RESPONSE PROPERTIES OF SINGLE NEURONS IN A NONSPECIFIC POLYSENSORY AREA OF THE CEREBRAL CORTEX OF THE RAT

By

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INTRODUCTION

The purpose of this research was to examine by means of extracellular microelectrode recording the response characteristics of single neurons in nonspecific polysensory areas of the cerebral cortex of the rat. Cortical areas from which potentials could be evoked by many different types of stimuli were first found in the cat (Amassian, 1954; Buser and Heinze, 1954; Albe-Fessard and Rougeul, 1955), and there is now an extensive literature dealing with this subject. Although there has been relatively little work done on other species besides the cat, nonspecific or polysensory evoked responses have also been recorded in the cerebral cortex of the rabbit (Shimazono, 1963) and that of the monkey (Albe-Fessard, Rocha-Miranda, and Oswaldo-Cruz, 1959; Bignall and Imbert, 1966). In the case of the rat, detailed characteristics of polysensory responses have been described and their distribution in the cortex has been mapped (Bliss and Petrinovich, 1964).

The interest in gross evoked responses recorded from polysensory areas has been accompanied by an interest in the response characteristics of the individual neural elements within these cortical areas. The first report of a polysensory area in the cat cortex (Amassian, 1954) included some observations on the activity of single cells in the same region. There have now been a number of microelectrode studies of neurons in polysensory areas of the cat cortex, as will be discussed more fully below. Again, there is little or no work on other species besides the cat. So far as is known to the present writer, no data from microelectrode recording in the polysensory areas of the rat cortex have been published.

The present research was therefore undertaken in the attempt to provide information about single unit responses in the polysensory areas of the rat cortex. Besides adding to the sample of species from which single cell activity in polysensory regions has been recorded, it was hoped that further information about the function of polysensory cortical areas in general might be obtained.

I. Terminology and definitions

There is a terminological difficulty which has arisen in the course of the work on nonspecific polysensory areas in the cat, and it concerns the name to be used in referring to these areas. By virtue of the fact that the polysensory areas lie outside the primary projection zones in the cat and the monkey, they lie within the areas classically referred to as "association cortex". The latter designation arose in the following way: The classical view of the organization of the cortical sensory projection areas was that of discrete, highly specific areas from which electrical responses to only one modality of sensory input could be elicited. Surrounding the specific projection areas (and the motor area) was cortex which appeared to be unresponsive to sensory stimulation. Because cortical areas from which no responses were evoked by peripheral stimuli were apparently devoted neither to sensory nor to motor functions, they seemed by default to represent the probable locus of action of the 'associative' or complex integrative functions of the brain (Flechsig, 1905; Buser, 1957). In the cat, the animal most widely used in electrophysiological recording, the non-primary or association areas occupy a large share of the total neocortical area. In the monkey the association

areas are even larger relative to the size of the specific sensory areas (Flechsig, 1905; Herrick, 1926). In lower mammals such as the rabbit and the rat, nearly the entire neocortex appears to be devoted to motor and specific sensory areas (Woolsey, 1952) leaving apparently very little cortex for associative purposes (Cajal, 1909). Thus the amount of association cortex appears to increase as the phylogenetic scale is ascended, a correlation which is compatible with the hypothesis that this type of cortex is devoted to 'higher' brain functions.

A somewhat different use of the term 'association' cortex or 'association' fibers or tracts arose from the work of the neuroanatomists, whose histological techniques demonstrated the existence of neural connections between the primary sensory zones and the cortical areas surrounding them (Cajal, 1909; Flechsig, 1905). Connections of this sort either in the cortex or at lower brain levels were termed 'associative' because they comprised structural associations between salient areas or nuclei and other topographically distinct areas or nuclei.

In the first report of polysensory responses evoked from a cortical area, Amassian (1954) chose to call the area a "somesthetic association area", because the area in question could be demonstrated electrophysiologically to have connections with the primary somesthetic cortex. Amassian called the responses evoked in the area by peripheral stimuli, "association positive responses". In later work on the same type of cortical response, other workers shortened the term to "association responses" (Thompson, Smith, and Bliss, 1963; Thompson and Shaw, 1964) or "associative responses" (Buser and Borenstein, 1957; Shimazono et al., 1963). The areas from which these polysensory responses were recorded were frequently referred to as

"association areas" (Bental and Bihari, 1963; Dubner and Rutledge, 1964) or "association response fields" (Thompson et al., 1963).

The use of the adjective "association" to designate electrophysiologically discrete sub-areas within the larger non-primary cortical domain can be the source of much confusion, for common usage is still to refer to all cortex outside of the primary areas as "association cortex" (Thompson, 1967). In the case of the primates (and to a lesser degree in cats), there are large areas of cortex which are not primary and which do not give "association responses". Another source of confusion is that the term "association" tends to presume functional characteristics which have not been demonstrated, (Buser and Bignall, 1957; Thompson, 1967). To avoid these difficulties, Buser and Bignall adopted the terms "non-primary areas" and "non-primary responses" in referring to all observations made outside the primary areas. Among the non-primary responses which they cite, "Type II" responses are equivalent to the "association responses" described above. The designation "non-primary" is not altogether adequate, however, for in the cat (and also, it will be shown, in the rat), the cortical areas from which "association responses" have been recorded overlap to some extent the primary motor cortex.

As will become evident in the following section, one of the main distinguishing characteristics of the so-called "association responses" is their nonspecific nature. Stimuli of different modalities can evoke maximal responses from one and the same cortical location. Another way of describing this property of responding, which is entirely different from the modality-specific properties of responses in the primary areas, is to call these nonspecific areas "polysensory". In the present paper,

therefore, responses of the type referred to above as "association responses" will be called simply, nonspecific or polysensory responses.

II. Nonspecific responses: Discovery and distinguishing characteristics

In the classical work on the cortical sensory projection areas, the elicitation of electrical responses to sensory stimulation was usually carried out under barbiturate anesthesia (Brazier, 1963; Mountcastle, 1968). It is now known that barbiturate anesthesia permits the evocation of the primary (shortest latency) electrical response from the specific sensory projection areas while tending to suppress responses of later occurrence (Adrian, 1941; Brazier, 1963). Further, there are some regions of the non-primary cortex which were thought to be unresponsive on the basis of observations made under barbiturate anesthesia, but from which electrical responses to peripheral sensory stimulation can in fact be elicited if barbiturate anesthesia is not used (Buser and Bignall, 1957). This fact was first discovered by Amassian (1954) while recording from the anterior lateral gyrus, a cortical area adjacent to the primary somatosensory projection area, using chloralose anesthesia. Amassian found that as little as 15 to 20 mg. I.V. of Nembutal was sufficient to abolish the nonspecific responses. Other workers, also using chloralose, found other responsive areas outside the classical primary areas (Buser and Heinze, 1954; Albe-Fessard, 1955; Thompson and Sindberg, 1960). Aside from their sensitivity to barbiturates, there are a number of characteristics which differentiate the responses of these non-primary areas from the responses of the primary, specific sensory areas.

(1) Perhaps their most significant characteristic is that they are nonspecific or polysensory. As was mentioned above, this refers to the ability of these response fields within the non-primary cortex to respond to diverse sensory stimuli. It has been shown that this convergence of input is heterotopic, in that different points on the body surface will elicit similar responses at a particular cortical locus, quite a different situation from that in primary somatic cortex where specific cortical points respond only to stimuli applied to specific body locations (Amassian, 1954; Buser and Borenstein, 1959; Albe-Fessard and Fessard, 1963). Even more striking, the convergence upon these non-primary areas is heterosensory, for entirely different sensory modalities can elicit well-marked evoked potentials (EPs) at one and the same point, again quite a different relationship from that which holds for the sensory-specific primary areas (Amassian, 1954; Albe-Fessard and Rougeul, 1955; Buser and Borenstein, 1959; Thompson and Sindberg, 1960).

(2) The nonspecific responses evoked at any given point by a stimulus of constant intensity are not reliable and consistent like the primary sensory EPs but instead are quite variable in waveform and amplitude (Amassian, 1954; Buser and Borenstein, 1959; Thompson and Shaw, 1964). Amassian (1954) reported three-fold changes in amplitude of the nonspecific responses, recorded under light chloralose with constant stimulus intensity, compared to around ten percent variability in primary response amplitudes recorded simultaneously to the same stimuli.

(3) Although it is possible to record nonspecific polysensory responses in unanesthetized cats (Buser and Borenstein, 1959; Albe-Fessard and Fessard, 1963; Shaw and Thompson, 1964), the responses are much smaller

in amplitude than when recorded under chloralose. Because of the problems of recording small electrical potentials from awake and active animals, and because of the amplitude variations mentioned above, there is great difficulty in distinguishing potentials evoked from the nonspecific cortical areas in unanesthetized preparations. The use of chloralose, because of its tendency to enhance activity of the central nervous system (Adrian, 1941; Albe-Fessard and Fessard, 1963), facilitates the recording of nonspecific responses. Some workers have concluded that chloralose anesthesia may be a necessity when very refined analysis of the nonspecific EPs is required (Denney and Thompson, 1967).

(4) In addition to their vulnerability to barbiturates, nonspecific EPs also show greater fragility than primary EPs under such deleterious influences as cooling and drying of the cortical surface or deteriorating physiological condition of the animal (Amassian, 1954; Buser and Borenstein, 1959).

(5) There is little relation between the amplitude of the evoked nonspecific responses and the intensity of the stimulus which evoked them (Amassian, 1954). The lack of correlation is not surprising considering the marked variability of the nonspecific potentials evoked by a constant stimulus intensity.

(6) The temporal characteristics of the nonspecific responses are quite different from those of primary responses. The nonspecific responses are of longer duration and latency than the primary EPs elicited by identical sensory stimuli (Amassian, 1954; Albe-Fessard and Rougeul, 1955; Thompson and Sindberg, 1960). Typical nonspecific response latencies recorded in the cat have been 15 to 40 msec for click, flash, or paw shock

stimuli, as compared with primary response latencies of approximately 10 msec for click, 12 msec for flash, and 5 to 8 msec for tactile stimuli (Buser and Borenstein, 1959). In addition, the nonspecific responses have longer absolutely and relatively refractory intervals following the first of two successive stimuli than do the corresponding primary responses, (Amassian, 1954), and they are not able to follow repetitive stimuli faster than about 5 per second.

III. Further observations on nonspecific responses in the cat

The first observation of nonspecific responses by Amassian (1954) established a technique of stimulation which has been used extensively in subsequent work concerned with polysensory responses. First, each stimulus consisted of a single brief presentation in a particular modality. Stimulus brevity is crucial if the potential evoked from the cerebral cortex is to be distinguished against the background of spontaneous or other on-going activity. Second, the stimulus modalities used by Amassian were the auditory, visual, and somesthetic. These three modalities continue to be the ones most commonly used in work with polysensory response systems. Third, the auditory and visual stimuli were diffuse and undifferentiated. For example, the light flash was not limited to any particular part of the visual field or spectrum. The auditory stimulus was a free field click, a form of acoustic stimulus for which precise specifications of frequency or intensity level are often left unstated, as was the case in Amassian's report. The use of diffuse auditory and visual stimuli has also continued to be characteristic of work with nonspecific responses, until a few quite recent attempts to

determine finer response capabilities, if any, which might exist in the nonspecific response areas. These recent experiments will be described below.

Soon after Amassian's work in the anterior lateral gyrus, Buser and Heinze (1954) confirmed his findings for this area and also reported convergence of auditory and visual stimuli in the suprasylvian gyrus of the unanesthetized cat. Their method entailed giving two stimuli of different modalities simultaneously. The intensity of each stimulus was adjusted to be just threshold. When both stimuli were given simultaneously, the resultant response was large and clear, providing striking evidence of facilitation between the two different sensory inputs. They commented on the long latency of the suprasylvian responses (20 to 50 msec) as well as on their duration (about 50 msec) which is long compared to the much briefer initial responses of the primary areas (Chang, 1959).

Following the report of Buser and Heinze, a long series of experiments was carried out by Buser and his colleagues in which the polysensory areas in the suprasylvian gyrus received more thorough investigation. Before following the progress of their work, however, we should take note of the publication in 1955 by Albe-Fessard and Rougeul of their finding of yet a different nonspecific area in the cat cortex, this one in the anterior sigmoid gyrus, overlapping the pre-central motor field. Albe-Fessard and Rougeul also recorded nonspecific responses in the anterior lateral gyrus area of Amassian and in two regions of the middle suprasylvian gyrus. Their stimuli consisted only of direct electrical stimulations of the sciatic nerve, and thus were not heterosensory. However, using both left and right sciatic nerves, they were able to demonstrate heterotopic

convergence upon a given cortical point, thus repeating Amassian's observations. They reaffirmed the long latency (15 - 20 msec) and the long duration (60 - 100 msec) characterizing the nonspecific responses, as well as the depressant effect of even small doses of Nembutal.

In 1956 Buser and Borenstein examined the role of chloralose in the elicitation of the nonspecific polysensory responses. Since these responses had first been observed in chloralosed animals, the possibility had been entertained that they represented an unnatural state of cortical activity and therefore might not be of significance for normal physiological functioning in the unanesthetized animal. Buser and Borenstein found that the nonspecific responses were very difficult to distinguish in the unanesthesized curarized preparation on the basis of one trial, but could be quite clearly seen if they used the technique of superimposing 10 or more successive oscilloscope traces on the same film. They attributed the difficulty of seeing the nonspecific EPs in single traces to two factors: (1) that there was more spontaneous activity in the unanesthetized preparation, thus making for a "noisier" baseline; and (2) that the nonspecific EPs in the unanesthetized preparation possess considerable variability which is even more pronounced than that already described for nonspecific EPs in chloralose preparations. These two observations have been confirmed repeatedly (Buser, Borenstein and Bruner, 1959; Denney and Thompson, 1967). Buser and Borenstein also noted that although a single point in the nonspecific area responded to stimuli of different qualities (paw shock, click, and flash), very dissimilar re-responses could be recorded from closely neighboring points. Thus they envisaged a mosaic distribution of nonspecific polysensory activity in

which each point from which activity was recorded had its own typical response waveform.

In an extensive series of studies by Buser and his colleagues (Buser, 1957; Buser and Borenstein, 1956, 1957, and 1959; Buser et al., 1959; Bruner, 1960; Bruner and Buser, 1960) the following observations were made:

Starting with an unanesthetized animal, the induction of chloralose anesthesia produces changes in the electrical phenomena recorded from the brain including (1) increased amplitude of both primary and nonspecific EPs; (2) a gradual disappearance of 'spontaneous' cortical activity; (3) simplification of the waveform of nonspecific EPs, and (4) a concentration in the distribution of the nonspecific EPs such that only those points giving maximal responses in the unanesthetized animal continue to respond under chloralose, while 'fringe' areas where unanesthetized EPs are small cease to respond under chloralose. The net effect of these changes is to make the polysensory response areas more sharply and clearly defined under chloralose, with a relatively larger inactive 'surround' than in the unanesthetized animal.

In several of this series of reports the attempt is made to find some degree of sensory specialization within the different nonspecific areas. For instance, Buser and Borenstein in 1957 reported that they found the optimal cortical locus for responses to simultaneous click and flash in the posterior part of the middle suprasylvian gyrus, while the best locus for paired click and shock was in the anterior suprasylvian gyrus. There is, however, a lack of agreement among the various papers regarding which polysensory areas respond best to particular sensory modalities. A later

paper (Buser and Borenstein, 1959) gives the suprasylvian gyrus as the location of two separate maximal response areas for visual stimuli and two different and separate maxima for tactile stimuli. Agreement is also lacking in regard to the precise locations within the suprasylvian gyrus of areas from which the nonspecific responses can be elicited. In addition one of the reports (Buser et al., 1959) suggests that the polysensory response field in the anterior suprasylvian is simply an extension of the one in the anterior lateral gyrus. While reflecting the difficulty inherent in the recording of nonspecific responses, these somewhat disparate observations highlight the variability as well as the wide distribution of the nonspecific responses in the cat. It remained for subsequent investigation to provide a comprehensive view of the interrelations of the polysensory areas.

A clear and integrated account of the different polysensory areas in the cat cortex has emerged from the work of Thompson and his colleagues. In 1960 Thompson and Sindberg published a report of nonspecific responses to auditory stimuli recorded in the anterior lateral gyrus, the pericruciate area, and two well-marked subregions within the suprasylvian gyrus. In each of the four nonspecific areas they found convergence of responses to stimulation at different regions of the cochlear nerve, thus demonstrating that the nonspecific areas lack the tonotopic organization characteristic of the primary auditory area (Woolsey and Walzl, 1942). Although Albe-Fessard and Rougeul (1955) had demonstrated hereotopic convergence of somatic inputs to the pericruciate area, this area was not shown to be polysensory until Thompson and Sindberg found that it responded to auditory stimuli. In addition, the work of Thompson and

Sindberg served to clarify the distribution of polysensory responses in the suprasylvian gyrus. Their conclusions regarding localization agree well with those reported earlier by Albe-Fessard and Rougeul using somatic stimulation. Later Thompson, Johnson and Hoopes (1963a) reported that exhaustive mapping of the cortical convexity during favorable conditions for recording nonspecific polysensory responses revealed no additional polysensory response fields. However, they did find polysensory responses on the medial wall of the hemisphere, clustered around the cruciate sulcus. Similar responses had been described in the anterior cingulate gyrus by Bruner (1960) and Bruner and Buser (1960). Thompson et al. suggested that these responses represent an extension of the pericruciate polysensory area onto the medial wall. Figure 1 is a diagram of the distribution of nonspecific polysensory areas in the cat cortex as summarized by Thompson and his colleagues, and shows their relation to the primary sensory and motor areas. Note that the pericruciate nonspecific area (PCA) overlaps the primary motor area (MI), although the two areas are not coextensive.

Thompson, Smith and Bliss (1963b) reported very high correlations between simultaneous response amplitudes in the different nonspecific areas (0.89 to 0.97 depending on stimulus modality) while the intercorrelations between simultaneous primary and nonspecific responses were near zero (-0.16 to 0.12). An analysis of recovery cycles for the nonspecific responses showed that these were much slower than for the primary responses, as had been pointed out earlier (Amassian, 1954; Albe-Fessard and Rougeul, 1955). Moreover, in all the nonspecific polysensory fields the recovery curves were the same regardless of the modalities of the

conditioning and test stimuli, thus indicating that blocking interaction occurred in each polysensory area without regard to modality of input. Thompson et al. concluded by suggesting that a single sub-cortical system was responsible for simultaneous EPs in the four different polysensory areas. The suggestion of a sub-cortical input to these areas was based in part upon the lack of correlation between responses in the primary and in the nonspecific areas. In addition, their own and earlier findings (Buser, 1957; Buser et al., 1959) revealed that responses in the nonspecific area are not dependent on the integrity of the primary cortical areas. Finally, a growing body of evidence indicated that thalamic nonspecific and/or association nuclei project to the nonspecific polysensory areas of the cortex (Albe-Fessard and Rougeul, 1955, 1958; Buser and Borenstein, 1956; Buser, et al., 1958, 1959; Prescott, 1963). Their hypothesis that "a peripheral stimulus delivered to any portion of the auditory, somatic, or visual receptive fields activates one and the same central association system in an undifferentiated manner" was based on the apparent equivalence in amplitude and waveform of potentials evoked at a given point by the different modalities of stimuli. Differentiation of response within the nonspecific polysensory areas will receive further discussion in the section on microelectrode studies of these areas, for analysis of single unit responses has made it possible to examine response characteristics in the polysensory areas with a finer resolution and greater sensitivity to detail.

The interesting question of how nonspecific polysensory areas in the cat may be related to behavior has been addressed in several ways. In work with chronic implanted electrodes in awake and unrestrained cats,

Shaw and Thompson (1964) found that the nonspecific EPs decreased during bodily activity. Novel stimuli of any modality, even of the same modality as the test stimuli, also produced a marked decrement in EP amplitude. In a second paper, Thompson and Shaw (1964) reported that the amplitude of EPs in the nonspecific areas was inversely proportional to the degree of behavioral "attention", defined by orienting responses made by the cats in response to infrequent click stimuli. In order to rule out the effects of movement per se, they presented the clicks only after the cat had remained quietly in one position for several minutes. A possible inference from this work is that nonspecific polysensory areas of the cortex may be involved in the organisms's response to novel or attention-getting stimuli.

Another interesting line of pursuit concerns the possible role of the nonspecific response areas in learning. Warren, Warren and Akert (1962) found that cats with bilateral lesions of the suprasylvian gyri were deficient in umweg learning, although the deficit may have been due to a generalized deterioration in visual perception rather than in the ability to learn. The lesions were referred to in this report as "prestriate lesions" and extended far enough posterior to encroach upon the parastriate cortex. In an experiment using the rather specialized paradigm of sensory pre-conditioning, Thompson and Kramer (1964) found that cats with complete ablation of all four nonspecific polysensory areas did not learn the criterion response, while control animals with lesions of the somatic sensory cortex were able to learn it easily. Because of the speed with which acquisition generally occurs in sensory preconditioning (commonly within 4 trials), Thompson and Kramer suggested that it is a type of learning highly dependent on stimulus novelty, with striking parallels between it

and the orienting response. These authors postulated that the reason for failure to learn on the part of the cats with lesions of the nonspecific response areas might be that they had lost the ability to respond to the novelty value of any stimuli, in particular the conditioned stimulus.

The number of studies devoted to the relation between nonspecific polysensory cortex and behavior in the cat is extremely small, a fact which was pointed out by Buser and Bignall in their 1967 review of nonprimary responses. As they emphasized, the situations are reversed for the cat and the monkey, for in the latter not much electrophysiological work has been done while a lot of behavioral data, particularly from ablation studies, is available. The homologies, if any, between nonprimary regions of the cat and monkey cortices have not yet been established (Thompson, 1967). Therefore it seems premature to attempt to generalize from one to the other with regard to either electrophysiological findings or the results of ablation studies.

The findings regarding nonspecific polysensory areas in the cat can be summarized as follows: Four well-defined areas in the cat cortex have been shown to give very labile, long-latency responses of long duration to auditory, visual, and somesthetic stimulation. These areas, as shown in Figure 1, lie in the anterior lateral gyrus (ALA), the pericruciate area (PCA), the anterior middle suprasylvian gyrus (AMSA) and the posterior middle suprasylvian gyrus (PMSA). While chloralose exalts the reactivity of all cortical areas, including the primary areas (Buser and Borenstein, 1957 and 1959; Albe-Fessard and Rougeul, 1958) and may thus be said to exaggerate the responses to peripheral stimuli, it appears that its use to facilitate the study of activity in the nonspecific polysensory areas

does not create response capabilities that do not exist during normal physiological functioning, for nonspecific or polysensory responses can be recorded in unanesthetized cats although it is more difficult to do so. There is some difference of opinion regarding the degree or quality of heterosensory convergence to the different polysensory areas, with some authors (Buser and Borenstein, 1957; Buser et al., 1959; Dubner and Rutledge, 1964) feeling that there are differences in the preferred sensory modality or modalities in a given response field, while other authors (Thompson et al., 1963a and b) feel that the responses in all of the polysensory areas are undifferentiated with regard to the different modalities. All authors are agreed, however, that convergence of different modalities is characteristic of all the nonspecific or polysensory areas. The existence of convergence and interaction between responses to stimuli of different modalities, together with the relative lack of correlation between stimulus intensity and response amplitude in the nonspecific polysensory areas, suggests that these areas may be cortical zones subserving integrative brain functions. This possibility is further reinforced by the few studies which have attempted to relate responses of the polysensory areas to behavior.

IV. Polysensory response areas in the rat cortex

It might seem unlikely that nonspecific or polysensory response fields could exist in the rat cerebral cortex. The convex surface of the rat brain appears to be nearly entirely committed to primary sensory and motor areas, as may be seen in part (a) of Figure 2. Thus, there would seem to be very little room to spare for any type of non-primary cortex. However, when a search was made for areas in the rat cortex from which nonspecific, polysensory responses might be evoked, such an area was found by Bliss and Petrinovich (1964). Using rats anesthetized with chloralose, they found that in the area shown in part (b) of Figure 2, well-marked surface responses could be evoked by click, light flash, and brief paw shock. These responses were very similar to the polysensory responses in the cat with respect to waveform and latency. In addition, the polysensory responses in the rat exhibited the high level of variability found earlier in the cat.

Bliss and Petrinovich performed response correlation analyses similar to those carried out earlier for the cat (Thompson, Smith and Bliss, 1963b). They compared response amplitudes in each of the primary areas with the amplitudes of the responses recorded simultaneously in the two polysensory areas. Correlations between the primary and either of the polysensory areas were nearly zero, while correlations between response amplitudes in the two polysensory areas were extremely high ($r = 0.92$ for the click stimulus, 0.88 for the flash, and 0.87 for shock). Thus, the rat nonspecific areas resemble those in the cat in their lack of correlation with primary response areas and in their high correlation with each other.

As these authors point out, the great variability in amplitude of the nonspecific EPs renders the high correlations between EPs in the two nonspecific areas especially striking.

In the same series of experiments, Bliss and Petrinovich demonstrated by means of interaction analyses similar to those which had been used for the cat (Thompson et al., 1963b) that the responses of the two polysensory areas appeared to be due to activation of a single system which functioned independently of the primary response systems. Using pairs of brief stimuli in which the first stimulus preceded the second by various intervals, they found that regardless of the modality of the first stimulus, the second stimulus could not elicit any response from the polysensory areas until an interval of at least 200 msec had elapsed. In the primary areas, by contrast, the second stimulus could evoke a response after an interstimulus interval as brief as 50 msec or less, depending on the modality. Thus in the rat as in the cat, the absolutely unresponsive period of the nonspecific EPs was significantly longer than the absolutely unresponsive period of primary EPs.

Finally, Bliss and Petrinovich found that apparently normal responses to all sensory modalities including the visual could still be evoked from the polysensory response fields in rats which had sustained complete bilateral ablation of primary visual cortex. This observation furnished additional evidence of the independence of nonspecific cortical responses from the primary cortical areas in the rat, and constitutes a further point of resemblance between the nonspecific responses in the rat and those in the cat. These authors concluded that their data demonstrated not only that nonspecific polysensory response fields exist in the rat

cortex, but also that these cortical fields show the same general characteristics as the nonspecific polysensory response fields in the cat. Recent work by Bliss (Personal communication, 1968) using unanesthetized rats indicates that the recording of nonspecific responses can be accomplished without chloralose, as in the cat, although again the superposition technique is necessary to make the responses stand out clearly.

In summary, although the work on rat polysensory response fields is not extensive, it appears to yield results highly similar to those found for the cat. The existence of cortical areas giving responses quite different from primary sensory responses appears well founded. As in the cat, the nonspecific or polysensory cortex in part overlaps but is not co-extensive with the motor cortex. Those characteristics of the gross EP which set the nonspecific areas apart from the primary cortex (polysensory responding, inability to follow rapid rates of stimulation, variability of response amplitude) also suggest the possibility that the nonspecific cortex is primarily involved in functions <u>other</u> than the accurate processing of stimulus quantity, numerosity, or quality. A reasonable hypothesis might thus be that, as is suspected for cat polysensory areas, the polysensory areas in the rat participate in complex or integrative functions.

V. Microelectrode studies of the nonspecific areas in the cat cortex

The attempt to analyze cortical functioning by means of gross EPs suffers from numerous difficulties, one of the most restrictive of which is a lack of precision. The gross EP or slow wave is a mass response from a large, unspecified population of neurons. A natural step therefore is to improve the resolution of the electrical 'picture' obtained by using microelectrodes to record isolated responses from single neurons.

