Journée du 4 juillet 1969

Deuxième séance

INFORMATION ET SYSTÈMES BIOLOGIQUES

III - STOCKAGE DE L'INFORMATION DANS LES SYSTÈMES NERVEUX

PRESIDENT J. Z. YOUNG

De la Physique théorique à la Biologie, C.N.R.S., 1971.

INTRODUCTION

J.Z. YOUNG

Our topic is called "Information storage in the nervous system" and I would like to call your attention to the ambiguity of our title. I think it is something that all of us, physicists, chemists, biologists and mathematicians can well discuss together. Words like "information" and "storage" are far from clear. I do not propose now to proceed to try to define them but I think it should be in our minds, that this is part of the area in which we could all perhaps contribute to understanding of nervous systems and others. I would like however to say a few words about the third part of our title "Information storage in the nervous system", because that is my particular subject. As Kandel says, the nervous system is a genetically programed system, pre-programed to take some appropriate action. I think we have been in some danger of forgetting this in the abstractions of talking about associative memory and other matters, we've tended to forget the nervous system as an adaptive device, pre-programed by its DNA, of course, to produce adaptive reactions. It's a multichannel system, as we've been often reminded of although one sometimes tends to forget it and to forget the problem which it brings to the theoretician. We are so used to talking about simple, single channel systems — computers and the like, where there are few processors of information and the information is passed along a small number of channels — that to think about a system which has this very large number of channels is a challenge that I think we have not always met in our discussions. There will be a divergence of opinion, today as to the encoding system of the nervous system. I think that some of you who are not biologists should realize that the points of view this afternoon will differ. My own view is that we can say rather firmly that the nervous system encodes by putting information about separate events into distinct channels. Certainly one of our speakers this afternoon will take an opposite view. But it is a very important difference from the encoding system with which perhaps you are more familiar. In the nervous system the mechanism of encoding is in general to put each item of information into a separate channel. It may seem a fantastically inefficient, indeed an absurd way, of proceeding, if you think about it. Nevertheless, at least in a large part, this seems to be the way the nervous system operates.

Now as to the memory, the memory also is a pre-programed part of the nervous system, programed by its DNA, to select between possible alternate actions those which are most appropriate in the light of past events. Therefore we have always to bear in mind the fact that the nervous system is informed not only by the outside world, but also by its own internal receptors (I don't think they've been mentioned yet : receptors for taste, for example, or for pain) which tell it what have been the results of the actions that have taken place in the past. This is a form of association, which is perhaps the most important for the nervous system, to associate an event with its results and to act appropriately in the future. In this way the nervous system builds what we can call a model of the events in the environment that are likely to happen and what their consequences are likely to be and hence can forecast and produce appropriate action in the future. I make no apology for this teleological formulation, which of course is quite commonplace in biology, I think we are all able to use these words without *arrière-pensée* now.

Finally, each species has its own type of memory system. Again a point we must remember : the organism does not always remember everything. It remembers only that which is relevant to its own particular form of life. Our own memory is so complex as is that of mammals with which we shall mostly be dealing this afternoon, that it is very salutory to be reminded of simpler forms of memory such as Dr. Kandel's beautiful example this morning. And we shall hear further about the memory of goldfishes and I may have a moment or two to say a word about octopuses — just to remind us that these are special purpose memories, each tailored to do a particular job for the animal. It's rather amusing for you to know that many of you have been walking on some highly programed memory systems if you've been to see the Palace of Versailles ! I wonder if any of you noticed — perhaps Dr. Maynard Smith did — the diggerwasps all over the courtyard here in front of the palace. There are thousands upon thousands of diggerwasps there, with their nests between the stones. Each of those wasps must remember the appearance of its hole, to which it brings back grubs, to feed the offspring which will presently emerge. If you wished to, you could study that particular memory system. I don't suppose it can remember much, but it must remember its particular hole and distinguish it from the holes made by all the other wasps there. Now with that diversion may I call upon Dr. Morrell.

De la Physique théorique à la Biologie, C.N.R.S., 1971.

NEURONAL INTEGRATIONS IN VISION

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Introduction

When a cat learns to associate a click with a light or a touch with a particular visual stimulus or discriminates one kind of visual stimulus from another, as judged by appropriate quantitative behavioral tests, we assume that there has occurred in the cat's nervous system an alteration in the relationship between, for instance, the auditory and visual systems or the visual and somatosensory systems, as the case may be. The present research is aimed at discovering the mechanisms of such a change in relationships.

It has now been clearly established that there are at least two stages, and probably many more, of information storage in the nervous system. Short-term memory in the range of 20-30 minutes is apparently subserved by electrical activity in nerve cells. It may be abolished by any intervention, i.e. electroconvulsive shock, concussion, deep anesthesia, etc., which interferes with the electrical activity of the brain. In contrast, long-term or permanent memory is resistant or impervious to all the interventions which suppress electrical activity. The development of the permanent stage is dependent upon the prior occurrence of the electrically sensitive stage. Thus, if electrical activity is blocked within a few minutes after exposure to a stimulus, all memory of that stimulus is erased. However, if electrical activity is allowed to continue normally for 15-20 minutes after stimulation and then blocked, subsequent testing reveals that memory for that particular event is quite preserved (Bures and Buresova, 1963; Deutsch, 1962; Gerard, 1961; John, 1961, 1967a, 1967b; McGaugh and Petrinovich, 1965; Morrell, 1961a, 1961b, 1963; Morrell and Naitoh, 1962; Russell and Ochs, 1963).

Our studies are concerned exclusively with the analysis of the neural mechanisms involved in short-term storage of information.

The mammalian visual system is especially well suited to an analysis of sensory coding. The elementary details of stage by stage connectivity have been extensively studied (Clare and Bishop, 1954; Doty, 1958; Hubel and Wiesel, 1959, 1961, 1962, 1963; Kuffler, 1953; Otsuka and Hassler, 1962; Polley and

Dirkes, 1963; Polyak, 1927; Talbot and Marshall, 1941; Thompson *et al.*, 1950; Vastola, 1961). An extraordinary degree of order and specificity has been found, not only at the lower levels, but extending into the cortical regions and even beyond the primary receiving area. Single cells have been shown to be extremely selective in their stimulus preferences and the required stimuli are generally quite complex (Barlow and Levick, 1965; Hill, 1966; Hubel and Wiesel, 1963; Lettvin *et al.*, 1959, 1961; McIlwain and Buser, 1968; Sterling and Wickelgren, 1969; Wickelgren and Sterling, 1969; Wurtz, 1969). Furthermore, polysensory interactions at single units have been shown by Jung and his co-workers (1958, 1961, 1963; Baumgarten and Jung, 1952) and Murata *et al.* (1965) to be an extremely pervasive feature of visual physiology.

Visual areas II and III have been described anatomically by Otsaka and Hassler (1962) and by Hubel and Wiesel (1965) as the zone immediately anterior and lateral to the primary visual area or striate cortex. These authors consider these areas homologous with areas 18 and 19 of Brodmann or parastriate cortex in man. Hubel and Wiesel (1965) have reported physiological observations on these cells which indicate highly complex receptive field organizations and highly selective stimulus preferences. In particular, these cells respond best to appropriately oriented lines, bars, edges or contours. We have confirmed these observations in detail. In addition, however, we have examined : a) the detailed microstructure of the cellular response pattern; b) sensitivity to non-visual modalities of sensation; c) the specificity of non-visual interactions; and d) modifiability of response pattern as a consequence of " prior experience ". " Prior experience " is herein defined as simultaneous presentation of two different stimuli, each of which, individually, elicited different response patterns.

The experimental preparation was the curarized, unanesthetized cat. Before the experiment, a sterile operative procedure was performed for implantation of a nylon receptacle which could be opened when desired for insertion of the microelectrode. At the same time, the animals were fitted with a cap of dental cement especially molded to receive the ear bars of the stereotaxic instrument. The arrangement was a modification of the " semichronic " technique of Hayward *et al.* (1964) described by Lindsley, Chow and Gollander (1967). Animals were immobilized with Flaxedil and artifically respired. Pupils were dilated with 0.5 % atropine and contact lenses were fitted to each eye. The " semichronic " technique (Hayward *et al.*, 1964; Lindsley *et al.*, 1967) permits rigid fixation of the head and eyes without any pressure upon the animal. Tungsten microelectrodes were used for extracellular single unit recording (Hubel, 1957).

All stimuli were 50 msec. in duration. Visual stimuli were projected on a screen 30 cm. distant from the eyes and could be delivered to each eye separately. Acoustic stimuli were 10 msec. clicks repeated for 50 msec. Tactile stimuli

were 10 msec. electric shocks lasting 50 msec. to the contralateral hind limb. Vestibular stimuli were produced by D.C. polarization of the labyrinth (anodal or cathodal) of 0.05 mamps through a Ag-AgCl electrode at the round window (Jung, 1963).

The interstimulus interval was randomly varied around a mean of 22.5 sec.

Data analysis was accomplished by playing tape recorded electrical activity through a LINC computer programmed to compute and display PST histograms (bin width manually selectable) out to 250 msec. after stimulus onset or 300 msec. after a prepulse placed on tape 50 msec. before stimulus onset.

The general plan of the experiment was as follows : For each cell encountered, the visual field was scanned manually with a 2 mm lighted baton or torch, much in the manner used in the clinical ophthalmological examination. All quadrants of gaze were covered. The response looked for was a change in the spontaneous discharge of the monitored cell. Such change could, of course, be excitatory or inhibitory (or both, one occurring after the other). In practice, it was easier to define a response where an excitatory component predominated. The excitatory portion of the receptive field was then carefully plotted and, in most cases, the inhibitory surround was also measured. Thereafter, the configuration of the target (now presented only within the excitatory receptive field) was changed repeatedly until one was found which gave the most vigorous discharge. That target was then selected as the optimum or " preferred " visual stimulus for the cell in question. Immediately following the determination of optimal visual stimulus, the cell's responsiveness to acoustic, tactile and vestibular input was examined. Out of the total of 890, 871 visually excitable cells also responded to one of the other three modalities of sensation. Very few cells responded to more than one non-visual modality; a few were trisensory in the sense of Buser and Bignall (1967), Buser and Imbert (1961) and Imbert *et al.* (1966) and of Jung (1961, 1963), Kornhuber and DaFonseca (1964) and Murata *et al.* (1965).

The receptive fields identified confirm quite precisely those measurements already published by Hubel and Wiesel (1965). The " preferred " stimulus configuration was extremely complex (yet still simple when compared to real life) consisting of edges, bars or lines of various lengths and orientation. When the optimal stimulus was used, mean cellular responses were quite stable (as measured by PST histograms of sums of 20 trials) even though there was obvious trial-to-trial variability and scatter of " latencies " and sometimes omission of some components.

Figure 1 illustrates the first 12 trials of the total of 20 used to compute the histogram shown in the lower half of the figure. There are obviously two bursts of activity evident when the tracings are displayed this way, i.e. looked at simultaneously, and, of course, two peaks in the histogram. Note, however, that if the tracings were examined individually, the second burst might not be

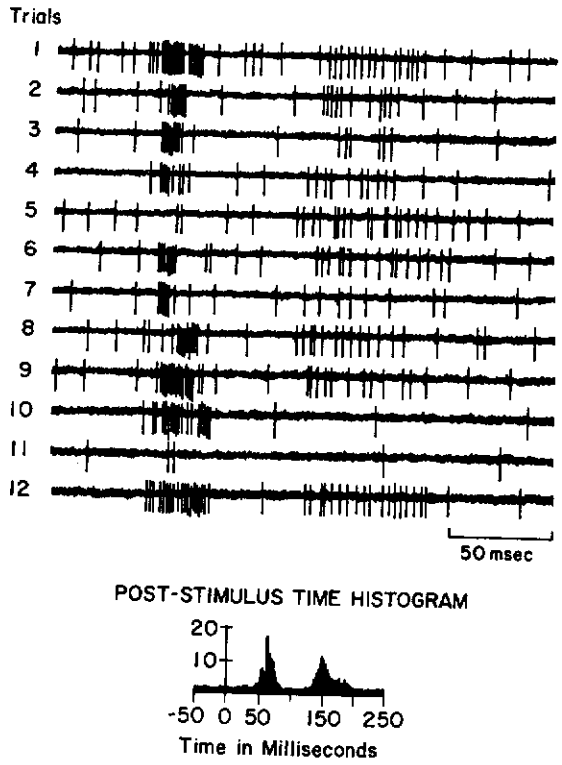

Fig. 1. Single unit extracellular records of the first successive 12 trials of the 20 trials which were summed to compute the PST histogram shown at the bottom of the figure. Each trial (250 msec segment of record triggered by stimulus onset) was displayed on a Tektronix 564 storage oscilloscope with the beam stepped down after each trace. When arrayed in this manner, i.e.: one above the other, it was obvious that there were two bursts of activity distinguishable from the relatively high rate of background spiking and these were reflected in the two peaks of the PST histogram. The different organization of each burst was also reflected by differences in amplitude and slope of the two histogram peaks. The portion of the histogram labeled — 50 msec to 0 represents unstimulated activity; the computation in this case having been initiated by the pre-pulse. It is important to note that if the single traces had been examined individually, the second burst might not be detected on trials 3, 7 and 10. On trial 5, the early burst failed to occur and on trial 11 there was no evidence at all of stimulus related discharge. Thus, in 5 out of the first 12 occasions the full pattern failed to appear. Binwidth equals 5 msec in this and all other illustrations in this paper. The calibration bar (the abscissa) at time zero equals 20 spikes in this and other figures unless separately specified. The cellular activity shown was this cell's response to its " preferred " visual stimulus. The latter was an obliquely oriented light slit in the right upper quadrant of gaze extending from 10° to 13° lateral to the vertical meridian. The excitatory visual receptive field is illustrated by the cross-hatched area in Figs. 9 and 10. Stimulus duration in this and all other figures was 50 msec.

detected in trials 3, 7 and 10; on trial 5 the early burst was undetectable and in trial 11 neither burst occurred. Each oscilloscope sweep was triggered by stimulus onset. The portion of the histogram labeled —50 msec. to 0 msec. represents " spontaneous " unstimulated activity, the computation in this instance having been initiated by the prepulse.

The PST histogram has the virtue of preserving the true time course of events (in contrast to the interval histogram) and, most important, preserves the trial-to-trial variability (in contrast to an " average " measurement).

When a stable response to a non-visual modality was discovered (or in a few cases a second visual but non-preferred stimulus configuration), the preferred stimulus was paired, i.e. presented simultaneously over the 50 msec. stimulus duration for 40 trials. These paired trials are what we herein define as " prior experience ". After the paired trials, the preferred visual stimulus was presented alone (testing for modification of response pattern). In most neurons (769), there was no effect on the post-pairing firing pattern, i.e. the " preferred " visual stimulus elicited a response virtually identical with that which occurred on initial presentation.

Thus, in the experiment illustrated by Fig. 2, the preferred visual stimulus evoked the discharge pattern summed in 20 trial blocks (1-20 and 21-40 of Fig. 2). Vestibular stimulation (Fig. 2, trials 41-60 and 61-80) yielded an entirely different pattern. Concomitant presentation of visual and vestibular stimulation (Fig. 2, trials 81-100 and 101-120) resulted in a third and quite distinctive histogram pattern. Nevertheless, upon retesting with the preferred visual stimulus, we obtained (Fig. 2, trials 121-140) exactly the same pattern originally elicited by that stimulus. Several reinterpolations of paired stimulation failed to induce a change in the cells' response pattern to visual or vestibular stimulation when the latter were presented alone. When such stability was encountered, as many reinterpolations of combined stimuli as were possible were attempted as time and the preparation would allow. In no single case was such " reinforcement " successful in eliciting modification; i.e. if modification was not evident after the first paired trials, it never occurred.

However, in 102 cells relatively striking and reliable changes in response pattern did occur after the initial pairing. All cells exhibiting response modification exhibited the alteration during the first testing sequence. Thus, there was no ambiguity about which cells would and which would not exhibit the change. More specifically, in these modifiable cells the histogram yielded by the testing stimulus alone resembled that elaborated by combined stimulation more than it did the control histogram for " preferred " stimuli upon initial presentation. Thus, there was a clear distinction, under the conditions of our experiment, of two separate populations : a majority of cells could be classified as extraordinarily stable cells reporting faithfully the stimulus configuration regardless of past history; and a smaller population, equally distinct, in which response

histograms were influenced by a specific past history. The degree of specificity will be illustrated below.

A prototypical example of modifiability

Figure 3 illustrates a prototypical example of response modification. This cell (64-128) was preferentially activated by a diagonal line of light at about

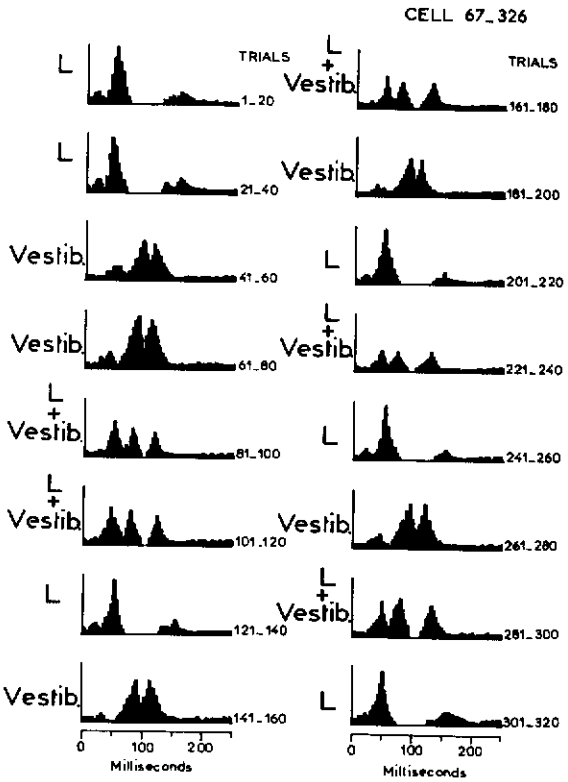

Fig. 2. Typical responses in a polymodal but non-modifiable neuron. Visual stimulation yielded a response configuration consisting of a sharp early peak, an inhibitory interval and very small late activity peaking about 150 msec after stimulus onset. Notations to the left of the histograms indicate the type of stimulation; trial numbers are listed to the right. The sequence of events should be read from the top to bottom on the left and then top to bottom on the right. This cell was typical in that it responded differently to visual (L) and non-visual (Vestib.) modalities and with a third pattern when the two (L + Vestib.) were combined. But the experience of paired stimulation had no effect on patterns subsequently elicited by either L or Vestib. alone. Visual stimulus was an obliquely oriented light slit in the left lower quadrant of gaze. Intensity of slit: 2.3 $\log_{10}$ cd/m^2; background: 0.03 $\log_{10}$ cd/m^2. Vestibular stimulus was a cathodal DC current 0.05 mA at the round window of the left ear. Its duration was 50 msec as with all other stimuli. Depth of the cell was 900 μ.

six degrees to the left of the vertical meridian. When so stimulated twenty times, the spike train summation yielded the uppermost histogram in Fig. 3. The single trace above the histogram was the response to the preferred stimulus which was most typical of the sum of twenty used to compute the histogram.

