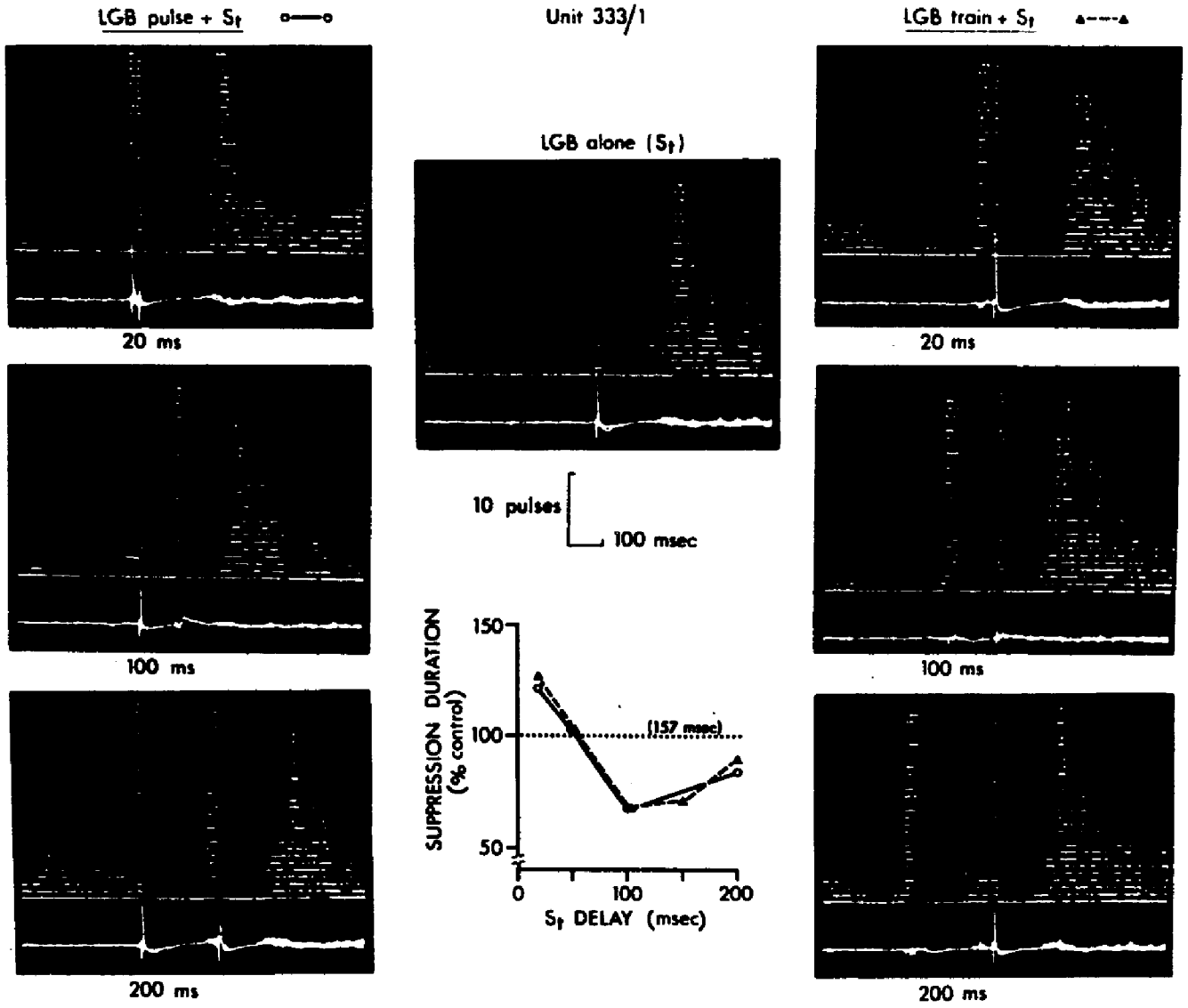


Fig. 8. A comparison of the effects of single vs. multiple conditioning shocks to LGB on spike suppression elicited by the LGB test shock (S_t) from a unit in the visual cortex.


LGB pulse + S_t
Unit 333/1
LGB train + S_t
LGB alone (S_t)
20 ms
20 ms
10 pulses
100 msec
100 ms
100 ms
SUPPRESSION DURATION (% control)
150
100
50
(157 msec)
0
100
200
S_t DELAY (msec)
200 ms
200 ms

single pulse, the identical effect was obtained. Again, the short interstimulus intervals (measured from the end of the conditioning train) produced a longer duration of suppression than the longer intervals. This was so in spite of other changes in the conditioning stimulus parameters: the pulse width was abbreviated (from .5 to .1 msec) and the intensity of each pulse was diminished (from 8V to 4V) to conform to the stimulus parameters used later for conditioning in MRF. Furthermore, the order of presentation for the multiple shocks was not randomized (as it was for the single conditioning shock). The fact that multiple conditioning shocks with the stated parameters and order of presentation had an effect that was identical to that generated by a single conditioning pulse to LGB indicates that the crucial parameter in this case was the interval between the last conditioning shock and the test shock. All the other instances of LGB conditioning thus used a single conditioning shock which was easier to administer.

Fig. 8 also illustrates that the afterdischarge following the conditioning stimulus and the suppression elicited by the test stimulus did not always interact in the algebraic fashion posited earlier. The abrupt interruption of the afterdischarge by the onset of suppression is vividly displayed in the histograms for the longest interstimulus intervals (bottom histograms on left and right in Fig. 8). The test-shock elicited suppression seems completely to override the powerful excitatory afterdischarge generated only a few milliseconds earlier.

The aspect of afterdischarge distributions following the test shock which seemed most clearly affected by variation of the stimulus

intervals was its skewness: the shorter the interstimulus interval, the longer the suppression duration following the test shock, and the more skewed the afterdischarge distribution. Without any information on additional aspects of the afterdischarge distribution, however, this appears to be but another way of describing the alterations in the period of suppression. The afterdischarge in Fig. 8 was of sufficient density to evidence that no simple relation between it (its degree, for example) and the prior suppression can be established for the short term (the 1 sec sweep duration). Measurements of the APL were not undertaken for these units (see explanatory footnote** on page 64).

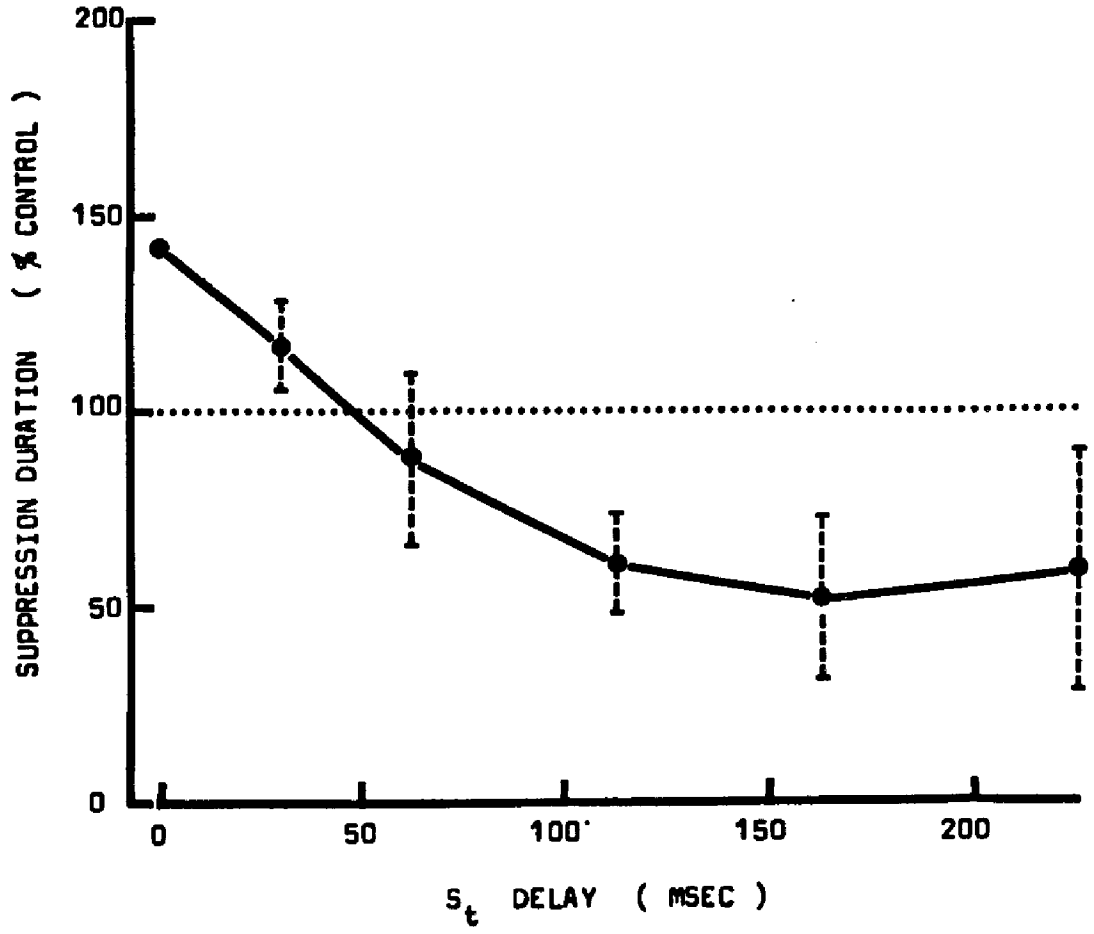
Fig. 9 furnishes a summary of the group results obtained upon conditioning in the LGB. The graph presents the mean duration of spike suppression (in terms of percent of control) plotted as a function of the test stimulus (S_t) delay, the length of the vertical lines representing the standard deviation at each delay. As the delay was increased, the duration of suppression declined from values which were initially higher than the control value. The transition from the prolonged suppression to its reduction occurred at a delay somewhere between 25 and 50 msec. The relatively larger scatter of the data at the longest interval (200 msec) indicates that a return to baseline values occurred at that interval for some units, while the decline in suppression duration was still progressing for others.

In no case for the 11 curves plotted (for 8 cortical and one adjacent unit in white matter) was there a negative instance to this sequence, although in three of the units evaluated early in this study no extension of suppression was observed as no interstimulus intervals less than 50 msec were sampled (Table III). One negative instance was observed in a subcortical recording locus.

Fig. 9. Group data: Relative changes in the duration of suppression elicited by a test shock to LGB (S_t) as a function of its delay from a conditioning stimulus to the same site in LGB. Black dots indicate mean values (in terms of percent of control) and vertical lines, the standard deviation at each delay. (N=11 sets of data obtained from 9 units.)

LGB Conditioning - Group data

N = 11



Conditioning in MRF: Effects of Interstimulus Interval

Fig. 10 illustrates the effects of tetanizing MRF on the duration of discharge arrest following the test shock to LGB. The oscilloscope tracings at the bottom show that when MRF and LGB stimuli were combined, discharge suppression, expressed in terms of percent of control, was abbreviated at brief interstimulus intervals (less than 50 msec) and extended at intervals of 50 msec and longer. Consequently, the time course for prolonged suppression was greater, but its extent, given the 200-300 msec range of intervals used in this study, was not established. The tracings also demonstrate an increment in the degree of afterdischarge, as well as a reduced latency to the peak of the afterdischarge spike distribution, at the shorter interstimulus intervals (see below).

The opposition between the effects of MRF and LGB conditioning is readily evident in the four units of Fig. 11, where conditioning in both loci was implemented in the same unit. The relatively high degree of variability observed among the units is confirmed in Fig. 12 which presents a summary of the group results for the positive findings with MRF conditioning (N=22, for 19 units). Additional positive instances were excluded from this summary (see Tables IV and V) because the control value was at 0 msec (no suppression); hence percentages could not be computed.

The transition from abbreviated suppression to its prolongation occurred just above the 50-msec interval, the highest degree of scatter also occurring at that interval. The possible contributors to the variability observed for MRF conditioning, such as Halothane level, ambient illumination, and the intensities of conditioning and test shocks, will be discussed in following sections.

Fig. 10. Effects of tetanizing MRF on the test response (S_t) elicited by a shock to LGB. The graph was based on data illustrated in the histograms obtained at the various delays indicated beneath the oscilloscope tracings. The relative duration of spike suppression was seen to increase as a function of the S_t delay.

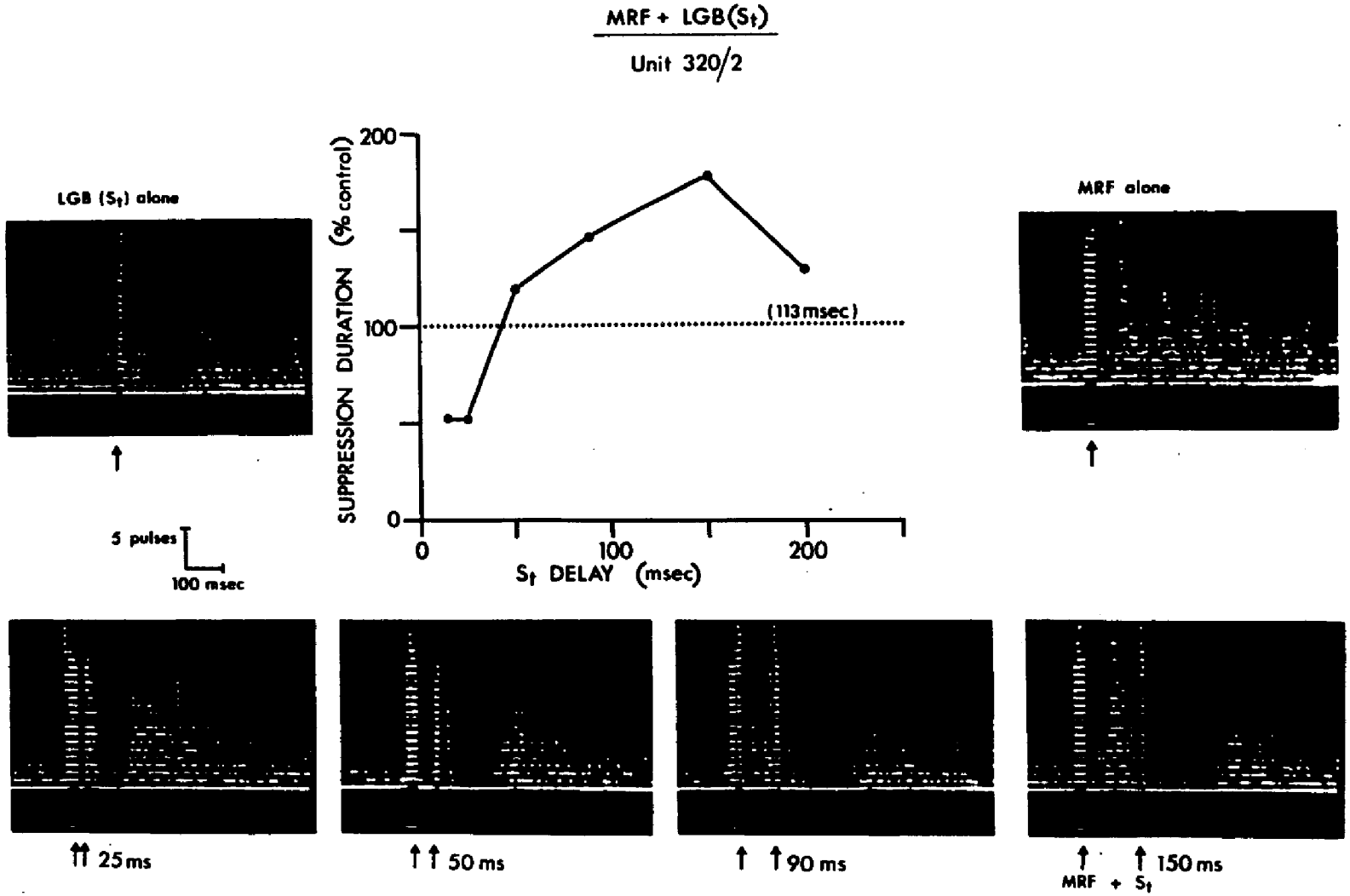

MRF + LGB(St)
Unit 320/2
LGB (St) alone
MRF alone
SUPPRESSION DURATION (% control)
200
100
0
(113 msec)
0
100
200
St DELAY (msec)
5 pulses
100 msec
25 ms
50 ms
90 ms
150 ms
MRF + St

Fig. 11. A comparison of the effects of MRF conditioning (solid line) vs. LGB conditioning (dashed line) in terms of the relative suppression period elicited by a shock to LGB. The data in each graph were obtained from the same unit, the left-hand graphs under low ambient illumination, the right-hand graphs at high levels of light adaptation.

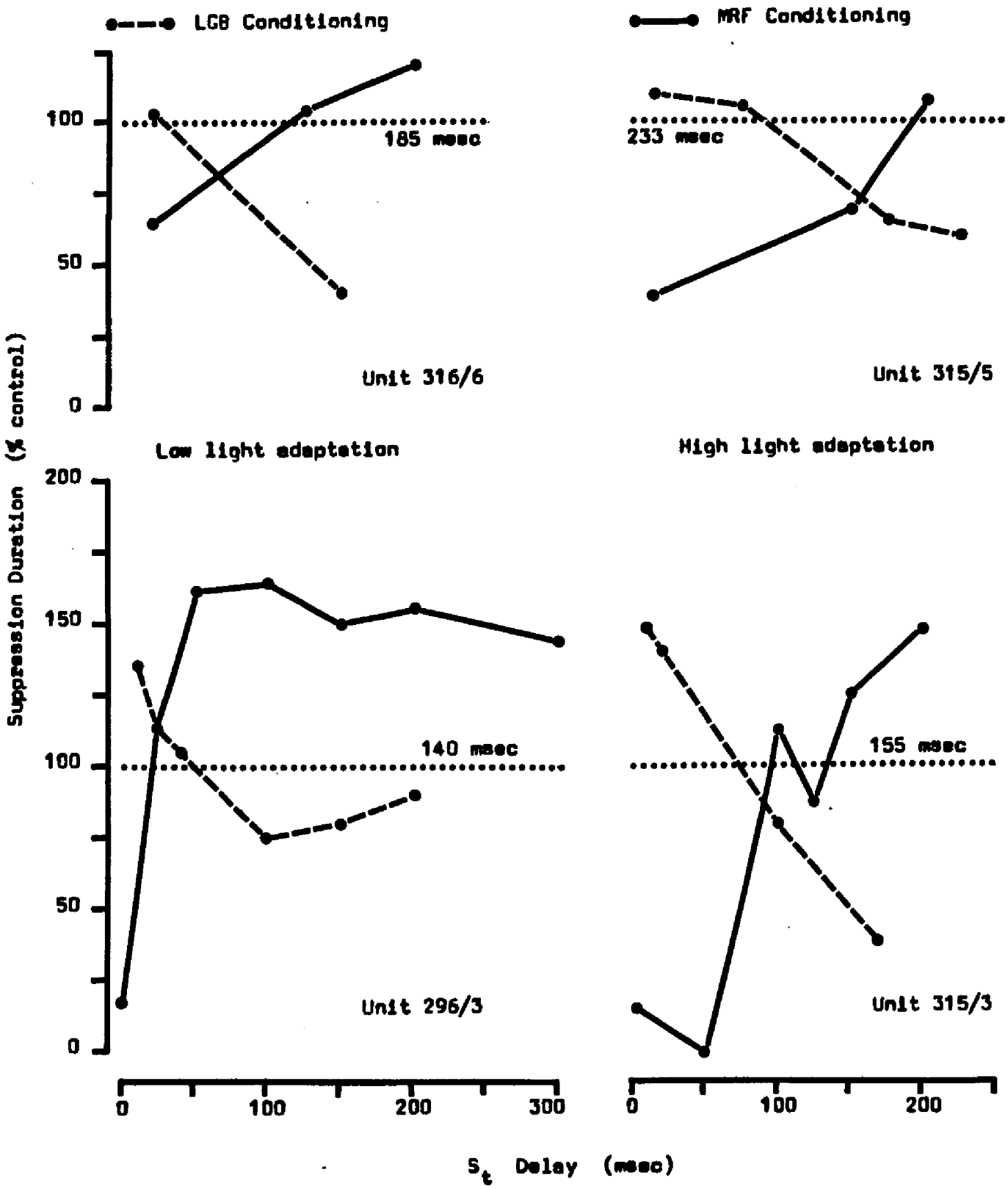
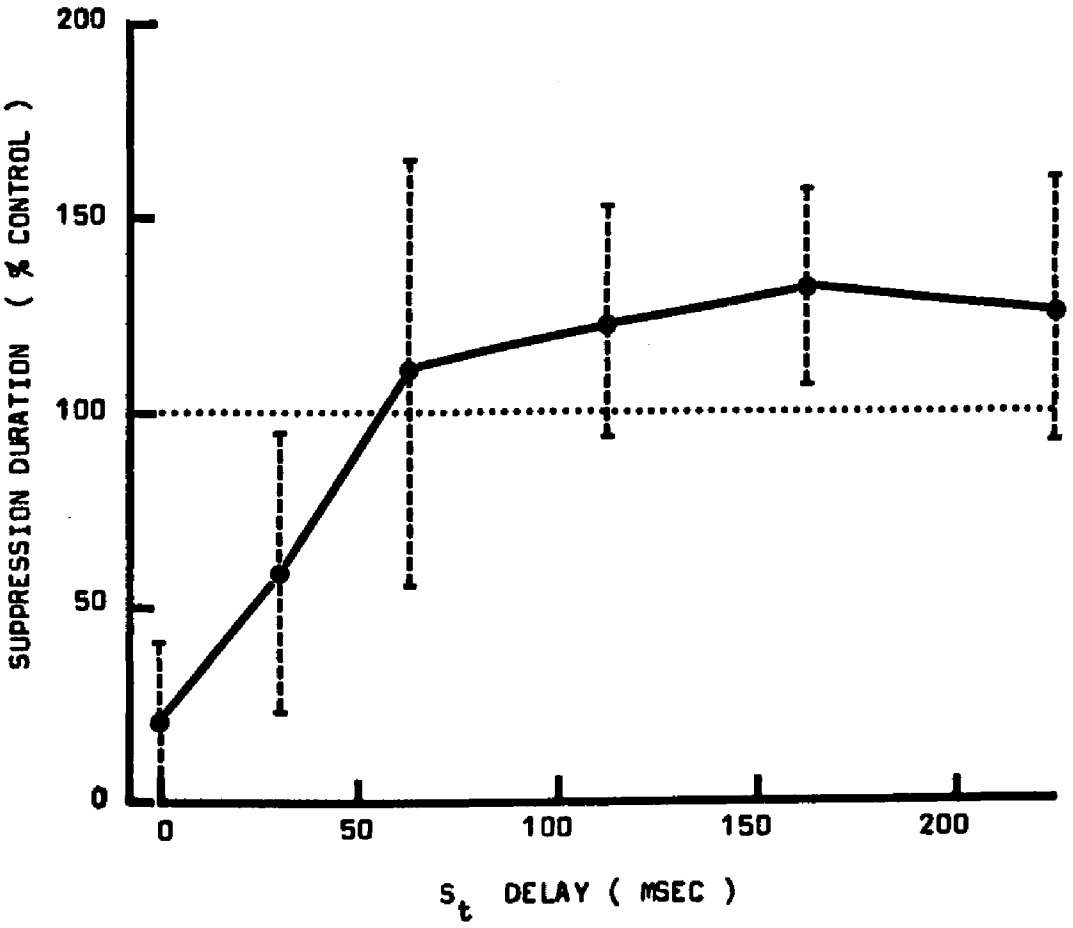