Before discussing the information about polysensory areas which has been gained from single-unit studies, it seems appropriate to acknowledge the limitations inherent in the microelectrode technique. First and perhaps most disconcerting is the problem of sample size. Considering the vast number of cortical elements, even in a restricted area of the cortex, it is apparent that even a sample numbering in the hundreds of neurons runs the risk of not being representative of the population from which it is drawn.

Secondly, the sample of neurons recorded from is undoubtedly biased. It is easier to record from large neurons than from small ones (Burns, Heron, and Pritchard, 1962; Dubner and Rutledge, 1964) because of the larger electrical signal generated by a larger cell (Scheibel, Scheibel, Mollica, and Moruzzi, 1955; Brazier, 1968) as well as because small neurons probably are most easily damaged and killed by contact with the electrode tip. Another source of bias lies in the differences in characteristic firing frequency of different cells, whether firing 'spontaneously' or in response to a known stimulus. Cells which fire infrequently are more likely to be by-passed, for they may not happen to be active when

the electrode tip is within recording distance of them.[1] The sources of bias are probably numerous and may include unsuspected factors in addition to such obvious ones as the configuration of the electrode tip, its electrical properties, and even the mechanical characteristics of the electrode carrier.

A third limitation in the use of microelectrodes is the difficulty in 'holding' a given cell once it is isolated. Various perturbations, such as the animal's breathing and heart-beat, as well as minute vibrations in the recording room or table or electrode carrier, conspire to move the electrode tip relative to the tissue surrounding it. A number of special techniques for controlling pulsation of the brain have been devised (Thompson, Lindsley, and Eason, 1966) with more or less success. However, losing a cell after a short recording interval is common experience. The limitation thus placed on replicability of results in the same unit is obvious. However, even more restrictive is the fact that whatever experimental design is used must be adapted to the overwhelming probability that the recording interval for any given unit will be brief. This places a severe restraint on the plan of the experiment, as will be discussed at greater length in the Methods section of this paper.

Additional difficulties arise in the interpretation of data obtained from microelectrode recording. It is common to find, in any given region of the central nervous system which gives gross evoked responses to sensory stimulation, that a substantial number of the cells encountered are

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[1]The present discussion is limited to extra-cellular microelectrode recording. A cell which does not fire at all could be detected by an intracellular microelectrode which records changes in D.C. level in addition to 'fast' electrical potentials. Somewhat different biases would apply therefore to intracellular microelectrode recording.

uninfluenced by any of the stimuli employed in a given experiment (Davies, Erulkar, and Rose, 1954; Katsuki, Sumi, Uchiyama, and Watanabe, 1958; Bental and Bihari, 1963; Bell, Sierra, Buendia and Segundo, 1964; Evans and Whitfield, 1964). This raises the question of whether the adequate stimulus was employed in the case of a cell classified as unresponsive.

Other parameters of the experimental arrangements, such as the interval between stimuli or the particular level or type of anesthetic used, may produce unintended effects upon the probability of cell firing. The condition of the animal is an obvious factor in determining the nature of cell activity, and the effects of physiological deterioration may be confounded with long-term changes in cell firing due to other possible causes such as habituation or conditioning. These limitations in the study of single units are mentioned only briefly here but will receive further comment in later parts of this paper.

A question which arose immediately when the convergence of different peripheral inputs had been demonstrated in the polysensory areas of the cat, was whether the convergence could be demonstrated at the unit level. The fact that at a given point the gross responses to different stimuli appear similar in waveform and about equal in amplitude does not necessarily mean that identical neurons are participating in the different responses. It could be inferred alternatively that there are separate neuron pools, each one responsive to a different sensory modality, which are intermingled in mosaic fashion. Still another alternative is that a combination of the two possibilities exists, with some neurons receiving convergent inputs and others responsive only to a particular sensory modality.

Microelectrode recording can help to answer this question. It has now been shown in a number of studies that there are many neurons in the polysensory areas of the cat cortex which respond to more than a single input (Amassian, 1954; Imbert, 1960; Buser and Imbert, 1961; Bental and Bihari, 1963; Shimazono et al., 1963; Dubner, 1966; Thompson et al., 1969). It is important to note that polysensory responding on the part of a given cell does not necessarily mean that that cell is the actual locus of convergence of the separate inputs. From extracellular records it is not possible to distinguish between cells which perform the integration of separate inputs and cells which merely receive the already-integrated inputs from some lower station in the afferent route to the cortex. The term 'projected convergence' has been used to describe the latter situation, in which integration occurs below the level of the units being observed (Albe-Fessard and Fessard, 1963). There is, however, evidence from intracellular recording (Dubner and Rutledge, 1964) that polysensory cells in nonspecific areas of the cat cortex do in a number of cases perform the integration of the heterogeneous inputs. Dubner and Rutledge observed that the direction and magnitude of evoked changes in cell membrane potential (EPSPs and IPSPs) were related to the modality of the stimulus. They found a small number of cells in which EPSPs resulted from one modality of stimulation and IPSPs from another. When both stimulus modalities were given together, there was clear evidence of the algebraic summation of the post synaptic potentials. Notwithstanding this evidence of convergence upon individual cortical neurons, it appears likely that projected convergence also occurs. Gross EP studies of thalamic and reticular zones thought to project to the polysensory cortical areas have shown convergence

of heterosensory inputs at these lower levels (Albe-Fessard and Rougeul, 1955, 1958; Buser and Bruner, 1956 b, 1960; Buser et al., 1958, 1959; Albe-Fessard and Mallart, 1960; Massion and Meulders, 1961; Albe-Fessard and Fessard, 1963; Prescott, 1963). Further, many single neurons in these subcortical areas have been found to be polysensory (Amassian and DeVito, 1954; Scheibel et al., 1955; Albe-Fessard and Fessard, 1963; Hotta and Kameda, 1963; Bach-y-Rita, 1964; Bell, Sierra, Buendia and Segundo, 1964; Hotta and Terashima, 1966 and 1965). Thus it should be kept in mind that cortical cells in the nonspecific areas whose activity indicates the integration of heterogeneous inputs are not necessarily the agents of that integration.

It has been reported that not all cells in the nonspecific cortical areas are polysensory, however. Cells whose responses were 'monosensory' have been described (Buser and Imbert, 1961; Bental and Bihari, 1963; Dubner and Rutledge, 1964; Dubner, 1966). It has been suggested that testing of these cells was not adequate to support the conclusion that they were monosensory, as only relatively short interstimulus intervals were used and longer interstimulus intervals are more favorable for cell responding (Bettinger, Davis, Meikle, Birch, Kopf, Smith and Thompson, 1967). Nevertheless, it appears possible that impulses generated by peripheral stimuli converge upon the polysensory cortical areas in at least three ways: (1) via afferent paths leading to separate and distinct pools of monosensory neurons within each polysensory area; (2) via other paths in which integration occurs sub-cortically; and (3) via afferent routes which converge upon the individual cortical neurons.

As has been pointed out by several authors (Albe-Fessard and Fessard, 1963; Buser and Bignall, 1967; Chow and Hutt, 1953), the convergence of

multiple inputs upon common neuron pools is a prerequisite for sensory or sensorimotor integration. Regardless of whether common neuron pools subserving heterosensory convergence in the polysensory areas exist subcortically or in the cortex itself, observation of neurons in polysensory cortex under various conditions of stimulation promises to extend our knowledge of integrative processes in the brain. Such observation makes it possible to identify parameters of stimulation which affect integration detectable in the responses of neurons in polysensory cortex.

Afferent pattern

One such parameter of stimulation is, quite obviously, sensory modality. While it is characteristic of many cells in the different nonspecific areas to respond to two or more modalities, it also appears quite often that cells respond differently to the different modalities. As Albe-Fessard and Fessard wrote of cells in the convergent zones of the thalamus, "noteworthy is the fact that every integrating neuron is characterized by a definite 'afferent pattern', one particular type of stimulus being, as a rule, more effective." (1963, p. 131). The fact of differential responding to different inputs has been elicited in several ways in the various studies of neurons in the polysensory cortex. Examples of unit activity have been reported in which the number of spikes per response or the interspike interval varied, depending on which of several different stimuli was presented (Amassian, 1954; Buser and Imbert, 1961; Dubner, 1966). A number of reports have remarked that differing response latencies to the different modalities are characteristic of individual cells (Amassian, 1954; Buser and Imbert, 1961; Shimzaono et al., 1963; Bettinger et al., 1967). A different method of characterizing responses deals with the

probability with which the cell will respond in a fixed number of trials, regardless of the number of spikes per response. Thus, if a certain stimulus is presented 10 times and the cell in question gives one or more spikes on each of 5 of those presentations, its response probability is given as 5/10 or 0.5 (if it fired one or more spikes on every stimulus presentation, its response probability to the given stimulus would be the maximum 1.0). This method of counting responses has been used by Dubner (1966) to describe the characteristic preferential responding of neurons in anterior lateral gyrus to click stimuli, and by Bettinger et al., (1967) to quantify the response capabilities of individual neurons which differed, in many cases widely, as a function of stimulus modality. Yet another approach to characterizing cell responses involves some representation of the temporal patterning of the cell's activity following a given stimulus. Post-stimulus time histograms plotting firing frequency in successive post-stimulus intervals have been used to categorize cell responses as 'excitatory' or 'inhibitory' (Bental and Bihari, 1963) or to demonstrate preferential responding to visual inputs in anterior middle suprasylvian gyrus (Dubner and Rutledge, 1964).

There is some suggestion that the 'afferent pattern' of a given neuron is not independent of anesthetic level. Dubner and Rutledge (1964) reported that a higher percentage of polysensory cells was observed in anterior middle suprasylvian gyrus in cats heavily anesthetized with chloralose (60 - 80 mg/kg) than in lightly anesthetized (35 - 50 mg/kg) or unanesthetized cats. A similar trend had been noted by Buser and Imbert (1961), in their report on the pericruciate area, although they found much higher percentages of responsive units in both anesthetized

and unanesthetized animals than had been found by Dubner and Rutledge. Evidence against attributing high levels of polysensory responding to the effects of chloralose has come from Bental and Bihari (1963) who observed nearly as large a percentage of polysensory units in unanesthetized cats as Dubner and Rutledge found in cats treated with chloralose, and from Bettinger et al. (1967) who used a level of chloralose (70 mg/kg) corresponding to what Dubner and Rutledge had designated as 'heavy', yet reported that all of the approximately 200 cells they observed in posterior middle suprasylvian gyrus were polysensory. Thus, either chloralose affects the different polysensory areas differently, or some other factor is responsible for the differences in number of polysensory cells found. Shimazono et al. (1963), while not commenting on this point directly, pointed out that cell responses are much clearer in cats under chloralose than in unanesthetized cats, partly because background or resting discharge rate is decreased, and partly because the latency of cell responses is more uniform. Thus it is possible that weak or indistinct polysensory responses were overlooked in some of the other studies using unanesthetized cats.

Another factor may be more important than anesthetic level in determining characteristics of the 'afferent pattern'. The results obtained by Bettinger et al. (1967) suggest that temporal parameters of stimulation are crucial in determining whether or not a given cell's responses will be polysensory. These authors found that for many cells in posterior middle suprasylvian gyrus the probability of responding increased as the interval between successive stimuli was lengthened over a range from one second to as much as 30 seconds or more. In a number of

cases the difference in response probability was very marked, with cells which responded to nearly every stimulus at interstimulus intervals (ISIs) of 10 seconds or more having response probabilities close to zero when the ISI was one or two seconds. Some of the cells reported by Bettinger et al. showed even more complex integrative properties. In the more complex cells, stimulus modality interacted with the ISI effect. For example, a particular cell might show low probabilities of responding to click and to flash at an ISI of one second. The same cell tested with an ISI of 10 seconds might then show a moderate level of response to the click and a maximal response to the flash. Bettinger et al. suggested that integrative response patterns such as those described above, because they depended on the recency of a stimulus as well as its modality, might represent the cellular coding of stimulus novelty and thus be involved in behavioral 'attention' or orienting on the part of the organism.

Cross-modality effects: facilitation and blocking

In addition to the possible effects of stimulus 'novelty', Bettinger et al. (1967) found that, for many cells in posterior middle suprasylvian gyrus of the cat, the probability of a cell's firing could be increased by combining two or three modalities to form a compound stimulus. In general, polysensory cells fired with higher probabilities to a compound made up of two stimuli given together than to either of the two stimuli given separately, and with still higher probabilities to the combination of all three (click, flash, and paw shock). Facilitation of response, usually measured in terms of increased number of spikes per response, had earlier been reported in the pericruciate (Buser and Imbert, 1961),

anterior suprasylvian (Dubner and Rutledge, 1964), and anterior lateral (Dubner, 1966) polysensory areas. Such observations recall the reports of cross-modal interactions at the gross EP level (Buser and Heinze, 1954; Buser and Borenstein, 1957; Thompson et al., 1963) as do observations of cross-modality blocking[1] effects on cell responses reported by the same authors and others (Bental and Bihari, 1963; Dubner and Rutledge, 1965; Shimazono et al., 1963). From experimentally varying the interval between two different stimuli it has appeared that optimal intervals for blocking are relatively long (50 - 250 msec) whereas maximal facilitation is obtained at shorter intervals (Dubner and Rutledge, 1964) or with the two stimuli presented simultaneously (Buser and Imbert, 1961; Bettinger et al., 1967).

These effects have been further elucidated by intracellular recording. Dubner and Rutledge (1965) observed long-lasting EPSPs (20 to 80 msec) and even longer IPSPs (30 to 300 msec) in cells of the anterior suprasylvian polysensory area during sensory stimulation. Presumably algebraic summation of such evoked synaptic potentials would be the basis for the cross-modality interactions described above, as is further supported by the similarity in time courses of EPSPs and facilitatory effects on the one hand and IPSPs and blocking effects on the other.

It has also been found that, for any given cell, stimuli of different modalities may differ in their ability to block a subsequent response of

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[1]Following the suggestion of Amassian (1953), the term 'blocking' is preferable to either 'occlusion' or 'inhibition', as it does not presuppose any underlying mechanism. At the unit level, 'occlusion' should be reserved for the case in which an excitatory input commands the cell's response so that other inputs are rendered ineffective. 'Inhibition' applies to the case in which an input to the cell acts to decrease the cell's excitability.

the cell to other stimulus modalities. Dubner and Rutledge (1964) reported that, for cells in the anterior suprasylvian polysensory area, visual stimuli were in general more effective than auditory or somatic stimuli in blocking responses to a subsequent stimulus. In these same cells, the auditory and somatic stimuli varied in their ability to block each other. Dubner (1966) found that cells in the anterior lateral gyrus were usually blocked for longer intervals by a click (up to 135 msec) than by a light flash (up to 90 msec). In both of the reports cited, the most effective blocking stimulus was also the stimulus which produced the strongest responses in terms of unit spike discharges. Thus the duration of blocking of subsequent responses following a given stimulus appears to be an indication of the relative effectiveness of that stimulus.

Specialized response capabilities of neurons in polysensory areas

As was mentioned earlier, nearly all studies of nonspecific polysensory areas have utilized diffuse, relatively undifferentiated stimuli in the form of light flashes, clicks, or peripheral electric shock. This tendency to avoid restricting the stimuli probably arose from the desire to engage as many responsive elements as possible, and was a natural result of not knowing what particular aspects of any sensory stimulus were likely to be definitive as far as nonspecific responses were concerned. Some recent work in two different polysensory areas, however, has succeeded in finding differential neuronal responding to small, circular spots of light located at different points within the visual field (Bignall, 1967; Dubner and Brown, 1968). Differential responses were obtained only near threshold illumination of the stimulus, when it was found that cells responded most vigorously to stimuli near the center

of the visual field. For brighter stimuli, location within the visual field was not a factor in determining the strength of the responses, which could be elicited by diffuse light flashes as in the traditional procedures.

It seems likely that other attempts to find differential responsiveness to precisely determined parameters of the stimulus will be made. Although diffuse light flash is a much more effective photic stimulus in the polysensory cortex than in primary visual cortex, (Dubner and Brown, 1968), the existence of highly specialized units in visual cortex (Hubel and Wiesel, 1965) and in other primary sensory areas (Mountcastle, 1957; Gerstein and Kiang, 1964) makes it reasonable to look for similarly complex response properties in the polysensory areas. The existence of units which are selectively responsive only to certain precisely limited types of stimuli might well account for the observations which been made in various polysensory areas of units which appeared to be totally unresponsive to flash, click or shock (Buser and Imbert, 1961; Dubner and Rutledge, 1964; Dubner, 1966).

From all of the types of response analysis described in the sections above, the picture of neuronal response characteristics which emerges is one in which many degrees of freedom are provided for the possible ways in which responses of neurons in the polysensory areas can vary. Not only the latency and the number of spikes per response, but also the statistical measures of response probability and distribution over time, appear to furnish potentially significant clues about the ways in which these cells process sensory information. Further, if neurons of the nonspecific cortical areas are implicated in complex operations of an integrative nature,

then it may be reasonable to anticipate that observation and analysis of their response properties will provide some degree of insight into the neural mechanisms underlying these complex operations.

VI. Aims of the present research

The present experiment using the rat was planned as an extension of the work of Bettinger et al. (1967) in the cat. The latter experiment was concerned with the effects of two parameters, stimulus modality and interstimulus interval, on the responses of neurons in polysensory cortex of the cat. Using the maps of polysensory cortex in the rat provided by Bliss[1] and Bliss and Petrinovich (1964), it was proposed to carry out extracellular microelectrode recording from single units in polysensory cortex of the rat while varying ISI and stimulus modality in a systematic fashion.

A general hypothesis to be tested in the present research was as follows: In those areas of the rat cortex which are electrophysiologically analogous to nonspecific polysensory areas in the cat cortex, there exist single units whose responses to sensory stimulation exhibit integrative properties similar to those described above for single units in the polysensory cortex of the cat. In particular, it was expected that polysensory units would be found, and that the response characteristics of such units might depend on stimulus modality and interstimulus interval, as in the cat.

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[1]Personal communication, 1968.

An additional question suggested by the findings in the earlier research in the cat involves the possibility of cell habituation. As was mentioned earlier, Bettinger et al. found that response probability was a function of interstimulus interval, with longer ISIs resulting in higher response probabilities. Particularly striking instances of this effect occurred whenever a new stimulus series was begun, often after a relatively long stimulus-free interval. On these occasions of initial stimulus presentations, cell response was almost never seen to fail. A reasonable explanation appeared to be that the cells habituated to a given stimulus during its repetition, even at relatively slow rates (such as one every 2 seconds), and that recovery occurred when the cell was allowed to 'rest' between stimulus series. As will be outlined in the Methods section, a procedure was designed to test this possibility.

Summary of the aims

For individual units in the cortical area referred to, it was proposed to:

(1) Examine the possibility of polysensory responding

(2) Determine whether or not responding is an increasing function of the interstimulus interval

(3) Examine the effects of compound stimuli (such as click plus shock or click plus flash) upon unit response

(4) Examine general response characteristics of units such as latency and temporal configuration.

The last point is an acknowledgement of the fact that relatively little electrophysiological work has been carried out in the rat. It was hoped that the present investigation would help to delineate basic characteristics of neural functioning in the rat.

Methods

I. Subjects and surgical preparation

The subjects were male hooded rats of the Long-Evans strain, ranging in weight from approximately 200 to 480 gm. Each rat was anesthetized with α-chloralose dissolved in heated propylene glycol, given intraperitoneally. The usual dose was 180 mg/Kg. This is an unusually large dose of chloralose, judging from dosages reported in other work with rats (Root and Hoffman, 1963; Bliss and Petrinovich, 1964).[1] In addition to to the chloralose, all rats received 0.04 mg. atropine sulfate intraperitoneally at the same time as the initial anesthetic injection and at intervals of 1/2 hour or more until the rat could be placed on artificial respiration. After a sufficient depth of anesthesia was reached, surgical preparation of the rats began with tracheotomy and cannulation of the external iliac vein for later use in intravenous injections. These preliminary preparations were done as quickly as possible so that the time lag until artificial respiration could begin would be minimal.[2] The rat was then placed in a headholder which held the rat's head rigid but allowed its height and angle to be adjusted. The rat's nose was held tightly by means of a bar that passed over the nose and clamped the incisors into a molded base plate. The angle of the head was adjusted so that the area of brain to be exposed would be in the horizontal plane. A midline incision was then made from between the eyes to the base of

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[1]For a discussion of the anesthetic technique required in this experiment, please refer to Appendix A.

[2]Please refer to Appendix B for a discussion of the problems of maintaining anesthetized rats under artificial respiration.

the neck, and the tissue overlying the skull was reflected to allow access to the left hemisphere. A small opening in the cranium was made with a small hand drill or with a scalpel used with great care as a chisel or gouge. The opening was then enlarged using rongeurs, until the desired area of the brain was exposed. The dura was reflected with minimal delay.[1] A dam of dental acrylic was built up around the exposure, and mineral oil at 38° C was used to cover the exposed brain surface. The mineral oil pool was maintained until after an electrode penetration was begun and a single unit had been isolated and was ready to be recorded. At that point the mineral oil was removed and replaced with agar (5% in normal saline), which helped to control cortical pulsations. The rat's right eye was sutured open and 1.0% opthalmic atropine applied topically.

During recording the rat's body temperature was monitored constantly by means of a rectal thermometer and maintained between 37° and 39° C. by a circulating hot water system (normal body temperature for the rat is 38.2° C). The brain exposure was visualized at 20X magnification through a binocular microscope and by this means cortical blood circulation could be monitored at frequent intervals. This provided a useful check on the adequacy of respiration and on the general condition of the animal. Penetration of the microelectrode into the cortical surface was always initiated under microscopic control.

At the beginning of recording, 0.4 cc of Flaxedil (20 mg/cc gallemine triethiodide, Davis and Geck) was given intravenously, and thereafter

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[1] If more than about 10 minutes elapse before removal of the dura is begun, the dura sticks to the cortical surface and pulls away blood vessels and grey matter when it is elevated.

supplementary doses were given as needed to maintain paralysis. Occasional recovery from paralysis was allowed to check anesthetic depth.

II. Stimulating and Recording Procedures

The procedures used for microelectrode recording as well as for stimulus presentations were different for the two portions of the research described below under the headings of Experiment I and Experiment II.

Experiment I

(a) Electrodes and recording

Electrical signs of unit activity as well as slow waves were recorded using tungsten microelectrodes made according to the method of Hubel (1957). The microelectrodes had tip diameters of approximately 1 μ and DC resistances in the approximate range of 4 to 20 MΩ. The cortical signals were led from the microelectrode directly into a Tektronix type 2A61 differential preamplifier plugged into one side of a Tektronix 565 dual-beam oscilloscope. Filter settings for single units were 600 to 6 K Hz, and for slow potentials were 0.6 to 600 Hz. The indifferent electrode was a metal clip attached to the cut edge of the rat's scalp, and signals from it were led into the other input stage of the differential amplifier. Thus the signal displayed by the oscilloscope represented the algebraic difference between voltage levels at the two electrode sites. The animal was enclosed in an electrically shielded metal cubicle, and all recording and stimulating equipment was outside the enclosure except for the loud speaker which delivered the clicks, the flash bulb unit, and the isolating transformer used to deliver foot shocks. With this arrangement the

electrical "noise" level was approximately 10 - 25 μV. and the amplitude of unit spikes was in the range 50 - 200 μV.

The microelectrodes were held in place by a Pryor micro-manipulator which was capable of advancing the electrode in the vertical plane a total distance of 1200 μ at the rate of 100 μ per revolution of the fine adjustment. For depths greater than 1200 μ the electrode carrier was lowered 1 mm and further advances performed by the fine adjustment. Oscilloscope displays of the bioelectric signals were photographed as they occurred by a Grass C-4 camera.

(b) Stimuli

The stimuli presented to the rat included single brief clicks, flashes of light, and brief shocks to the hind foot ipsilateral to the brain exposure. The clicks were produced by 0.1 msec square pulses from a Tektronix 161 pulse generator, led into an audioamplifier and thence into a horn speaker situated 12 in. from the animal's head. The loudness of the click was measured as follows: A Bruel and Kjaer condenser microphone Type 4133 (0.5 in. diameter) was placed in the same position as that occupied by the rat's head during an experiment. The click stimulus was presented exactly as during an experiment, at intervals of 1 sec. The output of the microphone was led to a low-level DC preamplifier (Tektronix type 63) plugged into the oscilloscope. Photographs were made of the display, as shown in Figure 3a . The sound pressure level of the click was obtained from the calibration of the microphone (1.30 mV/μbar) applied to the rms voltage measured from the oscilloscope display. The intensity of the clicks used in both Experiments I and II was 111.2 db SPL except when clicks of lower intensity were used in a few special cases

which will be mentioned. The sound pressure level of the ambient noise in the room where the experiment was conducted was measured using a Bruël and Kjaer sound level meter, and was found to be approximately 53 - 55 db SPL for frequencies up to 500 Hz, and to decrease from 49 db at 1000 Hz to 19 db at 10 K Hz. The main contributions to the ambient noise level were made by the ventilating fans in the oscilloscope and other electronic equipment, and by the artificial respirator which was quiet but discernible.

The light flashes were produced by a Xenon flashtube (Amglo type U-35-B) incorporated in a photostimulator manufactured for this experiment by the Research Instrument Service of the University of Oregon Medical School. No equipment was available to measure the intensity of the light flash directly, so an indirect method involving comparison with the output of a very recently manufactured Grass PS2 photostimulator was used. A photoelectric cell (boron-doped silicon solar cell, Hoffman Electronics type 55CL) was placed in the same position as that normally occupied by the rat's eye during an experiment. The Grass photostimulator was placed at the same distance from the rat's eye as the photostimulator used in the experiment. The output of the photocell in response to flashes from the Grass unit was led to the oscilloscope preamplifier and the display photographed. The amplitude of each of the intensity levels of the Grass photostimulator was measured in this way, yielding a set of points from which a curve was plotted relating photocell output to settings of the Grass photostimulator. The Grass unit was then removed and the photostimulator used in the experiment was put in the same place. The output of the photocell in response to the unknown flash intensity was then

photographed. Figure 3b shows the points plotted for the Grass intensity settings and the point corresponding to the flash used in the experiment. The flash used in the experiment was slightly less intense than the flash generated by the Grass unit at its lowest setting.

The electric shock stimulus was produced by a 0.2 msec. rectangular pulse from a Tektronix 161 pulse generator, led through a 1:4 isolating transformer and delivered by a pair of needle electrodes spaced approximately 3 mm apart and each inserted to a distance of about 3 mm into the basal surface of the rat's hind foot ipsilateral to the brain exposure. The shock intensity was controlled by a ten-turn dial controlling the output of the pulse generator. Calibration of shock intensity was carried out by means of current measurements through a 20 Ω resistor in series with the rat. Shock intensity was usually in the range 1.0 to 2.5 mA. Current settings for the shock were not equated between rats because it was considered more desirable to attempt to equate the magnitude of the twitch responses produced by the shock in the different animals by adjusting the current level. Before the administration of Flaxedil, the current level was set so as to produce a twitch response which was less than maximal but which involved more than just the leg receiving the shocks. Usually, slight twitches of the eyelids, vibrissae, and ears were observed in response to the shock. Pulse amplitude was monitored in a number of instances before and at the termination of recording. No changes over time were found in the waveform or the magnitude of the rectangular pulses delivered through the tissues of the rat's foot.