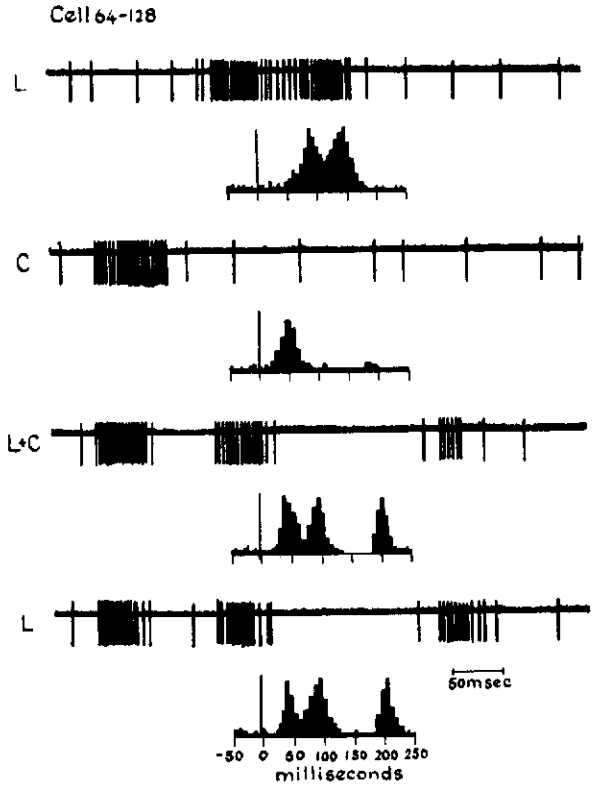

Fig. 3. A prototypical example of modifiability. This cell was encountered at a depth of 540 μ. It was preferentially activated by a diagonal line of light at about six degrees to the left of the vertical meridian. Intensity of the light: 1.8 $\log_{10}$ cd/m^2; background: 0.03 $\log_{10}$ cd/m^2. Above each histogram is shown the original record of a single trial (selected as the most representative of the 20 trials used to compute the histogram). Visual stimulation (L) yielded a particular temporal pattern of discharge. Acoustical stimulation (C, 30 db SPL at the cat's ear) resulted in a different pattern of firing having a single peak with a latency even shorter than the response to light. When the two stimuli were delivered simultaneously (L + C) an additional pattern was seen which appeared not to be a simple linear combination of responses to the two single stimuli but rather a total reorganization of firing pattern. After 40 such paired trials, the same visual stimulus as that used initially (L, lower) elicited a response pattern similar to that elicited by the paired stimuli (L + C) and unlike that which the stimulus had provoked on initial exposure (L, upper). The altered response lasted about 30 min, i.e.: time for 3 blocks of 20 trials each and then reverted to the original configuration of the response to light (L, upper).

The histogram had a late bi-phasic peak which is well illustrated in the single response (Fig. 3, L). The second histogram (Fig. 3, C) was the result of acoustic stimulation and had a single peak appearing even earlier than the response to light. When light and click were delivered simultaneously (Fig. 3, L + C), a reorganization of the temporal pattern of discharge took place which contained inhibitory intervals not seen before (especially between peak 2 and 3, Fig. 3, L + C) and which was difficult to regard as a simple summation of the effects of light and sound individually. Again, the single response above the histogram was chosen as that most representative of the sum of twenty used to compute the histograms. Following the paired trials, the preferred visual stimulus was presented alone (Fig. 3, L, fourth trace). The pattern of firing was similar to that elicited by the paired trials and relatively unlike that elicited by the same preferred visual stimulus before the pairing occurred.

Response modification in " polymodal " cells

The true time course of these events may be illustrated in Fig. 4. Visual stimulation resulted in a long, slow discharge of the cell, (Fig. 4, trials 1-40). Acoustical stimulation yielded a sharp, early peak (Fig. 4, trials 41-80). Repeated stimulation (Fig. 4, trials 81-100) resulted in a histogram identical with that which occurred on first exposure (Fig. 4, trials 1-40). Thus, the presentation of sound alone (Fig. 4, trials 41-80), or of time itself did not alter the cellular response as manifested in the post stimulus time histogram. Yet when light and sound were presented together (Fig. 4, L + C, trials 101-140) a third histogram type was obtained. Following the paired trials, the light alone elicited a response similar to that resulting from paired stimulation (Fig. 4, trials 141-200). As unreinforced visual stimulation continued (Fig. 4, 201-220), the pattern of discharge became gradually more and more similar to that originally elicited by the visual stimulus (Fig. 4, trials 241-260). However, acoustic stimulation (Fig. 4, trials 221-240) resulted in no change in the temporal discharge pattern (compare Fig. 4, trials 221-240 with trials 41-80) to acoustic stimulation when first applied (Fig. 4, trials 41-80). Since the light-evoked response was then similar to the initial response (compare Fig. 4, trials 1-40 with trials 241-260), a reintroduction of light-click pairing was instituted for twenty trials (Fig. 4, trials 261-280). The result of such reintroduction was the reappearance of the modified response (Fig. 4, trials 281-320) which persisted for as long as the cell was held in view.

Response modification in the case where the second stimulus elicits no overt response

Cell 64-196 (Fig. 5) was responsive to illumination of the contralateral eye (Fig. 5, trials 1-40) but not to illumination of the ipsilateral eye (Fig. 5, trials

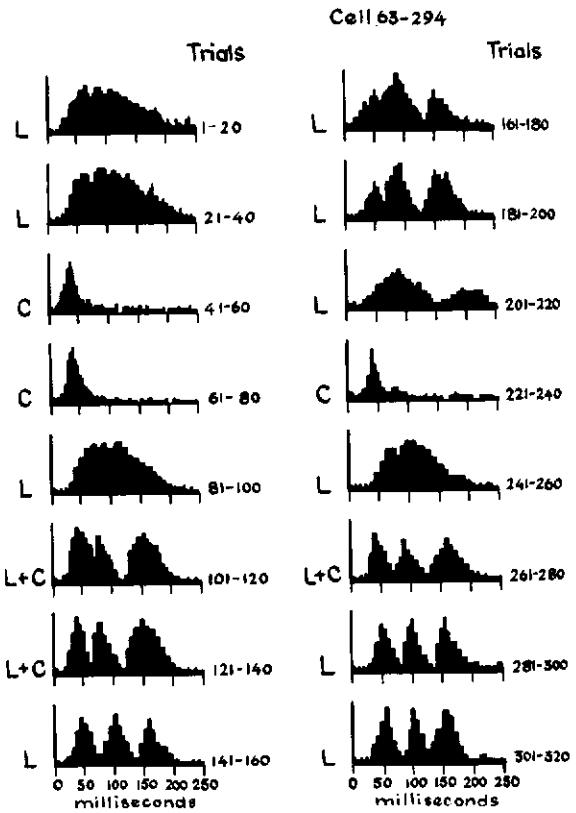

Fig. 4. Response modification in a polymodal cell. " Preferred " visual stimulus (L) for this cell, encountered at a depth of 1 mm, was a light line, light line : 1.5 $\log_{10}$ cd/m^2; background : 0.03 $\log_{10}$ cd/m^2, oriented from : 2:00 to 8:00 in its receptive field in the left lower quadrant of gaze. Click stimulus (C), 30 db above human auditory threshold in open field conditions, was also effective athough with a different pattern. This figure illustrates the PST histograms obtained throughout the entire course of observation of this cell. L + C indicates " preferred " visual and acoustic stimuli combined. Further explanation in text.
From : Morrell, 1967.

41-80). Yet when both eyes were stimulated (Fig. 5, trials 81-120) the response pattern differed from that attributable to stimulation of either eye individually. Thereafter, for some eighty trials (Fig. 5, trials 121-200) the response to contralateral eye stimulation differed from that obtained originally (Fig. 5, trials 1-40). There was still no response to ipsilateral eye stimulation (Fig. 5, trials 221-240). But after a brief repeated introduction of bilateral stimulation (Fig. 5, trials 261-280), the contralateral eye stimulus yielded, again, a pattern which approximated that resulting from paired stimulation (Fig. 5, trials 281-320).

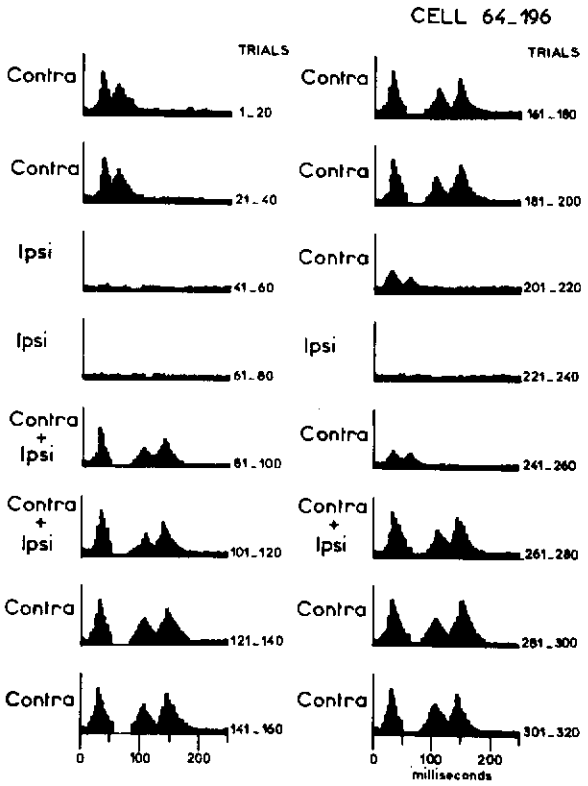

Fig. 5. Response modification in the case where the non-preferred stimulus was ineffective. Cell encountered at depth of 1 mm. Preferred visual stimulus for this cell was a light spot (2.8 $\log_{10}$ cd/m^2; background: 0.03 $\log_{10}$ cd/m^2) presented to the left or contralateral (contra) eye in the appropriate portion of the receptive field. Stimulation of the corresponding receptive field for the right eye (Ipsi) evoked no response at all. Nevertheless, binocular stimulation (Contra + Ipsi) yielded a different response pattern than had resulted from contralateral eye stimulation originally (Contra, trials 1-40). Following 40 trials of binocular stimulation, the response to stimulation of the contralateral eye alone (Contra, trials 121-200) shifted to the pattern first elicited by binocular stimulation. The alteration lasted 40 min or 4 blocks of 20 trials each before reverting to its original configuration. Further explanation in text.

Vestibular interaction

The preferred stimulus for cell 66-241 was a light line oriented from 11:00 to 5:00 in its receptive field. The vestibular stimulus was a 0.05 mAmp D.C. pulse, either anodal (A) or cathodal (C), applied to the left semicircular canals. The cell (Fig. 6) responded to the visual and to both types of vestibular stimulation — each with a different pattern. Combining the visual stimulus with vestibular A yielded a fourth histogram type (Fig. 6, trials 61-100). Following the paired presentations, the visual stimulus alone elicited a pattern (Fig. 6,

trials 101-160) closer to that resulting from paired stimulation (Fig. 6, trials 61-100) than to that yielded by visual stimulation alone (Fig. 6, trials 1-20) before pairing. Response to vestibular A alone (Fig. 6, trials 181-200) was unchanged. After some time, the discharge elicited by visual stimulation reverted to its original type (Fig. 6, trials 161-180 and 201-220). However, reintroduction of paired trials (Fig. 6, trials 221-240) restored the capacity of the visual stimulus to provoke a modified response (Fig. 6, trials 241-260 and 281-300).

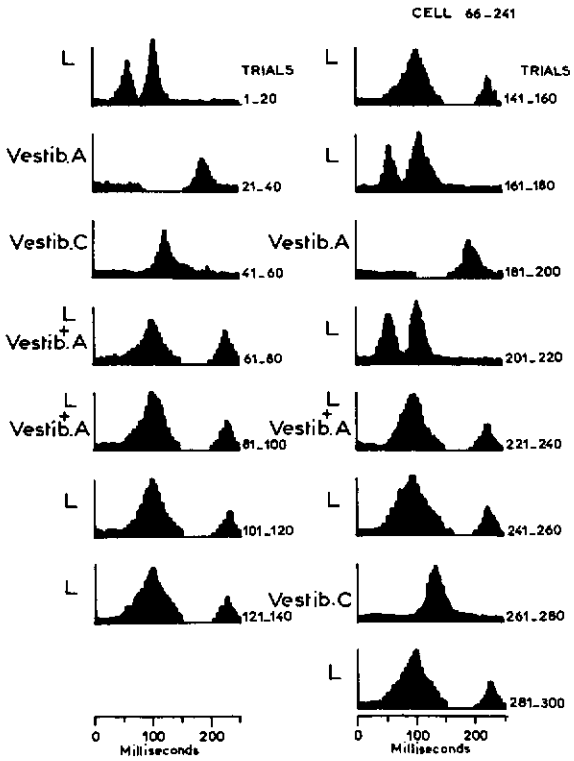

Fig. 6. Vestibular interaction. Cell 66-241 was encountered at a depth of 840 μ. Preferred visual stimulus was a light line oriented from 11:00 to 5:00 in a receptive field in the left upper quadrant. Luminance: 1.5 $\log_{10}$ cd/m^2; background, 0.03 $\log_{10}$ cd/m^2. Vestibular stimulus was a 0.05 mA D.C. pulse, either anodal (Vestib. A) or cathodal (Vestib. C) applied to the left semicircular canals. The cell responded to the visual (L) and to both types of vestibular stimulation - each with a different pattern. Combining the visual stimulus with Vestib. A resulted in a fourth histogram type. Following the paired presentations (trials 61-100), the visual stimulus alone elicited a pattern closer to that resulting from paired stimuli (trials 101-160) than to that originally evoked by the same visual stimulation. The entire time course of this effect is depicted in the serial PST histograms of this figure.

Differential specificity

Cell 64-107 (Fig. 7) was encountered at a depth of 1.3 mm below the pial surface. It had an extraordinarily rich response repertoire. There was a different response histogram for each of the following stimuli: a vertical bar (2.8 $\log_{10}$ cd/m^2) 6° in length moving from left to right in a dark room (VR-D); the same stimulus moving in the opposite direction (VL-D); the same stimulus

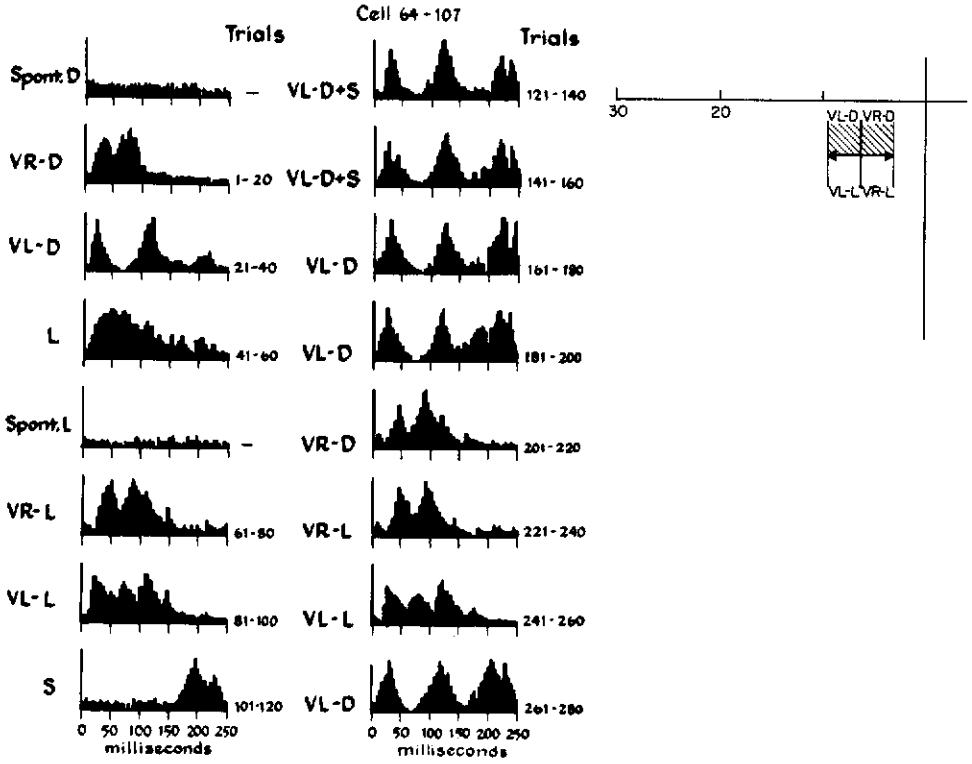

Fig. 7. Differential specificity. Cell 64-107 was encountered at a depth of 1.3 mm. Different response histograms were evoked when the vertical light bar, shown on the diagram to the left, in the receptive field also illustrated, having a luminance of 2.8 $\log_{10}$ cd/m^2, was moved to the right with the room lights dimmed (0.01 $\log_{10}$ cd/m^2, (VR-D); the same stimulus moving in the opposite direction (VL-D); the same stimulus moving to the right but with the room lights on (1.1 $\log_{10}$ cd/m^2) (VR-L); and the same stimulus moving to the left with the room lit (VL-L). The cell also responded simply to diffuse illumination of the room (L) and to an electric shock to the contralateral hindlimb (S). One of these stimulus configurations (VL-D) was paired with shock (S). The others served as controls for specificity. Histograms marked " Spont. L " and " Spont. D " represent sums of randomly chosen, 250 msec segments of record when the cell was unstimulated either in the dark room (D) or with the room lighted (L). See text for further explanation.
Modified from Morrell, 1967.

moving from left to right with the room lights on (1.1 $\log_{10}$ cd/m^2), (VR-L); and the same stimulus moving from right to left with the room lights on (VL-L). The cell also responded simply to diffuse illumination of the room (L) and to an electric shock to the contralateral hind limb (S). One of these stimulus configurations (VL-D) was paired with shock (S). The others served as controls for specificity. Histograms labeled " Spont. D " and " Spont. L " represent sums of randomly chosen 250 msec segments of record when the cell was unstimulated either in the dark room (0.01 $\log_{10}$ cd/m^2) (D) or with the room lit (L). The receptive field is shown in the diagram to the left in Fig. 7.

Response to paired stimulation (Fig. 7, VL — D + S, trials 121-160) appeared to be a simple summation of the light evoked activity (Fig. 7, VL-D, trials 21-40) and that produced by the shock alone (Fig. 7, S, trials 101-120). Nevertheless, following the paired trials, the VL-D stimulus alone (Fig. 7, trials 161-200) provoked response patterns similar to those elicited by combined stimulation. Thereafter, the response to each of the other three stimulus configurations (VR-D, VL-L and VL-D) could be compared to that obtained before pairing, i.e. in Fig. 7 compare trials 201-220 with trials 1-20; trials 221-240 with trials 61-80; and trials 241-260 with trials 81-100. Finally, the stimulus VL-D was again presented (Fig. 7, trials 261-280) and resulted in a histogram comparable to that of combined stimulation and different from that originally provoked by VL-D (Fig. 7, trials 21-40). In this case the modified pattern persisted for almost sixty minutes, 30 minutes having been employed to test the unreinforced or control stimuli.