LGB Conditioning
MRF Conditioning
100
50
0
185 msec
233 msec
Unit 316/6
Unit 315/5
Low light adaptation
High light adaptation
Suppression Duration (% control)
200
150
100
50
0
140 msec
155 msec
Unit 296/3
Unit 315/3
0
100
200
300
S_t Delay (msec)

Fig. 12. Group data: Relative changes in the duration of suppression elicited by a test shock to LGB (S_t) as a function of its delay from the end of the MRF train. Black dots indicate mean values, and vertical lines, the standard deviation at each delay. (N=22 sets of data obtained from 19 units.)

MRF Conditioning - Group data

N = 22



These findings were obtained for 63% of the replications in cortical (and adjacent) units so tested (Table IV). An additional 20% exhibited the same sequence in some variation (Table V). Seven percent of the units produced clear negative instances, in which the MRF-LGB combination induced a diminution of suppression throughout the temporal range (Table VI). In 10% of the units, no interactive effect was observed in response to the MRF and LGB inputs (Table VI).

(a) Effects of MRF alone. MRF activation, when initiated without an accompanying LGB pulse, usually produced a marked degree of enhancement of spontaneous spike discharge at the stimulus intensity used (4-5V; 5V for Unit 320/2 in Fig. 10). The latency of enhancement onset ranged between approximately 25-100 msec from the first pulse in the MRF train (30-msec gate), with fewer instances at the longer latencies. Occasionally, the latency to enhancement consisted of a period of discharge suppression as was the case in Unit 320/2. The duration of enhancement was, most commonly, several hundred msec long or observable until the end of the 1-sec trace, with increased frequencies of discharge often being clearly audible for several seconds thereafter, and sometimes for longer still. More limited periods of enhancement were seen as well, lasting for some 100 msec, for example. Brief periods of suppression were rarely observed within the context of spike enhancement generated by the MRF, but there often was an attenuation of enhancement tending to occur some 100-150 msec after the end of the MRF train. This was characteristically followed by the development of another peak of enhancement, signifying a bimodal distribution of the facilitatory effects of MRF activation (see distributions for MRF alone in Figs. 14 and 15 where the picture of MRF enhancement is representative of most of the neurons encountered). The attenuation of enhancement rarely descended below the spontaneous discharge frequency; when it did, it was

evaluated as a period of suppression generated by MRF alone. Despite this variability in the cortical unit's response to MRF activation, when the latter was combined with an LGB shock, the same sequence of events was almost inevitably reproduced, namely, a reduction of the period of suppression elicited by the LGB shock followed by its prolongation at the longer interstimulus intervals.

(b) MRF-LGB Interaction. A more detailed analysis of the effects of MRF-LGB interaction is useful for Unit 320/2 illustrated in Fig. 10. This unit is of particular interest because the same sequence of events was observed in spite of the somewhat unusual characteristics of its response to both LGB and MRF stimuli when independently presented. The response to LGB shock was unusual in its delayed onset of suppression which was nonetheless clearly present. The discharge enhancement produced by the MRF train was not only delayed as well, but preceded by an equally clearcut period of discharge suppression.

For those units which exhibited an unequivocal and prolonged enhancement of spike discharge following MRF activation, the administration of an LGB shock soon after the end of the MRF train predictably shortened the LGB-induced suppression. For some units, not only was suppression reduced, but an actual enhancement of spike frequency occasionally occurred at these short intervals. This was so for Unit 320/2 where the length of suppression was shortened and the initial spike response to LGB shock (prior to suppression) was noticeably enhanced - an outcome that was less predictable for this particular unit due to the initial suppression caused by MRF alone. Quite the opposite took place for Unit 320/2 at a longer MRF-LGB interval (e.g. at 150+ msec) where the LGB-elicited suppression was extended. It must be noted that

the prolongation of suppression at this (150-msec) delay, and even at the longest test-shock delays, occurred well within the range of intervals where MRF alone had generated enhancement of the spontaneous discharge. A simple superposition of the responses to MRF and LGB stimuli is thus an unlikely basis for the observed effects of MRF-LGB interaction. The abrupt interruption, by the LGB input, of the enhancement generated by the MRF train also militates against such explanation.

Inspection of alterations in the afterdischarge distributions in Fig. 10 discloses that the shortest MRF-LGB intervals generated a much higher rate of afterdischarge than had the LGB shock, by itself. Hence a uniform effect on both suppression and afterdischarge was operative at the short intervals: suppression was foreshortened and afterdischarge enhanced-- both effects being facilitatory. At the longest intervals for Unit 320/2, only suppression was affected; the rate of afterdischarge was not much altered. For other units, a uniform influence was observed at the longer intervals as well, when suppression was extended and the degree of afterdischarge reduced - an inhibitory effect throughout. For these units, an inverse relation may be said to describe the duration of suppression and the subsequent rate of afterdischarge. But this picture of homogeneity was somewhat complicated by the longer-term ($>$ 1 sec) influences on the afterdischarge - noted in the protocols for several units. For Unit 320/2, for example, the least off-'scope activity was recorded for the short interstimulus intervals (which had earlier exerted the uniformly excitatory influence); while the highest degree of longer-term activity was noted for the longer intervals (associated with an earlier suppressive influence).

MRF-LGB Interaction: Influence of Halothane

The data for the cortical units included in Fig. 12 were separated into two groups - one for which Halothane had been administered throughout (N=12) and another for which Halothane had been withdrawn following surgery (N=8). Despite the different composition of the two groups (see Table VII), a distinct similarity of potential import is evident in Fig. 13: Both functions exhibited the highest - and virtually identical - degree of variability at precisely the same interval (50+ msec). The scatter at all but one other interval was more extensive with Halothane. This may have resulted from the range of Halothane flow rates employed (.33-1.0%) and the larger number of cats in the group; or it may have been due to a greater intrinsic variability caused by Halothane itself. Some support for the latter view is provided by the data in Fig. 14 which illustrates the relation between the duration of suppression and the afterdischarge peak latency (APL), both with and without Halothane, for the same unit.

S_t delay was plotted against real time in Fig. 14 (i.e. in absolute values) to permit a clearer view of the relation between supression and the APL. While the duration of suppression and the APL seemed closely related when no Halothane had been administered, no such relation was observable with 1% Halothane. This finding was confirmed for most other such comparisons* (albeit not in the same unit, as above) and with other experimental conditions as well (LGB conditioning**, for example; see Table X).

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* Several units sampled per experimental condition were thought to satisfy the purposes of this comparison.

** It can now be stated that no APL measurements were presented for the data in Fig. 8 (LGB conditioning) as these data had been recorded with Halothane. No clear relation would therefore have been demonstrable between suppression and the APL (see Table X).

Fig. 13. Group data: Effects of Halothane administration on the spike suppression elicited by the LGB test shock (S_t) as a function of its delay from a conditioning train to MRF. Mean values for the relative duration of suppression are given by the black dots for the No Halothane condition and by the triangles for the Halothane condition. The standard deviation at each delay is given by the solid vertical lines for the No Halothane, and by the broken lines for the Halothane, conditions.

MRF Conditioning

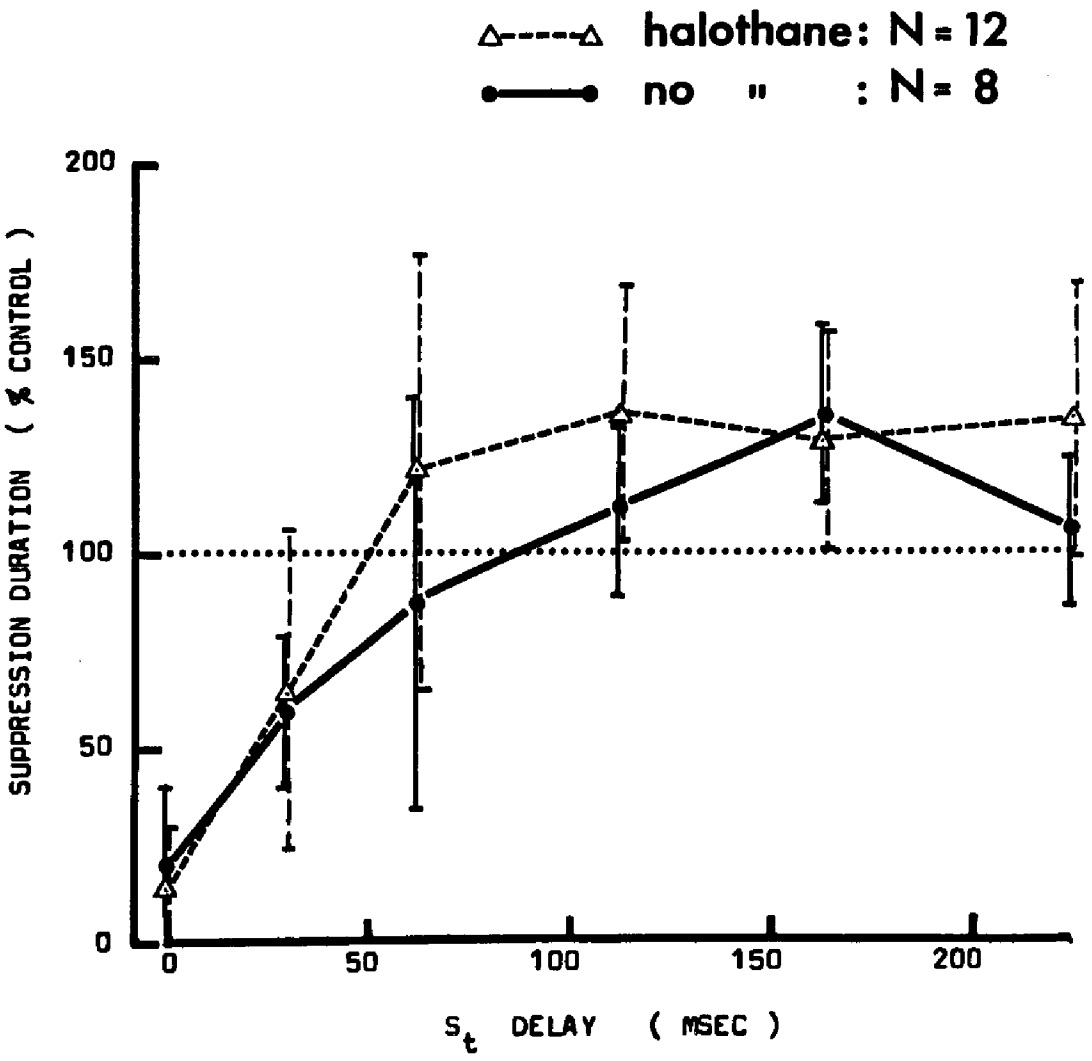
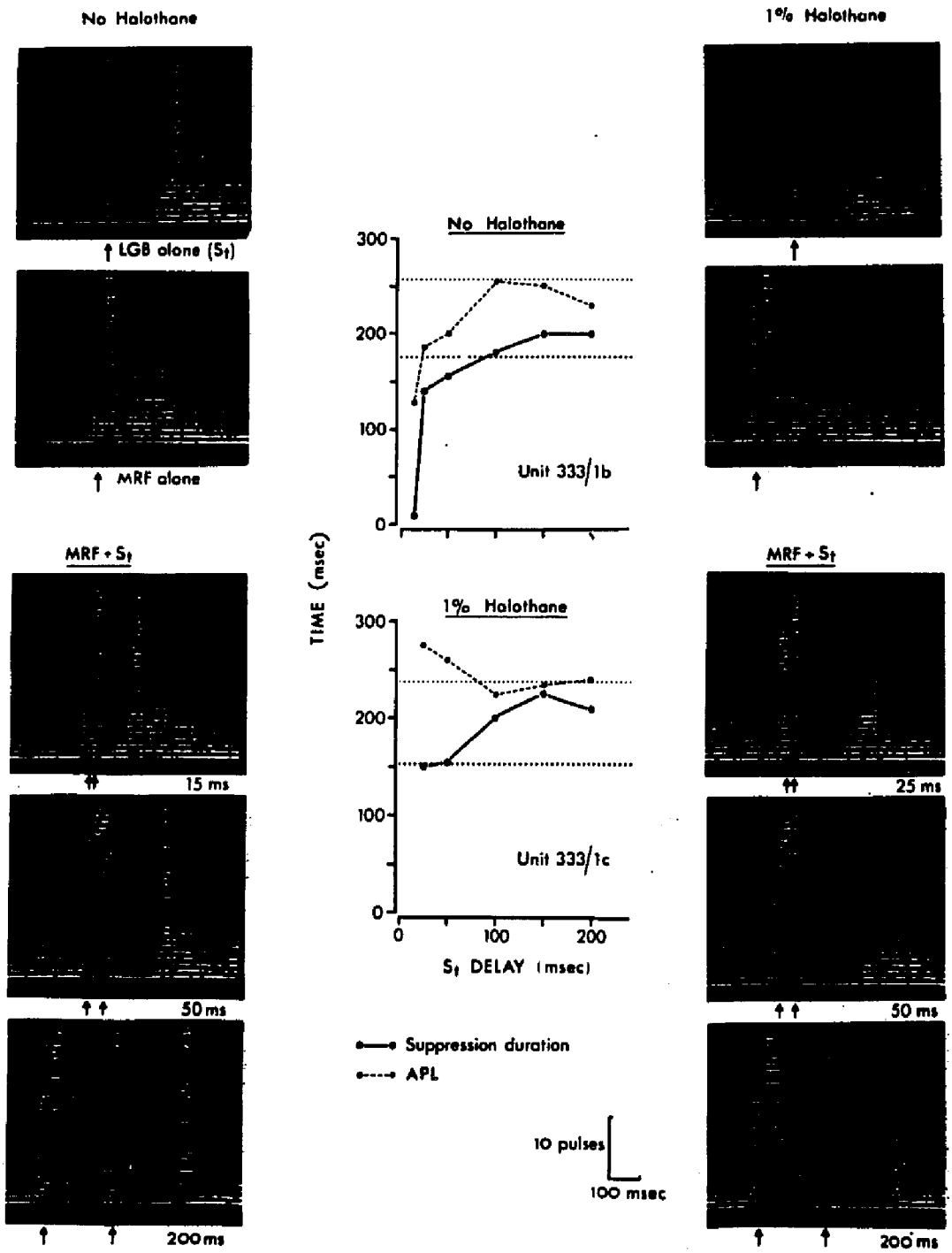


Fig. 14. A comparison of the influence of Halothane (at 0% and 1% in the left and right oscilloscope tracings, respectively) on the effects of the MRF-LGB interaction observed in Unit 333/1. The measures used, the duration of the LGB-elicited spike suppression (solid curves) and the APL (broken curves), were obtained as a function of the interstimulus interval.


No Halothane
1% Halothane
LGB alone (St)
MRF alone
MRF + St
15 ms
50 ms
200 ms
25 ms
50 ms
200 ms
No Halothane
1% Halothane
Unit 333/1b
Unit 333/1c
TIME (msec)
St DELAY (msec)
Suppression duration
APL
10 pulses
100 msec

MRF-LGB Interaction: Influence of MRF Intensity

Fig. 15 illustrates one of the effects produced by varying the intensity of the MRF train at a fixed MRF-LGB interval (45 msec here). The left-hand oscilloscope tracings show that as MRF intensity was increased from 1.5V to 6V, the duration of LGB-elicited suppression, which was initially longer than the control value (single trace on right), was progressively attenuated. A concomitant increase in the degree of afterdischarge and a decrease in its peak latency (APL) is readily seen in the same tracings. The effects of stimulating the MRF alone (tracings on right) will be discussed at the end of this section.

Similar, though not identical, results were obtained in three additional instances (Units 333/2, 425/12a, 425/12b in Table VIII). The similarity resided in the overall decline in suppression seen for these units over the range of MRF intensities administered. The difference lay in the increment in suppression seen in the mid-range of MRF intensities (clearly depicted in Fig. 18) which might better be characterized by an inverted-U, rather than by an inverse, relation. Only a much larger sample (N=8 here) and a more detailed assessment of the effects of MRF intensity would permit an appropriate characterization of the relationship. Still, the lower tetanizing voltages to MRF did tend, on the whole, to prolong LGB-evoked suppression, while the more intense conditioning trains tended to curtail it (Table VIII). It is noteworthy that the less intense MRF trains prolonged suppression.

Fig. 16 presents three sets of graphs illustrating the relation between the temporal (bottom graphs) and intensive (upper graphs) variables for three units. The MRF intensity curve for one of these, Unit 331/2, is the graph drawn from the oscilloscope traces in Fig. 15.

Fig. 15. An illustration of the effects of varying MRF intensity (a) at a fixed MRF-LGB interval (45 msec) - see oscilloscope tracings on the left - and (b) on the spontaneous activity (tracings on the right) derived from Unit 331/2 in visual cortex.