The stimuli were triggered by a system of Tektronix 162 waveform generators in such a way that any stimulus by itself or combinations of two or three together could be given at varying interstimulus intervals (ISIs). The ISIs most commonly used were 1, 2, 4, 8, and 10 sec. Additional ISI values of 1.2, 2.5, 3.2, 5.0, 6.3, 20 or 30 sec. were sometimes used.

The flash stimulator produced a faint noise which caused some units to fire. This effect was tested by placing an opaque screen in front of the flash, and noting whether the triggering of a flash produced any cell response. In cases where the sound of the flash stimulator produced cell responses, masking by the loud noise of an air jet was used during recording with visual stimuli.

(c) Stimulus programs

The usual procedure during an experiment was to give the auditory (A), visual (V), and tactile (T) stimuli simultaneously during the descent of the microelectrode. Such a compound stimulus, which will be referred to hereafter as "AVT", was repeated at intervals of 3.2 sec. throughout the search for, and isolation of, a single unit. It should be noted that if a stimulus of a single modality were chosen for use as a probe stimulus, a number of cells which responded primarily to the other modalities would never have been found. The use of a probe stimulus was mandatory because many cells, having "spontaneous" firing rates very close to or equal to zero, make their presence known only by the responses elicited from them.

After a cell was isolated a procedure to test its response characteristics was initiated. The response characteristics focused upon in Experiment I included whether or not a cell was polysensory (defined as

responding to more than one sensory modality), and the effect of the different ISIs upon responding. In addition the effects of combining two or more modalities to form compound stimuli were examined. The response measure chosen as the dependent variable was the all-or-none probability of responding on the basis of 10 trials, which will be described more fully in the section on data analysis below.

In order to test both specificity of response and the ISI effect in the shortest possible time, keeping in mind that many cells might not survive a lengthy testing procedure, a program was designed to measure a cell's response probability for each type of sensory input at a number of different ISIs. The procedure began by giving a series of 11 identical stimuli at any one ISI. During Experiment I the recording intervals of 100 or 200 msec were used. The stimulus was synchronized with the beginning of the oscilloscope sweep. Recording was photographic and consisted of camera exposures synchronized with the 100 or 200 msec. sweep durations of the oscilloscope. In cases where a cell was found to fire spontaneously, recordings were made of identical 100 or 200 msec. intervals ---the same ISI as that used for stimulation--- but with no stimuli presented. This was done to obtain some estimate of the probability of spontaneous firing occurring in the same intervals as those used for recording.

The stimulus program was as follows: For any given ISI, the single modalities were tested first and then the compound stimuli were tested.

(1) Single modalities. The order of presentation of the three modalities (A or V or T) was chosen at random. A series of 11 stimuli of a single modality was presented at a given ISI for each modality.

An interval of one min. without stimulation separated all stimulus series. As an example, letting "A_4" represent the click stimulus presented at four second intervals, Part (1) might go as follows:

11 A_4-----11 V_4-----11 T_4----

The dotted lines represent the one-minute rest intervals between individual stimulus series.

(2) Compound stimuli. For the four possible combinations, (AV, AT, VT, AVT) the order of presentation was chosen at random. A series of 11 stimuli of each such combination was presented, still at the same ISI as that used throughout Part (1). Again, 1 min. stimulus-free periods intervened between stimulus series. For example, letting "VT_4" represent the combination of flash and shock presented simultaneously at 4 sec. intervals, Part (2) might go as follows:

11VT_4----11 AV_4----11AVT_4----11 AT_4

After all ISIs and modalities or modality combinations had been tried in this way, cells which lasted long enough were tested for 'habituation'[1] by presenting a series of single stimuli, such as shock alone or click alone, at a relatively short ISI (for example, 2 sec.). In a few cases cells were given several habituation series at several different ISIs or stimulus intensities and in these cases the cells were permitted to recover to pre-habituation levels after each habituation series.

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[1]Defined as reversible response decrement due to stimulus repetition.

Reasons for changing from the procedures of Experiment I to those of Experiment II

As was mentioned briefly above, some of the cells observed in Experiment I exhibited spontaneous activity. As the research progressed, the amount of spontaneous activity observed and the number of cells exhibiting it increased. The reasons for the change in the level of spontaneous activity are not known. Possible explanations may include:

(1) A change in artificial respiration---a new respirator was acquired after several months and the respiratory rate was increased at that time from 50/min. to 70/min.

(2) Improved condition of animals in later experiments, owing to improved surgical preparation.

(3) Unknown changes in the animals as a result of environmental factors or changes in breeding or rearing procedures. A more thorough discussion of these points is given in Appendix C.

The spontaneous activity of units in polysensory cortex of rats treated with chloralose was not anticipated when Experiment I was planned, for earlier work on single units in polysensory areas of the cat had shown that spontaneous firing, although characteristic of unanesthetized preparations, was not recorded from cats under chloralose (Shimazono et al., 1963; Dubner and Rutledge, 1964; Bettinger et al., 1967). The procedures of Experiment I were not well suited to dealing with the spontaneous activity observed in the units for the following reasons:

(1) The problem of identifying a response in a spontaneously active cell becomes one of distinguishing whether or not a change in firing has occurred in response to the stimulus or whether it simply

represents spontaneous activity. The recording intervals of 100 or 200 msec were not long enough to provide an adequate basis for such a distinction. In addition, it was suspected that the duration of some responses might outlast the 100 or 200 msec recording intervals, and that therefore longer recording intervals should be used.

(2) The all-or-none response probability measure did not appear to be appropriate to spontaneously active units, as a unit which fired spontaneously on every trial was not capable of showing an increase in response probability due to stimulation. A measure incorporating the firing frequency of the cell appeared to be better adapted to the spontaneously active units.

(3) The stimulus-free control intervals recorded for the spontaneously active cells which were found in Experiment I did not seem to be the best available way of assessing the changes in spontaneous activity which were seen to occur within individual cells. Control periods closer in time to the actual stimulus seemed more appropriate. For this reason, a pre-stimulus control interval preceding every stimulus was incorporated in the design of Experiment II. Experiment II incorporated various procedural changes to take care of the objections described above. In addition the stimulus program was changed to provide more thorough testing with the various ISIs at any one modality. Other minor changes in procedural details are described below. In addition, a change was made in the type of electrode used for recording.

Experiment II

(a) Electrodes and recording

Glass microelectrodes were used in Experiment II. Glass capillary tubing (Pyrex, 0.8 mm OD) was drawn down to a tip diameter of less than 1 μ, with a long slender tapering shaft. The electrodes were filled with 3 molar NaCl. Electrical contact was made by means of a chlorided silver wire inserted into the open end of the microelectrode. This wire led to a Bak cathode follower. The animal was grounded by means of a second chlorided silver wire inserted into an open-ended glass tube, filled with the same 3 molar NaCl, firmly anchored in saline-dampened cotton which lay in contact with exposed tissue at the back of the neck. The electrical signal from the Bak unit was led to a Tektronix 122 differential preamplifier and from there led single-ended into the Tektronix 2A61 amplifier in the oscilloscope. The Bak unit and the 122 preamplifier were in the metal enclosure with the animal, but otherwise all arrangements were the same as with the metal microelectrodes. Electrical "noise" level was approximately 0.1 mV. and the amplitude of unit spikes was 0.8 to 1.0 mV. or more. Records of unit activity observed in Experiment II were preserved on magnetic tape for later play-back and analysis. The method of measuring responses in Experiment II involved the plotting of post stimulus time histograms and is explained in detail in the section on data analysis below.

(b) Stimuli

The stimuli used in Experiment II were the same as those used in Experiment I and included single clicks, shocks, and light flashes as well as all possible combinations of the three.

(c) Stimulus programs

As in Experiment I, 11 stimuli were presented in each series. The rest interval between series was shortened to 30 seconds. A given stimulus modality was now presented at a number of different ISIs before a new stimulus was presented. The values for ISI were 1, 2, 4, 8, and 10 seconds. For some cells an ascending order of ISIs was used followed after 1 min. by a descending order. For other cells the descending order preceded the ascending order. As an example, the click stimulus was presented in the following way:

11 A_1---11 A_2---11 A_4---11A_8---11 A_{10} (dotted lines represent 30 sec. rest intervals)

1 min. rest

11 A_{10}---11 A_8---11 A_4---11 A_2---11 A_1

After a long rest interval, typically 2 to 5 minutes, the shock and flash were each presented according to similar programs.[1] After the single-modality stimuli had been presented in this way, the modality combinations were tested in ascending series only. The order of presentation of the combinations was usually as follows:

AV (ISI 1, 2, 4, 8, 10 in succession)
1 min. rest
AT (ISI as above)
1 min. rest
VT (ISI as above)
1 min. rest
AVT (ISI as above)

If the cell was still viable after the foregoing procedure was completed, habituation series were given as in Experiment I.

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[1]Masking of the photo flash noise was done routinely during recording of V and VT series, and was carried out by means of an air jet noise as described for Experiment I.

III. Data analysis

Experiment I

The data of Experiment I were recorded on film. Each camera exposure represented one stimulus trial and showed one oscilloscope sweep lasting either 100 or 200 msec. The stimulus and the oscilloscope sweep were triggered simultaneously. During data analysis the film was analyzed with the aid of an enlarger which projected the image at 19 X. Spike latencies were read directly from the enlarged image.

A measure of all-or-none response probability was calculated as follows: Each stimulus trial was scored "1" if any spikes, regardless of the number, occurred during that trial. If no spikes occurred during that trial the score of "0" was recorded. The response probability was expressed as the sum of the scores for a given series of 10 trials, divided by the number of trials. Thus, if a unit responded with at least one spike in each of 4 trials out of the total 10, its response probability was counted as 4/10 or 0.4.

In order to obtain 10 trials all preceded by the same ISI, a series of 11 stimuli was actually given, and the response to the first stimulus was not counted for the purpose of examining ISI effect. Responses occurring on the first trial were included, however, in determinations of the latency of the unit's response to the different stimulus modalities. Responses on the first trial were also used in determining whether or not a cell responded to a given modality.

In order to decide whether a given cell was responsive to a particular stimulus modality, a response criterion was defined as follows: For a given

modality, each set of 11 trials under a particular ISI was considered as a block. In order to be counted as responding to the given modality, a unit had to meet two conditions:

(1) Unit firing had to occur in at least 3 trials in at least 1 block.

(2) Initial spike latencies in the 3 trials had to fall within a range no larger than 20 msec.

Experiment II

The data of Experiment II were recorded on magnetic tape. Subsequently, filmed records were made in the following way: During playback the tape recorder output signal was amplified and fed into a Schmitt trigger which transformed the recorded unit spike discharges into brief positive pulses. The procedure served to select the relatively high amplitude spikes of the unit under observation from the background noise and other low amplitude signals, such as other units from which electrical isolation of the unit under observation was not complete. From the transformed unit pulses, dot patterns (Wall, 1959) were made by imposing a brightening pulse on an otherwise dark oscilloscope trace whenever a unit pulse occurred. This was accomplished by feeding the Schmitt trigger pulses into a pulse-shaping circuit which produced brief positive pulses which were led to the grid of one beam of the oscilloscope. The positive pulses were sufficiently brief (.01 msec.) and of sufficient amplitude (25 V.) to register as small dots of light on film exposed to the 1 sec. sweep of the oscilloscope trace. Each sweep was initiated 200 msec. before the stimulus, thus providing a control record or prestimulus activity in addition to 800 msec. of post-stimulus activity. An artefact was added

to the trace to mark the occurrence of the stimulus. Ten successive trials under one stimulus condition (omitting the first trial of the usual 11-trial series) were photographed in one multiple exposure. Between each trial a stepping voltage applied to the vertical amplifier of the oscilloscope lowered the level at which the trace swept across the screen, so that successive traces occurred at successively lower positions on the oscilloscope face. The resulting photograph showed 10 horizontal arrays of dots, each array corresponding to a different stimulus trial. During photographing of the taped data, the record of cell activity and the output of the pulse-generating circuit were monitored visually by the experimenter using a second oscilloscope, to make sure that there was in fact an exact one-to-one correspondence between cell spikes and pulses applied to the grid.

Poststimulus time (PST) histograms were prepared from the photographed dot patterns in the following way: the filmed dot patterns were projected at 19 X magnification onto a grid whose vertical subdivisions corresponded to 50 msec. intervals in the oscilloscope trace. All the dots lying within a given 50 msec. interval (i.e. between two adjacent vertical lines of the grid) were counted, yielding a measure of firing frequency for each 50 msec. interval summed over the ten trials of one stimulus condition. Scores from the five different stimulus conditions corresponding to the five different ISIs under any one modality were then added to obtain the firing frequencies used to plot PST histograms of unit responding for a given modality. Each histogram thus represented the firing frequency of the cell in 50 trials. Histograms for both ascending and descending orders of ISI sequences were available for many cells. Firing frequencies obtained

from these PST histograms were used to determine whether or not a given cell responded to a particular modality. The criterion for a response was as follows: The peak-to-peak difference between the highest and the lowest points in the histogram in the first 400 msec. following the stimulus was measured. If this peak-to-peak difference was at least twice as large as the mean peak-to-peak fluctuation in the prestimulus control interval, the histogram was counted as showing a response to the stimulus in question.

For the purpose of assessing the effects of ISI upon cell responding, a measure of response magnitude based upon the firing frequencies in the individual ISI series was used. This measure is described in the Results section.

Results

The total number of units recorded in the present study was 94. Of these, 38 were recorded under the conditions of Experiment I and were obtained from a total of 87 rats. The remaining 56 units were recorded under the conditions of Experiment II and were obtained from a total of 45 rats. There were many more units that were observed but not included in the study, as the standard recording procedure was to postpone the beginning of recording until a unit had been held at least 10 minutes. The length of time a unit was held thereafter for recording varied from 10 minutes to more than 3 hours, with the large majority of units in the range from 30 to 90 minutes.

I. Location of units recorded

The location of each unit was determined by recording the transverse and longitudinal coordinates of the microelectrode tip relative to an arbitrary zero point. This point was taken to be the intersection of the coronal and sagittal sutures (bregma). The distance from the bregma to the lambdoid suture was measured in 35 rats, and the mean distance was found to be very close to 7 mm. A scale distance equivalent to 7mm was, therefore, used in drawing the idealized diagram of the rat brain shown in Figure 4 . The typical cortical exposure is shown in part a of this figure, with the bony landmarks providing visible reference points. It should be noted that the use of a plane rectangular coordinate system introduces some error into measurements on the curved surface of the cortex. As can be seen in part b of Figure 4 , electrode penetrations were

made at points lying within the approximate area described by Bliss[1] as giving polysensory gross evoked responses. Penetration sites were chosen so as to minimize damage to cortical blood vessels. No attempt was made to map the distribution of unit responses systematically, although the attempt was made to sample within the area as widely as possible. There were many penetrations in which no units could be found or isolated. The penetrations shown in Figure 4 b are those from which units were successfully recorded.

The depth at which a unit was recorded could be read from the knob of the fine adjustment of the micromanipulator, which completed one revolution when the vertical drive had traversed 100 microns. It is probable, however, that these depth measurements incorporate a large and unknown error factor. One source of inaccuracy is the tendency of the cortical surface to dimple when the electrode is first pushed through the pial membrane. Another is the extent to which further compression of the cortical tissue may occur as the electrode is advanced. An additional source of error in the present experiment was the use of a layer of agar to cover the brain. As the agar began to dry during the course of a long-lasting penetration, it sometimes clung to the microelectrode shaft, making further advance of the electrode somewhat erratic.

Responsive units did not appear to be confined to any particular cortical layer or depth. The cortex in the rat is approximately 2 mm thick in the area studied (König, 1963), and responsive units appeared to be found throughout that extent. Although the sample of units was most

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[1]Personal communication, 1968.

numerous in the upper and middle portions of the cortex, a number of cells were isolated more than 1000 μ below the surface of the cortex. No differences in responding appeared to be correlated with the depth at which the unit was located.

II. Criteria for the identification of single units

Unit spikes recorded during Experiment I, using tungsten microelectrodes, were usually initially negative in polarity. The criterion for identification of a single unit was a high degree of constancy in spike amplitude and waveform. Long-term changes in spike amplitude sometimes occurred, perhaps as the result of slow changes in the position of the electrode tip. As long as the change in amplitude was gradual and continuous and the waveform of the spike unaltered, the spike record was accepted as that of a single cell. Unit responses recorded during Experiment II, using saline-filled glass microelectrodes, were most often initially positive and biphasic. There were occasional long-term variations in waveform as well as amplitude with the glass microelectrodes, but identification of a single unit was not ambiguous because isolation was extremely clear. Although no attempt was made to measure spike amplitude precisely, it was evident that spikes recorded with the glass electrodes were generally of larger amplitude (0.5 - 5.0 mV) than those recorded with the tungsten electrodes (.05 - 0.2 mV). The changes in spike waveform which occurred with the glass electrodes were gradual alterations in smoothness or complexity, or gradual changes in the relative amplitudes of positive and negative phases. As in the case of the metal electrodes, it was felt that observed changes in spike amplitude or waveform using the glass microelectrodes

were probably due to changes in position of the electrode tip. However, such changes may also have been due to cell injury. It was noted that the rate of spontaneous[1] firing of some units increased over the recording interval, suggesting the possibility that local irritation due to the presence of the electrode tip tended to increase cell excitability. On the other hand, some units showed decreased spontaneous firing over time, and the most common observation was that of fluctuations in spontaneous activity which recurred at uneven intervals ranging from a few minutes to half an hour or more.

III. Typical unit activity following a stimulus

The most typical response of the units observed in the present experiment to a single brief stimulus consisted of three successive parts.

(1) The first change in unit activity was a brief increase in firing rate which occurred at a characteristic latency, usually within 20 to 100 msec, and was often very marked (Figure 5). Units which were not spontaneously active showed a "burst" response during a similar interval (Figure 6). As parts a and b of Figure 6 show, the number of spikes making up this initial brief response was quite variable. On some trials the unit fired once or a few times, and on other trials the unit responded with a larger number of spikes. This initial excitatory response was most characteristic for auditory and tactile stimuli. For visual stimuli, the initial excitatory response was often relatively small or absent.

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[1]'Spontaneous' is used here to refer to unit activity occurring in the absence of known external stimuli.

(2) Following the initial increase in firing rate, cells which showed some resting level of activity then showed a decrease in firing rate below the resting level. This inhibitory interval[1] typically lasted for 50 to 200 msec. or in some cases longer. Figure 7 shows PST histograms for several typical cells. It was not uncommon for the inhibitory interval to be very pronounced, as illustrated by Figure 7 . The histograms show that the frequency of firing during the inhibitory interval was near zero, even when 50 trials were summed together. The inhibitory interval appeared to be equally characteristic of all three modalities.

(3) Following the inhibitory interval there was a second, late increase in firing rate. There was more variability in this third position of the response, and some cells did not show it at all but appeared simply to return to their resting rate. As Figure 7 shows, this later phase of augmented firing following the inhibitory lull sometimes surpassed the initial response, although usually its amplitude was smaller than that of the initial response. The late excitatory response was also equally characteristic of all three modalities.

The examples shown in Figure 7 were recorded during Experiment II. Experiment I was designed for the recording of the early or "burst" responses, as was mentioned under Methods, and its recording intervals lasted only for the 100 or 200 msec. of the oscilloscope sweep triggered by the stimulus. A similar pattern of response can probably be assumed for the spontaneously active units in Experiment I; however, for the

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[1]No assumption regarding the locus of the inhibitory action is implied. The inhibitory action may be direct (on the observed cell) or indirect (on a prior cell which ordinarily exerts an excitatory influence on the observed cell).

audiomonitor often disclosed sounds of cell activity following soon after the end of the photographed sweep. Such activity would correspond in its timing to the late firing described above for the third portion of the response. In addition, it was not uncommon to see such late responses during the continuous visual monitoring of the oscilloscope trace that was possible before actual photographic recording began. As was mentioned earlier, the occurrence of such late activity apparently synchronized with the stimulus was one of the reasons for changing from the recording techniques of Experiment I to those of Experiment II.

IV. Cyclic firing tendencies

In addition to the initial increase in firing around 50 to 100 msec. and the later phase of increased firing following the inhibitory lull, some cells showed an additional wave or two of increased firing alternating in cyclic fashion with periods of decreased activity. These later alternations in firing frequency were less pronounced than the first three major phases described in the section above, and were not consistent in their appearance even within consecutive stimulus series for the same cell. Despite their high variability, they were clearly visible in a number of cases, of which Figure 8 shows an example. The presence or absence of cyclic firing may be a function of modality or of the ISI (Figure 9), although the present data bearing on this question are not numerous enough to support these possibilities with any certainty. It is also possible that the cyclic tendency was subject to fluctuations not related to the experimental variables in the present study.

V. Inhibitory intervals not preceded by early peak in firing frequency

Several cells were recorded whose characteristic response lacked the initial burst or firing increment, but instead began with the inhibitory interval. Figure 10 shows several examples. The cell shown in parts (a - c) of Figure 10 responded with the typical initial increase of firing to the auditory stimulus, although this initial response was quite small. Response patterns such as these suggest that whatever the mechanism responsible for the inhibitory interval, its actions are represented by a continuum of possible effects upon different cells. Some cells lie at one end of this continuum and exhibit relatively little inhibitory influence. Other cells, like the ones described in this section, lie at the other end of the continuum and exhibit an inhibitory influence so strong that evidences of the early firing burst are suppressed. Cells such as the ones illustrated here argue against the possibility that the inhibitory mechanism is a recovery effect following an increase in excitation, as these cells have no increased firing level from which to recover. Further discussion of the possible mechanisms underlying the observed response patterns is reserved for a later section.

VI. Latency of unit responses

In addition to the variability in number of spikes evoked from one trial to another, there is considerable variability in the latency of responding. Figure 6 shows the spike activity of a cell evoked by series of consecutive stimuli. The behavior of this cell is quite representative of the behavior of all the cells recorded. It is evident that, for any one modality, the early activity which appears to be evoked by the stimulus

is variable in its onset. Discounting those instances in which the cell was already in the midst of a burst of spikes when the stimulus occurred, it still appears that the characteristic latency of firing of this cell to any given stimulus can be stated only within rather wide limits.

In order to determine whether each modality was associated with a response latency characteristic of the population of cells in general, the interval between the stimulus and the first spike thereafter was recorded for each stimulus trial for each cell. The data of Experiment I and Experiment II were pooled for this purpose. Spikes occurring earlier than 10 msec. after the stimulus were discounted as being too early to represent possible activity evoked by that stimulus. Inspection of all the data indicated that the distributions of latencies corresponding to a particular stimulus for a given cell tended in a number of cases to be bimodal. In cases of this sort from Experiment II, in which PST histograms were available, it appeared that the early mode of the latency distribution corresponded well with the early peak in the frequency histogram, and the later mode of latency corresponded roughly to the peak of the later increase in firing described above. Because the later modes of the latency distributions exhibited more variability and usually represented fewer cases (as was also true for the later histogram peaks), only the early modal values of latency were used in calculating mean initial spike latencies for such cells. Table 1 gives for each stimulus the overall mean of the mean initial spike latencies to that stimulus. It can be seen from Table 1 that the latencies for the click (A) and the shock (T) were quite similar, and both fell mostly in the range of 30 to 70 msec. with means of 49.0 and 48.0 msec., respectively. The latency for the visual stimulus (V)

was longer and more variable. Most initial spikes following the visual stimulus occurred in the range 30 to 105 msec., with a mean of 69 msec.

Examples of single units showing longer response latencies to the visual stimulus are shown in Figure 11. Figure 11a, b contrasts a short latency click-evoked response with a long latency flash-evoked response in one cell. Figure 11c, d illustrates the response of a different cell which gave a short latency response to shock and long latency response to the flash.

Long latency responding to visual stimulation was also borne out by observation of the slow EPs recorded within the same general cortical area. Figure 12 shows slow potentials evoked by the three different stimuli, and indicates the same similarity in latency for the auditory and tactile EPs while illustrating the later appearance of the visual EP.

VII. Polysensory responding

The response criteria used in determining whether or not the units in Experiments I and II responded to a given modality were described in the part of the Methods section devoted to data analysis. Table 2 summarizes the activity of units recorded in Experiment I with regard to the type and amount of polysensory responding. It is clear from Table 2 that polysensory responding is the rule rather than the exception. Of the 35 units tested with all three stimulus modalities, 68.6% responded to more than one modality (total of entries ii, iii, iv, and v). Trisensory cells represented 37.1% of the total population (entry ii) and bisensory cells accounted for another 31.5%. Only 28.6% of the cells responded exclusively to one modality of stimulation. Most of the latter category were not

tested with every ISI, however, so it is possible that even they would have responded to more than one modality if the optimal ISI had been used.

It is also evident from the data summarized in Table 2 that most cells in this area of the cortex responded to auditory and to tactile stimuli (80% for each), whereas less than half of the number recorded (42.9%) were found to respond to the visual stimulus.

For the data of Experiment II, Table 3 summarizes the numbers of units found to respond to the different stimuli. The activity of each unit was classified according to which of the stimuli were presented and whether or not a response occurred. Among the total of 56 units recorded in Experiment II, 34 were tested with the auditory stimulus (A), 37 with the visual stimulus (V), and 42 with the tactile stimulus (T). It can be seen that each of these stimuli evoked responses in a high proportion of the units tested. The tactile stimulus appears to be the most effective, with 100% of the units tested with it showing a response. Table 4 summarizes the data in a somewhat different way, in order to show the degree of polysensory responding characteristic of the units in Experiment II. Of the 26 units tested with all three stimulus modalities, 22 were trisensory and 1 was bisensory. Of the 7 units tested with only two stimulus modalities, 6 were bisensory. There is no way of knowing whether the 20 cells tested with only one stimulus modality would have responded to the other stimulus modalities if they had been given the opportunity.

VIII. Response magnitude as a function of modality and ISI

It was evident from the earliest stages of the present research that the magnitude of unit responding was related to the stimulus modality and

to the interstimulus interval. Figure 6 illustrates these two effects for a cell recorded during Experiment I. The visual stimulus elicited responding on two trials at the ISI of 3.2 sec., and on four trials at the ISI of 8 sec. The auditory and tactile stimuli, both more effective for this cell, also elicited higher response probabilities at the 8 sec. ISI than at the 3.2 sec. ISI. Figure 13 illustrates the effects of stimulus modality upon the activity of a unit recorded during Experiment II. For this cell, T was very clearly the most effective stimulus. There appeared to be no response to V, and the response to A was intermediate. The effects of different ISIs can be seen in the dot patterns of Figure 14, where the series with A and with VT show particularly clear variations as ISI varies. Quantitative evaluation of the modality and ISI effects was carried out as follows:

Experiment I

In order to compare the effects of the different stimulus modalities and interstimulus intervals upon responses of units in Experiment I, the response probability of each cell for each stimulus and ISI was calculated according to the method described earlier. Each cell, therefore, had associated with it a set of probabilities, each probability being derived from a different combination of ISI and modality. The set of probabilities for a cell that was tested under a large number of stimulus conditions is shown in Table 5. The responses of this cell were representative of several characteristics of unit responding observed in both Experiment I and Experiment II. First, from the row means in Table 5, the tendency for the visual stimulus (V) to produce weaker responding can be seen; whereas the

mean response probabilities for A and T were roughly equivalent, the mean probabilities for V were generally lower. Second, the probability of responding appeared in many instances to be enhanced by combining two or three stimuli and presenting them together. The combination AVT showed this tendency most clearly, producing the highest mean response probability of any stimulus. The compound stimulus AT was also relatively more effective than the single stimuli presented alone. Third, the column totals at the bottom of the table indicate a tendency toward higher response probability with the longer ISIs. The highest mean response probability was obtained with an ISI of 10 sec. With the shorter ISIs, 1 sec. and 2 sec., relatively few responses were elicited.