Another cell exhibited another form of differential modifiability. It was encountered at a depth of 760 μ. The preferred visual stimulus was a light line (1,8 $\log_{10}$ cd/m^2) against a dark background (0.01 $\log_{10}$ cd/m^2). However, there were two effective orientations of the line (see diagram, Fig. 8). The orientation which was designated L.A. was within 2° of vertical; the other effective orientation was 5° from the horizontal and was designated L.B. The intermediate positions tested (shown as dotted lines in Fig. 8) did not alter the cellular firing pattern. Stimulus L.A. elicited the histograms shown in Fig. 8) (trials 1-20 and 21-40). Stimulus L. B. gave rise to a quite different temporal pattern of discharge (Fig. 8, trials 41-60 and 61-80) which was characterized by burst activity which had an earlier peak than that caused by L.A. and was followed by a pronounced inhibitory interval lasting 60-75 msec. The cell was also responsive to vestibular stimulation (0.8 mA D.C. applied to the contralateral round window), either anodal (A) (Fig. 8, trials 81-100) or cathodal (C) (Fig. 8, trials 121-160). Following the pairing, stimulus L.A. was applied alone for three groups of 20 trials each (Fig. 8, trials (161-220). A late component, apparently derived from vestibular C (see Fig. 8, trials 101-120) persisted in the patterned response provoked by the L.A. visual stimulus alone. The control visual stimulus, L.B., did not elicit such a change (Fig. 8, trials

221-240 compared with trials 41-80), the response being essentially like that which occurred on first application. Nor was there any change of response to vestibular A (Fig. 8, trials 241-260) or vestibular C (Fig. 8, trials 261-280) when each was presented separately and without combination with light. However, repairing of vestibular C with L.A. (Fig. 8, trials 281-300) again yielded

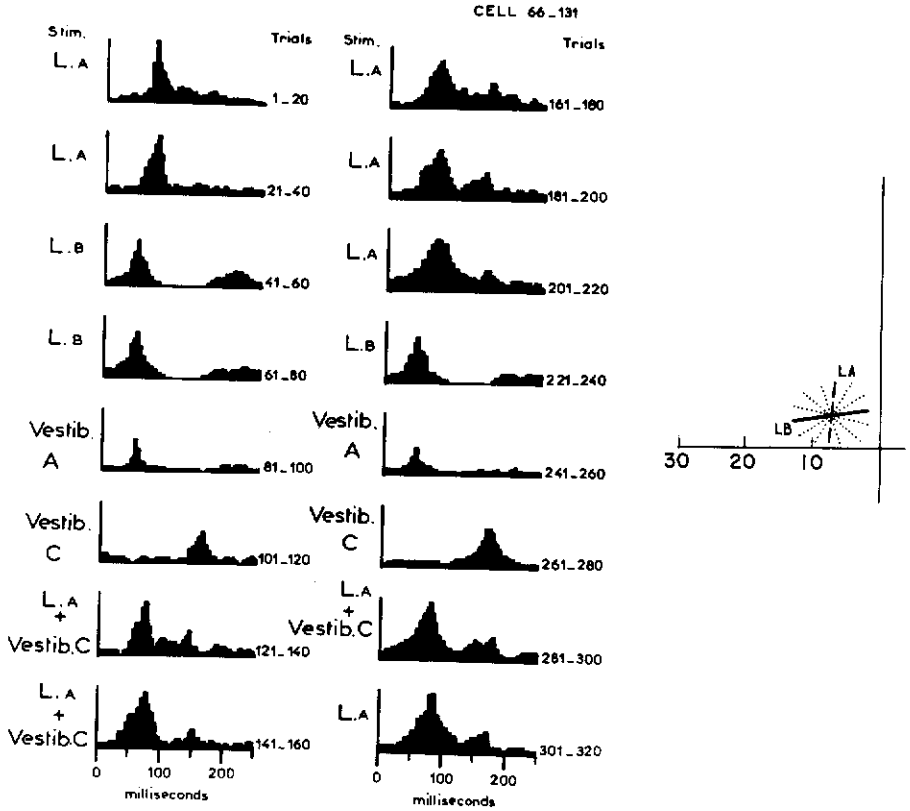

Fig. 8. Further differential specificity. Cell 66-131 was encountered at a depth of 780 μ. Preferred visual stimuli for this cell consisted of light lines (1.8 $\log_{10}$ cd/m^2) (background: 0.01 $\log_{10}$ cd/m^2). Two orientations L. A (dashed line) and L. B (solid line) were differentially effective while intermediate positions (shown as dotted lines in the diagram) were ineffective. The cell also responded to vestibular stimulation, anodal (Vestib. A) or cathodal (Vestib. C) differentially (0.8 mA D.C. to contralateral round window). Stimulus L. A was paired with Vestib. C (trials 121-160), stimulus L. B serving as a control for specificity. Subsequent testing with L. A alone (trials 161-220) revealed the usual evidence of modifiability. Testing with L. B alone revealed (trials 221-240) no evidence of modified histogram pattern. Furthermore, testing with Vestib. A alone or Vestib. C alone yielded no evidence of change consequent to the pairing experience. Thus, only the response to the visual stimulus which had been combined with stimulation via another modality exhibited a change in cellular discharge pattern.

the modified histogram and the modification persisted for the next set of 20 trials when L.A. was presented alone (Fig. 8, trials 301-320). Here, again, it seems that only the particular visual stimulus that had been combined with the vestibular activation was capable of eliciting the modified response pattern. Vestibular stimulation, either the one which had been combined with light (vestibular C) or the " control " stimulus, (Vestibular A) failed to produce the modified response. The latter was also true of the " control " visual stimulus (L.B.).

The specificity of non-visual input of visual cells : the dimension of acoustical space

Most investigators have regarded non-visual input to visual cells as being conducted through pathways, e.g., reticular formation of thalamus and mesencephalon, classically considered to be non-sensory specific (Abrahamian *et al.*, 1963; Bergamini and Bergamasco, 1967; French, 1960; Jasper, 1960, 1961; John, 1961; Kornhuber and Da Fonseca, 1964; Lomo and Mollica, 1962; Machne and Segundo, 1956; Moruzzi and Magoun, 1949; Rose and Lindsley, 1968; Scheibel et al., 1955; Scheibel and Scheibel, 1967; Segundo and Machne, 1956; Skrebitskii and Gapich, 1967, 1968; Steriade, 1970; Thompson *et al.*, 1963a, 1963b). These are pathways in which the quality and sign of the sensation was thought to be essentially lost and the function of such afference to be the modulation of arousal, attention, etc. We, ourselves, regarded the matter in the same way and that is why we chose to use trains of clicks, electric shocks to the hind limb and vestibular polarization as the non-visual stimuli. These were as unspecific as possible while still representing activity of another sensory modality. Moreover, there is no doubt that sleep, wakefulness, or the various stages of sleep (Evarts, 1963, 1967; Hubel, 1959a, 1959b, 1960; Huttenlocher, 1960, 1961; Jouvet, 1967; Wurtz, 1969) as well as administration of barbiturates (Erulkar *et al.*, 1956; Jarcho, 1949; Lömo and Mollica, 1962; McIlwain, 1964, Mountcastle et al., 1963; Murata *et al.*, 1965; Poggio and Mountcastle, 1963; Robertson, 1965; Verzeano *et al.* 1955; Wurtz, 1969) drastically alter the responsiveness of cells at both the lateral geniculate nucleus (LGN) and at the cortical level in a very general way. On the other hand, Spinelli *et al.* (1968) reported that there was tonal or frequency specificity in the acoustical input to striate cells; acoustically driven striate cells each had a " best-frequency " to which it responded and showed relatively little response to other frequencies. This result suggested that rather specialized attributes of the acoustical stimulus were being conveyed to the visual system.

Our own observations on cells of areas 18 and 19 revealed another specific aspect of the acoustical stimulus, namely its location is space. This feature had been ignored in all of our previous studies in which the sound was delivered

from a loudspeaker mounted high on the wall contralateral to the exposed visual cortex. A rearrangement of the equipment resulted in positioning of the loudspeaker on the opposite or ipsilateral wall. In subsequent experiments the effectiveness of the acoustical stimulus dropped precipitously; the only variable

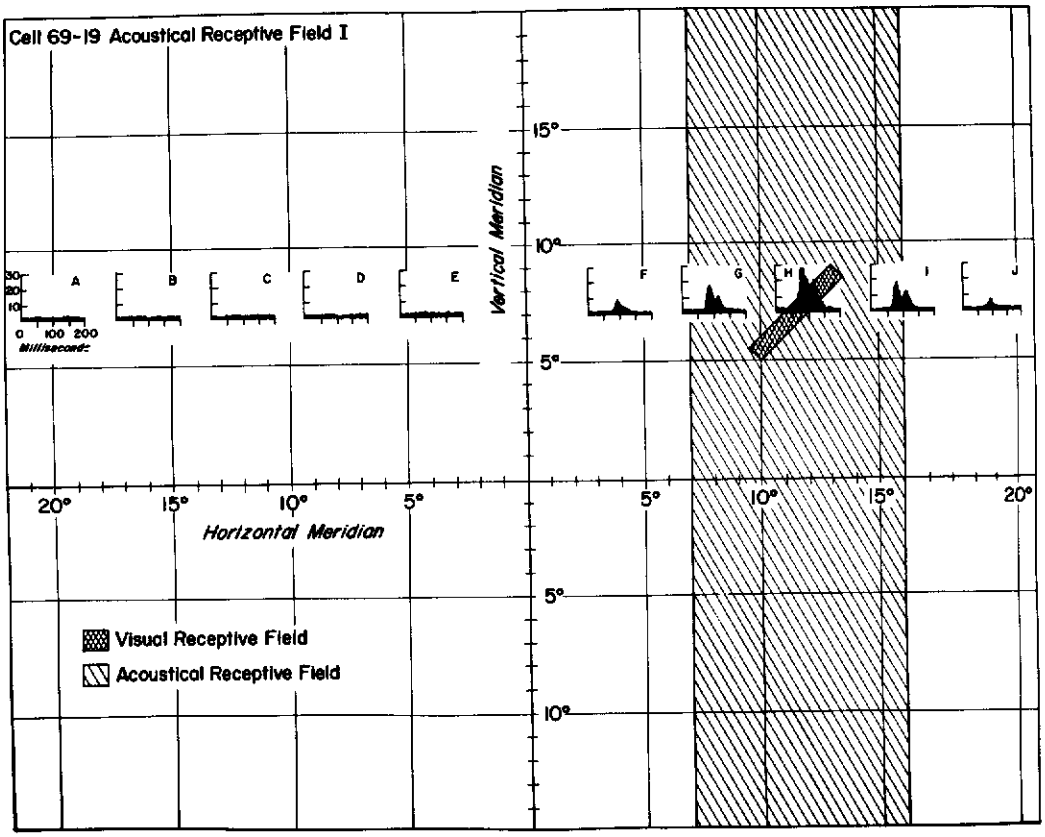

Fig. 9. Visual and acoustical receptive fields superimposed. Horizontal dimension. PST histograms to acoustical stimulation (50 msec train of 10 msec clicks) delivered from small focused loudspeakers mounted on the wall immediately behind the tangent screen on which the visual images were projected. The center of the histogram display corresponds to the site of the sound source as projected on the tangent screen. Thus, the histogram labeled " A " was located 20° to the left; " B " was 16° left; " C " was 12° left; " D " was 8° left, " E " was 4° left; " F " was 4° right; " G " was 8° right; " H " was 12° right; " I " was 16° right; " J " was 20° right. All sites were 7° above the horizontal meridian. Excitatory visual receptive field was an obliquely oriented light line in the right upper quadrant and is indicated by the cross-hatched area. The area marked by diagonal lines represents what we herein call an acoustical receptive field. The PST histograms of acoustical responses in this and the succeeding three figures, i.e.: Figs. 9-12, were composed of sums of 40 trials (as compared with 20 trial sums in the preceding 8 figures) and the calibration bar at time zero represents 30 counts (instead of 20). Analysis interval: 200 msec.

having changed being the location of the sound source. We then obtained a small focused loudspeaker mounted in a metal sleeve of 2.5 cm diameter which could be positioned at any site behind, above or below the screen on which the visual images were projected. Without dwelling on details, since the full data will be presented elsewhere, it was clearly evident that the most effective sound source for acoustical activation of visual neurons was one located in that cell's receptive field for visual stimuli. For example, a cell having an excitatory

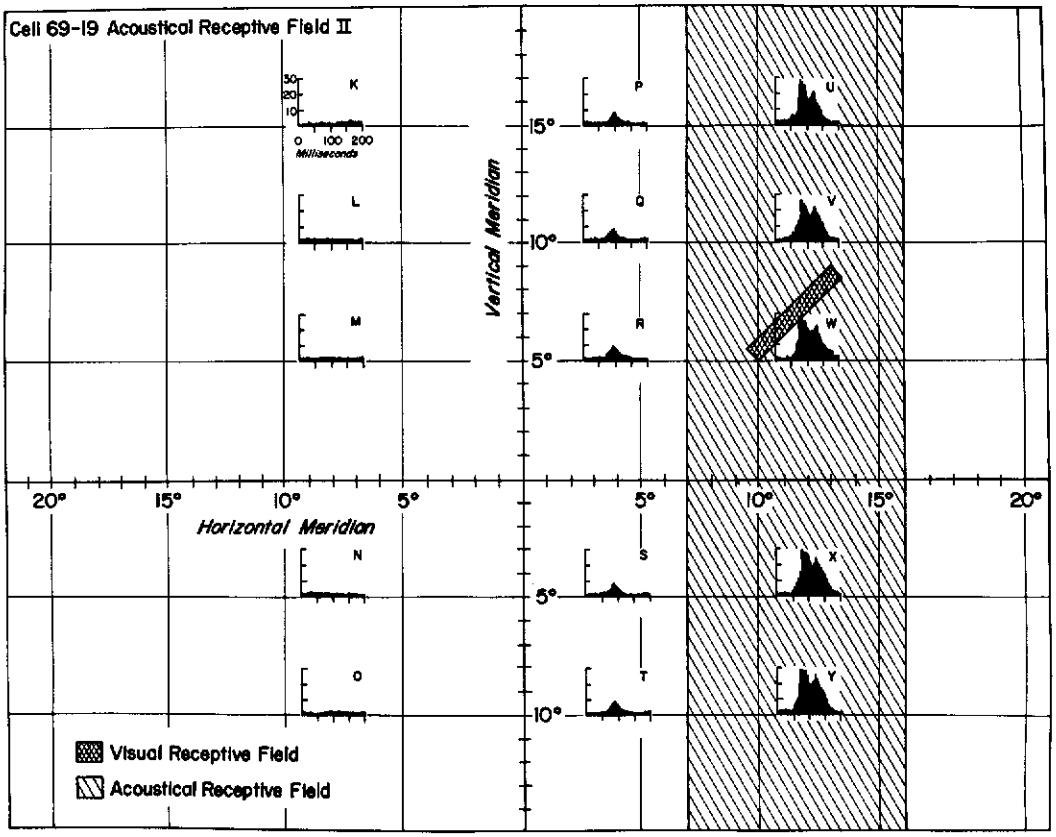

Fig. 10. Visual and acoustical receptive fields superimposed. Vertical dimension. Same cell as in Fig. 9. PST histograms of acoustical responses elicited by focused loudspeakers placed at sites on the tangent screen corresponding to the center of the histogram. Thus, sites " K ", " L ", " M ", " N " and " O " were all 8° left lateral and at, respectively, 15°, 10° and 5° above the horizontal meridian and 5° and 10° below it. Sites " P ", " Q ", " R ", " S " and " T " were all 4° right lateral and at, respectively, 15°, 10°, 5° above the horizontal meridian and 5° and 10° below it. Sites " U ", " V ", " W ", " X " and " Y " were all 12° right lateral and at, respectively, 15°, 10°, 5° above the horizontal meridian and 5° and 10° below it. The visual receptive field is indicated by cross-hatching. Visual responses from a light slit placed in the indicated region may be seen in Fig. 1, which illustrates the visual responses from the same cell.

receptive field 10-12° lateral to the vertical meridian gave its most vigorous acoustical response when the sound source was also 10-12° lateral to the vertical meridian. The borders of the receptive field for sound were not as precise as those for light and we failed to demonstrate a true inhibitory surround. Maximal acoustic response occurred when the loudspeaker was within the excitatory visual receptive field but weaker responses were detectable over a range of at least ± 5°. Responses invariably disappeared when the sound source was placed on the other side of the vertical meridian. Only the lateral dimension was significant. Displacements of the sound source above or below the horizontal meridian while maintaining the same deviation from the vertical meridian had no additional effect.

Figure 9 exhibits PST histograms of the cellular discharge to acoustical stimuli (in each case 40 presentations of 50 msec click trains) as a function of position on the tangent screen used to project visual images. The " preferred " visual stimulus was an obliquely oriented light slit in the right upper quadrant of the field extending from 10°-13° lateral to the vertical midline. When the light slit was positioned slightly to the right or left of site indicated, there was a pronounced inhibition of discharge; other sites had no effect whatsoever. As can be seen from the accompanying histograms the borders of the acoustically responsive zone were not as sharp and there was no evidence of an inhibitory surround. The shaded area of Fig. 9 represents the zone of effective acoustic stimulation. It is notable that within that zone stimulations above and below the horizontal meridian gave similar results (Fig. 10). Another cell in the same penetration was activated by a differently oriented visual stimulus (Fig. 11) and had a smaller receptive field closer to the vertical meridian. Histograms of acoustically-evoked activity are displayed at various sites along the horizontal meridian (Fig. 11 A, B, C, D, E). Similarly, the histograms of cellular firing at various sites along the vertical meridian are illustrated in Fig. 12 F through Q. The acoustical receptive field is shown as the shaded area superimposed on the tangent screen map (Figs. 9, 10, 11, 12). The cell shown in Figs. 11 and 12 had a narrower zone of acoustic sensitivity than the cell in Figs. 9 and 10. It is important to stress that the boundaries are not as sharp as they appear in the diagram and such relative differences as were noted between these two cells depend upon the use of the small focused loudspeaker mentioned above for their demonstration. Moreover, a certain subjective element enters into the determination of what constitutes an acoustical receptive field boundary. This is well exemplified by the histogram patterns in Fig. 9. The histogram for position " H " had the largest number of counts. Histograms " G " and " I " contained fewer counts but maintained the basic shape of histogram " H ". Therefore, " G ", " H " and " I " were all considered within the acoustical receptive field. The histograms for positions " F " and " J " do, in fact, reveal an acoustical response but it was very small and did not have the same shape

as " G ", " H " and " I ". The decision to place " F " and " J " outside the boundary of the receptive field was purely arbitrary and may have to be reconsidered as more parametric details become available.