MRF INTENSITY – LGB delay constant at 45 msec

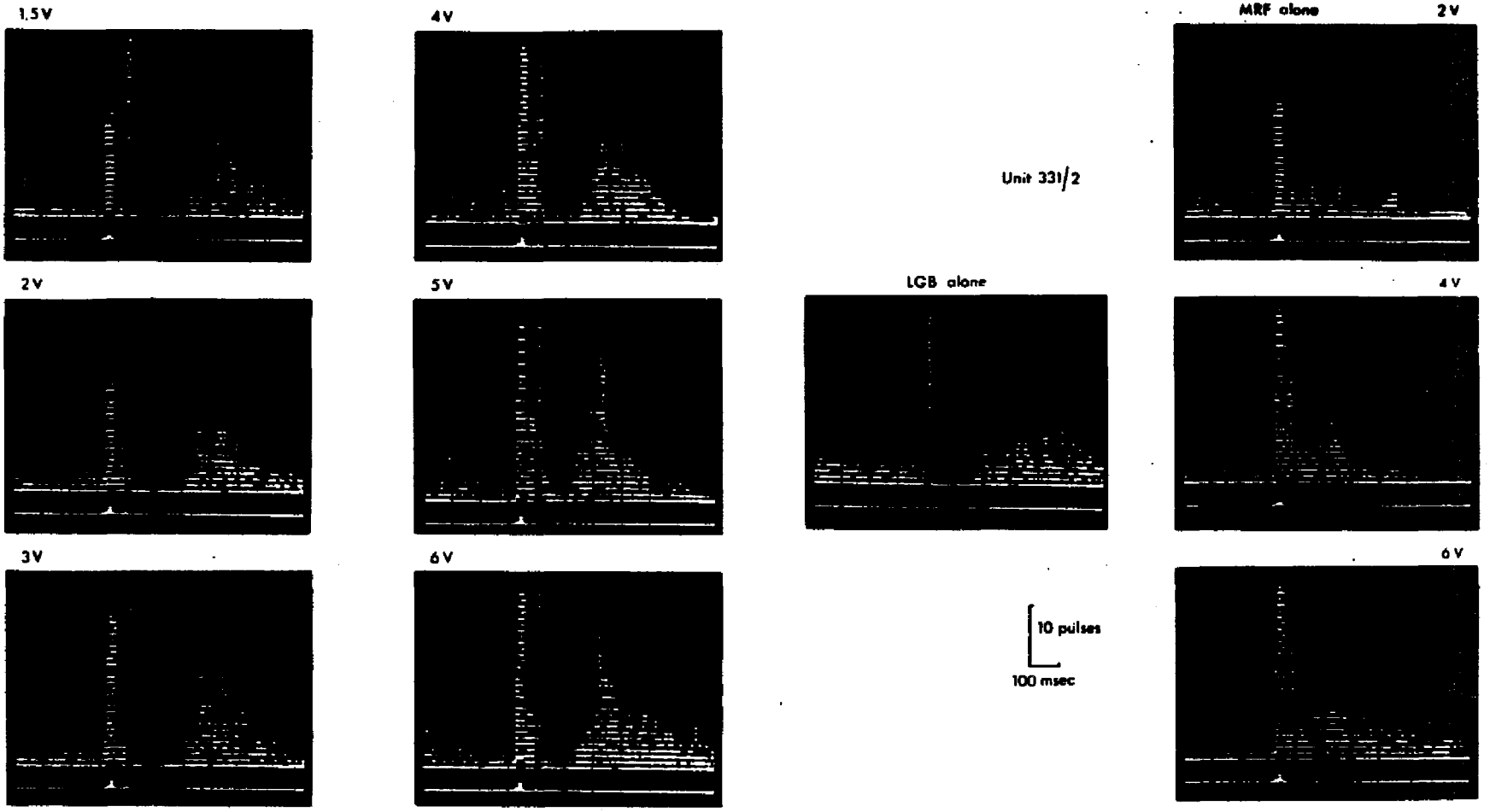
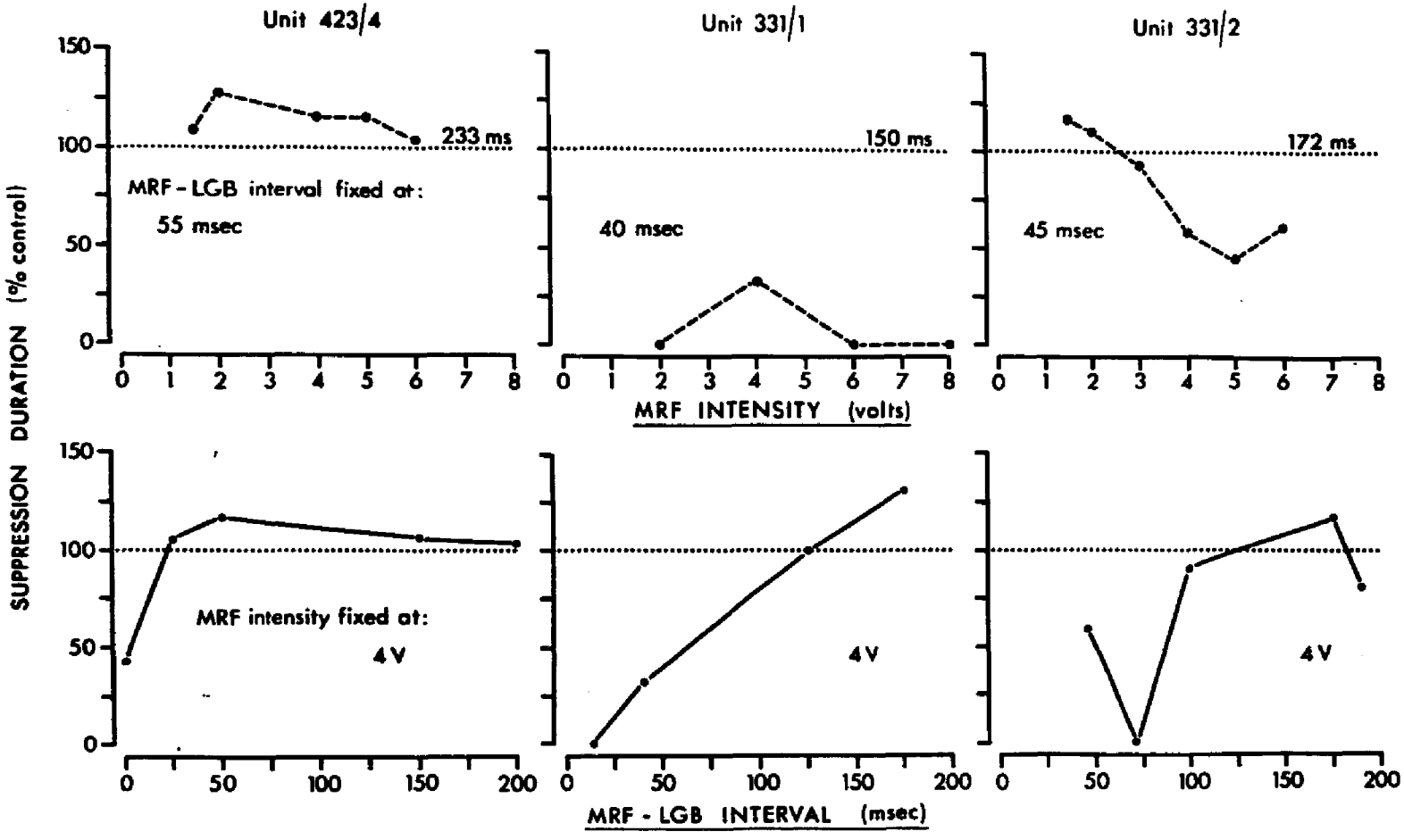


Fig. 16. The three upper graphs illustrate the effects of MRF intensity (along the abscissa, in volts) on the suppression duration of the test response (in percent of control), for a fixed MRF-LGB interval. The influence of MRF intensity appears to depend upon the relation of the fixed MRF-LGB interval to the 'transition' interval (see text). The latter can be seen on the bottom graphs where suppression is shown as a function of the MRF-LGB interval. When the MRF-LGB interval employed was longer than the transition interval (as in Unit 423/4), suppression was lengthened throughout. When the fixed interval was shorter than the transition interval (Units 331/1 and 331/2), suppression was generally shorter than the control value. The effectiveness of MRF intensity as such is clear only in Unit 331/2, where the duration of suppression was abbreviated as a function of increasing MRF intensity.


Unit 423/4
Unit 331/1
Unit 331/2
SUPPRESSION DURATION (% control)
150
100
50
0
233 ms
150 ms
172 ms
MRF - LGB interval fixed at:
55 msec
40 msec
45 msec
0 1 2 3 4 5 6 7 8
MRF INTENSITY (volts)
MRF intensity fixed at:
4 V
4 V
4 V
0 50 100 150 200
MRF - LGB INTERVAL (msec)

Clearly, the two other intensity curves are unlike it, in exhibiting either a relatively constant prolongation of suppression over all MRF intensity values (Unit 423/4) or, conversely, a diminution of suppression throughout the intensity range (Unit 331/1). The constancy of the effects indicates that these were determined more by the temporal parameter (the fixed MRF-LGB interval) than by the MRF-intensity variable which failed to markedly affect the duration of LGB-elicited suppression in these units. However, if the inverted-U function were descriptive of the relation between suppression and MRF intensity, these two units could not be readily excluded from among the positive instances (thus augmenting their number to 6/8*).

The normal procedure for examining the influence of MRF intensity would require the selection of a particular MRF-LGB interval. Since the test-stimulus delay had a marked effect on its subsequent suppression, it was decided to set that interval at or near the value corresponding to the control condition - that is, where the curves tend to cross the dotted line (bottom graphs in Fig. 16). This was designated the 'transitional' interval. Prior to the actual data analysis, however, there was no means of accurately selecting such an interval and the data seem to reflect that fact. For Unit 423/4 (in Fig. 16), for example, the chosen MRF-LGB interval (55 msec) was longer than the transitional interval (bottom graph) and thus might have tended to bias the results toward prolongation of suppression, as was the case (top graph). Conversely, the 40-msec interval selected for Unit 331/1 (same Fig.) was

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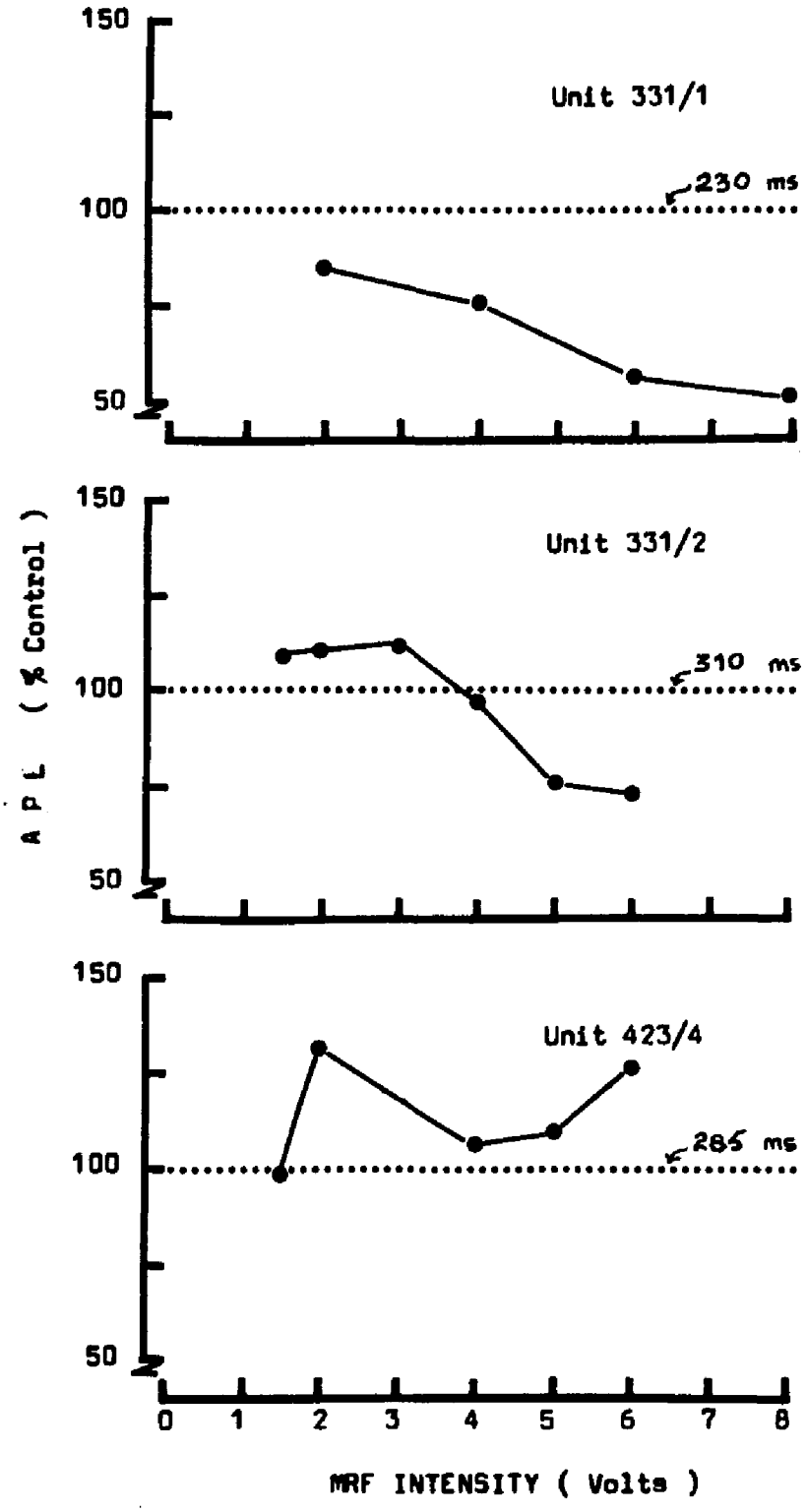
* In the two remaining instances, the results for Unit 423/1 were ambiguous in exhibiting a declining function except for the highest MRF-intensity value, while Unit 423/3 was a decidedly negative instance in having given rise to an ascending suppression function, with prolonged suppression over all MRF intensities.

far shorter than the actual transitional interval (bottom graph) and the opposite bias, toward abbreviation of suppression, was seen here (upper graph). The same bias is evident for Unit 331/2 where the 45-msec interval would have been expected to introduce a bias toward diminution of suppression (bottom graph). This was confirmed (upper graph) since the majority of points were below the control value.

The major difference between the intensity curves obtained for Unit 331/2 and the others in Fig. 16 is the apparent effectiveness of the MRF-intensity variable for 331/2 as opposed to its ostensible failure in exerting any influence on those units where a relatively uniform outcome was observed over all intensity values . But inspection of the APL functions in Fig. 17 reveals that MRF intensity did in fact influence some aspect of Unit 331/1's response: for this unit, an inverse relation was obtained for MRF intensity and the APL. This was so for Unit 331/2 as well. Halothane had been withdrawn prior to recording from these units. All other units so tested had been recorded under Halothane. Only one of these exhibited a clearcut influence of MRF intensity on the APL (Unit 425/12[a] in Table VIIIa). Interestingly, an inverse relation was descriptive of the APL results as opposed to the inverted-U relation seen for suppression (see Fig. 18 for the latter). These observations confirm the earlier description of (1) a dissociation introduced by Halothane between the findings for suppression and the APL; and (2) the variability of the APL itself, also brought about by Halothane.

Fig. 17. The influence of MRF intensity on the APL (in percent of control) associated with the three units represented in Fig. 16. The actual value (in msec) for the APL following the LGB shock alone is shown, for each unit, on the dotted line demarcating the control (100%) value.


150
100
50
Unit 331/1
230 ms
150
100
50
Unit 331/2
310 ms
150
100
50
Unit 423/4
285 ms
0 1 2 3 4 5 6 7 8
APL (% Control)
MRF INTENSITY (Volts)

(a) The Effects of MRF Alone: An Amendation. The observation that MRF appears mainly to enhance the maintained discharge may now be amended in viewing the right-hand tracings in Fig. 15: a comparison of the levels of spike discharge preceding each MRF train reveals a decline in spike frequency with increasing MRF intensities. Since each histogram was compiled from 16 separate trials, and the intertrial interval was 4 sec here, a long-latency suppression with long time course appears to have been in effect at the highest MRF intensity (6V), one that was cumulative from trial to trial. With the less intense MRF trains, this latency to suppression appears to have been shorter: note the development of spike suppression toward the end of the 4V trace, some 500 msec after the end of the MRF train. At 2V, however, there is only a mere hint of spike suppression toward the end of the trace (and not much enhancement either), yet a conditioning stimulus of that intensity tended most markedly to prolong the LGB-evoked suppression of spike discharge.

In sum, MRF apparently exerts both excitatory and inhibitory influences on the spontaneous (as vs. the evoked) cortical discharge - a fact long reported in the literature. The excitatory influence was certainly the more conspicuous in our extracellular records when MRF alone was activated. With MRF-LGB interactions, on the other hand, the excitatory effects were dominant only at short interstimulus intervals and high MRF intensities. The suppressive effects of the conditioning-test stimulus interactions at the longer intervals and with weaker conditioning trains pose a dilemma which may not be explicable without recourse to an overriding inhibitory effect generated by the MRF at these parameters.

ADDITIONAL OBSERVATIONS

MRF-LGB Interaction: Influence of Test-Shock Intensity

The degree of either the prolongation or the abbreviation of LGB-elicited suppression was observed to vary markedly in relation to the control level from cat to cat (e.g. 296 vs. 315 in Fig. 11) and from unit to unit in the same cat (Units 3 and 5 in Cat 315, same Fig.). Both level of background illumination* and administration of Halothane may have contributed somewhat to this variability. Still, the functions drawn from Units 296/3 and 315/5 (in the same Fig.), where the actual control values were 140 and 233 msec respectively, suggest that the intensity of the test shock (the duration of suppression generated by it) may have been a relevant factor (in addition to the intensity of the MRF train which has just been shown to exert a substantial influence on the LGB-evoked spike suppression).

A comparison of MRF-LGB interaction at two different test-shock intensities was carried out in the same unit to determine whether the relative degree of suppression was dependent upon the test-shock intensity level. The two sets of curves for Unit 425/12 in Fig. 18 demonstrate that the higher test-shock intensities resulted in a smaller relative increment in suppression and a concomitantly greater decrement in suppression than the lower test-shock intensities, and that this was upheld for both the temporal and intensive MRF-LGB manipulations. This was confirmed in Unit 423/4 for the temporal interaction.

These data suggest that there is a ceiling to the amount of suppression that the MRF-LGB interaction will generate. Since the test stimulus

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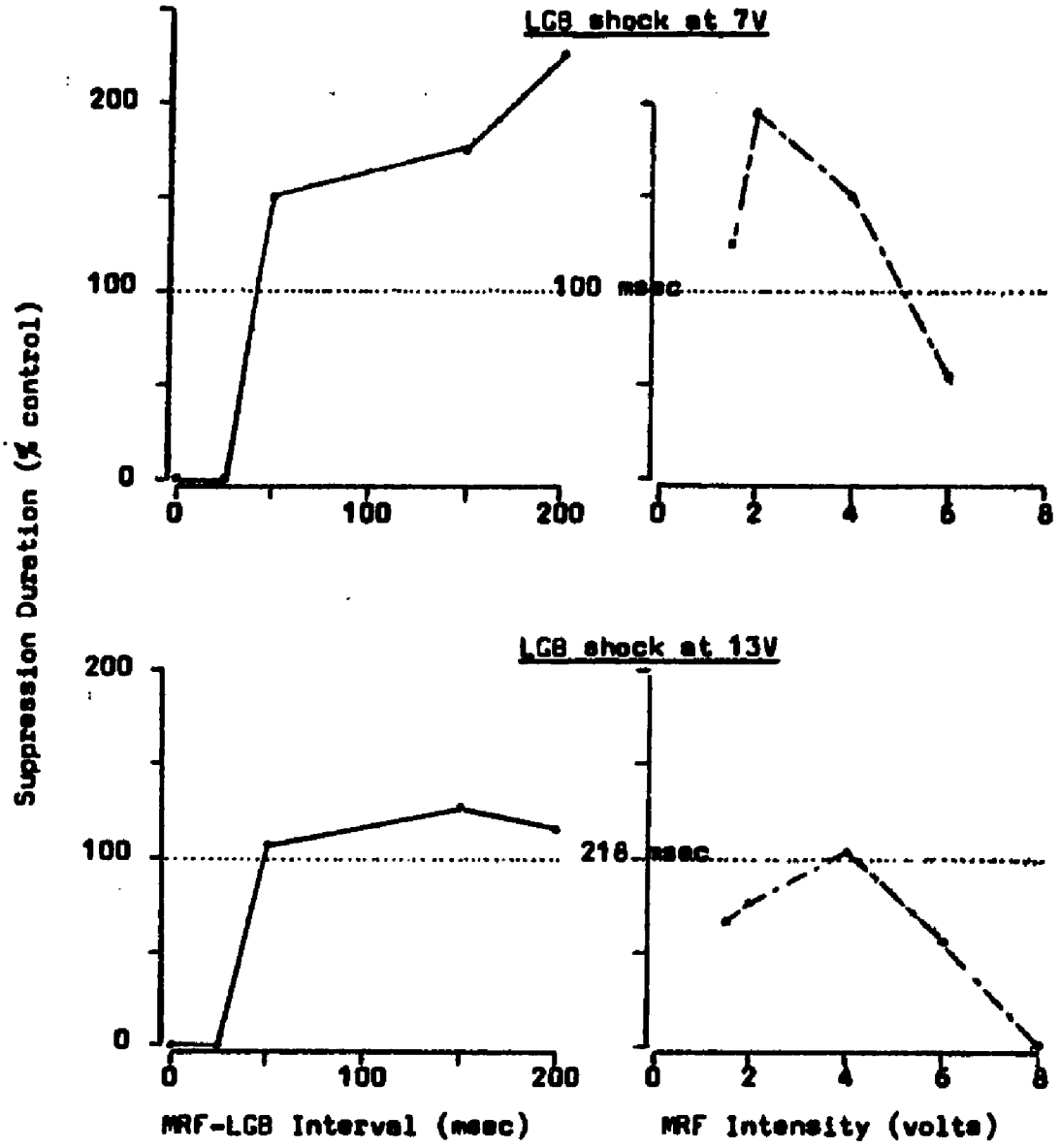
* Alterations in background luminance affected both the LGB-evoked suppression and the unit's maintained discharge in an opposite manner in different units. Yet these differences were not reflected in the nature of the influence of MRF conditioning.