Figure 15 shows the means of the response probabilities of all cells recorded in Experiment I, plotted as a function of stimulus modality and ISI. Figure 15 illustrates the relatively greater effectiveness of the tactile and auditory stimuli compared to the visual stimulus. The tendency of response probability to increase with increasing ISI was also evident for the auditory and tactile stimuli, although this tendency does not appear to characterize the visual stimulus.

Experiment II

The data from Experiment I support the generalization that the auditory and tactile stimuli were more effective than the visual stimulus, both in terms of numbers of cells responding to each stimulus and in terms of the response probabilities of the individual cells. A more precise comparison between the different modalities and ISIs was possible using the data of Experiment II, for the number of cells which had undergone testing with all stimulus modalities and ISIs was large enough to afford

the use of statistical comparisons between the different stimulus conditions.

Measures of response magnitude for Experiment II were obtained in the following way: The 50 msec. interval showing the highest firing frequency following the stimulus was identified for each cell from inspection of its PST histograms. The firing frequencies in this interval were then counted for each ISI and stimulus modality for each cell. These counts represented the total number of times the cell fired in the chosen 50 msec. interval, summed over the 10 stimulus trials at any one ISI. From these same 10 trials, the mean firing frequency of the four 50 msec. control intervals preceding the stimulus was calculated. This mean control value was subtracted from the mean response frequency measure. The resulting difference scores were thus adjusted to some extent for the differing levels of spontaneous activity preceding the stimulus. Such an adjustment was desirable because the level of spontaneous activity varied considerably from one unit to another and even within one unit from time to time.

As was described in the Methods section, for each separate stimulus modality, some cells were tested with an ascending order of ISIs, starting with an ISI of 1 sec. and proceeding thereafter with ISIs of 2, 4, 8, and 10 sec. in succession. Other cells tested with the same stimulus received a descending order of ISIs, beginning at 10 sec. and decreasing to 1 sec. at the end. When a cell was held long enough, it was tested with both orders. Some of these cells received the ascending order first, followed by the descending order, while other cells started with the descending order and ended with the ascending order. Thus, the data for any one

stimulus modality were collected under four different ISI orders: ascending first, ascending second, descending first, and descending second.

The first analysis of the data, therefore, examined the possibility that there was an effect of ISI order upon response magnitude and, in addition, tested whether there was a significant effect due to ISI. In order to do this, the difference scores for all cells tested both with ascending and with descending ISI series for a given modality were submitted to analysis of variance, using a 2 x 2 x 5 factorial design for repeated measures (Winer, 1962). The first factor was the direction of ISI sequence (either ascending or descending). The second factor was the order of priority (ascending first or descending first). The third factor represented the five different values of ISI (1, 2, 4, 8, or 10 sec.). Each cell was represented by a score under each ISI and under both ascending and descending ISI sequences, while no cell could be recorded under both the ascending-first and descending-first orders. A separate analysis was done for each of the three stimulus modalities. Tables 6, 7, and 8 summarize the analyses of variance for each of the three modalities. Neither the direction nor the order of ISI series was found to exert a significant effect on the responses. The ISI was found to a significant factor for the auditory ($p < .001$) and tactile ($p < .05$) modalities, but not for the visual stimuli. This finding corroborates the effect which was first noted for the data in Experiment I (Figure 14), namely, that the probability of responding to auditory and tactile stimuli was affected by the ISI, whereas the probability of response to the visual stimuli appeared to be unaffected by this variable.

The ISI order having been shown to be inconsequential, it was then permissible to pool the data collected from all cells undergoing complete ISI series for all modalities. The aim was to have an analysis in which possible interaction effects between ISI and modality could be tested. Nineteen cells in Experiment II were held long enough (1 1/2 to 2 hours) to permit the recording of complete ascending and descending orders of all ISIs for all three stimulus modalities. Data from the ascending and the descending sequences for a given modality were combined to yield a single difference score similar to that computed for each cell for the first analysis described above. These scores were analyzed by means of a 3 x 5 factorial design with repeated measures (Winer, 1962). Stimulus modality was the first factor with three levels corresponding to A, V and T. The second factor was that of ISI with its five different values. Each single unit was represented by a score in each cell of the 3 x 5 table (each of the 5 ISIs x each of the 3 modalities). Table 9 summarizes the analysis of variance for the nineteen units recorded under all modalities and ISIs. Both modality ($p < .05$) and ISI ($p < .01$) were found to exert a significant effect on response magnitude. Figure 16 shows the mean response magnitude for each modality plotted as a function of ISI. Once again, the visual stimulus elicited the lowest level of responding. Although all curves show a tendency to increase with increasing ISI, this effect is clearest for the auditory modality. Mean responses to V do not increase monotonically but show a downward trend at ISI = 10 sec.

Individual comparisons between the means for each modality showed that the only significant difference was between the means for tactile and visual stimuli ($p < .05$). The mean for V was not significantly

different from the mean for A, nor was A significantly different from T. Individual comparisons between the means for the different ISIs revealed that the significant effect due to ISI was the result of a significant difference between ISIs of 1 sec. and the two longest ISIs, 8 sec. and 10 sec. From inspection of the graph, it appears that most of this significant difference between the short and long ISIs was contributed by the responses to A. However, none of the interactions proved to be significant.

IX. Integrative responses

In many individual cases the response probabilities of cells in Experiment I were higher for compound stimuli (AV, AT, VT, AVT) than for the single stimulus modalities (see Table 5 which gives as an example the response probabilities of an individual cell). The curves of the mean probabilities for the whole group of cells, however, reveal that the combinations AT and AVT are the only ones for which increased responding was characteristic of the group as a whole. These curves are shown in Figure 17 . The curve for VT is nearly identical with that for T alone. The curve for AV is nearly identical with that for A alone. Thus, the addition of visual stimulation does not seem to have increased the probability with which these units responded over the level that would be expected for the auditory or tactile stimuli by themselves. Similarly, the curve for AVT is quite close to that for AT, indicating that the addition of V to the complex AT does not produce much additional effect on cell responding.

The conclusion from the data of Experiment I would thus seem to be that the cells in this sample population integrate the inputs from the

auditory and tactile modalities, but not the visual modality, at least under the condition of simultaneous stimulus presentation used in the present experiment.

This is surprising because the data of Experiment II indicate, even more clearly than the data for Experiment I, that the visual input by itself is capable of driving the cells in this area of the rat brain (Figures 7 and 11). Nevertheless, when the histograms of responses to the compound stimuli are compared with the histograms of the same cells responding to A, V, or T alone, it becomes evident that many cell responses to the compounds AV, AT, and VT are dominated or wholly commanded by the responses typical for the auditory or tactile stimuli when given separately. Figure 18 shows several examples in which the histograms of the responses to compound stimuli can be compared with the histograms derived from the two stimuli given separately. It can be seen that the histograms for the compounds look very similar to the histograms for the corresponding auditory or tactile stimulus when given alone. Such examples support the conclusion from Experiment I regarding the lack of integration of visual input. On the other hand, there are a few examples of the case in which a compound which includes V appears to show combined effects both of V and of the other stimulus of the pair, as shown in Figure 19 . It does appear, therefore, that the visual stimuli are not completely incapable of affecting the response magnitude of the cells even when competing with the auditory or tactile inputs. Possibly, this indicates that the PST histogram is a more sensitive index of integrative responding than is the all-or-none response probability measure. However, the data from Experiment II are not ample in regard to the effects of compound stimuli. Altogether, only

17 of the 56 cells in Experiment II were held long enough to undergo not only complete testing with the single stimuli, but also the subsequent testing with stimulus compounds. Since the responses to any two individual stimuli must be very clear in order for the histogram of the corresponding compound to show clear resemblance to either, some of the data from testing with compound stimuli do not yield much information regarding integrative responding because the component responses are not by themselves easily recognizable.

Some additional information regarding the effects of the compound stimuli upon unit responding is furnished by a comparison of the response latencies to the different compound stimuli. The mean latencies of the initial spikes following the different compound stimuli are shown in Table 10. Entries in the table are based on data from both Experiment I and Experiment II and were calculated according to the method described earlier (p. 60). It can be seen from the table that initial spike latencies are shortest for the combinations AT and AVT. The addition of V to either A or T appears to have little or no effect on latency. Variability in latency also appears to be a function of the stimulus condition. Except for the combination AV, the standard deviations of the latency distributions appear to be lower for the compound stimuli than for the single stimuli. Although the latency of responding is not information which is available to the responding system, the response latencies appear to be a useful index of stimulus effects which will receive further discussion below.

X. Habituation

As was mentioned in the Introduction, the observation in the cat of lower response probability at shorter ISIs had suggested the possibility that habituation was occurring at the shorter ISIs. The data from the present experiment have confirmed the same ISI effect for the units observed in the rat brain, at least for the auditory and tactile modalities, and the question again arises whether the response decrement at the shorter ISIs is attributable to habituation.

Further information regarding the possible occurrence of habituation can be derived in several ways. One way is to look at the individual ascending and descending ISI series (Table 11) to see whether response decrement was more marked at the end of the descending series than at the beginning of the ascending series. If habituation were responsible for the response decrement at short ISIs, we would expect that its effects might be more marked for the 11 stimuli presented at the 1-sec. ISI terminating the descending series, for this set of stimuli occurred after the cell had undergone testing at all other ISI values (a total of 44 stimuli). Moreover, the cell had a stimulus-free rest interval of at least 2 min. preceding the ascending series, whereas the stimulus-free interval preceding the 1-sec. ISI series which terminated the descending series was only 30 sec. The conditions of the descending ISI order thus were more favorable for obtaining habituation than was the case for the ascending order.

This argument led to the a priori hypothesis that the response level for the ISI of 1 sec. should be lower for the descending than for the ascending order. Since this hypothesis was formulated prior to the

opportunity to inspect the data, it is permissible to test the difference between the means of the ascending versus the descending order, even though there were no significant effects due to order found in any of the three analyses (Tables 6, 7, and 8).

The mean responses obtained for each modality at the 1-sec. ISI are shown in Table 11. It is evident, for the auditory and tactile modalities, that the response magnitudes recorded at the end of the descending series are indeed lower than those recorded at the beginning of the ascending series. The differences, however, are not large. Neither proved to be significant ($p \leq .05$). The difference between the means for the visual modality is large but in the opposite direction from that predicted. This difference proved to be statistically significant ($p < .05$) but probably should not be accepted as being necessarily of physiological significance. The a posteriori nature of the hypothesis being tested, in the case of a difference in sign opposite to that predicted, impugns the tenability of any inferences that may be drawn.

The hypothesis that the response magnitudes at the end of the descending order were smaller than those at the beginning of the ascending order must, therefore, be rejected. A possibility remains that habituation was responsible for the low response magnitudes at all the 1-sec. ISIs, but that the expected difference between response magnitudes for the two different stimulus orders at the 1-sec. ISI did not appear because there was sufficient time for recovery between each stimulus series, even when the rest interval was only 30 sec.

An additional and entirely different approach to the question of whether or not habituation can occur in the unit responses of the type

observed in the present experiment was used for a small number of cells. Although the data are not numerous, they are presented here because they are suggestive of changes in unit responding which may be specific to the habituation process. The method for looking at possible habituation was as follows: If a cell lasted throughout all the testing with different ISIs and modalities and still appeared to show no signs of deterioration either in its responding or in its spontaneous activity, it was then tested with a long series of stimuli repeated at a uniform, short ISI. Such a train of repeated stimuli constitutes the classic paradigm for obtaining response habituation.

A total of 10 cells received stimulus series long enough to provide an adequate test (60 to 220 trials, various stimulus modalities). Of these 10 cells, 6 showed no decrease in response magnitude over the total trial series, although many instances of fluctuating between high and low levels were observed. Two cells showed progressive response decrements over the series of trials, but recovery data which are necessary to support the inference of habituation are lacking. One of these cells ceased to respond at all at the end of 130 trials and so its decreasing responsiveness may have been indicative of deterioration rather than habituation. The other cell continued to fire with a high spontaneous rate for at least 30 min. after the 125-trial habituation series ended. Despite the lack of recovery data for this cell, its diminishing response curve is shown in Figure 20 as an illustration of the marked fluctuations in response level which often occur in extended series of trials, regardless of whether or not habituation occurs. It is worth noting that if the stimulus sequence had been terminated after 15 trials, the impression would have been created

that rapid and marked habituation had occurred. This would have been a misleading impression, as the next block of 5 trials shows. Notwithstanding the fluctuations in response level shown by this cell, the progressive decrement in its response level over the series of 125 trials is suggestive of habituation.

The behavior of the remaining two out of the 10 cells is shown in Figures 21 and 22. Unit # 48-2 was tested at two intensity levels of the tactile stimulus, using the same ISI of 3.2 sec. for both. The higher intensity series was given first. Both habituating series were followed by recovery series in which the trials were spaced 10 sec. apart. This unit shows progressive response decrement for both intensities of the stimulus, although for the low intensity the initial response level is low enough that further decreases could not be very large. The behavior in the last trial blocks of both intensity series makes interpretation of the trend in response level difficult, for responding appears to return to its initial level. After the recovery series following the lower-intensity habituating series, 30 trials were given with the initial high intensity and ISI of 3.2 sec. The resulting jump in response level can be seen, followed by two more blocks of trials in which response level again decreased.

The observations cited above for unit # 48-2 constitute rather equivocal evidence for habituation. The data for the last unit, # 55-2 (Figure 22) are, however, clearly indicative of habituation. This unit was tested with the auditory stimulus at two intensity levels and three different ISIs. Following each habituation series, recovery to pre-habituation levels was observed. The order in which each series was given is

noted in the figure. Figure 22 shows that response probability decreased as each stimulus series was prolonged, thus meeting one requirement for habituation. According to the analysis of habituation characteristics given by Thompson and Spencer (1966), habituation occurs more rapidly at fast repetition rates than at slower ones. Figure 22 also shows that the response decrement occurred faster for the lower intensity series at the 2.5-sec. ISI than for the higher intensity series at the same ISI. This observation agrees with another feature characterizing habituation as described by Thompson and Spencer, namely that the rate at which habituation occurs is inversely related to the strength of the habituating stimulus.

It can be seen from Figure 22 that decreases in the level of responding are already evident in the first points plotted, which represent the respective response probabilities based on the first block of 10 trials. The progressive response decrement which is evident in the curves of Figure 22 is thus already manifest within the number of trials commonly used in collecting the data of Experiments I and II.

Discussion

The data indicate that many individual cells in the polysensory area of the rat cortex are responsive to auditory, visual, and tactile inputs. Thus the question of whether convergence is present at the unit level is answered in the affirmative. It appears that most of the single units in this area are polysensory, inasmuch as the majority of units in the present study were fired by at least two modalities (usually, the auditory and tactile), and a large number of these were fired by all three modalities tested. The PST histograms for the cells which survived only long enough to be tested with one stimulus modality do not appear to differ in any systematic way from those tested with more than one stimulus. Presumably, a large proportion of the units tested only with one stimulus would have proved to be polysensory if testing with a second or third modality had been possible for them.

I. Characteristics of polysensory cells

Degree of convergence

The term 'polysensory' has been used in the present context to refer to any cell responding to more than one modality. Within that category, however, cells can be subdivided into a group which responds to all three modalities (trisensory cells) and a group which responds only to two modalities (bisensory cells). Of the total of 61 cells from both Experiment I and Experiment II which were tested with all three stimulus modalities, 35 were trisensory. Of the remaining cells, 12 were bisensory, leaving only 14 cells which responded only to one modality and thus were not polysensory. Based on this sample, the trisensory cells can be seen

to outnumber the other types of cells in the area sampled, and thus it appears likely that responsiveness to a diversity of stimulation is important in the functioning of this part of the rat's brain.

A larger percentage of cells was found to be polysensory in Experiment II than in Experiment I (87.9 % vs. 68.6 %). It is possible that the PST histogram was a more sensitive measure of responding for the cells studied in the present experiment, because it made available information gained from the temporal pattern of responding. The PST histograms demonstrated late inhibition and even later excitatory responses which were not observable using the response probability measure and short recording intervals of Experiment I. Thus, some of the units in Experiment I which did not appear to be responsive to a particular modality of stimulation, might have shown inhibitory intervals or late excitatory responses if these had been investigated. This suggestion applies most forcefully to the responses to visual stimulation. The PST histograms showed that visual responses often consisted of weak early excitatory responses, while the later inhibitory and excitatory responses were clear and well marked. Thus the short recording intervals of Experiment I discriminated more severely against the visual responses than against the other two modalities.

Modality differences

Of the three stimulus modalities, the tactile stimulus in general was found to produce the largest early excitatory responses. Its greater effectiveness in eliciting the early excitatory response is evident from the following observations:

(1) In Experiment II response magnitudes to T were in general higher than to A or to V (Figure 16). In addition, a larger number of cells responded to T. Of those cells tested with T, 100% responded to the stimulus. The corresponding figures for the percentage of cells responding to V or to A are 83.8% and 85.3% respectively.

(2) The tactile stimulus produced more clearly-marked, consistent "burst" responses in a large number of cases (examples are shown in Figures 5, 6, 11, and 14).

The relative ineffectiveness of the visual stimulus in evoking early excitatory responses is evident not only in the mean response magnitudes plotted in Figures 15 and 16, but also in the smaller number of units responding to V in Experiment I (Table 2). Whereas 80% of all cells tested with either A or T responded to the stimulus, only 42.9% of the cells tested with V responded to V.

In addition, the latencies of responses to the different stimuli support the generalization that the visual stimulus appears to be the least effective. The inverse relation between stimulus strength and the variability of response latency is well known (Amassian and Waller, 1958; Brazier, 1968). As Table 1 shows, the latencies for the visual stimulus exhibit the highest degree of dispersion.

The observations that T was most effective and V was least effective might be explained on the basis that T was a relatively stronger tactile stimulus than either A or V with respect to their respective stimulus dimensions. Lacking cross-modality intensity comparisons in rats for the stimuli used in the present experiment, it is possible only to make the following arguments against this suggestion: Although T was probably

more intense than any tactile stimulus normally encountered by rats, the same was true of A and V. Both A and V were very intense stimuli by the standard of what is normal for the rat.

Another possible explanation for the relative dominance of the tactile modality is that the cells recorded were sampled from areas SI or SII in the rat. Area SII can be ruled out on the basis that its anatomical location is quite far ventral to the area investigated in the present research. Area SI overlaps the area explored in the present research. However, units in SI have been shown to have very discrete receptive fields in the cat (Mountcastle, Davies and Berman, 1957). If the same situation applies to the rat, then only a small fraction of the units observed in the present study could have been within the representation of the hind foot. Furthermore, representation in SI is mainly contralateral, whereas the stimulation used was the ipsilateral foot.

Temporal pattern of responding

A typical response pattern was observed for the cells in the present experiment. The pattern consisted of three successive elements: (1) an early excitatory response or "burst"; (2) an inhibitory interval or period of decreased responding; (3) a late excitatory response.

The inhibitory interval might possibly by explained on the basis of temporary exhaustion of the cell's firing ability following a large burst of activity. However, the observation of cases in which inhibitory intervals occurred without prior excitatory responses (Figure 10) argues against this view. Evoked hyperpolarization of cells in the anterior suprasylvian polysensory area of the cat cortex was observed by Dubner and Rutledge during intracellular recording (1965). They reported a number of cases in which the hyperpolarization was not preceded by any excitatory response. The periods of hyperpolarization which they observed lasted from 30 to 300 msec., which is comparable to the durations of inhibitory intervals observed in the present experiment.

The occurrence of an inhibitory interval following an initial excitatory response is not uncommon for single cells in various neural structures (Albe-Fessard, 1962; Creutzfeldt, Rosina, Ito, and Probst, 1969). As pointed out by Albe-Fessard (1962), the mechanism underlying the inhibitory interval may be either an intrinsic mechanism in the cell or an extrinsic effect due to external influences upon the cell. Furthermore, extrinsic inhibitory effects may act either directly on the cell in question, or may be "distant", acting upon other neural elements which are normally excitatory to the cell in question. Dubner and Rutledge showed, in their intracellular records from neurons in the anterior suprasylvian gyrus of the cat under chloralose, that inhibition of the cells they observed could occur in several ways. Inhibition acting directly upon the cell being observed was apparent in cases showing the algebraic summation of EPSPs and IPSPs. Distant inhibition was inferred in cases where no hyperpolarization was observed during evoked decreases in spontaneous firing.

The occurrence in the units observed in the present study of late excitatory responses following the inhibitory interval could signify a "rebound" effect following inhibition, or it might represent a new wave of excitation reaching the cortex from below. Similar late firing bursts have been observed in the cat under chloralose (Albe-Fessard and Buser, 1955; Dubner, 1966). The study by Dubner used a technique of extracellular polarization to increase the excitability of the cells in the anterior lateral gyrus. Under this condition of exaggerated excitability, the cells showed inhibitory effects lasting 150 to 200 msec. following short latency excitatory activity elicited by the auditory, visual, or tactile stimuli. In addition, some cases of late firing following the inhibitory interval were noted, including some examples of oscillatory firing which appear to have been similar to the cyclic responses reported in the present experiment.

The possible physiological significance of temporally adjacent excitatory and inhibitory response intervals is an interesting subject for speculation. The occurrence of the inhibitory interval could serve as a contrast mechanism to emphasize whatever information is conveyed in the early excitatory burst. Even for the most vigorously responding cells, the evoked firing rate was never very high. The highest histogram peaks represented counts in the range of 150 to 180 spikes per 50 msec. interval, summed over 50 trials. These counts are equivalent to 3 or 5 spikes per 50 msec. interval in one trial, and only for that one of the 50 msec. intervals in which peak responding occurs. In view of this relatively low rate of firing, some sort of contrast mechanism would seem to be of value in improving the clarity of the message transmitted by the cell.

Effects of varying the ISI

The effect of ISI upon the response magnitudes observed in the present experiment was not as simple as the effect observed in the cat (Bettinger et al., 1967). Although the responses to auditory and tactile stimuli occurred with higher probability and attained greater firing frequencies at the longest ISI as compared to the shortest, the responses to visual stimuli did not show this effect. If anything, the visual modality showed a decreased response magnitude at the longest ISI (Figure 16). It is difficult to conceive of the physiological significance of this difference between the visual and the other modalities. While the ISI effect can be thought of as a possible neural substrate for habituation, as discussed briefly in the Introduction, it is not clear why such a mechanism would not apply to visual stimulation. The depressant effect of brief ISIs upon response magnitude has been noted in connection with gross EPs of the polysensory cortex in cat (Albe-Fessard and Rougeul, 1958; Albe-Fessard and Fessard, 1965). It has also been advanced as the probable reason for the low incidence of polysensory units found in some of the single-cell work with cats (Bettinger et al., 1967). This characteristic, referred to as "fatiguability", has been described as being representative of cortical and subcortical convergent structures in general (Albe-Fessard and Fessard, 1963). The generality of the phenomenon in the cat, both at the unit level and at the level of gross EPs, makes it doubly surprising not to find it for the visual modality in the rat. In view of the relative weakness of the visual responses in the rat, perhaps the failure to find the ISI effect for the visual response is indicative merely of an inadequate sample.

Information transmitting capabilities

A different mode of functioning is apparent for the units in the polysensory cortex as compared with those in the primary cortical areas. Based on what has been found for primary units in the cat, the response of a single unit on one trial can be viewed as an information transmitting event with sufficient clarity and signal-to-noise ratio (Katsuki et al., 1958; Mountcastle et al., 1957; Hubel and Wiesel, 1959) that its message in that one trial is theoretically available for processing by other elements of the nervous system to which it projects. For the purpose of the present discussion, we will assume that the redundancy exemplified by the actual existence of many neurons all transmitting the same message relating to the same stimulus trial is irrelevant. In contrast to the situation in primary cortex, the responses of single units in polysensory cortex do not appear to be efficient transmitters of messages in only one trial. Again, it should be recalled that the PST histograms shown in the figures are based on 50 trials for each modality, and that the count for each interval is the sum of the unit spikes generated in that time interval over the total 50 trials. Reference to the scale on the ordinate of the histograms shows that the counts in many cases are less than 50. Thus, whatever information is conveyed by the magnitude and duration of the excitatory and inhibitory periods which are evident in the histograms is not available in one trial. This information is available on a statistical basis only, whether derived from the responses of one unit summed over a number of trials or derived from the summed responses of many neurons on one trial. The latter eventuality is most likely the more physiologically significant, for the structure of the nervous system

appears to be founded on a high degree of redundancy provided by many elements performing similar functions simultaneously. However, the former type of information retrieval over a period of time or over numerous stimulus trials could be involved in some aspect of the functions, as yet unknown, which are peculiar to the polysensory cortex. For instance, it might reasonably be implicated in learning or other types of behavioral plasticity in which a number of trials is necessary to produce a change in the organism's behavior.

II. Comparison between single cell and gross EP data

The units observed in the present study were not found to be equally responsive to all three modalities of stimuli. It is difficult to reconcile this observation with the conclusion drawn from gross EP recording in the rat, that the polysensory area appears to respond equally and in an undifferentiated manner to the different modalities of stimuli (Bliss and Petrinovich, 1964). It will be recalled that a similar discrepancy exists in the case of polysensory cortical areas in the cat. On the basis of gross EP recording, some investigators have concluded that a single system undifferentiated with regard to modality and projecting equally to all the polysensory cortical areas in the cat is responsible for the activity evoked in these areas (Thompson et al., 1963 a and b). This conclusion was based upon the high correlations of amplitude and waveform between EPs recorded simultaneously in the different polysensory areas, and also upon the apparent similarity in waveform and amplitude of EPs to different stimuli recorded at the same point. In addition, the ability of stimuli of different modalities to block each other equally well regardless of

the order of presentation supported the concept of a single activating system. By contrast, experiments conducted at the single unit level in the cat have found highly differentiated responding among individual cells in any one polysensory area (Bental and Bihari, 1963; Dubner and Rutledge, 1964; Dubner and Brown, 1965; Bettinger et al., 1967) and also have indicated general differences between the different areas with respect to the effectiveness of the different modalities (Dubner and Rutledge, 1964; Dubner, 1966). It is possible that in the studies referred to, such differences in responding were a consequence of intensity differences between the stimuli of different modalities. In the present study, the fact that nearly all cells showed well-marked inhibitory responses to all three modalities of stimuli is in accord with the suggestion of a single undifferentiated projection to the polysensory cortical area. Such a projection might originate in nonspecific areas of the thalamus of the rat, as has been suggested for the cat (Albe-Fessard and Rougeul, 1955 and 1958; Buser et al., 1958 and 1959). However, the early excitatory responses of the cells observed in the present study showed marked differences in magnitude as a function of stimulus modality. Some other projection system must, therefore, be adduced to account for the early excitatory responses. It would be difficult to explain why the synaptic potentials generated by both systems would not be equally represented in the gross EP. The observations in the present study thus do not appear to clarify the relation between single unit responses and the gross EPs in the polysensory cortical area.