So far we have been unable to demonstrate tuning curves for these cells; the spatial distributions described obtained for clicks and also for pure tone bursts from 10khz to 50khz. Therefore, these cells appear to be a separate population from that discovered by Spinelli *et al.* (1968) in that they are sensitive to acoustical space rather than to pitch. Other possible parameters have not yet been investigated. In particular, it should be noted that since the visual

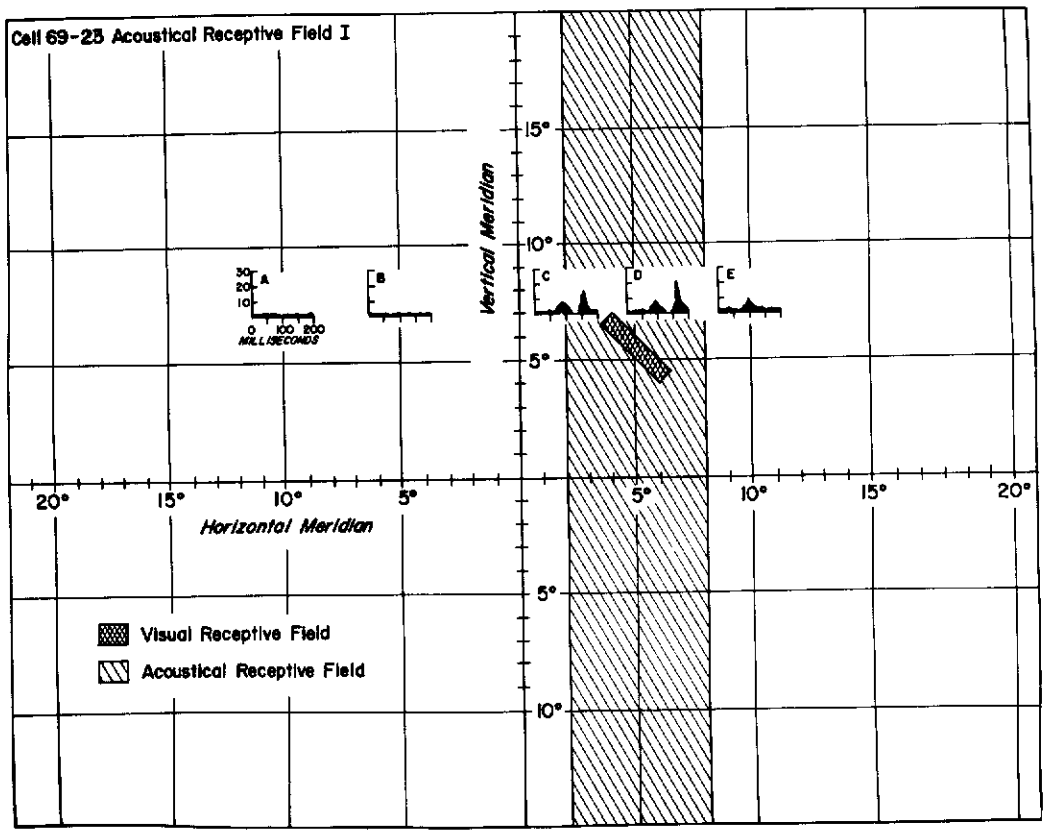

Fig. 11. Visual and acoustical receptive fields superimposed. Horizontal dimension. Another cell in the same penetration. Visual receptive field extends from 6° to 4° right lateral with an obliquity opposite from that of the preceding cell (Figs. 9 and 10). PST histograms to acoustical stimulation from focused loudspeakers placed at sites indicated by the center of the histogram display. Thus, sites " A ", " B ", " C ", " D " and " E " were all at 7° above the horizontal meridian, and were at, respectively, 10° and 5° left lateral and 2°, 6° and 10° right lateral. Visual receptive field indicated by cross-hatching; acoustical field by diagonal lines.

displays were designed for tangent screen projection rather than for a perimeter and the acoustical stimulus sites were superimposed upon the visual field coordinates, all sites were not equidistant from the ears. Nevertheless, in Fig. 9, for instance, loudspeaker positions " C " and " H " were both displaced 12° from the vertical meridian, yet the difference between the two histograms was striking. Position " F " was nearer to the animal than position " H " and position " J " much further away. Yet the loudspeaker at position " H " yielded

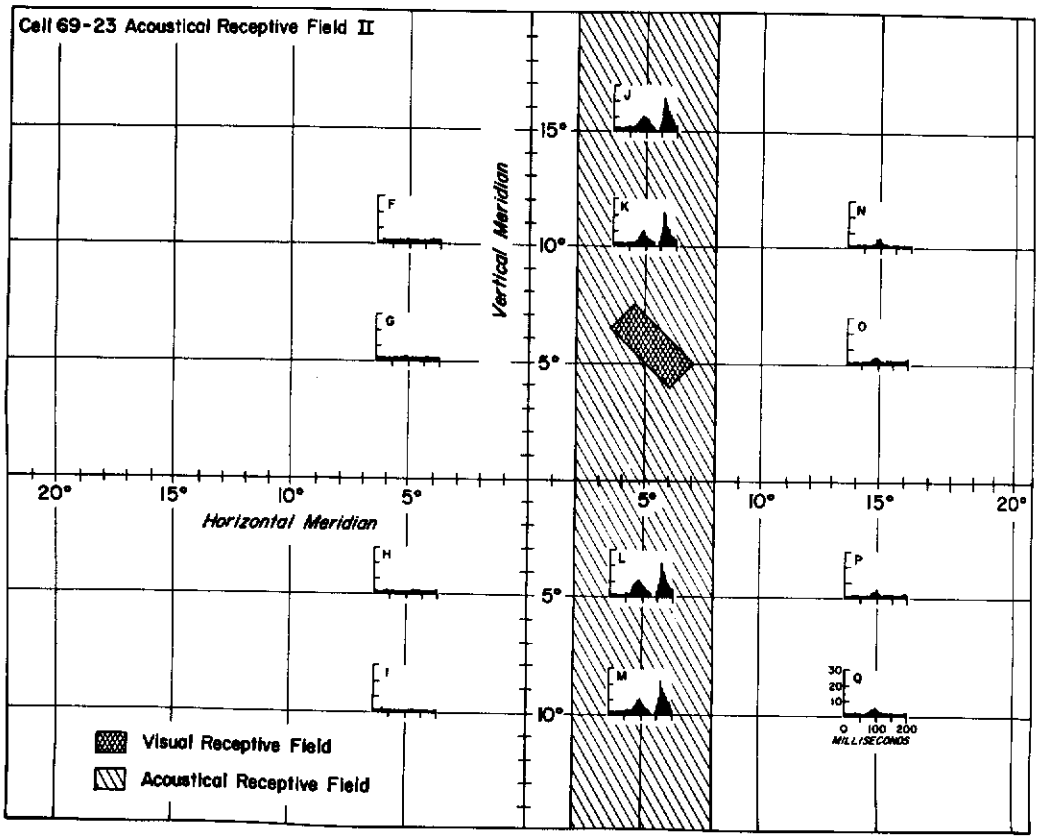

Fig. 12. Visual and acoustical receptive fields superimposed. Vertical dimension. Same cell as in Fig. 11. PST histograms to acoustical stimulation from focused loudspeakers placed at sites upon the tangent screen indicated by the center of the histogram display. Thus, sites " F ", " G ", " H " and " I " were all 5° above and 5° and 10° below the horizontal meridian. Sites " J ", " K ", " L " and " M " were all at 5° right lateral and were, respectively, 15° and 10° above and 5° and 10° below the horizontal meridian. Sites " N ", " O ", " P " and " Q " were all 15° right lateral and were, respectively, 10° and 5° above and 5° and 10° below the horizontal meridian. The acoustical receptive field in this cell was narrower than in the example of Figs. 9 and 10, but shares with the latter the property that the cellular responsiveness does not discriminate stimuli displaced along the vertical dimension but does so sharply along the horizontal.

the most vigorous discharge, while stimulations at " F " and " J " evoked very similar and smaller activity patterns. Thus, it seems unlikely that the spatial differences observed can be accounted for by any simple scale for distance of sound source.

Discussion

The microstructure of the temporal pattern of cellular discharge as examined by computation of PST histograms revealed an extraordinary richness and diversity of detail as well as a remarkable stability of pattern when the same stimulus was applied in serial replications. For most cells the stability of response for given stimuli persisted despite applications of combined stimuli which, in a small proportion of cells, resulted in response modification. The most important observation which the use of the PST histogram allowed was that in polymodal cells each and every qualitatively different stimulus resulted in a different and distinctive temporal pattern of discharge. Thus, a visual cortical neuron, which was also responsive to acoustical stimulation, responded in a different manner depending on the location of the sound source (Fig. 9, compare F or J with G. H. or I. Cells responsive to more than one visual stimulus (Figs. 7 and 8) produced unique histograms for each effective stimulus configuration and, furthermore, non-visual stimuli impinging on the same cells (tactile or pain, in the case of Fig. 7 and vestibular in the example of Fig. 8) elicited still further unique and characteristic histogram patterns. Even the direction of vestibular polarization affected response patterns in different ways (Figs. 6 and 8). The same acoustical stimulation provoked one kind of response in one cell (Fig. 4) and other kinds in other cells (Figs. 9 and 11). In short, cellular discharge patterns appear to be quite specific both for each particular cell and for each effective stimulus.

When looked at in this manner, it seems extremely hazardous to classify the various afferent drives engaging visual neurons into simply "specific" and "unspecific" influences. In an early paper, Jung (1961) cogently summarized the argument for a specific vestibulovisual interaction as necessary to the precise regulation of visual function. This was quite apart from any diffuse, non-specific arousal. Furthermore, at that time Jung suggested that many of the neural mechanisms mediated by the brain stem reticular formation and loosely termed "non-specific" were, in fact, highly specific behaviors. That suggestion has received ample experimental confirmation, both in man (Morrell, 1967) where the topological distribution of cortical desynchronization was precisely concordant with the primary geniculocalcarine afferents activated by a localized visual stimulus (Polyak, 1927) and in several animal species (Gumnit, 1960; Jasper, 1960, 1961; Jasper *et al.*, 1960; Morrell, 1961 *a*).

Indeed, it often seems that when so-called "unspecific" neural systems are challenged in physiological ways and their ensuing responses thoroughly exa-

mined, some surprisingly specific features may be detected. This may not always be the specific quality intitially expected as shown, for instance, in Figs. 9-12, where the specificity lies in the spatial rather than the frequency dimension of acoustical stimuli. Certainly, in these examples of non-visual input to visual cells, the term "unspecific" seems inappropriate. The rough anatomical distinctions derived from work with gross evoked potentials (for reviews, see Albe-Fessard and Fessard, 1961; French, 1960; Jasper, 1960, 1961; Rose and Mountcastle, 1959) led to the hypothesis made explicit by Abrahamian *et al.* (1963), Bergamini and Bergamasco (1967), Rose and Lindsley (1968) and Uttal and Cook (1964), that short latency responses are of "lemniscal" origin while long latency responses arise from parallel activation of "extralemniscal", bilaterally projecting, modality non-specific, mesencephalic and thalamic reticular systems. The same distinctions were applied to single unit studies by Kornhuber and Da Fonseca (1964) but to this writer, they no longer seem adequate to encompass the vast range, variety and complexity of observations now becoming available through the application of computer technology to the analysis of single unit activity. A case in point is the very different picture observed by Dubner and Rutledge (1964) when they examined single units of the same association cortex in which Thompson *et al.* (1963 *a*, 1963 *b*) concluded that there was a "central association system" which was modality non-specific and was activated by extralemniscal pathways. However, examination of single units receiving biomodal or trimodal convergence revealed that each cell had biases in terms of what modality most effectively engaged it and that cellular response patterns differed depending upon which stimulus modality was used to activate the cell (see also Dow and Dubner, 1969).

The case is similar in parastriate neurons. Thus, although the parastriate area is clearly a zone having mainly visual function organized on a receptive field plan, even visual afferents do not command the cell's behavior in a simple reflex manner. Non-visual afferents impinging on visual cells elicit different output patterns and, presumably, themselves have a specificity along some dimension. Responses to other modalities which engage visual neurons are not distinguishable by latency, duration or maximal initial reaction (to use the criteria set forth by Kornhuber and Da Fonseca, 1964). There are only two criteria by which we can distinguish the effect of non-visual from visual input to visual cells. These are 1) sensitivity to barbiturate anesthesia, respiratory and cardiac distress and sleep (Abrahamian *et al.*, 1963; Erulkar *et al.*, 1956; Murata *et al.*, 1965), all of which diminish the response to non-visual input but leave the response to visual input relatively unaltered (Hubel and Wiesel, 1965 *b*; Robertson, 1965), and 2) the one-way character of results on cellular modification described above and discussed below.

In short, none of our results suggest a lack of specificity either for cell or for signal. Therefore, we prefer the more neutral terms primary and secondary as used by Buser (Buser and Bignall, 1967; Buser and Borenstein, 1959; Buser and Imbert, 1961), Albe-Fessard (Albe-Fessard and Fessard, 1963; Albe-Fessard and Rongeul, 1958, Mallart *et al.,* 1961), Amassian (Amassian, 1953, 1954; Amassian and De Vito, 1954), and Jung (1961). Until more experimental data enabling a detailed and meaningful classification becomes available, we consider that for visual cells the preferred visual stimulus is primary and all non-visual activations are secondary. For some cells, there was more than one "preferred" visual stimulus (Figs. 7 and 8).

Yet even this distinction is unsatisfactory. The designation of a "preferred" stimulus is limited by the investigator's inventiveness in compiling a stimulus repertoire and by a subjective estimate of the response magnitude. Magnitude, in turn, is hardly a meaningful scale on which to compare patterns. As noted above, the stimuli we use are relatively complex but still extremely simple when compared to those of real life. How will the cell having an active discharge to a certain orientation of line or edge respond to a picture of a mouse. Or, even better, a live mouse, with its olfactory, tactile and motile features? Similar difficulties apply to the selection of non-visual, interaction stimuli. The previously unguessed specificity of the spatial aspect of acoustical stimuli (Figs. 9-12) raises the question of whether specificities exist in some dimension for tactile, noxious and vestibular input to visual cells. No answer to that question can yet be given because the required experiments have not been done.

Auditory physiologists generally have devoted much more attention to mechanisms of pitch discrimination than to those for localization of a sound. Nevertheless, there is a considerable body of literature relating to the latter problem (Brugge *et al.,* 1969; Erulkar *et al.,* 1956; Galambos *et al.,* 1959; Geisler *et al.,* 1969; Goldberg and Brown, 1968, 1969; Kass *et al.,* 1967; Masterton and Diamond, 1964; Masterton *et al.,* 1968; Moushegian *et al.,* 1967; Neff, 1962; Neff and Diamond, 1958; Nelson and Erulkar, 1963; Rose *et al.,* 1966; Rosenzweig, 1954; and for an excellent and comprehensive review of the clinical literature, see Walsh, 1957). In general, it appears that stimulus coding for the location of sound depends upon very small differences in time of arrival at each ear. Cells in the superior olivary complex are sensitive to time differences in the range of microseconds. Such information must then be relayed to visual cortex, perhaps through auditory cortex or, possibly, via the inferior colliculus to superior colliculus and then on to visual cortex. To our knowledge, there has been no investigation of any kind of acoustical response in the superior colliculus, let alone responses depending upon directionality of sound source.

Whatever the pathway, there is a certain biological sense about the fact that many parastriate cells are sensitive to spatial features of the acoustical input

and, in particular, are concerned with sound sources roughly coincident with the same sector of space which contains that cell's visual receptive field.

The equally obvious lack of discrimination in the up-down dimension is consistent with the observation that the intact, behaving cat cannot learn a discrimination based upon altitude alone unless it tilts the head, thereby adding a lateral dimension to the stimuli. (Our cats were paralyzed with heads rigidly fixed in the horizontal plane.) It is also possible that "feature-detector" cells for altitude of sound source are present but in such small numbers that we failed to encounter them.

The notion that temporal pattern of discharge may provide a code by which the nervous system preserves qualitative features, local sign and modality specificity in polymodal cells is not new and has been suggested by many investigators (Adey *et al.*, 1954; Adrian, 1949; Amassian, 1953, 1954; Amassian and De Vito, 1954; Burns, 1955, Granit, 1955; Machne and Segundo, 1956; Segundo and Machne, 1956; Tove and Amassian, 1958; von Békésy, 1959; Wall, 1959, 1961). The statistical homogeneity of the typical patterns (For a cell and for a stimulus) shown in the preceding figures affords strong support for that notion. Nevertheless, it must be clearly stated that these cells do not exhibit the kind of synaptic security which was demonstrated by Mountcastle *et al.* (1963) and Poggio and Mountcastle (1963) for cells of the ventrobasal complex. Although all could be driven by particular visual stimuli within well-defined receptive fields as previously noted (Morrell, 1967), each stimulation did not yield exactly the same cellular discharge pattern. Thus, in Fig. 1 the PST histogram clearly indicates two peaks of activity. Yet, when examined individually, trials 3, 7 and 10 failed to show the second burst; in trial 5 the early burst was not detectable and in trial 11 neither discharge occurred. Clearly, therefore, at any given time, on any particular occasion, the responsiveness of a nerve cell cannot be relied upon to specify the nature of an experience. Obviously any complex organism must rely on parallel processing in thousands of elements along hundreds of channels to adequately analyze an external event. No single channel need be depended upon for most activities of everyday life. The observed relationship between the input and the output of a cell has been described as "probabilistic" (Morrell, 1967), i.e.; as having a statistical stability in the time course of firing with respect to a stimulation. The term "probabilistic" is descriptive only and does not imply any particular conclusion about the nature of the "noise" in the system. It is possible that a completely deterministic system, but one in which many variables are unknown, would appear probabilistic to the limited viewpoint of a microelectrode sampling the output of one single cell. Nor, of course, do these observations exclude the possibility of some fundamental stochastic property operating at the level of synaptic transmission. All that can be said at this stage is that it is not necessary to

introduce any fundamental indeterminacy in the system to account for all the available data (Bullock, 1967; Kennedy *et al.*, 1966).

The next most important observation which these experiments allowed was that concerned with response modification in a relatively small but significant proportion of cells. The general stability of cellular responses in visual cortex makes those cells exhibiting response modification stand out clearly. The distribution of modifiable cells was not random; it was quite orderly. These cells were almost always encountered in groups and such groups were invariably found in columnar penetrations of the microelectrode. In many penetrations, some seven cells of this type have been found; the largest number of modifiable neurons encountered in a single penetrations was 15. What can be the meaning of columnar organization for this type of cell? In the first place, such an arrangement makes it possible for these cells to take advantage of the information built into the basic connectivity of the system according to genetic rules. Secondly, it means that these cells feed information outward, either to subcortical nuclei or to relatively distant cortical regions, but do not interact with their immediately adjacent cortical neighbors. This supposition is in accord with almost all other observations on the functional properties of cortical cells Hubel and Wiesel, 1963; Powell and Mountcastle, 1959). Nevertheless, the number of cells which exhibit response modification is small, i.e.; 10-12 % of total cells sampled. It is interesting that all investigators who have looked at this problem have found a similar percent (Adám *et al.*, 1966; Adkins, Morse and Towe, 1966; Bishop, 1965; Bishop *et al.*, 1959; Bures and Buresova, 1967; Buchwald *et al.*, 1966; Chow *et al.*, 1968; Erulkar and Fillenz, 1958, 1960; Hill, 1966; Hori *et al.*, 1967; Horn, 1965; Hubel *et al.*, 1959; Kandel, 1967; Kandel and Spencer, 1968; Kamikawa *et al.*, 1964; O'Brien and Fox, 1969 *a*, 1969 *b*; Weingarten and Spinelli, 1966; Yoshii and Ogura, 1960). Chow, Lindsley and Gollander (1968) demonstrated alterations in firing pattern in lateral geniculate cells consequent to a specific prior experience which were very similar to those reported here and in Morrell (1967). They also found that such changes occurred in about 10-12 % of the population and that such cells were always encountered in groups.