Fig. 18. The effects on LGB-evoked suppression of varying the MRF-LGB delay (left-hand graphs) and the MRF intensity (right-hand graphs) at two values of the LGB test shock: a low LGB intensity for this unit, at 7V, in the upper graphs and a high LGB intensity, at 13V, in the lower graphs. The actual duration of suppression produced by the LGB shock alone was 100 msec for the 7V shock and 218 msec for the 13V shock, as noted on the graphs.

Unit 425/12

MRF intensity at 4 volts MRF-LGB interval at 50 msec



intensities employed throughout this study were relatively high (as noted earlier), the observed prolongation of suppression -relative to control - induced by MRF conditioning must have been less marked than it would have been with less intense test shocks.

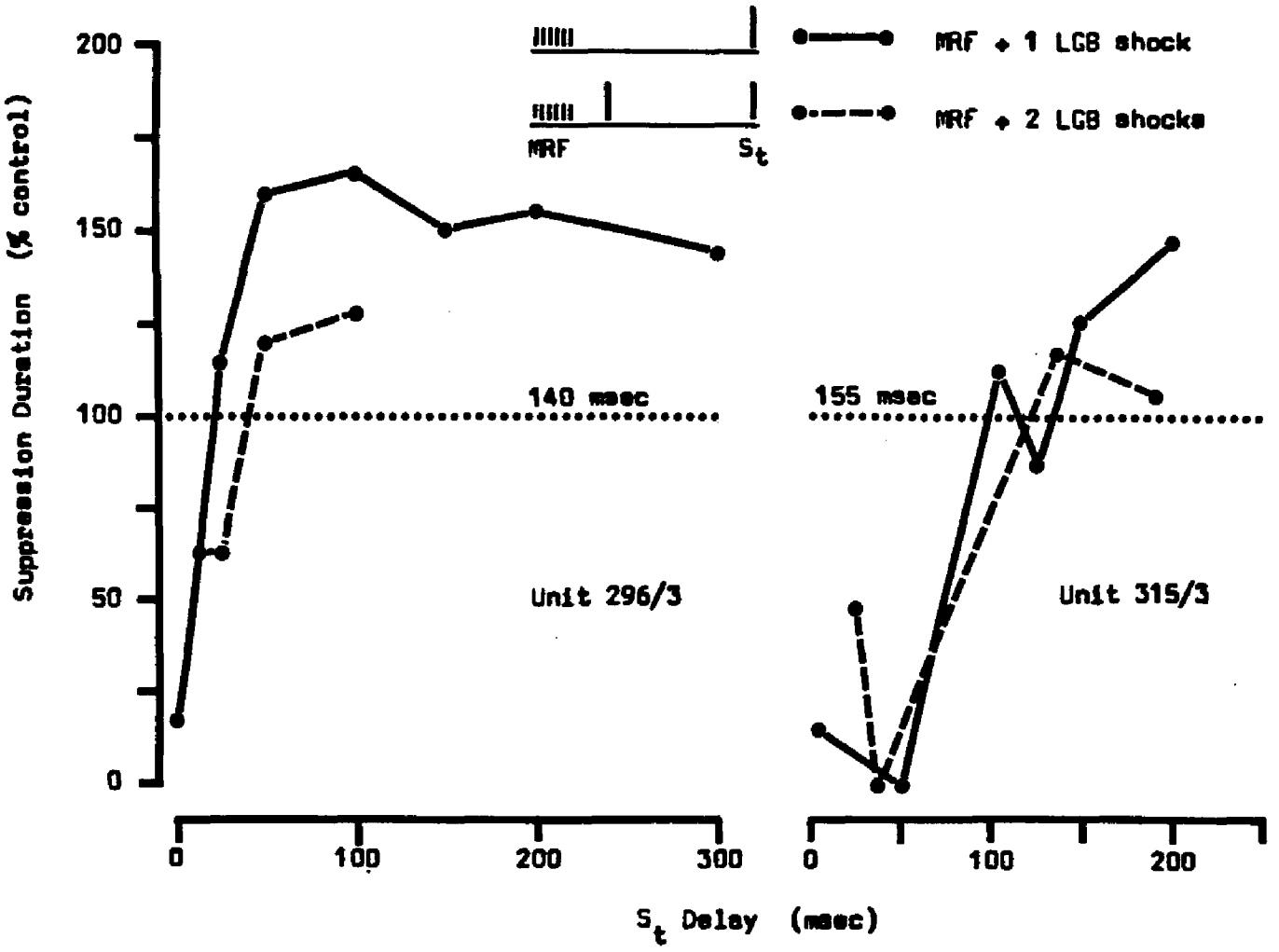
MRF-LGB Interaction: Dual LGB Shocks

In a few units, MRF conditioning was implemented with dual LGB shocks. In earlier studies, the cortical excitability cycle for gross evoked potentials was found to differ for single and dual LGB shocks preceded by MRF activation (e.g. Chalupa et al, 1973). The influence of MRF on the response to the second stimulus appeared to be independent from its effect on the first. In this study, an attempt was made to evaluate the response of single units under similar circumstances.

Fig. 19 demonstrates that the only observable (and very minor) difference in the alterations caused by MRF activation in the duration of suppression following single and double shocks to LGB lay in the magnitude and not the nature of the effect. As with the single LGB shock, suppression elicited by the second LGB stimulus was reduced at the shorter MRF-S_t delays and prolonged for the longer intervals - although both the reduction and prolongation of suppression may have been somewhat attenuated with the interpolation of the additional LGB shock. Another difference lay in the longer latency to suppression following the second LGB shock.

A comparison of the length of suppression elicited by the first and second LGB shocks following MRF activation reveals a biphasic effect - as was suggested by the earlier data for MRF and single LGB shock.

Fig. 19. A comparison, in two units, of the effects of MRF conditioning on the spike suppression elicited by a single test shock (solid line) with that elicited by the second of two LGB shocks (dashed line). The delay between the end of the MRF train and the first LGB shock was held constant (at 0 msec for Unit 296/3 and 15 msec for 315/3).


MRF + 1 LGB shock
MRF + 2 LGB shocks
MRF
S_t
Suppression Duration (% control)
200
150
100
50
0
140 msec
155 msec
Unit 296/3
Unit 315/3
0
100
200
300
S_t Delay (msec)

That is, when the two LGB shocks were separated from the MRF train by a short and long delay respectively, suppression after the first shock was abbreviated whereas suppression after the second was extended. Thus it appears that when the two opposing influences of MRF and LGB conditioning are pitted one against the other, the effectiveness of MRF priming is the greater, even when the LGB stimulus is administered in the same locus as the test shock and is closer to it in time. The MRF-S_t delay appears to have been the crucial parameter. The use of dual shocks was discontinued after confirmation of the foregoing (see Table IX).

Recording from the Midbrain

When cortical recording was no longer feasible due to pulsation or other interference, attempts were made to locate units responsive to LGB stimuli subcortically, especially in the region of the mesencephalon. A number of such units (7/11) responded with a period of suppression to LGB shock, although the duration of suppression was generally briefer, even when the LGB shock intensity was increased (Tables I and II).

When MRF conditioning was employed in conjunction with LGB shock*, 5/7 units in the vicinity of the central grey, superior colliculus, and posterior commissure, produced response sequences much like those seen in cortex where an initial diminution of suppression was followed by its prolongation (Table IX). The cortical events were more clear-cut, however, and appeared to precede those in the midbrain, as suggested

* It was possible both to stimulate and record in the midbrain since recording was always carried out contralaterally to the stimulation sites.

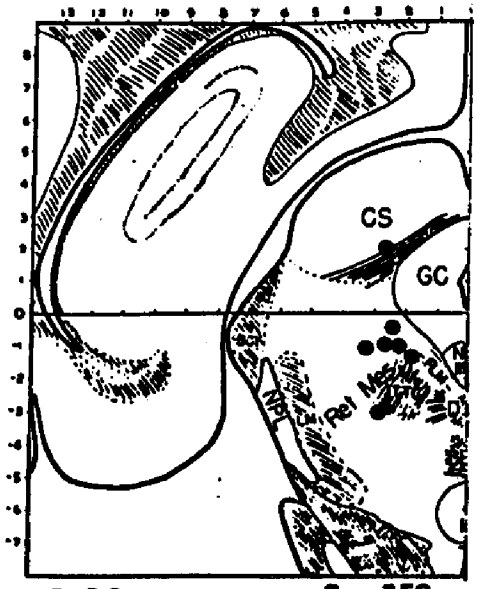
either by a delayed onset of suppression or by the development of changes in the cortical EEG prior to alterations in the mesencephalon. The negative instances were unsystematic but tended to show a diminution of suppression following MRF conditioning.

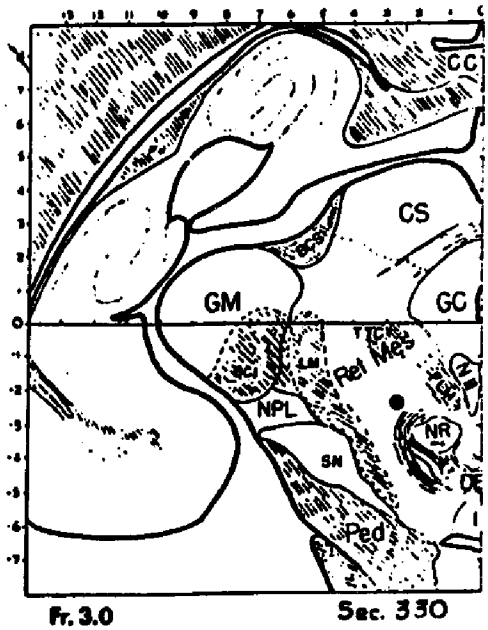
Histology

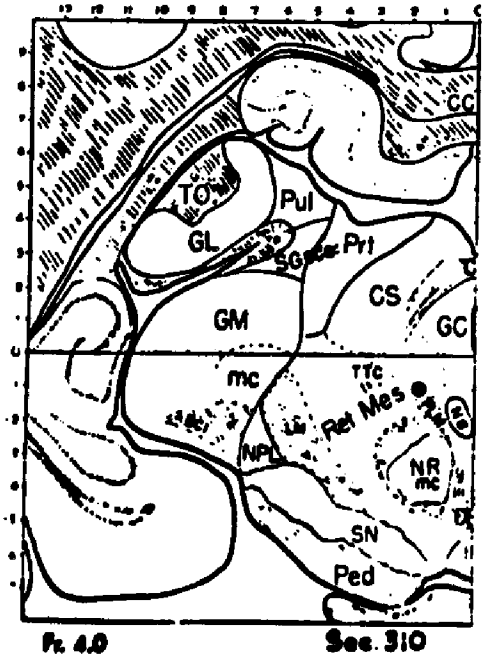
The midbrain stimulating loci for 64% of the units monitored in this study were examined microscopically and plotted on coronal sections (A2.0 - A4.0) traced from the stereotaxic atlas of Jasper and Ajmone-Marsan (1954). Fig. 20 shows that the majority of our midbrain placements were located above the central tegmental tract, with some placements likely in the nucleus cuneiformis (Taber, 1961) and others abutting on the path of the medial longitudinal fasciculus adjacent to the central grey. Photographs of representative electrode locations for the MRF in two units are shown in Fig. 21. Discussion of the placement in superior colliculus will be found in Appendix A.

The placement near the red nucleus (A3.0) generated different effects from other stimulating loci. But that may also have been the case because the LGB placement for that cat (335) was established as having been just below the LGB, in the nucleus reticularis of the thalamus. All other histologically verified LGB placements (again, for 64% of the units) were located medially in LGB, often on the border of, and at times within, the optic tract (see Fig. 21). The medial LGB projects, of course, to the lateral portion of Area 17 and the medial portion of Area 18 - the vertical meridian being on the boundary between Areas 17 and 18 - which was the general location of our recording microelectrodes (see Fig. 2).

Fig. 20. Sampling of mesencephalic stimulating loci plotted on serial coronal sections from the stereotaxic atlas of Jasper and Ajmone-Marsan (1954). CS, superior colliculus; FLM, medial longitudinal fasciculus; GC, central grey matter; NR, red nucleus; Ret Mes, mesencephalic reticular formation.


CS
GC
Rel
Mes
NPL
Fr. 2.0
Sec. 350


CC
CS
GM
GC
Rel
Mes
NPL
NR
SN
Ped
Fr. 3.0
Sec. 330


CC
TO
Pul
GL
SG
Prt
CS
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GC
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TTc
Rel
Mes
NPL
NR
mc
SN
Ped
Fr. 4.0
Sec. 310

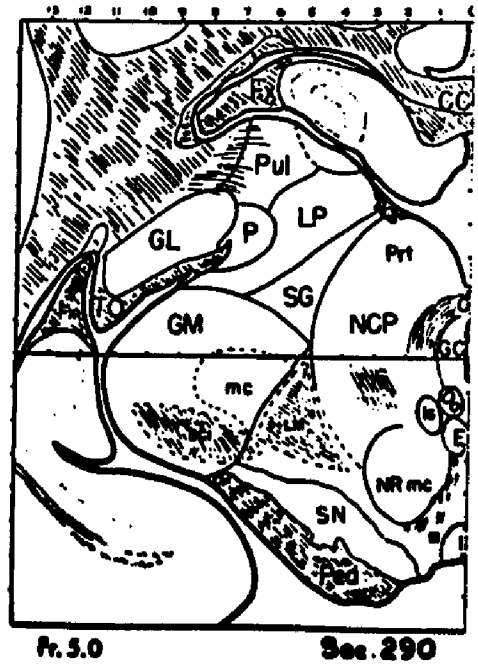
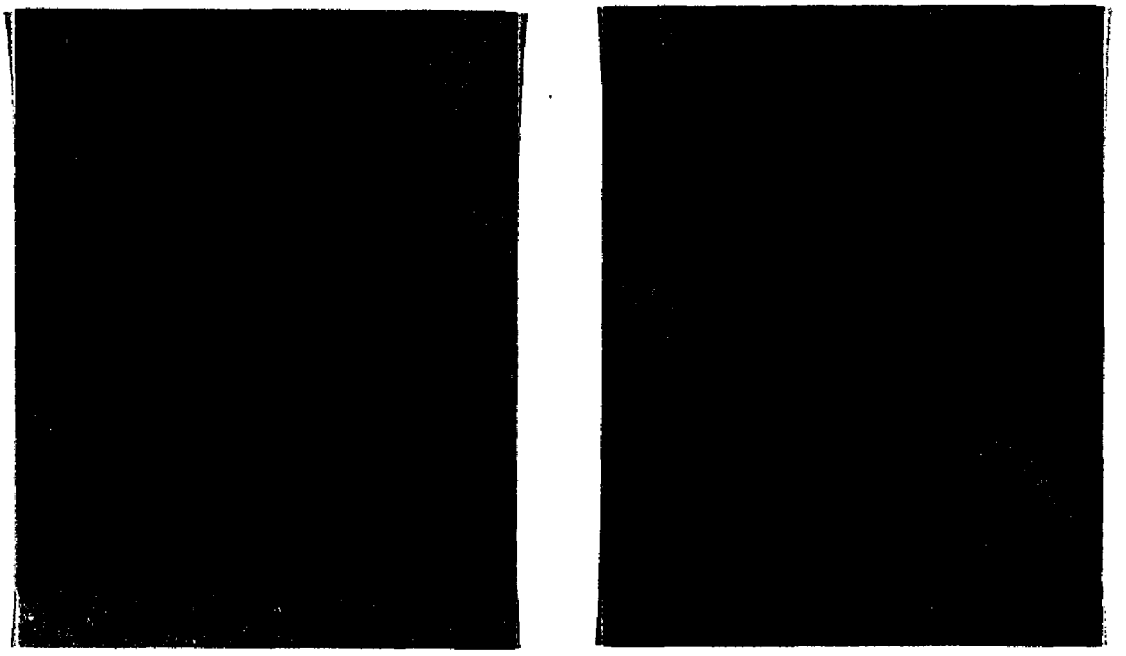
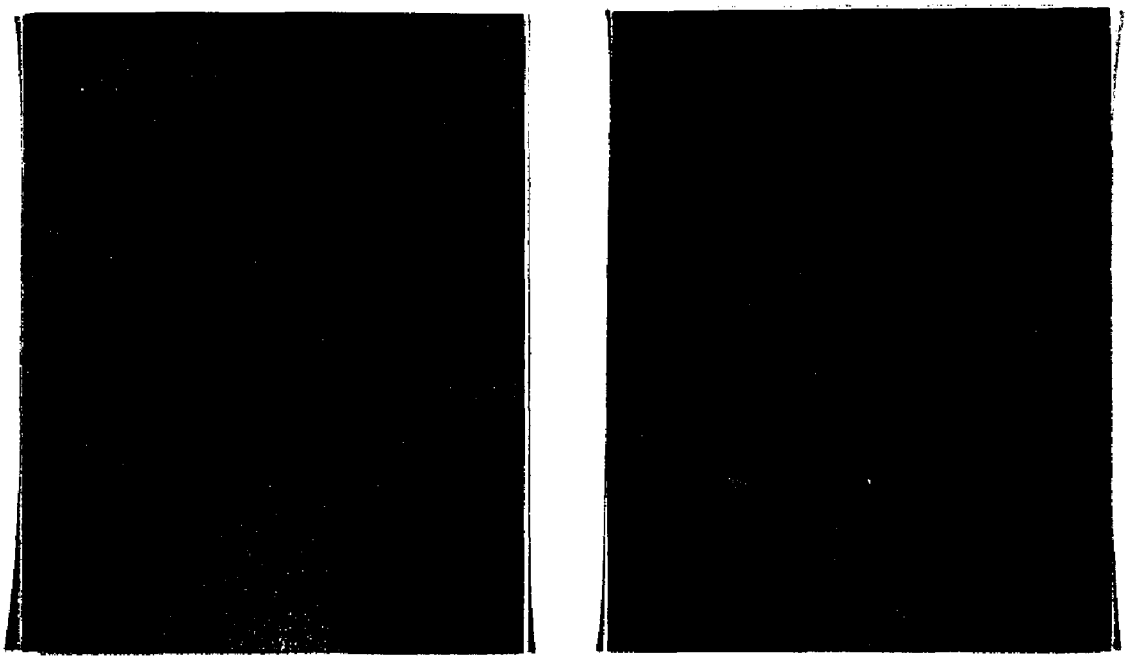

CC
Pul
GL
P
LP
Prt
TO
SG
GM
NCP
mc
NR mc
SN
Ped
Fr. 5.0
Sec. 290

Fig. 21. Representative stimulating loci in left LGB (upper photographs) and contralateral MRF (lower photographs) for two cats (319 on the left and 333 on the right).

LGB Loci



MRF Loci



Cat 319 Cat 333

DISCUSSION

The results of the present study demonstrate that MRF activation can either curtail or prolong the inhibitory portion of the evoked response recorded from a single unit in the cat's visual cortex. The literature has long reported either excitatory or inhibitory effects of the MRF on the cortical neuron's resting discharge. This observation has stood in marked contrast to the reports on the MRF's influence on evoked neuronal responses in visual cortex. With several notable exceptions, the principal finding for evoked cortical discharges has been facilitatory. Furthermore, even when MRF activation was seen to generate both excitation and inhibition, these were rarely observed in the same cortical neuron. The distinctive effects were therefore ascribed to the character of the monitored unit rather than to any systematic variation in the MRF stimulation administered. This construction deprives the MRF of a causal role in the kinds of alterations seen in cortical units following its activation. In the present study, on the other hand, the results were clearly dependent upon the parameters of stimulation applied to the MRF. This fact implicates the MRF much more significantly in the nature of the cortical events following its activation. It also allows the depiction of a relation between events at the unit and more molar levels - a somewhat more specific relation, as we shall see, than the literature has heretofore afforded.