III. Responses to compound stimuli as indices of integrative processes

Features of cell responses such as magnitude and temporal pattern presumably make it possible for a cell to transmit a variety of information about the various sensory inputs. These features might thus be described as the cell's "efferent pattern". A different question concerns the features of the input to which the cell is capable of responding. As was pointed out in the Introduction, such features of the stimulus as modality or ISI constitute an "afferent pattern" which defines conditions under which the cell is most likely to respond or which evoke the largest responses from the cell.

The role of polysensory inputs in the afferent pattern of the cells in the present experiment has already been mentioned. It was noted that the tactile modality appeared to be a dominant component in the afferent pattern of these units. A further question, however, concerns the effects of the compound stimuli (AV, AT, VT and AVT) on unit responding. The data of Experiment I indicated that for many units in the polysensory cortex, the compound stimuli AT and AVT produced higher response probabilities than the single stimuli did when presented separately. The effects of the compound stimuli as shown in Figure 17 suggest that the auditory and tactile inputs were integrated at some stage in the afferent path when stimuli of these modalities were presented simultaneously. The observation that the visual input did not appear to be integrated in a similar fashion is puzzling. Again, the intensity of the visual stimulus may be an explanatory factor. It is possible, however, that the timing of the afferent impulses from visual stimulation was such that they reached the cortex just at the time when the shorter-latency auditory or tactile

responses had produced profound inhibition. The longer latencies to the initial spikes following visual stimulation and the observation that the initial excitatory peaks in the histograms occurred later for the visual than for the tactile or auditory modalities are consistent with this explanation.

The longer latencies of responding to visual stimuli require some explanation. It seems unlikely that retinal delay or the length of the afferent path can account for the long latencies. In the cat the latencies of response in the polysensory cortex to visual stimuli are much shorter (Buser et al., 1959). The afferent path to the polysensory cortex for visual stimuli in the rat has not received electrophysiological study, so far as is known to this writer. Therefore, sources of central delay for visual stimulation remain to be identified.

The evidence of integration of the different sensory inputs in the firing patterns of units in Experiment II was equivocal. Some PST histograms for compound stimuli looked as though the separate modalities were indeed integrated by the cell, to produce histograms different from those produced by either stimulus separately. Other histograms for compound stimuli looked very similar to the histogram for the dominant stimulus when presented alone, as though the dominant stimulus effectively blocked the reception of the other modality of input. No single generalization thus appears to be applicable to the magnitude or pattern of responses to the compound stimuli, apart from the fact that responses to the compound stimuli exhibited early excitatory, later inhibitory, and late excitatory components similar to those observed for the single modalities. However, the latencies of initial spikes following the stimulus were shorter for

for the compound stimuli than for single stimuli (Table 10). In addition, the variability in latency was lower for almost all compound stimuli. It is noteworthy that the stimulus compounds tended to produce response latencies which were shorter than those of the separate component stimuli. It might have been expected that a stimulus compound would elicit a response at whichever was the shorter of the characteristic latencies of its components. Instead, the different compound stimuli had their own characteristic latencies. The fact that latencies for the combination AVT were the shortest and least variable suggests that this was the most effective stimulus among those tested. The further implication is that, for cells in the polysensory cortex, increasing the diversity of the inputs to a given cell is equivalent to increasing the intensity of a single input.

In summary, it appears that not only are the cells in this area of the cortex characteristically polysensory, but also that their responses are capable of reflecting complex aspects of the interactions between different sensory inputs to the organism. The possible participation of these neurons in specific examples of intersensory responses at the gross behavioral level remains to be examined and can only be suggested here. It is, however, concluded that the cells studied in this investigation appear to provide a likely physiological substrate for the performance of such behavioral responses.

Summary and Conclusions

Responses of single neurons in a nonspecific polysensory area of the cerebral cortex of the rat were studied by means of extracellular microelectrode recording. The responses were evoked by auditory (A), visual (V), and tactile (T) stimuli given alone or in combination. The stimuli consisted of single brief clicks, light flashes, and electric shocks to the paw. Stimulus programs were designed to examine the effects of stimulus modality and interstimulus interval (ISI) upon cell responding. Values for the ISI were 1, 2, 4, 8, and 10 sec. The experiment undertook to test two hypotheses suggested by observations in polysensory cortex of the cat: (1) that individual units in the polysensory cortex of the rat are polysensory (i.e., respond to more than one modality), and (2) that the degree of responding is an increasing function of the ISI.

The study consisted of two parts, referred to as Experiment I and Experiment II. In Experiment I an all-or-none response probability measure based on 10 stimulus trials was used as an index of cell responding under the various conditions. Units were recorded photographically and the recording intervals were limited to the 100 or 200 msec. following the stimulus. In Experiment II a response measure based on the peak frequency in a poststimulus time (PST) histogram was used as an index of cell responding. Unit responses were recorded on magnetic tape and the total interval used in analyzing the spike activity consisted of the 200 msec. preceding the stimulus and the 800 msec. following it.

The responses of most units in Experiment II displayed a characteristic temporal pattern, consisting of an early excitatory phase, a subsequent

inhibitory interval or depression in firing rate, and a later excitatory response. Reasons were discussed for considering that the same pattern characterized many units in Experiment I despite the fact that the recording intervals of Experiment I were not long enough to show such a pattern.

Instances of units showing variations from the typical response pattern were presented and their implications for the possible mechanism underlying the pattern of responding were discussed.

The latencies of the initial spikes following each type of stimulus were measured. The mean latency for the response to A was 48.0 msec. and to T was 49.0 msec. The mean latency of response to V was 69 msec. In addition to being longer, the latencies to V showed greater variability.

The results of both Experiments I and II supported the first hypothesis, in that 68.6% of the units in Experiment I and 87.9% of those in Experiment II were found to be polysensory. A majority of the polysensory units in both experiments were trisensory (35 out of 47) and the remaining 12 polysensory units were bisensory.

The three stimuli were not equally effective in eliciting unit activity. The paw shock was found to be the most effective for the cells sampled, and the light flash was the least effective for most units. The click was intermediate in its ability to evoke unit responses. The possibility that differences in intensity were responsible for this effect was discussed.

The second hypothesis, that the magnitude of responding is an increasing function of the ISI, was supported by responses to A and T, but not by responses to V. Although mean response magnitudes for A and T were increasing functions of the ISI, response magnitudes to V did not show a systematic increase.

The responses to the compound stimuli AV, AT, VT, and AVT were examined with respect to latency and magnitude. Response latencies were shortest for the compounds AT and AVT. The mean latency for AT was 37.5 msec. and for AVT was 36.9 msec. Thus, these latencies were shorter than for any of the stimuli given separately. The addition of V to A, to T, or to AT produced little or no change in mean response latency. A similar lack of effect for V was noted in the mean response probabilities of Experiment I. The probabilities of response to A, to T, and to AT were highly similar to those for AV, AT, and AVT, respectively. The PST histograms for the data in Experiment II revealed no consistent differences between the responses to compound stimuli and those to the individual stimuli presented separately. However, the number of cases representing any stimulus compound was relatively small in Experiment II.

It was concluded that the majority of the cells sampled in the present experiment, in addition to being polysensory, appeared to be integrating simultaneous auditory and tactile inputs. Evidence regarding the integration of the visual input with other modalities was inconclusive.

Some preliminary observations on the possible occurrence of habituation in the cells in the polysensory cortex of the rat were presented. These observations, together with the evidence of polysensory responsiveness and integration of inputs from different modalities, support the inference that the polysensory cortex of the rat is likely to be active in complex or integrative brain functions, particularly those involved in responding to diverse sensory inputs.

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APPENDIX A: Anesthesia

The chloralose used for the first 45 Ss was manufactured by Prolabo Laboratories, Rhone, France. Each anesthetic dose was mixed fresh for that day's experiment. The first few rats were given a dose of 110 mg/Kg IP. This dose proved to be insufficient, so the dose level was increased a small step at a time from one rat to the next, until a dose level was reached at which most if not all the rats were anesthetized within 30 min. after the injection, and at which no deaths occurred which were thought to be the result solely of the anesthetic. This dose level, as mentioned earlier, was 180 mg/Kg. When a new source for α-chloralose was used (Rossiger, New York), the dose level was decreased (to 120 mg/Kg. in one rat, to 150 mg/Kg in another) as it had been suggested that the Prolabo chloralose might have lost strength due to age. However even using the new chloralose it was found necessary to use 180 mg/Kg. A third brand of chloralose, (Merck, Darmstadt, Germany) was also tried and it too required a dose level of 180 mg/Kg to be effective.

The conclusion therefore seems justified that the usually quoted dose level of chloralose for the rat (55 mg/Kg, Barnes and Etherington, 1966) is not adequate for the particular strain or particular family of rats used in this experiment. Another possibility is that the dose levels quoted in the literature have been derived for albino rats, and that hooded rats in genera l may require a higher dose level.

APPENDIX B: Artificial respiration

In view of the wide agreement regarding the vulnerability of rats and other rodents to respiratory failure under anesthesia, it is of particular interest that reducing the delay between anesthesia and artificial respiration effected a remarkable improvement in the survival time and physiological condition of preparations used in the present research. For the first 47 rats used in this experiment, artificial respiration was not begun until after Flaxedil was given, usually 2 to 3 hours after the anesthetic took effect. This was after all surgical and other preparatory procedures were complete and electrical recording from the brain was to begin. Of these rats 38% died either before reaching the point of giving Flaxedil or soon after beginning recording. Starting with rat no. 48, artificial respiration was begun as soon as the tracheal cannula was in place, or else just subsequent to the venous cannulation. The time lag between surgical anesthesia and the beginning of artificial ventilation was thus reduced to approximately 30 min. Of the rats anesthetized subsequent to rat no. 48, only 23% died prematurely. The typical preparation appeared to remain in excellent condition up to the point at which the experiment was terminated upon the decision to sacrifice the rat, often 12 to 15 hours after the initial anesthetic dose.

It would thus seem that one way to improve the survival time of rats which must be anesthetized, is to arrange for their artificial ventilation as early as possible. It is apparently not necessary to wait for a paralyzing agent to inactivate the rat's own respiratory

mechanism before beginning artificial respiration, at least not when chloralose is used. One does not see double breathing or other signs of the rats' fighting the ventilatory rhythm imposed upon them.

APPENDIX C: Changes in spontaneous activity during the course of the experiment

The change in spontaneous activity did not appear to be related to any variable under the experimenter's control. It is possible that the spontaneous activity increased because of an improvement in the surgical technique of the experimenter, together with a concomitant shortening of the delay from induction of anesthesia to recording of unit activity. Against the latter point, however, is the fact that there was no decrease in spontaneous activity as the anesthetic effects diminished over time. Another possible source of a difference in spontaneous rates between Experiment I and Experiment II is the use of different artificial respirators. The respirator used in Experiment II was specifically designed for small animals such as rats and it may, therefore, have produced a more appropriate level of ventilation of the rats' lungs. Against this suggestion is the observation that the spontaneous rate increased gradually and progressively over time, rather than showing a sharp change in level when the change was made from the first to the second respirator. A similar argument can be used against the possibility that the differences in spontaneous rate were due to the different brands of chloralose used.

The most likely reason for the progressive change in spontaneous rate, apart from the possible improvement in surgical technique mentioned earlier, would appear to be some undetermined factor in the rats' physical condition which changed gradually over time. As an example of such a factor, a subacute respiratory infection was found to be present in the rat colony during the time that this experiment was in progress. Although

the rats showed no external symptoms of the infection and postmortem examination failed to reveal any gross signs of illness, the rats during this time were unable to survive more than a few hours at most under the anesthesia and surgery used in this experiment. After several weeks of treatment with an antibiotic in the drinking water, the rats showed remarkable improvement in their ability to survive anesthesia and surgery. Thus, it appears that there can be significant differences in the rats' physiological well-being unaccompanied by any external signs. It, therefore, seems possible that the change in spontaneous rate may have been related to some change in the general health of the rats which affected neural activity under anesthesia.

APPENDIX D
Numbers of units contributing to the means illustrated in Figure 15 and Figure 16

Figure 15

Stimulus	ISI	Mean	Number of units
A	1	1.4	5
	2	3.1	18
	4	4.6	21
	8	3.8	9
	10	5.3	8
V	1	2.2	5
	2	1.9	20
	4	2.1	22
	8	2.4	9
	10	1.7	9
T	1	2.3	6
	2	3.7	19
	4	5.1	21
	8	3.6	10
	10	4.3	7

Figure 16 A, V, T entries are the same as those above.

AV	1	1.14	6
	2	3.14	14
	4	4.5	17
	8	4.2	9
	10	5	8
AT	1	3.4	5
	2	5.5	15
	4	6.6	19
	8	6.5	8
	10	7.3	7
VT	1	3.2	5
	2	3.7	15
	4	5.0	20
	8	3.5	8
	10	3.4	7
AVT	1	3.0	12
	2	4.5	17
	4	7.5	20
	8	6.4	9
	10	7.0	7

Table 1 Mean initial spike latency for each stimulus modality

A	V	T
49.0 msec	69.12 msec	48.0 msec
S.D. = 19.45	S.D. = 36.95	S.D. = 20.49
n = 65	n = 60	n = 69

Standard deviations and number of units contributing to means are listed in order below each mean.

Table 2 Number of cell in Experiment I responding to the different stimulus modalities and combinations

i	ii	iii	iv	v	vi	vii	viii	ix
Total # of cells tested with all stimuli (A,V,T)	# cells resp. to A,V,T	# cells resp. to A,T but not V	# cells resp. to A,V but not T	# cells resp. to V, T but not A	# cells resp. only to A	# cells resp. only to V	# cells resp. only to T	# cells resp. to none of A,V,or T
35 (100%)	13 (37.1%)	10 (28.6%)	1 (2.9%)	0 (0%)	4 (11.4%)	1 (2.9%)	5 (14.3%)	1 (2.9%)

Total # cells resp. to A and V (ii + iv)	Total # cells resp. to A and T (ii + iii)	Total # cells resp. to V and T (ii + v)	Total of all cells resp. to A (ii + iii + iv + vi)	Total of all cells resp. to V (ii + iv + v + vii)	Total of all cells resp. to T (ii + iii + v + viii)
14 (40.0%)	23 (65.7%)	13 (37.1%)	28 (80.0%)	15 (42.9%)	28 (80.0%)

Data only from units tested with all 3 modalities. The number of trials for a given modality varied between units and depended upon the number of different ISIs at which a unit was tested.

Table 3 Number of cells in Experiment II responding to each modality tested.

	A		V		T	
	Tested	Responded	Tested	Responded	Tested	Responded
Number of Units	34	29 (85.3%)	37	31 (83.8%)	42	42 (100%)

Table 4 Polysensory responses of units in Experiment II

Number of cells	Tested	Responding to all stimuli tested	Response of remainder
Stimulus condition tested			
All 3 stimuli (A; V; T)	26	22 (84.6%)	1 cell - V & T 3 cells - T only
Two stimuli (A; V) or (A; T) or (V; T)	7	6 (85.7%)	1 cell - T only
One stimulus only (A); (V); or (T)	20	18 (90%)	2 cells - tested to V, no response
	3	Fired too infrequently to determine whether response occurred.	
Total number of cells in Experiment II	56		

Table 5 Response probabilities of a single unit recorded during Experiment I

ISI (sec)	1	2	4	8	10	Mean
Stimulus						
A	.4	.1	.5	.5	.6	.42
V	.4	.0	.2	.1	.1	.16
T	.2	.1	.9	.2	.6	.40
AV	.1	.2	.7	.6	.5	.42
AT	.4	.2	.7	.8	.8	.58
VT	0	.4	.3	.2	.7	.32
AVT	.5	.4	.6	.7	.10	.64
Mean	.29	.20	.56	.44	.61	

Table 6 Summary of analysis of variance for the histogram difference scores for the auditory stimulus

Source	SS	df	MS	F
Between Subjects		26		
A	11.08	1	11.08	0.12
Ss within groups	2,279.4	25	91.18	
Within Subjects		243		
B	0	1	0	
AB	0.126	1	0.126	
B x Ss in groups	391.08	25	15.64	
C	485.60	4	121.40	6.71**
AC	36.13	4	9.03	0.50
C x Ss in groups	1,808.73	100	18.09	
BC	39.78	4	9.95	0.50
ABC	70.63	4	17.66	0.71
BC x Ss in groups	2,493.48	100	24.93	

**p .01 ($F_{.99}$ = 3.65, df = 4, 60)

A = Order (ascending 1st or 2nd)

B = Sequence (ascending vs descending)

C = ISI

Table 7 Summary of analysis of variance for the histogram difference scores for the visual stimulus

Source	SS	df	MS	F
Between Subjects		25		
A	61.07	1	61.07	0.03
Ss within groups	45,043.80	24	1,876.83	
Within Subjects		234		
B	13.81	1	13.81	1.66
AB	13.20	1	13.20	1.59
B x Ss in groups	199.11	24	8.30	
C	36.32	4	9.08	0.81
AC	52.28	4	13.07	1.16
C x Ss in groups	1,077.72	96	11.23	
BC	42.25	4	10.56	0.14
ABC	52.99	4	13.25	0.18
BC x Ss in groups	7,000.27	96	72.92	

A = Order (ascending 1st or 2nd)

B = Sequence (ascending vs. descending)

C = ISI

Table 8 Summary of analysis of variance for the histogram difference scores for the tactile stimulus

Source	SS	df	MS	F
Between Subjects		27		
A	281.76	1	281.76	0.50
Ss within groups	14,629.30	26	562.66	
Within Subjects		252		
B	2.27	1	2.27	0.13
AB	10.96	1	10.96	0.63
B x Ss in groups	450.13	26	17.31	
C	132.53	4	33.13	2.82 *
AC	80.16	4	20.04	1.70
C x Ss in groups	1,223.50	104	11.76	
BC	18.04	4	4.51	0.13
ABC	42.08	4	10.52	0.31
BC x Ss in groups	3,547.24	104	34.11	

*p .05 ($F_{.95}$ = 2.52, df = 4, 60)

A = Order (ascending 1st or 2nd)

B = Sequence (ascending vs descending)

C = ISI

Table 9 Analysis of variance, response magnitudes for all cells tested with all stimulus modalities and all ISIs

Source	SS	df	MS	F
Between Subjects	5,290.55	18	293.92	
Within Subjects		266		
ISI	194.99	4	48.75	3.71**
ISI X subjects	947.32	72	13.16	
Modality	1,331.27	2	655.64	3.93*
Modality X subjects	6,099.35	36	169.43	
ISI X Modality	130.05	8	16.26	1.91 †
ISI X Modality X subjects	1,225.93	144	8.51	

*p .05 ($F_{.95}$ = 3.26, df = 2, 36)

**p .01 ($F_{.99}$ = 3.60, df = 4, 70)

† $F_{.95}$ = 2.00, df = 8, 150

Table 10 Comparison between mean initial spike latencies for each compound stimulus as for each separate stimulus modality.

Stimulus	A	V	T	AV	AT	VT	AVT
Mean latency	49.0	69.1	48.0	48.9	37.3	44.3	36.9
S.D.	19.5	36.9	20.5	25.7	16.2	15.0	14.0
n	65	60	69	43	44	43	39

n = number of units contributing to each mean

S.D. = Standard deviation

Table 11 Mean response magnitudes for each ISI under the different conditions of ascending and descending ISI sequences

Stimulus	A					V					T				
ISI	1	2	4	8	10	1	2	4	8	10	1	2	4	8	10
Ascending sequence (ISI = 1, 2, 4, 8, 10)	1.85	2.93	3.81	5.81	5.34	1.94	2.53	2.70	2.52	1.61	6.86	6.34	7.62	9.00	8.13
Descending sequence (ISI = 10, 8, 4, 2, 1)	1.32	3.62	5.02	5.03	4.78	2.93	2.59	1.68	4.08	2.62	6.13	6.97	7.39	7.27	8.17

Figure 1. The relation between primary cortical areas and the association response fields in the cortex of the cat.

AI - auditory area I

AII - auditory area II

Ep - ectosylvian auditory area

SI - somatic sensory area I

SII - somatic sensory area II

MI - somatic motor area I

VI - visual area I

VII - visual area II

ALA - anterior lateral association area

AMSA - anterior middle suprasylvian association area

PMSA - posterior middle suprasylvian association area

PCA - pericruciate association area

(Redrawn from Thompson, 1967)

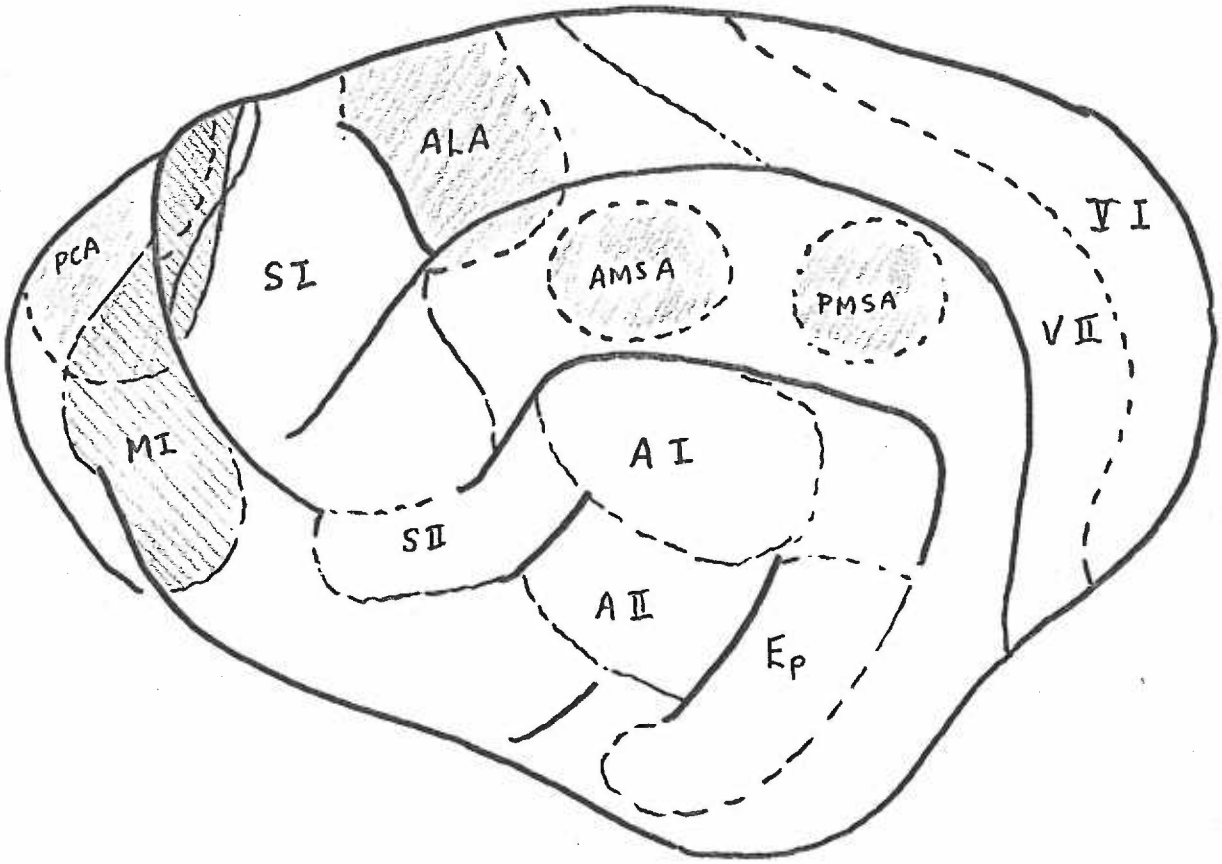
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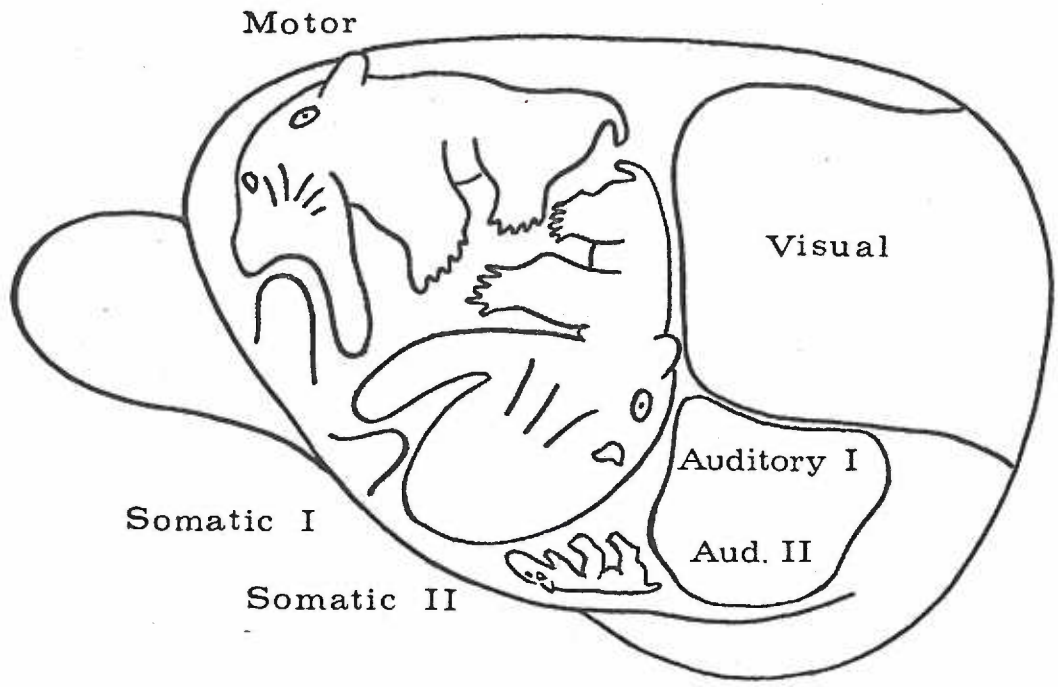
Figure 2. The relation between primary cortical areas and the nonspecific polysensory area in the rat cortex.