Nevertheless, we really have no means of knowing whether the proportion we and others have found (roughly 10-15 %) represents a realistic estimate of that portion of the population having "plastic" properties. There are indeed several reasons to consider that this estimate may be erroneously low. Thus, the recognition of pattern required the summed PST histogram method of data analysis. This, in turn, required that the same cell be held for many hours to provide all the necessary controls and comparisons. In many cells, we may not have hit upon the adequate or optimal stimulus. Moreover, the testing method employed to demonstrate response modification involved essentially an extinction series and may have resulted in a more rapid loss of the modified

pattern than would have occurred had we used intermittent reinforcement or an entirely different method of testing. Varying the time interval between stimuli might also have increased the yield of modifiable neurons. Finally, these cats were naive to begin with. The proportions might be quite different had we pretrained the animals behaviorally with a number of the stimuli later used in testing.

An additional feature of this experiment deserving of comment is the fact that response modification only occurred when the "preferred" visual stimulus was administered. For instance, if the cell was optimally sensitive to a particular configuration of luminous stimulation and also to acoustical stimulation, and when the two were combined, a third firing pattern occurred (as in Figs. 2 and 4), only the "preferred" visual stimulus elicited a pattern change. Presentation of the non-preferred member of the pair alone never evoked a pattern similar to that yielded by the pair. Thus, the alteration was evident only when the cell's responsiveness was tested by application of the preferred visual stimulus. Why this one-way effect should obtain is not at all clear. However, the observation leads to the prediction that a similar experiment conducted in auditory cortex would yield a modification limited to response to the acoustical volley. The visual stimulus alone in the latter case should be incapable of eliciting or maintaining the modified response.

In the past (Morrell, 1967), we have hesitated to label the modification phenomenon with the term "conditioning". The latter involves the establishment of a permanent engram; and we particularly do not have evidence that the microstructure of a cellular firing pattern is the physical substrate of enduring memory. We have considered it much more likely that temporal patterns of cellular discharge do represent the initial or short-term or electrically sensitive stage of information storage in brain. The time intervals involved are of the same order of magnitude as the so-called "consolidation time" (Chamberlain *et al.*, 1963; Deutsch, 1962, Di Giorgio, 1929; Gerard, 1961; McGaugh and Petrinovich, 1965) and the "heterosynaptic facilitation" of Kandel and Tauc (1965).

We have said (Morrell, 1967) that it seems most *unlikely* that retrieval or recognition requires the cellular recreation of these temporal patterns of discharge. The demonsration by Lindsley, Fehmi and Adkins (1967) which showed that monkeys could recognize objects with which they had been trained in 10 msec. or less was cited as evidence to support that opinion. The cellular activities we have described often last as long as 250 msec.

Nevertheless, at this time, it seems appropriate to point out also that our microelectrode samples the activity of one single cell and from that standpoint the pattern may take 250 msec. to unfold. But clearly the cat's action does not depend on any single cell. Suppose that the multiple parallel chains in the cat's nervous system abstract a spatially dispersed, almost instantaneous, analog of

the cellular firing patterns which we detect in the temporal dimension (see Maffei, 1968).

A further speculation, now being tested, goes as follows. New information as registered in the nervous system is first preserved as a temporal pattern of neural activity (short-term memory having the duration of the "consolidation" phase). During this period, the permanent storage (presumably anatomical and biochemical) phase begins. Permanent storage has no reflection in electrical events. However, each time the information is retrieved either for comparison with new input or by central interrogation, the memory read-out occurs and is reflected in neuronal activity having essentially the pattern of that which occurred during initial storage. The distribution of the pattern through time is what we can demonstrate by the PST histogram display. Presumably, there is also an analogous organization of activity across a spatial domain. It is the latter which allows for rapid retrieval; the former activity has the same result as it had originally; that is, it makes more of the stuff of which the permanent storage is made. Thus, each retrieval propagates and disseminates the permanent storage, building it in more and more securely. Such a mechanism seems to fit with an enormous body of behavioral data (see John, 1967). In this view, the electrical configuration of neuronal discharge represents an "active" form of the memory trace emitted by the animal either spontaneously, or when called for by an external stimulus. The "resting" form of the memory trace presumably is represented by anatomical or chemical changes at a molecular or even sub-molecular level. This hypothesis predicts, then, that in a highly trained animal each recollection of the training stimulus would be accompanied by an electrophysiological change comparable to that described herein. Some evidence in favor of this notion has been presented by John (1967).

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NEURAL CORRELATES OF MEMORY *

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If we insert a number of fine wires, insulated except for the tip, into the brain and connect them to high gain amplifiers, such electrodes detect potentials on the order of tens of microvolts which fluctuate at frequencies ranging up to about 50-60 cycles per second. These potentials probably represent the fluctuations of membrane potentials integrated across large numbers of brain cells around the tip of the electrode, and reflect the excitatory or inhibitory influences impinging on these cells rather than their actual firing. Electrodes in different brain regions typically detect potentials which fluctuate rather independently. If a strong sensory stimulus, such as a click or a flash, is presented to the animal, a perturbation with definite chraacteristics occurs in the potentials recorded from some regions. This phase-locked oscillation is called an *evoked potential.*

For some years, we have studied the changes in evoked potentials which occur as various stimuli are made behaviorally significant for an animal. These experiments involve chronic implantation of 34 electrodes into different brain regions, followed by long-term studies of evoked potentials caused by two signals which differ in their repetition rate, such as flashes at two different frequencies, and which are the cue for two different behaviors. Some of our animals have been studied since 1962.

Suppose we teach a cat that he can get food whenever he presses a lever. While he performs this learned task, alert and highly motivated, an overhead light flickers, causing a rhythmic fluctuation of the intensity of his whole visual field.

Figure 1 shows that this meaningless stimulus causes evoked potentials which are localized to only a few regions of the brain, such as channel 2 which is the lateral geniculate body, a thalamic nucleus in the visual system. The

* The work described in this paper has been supported by Research Grant MH-08579 from the National Institute of Health.

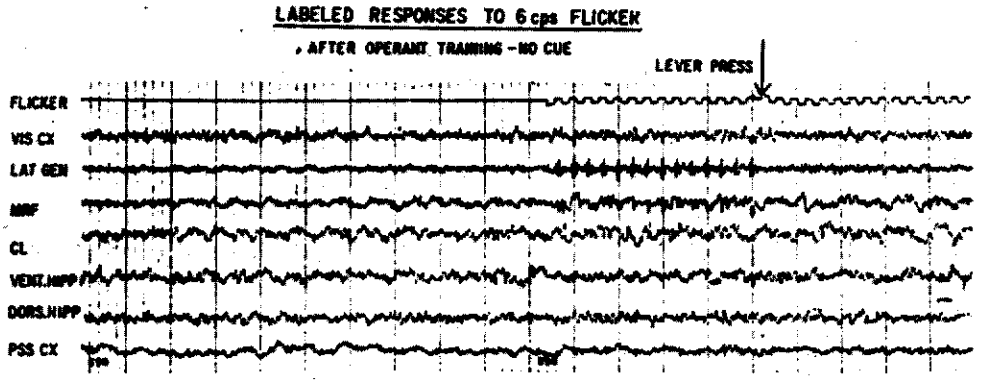

Fig. 1. Effect of 6-cps flicker presentation to cat after it had learned that milk could be obtained whenever a lever was pressed. Flicker had no signal value at this stage. Notice how little labeled activity was elicited by the flicker except in the lateral geniculate. Note disappearance of response in lateral geniculate due to internal inhibition, as cat presses lever and waits for milk.
(From John, " Mechanisms of Memory ", 1967)

activity of different brain regions is markedly independent. Now suppose that the animal is taught that a lever press during flicker at this frequency will be punished by withholding the opportunity to get food. The flicker has become a negative conditioned stimulus.

Figure 2 shows that this significant signal now causes evoked potentials in many brain regions which were unresponsive. Although some brain regions

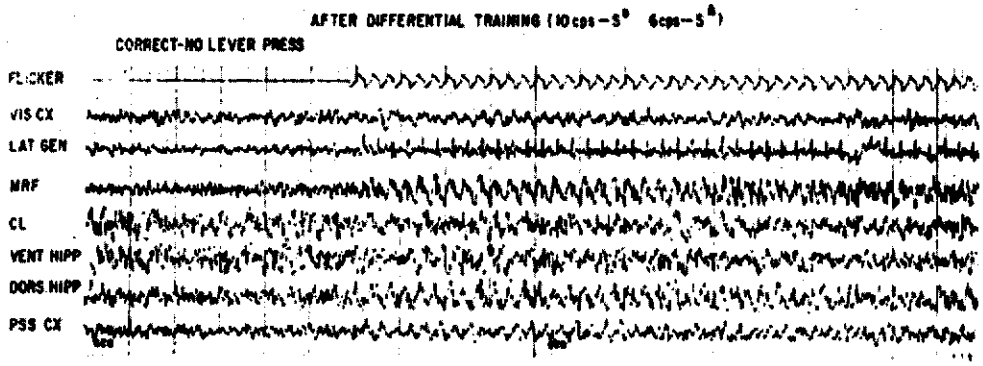

Fig. 2. Effect of 6-cps flicker after elaboration of frequency discrimination, using 10-cps flicker as positive signal and 6-cps flicker as negative signal. These records were obtained during correct inhibition of lever press during 6-cps flicker. Note marked enhancement of labeled potentials at the stimulus frequency after differential training, and frequency specificity of the brain activity.
(From John, " Mechanisms of Memory ", 1967)

still display no response to the stimulus, a group of regions show rather similar responses. The apparent coupling between different parts of the system seems to have increased. The increased similarity can be demonstrated quantitatively in a number of ways, such as by the decrease in the dimensionality of the electrical ' signal space ' which can represent the set of evoked responses. This observation is well established, having been reported by numerous laboratories [1]. In overtrained animals, similarity between certain brain regions can be extremely striking. This is seen most clearly if a number of evoked responses are averaged, which effectively increases the signal to noise ratio, as seen in the figure 3.

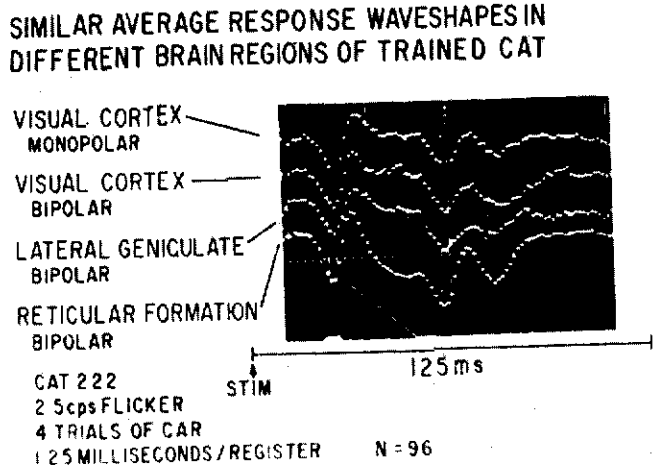

Fig. 3. Average response waveshapes recorded from different derivations in a trained cat. Note the marked similarity of the potentials in different brain regions.

(From John, " Mechanisms of Memory ", 1967)

It should be emphasized that other brain regions may show quite different activity at the same time that a subset of anatomical structures displays such similarity. These non-similar loci may be located geometrically between loci showing similarity. Thus it is unlikely that such similarity can be attributed to volume conduction from some large single source. Nonetheless, we considered it important to learn what patterns of neural discharge occurred under such circumstances. As Dr. Morrell has explained, neural discharge can be observed as fast, relatively large voltage spikes, recorded from fine microelectrodes.

Depending upon the tip size and the amplification, microelectrodes can record from single neurons or from groups of neurons. We have developed a chronically implanted microdrive which can move a closely spaced pair of microelectrodes vertically through the entire thalamus of the cat [4]. The electrodes can be held in a given position motionless for as long as desired,

and can be moved in very small increments. By use of appropriate filters, such electrodes can provide information about the discharge of nerve cells as well as about the slow wave or evoked potential activity in a brain region. Low pass filtering provides the evoked potential from the region, while the output of a high pass filter contains the spikes produced by multiple neurons near the electrode tip. By use of pulse height discriminators, spikes of specified amplitude can be segregated and studied. We consider these amplitude specified spikes to correspond to the discharges of a group or ensemble of neurons located within a certain distance of the electrode tip. With these methods, we have studied the average evoked potentials and simultaneously recorded post-stimulus time histograms of neural ensembles as microelectrodes were slowly advanced through large distances in both trained and untrained cats [3, 5]. Such studies take 8 to 10 months per animal and are carried on in the freely moving unrestrained state. The results show good relationships between evoked potential waveshape and ensemble post-stimulus histogram contour. In general, when the evoked potential swings in one direction, the probability of firing in the ensemble increases, and when it swings in the opposite direction, the probability of firing decreases. Changes in the evoked potential waveshape are usually accompanied by changes in the local firing pattern. It is worth emphasizing that under conditions such as those used in our studies, single cells show extreme variability in their firing patterns while groups of cells display striking invariance. All data discussed were based on averages of 500 responses and were reproducible. After a traverse has been made through a region of the brain, it is possible to define each peak and trough of the evoked potentials and post-stimulus histograms and to measure their amplitude at each electrode position. Gradients can now be constructed for each of these components separately, plotting amplitude of response vertically versus depth of electrode penetration along the horizontal axis.

Figure 4 shows the gradients obtained from a traverse of 10,000 microns in an untrained animal. The irregular contour of these gradients shows that

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Fig. 4. Amplitude gradients (left graphs) and latency gradients (right graphs) from an untrained animal. Graphs on the left side illustrate the amplitude gradients of positive (P) and negative (N) AER components and PSH peaks (see key), computed for Cat 1, 2-cps. Successively later components are depicted from top to bottom graph. In each graph, amplitude on the component is plotted as horizontal displacement. At bottom are presented the correlation coefficients rij between response waveshape at adjacent electrode positions.

Each graph on the right side shows the latency distribution of the P and N AER component and the PSH peak whose amplitude gradients are found in the graph at the same level on the left side of the figure. Component latency is plotted along the abscissa, while depth of penetration is represented along the ordinate.

(From John and Morgades, *Comm. Behavioral Biol.*, 1969)

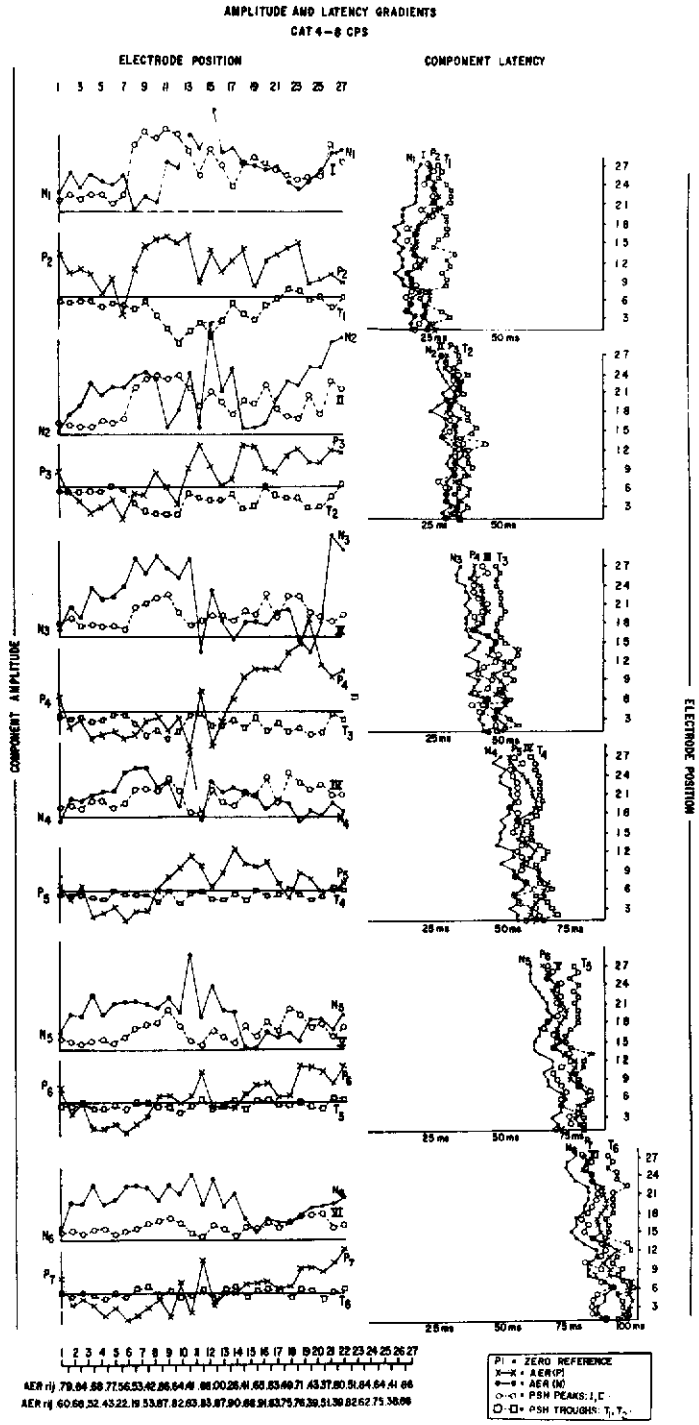
AMPLITUDE AND LATENCY GRADIENTS
CAT 4—8 CPS
ELECTRODE POSITION
COMPONENT LATENCY
COMPONENT AMPLITUDE
ELECTRODE POSITION
1 3 5 7 9 11 13 15 17 19 21 23 25 27
25 ms
50 ms
75 ms
100 ms
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
AER rij 79 84 88 77 56 53 42 86 64 41 66 00 26 41 66 83 49 71 43 37 80 51 64 64 41 66
AER rij 60 66 32 43 22 19 53 87 82 63 83 87 90 66 91 63 75 76 39 51 39 82 62 75 38 66
Pi = ZERO REFERENCE
AER(P)
AER (N)
PSH PEAKS: I, C
PSH TROUGHS: T1, T2

Fig. 4

there was marked *heterogeneity* of response to this stimulus throughout the mapped region, both with respect to the evoked potential and to the ensemble firing patterns. The graphs to the right show that there was also appreciable variation in component latency across the domain. The traverse included the lateral geniculate.

Figure 5 shows the gradients obtained from a traverse of 4000 microns through the lateral geniculate in a trained cat. The smooth contour of these gradients shows that there was marked homogeneity of response to this conditioned stimulus throughout the mapped region, both with respect to evoked potentials and to ensemble firing patterns. The graphs to the right show that there was little variation in the latency of a component across the domain.

The trained cats had learned to discriminate between two different flicker frequencies which were the cues for two different behaviors. At each electrode position in the traverse, characteristic evoked potential waveshapes and firing patterns were elicited by the two different signals. This figure shows that the average of the responses to the two different stimuli, summed across the entire traverse, are different at very high levels of significance. In other words, signal 1 elicited firing pattern 1 across the domain, while signal 2 elicited firing pattern 2. It should be stressed that not all neurons responded to the two signals. Only a fraction of the cells in any region were responsive, and that fraction varied from region to region. However, responsive groups had the same characteristic firing patterns no matter where they were located.