We noted earlier that most unit studies have concentrated on the MRF's influence on the initial excitatory portion of the unit's response to input, the very portion of the cortical response that is now known to be least susceptible to modification by 'non-specific'

input. This last has been established for gross potentials (e.g., Creutzfeldt and Kuhnt, 1973; Fuster and Docter, 1962) and for micropotentials as well (Evarts, 1963). For extracellular analyses, the later components of the evoked cortical response, those that have been shown to be the most labile, the most amenable to manipulation, were simply the discharges occurring at longer latency, often following a period of suppression of spike discharges (Evarts, 1963; Narikashvili et al., 1965; Skrebitsky, 1969).

The unitary response in visual cortex to either electrical or adequate stimuli is by now known to comprise more than an initial excitatory discharge (e.g., Creutzfeldt et al., 1969). In fact, an inhibitory component seems so inherent a part of the response to visual input that it is often present even when an excitatory component is not (Creutzfeldt and Kuhnt, 1973; Kuhnt and Creutzfeldt, 1971; Watanabe et al., 1966). Consequently, the cortical response elicited by a shock to the LGB proved to be an appropriate tool for evaluating the effects of MRF activation on cortical inhibition: its most distinctive property being a relatively long and variable period of spike suppression. Such suppression of spike discharge has been correlated, on numerous occasions, with membrane hyperpolarization (e.g., Li et al., 1960; Tasaki et al., 1954; Watanabe et al., 1966). It is thus aptly viewed as an inhibitory phenomenon and will be so designated hereafter.

The MRF's influence on ongoing inhibition in visual cortex has rarely been assessed perhaps because spontaneous IPSPs constitute only a fraction of 5-15% of all cortical PSPs during resting activity (Creutzfeldt et al., 1966). Since IPSPs are much more commonly elicited by sensory input, MRF effects on cortical inhibition are best evaluated

with evoked, rather than with spontaneous, inhibitory activity. In the present work, evaluation of evoked inhibition has shown it to be remarkably sensitive to manipulations of the MRF in both the temporal and intensive domains.

The interstimulus interval (MRF-S_t delay) was the most thoroughly explored variable in this study, and its effect the most robust; while the effects of MRF intensity were probably the most labile and sensitive to parametric shifts (at different values of the interstimulus interval, for example). The short interstimulus intervals and high-intensity MRF trains contracted the inhibitory period, while the longer intervals and weaker MRF trains prolonged it. The relative degree of reduction or prolongation of inhibition also depended upon the intensity of the test shock. Prolongation of inhibition by the MRF was much more pronounced with weak test shocks, while reduction of inhibition was the more marked influence at higher test-shock intensities. The use of dual LGB shocks following the MRF train demonstrated that the effect of MRF conditioning was truly biphasic. The responses to the two LGB shocks were differentially affected as a function of each one's delay from the end of the MRF train: the inhibitory period elicited by the first (and short-interval) LGB shock was foreshortened, while that elicited by the second (and longer-interval) shock was lengthened. These findings suggest, as have several other recent reports (e.g., Henry and Bishop, 1971), that a variety of questions concerning inhibitory phenomena can be answered by means of the extracellular technique - particularly when the intracellular method has proved as refractory as it apparently has in the investigation of reticulocortical interactions.

The functional significance of evoked inhibition is generally discussed in the context of receptive fields. But, as Henry and Bishop (1971) have remarked:

> . . . it is unfortunate that the idea of a straightforward relationship between "on" discharges and excitation on the one hand and "off" discharges and inhibition on the other should have become so deeply embedded in the literature.
>
> . . . inhibition is not to be equated exclusively with "off" areas. More frequently, we have found that inhibitory phenomena exist as separate and distinct components in the receptive field without any necessary relationship with either "on" or "off" areas. (p. 4)

We shall therefore cite several studies which have examined inhibition straightforwardly either through intracellular recording or by monitoring spike suppression with the extracellular technique. Each of these will demonstrate the considerable import of the inhibitory component of the neuron's response. We shall then return to the receptive-field framework where the meaning of our findings must, however provisionally, be located.

Evoked inhibition, monitored extracellularly, is an ubiquitous response, well documented in a variety of species, and recorded throughout cortex, subcortically, and more peripherally as well (e.g., Gerstein, 1969; Li, 1956; McLennan, 1970; Polyanskii, 1967; Tasaki et al., 1954; Toyama and Matsunami, 1968). In an intracellular study, Kuhnt and Creutzfeldt (1971) showed that increasing photic intensities augmented the amplitude and duration of IPSPs in visual cortex while the short initial EPSP only rarely reached threshold. At the highest flash intensities, the primary EPSP was in fact cut off, ostensibly by the more ppwerful IPSP, and the initial spike response was completely suppressed.

Gerstein (1969) demonstrated that, of the three response components he had monitored (apparently identical to those observed in the present work), alterations in the inhibitory phase alone exhibited a highly systematic relation to variations in the adequate stimulus. He had recorded from units in the dorsal cochlear nucleus of the cat, following short tone bursts at a series of frequencies. Neither the initial excitatory discharge, nor the later discharges, exhibited any such relation. These observations suggest that, for some sensory channels and/or stimulus attributes, the inhibitory portion of the response may be more informative than the prior and subsequent excitatory discharges.

The importance of neuronal afteractivity for sensory processing has been emphasized by many (e.g., Jasper, 1966; Libet et al., 1967; Wagman and Battersby, 1964). Afteractivity, as ordinarily conceived, refers to excitatory responses succeeding the first-observed time-locked response to a stimulus. In this work, however, as in Gerstein's, attention is drawn to the inhibitory sequelae of input by virtue of the observed dissociation of the inhibitory component from the excitatory activity both preceding and following it, in its being, at times, the response component uniquely related to variations in the stimulus.

Once it is clear that the unit's 'response' comprises a series of events - to wit, an initial excitatory discharge, consequent spike suppression and later discharge (the 'afterdischarge') - then modification of any portion of the series may prove to be as revealing, if not more so, as an account confined to the initial excitatory discharge. It will be recalled, for example, that when Halothane had been withdrawn prior to the experimental treatments, alterations in the period of spike suppression were clearly predictive of modifications in the later spike discharges (specifically, in the afterdischarge peak latency). This was

not the case when Halothane was maintained throughout the experimental treatments - a datum that warrants further study as it indicates that the relations among the various components may be instructive.

While all inputs into cortex are thought to be excitatory, it has been proposed that intracortical connections are largely inhibitory (Hess et al., 1975). Some recent and highly provocative studies suggest that intracortical inhibition may play a larger role in sensory coding than the ancillary function that is often accorded it. Brooks and Jung's (1973) point of view will serve to illustrate this last:

> It is questionable whether inhibition or suppression of activity . . . has much information value per se, although there are several types of inhibition occurring subcortically which may function in accentuating excitation. (p.334)

Their view of the "sharpening" role of inhibition is the standard one. But it neglects the role of inhibition in "shaping" or increasing the selectivity of the neuronal response to input (Benevento et al., 1972).

When Pettigrew and Daniels (1973) administered a GABA-inhibitor, bicuculline, and examined the response properties of single neurons in the cat's visual cortex, they found that the receptive-field properties of complex and hypercomplex cells were dramatically altered. Removal of GABA-mediated inhibition apparently transformed the more complex cells in Hubel and Wiesel's (1965) hierarchy into units with properties not dissimilar to those of an afferent fiber from the LGB. The parallel input from LGB known to impinge on each category of cortical cell, from the simple to the hypercomplex (Stone, 1972), may thus provide an infrastructure over which the higher orders of complexity are superimposed by means of intracortical inhibitory mechanisms. If so, the response specificity characterizing cortical 'feature detectors' would be determined, in the main, by inhibition.

Only further study can establish the specific part played by cor-

tical inhibition in the neural coding of input. Nonetheless, since Hartline's demonstration of lateral inhibitory interactions in the eye of Limulus, it has become habitual to conceive of inhibitory function in the visual system (and elsewhere) as subserving contrast and contour enhancement (Ratliff, 1972). To facilitate the ensuing discussion of our findings, we shall follow that precedent and regard the organization of the LGB-evoked response sequence - excitation (?) followed by inhibition and renewed excitation - as a temporal expression or consequence of the spatial properties of the system. Any modifications of the inhibitory period will hence be interpreted as an effect primarily on interneuronal or spatial contrast mechanisms and, as such, on the response specificity of cortical neurons. But mechanisms subserving spatial contrast affect succeeding events. And the very process, inhibition, which helps circumscribe or define the event in space will define it in time as well. Hence a brief consideration of the role of the inhibitory period in intraneuronal or temporal contrast follows next.

LGB Conditioning

LGB conditioning was implemented both to provide a basis of comparison (a 'control') for the influence of MRF activation as well as to assess the effect of prior inhibition on the neuron's responsiveness to subsequent input. This last was to have confirmed the reality of the putative contrast mechanism in the temporal domain. Unfortunately, as has been noted earlier, the questionable nature of the initial spike responses in this study has precluded such analysis. Where it is known, however, that membrane hyperpolarization underlies the inhibitory pause, as is the case for spike suppression generated by an LGB shock, it may be confidently assumed that the unit's responsiveness will be attenuated. Polyanskii (1967) showed this was so in neurons of the visual cor-

tex whose excitability cycles he had studied in waking rabbits. Most visual cortical neurons in rabbits respond to light flashes with a sequence of events identical to the response we have described: an early discharge followed by inhibition and a fairly long afterdischarge. When double flashes were administered at increasing intervals, the response to the test flash was inhibited for some 90 msec, followed by a gradual period of recovery at intervals of 90-130 msec. After this period of recovery, the number of spikes in the test response increased above the control values, prior to a restoration of the original values at 200-250 msec. The time course of these modifications indicates that the inhibitory period does in fact reduce the unit's responsiveness, while the afterdischarge apparently facilitates it - evidence that a mechanism for (neural) contrast enhancement is intrinsic in the cortical response to input.

Our results suggest that the efficacy of this mechanism is enhanced both by LGB stimuli of increasing intensity as well as by conditioning in LGB at the shorter intervals. The accuracy of this interpretation is underscored by von Békésy's (1967) repeated demonstrations, for several sensory modalities, that strong stimuli, or stimuli with rapid onset or increased frequency (i.e., short interstimulus intervals), were required to produce lateral inhibition behaviourally. Our results with LGB conditioning are consistent with von Békésy's observations: as interstimulus intervals were reduced, that is, as stimulus frequency was effectively increased, the consequent inhibition was lengthened.

Using direct cortical stimulation, McLennan (1970) also reported that longer periods of inhibition (far longer than those seen in the

present work) followed trains of stimuli (at 10-100 Hz) rather than single stimuli. Interestingly, Libet et al. (1967) pointed out that the production of conscious sensation was more readily accomplished by repetitive electrical stimuli rather than by single shocks to the VPL or directly to cortex, even when the single shocks were of far greater intensity. Furthermore, the stimulus trains had to be delivered at relatively high frequencies (generally, at 60 pulses per sec for .5 sec or longer) to ensure their effectiveness. It seems that the very conditions which favour the production of increased inhibition, whether physiologically or behaviourally ascertained, also favour the conscious appreciation of stimuli.

High-frequency activation of the MRF has long been associated with the production of behavioural alertness, if not consciousness*. A parallel may well exist between the iterative stimulation needed for the conscious detection of stimuli and the nature of the influence exerted through high-frequency activation of the MRF.

MRF-LGB Interaction

The expectation was raised earlier that, because of the higher thresholds and longer latencies associated with inhibitory processes in cortex, a diffuse excitatory input such as that thought to arise from the MRF would allow inhibitory mechanisms to become more manifest. This is indeed the case: the LGB-evoked spike suppression was prolonged after MRF conditioning, but only at low MRF intensities or relatively

* Although the MRF is no longer considered to be solely responsible for the behavioural arousal continuum (Valenstein, 1969), it still is thought to contribute to its expression in some undetermined way.

long after it had been discontinued. Conversely, at high MRF intensities and short MRF-S_t delays, spike transmission was enhanced after the test stimulus. These findings are not suggestive of a direct relation between the intensity of MRF activation of cortical inhibitory neurons and the effectiveness of their output.

The findings at the brief MRF-LGB intervals (or with the more intense MRF trains), where suppression was abbreviated, may be sufficiently well explained by a superposition or algebraic summation of the responses to the two inputs presented independently. But such summation of the two responses at the longer MRF-LGB intervals (or with the weaker MRF trains) cannot account for the observed prolongation of suppression seen after the LGB shock: at those intervals, MRF activation alone still enhanced the degree of the resting or maintained cortical discharge. Enhancement (MRF-generated) plus suppression (LGB-generated) do not equal longer suppression. Rather than a passive convergence of the specific and extravisual inputs at some point in the system, an interactive relation must be responsible for the prolonged suppression at the longer MRF-LGB intervals (and with the weaker MRF trains).

Several mechanisms may underlie this interaction: (1) an exhaustion of synaptic transmitters due to prior facilitation; (2) defacilitation; (3) postsynaptic inhibition following MRF activation, manifesting itself most clearly in the extracellular record through interaction with specific input. Intracellular recording might readily resolve the issue but, to our knowledge, has not as yet been conducted in this area of investigation. Furthermore, as the plausibility of each of these hypotheses is evaluated in turn, it ought to become evident that the extracellular record itself indicates that the last of these is the least suspect.

The particular temporal pattern almost invariably produced by the MRF-LGB interactions (without regard to cortical layer or type of unit

sampled*), namely, the initial curtailing of suppression followed by its extension, suggests a possible explanation. It implies that the high degree of facilitation initially generated by MRF activation perhaps exhausted the synaptic transmitters, or caused a form of presynaptic inhibition, which expressed itself in the consequent lengthening of the duration of spike suppression. Several findings militate against this interpretation. The most pertinent is the observation that low-intensity MRF activation, which most effectively prolonged the duration of evoked inhibition, hardly generated any facilitation of the maintained discharge (Fig. 15). This condition (weak MRF activation) would be less likely to exhaust synaptic transmitters than would strong MRF activation, yet it was the weak activation which had the more powerful inhibitory influence. On one occasion, moreover, a single MRF conditioning shock was used (again, a weaker stimulus than the longer train): the only observed effect was a prolongation of suppression at all interstimulus intervals tested (data in Table IX). It is thus unlikely that prolongation of spike suppression seen at the longer MRF-S_t delays was a direct consequence of the prior facilitatory action. One must look toward other explanations.

When the LGB shock was presented alone, and its intensity was augmented, increasing periods of inhibition were ordinarily succeeded by correspondingly higher degrees of afterdischarge. This relation between inhibition and afterdischarge was subverted by MRF conditioning (and sometimes by LGB conditioning as well). With MRF conditioning, the shorter suppression periods were followed by the higher rates of afterdischarge. Significantly, the longer suppression periods were rarely

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* Since most of our units exhibited a distinct resting discharge, our sample of units could not have included many 'simple' cells (Henry and Bishop, 1971).

followed by a corresponding diminution of the degree of afterdischarge - an observation which tends to undercut the defacilitation hypothesis: for if defacilitation manifested itself in the prolongation of suppression, a corresponding attenuation of the immediately succeeding afterdischarge might have been anticipated. Furthermore, since MRF alone still facilitated the neuron's discharge at these longer intervals, defacilitation would have had to be caused by an interactive relation between the MRF and LGB inputs. The lack of symmetry in the relations between suppression and afterdischarge further attests to the operation of different mechanisms at the short and long interstimulus intervals. Moreover, the high degree of variability seen at the 'transitional' interval (ca 50 msec) may signal the onset of the non-linearity suggested by the prolongation of suppression. If the 'transitional' interval does in fact reflect the onset of an interactive relation between the responses to MRF and LGB inputs, then a thorough evaluation of MRF influences at the longer intervals - a rarity in the majority of unit studies conducted in the area - would appear indispensable for a determination of the mechanisms involved.

If neither the 'synaptic exhaustion' nor the defacilitation hypothesis is persuasive, we are left with the possibility, for which there appears to be no negative evidence, that some underlying inhibitory process must have developed following MRF activation, to surface in the observed prolongation of spike suppression at the longer intervals, but only when inhibition had first been triggered by specific input. In other words, the MRF may exert an inhibitory effect on the cortical unit, an effect possibly independent of the LGB-evoked inhibition (witness the suppression of the cortical unit's maintained discharge at relatively long delays) but often made manifest, in the extracellular record, only in conjunction

with the LGB-evoked response.

Time seems to be essential for the elaboration of reticulocortical influence. The long latencies reported in the literature and often observed in this work as well (as long as 50-100 msec from the beginning of the MRF train*) for the onset of reticular effects in visual cortex have not been accounted for to date. Other than the time possibly required for the manifestation of the physiological effects of iterative stimulation, the long latencies suggest the existence of a rather indirect pathway to cortex. There have been intimations of massive mesencephalic input into cortex of extremely fine unmyelinated fibers whose diameters are so small as to be almost beyond the resolution of the light microscope (e.g., Curtis, 1972, in Discussion, p.322). These would presumably subserve very slow conduction. However, many authors, including Szentagothai (1973), have expressed reservations about the evidence for such direct MRF input into the visual cortex.

While the evidence for direct MRF projections to the LGB is more substantial (Bowsher, 1970), the same problem of time arises: the latency of the LGB response to MRF activation is of the same order of magnitude as the latency of the cortical response (see Tatton and Crapper, 1972). This fact does not rule out a mediation by LGB of the reticulocortical effects, but it does decrease the likelihood that the LGB is the sole intermediary. Although numerous workers have investigated the MRF's influence on LGB neurons, few have provided data that are fully compatible with, or that would adequately account for, the observations we have made at cortex. For example, both Satinsky (1968) and Tatton

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* The reference is to the onset of the MRF's enhancement of the cortical unit's resting discharge frequency. The longer latencies observed in this study include the occasional suppressive effect seen prior to such enhancement (see Results).

and Crapper (1972) observed dual effects in LGB neurons following MRF activation. Their observations, however, were largely derived from the resting (rather than the evoked) activity of LGB units. Furthermore, their dual effects were not confined to a particular sequence - some units exhibited an initial suppression followed by facilitation, and vice versa.

Singer and Dräger (1972) examined the effects of MRF activation on intracellular responses in LGB to stimulation of the optic tract (OT). When a stimulus to MRF was administered 60-200 msec prior to the OT shock, the hyperpolarization following the LGB action potential was reduced in amplitude and duration. No mention was made of any MRF effects on the LGB response preceding the 60-msec interval. However, in discussing the effects of MRF activation on the resting activity of LGB neurons, Singer and Dräger mentioned that a slight firing rate decrease was occasionally observed immediately (20-60 msec) after the MRF stimulus. These data suggest a possible basis for our observations at cortex, in being unidirectional (although opposite in sign): inhibition (?) preceded facilitation in their study.

The MRF's influence on the LGB is undoubtedly reflected at cortex. But in order to strengthen the case for the LGB as sole intermediary for the reticulocortical effects, a study (preferably intracellular) would have to be conducted, using identical stimulus parameters or concurrent recording for LGB and cortex. Furthermore, an interactive relation between the MRF and visual inputs, such as that observed at the longer interstimulus intervals for cortical units, would have to be discerned at the level of the LGB. In sum, given the amount of divergent data, the intervention of additional structures is more than likely - a consideration insufficiently explored in the literature.

One such structure is the nucleus reticularis of the thalamus (henceforth abbreviated NRT). The NRT is situated over the surface of dorsal and metathalamus such that most thalamocortical and corticothalamic fibers must traverse its dendritic fields to reach their destinations (Scheibel and Scheibel, 1966, 1967a, 1967b). The Scheibels have speculated that the NRT is strategically located to perform the gating or filtering function considered necessary by them for mechanisms subserving attention. Data have accumulated over the past several years tending to support their point of view (see Schlag and Waszak, 1970, 1971; Waszak, 1974).