(a) Primary cortical areas. (Redrawn from Woolsey, 1958)

(b) The nonspecific polysensory area. (Redrawn from Bliss, personal communication, 1968)

B - bregma

L - lambda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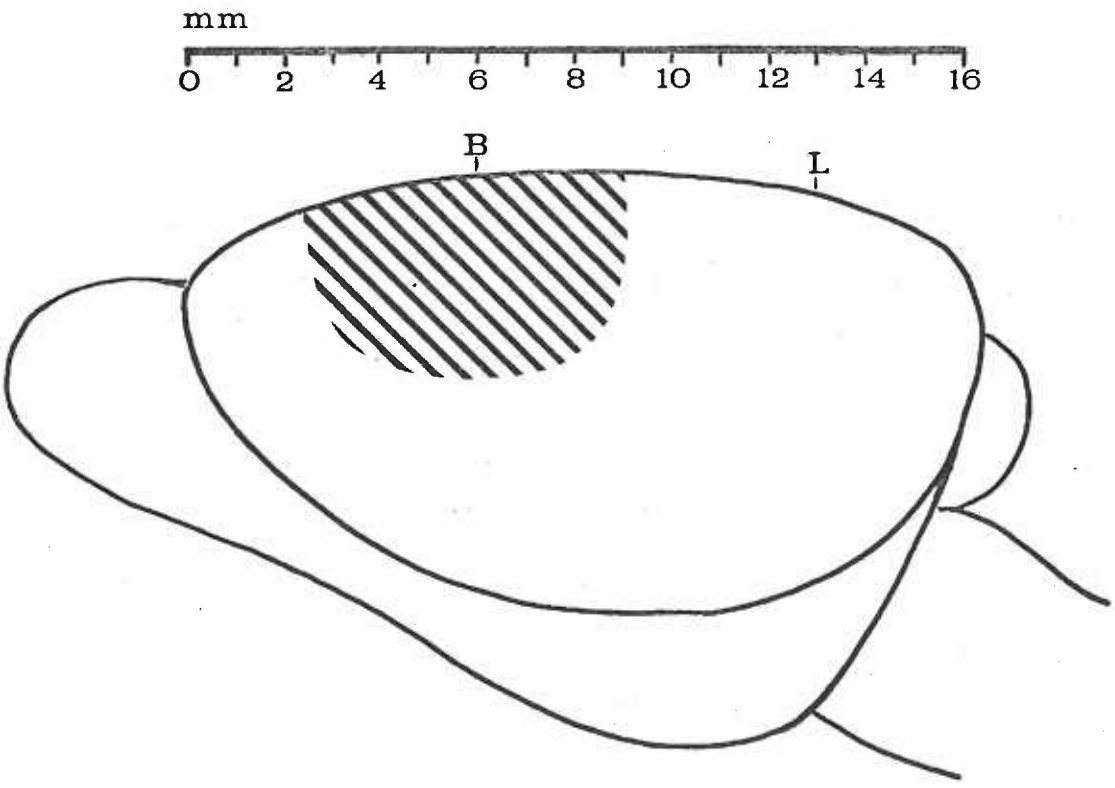
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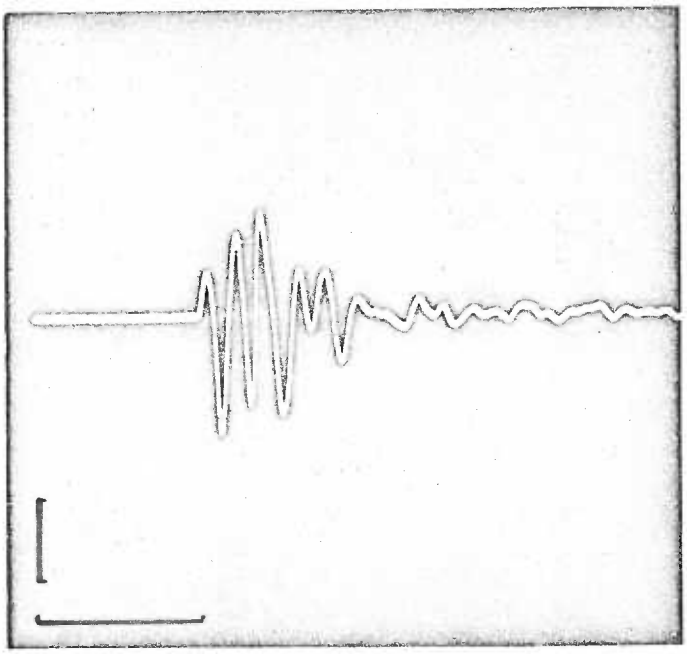
Figure 3. Calibration of the click and flash stimuli.

(a) The oscilloscope display of a single click stimulus. Calibrations: 50 mv., 1 msec.

(b) The relation between voltage output of the photocell and intensity settings of the Grass Photostimulator. The voltage output corresponding to the flash from the stimulator used in the experiment is shown as a solid dot on the extrapolated curve for the Grass unit.



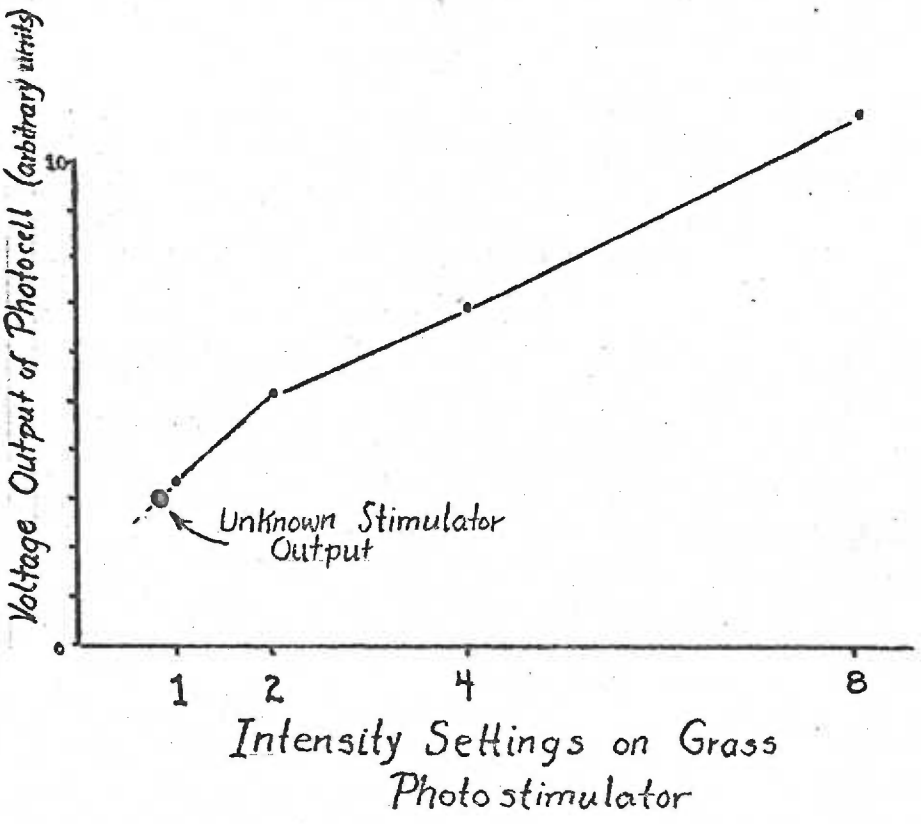
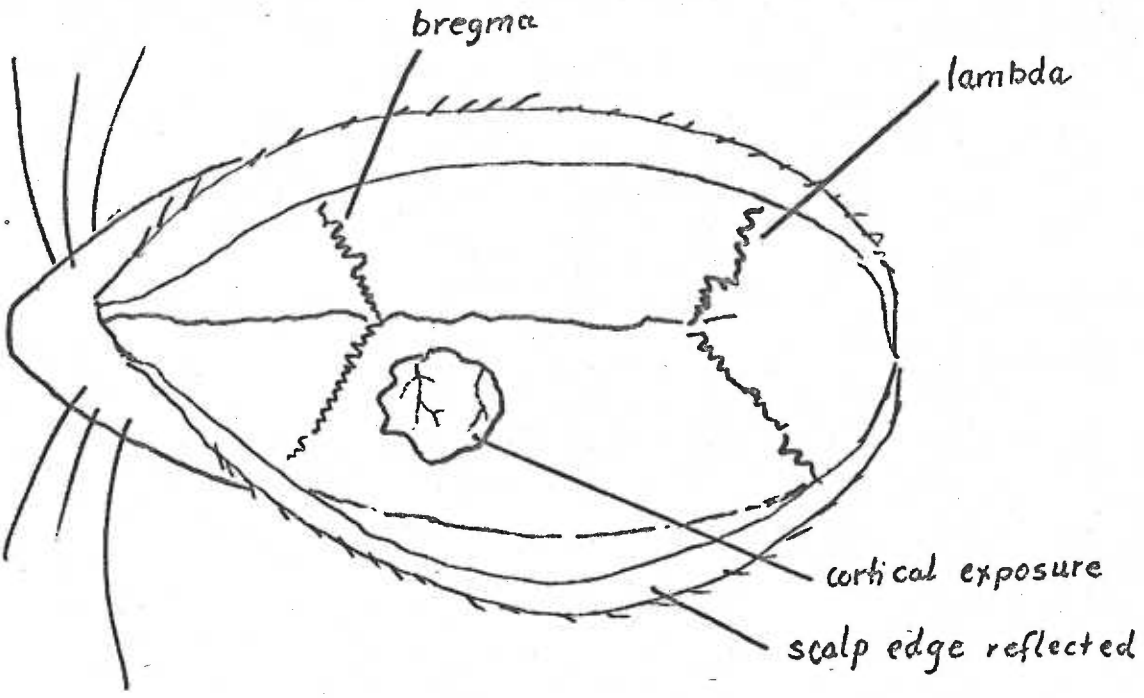

Voltage Output of Photocell (arbitrary units)
10
0
Unknown Stimulator Output
1
2
4
8
Intensity Settings on Grass Photostimulator

Figure 4. (a) Diagram of a typical cortical exposure made in the present experiment. Sutures used as reference points:

B - Bregma

L - Lambda

(b) Electrode penetrations from which the units reported in the study were recorded.


bregma
lambda
cortical exposure
scalp edge reflected

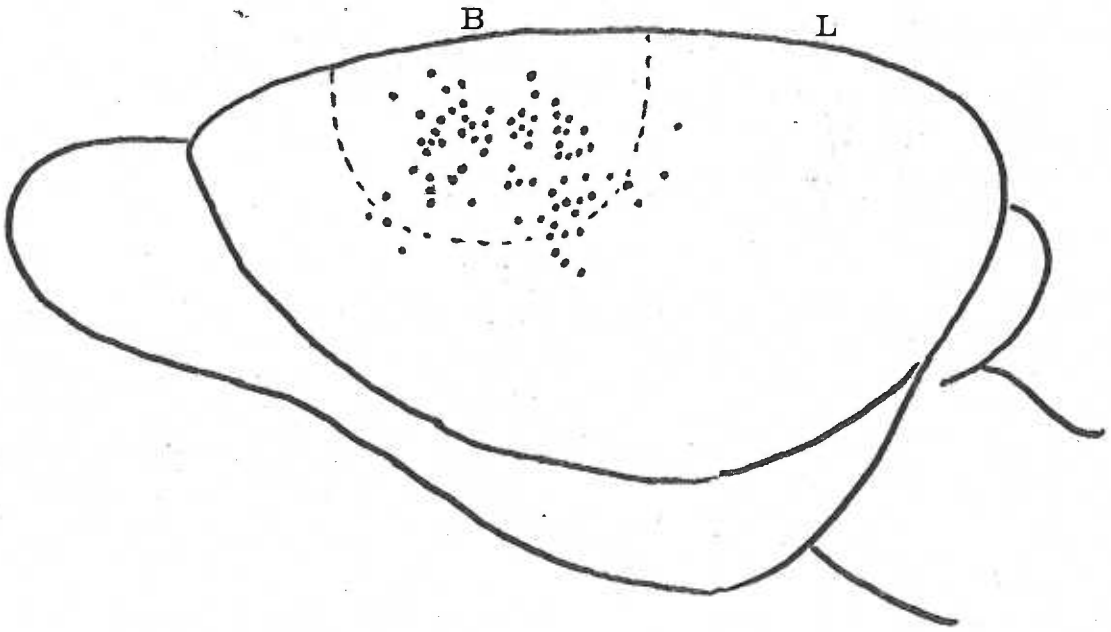

B
L

Figure 5. Activity of a single unit recorded during Experiment II. Responses to auditory, visual, and tactile stimuli. A series of 11 responses to each stimulus modality at an ISI of 3.2 sec is shown. The first trial is at the top of each series. The stimulus occurred at the beginning of each trace. All traces were 200 msec in duration. A - auditory; V - visual; T - tactile. Spike polarity shown positive upwards.

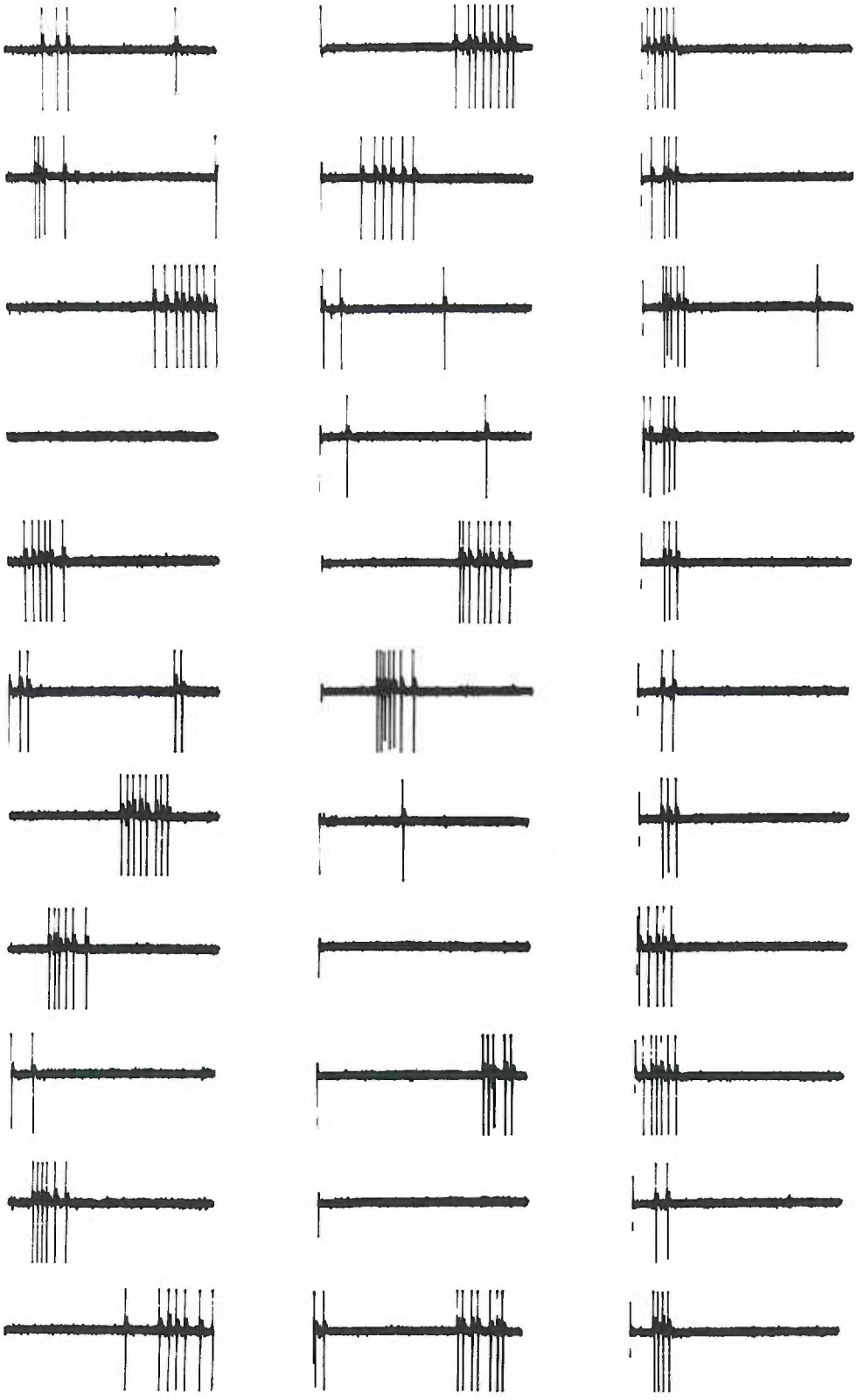
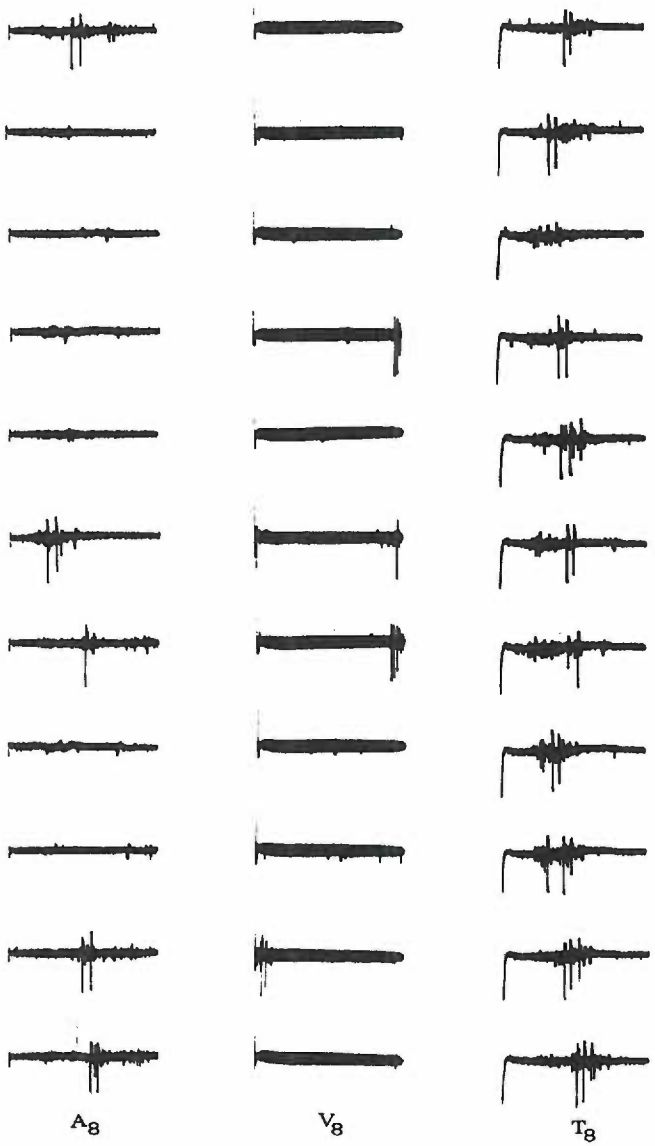

A
V
T

Figure 6. Activity of a unit recorded during Experiment I. Responses to auditory, visual, and tactile stimuli at two different ISIs.

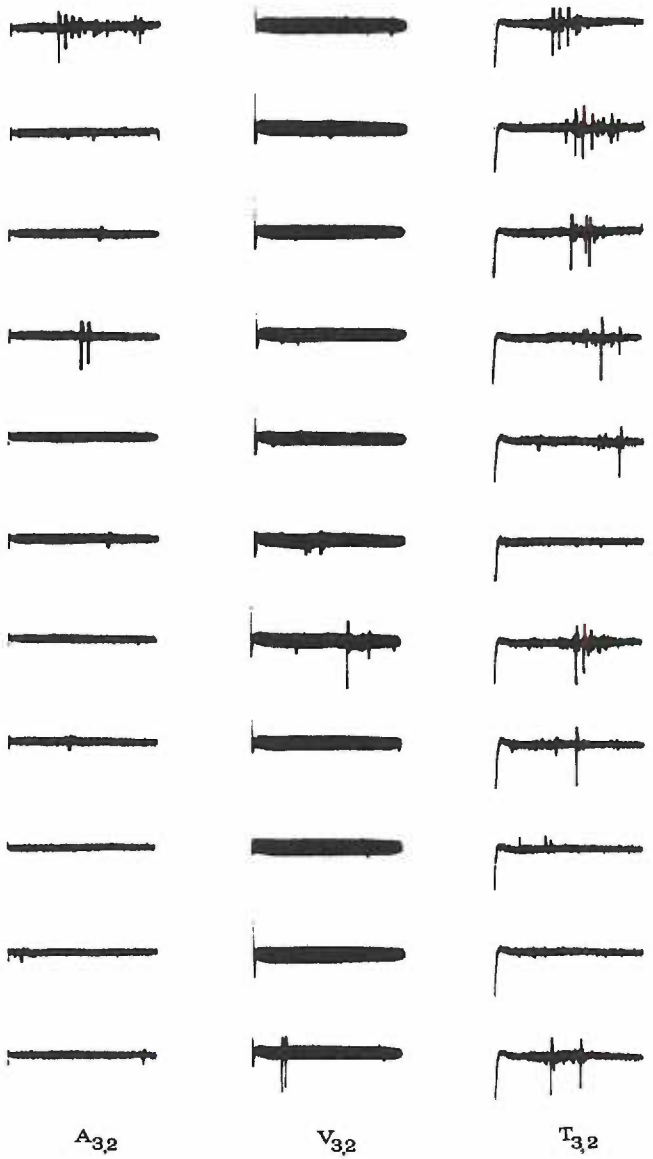
(a) ISI of 8 sec.

(b) ISI of 3.2 sec.

Series of 11 responses to each modality, with the first trial at the top for each series. The stimulus occurred at the beginning of each trace. Sweep duration was 100 msec for A and T, 200 msec for V. Spike polarity, positive upwards. Spikes have been retouched.



(a)

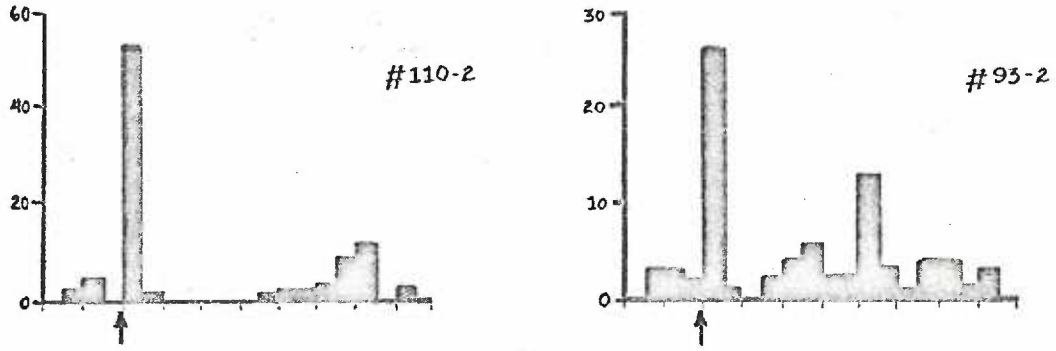


(b)

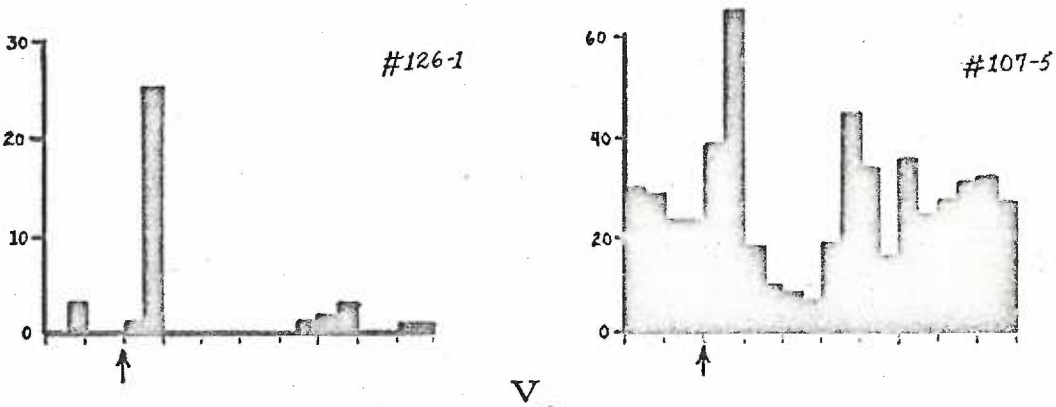
Figure 7. PST histograms of typical units in response to different modalities of stimulation.

The numbers on the ordinate represent counts per 50 msec interval. Intervals marked below the abscissa, 100 msec. The arrow indicates the occurrence of the stimulus. Each unit is identified by a number corresponding to the experiment in which the unit was recorded.

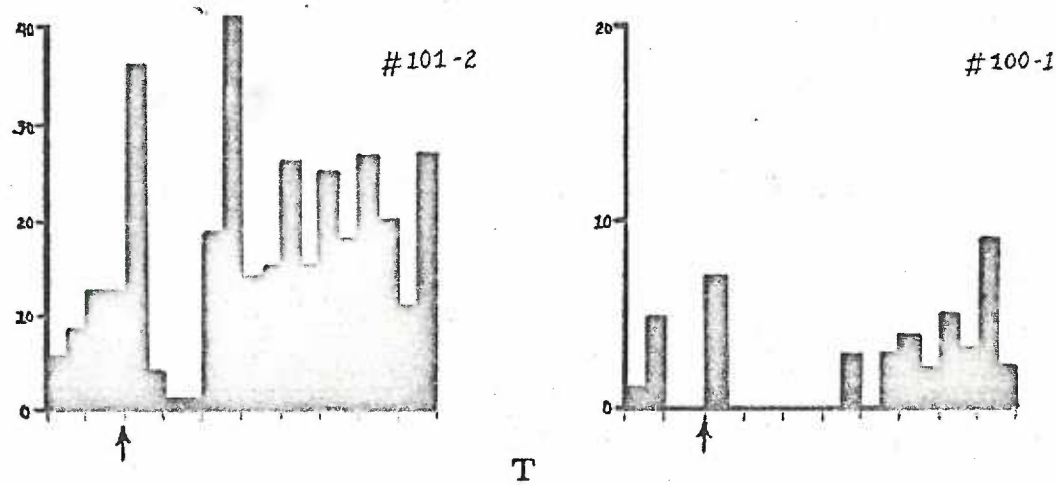
A: auditory, V: visual, T: tactile.


60
40
20
0
#110-2
30
20
10
0
#93-2

A


30
20
10
0
#126-1
60
40
20
0
#107-5

V


40
30
20
10
0
#101-2
20
10
0
#100-1

T

Figure 8. Dot patterns showing the responses of a single unit to various stimuli.

Each line of dots is the record of spike discharges during a single trial, and represents an oscilloscope sweep lasting 1 sec. The occurrence of the stimulus is represented by the vertical column of dots corresponding to the stimulus artefact. The sweep was initiated 200 msec. before each stimulus. The first trial is at the top of each array of 10 trials under one ISI. A cyclic firing tencency can be seen in many of the displays, particularly in the displays corresponding to A_4 and to the compound stimuli. Stimuli in each display were as follows: (A) - spontaneous activity; (B) - A_4; (C) - V_{10} i; (D) - T_2; (E) - AV_4; (F) - AT_8; (G) - VT_{10}; (H) - AVT_2. The subscript refers to the ISI. The particular ISI value for which responses were the clearest was selected in each case. Dots were retouched in some cases.


A
B
C
D
E
F
G
H
100 msec

Figure 9. The effects of the ISI upon the cyclic firing tendency of one cell.

The stimulus was T in every array. Cyclic firing is especially evident in (D) and (F).