Perhaps the most intriguing feature of this extensive representational system is that the similarity of response is dynamic, not static. When a novel stimulus is presented, or when a trained animal makes a mistake, we see that certain brain regions depart from this common pattern and display markedly different activity. Thus we began to suspect that part of the picture of homogeneous response observed in trained animals was caused by the release of a pattern of electrical activity stored in memory. This can be seen in this figure, which compares the potentials recorded from a differentially trained cat during correct and erroneous behavior. On the left we see that during correct avoidance response to a 7/s flicker, rhythmic potentials at the stimulus frequency are elicited in many regions. On the right, we see that when an erroneous approach response appropriate to a differentiated 3/s flicker is elicited by the 7/s flicker, the cortex displays marked activity at the *wrong* frequency [7].

A similar phenomenon can be seen during generalization. Here we see average evoked responses which, on the top row, were obtained during correct

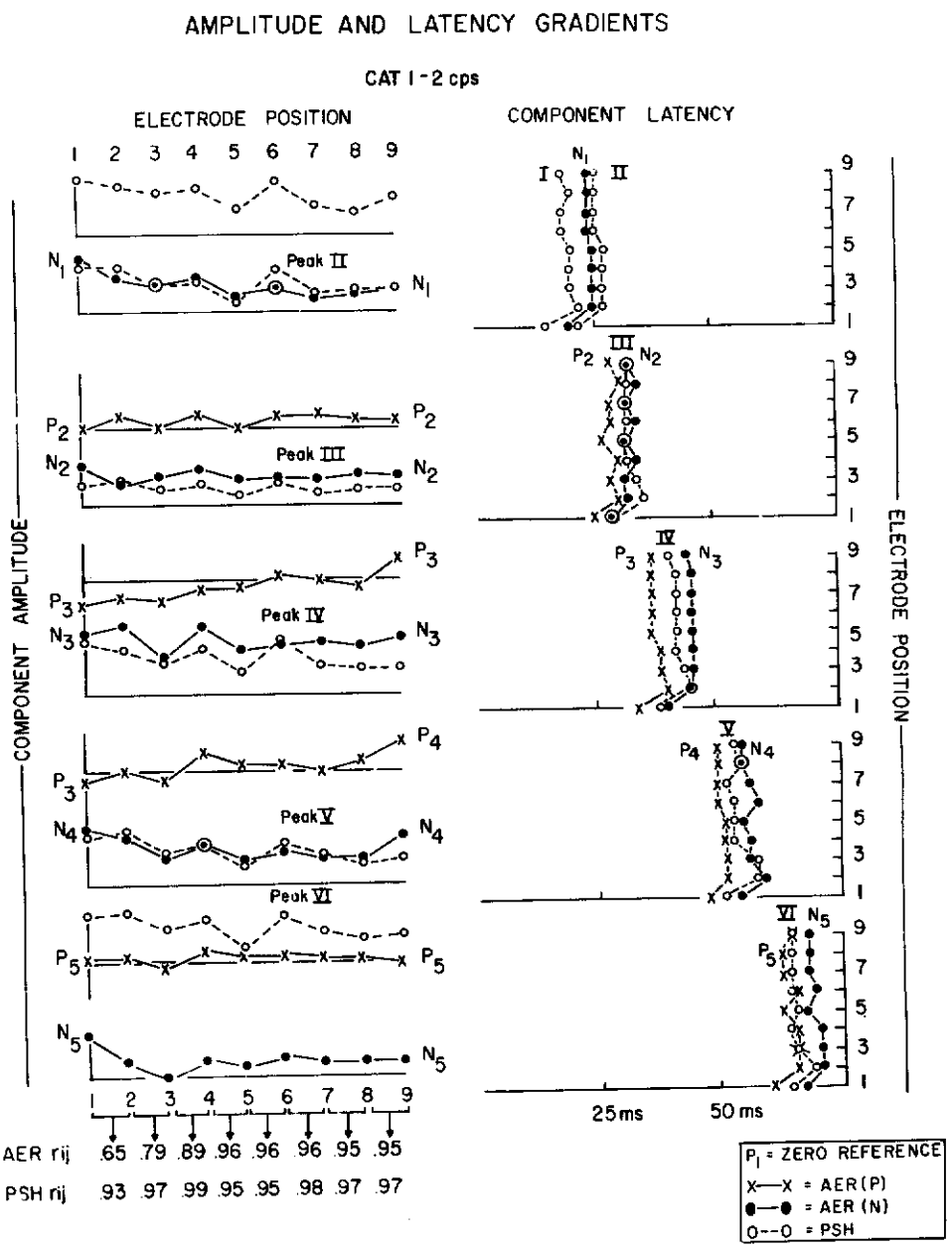

Fig. 5. Gradients as shown in Fig. 4, but from a trained cat, which obtained food by pressing one lever in response to a 2-cps flicker and a different lever in response to an 8-cps flicker.

performance of a conditioned response to a 10/s flicker. On the bottom row, we see evoked response caused by a novel 7/s flicker which the animal ignored. In the middle row is shown the evoked potential caused by the 7/s flicker when 'generalization' occurred and the animal performed the behavioral response learned to the 10/s signal. We considered component I to reflect afferent input of information, and components II and III to reflect the activation of memory about that input [9].

Figure 6 shows the counterpart of this phenomenon on the level of neural firing. These records were obtained in the lateral geniculate. The upper dotted

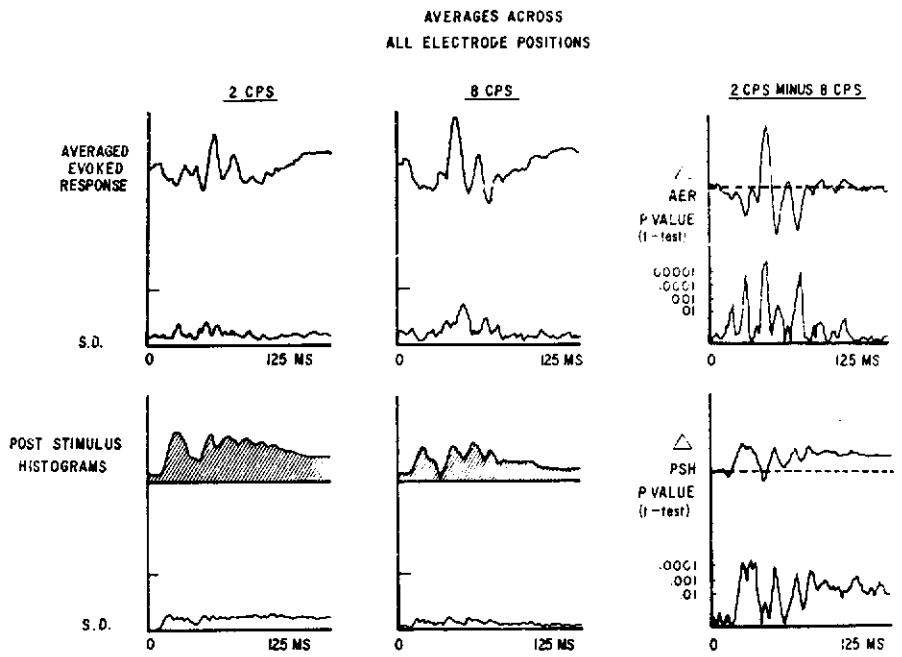

Fig. 6. *Upper left:* the top curve in this graph shows the *average* of the AERs elicited by the 2-cps CS across all electrode positions in the mapped region, while the lower curve shows the standard deviation of the group of AERs; *Lower left:* the top curve shows the *average* of the PSHs elicited by the 2-cps CS across the same electrode positions and the lower curve shows the standard deviation; *Upper middle:* The *average* AER to the 8-cps CS and the corresponding standard deviation; *Lower middle:* The *average* PSH to the 8-cps CS and its standard deviation; *Upper right:* The top curve shows the difference waveshape resulting from the subtraction of the average AER to the 8-cps CS from the average AER to the 2-cps CS. The lower curve shows the p value, as computed by the t-test, for each point of the difference wave; *Lower right:* The top curve shows the difference waveshape resulting from the subtraction of the average PSH to the 8-cps CS from the average PSH to the 2-cps CS. The lower curve shows the p value for each point of the difference.

(From John and Morgades, *Comm. Behavioral Biol.*, 1969)

curve shows the evoked potential elicited by a 2/s flicker used as the conditioned signal during a set of trials resulting in correct performance of a lever press for food. The dotted histogram shows the firing pattern of the neural group under study. The solid curve shows the evoked potential caused by presentation of a novel 1/s flicker to which behavioral generalization subsequently occurred. The shaded histogram shows that the neural firing pattern caused by the novel stimulus during generalization was quite the same as the neural response to the actual conditioned stimulus. On the bottom of the figure, we see the evoked potential and post-stimulus histogram caused by the same 1/s test signal when generalization failed to occur. Note the alteration of the later components.

These results might mean that during generalization a specific firing pattern and potential waveshape were released from memory, recapitulating the usual response of the brain to a familiar event, or might be due to alterations of excitability caused by aroused attention, incipient movement or levels of motivation. In order to distinguish between these alternatives, we devised a technique which we call ' differential generalization ' [8].

For example, a cat is taught to press the lever on the right side of a work panel to get food after presentation of a 1/sec flickering light in a dimly lit cage. Let us call this V_1 CR. Presentation of a 2/sec flickering light means that the

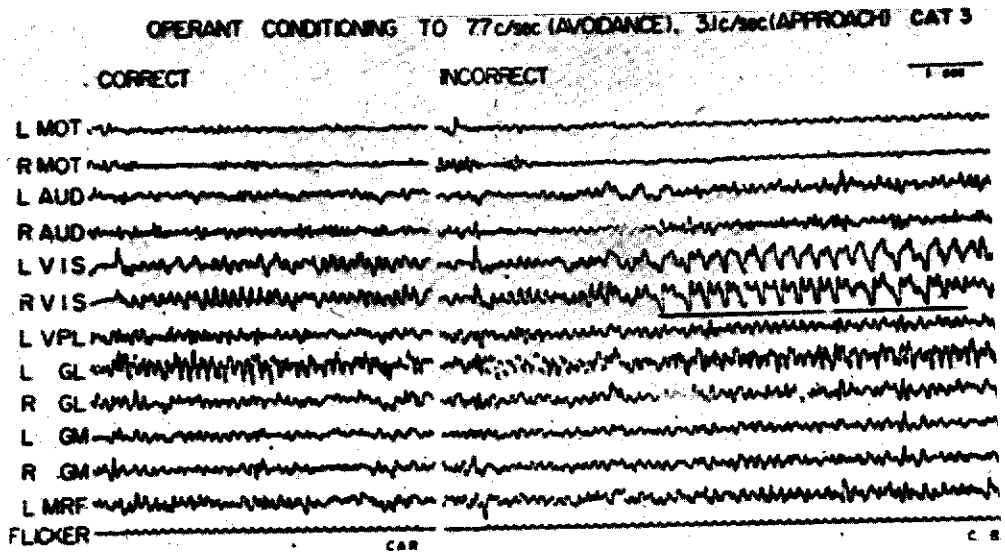

Fig. 7. Recordings obtained from a differentially trained cat in response to presentation of a 7.7 cps flicker CS: *Left:* during correct performance of the CAR appropriate for the 7.7-cps flicker stimulus; *Right:* during erroneous performance of a food response (CR) which would have been appropriate had the flicker signal been at 3.1-cps.

animal should press a different lever on the left side of the panel to avoid electrical shock (or perhaps to get food from a different dipper). Let us call this V_2CAR. After much overtraining, sometimes lasting more than a year, we are ready to study differential generalization. During a random sequence of presentations of V_1 and V_2, we occasionally introduce a neutral stimulus, V_3, which is a 1.5/sec flicker exactly midway between V_1 and V_2. Sometimes this stimulus elicits one learned behavior (CR); sometimes it elicits the other behavior (CAR). This experiment has been done using a wide range of training frequencies and a variety of behaviors, with similar findings in every animal.

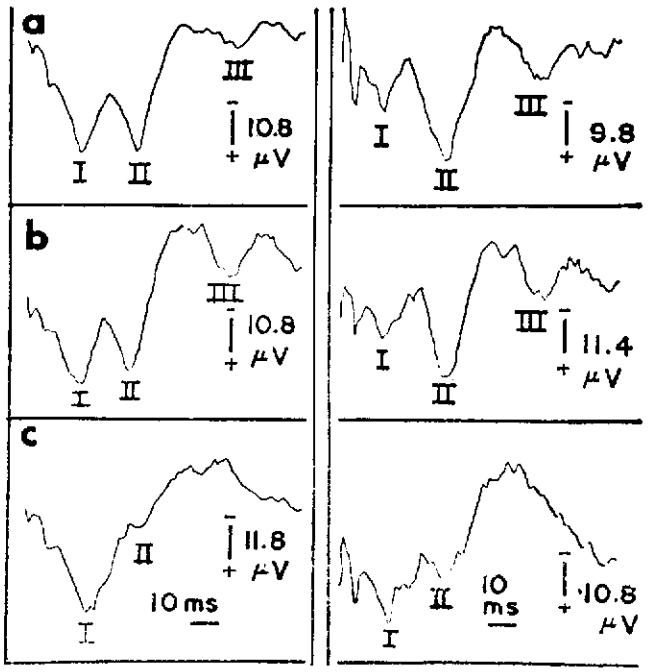

Fig. 8. Average response computations obtained from the lateral geniculate nucleus reticularis of the cat under various conditions during the same experimental session. All averages in this illustration are based upon 42 stimulus repetitions from a number of behavioral trials. Analysis epoch was 62.5 msec. *Upper row:* Average responses evoked in structures by the 10-cps conditioned stimulus (flicker) actually used in training, during repeated correct behavioral performances. *Middle row:* Average responses evoked by a novel 7.7-cps flicker, during repeated generalization behavior. Test trials with the 7.7-cps stimulus were interspersed among trials with the actual 10-cps conditioned stimulus, and were never reinforced. *Bottom row:* Average responses evoked by the 7.7-cps flicker on presentations when no generalization behavior was elicited. Note the similarity of the waveshape elicited by the actual conditioned stimulus to the response evoked by the novel stimulus during generalization. Notice the absence of the second positive component in the evoked potential when generalization failed to occur.

(From John, " Mechanisms of Memory ", 1967)

Two interesting facts emerge from such studies: First, the evoked potential waveshape when V_3 results in performance of one conditioned response, let us call it V_3CR, in some regions is significantly different from the evoked potential observed when the same physical stimulus V_3 is interpreted differently and elicits the other behavior, V_3CAR. Therefore, the shape of the evoked potential is not determined solely by the physical stimulus. Second, the evoked potential obtained during V_3CR closely resembles the waveshape elicited during V_1CR. Conversely, the waveshape during V_3CAR closely resembles that elicited during V_2CAR. The results are illustrated in the figure. Each set of four average responses comes from a different animal. In each case, the first waveshape shows the evoked response during V_1CR while the fourth wave comes from V_2CAR. Both the second and third waveshapes were elicited by V_3; the second during V_3CR and the third during V_3CAR. The intermittent line between V_3CR and V_3CAR indicates the intervals for which the two evoked responses are statistically different at the level $p < 0.01$. These results suggest that the novel input V_3 activates a neural system which releases an electrical pattern as if a particular familiar input were actually present. This released pattern reproduces

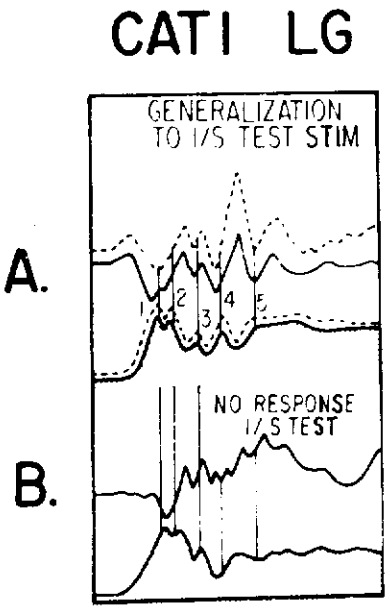

Fig. 9. *Upper half:* AER and PSH recorded during 18 trials resulting in CR to the 2-cps CS (dotted curves) and during 32 trials resulting in generalization to a 1-cycle test stimulus (solid curves). The test stimuli were randomly interspersed between presentations of 2-cps and 8-cps in a long experimental session. *Lower half:* AER and PSH obtained during 17 trials resulting in failure to generalize to the test stimulus.

(From John and Morgades, *Exptl. Neurol.*, 1969)

the usual effect of the familiar event. These effects are therefore specific and cannot be attributed to arousal, attention or other unspecific factors.

These various findings suggest that 1) the activity of extensive neural regions is altered during learning, so that similar processes are distributed through different regions; 2) conditioned stimuli cause specific average firing patterns to occur in distributed neural groups, which may constitute a representational system; 3) the neural mechanism established during learning is capable

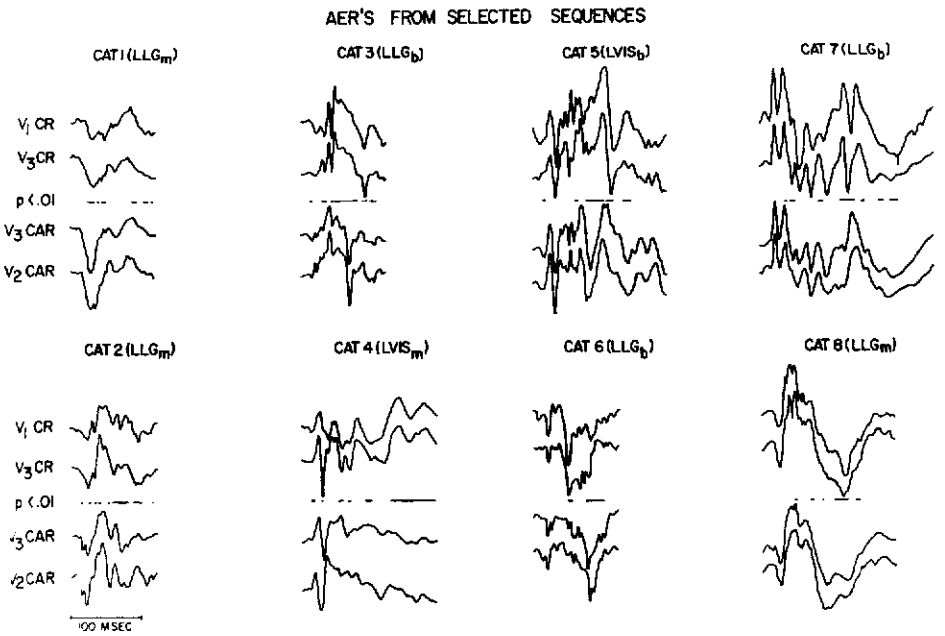

Fig. 10. Average response waveshapes recorded from one structure in each experimental animal. The averages were based upon homogeneous sequences of evoked potentials selected by the experimenter from the last 4 seconds of multiple decision-making trials. (The validity of the selection procedure has since been substantiated by computerized analysis for non-homogeneity and computerized sorting of the evoked potentials into appropriate classes.) The decision-making trials resulted in correct performance of a lever-press for food during presentation of flicker at frequency 1 (V_1CR), correct performance of a lever-press to avoid shock during presentation of flicker at frequency 2 (V_2CAR), or during presentations of flicker at an intermediate frequency 3, generalized approach (V_3CR) or avoidance (V_3CAR). Interrupted line between the second and third waveshape in each group indicates those intervals during which the significance of the difference between V_3CR and V_3CAR exceeds the 0.01 level. LLG, left lateral geniculate body; LVIS, left visual cortex; subscript *b* indicates bipolar derivation taken between two electrodes 1 mm apart. Frequencies were as follows: Cats 1 and 2, $V_1 = 7.7$, $V_2 = 3.1$, $V_3 = 5.0$; Cat 3, $V_1 = 3{,}1$, $V_2 = 7.7$, $V_3 = 5.0$; Cats 4, 5 and 8, $V_1 = 5$, $V_2 = 2$, $V_3 = 3.1$; Cat 6, $V_1 = 2.5$, $V_2 = 1.0$, $V_3 = 1.75$; Cat 7, $V_1 = 1.0$, $V_2 = 2.5$, $V_3 = 1.75$. Sample size was variable, with an average of 15.