In its dorsal leaf, the MRF sends a major output to the NRT, its influence being inhibitory (Yingling and Skinner, 1975; Skinner and Yingling, 1976). NRT neurons display a firing pattern which is the converse of the pattern observed in the specific thalamic nuclei (Schlag and Waszak, 1970). It has been postulated that the NRT output to thalamic structures is inhibitory (see Schlag and Waszak, 1970). Hence activation of the MRF would set up a complex series of events in NRT, LGB, and, as a result, in visual cortex as well. To complicate matters further, there remains the question of the MRF's ventral leaf (Scheibel and Scheibel, 1967b) and its possible influence - albeit indirect - on visual cortex. Several studies have shown a dissociation between the MRF's effects on LGB and visual cortex. Among these, Tatton and Crapper (1972) have reported that, although the MRF stimulus loci which produced alterations at both LGB and cortex overlapped, the LGB loci were circumscribed within a more widespread region mediating cortical desynchronization; "The locations at which the TG [tegmental-geniculate] alterations were obtained constitute a more localized region within the larger mesencephalic area mediating [cortical] 'alerting'." (p. 383).

Our records for MRF alone often exhibited a bimodal distribution of spikes. Such a pattern may reflect either a series of complex interactions elaborated in time over a circuit such as that described above for the NRT. Or it may reflect the modulation of cortical events by several input pathways, with different numbers of interpolated synapses. All of these possibilities await investigation.

Our electrodes were situated largely in the region of the nucleus cuneiformis which extends rostro-caudally through the entire mesencephalon just below the tectum (Taber, 1961). This region has been described as relatively undifferentiated, with considerable dendritic overlapping and characteristic intermingling of dendrites and passing fibers (Ramón-Moliner and Nauta, 1966). Thus stimulation in this region could hardly avoid activation of both local neurons and passing fibers. Although "the reticular core has finally begun to outlive its image as a mindless monolith" (Scheibel and Scheibel, 1977), Ramón-Moliner and Nauta (1966) have designated it the "isodendritic core of the brain stem," its morphological features regarded by them as "justifying a unitary concept even in the absence of any physiological data"(1966, p. 320) which are, of course, abundant.

"Isodendritic" neurons are characterized by multimodal inputs (Ramón-Moliner and Nauta, 1966). The classical schema of collateral inputs into the MRF from primary sensory pathways, resulting in both 'specific' and 'nonspecific' activation of cortex, has been questionable for some time. A number of investigators have been unsuccessful in their search for collaterals from, for example, the optic pathways. Yet multimodal sensory, as well as motor, inputs are known to converge upon the MRF (e.g., Amassian and Devito, 1954; Bell et al., 1964; Scheibel and Scheibel, 1977). More recently, a schema of a different order has

emerged, to some extent as a result of investigations on the vertebrate tectum (see Ingle and Sprague, 1975; Scheibel and Scheibel, 1977). Portions of the MRF and the deeper layers of the mammalian superior colliculus may be viewed as a minibrain - with overlapping sensory and motor maps furnished by centrifugal fibers specialized for stimulus localization: a semi-final common path of sorts which guides the orienting-escape continuum of the mammal's behaviour (see Ingle and Sprague, 1975; Scheibel and Scheibel, 1977). Stimulation of colliculus and the MRF will cause the animal to orient (Fuster and Uyeda, 1962; Ingle and Sprague, 1975). Schaefer (in Ingle and Sprague, 1975) demonstrated that stimulating colliculus will cause the normal or decorticate cat to orient toward the appropriate spatial locus at low stimulus intensities and to escape at the higher intensities. Thus, orienting and increased inhibition at cortex may well be correlated; and increased inhibition presumably sharpens and shapes sensory mechanisms at the cortical level. Escape, on the other hand, would be associated with decreased inhibition - with facilitation, in fact, at cortex, and clearly with facilitation of the motor output as well. Our study can be viewed as having examined the activity of that portion of the cortico-mesencephalic-cortical loop subserving the outcome of the mesencephalon's choice between orienting and escape: that is, its choice between staying put, with its attendant analysis of the environment, and action, at the expense of analysis. The following discussion elaborates this view.

As we have interpreted the cortical response to an LGB shock, the period of spike suppression or inhibition mainly reflects the neuronal interactions which lead to the establishment of contrast and response specificity in the local neuronal pool. When MRF (or SC: see Appendix A) activation reduced the inhibitory period, not only was 'contrast' reduced but, as a result, the configuration of the test response (the sequence

of excitation, inhibition, and renewed excitation) often lost its distinctive character. This is evident in Figs. 14 and 22 where the spike distribution at the shortest interstimulus interval resembles the histogram generated by the conditioning stimulus per se much more than it does the response distribution to the test shock. As noted earlier, this last could have resulted from a simple superposition of the two response distributions. Conversely, the longer intervals and weaker MRF stimuli tended to enhance the distinctiveness of the response to an LGB shock. The various components of the response became still more clearly demarcated, either through lengthening of the inhibitory period or, occasionally, through a marked skewness of the afterdischarge distribution (as in the lower left histogram in fig. 14). When two levels of intensity were used for the test shock, contrast was enhanced most dramatically for the weaker test stimulus.

Without knowing which aspect of the unit's response 'encodes' the stimulus, it would appear to be rash to assume that facilitation of spike transmission by the MRF necessarily improves sensory processing. Several authors, Evarts (1961) among them, have proposed that enhancement of inhibitory activity may in fact improve the signal-to-noise ratio in neural processing. Significantly, the facilitation brought about by MRF activation has been seen to obscure otherwise clearcut responses to repetitive photic flashes (Narikashvili et al., 1966).

The standard experiments cited as evidence for the MRF's positive contribution to sensory processing are those of Lindsley (1958) and Fuster (1958; Fuster and Uyeda, 1962). Lindsley demonstrated an enhanced test response when dual photic flashes, separated by an interval of 50 msec, followed MRF activation. Fuster and Uyeda reported that MRF activation improved monkeys' performance on a tachistoscopic discrimination task. However, Lindsley's results were obtained only after MRF activation

had been discontinued and not during its implementation.

Fuster and Uyeda carefully pointed out that they had used an MRF train at low intensity after Fuster's (1958) report of impaired performance at high MRF intensities. Thus the MRF parameters in both sets of experiments were those that tended to lengthen evoked inhibition in our study. It appears that there is no substantial evidence that a generalized facilitation of spike transmission in cortex, effected by the MRF, is responsible either for the enhanced recovery cycle of gross potentials or for the improved behavioural performance of Fuster's monkeys.

There is some evidence, on the other hand, that the normal waking state - to which the MRF is thought to contribute - is associated with a prolongation of evoked inhibition in cortex. This was shown by Evarts (1961) for the cortical extracellular response evoked by a shock to the optic radiations. The evoked inhibitory period was longer during wakefulness than during sleep, in the unrestrained cat. Evarts qualified this observation by pointing out that the waking state he had studied differed from the state of intense arousal which may follow strong electrical stimulation of the reticular formation. Furthermore,

> One factor which has an important bearing on patterns of neuronal discharge during waking is the amount of sensory stimulation which the cat is receiving. If one records unit activity from the visual cortex during sleep when the cat's eyes are closed, and during arousal when the cat has suddenly opened its eyes and looked about, one frequently finds that arousal is associated with a burst of activity. On the other hand, when the sensory input is restricted during both waking and sleep, a majority of units show decreased spontaneous activity upon arousal. . . . In the waking conditions of the present experiments, the cats have been in the soundproof experimental room a number of times, have been familiarized with their environment, and appear to be uninterested in their surroundings. (Evarts, 1961, in Discussion on p. 184.)

In effect, depending upon whether the animal's waking state was more or less alert or aroused, opposing results were observed for the resting

cortical discharge, corresponding to our observations on the cortical response to input.

Bradley (1961, in Discussion on p. 183) noted that stimulation of the reticular formation at threshold intensity produced wakefulness, while supraliminal stimuli tended to induce a state of excitement or escape reactions. Several investigators have shown the disruptive impact of high-intensity MRF stimulation in both the behavioural (e.g., Sterman and Fairchild, 1967) and neuronal domains. Verzeano (1961, in Discussion on p. 183), for example, found that increasing the intensity of MRF trains (at 200-300 Hz) to 4 volts amplitude (precisely our parameters for the temporal condition) resulted in a disruption of the propagation of unit activity, as monitored by multiple microelectrodes. The same neuronal events were observed, moreover, when the animal was excited, even when no artificial stimulation had been administered.

The parallel suggested by the above findings between the physiological events and the well-known behavioural expressions of the arousal continuum needs little elaboration. Moderate levels of arousal are characterized by optimal behavioural performance (for most tasks), while the lowest and highest arousal levels are associated with behavioural disruption, albeit for different reasons at the low (sleep) and high ends of the continuum. It is tempting to view the MRF effects on cortical units at the lower intensities and longer interstimulus intervals in this study as resembling neuronal activity during moderate arousal; and the MRF's effects at the higher intensities and shorter intervals as 'disruptive.' The temptation is magnified both by our results showing an inverse or 'inverted-U' relation when MRF intensity was varied and by the prevalent interpretation of evoked inhibition

as subserving a clearer representation of input. The conditions giving rise to enhanced neuronal contrast and response specificity would thus be located at the lower to moderate regions of the arousal spectrum, while those reducing contrast and selectivity would be found within the range of high arousal (and sleep): a relation that is readily tested in the unrestrained or unanaesthetized animal.

If enhanced contrast and selectivity are beneficial for sensory processing, can reduced contrast (the 'disruption' referred to above) have its own utility? It is helpful to remember that intensification of contrast in the nervous system is achieved at a cost, and that is a loss of information, of detail, and of sensitivity. Conversely, attenuation of inhibition, reduction of contrast, is often associated with a heightened sensitivity (see, e.g., Brooks and Jung, 1973, p. 399). Interestingly, Pettigrew and Daniels (1973) showed that removal of GABA-mediated inhibition resulted in a marked increase in the complex cell's resting and evoked activity - this, alongside its loss of selective responsiveness.

The hypothesis that the MRF increases discriminative power through lengthened inhibition on the one hand, and sensitivity through reduced inhibition on the other, is testable in both the physiological and behavioural domains - although most convincingly, and with greatest difficulty, in the latter. The behavioural context for which a high arousal accompanied by increased sensitivity would be appropriate - even at the expense of discriminative accuracy - is described by unfamiliarity and threat. The detailed registration of edges and contours is less to the point, in such circumstances, than the detection and localization of sudden movements, especially those in the periphery of vision.

Enhancement of spike transmission by the MRF would facilitate just that response component - the initial spike burst - which, according to von Békésy (1967), subserves stimulus localization.

The initial spike burst is also the mark of the excitatory receptive-field center. Enlargement of that center through MRF activation would signify an increased sensitivity (or impaired resolution); its reduction would represent the converse. MRF activation has already been shown to enlarge receptive fields in the LGB - under scotopic conditions, and with fields largely beyond the area centralis (Meulders and Godfraind, 1969). The existence of different cell groupings in the retina, and their distinct central projections (Fukuda and Stone, 1974), raises the question of differential MRF effects on these cells. The question is of particular interest since the slow-conducting X-cells, concentrated in the area centralis, are thought to mediate high visual resolution, while the fast-conducting Y-cells are probably important for peripheral vision. Area 18 receives input only from the Y-cells and this fact may account for Orem and Feeney's (1971) report on a rostrocaudal difference in MRF effects on visual cortex (see Review of the Literature).

Parameters other than alterations in receptive-field size might also be used to illuminate the question of MRF influence on sensitivity as vs. resolution: decreased directional selectivity, for example, would signify an increased sensitivity but an impaired discriminative function for a particular neuron (see Robertson, 1965). Contrast thresholds of grating patterns could be examined under different levels of arousal and the sharp tuning to spatial frequency characteristic of neu-

rons in the visual cortex (Campbell, 1974) could be evaluated for alterations induced by MRF activation; both would provide an indication of changes in inhibitory function with variations in arousal or electrocortical activation. But only a study in which both neuronal and behavioural measures were undertaken concurrently could substantiate our central thesis: that significant characteristics of electrocortical activation and arousal, particularly those associated with sensory discrimination, depend for their optimal expression on an increment in inhibitory function in cortex.

If the degree of inhibitory participation in cortical activity can be and is regulated in some generalized fashion by the MRF, the implications of such regulation are necessarily broad. Our findings may, for example, be relevant to such refractory clinical entities as epilepsy and pain.

Some types of seizures are thought to result from a failure of inhibitory control (Kuhnt and Creutzfeldt, 1971). The incidence of seizures is associated, moreover, with arousal in tending to occur more frequently during sleep and under stress (i.e., at both ends of the arousal continuum). Attempts have been made to treat epileptic conditions with electrical stimulation of diverse C.N.S. structures, with varying degrees of success. Our findings indicate that, should MRF stimulation be undertaken to enhance inhibitory activity, both its parameters and the nature of its relations with other stimuli cannot be neglected. Frequency of visual stimulation is known to be an important parameter for seizure induction. In this connection, we have seen that MRF conditioning completely reversed the slope of the dual LGB function

(Fig. 19), thus essentially reversing the effect of stimulus frequency in the visual pathway. The force of MRF conditioning superseded the influence of a conditioning stimulus in the sensory pathway. Hence the regulation of contrast or inhibition for any given stimulus configuration appears to be dominated by concurrent activity in extravisual structures rather than by prior events in the geniculostriate system itself. This must mean that neural mechanisms subserving temporal phenomena, such as the CFF, ought to be investigated in the awake, functioning organism. Otherwise, spurious results are likely to be obtained, depending upon the degree of MRF involvement in the preparation studied.

The particular link between arousal and its regulation of inhibition here postulated may also be consonant with the production of analgesia through stimulation of midbrain structures (Balagura and Ralph, 1973; Mayer et al., 1971; Melzack, 1973; Reynolds, 1969). Although a disquisition on this last is beyond our purview, it should be noted that our results were obtained through stimulation of the region of the central tegmental tract, adjacent to the central grey, the very region where stimulation effected a marked analgesia in Reynolds' (1969) study. Furthermore, to achieve their analgesic effects, Balagura and Ralph (1973) applied a low-intensity stimulus to the mesencephalon.

In conclusion, the orderliness of our findings suggests that, in selecting evoked inhibition as our dependent variable, we have located the cortical mechanism most susceptible to MRF regulation. The MRF's signal contribution to cortical function may reside in its regulation of cortical inhibition.

APPENDIX A

SC-LGB Interaction and Photic Test Stimulus

The electrode placement in superior colliculus (SC) - at A2.0 in Fig. 20 - was intended for it, in view of Tatton and Crapper's (1972) observation that the most dorsal midbrain point at which they had obtained cortical alerting, with no concomitant alterations in LGB, corresponded to the ventral portion of the deep layer of the superior colliculus. The deep layers of SC are thought to be intimately related, both functionally and morphologically, to the underlying MRF (Ingle and Sprague, 1975).

Several studies have demonstrated the similarity of conditioning in SC and MRF on the gross cortical response to visual input (e.g., Brown and Marco, 1967; Chalupa et al., 1973). In our study, although the effect on the spike frequency distributions of the same cortical unit was not identical after activation of these structures, a pronounced degree of enhancement was observed for both. Two curves for SC-LGB interaction were plotted as in Fig. 22. They confirmed the similarity of MRF and SC conditioning at the unit level. Furthermore, the histograms demonstrate that the inhibitory effect (i.e., the prolongation of spike suppression) is as prominent, if not more so, with SC conditioning: the periods of suppression were markedly extended, at shorter interstimulus intervals.

Two additional units were monitored with SC conditioning and a long photic flash as the test stimulus. Remarkably similar results were obtained using photic stimulation, as is evident in Fig. 23: For the test stimulus alone (upper left-hand histogram), there were very brief, barely discernible, periods of discharge suppression shortly after both

Fig. 22. Influence of conditioning in superior colliculus (SC) on LGB-evoked spike suppression. The ipsilateral MRF had been fulgurated at 0.5 mamp for 25 sec prior to SC stimulation.

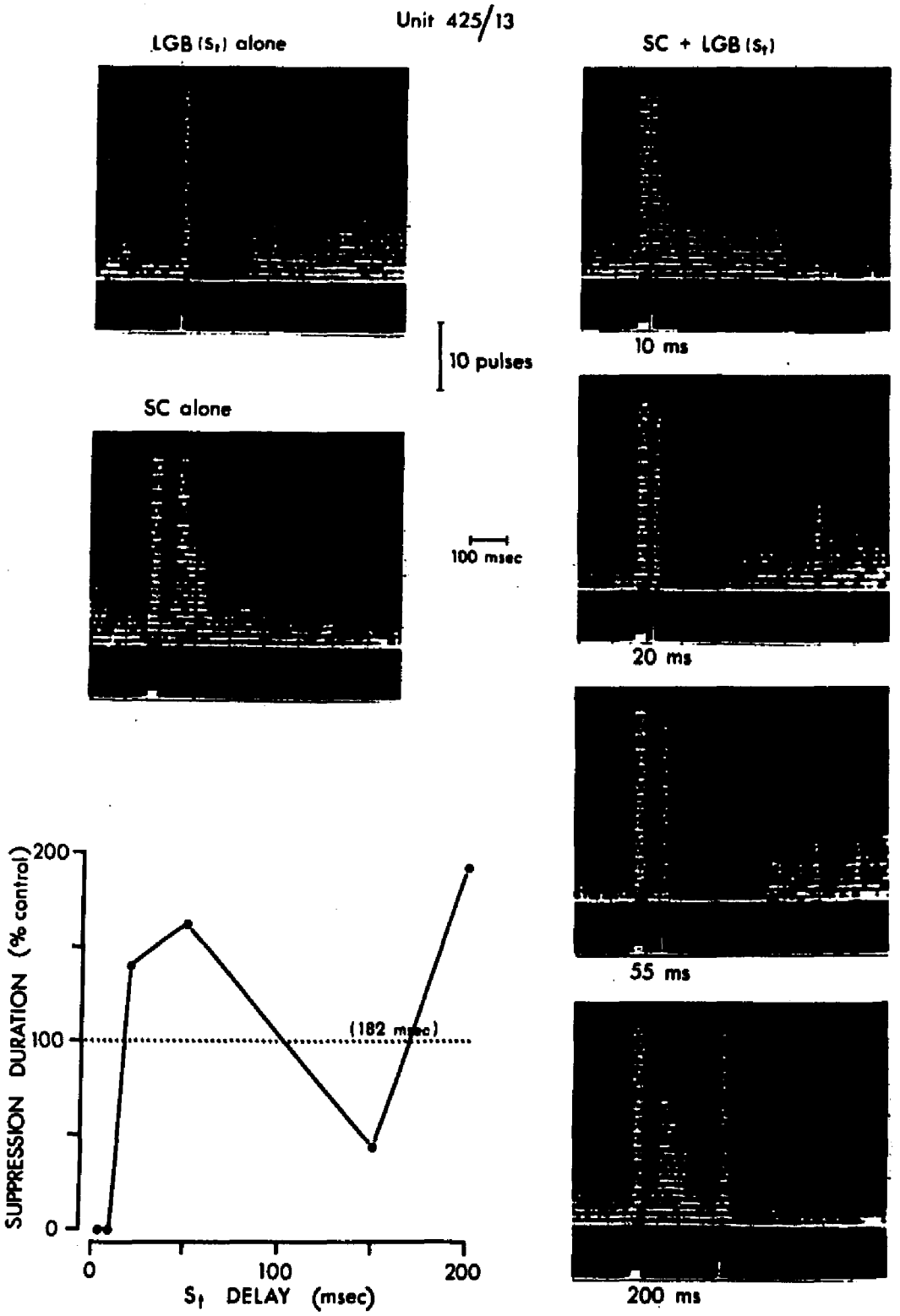
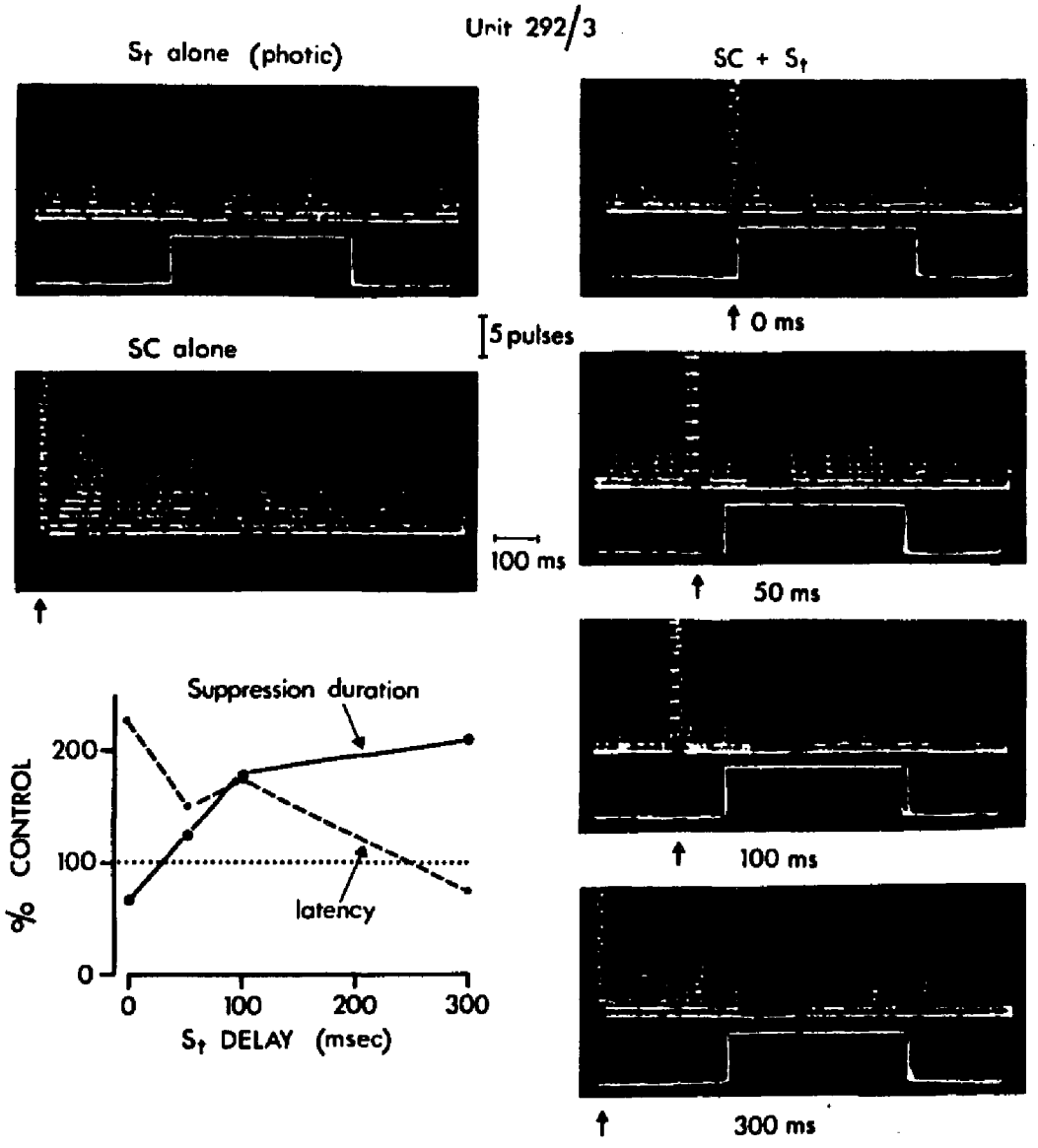