(A) spontaneous activity

(B) T_1

(C) T_2

(D) T_4

(E) T_8

(F) T_{10}

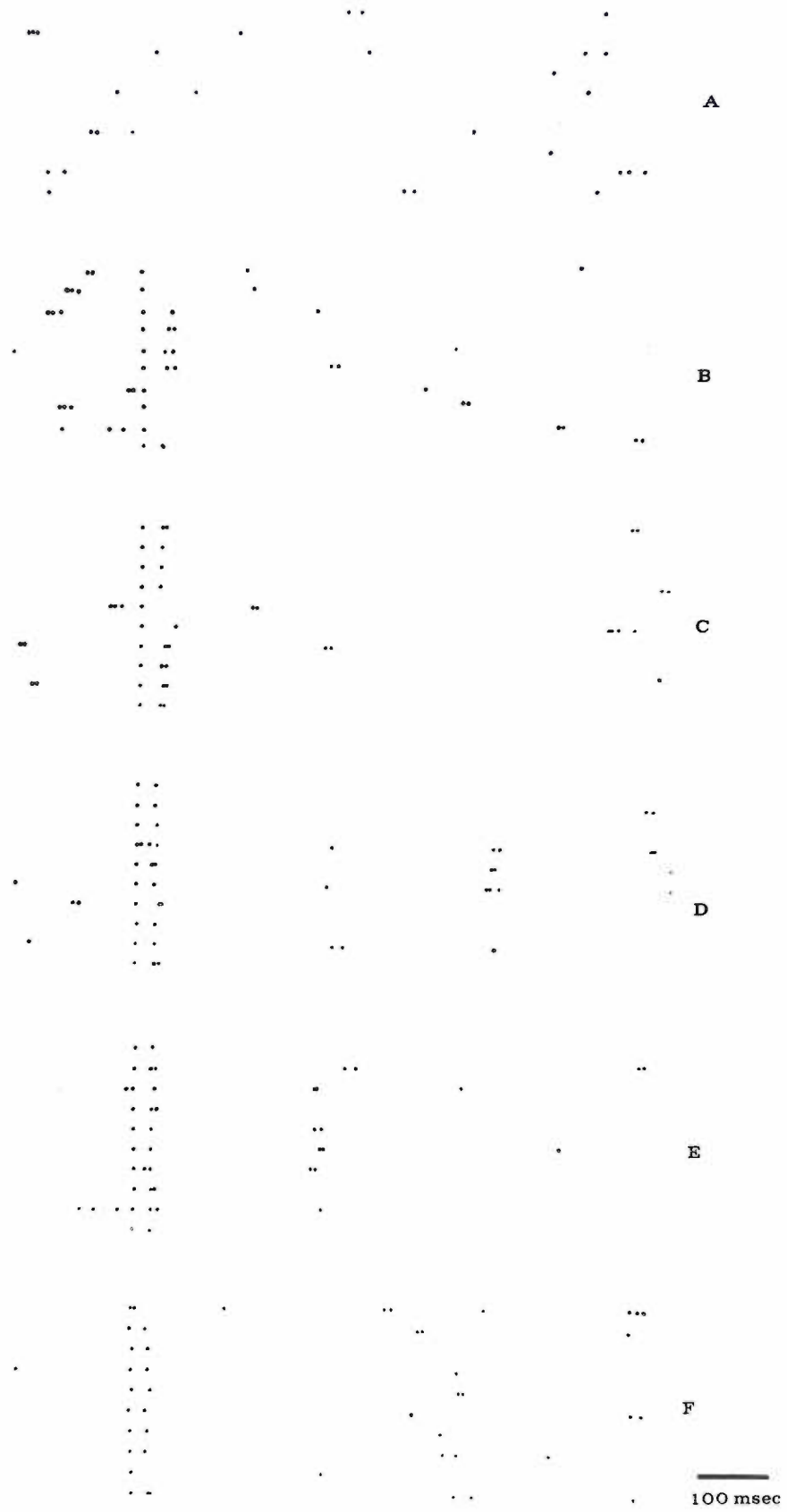

A
B
C
D
E
F
100 msec

Figure 10. Responses of two different cells showing inhibitory interval not preceded by an early excitatory response.
The histograms show the responses of the cell to 50 trials with the same stimulus modality as that used in the 10 trials shown in each dot pattern to the left. The arrow marks the occurrence of the stimulus. Intervals along abscissa, 50 msec.

Unit # 105-2:

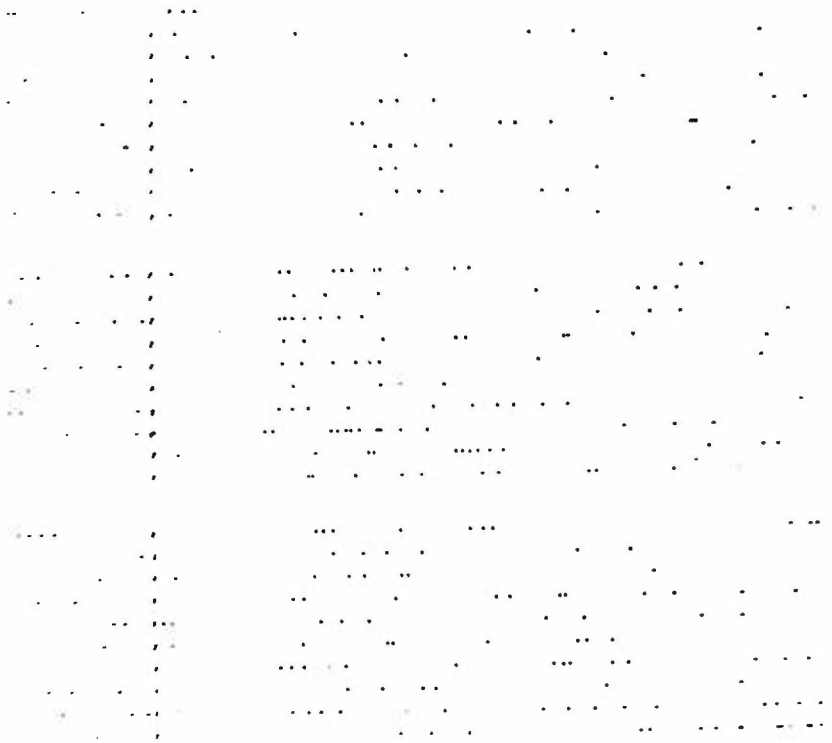
(A) Dot pattern, A_2

(B) Dot pattern, T_2

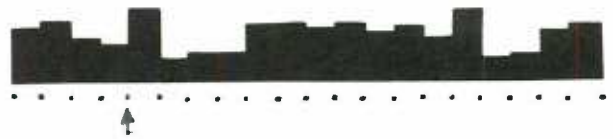
(C) Dot pattern, VT_2

Unit # 103-2:

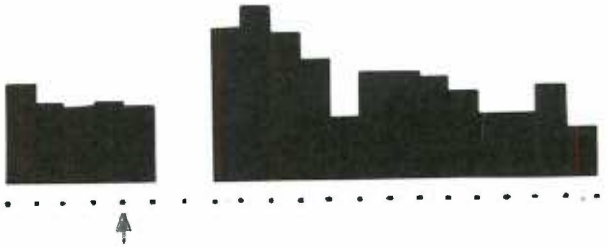
(D) Dot pattern, T_{10}



#105-2



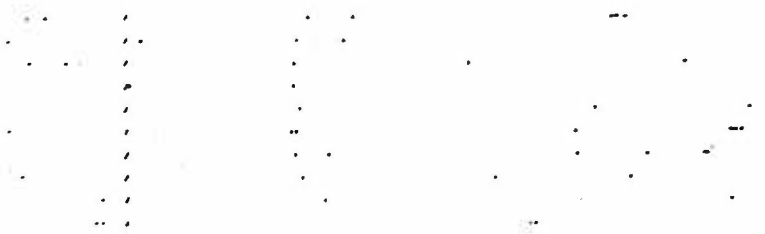
A



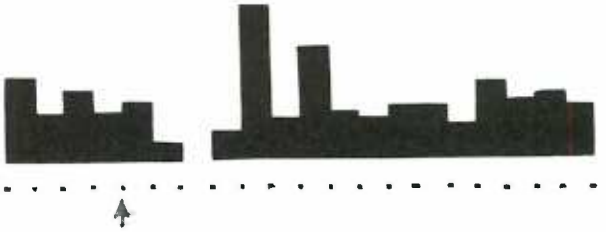
B

C

100 msec



#103-2



D

Figure 11. Responses of two different cells showing later responding to V than to A or T.

The histograms and dot patterns are drawn on the same time scale to facilitate comparison. Intervals along abscissa, 50 msec.

(a) A unit exhibiting later responses to V than to A.

(A) Dot pattern: 10 trials with A

Histogram: 50 trials with A under all ISIs

(B) Dot pattern: 10 trials with V

Histogram: 50 trials with V under all ISIs

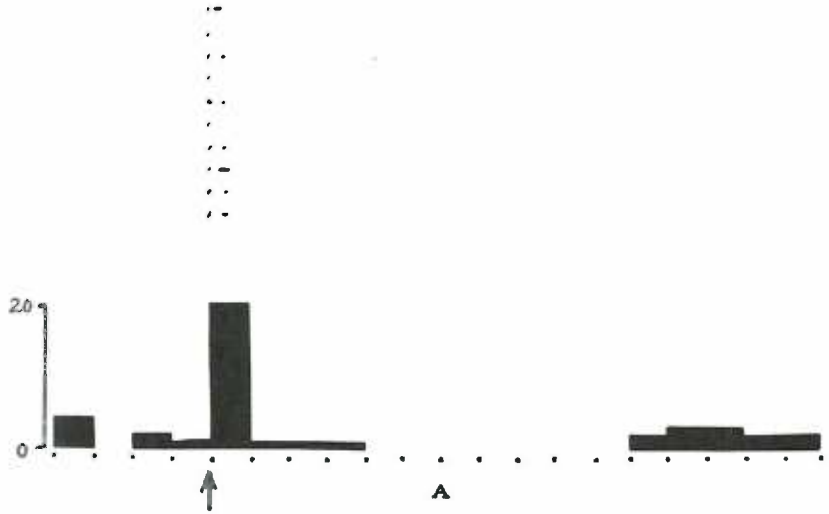
(b) A different unit exhibiting later responses to V than to T.

(A) Dot pattern: 10 trials with T

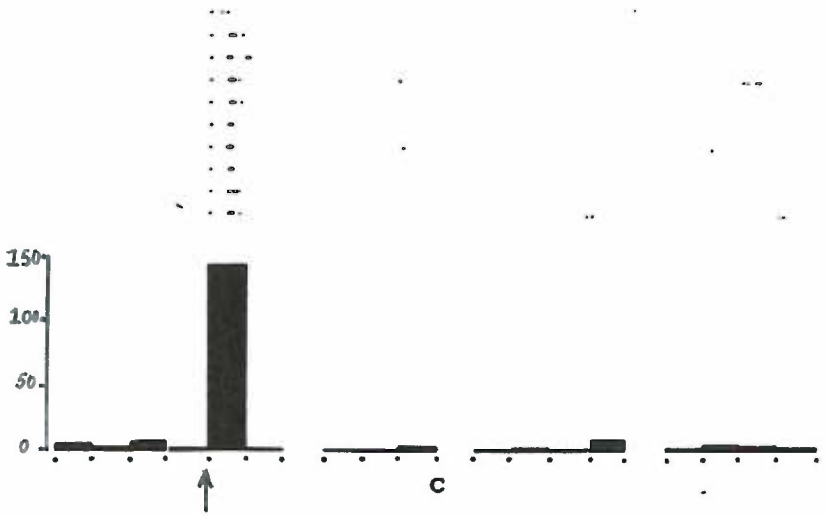
Histogram: 50 trials with T under all ISIs

(B) Dot pattern: 10 trials with V

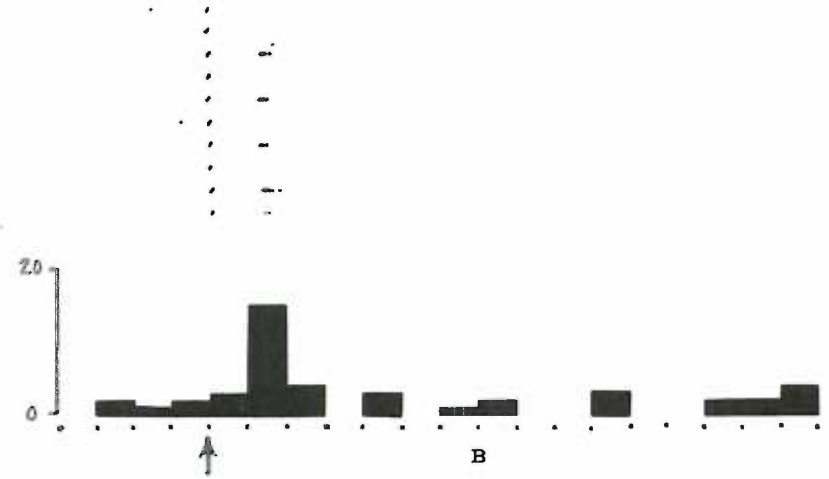
Histogram: 50 trials with V under all ISIs



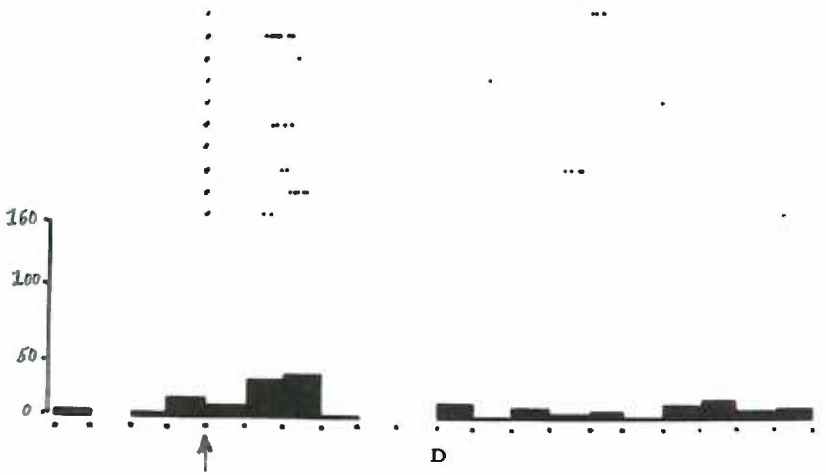
#114-1



#114-3



(a)



(b)

Figure 12. Slow evoked potentials to the three different stimuli recorded at one point within the nonspecific polysensory cortex.

A - auditory

V - visual

T - tactile

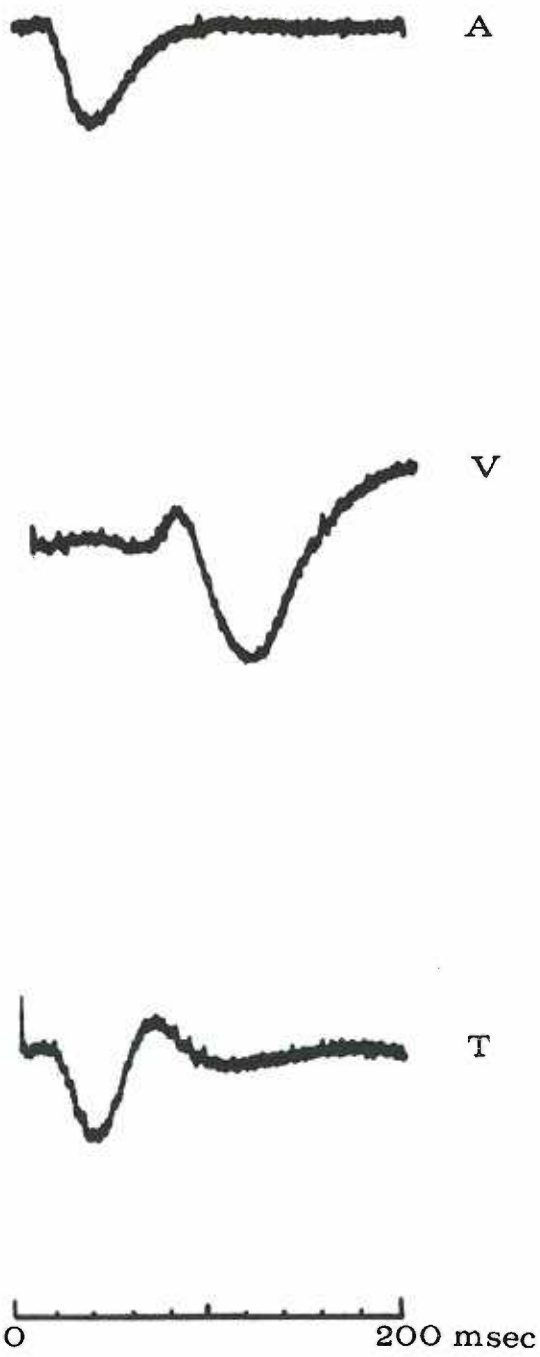
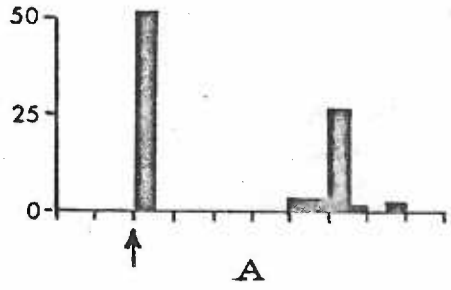
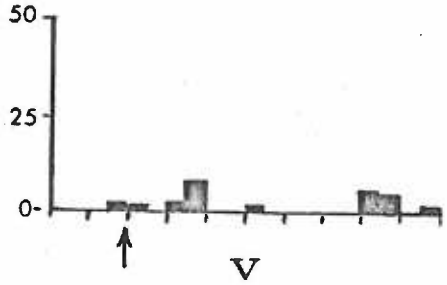

A
V
T
0
200 msec

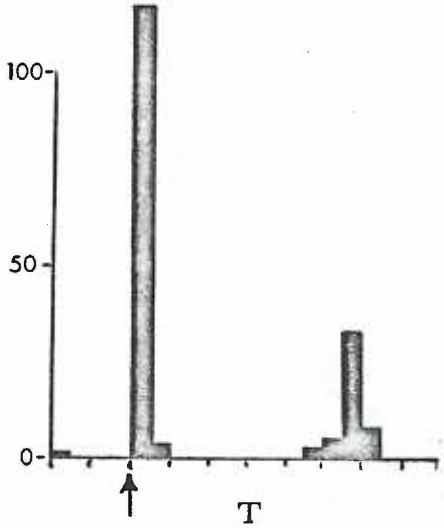
Figure 13. The effects of stimulus modality on the response of a single unit.

Each histogram represents 50 trials with the stimulus modality indicated, under all ISIs. Numbers on the ordinate represent counts per 50 msec. Note the difference in scales. Intervals along abscissa, 100 msec.





#108-1



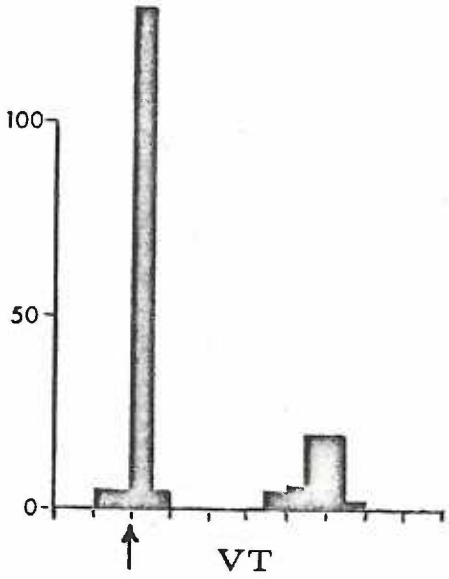


Figure 14. Dot patterns of a single cell showing the effect of ISI on responding to three different modalities.

(A) A_1	(F) T_1	(K) VT_1
(B) A_2	(G) T_2	(L) VT_2
(C) A_4	(H) T_4	(M) VT_4
(D) A_8	(I) T_8	(N) VT_8
(E) A_{10}	(J) T_{10}	(O) VT_{10}

The arrows mark the occurrence of the stimulus. This unit showed no spontaneous activity whatsoever, so no prestimulus control interval is shown for any of the dot patterns in this figure.

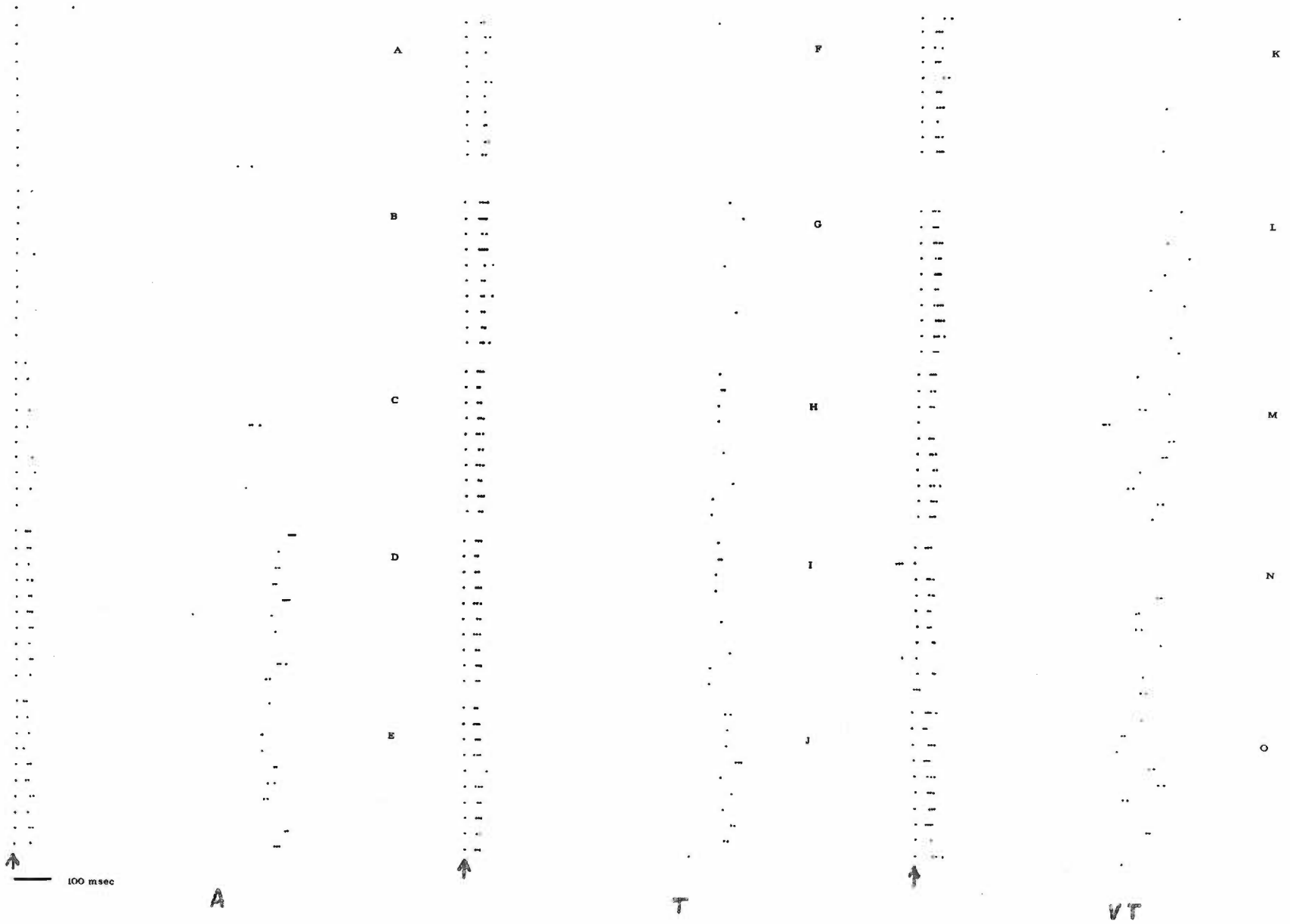

A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
100 msec
A
T
VT

Figure 15. Mean response probabilities of cells in Experiment I as a function of ISI and stimulus modality.

The number of units contributing to each point plotted in the graph is given in Appendix D.

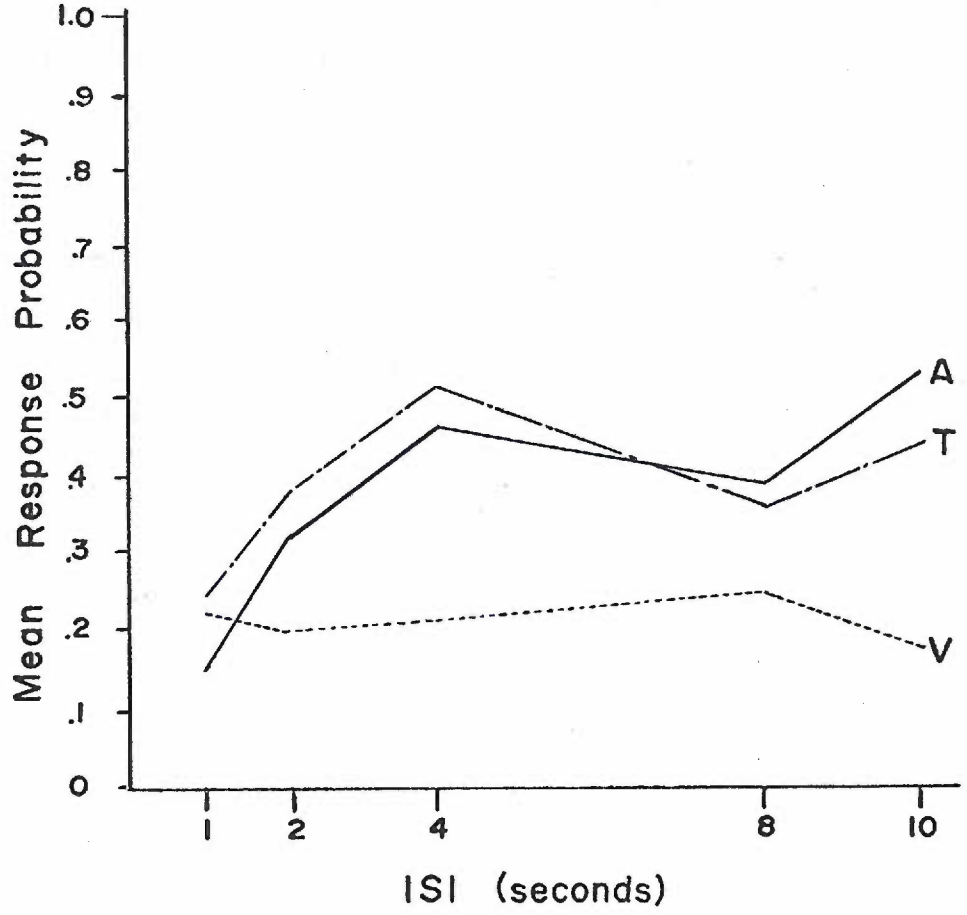

Mean Response Probability
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
A
T
V
1
2
4
8
10
ISI (seconds)

Figure 16. Mean response magnitudes of cells in Experiment II as a function of ISI and stimulus modality.

Each point represents mean response magnitudes from the same group of 19 cells.