(From John, Shimokochi and Bartlett, *Science*, 1969)

of reproducing the usual effect of a stimulus in its absence. This suggests that the electrical 'readout' from memory may literally reproduce the pattern which was 'read in'.

These phenomena may not be functionally critical for learned responses to occur, merely reflecting a correlation with unknown but primary mechanisms, or may actually provide an insight into the mechanisms mediating retrieval of memory in the brain. In the latter case, these data suggest that the information relevant to two signals may be represented by two different statistical patterns in the orderly fluctuations of firing in the same neural population through time, rather than by discrete events occurring in different specific cells.

To help you evaluate this phenomenon, we have prepared a film which shows the sequence of potentials caused by V_3 during differential generalization [2]. These potentials are raw data displayed on an oscilloscope, with no computer processing. You will see a few examples of potentials during V_1CR and V_2CAR. A light at the bottom of the oscilloscope face is vertically below the particular component which we consider the readout potential. After a few teaching trails, a series of V_3 presentations will be presented. When the scope face goes blank and a question mark appears, the animal performed a response. The audience can then predict what the animal actually did *.

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* The film which was shown at this point in the conference is available for interested groups to view.

De la Physique théorique à la Biologie, C.N.R.S., 1971.

DISCUSSIONS

M.U. PALMA : From Dr. Morrell's slides, I had the feeling of the existence of a spontaneous rhythm, within some 50 or 100 milliseconds, some kind of echo. I would like to know if this is true, and what this means.

J.Z. YOUNG : I would like to ask Dr. Roy John how long does it go on responding to the V_3 stimulus. They get no reward for this ?

E. ROY JOHN : V_3 is occasionally interspersed in a random sequence of V_1 and V_2. You cannot include many V_3 trials in a day, or it is no longer generalization. When an animal has been tested a few times with V_3, we begin a random reinforcement of V_3, an aperiodic and unsystematic reinforcement; there is no rhyme or reason to it. Thus, we can keep him going for quite awhile as though he had hypotheses he was testing.

H.C. LONGUET-HIGGINS : Is Professor Roy John ready to commit himself to a view as to whether the lateral geniculate is the seat of any plastic changes which might occur during the learning process ?

E. ROY JOHN : We've put 96 electrodes in different brain areas in the population of cats in whom we observed this phenomeon, and we have observed statistically significant differences between V_3CR and V_3CAR in 65 out of the 96 placements. Furthermore, suppose you assume that the evoked potential waveshape when the animal produces a previously learned behavior to an indifferent stimulus hypothetically contains ' read-in ' about the stimulus plus ' read-out ' from memory. Substract from that waveshape the evoked potential caused when the same indifferent stimulus elicited no behavior from the animal, which is an approximation of ' read-in ' alone. Thus, subtracting ' read-in ' from ' read-in plus read-out ' should yield a different waveshape whose latency shows the process appears in time [6]. If memory were localized, the difference waveshape with the shortest latency should arise in the place where the process exists, and then it should propagate. The results of that measurement are distressing. They indicate that there is an extensive system which includes the mid-line thalamus, the mesencephalic reticular formation and the cortex of the sensory modality, all of which change mode earliest. The difference waveshape is then found later and later as one goes to the other structures, and it appears last in lateral geniculate where we viewed it today. Unfortunately, the reason I say the results are distressing is because with measurements which we

pushed to 600 microseconds per register, it appears as though the cortex and reticular formation change state at the same time. We cannot see a significant difference in the latency of the process in those two places.

J.Z. YOUNG : So you would conclude that, by saying that, there was no localization.

E. ROY JOHN : I am not willing to conclude that yet. We are planning a series of experiments similar to these in which pattern recognition techniques will be used with a high speed computer to try to identify the appearance of these read out waveshapes in different anatomical regions. As the computer identifies their appearance, it will mobilize a disruptive electrical input which will stimulate the electrode where this process is arising, in an attempt to disrupt the organized activity of the structure from which we are recording. It is my hope that that experiment will find some region with which one cannot interfere if retrieval is to occur in a generalization paradigm.

J.Z. YOUNG : Have you any more questions ? Yes, Dr. John.

E. ROY JOHN : Can I just add one provocative word to try to arouse some of my colleagues. The read-out process which we see is massive. It is, as I pointed out, a factor of four to five larger than the evoked potential which we thought was the important thing going on in the lateral geniculate. This process, which is precisely a thing which you could never see in an anesthetized or untrained animal, has a much more compelling amplitude, and a signal to noise ratio which is much higher than the evoked potential. The impression one gets is that the huge read-out potential is accomplishing tremendous coherence in a set of cells. Very phased discharge is taking place, a very high level of organization is imposed on the nucleus which is undergoing this process. This is part and parcel with the rest of the story which I showed you, which says that the changes which take place are distributed, which says that if you look at a single cell its behavior is highly variable in the unanesthetized or unrestrained animal, yet when you look at the ensemble you see invariants. The question we really have got to resolve is whether the information being processed and retrieved in a nervous system under such circumstances consists of the firing of some particular cell, which Professor Fessard once called the " ultimate pontifical neuron ", which is the neuron which says " yes, I know " or whether it is the statistical characteristics, the time rate of change of entropy in a system which defines the message, with the message being contained by no component in it at all. The components are in fact relatively unimportant. I think that the data I have shown you suggests that the latter alternative must be considered seriously. I may be wrong, but it should be considered seriously.

M.U. PALMA : I would like to remark in this respect that when you have, say, " n " channels through which you pass identical (and phased) signals which are noisy, then if all the signals add up it is very easy to see that the signals just add up, and the noise adds as the square root of " n ", so that this improves the signal-to-noise ratio by a factor $\sqrt{n}$.

J.Z. YOUNG : Any more comments ? No ? Well, thank you very much indeed, our speakers have shown us some of the difficulties and the possibilities of the study of the electrical activity of the nervous system. I hope this will be fruitful in stimulating suggestions as to how methods may still be improved.

De la Physique théorique à la Biologie, C.N.R.S., 1971.

EFFECTS OF ANTIBIOTICS ON LONG-TERM MEMORY FORMATION IN THE GOLDFISH (*) (**)

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1. Introduction

The use of disruptive agents such as trauma, electroconvulsive shock and convulsant durgs as experimental probes in improving our understanding of brain memory mechanisms is well known. On the basis of growing insusceptibility to a specific treatment as a function of time following learning, the process of consolidation, or fixation of memory is inferred. Depending upon the training task, the experimental animal and the disruptive agent, variable effects on retraining at some later time are seen. Gradients varying from a few seconds to many hours in duration are derived, representing the growing resistance of a new memory to disruption during the post-training period. It is immediately apparent that to explain the many time courses of consolidation reported, there must either be many stages of consolidation, the disruption of any of which can modify an animal's ability to perform a learned behavior, or each agent must artifactually interfere with memory in a way that more characterizes its mode of action than it describes a physiological process involved in memory formation. Since all of the above agents temporarily interrupt gross brain function by producing convulsions and/or unconsciousness, a simple explanation of their action involves the dissolution of "reverberating" electrical circuits within the neuronal network which ultimately would have become converted to some more stable form had the process not been interrupted. That the permanent form of memory should be chemical has been suggested by a number of considerations. The long lasting nature of memory suggests it ultimately resides in a form resistant to various natural forces

* The research reported in this chapter was supported by grants from the National Institute of Mental Health and the National Science Foundation. The able assistance of Mr. Paul Klinger is gratefully acknowledged.

** The findings reported here were also presented at a symposium on animal memory at Dalhousve University, Nova Scotia, Canada in June, 1969.

tending to randomize molecular arrangements, i.e. covalent chemical bonds. Such bonds are known to mediate the storage of genetic material. The DNA that contains coded instructions for the synthesis of specific enzymes is resistant to physical agents as well as to the enzymes that act on the rapidly-turning over intracellular components engaged in energy production for cellular function. More direct evidence for a molecular basis of memory stems from experiments made possible by the recent availability of antibiotic agents that block macromolecular processes in animal cells. These novel substances, to be considered in some detail, have been shown to block memory formation when they are applied to the brain. Unlike previously and annestic agents described above, they do not produce gross neurologic disturbance.

2. The antibiotic inhibitors of macromolecular synthesis

The molecular business of a cell might conveniently be divided into two categories : those related to growth (including cellular reproduction), and those related to energetics — the conversion of food to useful energy. The machinery for reproduction and growth is located principally within the nucleus of the animal cell, while energy metabolism goes on in various extranuclear structures. The interrelationship of these two functions of cells is complex. The nucleus regulates the level of key metabolic enzymes, and thus plays a role in cellular energetics as well as growth. The macromolecular synthesis of growth can on the other hand not occur without the presence of high energy substances provided by the cytoplasm, such as ATP. Despite this interdependence, specific chemical agents exist that can selectively block a given step of growth alone or of metabolism alone and the effects of such agents may be analyzed to give further insight into these two domains of cellular physiology.

Disruption of energy metabolism of the brain of higher animals by such substances as cyanide or carbon monoxide produces often irreversible effects and does not appear to be a useful means of understanding brain function. Blockers of macromolecular synthesis are relatively new chemical tools. They were first discovered and explored for their possible use of antiinfectious and anticancer agents. In nature, they presumably arose via natural selection and mutation and provide armamentarium for microorganisms and some higher life forms. Their secretion by a microorganism into its growth medium results in the inhibition of growth of neighboring organisms. The specific molecular mechanism by which such metabolic monkey wrenches work varies but in general each agent has a single selective molecular site at which it acts. These agents are therefore useful experimental probes. Of particular interest are those agents that block DNA, RNA or protein synthesis.

Since the mechanism of the synthesis of DNA, RNA and protein bears strong resemblance in all living material, it is not surprising that many of these

antibiotic blockers of macromolecular synthesis are biologically active in animal as well as in bacterial systems. For example, arabinosyl cytosine selectively blocks DNA synthesis (replication) in bacteria as well as in higher animals. Actinomycin D has no effect on replication, but by combining with DNA, prevents its use as a template for RNA synthesis (transcription). These activities are confined to the nucleus of the eukaryotic cell. Translation, the synthesis of protein by ribosomes, although a part of the cellular growth process, occurs mainly in the cytoplasm of the cell. It may be blocked by a number of agents including puromycin and the cycloheximides. Proteins are the final effectors and express their function via their catalytic (enzymic) activities. The extranuclear site in which most proteins are made is the polysome, which may be considered a factory in which a coded messenger RNA (mRNA) is sequentially read as it passes down the assembly line, by a series of workmen (the ribosomes), each of whom assembles amino acids into an identical continuous sequence determined by the mRNA. The existence of 20 known amino acids which can be coded and the usual length of proteins (100 + amino acids) make possible more unique proteins than there are atoms on earth to assemble. In the polysome, mRNA determines which combination of amino acids will be put together and in a given polysome the same mRNA can give rise to as many molecules of a given protein as there are ribosomes. The antibiotic, puromycin interferes with this process by attaching itself to the growing peptide chain. The peptidyl puromycin formed leaves the polysome. This antibiotic thus chops off incomplete fragments of protein. The glutarimide inhibitors, cycloheximide (CXM) and acetoxycycloheximide (AXM), slow down the assembly process. They therefore also block formation of peptidyl puromycin. Both puromycin and the cycloheximides have the net effect of preventing the formation of proteins and hence cellular growth as well. They also block some forms of cellular regulation, such as enzyme induction. Although they act by different mechanisms, the net effect is the inhibition of protein synthesis.

The neuron, like other cells, synthesizes RNA and protein. The polysomes are near the nucleus, in the perikaryon, but active neuronal metabolism may be occuring at some distance in presynaptic terminals separated from the rest of the cell *via* an axon which might be as little as a few microns or as much as a meter away. Regulation by the nucleus may require transport of macromolecules *via* the axon.

3. Effects of antibiotics on learning and memory in the goldfish

Several years ago, we developed a technique for the intracranial injection of various materials in a 5-10 microliter volume into unanesthetized goldfish (Agranoff and Klinger, 1964). By means of isotopic studies we found that injections of antibiotics such as puromycin (170 μg) or acetoxycycloheximide

(AXM, 0.2 μg) inhibited protein synthesis throughout the brain to about 20 % of normal for several hours, with recovery in about 1 day (Brink, Davis and Agranoff, 1966; Lim, Brink and Agranoff, 1971). Despite this drastic effect on protein synthesis, there was little change in the gross behavior of the animals. In fact, injected goldfish could be trained in a shock avoidance task with no gross evidence of impairment in performance (Agranoff, Davis and Brink, 1965). The apparatus we used in our initial studies (Task I) was modeled after a two-way shuttlebox of Bitterman (Behrend and Bitterman, 1964) and differed mainly in that in our task, fish were given a discrete number of trials rather than trained to a criterion. Animals were given 20 trials on Day 1 of an experiment, were returned to home tanks, then given 10 retraining trials 3 days later (Day 4). Between training sessions, fish were stored in individual plastic home tanks and were maintained without feeding in continuous light. Possible influences of daily rhythms on behavior or on drug effects have not been investigated systematically, but there was no indication that the time of day influenced the experimental results. One-minute trials were given in blocks of 5, and the blocks alternated with 5 minutes of darkness in the shuttlebox. At the beginning of a trial, a light (Sylvania 120PSB) went on the side of the shuttlebox in which the fish had been placed and 20 seconds later, intermittent electrical shock (0.2 sec; 3 v; 60 cps at 0.1 mA) was administered through the water. At the end of the 40th second, both light and electrical shock in the lighted end of the apparatus were terminated whether the fish had avoided or escaped the shock. The shock was transmitted across the barrier to the opposite side of the shuttlebox to a negligible extent. After 20 additional seconds, the next trial was initiated with onset of light on the side of the shuttlebox to which the fish had swum during the first 20 seconds, avoiding the shock, or had escaped. Fish averaged about 2 avoidances in the first 10 trials, about 4 in the next 10 and 6 on retraining on Day 4. Groups of fish retrained at later times, as much as several weeks after the initial 20 trials, showed the higher avoidance scores characteristic of trials 21-30 seen on Day 4. Other groups, given trials 21-30 on Day 1, immediately following trial 20, performed similarly. The interval between trial 20 and 21 thus had little or no effect on the total avoidance score for the subsequent block of 10 trials. There was considerable variability in the number of avoidances from fish to fish as well as in the means from group to group. We used a regression equation to predict Day 4 scores for each fish on the basis of performance in the first 20 trials (Davis, Bright and Agranoff, 1965). The regression was empirically derived from Day 1 and 4 scores of 189 control fish. Predicted avoidance scores for Day 4 for each fish was substracted from the achieved score as a measure of memory loss. This method of computation aided in comparing effects on fish differing in absolute levels of avoidance responding within a group as well as in comparing groups of fish that differ in the average number of avoidances during training. Undoubtedly, many factors

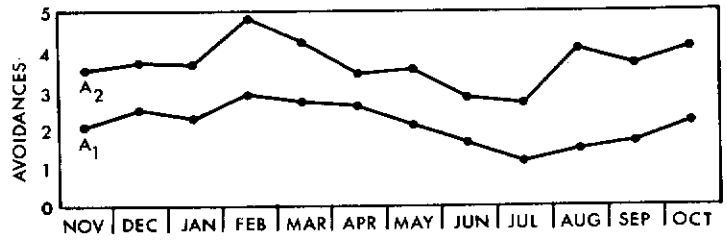

Fig. 1. Seasonal variation in avoidance responding for groups of fish trained in Task 1. A_1 = avoidances on trials 1-10. A_2 = avoidances on trials 11-20. Day 4 scores (not shown) were predicted by a regression analysis (from Agranoff and Davis, 1968).

contribute to this variability. We have observed a distinct seasonal variation in performance. This is reflected in Fig. 1 (Agranoff and Davis, 1968). Even with the regression, avoidance scores were sufficiently low in the summer months to discourage us from running behavioral experiments.

TASK I. The effect of injection of puromycin at various times following training of Task I are summarized in Table 1. The fish injected after one hour had been returned to home storage tanks following training. Our major findings (Agranoff *et al.*, 1966) using this task were : 1) Puromycin or AXM when injected immediately following training on Day 1 produced a marked decrease in responding on Day 4. The same amount of antibiotic given 1-2 hr following trial 20 had no effect. Thus the effect of the injections were temporally related to training, consistent with consolidation hypotheses of memory formation. The injection of saline immediately following training had no effect on memory, while graded lower dosages of puromycin had smaller effects. 2) When the agent was injected before training, there were no observable neurological effects as alluded to above. Furthermore, there was relatively little effect on Day 1 scores, and yet we found marked memory loss on Day 4. 3) Animals allowed to remain in the training apparatus instead of being returned to home tanks following training remained susceptible to puromycin long after they ordinarily would have " fixed " memory (Davis and Agranoff, 1966). Animals remaining in the

TABLE 1

Task I : Consolidation

Puromycin dihydrochloride (170 µg) was injected IC in 10 µl.

Treatment, day 1	Retention, day 4	N
None	0	72
Puro, 0 delay	− 2.7(*)	36
Puro, 1 H delay	− 0.1	35

* Significant at p. < .01.

shuttlebox for periods up to 3 hrs and not injected showed no memory loss. This striking result suggested that the return to the home tank triggered the onset of the fixation process. 4) Actinomycin D blocked RNA synthesis selectively during the first 2 hr following its intracranial injection. At later times, protein synthesis was also blocked. This drug also produced a block in memory (Agranoff, Davis, Casola and Lim, 1967). These results (Agranoff and Klinger, 1964; Brink *et al.*, 1966; Lim *et al.*, 1971; Agranoff *et al.*, 1965) were interpreted to mean that the formation of long-term memory required ongoing RNA and protein synthesis but that initial acquisition did not. Further discussion of these results and their interpretations are presented below. 5) Electroconvulsive shock was effective over a similar temporal gradient. The period of susceptibility to ECS could be extended by cooling animals from 19° to 9° in the posttrial period (Davis *et al.*, 1965). Cooling alone did not produce amnesia. 6) When puromycin or AXM was given immediately following training, there was no immediate loss of memory. The amnesia developed over a period of 2-3 days.

TASK II. Some experiments were performed using shuttleboxes in which fish were trained to swim into the lighted rather than into the darkened side of the shuttlebox. This is a more difficult task as judged by avoidance scores (Agranoff and Davis, 1968) but animals could be trained, and memory formation was disrupted with puromycin as in Task I. Task III, described below, is also more difficult than Task I for the goldfish and has been in use in our laboratory for the past 2 years.