Unit 425/13
LGB (S_1) alone
SC + LGB (S_1)
10 pulses
10 ms
SC alone
100 msec
20 ms
55 ms
200 ms
SUPPRESSION DURATION (% control)
200
100
0
(182 msec)
0
100
200
S_1 DELAY (msec)

fig. 23. Influence of collicular (SC) conditioning on spike suppression (and its latency) elicited by a photic stimulus. The arrows beneath the oscilloscope tracings indicate the end of the SC train, while the on- and offset of the photic stimulus are depicted in the square waves on the tracings.


Unit 292/3
S_t alone (photic)
SC + S_t
5 pulses
0 ms
SC alone
100 ms
50 ms
Suppression duration
200
100
0
% CONTROL
latency
0
100
200
300
S_t DELAY (msec)
100 ms
300 ms

the onset and cessation of illumination (which lasted 450 msec). These periods of suppression to light alone might not have been identified as such had the effect of SC conditioning, where the suppression became prominent, not been examined. Suppression to the photic flash occurred with a minimum latency of 30 msec. A reciprocal relation was obtained between the duration of suppression and its onset latency (same Fig.). The afterdischarge was not really discernible after the photic stimulus, nor was it made more manifest by the SC conditioning.

APPENDIX B

TABLE I

LGB ALONE

Cat/Unit	A-P/L*	Depth	Probable Locus	% Halothane	Suppression Duration (msec)
271/1	A3/L3	17.0d*	M*	0.5	60
271/2	A3/L3	17.2d	M	0.5	50
274/1	A3/L2.5	1.3d	C	0.5	185
274/2	A3/L2.5	2.2d	C	0.5	162
274/4	A2/L2.5	4.0d	WM	0.5	100
275/1	A4/L2.5	2.0d	C	0.5	25
275/2	A4/L2.5	2.2d	C	0.5	47
275/3	A4/L2.5	1.2d	C	0.5	60
275/6	A4/L2.5	17.0d	M	0.5	0
281/1	A4/L3	3.1d	WM	0.8	0
281/2	A4/L3	5.3d	WM	0.8	0
281/4	A4/L3	2.8d	WM	0.8	100
287/1	A3/L2.5	13.0d	M	0.75	7
294/1	A3/L2.5	2.4d	C	0.5	155
296/1	A3/L2	1.6d	C	0.33	183
296/2	A3/L2	1.6d	C	0.33	55
296/3	A3/L2	2.7d	C	0.33	140
302a/1	A3/L2.5	——	—	—	175
302a/2	A3/L2.5	3.0d	WM	—	212
315/1	A1/L2.5	5.7d	WM	0.8	80
315/2	A2/L2.5	15.7p	M	0.8	90
315/3	A2/L2.5	1.5p	C	0.8	155
315/4	A2/L2.5	0.65p	C	0.8	160
315/5	A2/L2.5	0.63p	C	0.8	233
316/1	A4.5/L2	3.25p	C	1.0	175
316/3	A4.5/L2	12.7p	M	1.0	105
316/4	A4.5/L2	1.59p	C	1.0	90
316/5	A4.5/L2	1.56p	C	1.0	215
316/6	A4.5/L2	1.50p	C	1.0	185
316/7	A2/L2.5	1.9p	C	1.0	0

* See legend following Table.

Cat/Unit	A-P/L	Depth	Probable Locus	% Halothane	Suppression Duration (msec)
316/8	A2/L2.5	9.0p	WM?	1.0	0
316/9	A2/L2.5	9.1p	WM	1.0	0
316/10	A2/L2.5	15.0p	M	1.0	0
316/12	A2/L2.5	4.7p	WM-C?	0	220
316/13	A2.5/L5	0.75p	C	0	200
319/1	A4.5/L2.5	3.3p	WM-C?	0	168
319/2	A4.5/L2.5	3.5p	WM-C?	0	218
319/3	A4.5/L2.5	3.6p	WM-C?	0	300
319/4	A4.5/L2.5	3.7p	WM-C?	0	160
320/1	A4.5/L2	2.2p	C	0	0
320/2	A4.5/L2	2.7p	C	0	113
320/3	A4.5/L2	14.8p	M	0	210
320/4	A4.5/L2	15.6p	M	0	0
328/1	A3.5/L2.5	2.2p	WM	0.4	0
328/2	A3.5/L2.5	4.0p	WM	0.4	0
328/3	A3.5/L2.5	15.3p	M	0.4	0
328/4	A3.5/L2.5	16.2p	M	0.4	70
328/5	A3.5/L2.5	1.45p	C	0.4	0
328/6	A3.5/L2.5	1.36p	C	0.4	0
328/7	A2.5/L2.5	3.75p	WM	0.4	0
328/8	A2.5/L2.5	3.62p	WM	0.4	0
328/9	A2.5/L2.5	3.53p	WM	0.4	20
331/1	A2/L3	5.31d	WM	0	150
331/2	A2/L3	1.35d	C	0	172
331/3	A2/L1.5	5.59d	C	0	115
333/1a	A4/L2	1.59p	C	0	180
333/1b	"	"	"	"	175
333/1c	"	"	"	1.0	154
333/1d	"	"	"	"	157
333/1e	"	"	"	0	178
333/2	A4/L2	1.47p	C	0	128
333/3	A4/L2	1.43p	C	0	150
335/1	A1/L3.5	1.31d	C	0	115
335/2	A1/L3.5	3.3d	WM	0	0

Cat/Unit	A-P/L	Depth	Probable Locus	% Halothane	Suppression Duration (msec)
335/3	A1/L3.5	3.5d	WM	0	230
335/4	A1/L3.5	4.9d	WM	0	118
335/5	A1/L3.5	2.64d	WM	0	0
335/6	A1/L3.5	2.64d	WM	0	0
335/7	A1/L3.5	2.58d	WM	0	150
335/8	A1/L2.5	1.53d	C	0	0
335/9	A1/L1.5	0.46d	C	0	155
335/10	A1/L1.5	2.27d	C	0	0
335/13	A4/L2.5	1.77d	C	0	0
423/1	A3/L1.5	3.55d	C	0.7	206
423/3	A3/L1.5	3.1d	C	0.7	188
423/4b	A3/L1.5	2.9d	C	0.7	233
425/1	A2.5/L1	1.68d	C	1.0	145
425/2	A2.5/L1	1.81d	C	1.0	103
425/4	A2.5/L1	1.25d	C	1.0	100
425/6	A2.5/L1	2.94d	C	0.5	260
425/7	A3.5/L2	2.62d	C	0.5	0
425/8	A3.5/L2	1.72d	C	0.5	190
425/9	A1.5/L2	1.33d	C	0.5	95
425/10	A1.5/L2	1.72d	C	0.5	250
425/11	A1.5/L2	2.07d	C	0.5	145
425/12b	A1.5/L2	2.87d	C	0.5	100
425/13	A1.5/L2	1.83d	C	0.5	182
		PHOTIC STIMULUS ALONE			
287/2	A3/L2.5	13.0d	M	0.75	50
292/3	A4/L1.5	2.0d	C	0	103
292/4	A4/L1.5	1.7d	C	0	70
290/3	A2.5/L2	12.0p	M	0.5	200

Legend:

A-P/L: A-P, anterior-posterior plane; L, laterality

Depth readings: d, below dura mater; p, pia mater

Probable locus: C, cortex; M, midbrain; WM, white matter below or adjacent to cortex

TABLE II

Suppression Duration (msec) as a Function of LGB Intensity

	Voltage*														
Cat/Unit	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15
274/1					135		185								
333/1e				30	115	115	140		195	160	205				
335/4						50		118		135					
423/1	80	170		195	180	190		210							
423/3	125	105		160		145		175							
423/4	0	120		195		120		215		225					
425/4										0			60		100
425/7							0		25		45				
425/8							130		190		240		205		
425/12					0		200		190		255		220		
425/13					120		182		135		270				
271/1			0			60				65	-Midbrain unit				
425/1 -negative instance (unorthodox gross response as well)							30		78		0		145		100

* Values of stimulus intensity presented in quasi-random fashion except in Units 333/1e and 425/4 where they were administered in rank order.

TABLE III

LGB CONDITIONING

Suppression Duration in Percent of Control (LGB alone)

			Interstimulus Interval (msec)							
Cat/Unit	R or S	LGB alone (msec)	0-10	20-40	50-75	100-125	150-175	200-250	300	400
274/1	S	185			41	57				
274/2	R	162			80	43		65	83	68
275/2	R	47			96	43		0		
281/4	S	100			110	60	25	25		
296/3	R	140	136	111		76	81	89		
315/3	R	155	148	135		81	39			
315/5	R	233		109	107		67	59		
316/6	R	185		103			41			
333/1d	R	157		121	102	67		83		
333/1d-T*	S	157		127	102	67	70	88		
333/1e-T	R	178		112	70	59	42	59		
			—	—	—	—	—	—		
		Σ	284	818	708	553	365	468		
		$\bar{X}$	142.0	116.9	88.5	61.4	52.1	58.5		
		S.D.		9.9	22.1	12.5	19.0	29.6		

*T = Multiple conditioning shocks (train)

TABLE IV

MRF CONDITIONING: Positive Instances

Suppression Duration in Percent of Control (LGB alone)

		Interstimulus Interval (msec)*						
Cat/Unit	LGB alone (msec)	0-10	20-40	50-75	100-125	150-175	200-250	300
281/4	100		0	110	115	130		
296/3	140	18	114	161	164	150	154	143
315/3	155	16		0	100	126	148	
315/5	233	39				69	107	
316/4	90		67	211				
316/5	215		37		181			
316/6	185		65		103		122	
319/2	218	64		103		119		
320/2	113	53	53	119	146	177	128	
331/1	150	0	32		100	137		
331/2	172		58	0	90	116	81	
331/3	115	0	39		139	161	120	
333/1a	180	31	67		92	113	86	
333/1b	175	10	80	89	103	114	114	
333/1c	154		97	101	130	146	136	

* Order of presentation was quasi-random.

Cat/Unit	LGB alone (msec)	Interstimulus Interval (msec) 0-10	20-40	50-75	100-125	150-175	200-250	300
333/2	128	35		141		141		
333/3	150		87			117		
423/1	206	0	95	87		117	107	
423/3	188	0		157		141	120	
423/4	233	43	105	116		106	103	
425/12a	218 @13V	0	0	108		128	117	
425/12b	100 @ 7V	0	0	150		175	225	
	Σ	309	996	1653	1463	2483	1868	
	$\bar{X}$	20.6	58.6	110.2	121.9	130.7	124.5	
	S.D.	21.3	35.4	53.5	28.6	24.8	33.0	

Additional positive instances with control (LGB alone) at 0 msec*:

281/2	0			40	75			
320/1	0		0				170	
328/1	0	0		0	183		160	
328/6	0		0	0	210			

* Percent of control unobtainable, therefore suppression values given in msec.

TABLE V

MRF CONDITIONING: Dubious Instances

Suppression Duration in Percent of Control (LGB alone)*

Cat/Unit	LGB alone (msec)	Interstimulus Interval (msec) 0-10	20-40	50-75	100-125	150-175	200-250	Comments
302a/1	175		57		97			- greater than 100 msec train to MRF and
302a/2	212		80		97			longer intervals not sampled
315/1b	80		44		131		113	- ambient illumination differed for control and experimental conditions
333/1a	178	51		98	98	107	87	
423/4	125	0	208		176	136	0	- reversal of effect at longest interval
335/2	0					125	0	- " " " " " "
335/5	0		0	75	220	0		- " " " " " "
335/8	0		0	0	0	55	0	- " " " " " "

Histological verification disclosed that the electrode tip (used for the test shock) was actually located in the reticular nucleus of the thalamus for the last three units, 335/2, 335/5, and 335/8.

* Where control value at 0 msec, suppression values given in msec as well (since percentages unobtainable).

TABLE VI

MRF CONDITIONING: Negative Instances

Suppression Duration in Percent of Control (LGB alone)*

		Interstimulus Interval (msec)							
Cat/Unit	LGB alone (msec)	0-10	20-40	50-75	100-125	150-175	200-250	300	Comments
319/1	168	103		101	104		95	104	- MRF ineffective: control level throughout
328/7	0		0		0	0			- " " " " "
328/8	0		0		0	0			- " " " " "
315/1a	83	96	24		90		88		- " " " " " with one exception
275/2	45			11	11		33		- decreased suppression throughout
328/9	20	0		0	0	0			- " " "
425/2	103	0					0		- " " "

* Where control value at 0 msec, suppression values given in msec (since percentages unobtainable).

TABLE VII

MRF CONDITIONING: EFFECTS OF HALOTHANE

With Halothane: Suppression Duration in Percent of Control (LGB alone)

Cat/Unit	LGB alone (msec)	Interstimulus Interval (msec) 0-10	20-40	50-75	100-125	150-175	200-250	300	% Halothane
296/3	140	18	114	161	164	150	154	143	0.33
315/3	155	16		0	100	126	148		0.8
315/5	233	39				69	107		0.8
316/4	90		67	211					1.0
316/5	215		37		181				1.0
316/6	185		65		103		122		1.0
333/1c	154		97	101	130	146	136		1.0
423/1	206	0	95	87		117	107		0.7
423/3	188	0		157		141	120		0.7
423/4	233	43	105	116		106	103		0.7
425/12a	218 @ 13V	0	0	108		128	117		0.5
425/12b	100 @ 7V	0	0	150		175	225		0.5
	Σ	116	580	1091	678	1158	1339		
	$\bar{X}$	14.5	64.4	121.2	135.6	128.7	133.9		
	S.D.	16.8	41.0	56.1	32.3	28.3	34.5		

No Halothane:

Cat/Unit	LGB alone (msec)	Interstimulus Interval (msec) 0-10	20-40	50-75	100-125	150-175	200-250	300
320/2	113	53	53	119	146	177	128	
331/1	150	0	32		100	137		
331/2	172		58	0	90	116	81	
331/3	115	0	39		139	161	120	
333/1a	180	31	67		92	113	86	
333/1b	175	0	80	89	103	114	114	
333/2	128	35		141		141		
333/3	150		87			117		
Σ		119	416	349	670	1076	529	
$\bar{X}$		19.8	59.4	87.3	111.7	134.5	105.8	
S.D.		21.0	18.8	53.6	22.2	22.6	18.8	

TABLE VIII

MRF INTENSITY

Suppression Duration in Percent of Control (LGB alone)

Cat/Unit	LGB alone (msec)	MRF Intensity (in volts)* 1.5	2.0	3.0	4.0	5.0	6.0	8.0	MRF-St Interval (msec)
331/1	150		0		32		0	0	40
331/2	172	116	110	93	58	44	61		45
333/2	128		137		141		86		50
423/1	203	128	118		74		128		55
423/3	188	141			157		162		65
423/4	233	107	127		116	116	105		55
425/12 b	100 @ 7V	125	195		150		55		50
425/12 a	218 @13V	71	78		108		57	0	50

*administered in quasi-random order except for Unit 331/2

TABLE VIII a

MRF INTENSITY

Afterdischarge Peak Latency (APL) in msec.

Cat/Unit	LGB alone	MRF Intensity (in volts) 1.5	2.0	3.0	4.0	5.0	6.0	8.0	% Halo.
331/1	230		195		175		130	120	0
331/2	310	335	340	345	300	235	225		0
333/2									0
423/1	250	300	295		325		325		0.7
423/3	313	325			355		360		0.7
423/4b	285	280	375		305	310	360		0.7
425/12b	250	350	295		340		340		0.5
425/12a	346	475	400		450		375	310	0.5

TABLE IX

ADDITIONAL OBSERVATIONS

MRF CONDITIONING: DUAL LGB SHOCKS

Suppression Duration in Percent of Control (LGB alone)

Cat/Unit	LGB alone (msec)	S_t Delay (msec) 0-10	20-40	50-75	100-125	150-175	200-250
296/3	140	64	64	121	127	124	Long latency to suppression
315/3	155		48 & 0		116	106	
316/6	185		68			116	

For all 3 units, suppression after the first LGB shock was reduced.

SINGLE MRF CONDITIONING SHOCK + SINGLE LGB TEST SHOCK

423/1	206	112 (replicated)				124	126

10-MIN MRF CONDITIONING AT 3 Hz

423/3	188	125						
		125:	recorded	3 min.	later	without	MRF	conditioning
		128:	"	"	"	"	"	"
		104:	"	"	"	"	"	"

TABLE IX (Continued)

Suppression Duration in Percent of Control (LGB alone)

SC CONDITIONING: LGB TEST SHOCK

Cat/Unit	LGB alone (msec)	S_t Delay (msec) 0-10	20-40	50-75	100-125	150-175	200-250	300
294/1	155			148		194		
425/13	182	0	140	162		44	192	

SC CONDITIONING: PHOTIC TEST STIMULUS

292/3	103 -onset	53		102&194	146			170
"	125 -offset	60		32 100	88			136
292/4	70 -onset				193			

MRF CONDITIONING: MIDBRAIN RECORDING*

275/6	No response			0+	0+		
287/1	7	0		63	0		
315/2	90				43		70
316/3	105		20	0+	0	120 - long-latency supp.	
316/10	0		0+		175		
320/4	0	10			35	35	13
328/3	0					210 - drastic supp. of activity in general	

* Suppression duration in msec.