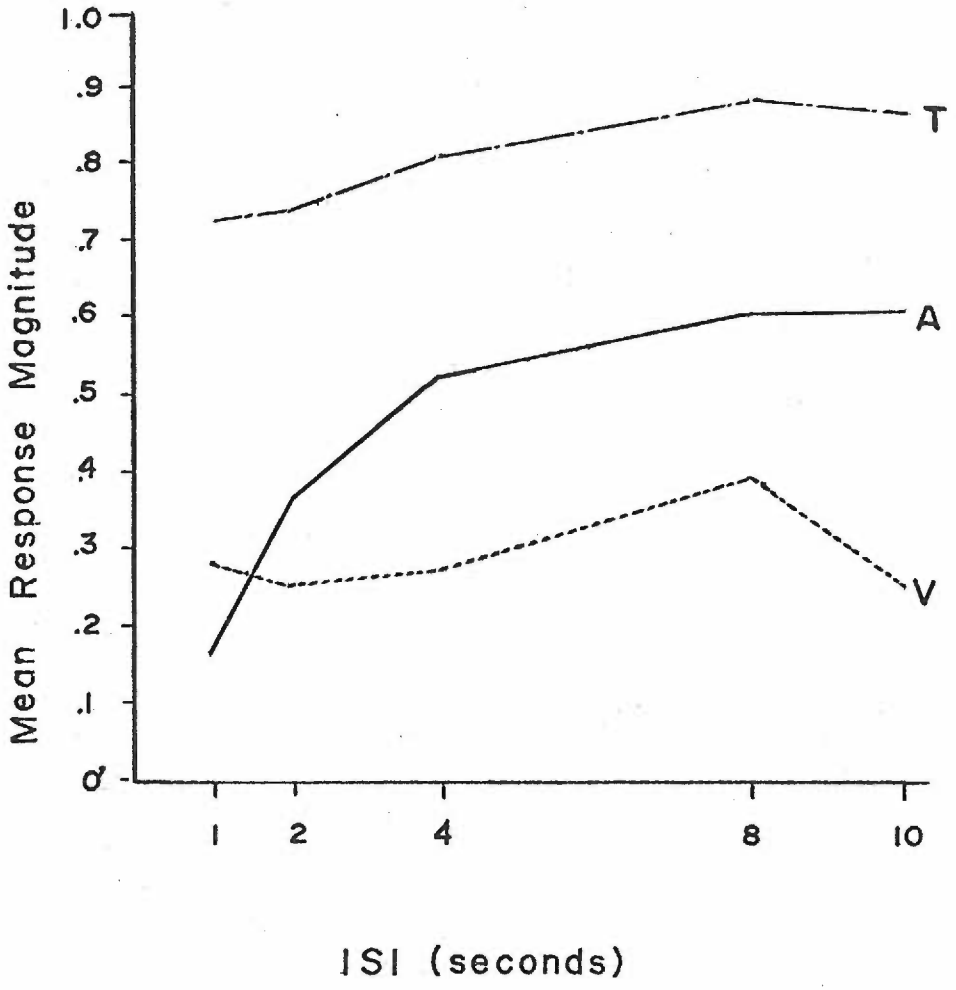

1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
Mean Response Magnitude
T
A
V
1
2
4
8
10
ISI (seconds)

Figure 17. Mean response probabilities of cells in Experiment I showing the effect of stimulus combinations.
The curves for A, V, and T are identical with those shown in Figure 15. Note the expanded scale on the ordinate.

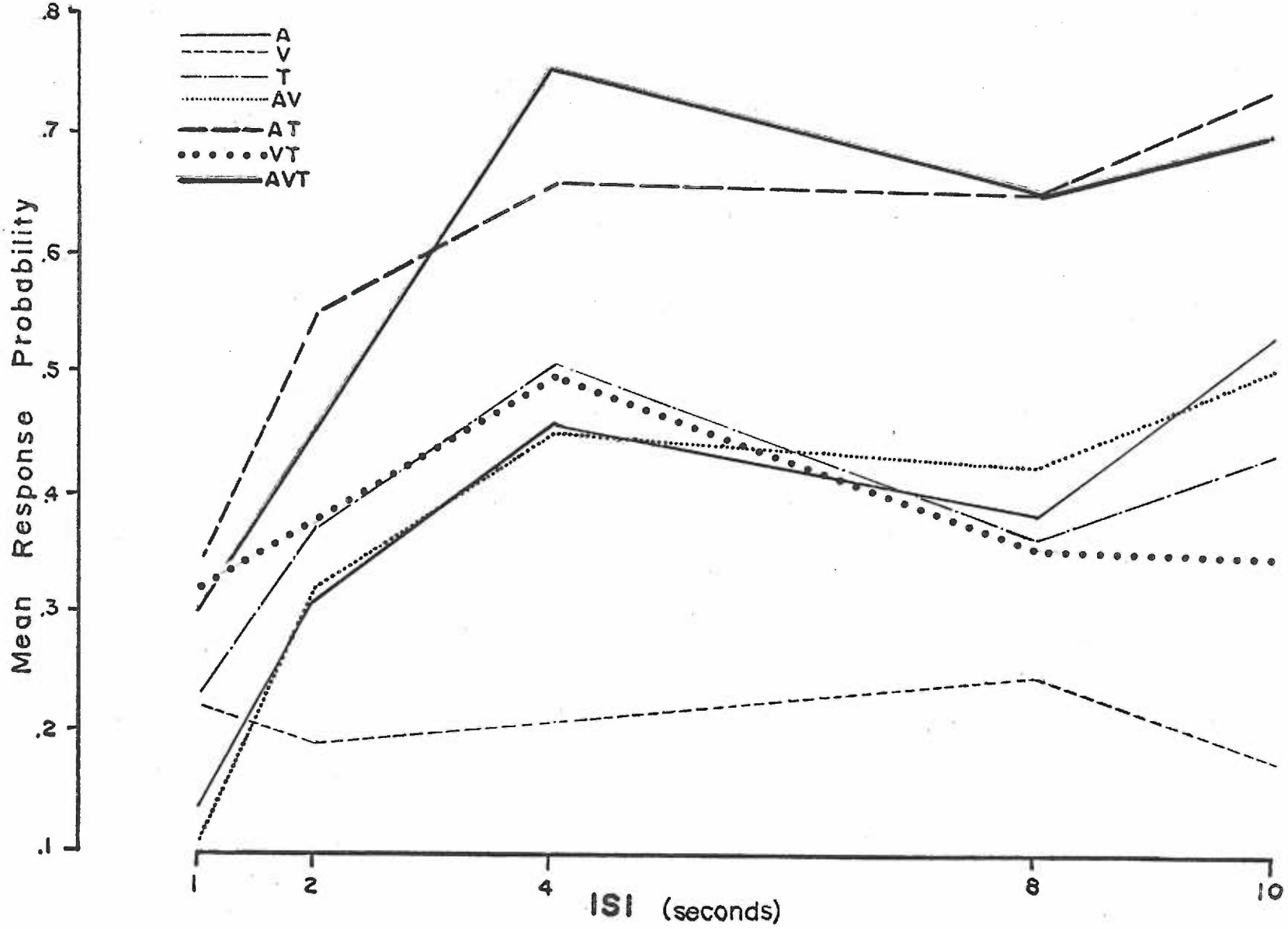
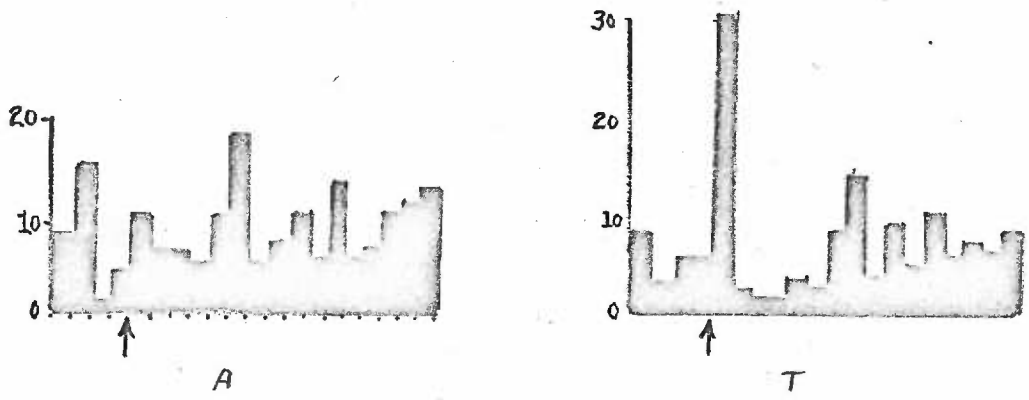

A
V
T
AV
AT
VT
AVT
Mean Response Probability
.8
.7
.6
.5
.4
.3
.2
.1
1
2
4
8
10
ISI (seconds)

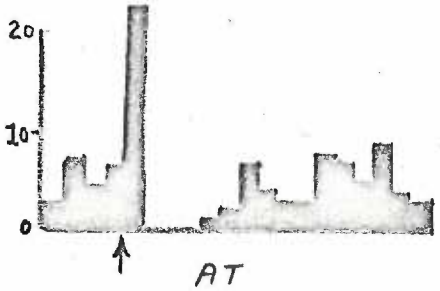
Figure 18. PST histograms of unit responses to compound stimuli. Histograms of responses to the separate stimulus modalities are shown for comparison. The response to the compound stimulus appears similar to that for a single stimulus modality.

(a) Unit # 94-2: Responses to A, T, and AT

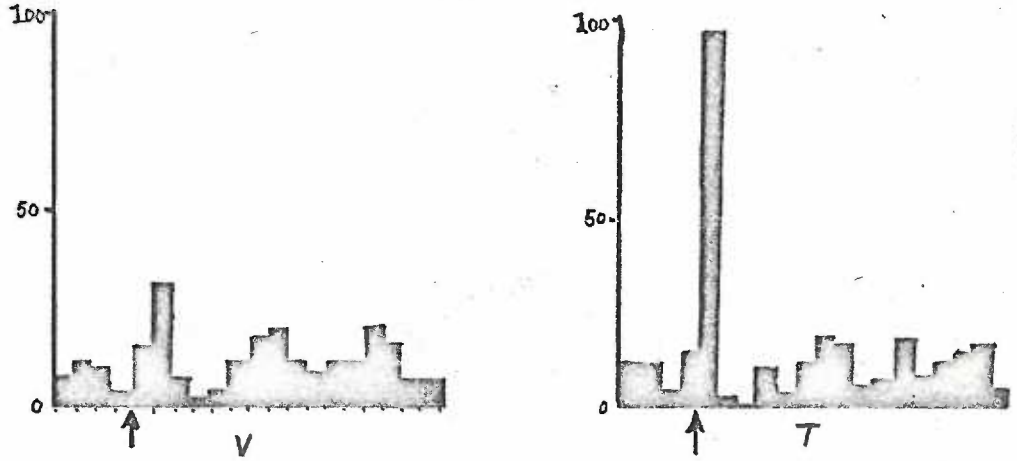
(b) Unit # 96-2: Responses to V, T, and VT



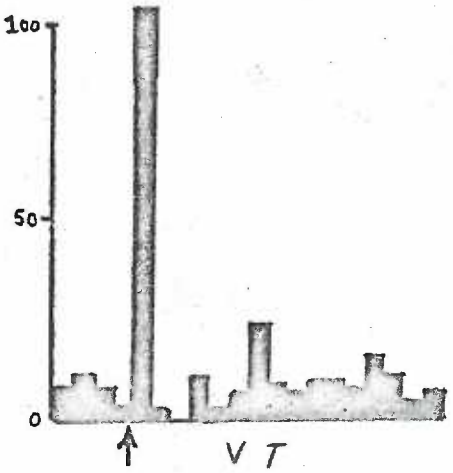
H94-2



(a)



H96-2

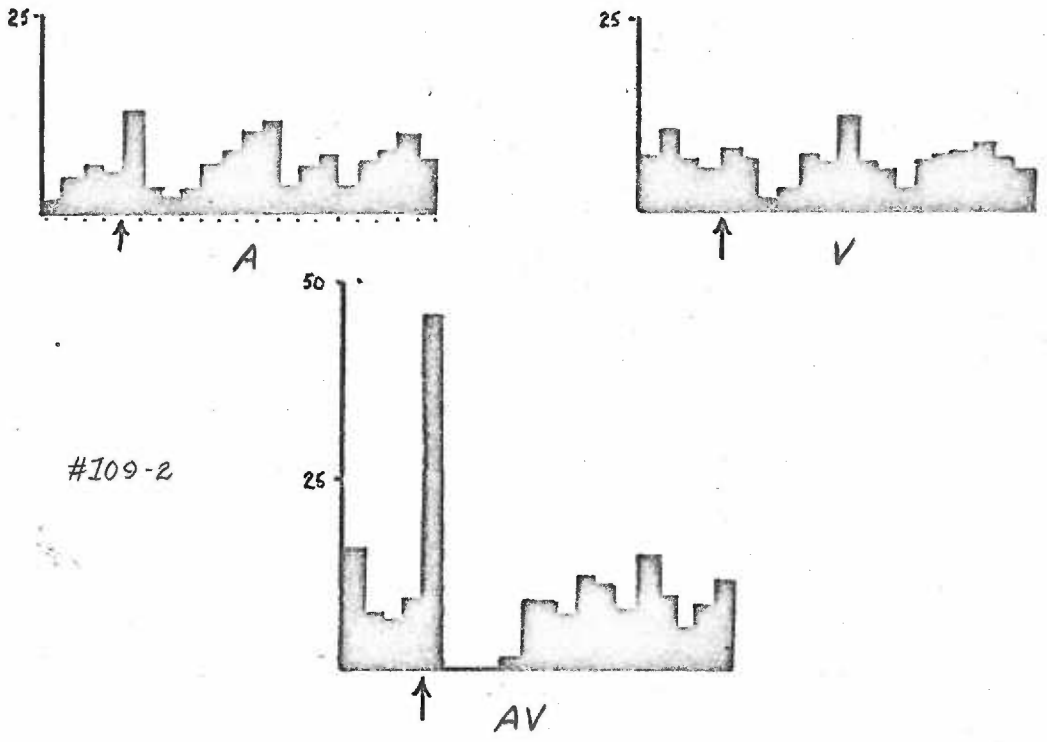


(b)

Figure 19. PST histogram of unit response to compound stimuli. The response to the compound stimulus appears to differ from that evoked by either one of the component stimuli by itself.

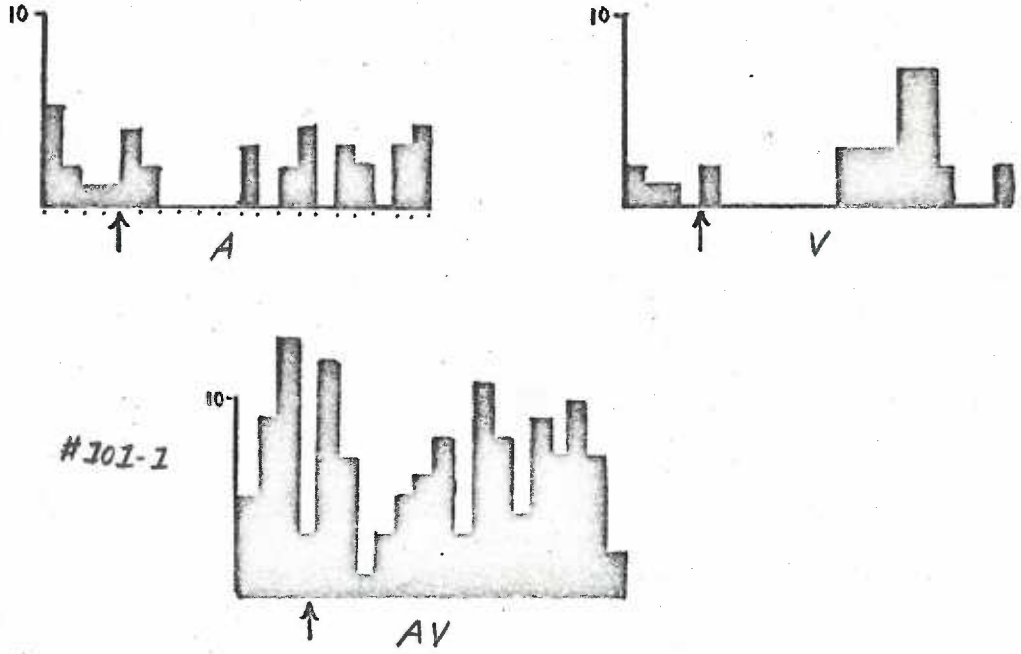
(a) Unit # 109-2 : Responses to A, V, and AV

(b) Unit # 101-1 : Responses to A, V, and AV



#109-2

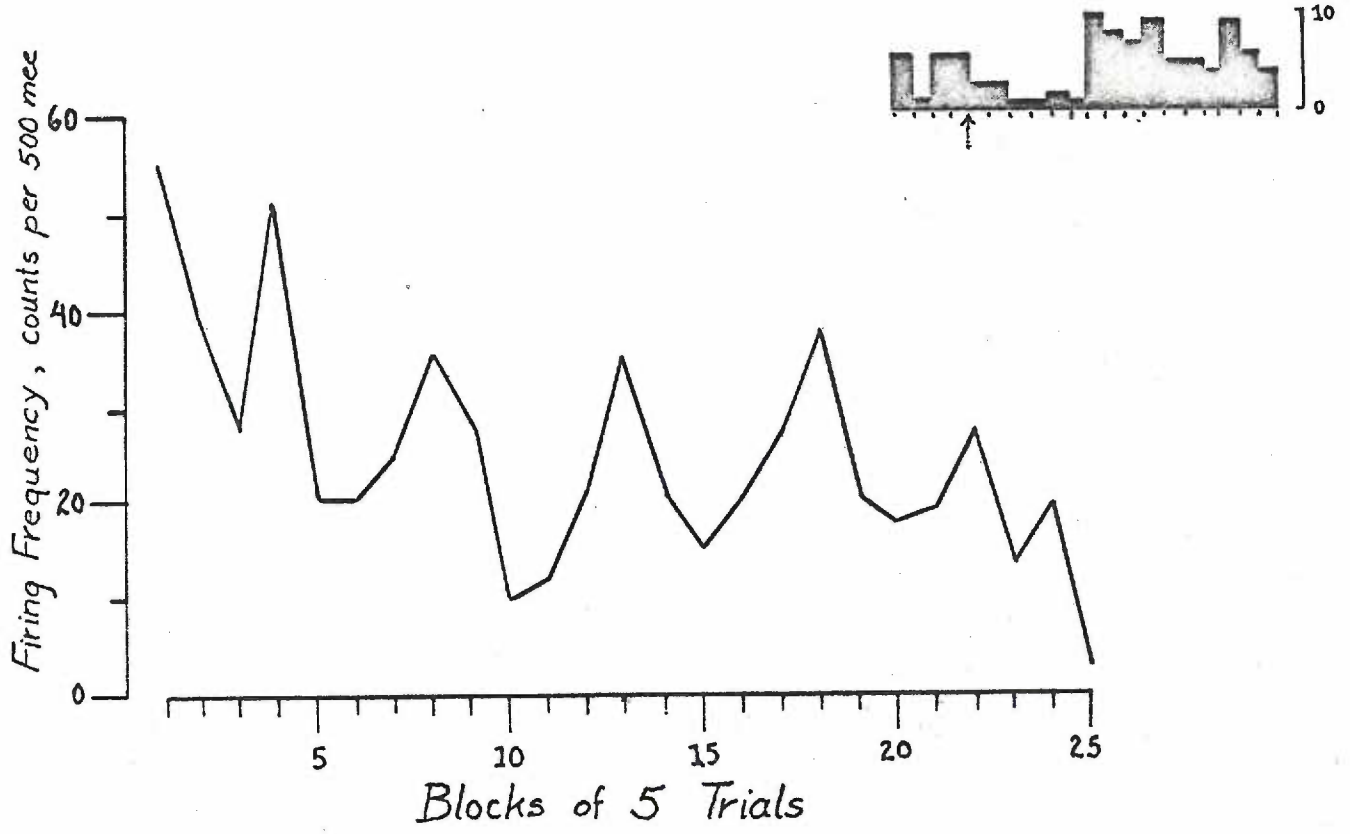
(a)



#101-1

(b)

Figure 20. A habituation series of stimuli for a unit in Experiment II. Note the marked fluctuations in firing frequency between different trial blocks. Inset: PST histogram based on first 50 trials of habituation series. Note that this unit does not show the early excitatory response but shows a late excitatory response ca. 300 msec. For the habituation series, firing frequency was counted in the 500 msec period following each stimulus. Stimulus: A_2 .

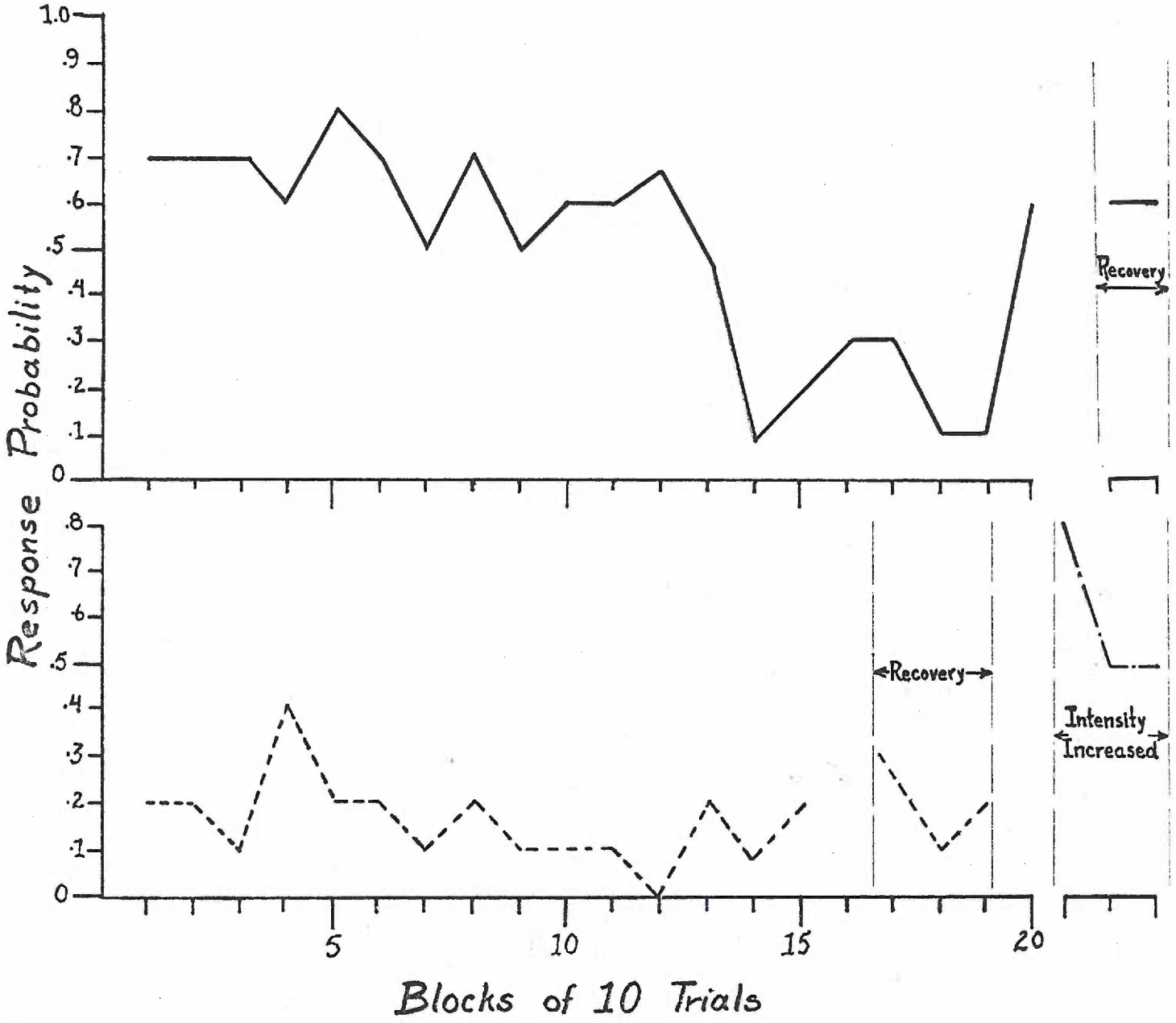

Firing Frequency, counts per 500 msec
60
40
20
0
5
10
15
20
25
Blocks of 5 Trials
10
0

#96-2

Figure 21. A series of habituation stimuli in a unit in Experiment I.

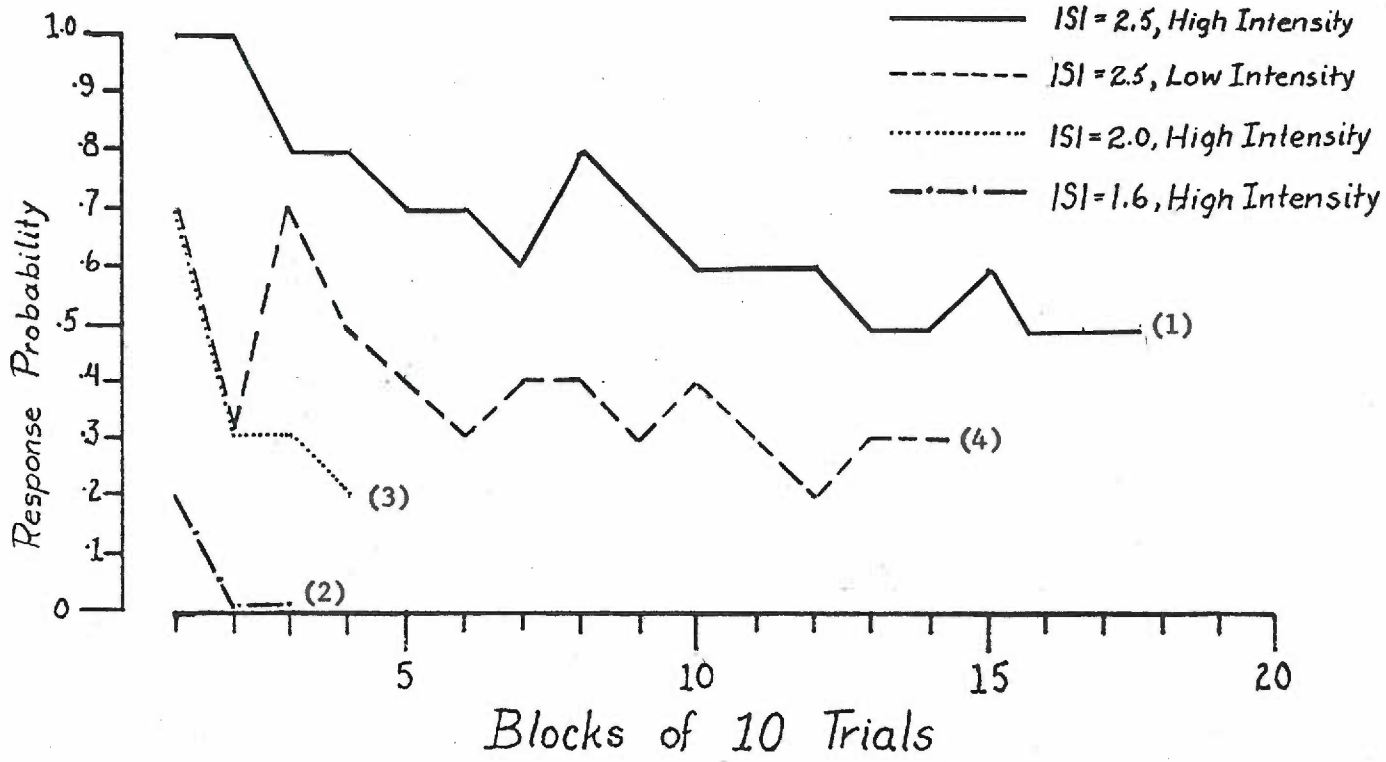
(a) Upper graph, 200 trials with $T_{3.2}$, followed by recovery interval at T_{10}

(b) Lower graph, 150 trials with $T_{3.2}$ at lower intensity than in part (a), followed by recovery interval at T_{10}, followed by 30 trials with $T._{3.2}$ at original higher intensity.


1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
Response Probability
Recovery
(a)
.8
.7
.6
.5
.4
.3
.2
.1
0
Recovery
Intensity Increased
(b)
5
10
15
20
Blocks of 10 Trials

#48-2

Figure 22. Habituation series with the auditory stimulus for a unit in Experiment I. Note that the differences in the speed with which response decrement develops appear to be related to the stimulus intensity and to the ISI. The small numbers in parentheses beside each curve indicate the order in which each habituation series was given.


ISI = 2.5, High Intensity
ISI = 2.5, Low Intensity
ISI = 2.0, High Intensity
ISI = 1.6, High Intensity
Response Probability
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
(1)
(2)
(3)
(4)
5
10
15
20
Blocks of 10 Trials

#55-2