TABLE X

SAMPLES OF AFTERDISCHARGE PEAK LATENCY MEASURES FOR SEVERAL CONDITIONS IN MSEC

Cat/Unit	LGB alone	% Halo.	LGB INTENSITY (in volts) 1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0
333/1e		0				140			200		250	265	280		
423/4		0.7	170	225		275		280		290		270			
425/12		0.5					0(140)		250		325		285		346

			LGB CONDITIONING: S_t Delay (in msec) 0-10	20-40	50-75	100-125	150-175	200-250	300
333/1d	237	1.0		240	240	195		250	
333/1d-T	237	1.0		250	210	200	170	210	
333/1e-T	220	0		250	220	190	150	175	
			MRF CONDITIONING						
320/2	245	0	175	135	225	275	260	340	
331/1	230	0	160	175		275	205		
331/2	310	0		270	260	260 300		345	
333/1a	298	0	140	170		250	270	255	
333/1c	238	1.0		275	260	225	235	240	
423/3	313	0.7	0		355		325	310	
423/4b	276	0.7	325	325	305		278	255	
425/12a	346	0.5	50	310	450		420	335	
425/12b	250	0.5	40	0	340		370	360	

BIBLIOGRAPHY

Akimoto, H., Saito, Y., and Nakamura, Y. Effects of arousal stimuli on evoked neuronal activities in cat's visual cortex. In: The Visual System: Neurophysiology and Psychophysics, R. Jung and H. Kornhuber (Eds.). Berlin-Göttingen-Heidelberg: Springer-Verlag, 1961, 363-374.

Alter, I. and Battersby, W.S. Temporal dispersion of unit discharges in visual cortex due to MRF-LGB interaction. The Physiologist, 1973, 16(3). (Abstract)

Amassian, V.E. Microelectrode studies of the cerebral cortex. Int. Rev. Neurobiol., 1961, 3, 67-136.

Amassian, V.E. and DeVito, R.V. Unit activity in reticular formation and nearby structures. J. Neurophysiol., 1954, 17, 575-603.

Balagura, S. and Ralph, T. The analgesic effect of electrical stimulation of the diencephalon and mesencephalon. Brain Res., 1973, 60, 369-379.

Bartlett, J.R. and Doty, R.W. Influence of mesencephalic stimulation on unit activity in striate cortex of squirrel monkeys. J. Neurophysiol., 1974, 37, 642-652.

Békésy, G. von. Sensory Inhibition. Princeton, N.J.: Princeton Univ. Press, 1967.

Bell, C., Sierra, G., Buendia, N., and Segundo, J.P. Sensory properties of neurons in the mesencephalic reticular formation. J. Neurophysiol., 1964, 27, 961-987.

Benevento, L.A., Creutzfeldt, O.D., and Kuhnt, U. Significance of intracortical inhibition in the visual cortex. Nature new Biol., 1972, 238, 124-126.

Bowsher, D. Reticular projections to lateral geniculate in cat. Brain Res., 1970, 23, 247-249.

Bradley, P.B. (See Evarts, 1961)

Bremer, F. Neurophysiological mechanisms in cerebral arousal. In: The Nature of Sleep. CIBA Found. Symp., G.E.W. Wolstenholme and M. O'Connor (Eds.). Boston: Little, Brown & Co., 1961a, pp. 30-50.

Bremer, F. Neurogenic factors influencing the evoked potentials of the cerebral cortex. In: Sensory Communication, W.A. Rosenblith (Ed.). Cambridge, Mass.: M.I.T. Press, 1961, 675-698.

Bremer,F. and Stoupel, N. De le modification des réponses sensorielles corticales dans l'éveil réticulaire. Acta Neurol. Psychiat. Belg., 1958, 58, 401-403.

Brooks, B. and Jung, R. Neuronal physiology of the visual cortex. In: Visual Centers in the Brain. Handbook of Sensory Physiology, Vol. VII/3B, R. Jung (Ed.). Berlin-Heidelberg- New York: Springer-Verlag, 1973, 325-440.

Brown, T.S. and Marco, L.A. Effects of stimulation of the superior colliculus and lateral thalamus on visual evoked potentials. EEG clin. Neurophysiol., 1967, 22, 150-158.

Burns, B.D. The Uncertain Nervous System. London: Edward Arnold, 1968.

Campbell, F.W. The transmission of spatial information through the visual system. In: The Neurosciences: Third Study Program, F.O. Schmitt and F.G. Worden (Eds.). Cambridge, Mass. and London: M.I.T. Press, 1974, 95-103.

Chalupa, L.M., Battersby, W.S., and Frumkes, T.E. Some subcortical determinants of visual cortical excitability in the cat. Inter. J. Neurosci., 1973, 5, 1-13.

Colonnier, M.L. The structural design of the neocortex. In: Brain and Conscious Experience, J.C. Eccles (Ed.). New York: Springer-Verlag, 1966, 1-23.

Creutzfeldt, O.D., Fuster, J.M., Herz, A., and Straschill, M. Some problems of information transmission in the visual system. In: Brain and Conscious Experience, J.C. Eccles (Ed.). New York: Springer-Verlag, 1966, 138-164.

Creutzfeldt, O. and Jung, R. Neuronal discharge in the cat's motor cortex during sleep and arousal. In: The Nature of Sleep. CIBA Found. Symp., G.E.W. Wolstenholme and M. O'Connor (Eds.). Boston: Little, Brown & Co., 1961, 131-170.

Creutzfeldt, O.D. and Kuhnt, U. Electrophysiology and topographical distribution of visual evoked potentials in animals. In: Visual Centers in the Brain. Handbook of Sensory Physiology, Vol. VII/3B, R. Jung (Ed.). Berlin-Heidelberg-New York: Springer-Verlag, 1973, 595-646.

Creutzfeldt, O.D., Rosina, A., Ito, M., and Probst, W. Visual evoked response of single cells and of the EEG in primary visual area of the cat. J. Neurophysiol., 1969, 32, 127-139.

Creutzfeldt, O., Spehlmann, R., and Lehmann, D. Veränderung der Neuronaktivität der visuellen Cortex durch Reizung der Substantia reticularis mesencephali. In: The Visual System: Neurophysiology and Psychophysics, R. Jung and H. Kornhuber (Eds.). Berlin-Göttingen-Heidelberg: Springer-Verlag, 1961, 351-363.

Curtis, D.R. (See McIlwain, 1972)

Demetrescu, M., Demetrescu, M., and Iosif, G. The tonic control of cortical responsiveness by inhibitory and facilitatory diffuse influences. EEG clin. Neurophysiol., 1965, 18, 1-24.

Dumont, S. and Dell, P. Facilitation réticulaire des mécanismes visuels corticaux. EEG clin. Neurophysiol., 1960, 12, 769-796.

Evarts, E.V. Effects of sleep and waking on activity of single units in the unrestrained cat. In: The Nature of Sleep. CIBA Found. Symp., G.E.W. Wolstenholme and M. O'Connor (Eds.). Boston: Little, Brown & Co., 1961, 171-187.

Evarts, E.V. Photically evoked responses in visual cortex units during sleep and waking. J. Neurophysiol., 1963, 26, 229-248.

Fessard, A. The role of neuronal networks in sensory communications within the brain. In: Sensory Communication, W.A. Rosenblith (Ed.). Cambridge, Mass.: M.I.T. Press, 1961, 585-606.

Fifková, E. and Maršala, J. Stereotaxic atlas for the cat. In: Electrophysiological Methods in Biological Research, 3rd. rev. ed., J. Bureš, M. Petrán, and J. Zachar (Eds.). New York: Academic Press, 1967, Appendix 1.

Fukuda, Y. and Stone, J. Retinal distribution and central projections of Y-, X-, and W-cells of the cat's retina. J. Neurophysiol., 1974, 37, 749-772.

Fuster, J.M. Effects of stimulation of brain stem on tachistoscopic perception. Science, 1958, 127, 150.

Fuster, J.M. Excitation and inhibition of neuronal firing in visual cortex by reticular stimulation. Science, 1961, 133, 2011-2012.

Fuster, J.M. and Docter, R.F. Variations of optic evoked potentials as a function of reticular activity in rabbits with chronically implanted electrodes. J. Neurophysiol., 1962, 25, 324-336.

Fuster, J.M. and Uyeda, A.A. Facilitation of tachistoscopic performance by stimulation of midbrain tegmental points in the monkey. Exp. Neurol., 1962, 6, 384-406.

Garey, L.J. and Powell, T.P.S. An experimental study of the termination of the lateral geniculo-cortical pathway in the cat and monkey. Proc. roy. Soc. B, 1971, 179, 41-63.

Gerstein, G.L. (see Perkel and Bullock, 1969)

Gray, E.G. Axo-somatic and axo-dendritic synapses of the cerebral cortex: An electron-microscopic study. J. Anat., 1959, 93, 420-433.

Grundfest, H. The interpretation of electrocortical potentials. In: Pavlovian Conference on Higher Nervous Activity, N.S. Kline (Ed.). Ann. N.Y. Acad. Sci., 1961, 92 (3), 877-889.

Henry, G.H. and Bishop, P.O. Simple cells of the striate cortex. In: Contributions to Sensory Physiology, Vol. 5, W.D. Neff (Ed.). New York: Academic Press, 1971, 1-46.

Hess, R., Negishi, K., and Creutzfeldt, O. The horizontal spread of intracortical inhibition in the visual cortex. Exp. Brain Res., 1975, 22, 415-419.

Hubel, D.H. and Wiesel, T.N. Receptive fields and functional architecture in two nonstriate visual areas (18 and 19) of the cat. J. Neurophysiol., 1965, 28, 229-289.

Ingle, D. and Sprague, J.M. Sensorimotor function of the midbrain tectum. Neurosci. Res. Prog. Bull., 1975, 13, 167-288.

Jasper, H.H. Implications for the neurological sciences. In: Electrical Stimulation of the Brain, D.E. Sheer (Ed.). Austin: Univ. of Texas Press, 1961, 557-562.

Jasper, H.H. Brain mechanisms and states of consciousness. In: Brain and Conscious Experience, J.C. Eccles (Ed.). New York: Springer-Verlag, 1966, 256-282.

Jasper, H.H. and Ajmone-Marsan, C. A Stereotaxic Atlas of the Diencephalon of the Cat. Ottawa: Nat. Res. Council of Canada, 1954.

Jones, E.G. and Powell, T.P.S. Anatomical organization of the somatosensory cortex. In: Somatosensory System. Handbook of Sensory Physiology, Vol. II, A. Iggo (Ed.). Berlin-Heidelberg-New York: Springer-Verlag, 1973, 579-620.

Jung, R. Neuronal integration in the visual cortex and its significance for visual information. In: Sensory Communication, W.A. Rosenblith (Ed.). Cambridge, Mass.: M.I.T. Press, 1961, 627-674.

Klüver, H. and Barrera, E. A method for the combined staining of cells and fibers in the nervous system. J. Neuropath. exp. Neurol., 1953, 12, 400-403.

Kuhnt, U. and Creutzfeldt, O.D. Decreased post-synaptic inhibition in the visual cortex during flicker stimulation. EEG clin. Neurophysiol., 1971, 30, 79-82.

Li, C.L. The inhibitory effect of stimulation of a thalamic nucleus on neuronal activity in the motor cortex. J. Physiol., 1956, 133, 40-53.

Li, C.L. Cortical intracellular synaptic potentials. J. cell. comp. Physiol., 1961, 58, 153-168.

Li, C.L. Cortical intracellular synaptic potentials in response to thalamic stimulation. J. cell. comp. Physiol., 1963, 61, 165-179.

Li, C.L. and Chou, S.N. Cortical intracellular synaptic potentials and direct cortical stimulation. J. cell. comp. Physiol., 1962, 60, 1-16.

Li, C.L., Ortiz-Galvin, A., Chou, S.N., and Howard, S.Y. Cortical intracellular potentials in response to stimulation of lateral geniculate body. J. Neurophysiol., 1960, 23, 592-601.

Libet, B., Alberts, W.W., Wright, E.W. Jr., and Feinstein, B. Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. Science, 1967, 158, 1597-1600.

Lindsley, D.B. The reticular system and perceptual discrimination. In: Reticular Formation of the Brain, H.H. Jasper (Ed.). Boston: Little, Brown,& Co., 1958, 423-434.

Lindsley, D.B. The reticular activating system and perceptual integration. In: Electrical Stimulation of the Brain, D.E. Sheer (Ed.). Austin: Univ. of Texas Press, 1961, 331-349.

MacKay, D.M. Evoked brain potentials as indicators of sensory information processing. Neurosci. Res. Prog. Bull., 1969, 7(3), 181-276.

MacKay, D.M. and Jeffreys, D.A. Visually evoked potentials and visual perception in man. In: Visual Centers in the Brain. Handbook of Sensory Physiology, Vol. VII/3B, R. Jung (Ed.). Berlin-Heidelberg-New York: Springer-Verlag, 1973, 647-678.

Mayer, D.J., Wolfle, T.L., Akil, H., Carder, B., and Liebeskind, J.C. Analgesia from electrical stimulation in the brainstem of the rat. Science, 1971, 174, 1351-1354.

McIlwain, J.T. Nonretinal influences on the lateral geniculate nucleus. Inves. Ophthalmol., 1972, 11(5), 311-322.

McLennan, H. Inhibitions of long duration in the cerebral cortex. A quantitative difference between excitatory amino acids. Exp. Brain Res., 1970, 10, 417-426.

Melzack, R. The Puzzle of Pain. Great Britain: Penguin Books, 1973.

Meulders, M. and Godfraind, J.M. Influence du réveil d'origine réticulaire sur l'étendue des champs visuels des neurones de la région genouillée chez le chat avec cerveau intact ou avec cerveau isolé. Exp. Brain Res., 1969, 9, 201-220.

Moruzzi, G. and Magoun, H.W. Brain stem reticular formation and activation of the EEG. EEG clin. Neurophysiol., 1949, 1, 455-473.

Narikashvili, S.P., Arutyunov, V.S., and Moniava, E.S. Influence of reticular impulses on unit activity in the visual cortex. Zh. vyssh. nerv. Deyat., 1965, 15, 1004-1013. (Russ.)

Narikashvili, S.P., Moniava, E.S., and Arutyunov, V.S. Mechanism of the influence of the reticular formation on cortical neurons. Fiziol. Zh. SSSR im. I.M. Sechenova, 1966, 52, 660- . (Russ.)

Orem, J. and Feeney, D.M. Reciprocal reticular influences on cells in rostral and caudal visual cortex of the cat. Brain Res., 1971, 30, 200-203.

Otsuka, R. and Hassler, R. Über Aufbau und Gliederung der corticalen Sehsphäre bei der Katze. Arch. Psychiat. Nervenkr., 1962, 203, 212-234.

Perkel, D.H. and Bullock, T.H. Neural coding. In: Neurosciences Research Symposium Summaries, Vol. 3, F.O. Schmitt, T. Melnechuk, G.C. Quarton, and G. Adelman (Eds.). Cambridge, Mass. and London: M.I.T. Press, 1969, 405-527.

Pettigrew, J.D. and Daniels, J.D. Gamma-aminobutyric acid antagonism in visual cortex: different effects on simple, complex, and hypercomplex neurons. Science, 1973, 182, 81-83.

Polyanskii, V.B. Cycles of excitability in neurons of visual cortex in waking rabbits in response to double flashes. Zh. vyssh. nerv. Deyat. im. I.P. Pavlova, 1967, 17, 714-721. (Russ.)

Ramón-Moliner, E. and Nauta, W.J.H. The isodendritic core of the brain stem. J. comp. Neurol., 1966, 126, 311-336.

Ratliff, F. Contour and contrast. Scientific American, 1972, 226, 91-101.

Reynolds, D.V. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science, 1969, 164, 444-445.

Riggs, L.A. Vision. In: Woodworth and Schlosberg's Experimental Psychology, 3rd ed., J.W. Kling and L.A. Riggs (Eds.). New York: Holt, Rinehart and Winston, 1971, 273-314.

Robertson, A.D.J. Anaesthesia and receptive fields. Nature, 1965, 205, 80.

Satinsky, D. Reticular influences on lateral geniculate neuron activity. EEG clin. Neurophysiol., 1968, 25, 543-549.

Scheibel, M.E. and Scheibel, A.B. The organization of the nucleus reticularis thalami: a Golgi study. Brain Res., 1966, 1, 43-62.

Scheibel, M.E. and Scheibel, A.B. Structural organization of non-specific thalamic nuclei and their projection toward cortex. Brain Res., 1967a, 6, 60-94.

Scheibel, M.E. and Scheibel, A.B. Anatomical basis of attention mechanisms in vertebrate brains. In: The Neurosciences: A Study Program, G.C. Quarton, T. Melnechuk, and F.O. Schmitt (Eds). New York: The Rockefeller Univ. Press, 1967b, 577-602.

Scheibel, M.E. and Scheibel, A.B. The anatomy of constancy. In: Tonic Functions of Sensory Systems, B.M. Wenzel and H.P. Ziegler (Eds.). Ann. N.Y. Acad. Sci., 1977, 290, 421-435.

Schlag, J. and Waszak, M. Characteristics of unit responses in nucleus reticularis thalami. Brain Res., 1970, 21, 286-288.

Schlag, J. and Waszak, M. Electrophysiological properties of units of the thalamic reticular complex. Exp. Neurol., 1971, 32, 79-97.

Singer, W. and Dräger, U. Postsynaptic potentials in relay neurons of cat LGB after stimulation of MRF. Brain Res., 1972, 41, 214-220.

Skinner, J.E. and Yingling, C.D. Regulation of slow potential shifts in nucleus reticularis thalami by the mesencephalic reticular formation and the frontal granular cortex. EEG clin. Neurophysiol., 1976, 401, 288-296.

Skrebitsky, V.G. Nonspecific influences on neuronal firing in the central visual pathway. Exp. Brain Res., 1969, 9, 269-283.

Steriade, M. Ascending control of thalamic and cortical responsiveness. Int. Rev. Neurobiol., 1970, 12, 87-144.

Sterman, M.B. and Fairchild, M.D. Modification of locomotor performance by reticular formation and basal forebrain stimulation in the cat: evidence for reciprocal systems. Brain Res., 1966, 2, 205-217.

Stone, J. Morphology and physiology of the geniculocortical synapse in the cat: the question of parallel input to the striate cortex. Inves. Ophthalmol., 1972, 11, 338-346.

Szentágothai, J. Synaptology of the visual cortex. In: Visual Centers in the Brain. Handbook of Sensory Physiology, Vol. VII/3B, R. Jung (Ed.). Berlin-Heidelberg-New York: Springer-Verlag, 1973, 270-324.

Taber, E. The cytoarchitecture of the brain stem of the cat. I. Brain stem nuclei. J. comp. Neurol., 1961, 116, 27-69.

Tasaki, I., Polley, E.G., and Orrego, F. Action potentials from individual elements in cat geniculate and striate cortex. J. Neurophysiol., 1954, 17, 454-474.

Tatton, W.G. and Crapper, D.R. Central tegmental alteration of cat lateral geniculate activity. Brain Res., 1972, 47, 371-387.

Towe, A.L. and Harding, G.W. Extracellular microelectrode sampling bias. Exp. Neurol., 1970, 29, 366-381.

Toyama, K. and Matsunami, K. Synaptic action of specific visual impulses upon cat's parastriate cortex. Brain Res., 1968, 10, 473-476.

Toyama, K., Matsunami, K., Ohno, T., and Tokashiki, S. An intracellular study of neuronal organization in the visual cortex. Exp. Brain Res., 1974, 21, 45-66.

Uchizono, K. Characteristics of excitatory and inhibitory synapses in the central nervous system of the cat. Nature, 1965, 207, 642-643.

Valenstein, E.S. Biology of drives. In: Neurosciences Research Symposium Summaries, Vol. 3, F.O. Schmitt, T. Melnechuk, G.C. Quarton, and G. Adelman (Eds.). Cambridge, Mass. and London: M.I.T. Press, 1969, 1-107.

Velyka, R.R. Role of mesencephalic reticular formation in organization of cortical neuronal activity during specific stimulation. Fiziol. Zh., 1966, 12, 795- . (Russ.)

Verzeano, M. (see Evarts, 1961)

Wagman, I.H. and Battersby, W.S. Neural limitations of visual excitability. V. Cerebral afteractivity evoked by photic stimulation. Vision Res., 1964, 4, 193-208.

Waszak, M. Effects of barbiturate anaesthesia on discharge pattern in nucleus reticularis thalami. Pharmacol. Biochem. Behav., 1974, 2, 339-345.

Watanabe, S., Konishi, M., and Creutzfeldt, O.D. Postsynaptic potentials in the cat's visual cortex following electrical stimulation of afferent pathways. Exp. Brain Res., 1966, 1, 272-283.

Woolsey, C.N. Comparative studies on cortical representation of vision. Vision Res., Supp. No. 3, 1971, 365-382.

Yingling, C.D. and Skinner, J.E. Regulation of unit activity in nucleus reticularis thalami by the mesencephalic reticular formation and the frontal granular cortex. EEG clin. Neurophysiol., 1975, 39, 635-642.