TASK III. The shuttleboxes are identical to the ones used in Task I and II except that a clear plastic gate is present over the center barrier and must be deflected by the fish upon crossing. The gate was initially inserted to make the task more difficult in the hope that there would be a greater difference in response scores between Day 1 and Day 4 and also to discourage intertrial crossing. In this task, following 5 minutes of acclimatization in the shuttlebox, 20 one-minute trials are given in a single block. A 15 second avoidance period is initiated by a light signal on the side of the shuttlebox in which the fish is located. Whether the fish avoids during the first 15 seconds or escapes in the subsequent 20-second shocking period, photodetectors on either side of the

1. In Task III, a separate regression is calcualted for two groups of fish, those that demonstrate at least one avoidance response on Day 1 (a) and those that do not (b). Avoidances (A), failures to escape (F) and number of shocks received (S) during trials 1-10 or 11-20 on Day 1 are designated by the subscripts 1 and 2 respectively. The predicted score for group b on retraining, $PA_3 = 5.628 + .129\,(A_1) + .332\,(A_2) - .247\,(F_1 + F_2) - .016\,(S_1) + .030\,(S_2)$. For group a, $PA_3 = 5.082 + .098\,(F_1) - .339\,(F_2) - .042\,(S_1) + .026\,(S_2)$. The calculations are based on a multiple-regression equation with multiple predictors (McNemar, 1969).

barrier register the response and terminate the trial, leaving the fish in darkness until the beginning of the next minute. Twenty such shuttleboxes are interfaced at the present time to a PDP-8 computer which programs the trials and records the responses of each fish on punched tape. Latencies are recorded in tenths of seconds. Additional programs facilitate storage of data and calculation of regression equations from groups of control fish run every week. Several thousand fish were studied with the automated apparatus during a 1.5 year period. When control fish perform significantly differently from predicted Day 4 scores

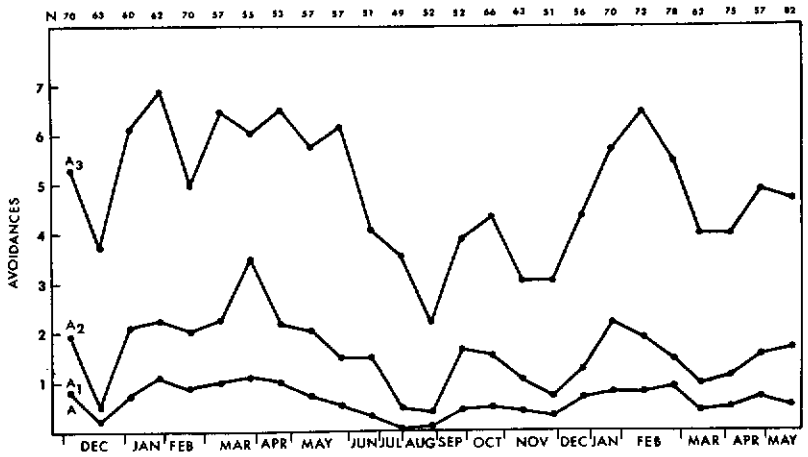

Fig. 2. Seasonal variation in avoidance responding for groups of fish trained in Task III. A_1 and A_2 as in Fig. 1. A_3 = avoidances in trials 21-30 on Day 4.

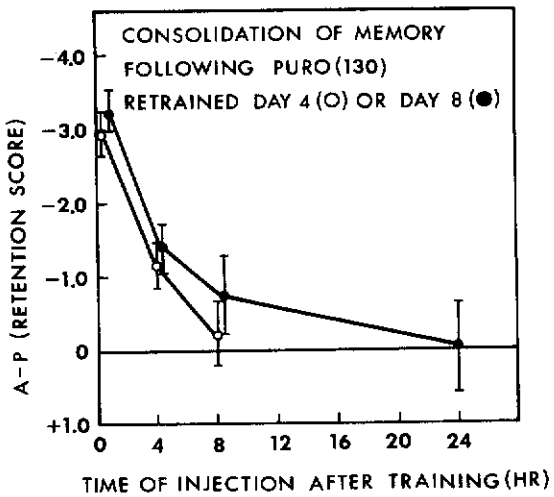

Fig. 3. Effect of varying the time of intracranial injection of puromycin on Day 1 on memory as tested on Day 4 or on Day 8 (some of the fish in this group were retrained Day 7). Retention score is obtained as in Table 1.

TABLE 2

Task III: Consolidation

Puromycin dihydrochloride (130 μg) or saline in 10 μl was given IC 1 h before training.

Treatment day 1	Retention day 4		Rétention day 7-8	N
Puro, 0 delay	− 2.96(*)	82	− 3.29(*)	36
Puro, 4 h delay	− 1.15(*)	80	− 1.40(*)	27
Puro, 8 h delay	− .23	53	− .76	24
Puro, 24 H delay†			− .04	27

* Significant at $p < .01$.

† From Davis and Klinger (1969).

on the basis of an annual regression equation [1], experimental groups for that week are not used. Examination of control groups run in Task III (Fig. 2) reveals examples of deviations from the expected response scores of control groups, e.g., the last week in February.

Results of memory studies are in general agreement with our earlier findings with Tasks I and II, but with some interesting differences as follows: 1) In contrast to our results in Task I, we have found that groups given 170

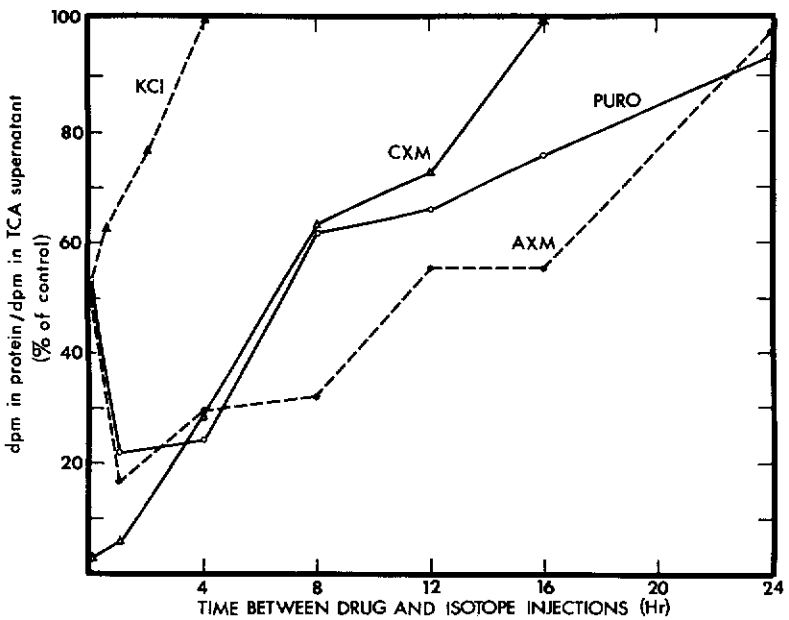

Fig. 4. Effect of intracranial injection of various agents on incorporation of leucine into brain protein (Lim *et al.*, 1971).

μg of puromycin 24 hr after training show some apparent sickness in Task III as judged by performance on Day 4. Using 130 μg of puromycin in Task III (Table 2), there is no evidence for sickness, although this dose does not produce a complete memory loss. That is, Day 4 scores are not as low as scores for trials 1-10 on Day 1, but highly significant deficits are seen. Tables 1 and 2 show that the " consolidation time " with puromycin in Task III is considerably longer than that seen for Task I. Animals given puromycin but retrained 7-8 days later show a similar deficit. Although AXM had previously been demonstrated to produce amnesia in Task I, in view of the scarcity of this material, we used injections of 10 μg of the less potent compound, CXM, in further experiments in Task III. As can be seen from Fig. 4, this amount of the agent, 50 times the milligram amount of AXM used previously, produced a more intense depression of protein synthesis but of shorter duration (Lim *et al.*, 1971). CXM produced little memory deficit by Day 4 but a degree comparable to that seen with puromycin is obtained upon retraining on Day 8 (Fig. 5). The " short-term memory decay " appears to occur some time after Day 6. This delayed action of antibiotics has been previously observed with AXM (Agranoff, 1970a). There may be some evidence of this delayed onset of amnesia in studies in which the various blocking agents were given to fish following 20 min in the shuttleboxes (but without training trials) on Day 2, with retesting on Day 8 rather than Day 4 (Davis and Klinger, 1969).

The puromycin effect and state-dependent learning. Experiments were performed to see whether some of the effects of puromycin could be accounted

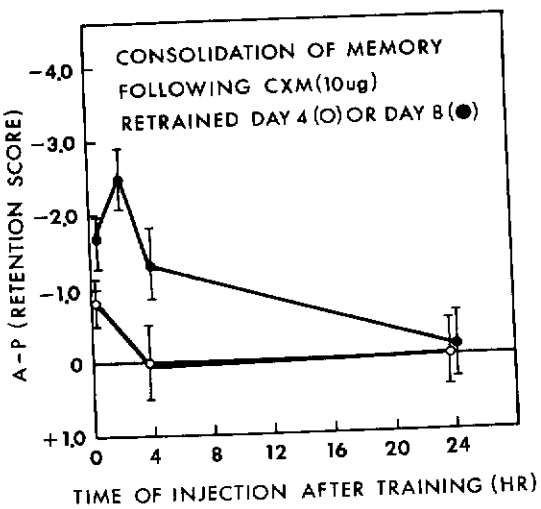

Fig. 5. Effect of varying the time of intracranial injection of 10 μg of cycloheximide on Day 1 on memory as tested on Day 4 or on Day 8. Retention score is obtained as in Table 1.

for by " state-dependent " learning (Overton, 1968). For these experiments, the antibiotic was given just before a training session. It can be seen from Table 3 that puromycin given both before training and before retraining had no significant effect on the amnesia and that puromycin itself given only before retraining, had no significant amnestic effect. The latter experiment suggests that inhibition of protein synthesis by 80 % does not affect the retrieval process.

Effect of anesthesia. As discussed below, the effects of blocking agents might be attributed to their non-specific noxious effects by an interference mechanism. To test this possibility, Finquel (MS-222) was administered following training. If the antibiotic exerts its effect in a heavily sedated animal, it is not likely that any noxious effects of the antibiotic will act as an unconditioned stimulus. It can be seen from Table 4 that the anesthetic itself had no effect on retention or on the puromycin-induced amnesia.

TABLE 3

Task III : Dual injection

Puro (130 µg) or saline in 10 µl was given IC 1 h before training.

Treatment		Rétention, day 4	N
Day 1	Day 4		
Puro	-	− 2.96(*)	82
-	Puro	− .81†	28
Puro	Puro	− 3.02(*)	20
Puro	Saline	− 2.50(*)	21

* Significant at $p < .01$.
† Significant at $p < .05$.

TABLE 4

Task III : Effect of Finquel

Fish were placed in tanks with 50 mg Finquel (MS-222)/L for 4 H. Puromycin dihydrochloride (130 µg) was injected IC in 10 µl.

Treatment, day 1	Rétention, day 4	N
Finquel, 0 delay	+ .04	54
Finquel + Puro, 0 delay	− 2.71(*)	52
Finquel, 0 delay Puro, 4 HH delay	− 1.43(*)	46

* Significant at $p < .01$.

4. Possible mechanisms

An hypothesis consistent with the present results is that normal ongoing RNA and protein synthesis are required for the consolidation of memory. The questions then arise 1) what is the evidence for the existence of the consolidation process itself and 2) are the agents reported on here exerting their amnestic effects via their block of macromolecular synthesis, or by some other meams ?

In regard to the existence of a consolidation phenomenon, it should first be noted that this is still an area of scientific controversy. Agents administered at various times after training and causing a decrement in subsequent performance could be doing so not by preventing the formation of memory, but rather by exerting some sort of interference — behaviorally, by acting as an US to produce conditioned fear or conditioned inhibition; electrically by generating neuronal noise, or by some other means. Consolidation and interference mechanisms may give very different interpretations to a given experiment. For example it has been postulated that electroconvulsive shock does not interfere with memory at all in some circumstances but simply blocks temporarily the performance of a newly learned task. In other instances, it would seem very difficult to distinguish experimentally between interference and consolidation hypotheses. For example, an agent that inhibits protein synthesis may block memory by preventing the formation of a substance needed for the ultimate expression of memory. It might alternatively cause the formation of faulty proteins or reduce the formation of a particular protein to the extent that other proteins produced before or after the period of inhibition interfere with its expression.

The present experiments on the effect of antibiotics on fish behavior tend to support in general the concept of consolidation. Unlike ECS and the convulsant drugs, antibiotics can exert their chemical effects without gross behavioral effects. We can therefore administer the agents pre-session. Such experiments, not previously possible, show that amnesia can be produced as a result of pre-session treatment. In order to explain such an effect by some mechanism other than by a blocking consolidation, it becomes necessary to propose beckward conditioning in which the agent acts as an US or proactive effects of the agent on learning. Experiments in which puromycin was used together with Finquel appear to support the idea that the antibiotic is not exerting its effect by acting as a stimulant and also as discussed below, is not acting as a convulsive agent.

Whether or not the antibiotic agents exert their effect on memory by blocking macromolecular synthesis or by some other mechanism is a question which must be enswered in order to interpret the biological significance of behavioral experiments in which they have been used. While it is possible that

macromolecular synthesis somehow mediates a part of the consolidation phenomenon, it might be via some global aspect of brain metabolism such as respiration (Jones and Banks, 1969). It is also possible that consolidation requires one of the known neurotransmitters, whose concentration is regulated via protein synthesis (Weiner and Rabadjija, 1968). Puromycin has been reported to potentiate the convulsant action of metrazole in mice and we have found this to be true in fish as well (Agranoff, 1970b). The possibility that the convulsant property of puromycin contributes to the amnestic effect is diminished by our finding that puromycin-aminonucleoside has a similar potentiating effect on convulsions, but not on memory or on protein synthesis.

Since CXM, AXM and puromycin have all been demonstrated to produce amnesia in the goldfish, and since each of these agents also blocks protein synthesis in the goldfish brain, parsimony at present dictates that the block in protein synthesis produced is causally related to the memory loss. In comparing the amnestic effects of puromycin and CXM in the present studies, we see that the agent's effect on protein synthesis are over by 24 and 16 hours respectively. Nevertheless amnesia may not develop for some days thereafter. In fact, amnesia due to CXM, a shorter acting agent, takes longer to appear than does that with puromycin. Verification of a correlation of the inhibition of protein synthesis with the susceptibility to amnesia could be established by injection at various times pre-session. For example we expect CXM given 16 hours pretrial to have no effect on memory. Such studies are presently under way with the use of Task III.

The interrelationships of the time of injection of an antibiotic, its known duration of chemical effect and the time of retesting the experimental animal were examined in the hope of giving some insight to the mechanism of the memory-blocking process. It is noted that the effects on protein synthesis of CXM and puromycin are over in less than a day, that the disruptible period is over within a few hours post-session and that the amnesia may take several days to develop. When CXM is given 4 hours posttrial, little amnesia is found on Day 4 while a significant deficit is detected on Day 8. The diagrammatic representation seen in Fig. 6 is consistent with our findings. We suggest that there is a time (the consolidation period) following training in which there is within the nervous system a strengthening of newly acquired information which proceeds exponentially. The onset of this period for avoidance learning may be triggered by a lowering of arousal accompanying termination of a session and removal to the home tank. On termination of the consolidation period, the strengthening process proceeds linearly until it reaches some final asymptotic level. Examples of how various agents might exhibit their effects are also shown in the diagram. While the diagram serves as a framework that is consistent with our experimental results, it is perhaps also useful to review what it does not tell us. It does not answer the question of whether memory requires formation of a

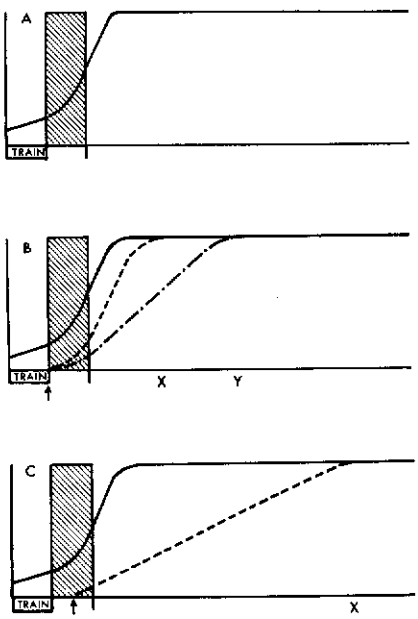

Fig. 6. Diagrammatic representation of effects of disruptive agents on associate strengh (ordinate) or recently acquired behavior. During the postsession period (shaded area), an amplification process exponentially increases its physiological expression, presumably synaptic, and establishes the rate at which strengthening continues until an asymptotic level is reached. (A) Unblocked learning and consolidation. (B) When disruption follows training, a weakening or interfering subtractive process relevant to the training is generated and also strengthens until it too reaches its asymptotic level. At this time (X), the learned behavior can no longer be elicited. A weaker disruptive agent completes its effect on memory at a later time (Y). (C) When disruption begins after partial fixation, the interference process is subjected to amplification for a shorter period of time. It is therefore expected that an agent, administered some time after the onset of fixation, will ultimately produce a maximal effect on memory but will exhibit a prolonged " short-term memory decay ". Long-lasting partial deficits in performance could be produced by interaction of several such processes.

specific protein or simply the participation of protein synthesis in some aspect of the memory process. The fact that the agents block memory at all does support a role for growth process and by implication for a genetic basis for the " engram ", the organic basis of memory.

DNA contains the information for the generation of an entire individual including the specification of all the connections in the brain. Within these specifications must also be the capability for changes evoked in the learning experience. It is proposed that the blocking agents prevent this evocation as they block enzyme induction, cellular differentiation and other processes under nuclear control.

Ultimately, we would like to understand behavioral changes in the nervous system on a molecular basis. Since the blocking agents appear to act reversively, a first step might seem localization of effects in the fish brain. While such experiments have not yet been performed, it should be remembered that after half a century of searching, electrical and anatomical correlates of learning are still highly speculative. It is too early to say whether the blocking agents will be a more useful tool for localization. It is already apparent however, that they have given us a valuable tool for studying of the memory process — one that separates two distinct phases of memory formation.

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De la Physique théorique à la Biologie, C.N.R.S., 1971.

STOCKAGE PHYSIQUE DE L'INFORMATION

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1. L'information est habituellement stockée sous la forme d'arrangements fixes d'éléments dans l'espace, ou d'orientation d'éléments anisotropes. C'est alors une information dormante, qui exige pour être utilisée un apport d'énergie libre. Il est possible de conserver aussi, pendant des temps courts, l'information sous une forme dynamique, mais il s'agit alors en réalité d'un message plus ou moins retardé dans sa délivrance, ou circulant en circuit fermé en attendant d'être utilisé. Dans le premier cas, le support est généralement solide, ou au moins un corps conservant certaines relations topologiques. Dans le second cas il peut s'agir de fluides ou de champs.

2. L'inscription de l'information dans la mémoire statique ou dans le message se fait par éléments binaires 0 et 1 successifs ou simultanés, dans un dispositif spatiotemporel préexistant, soit en fait, soit virtuellement. Ce dispositif spatiotemporel de la mémoire correspond élément par élément au dispositif inscripteur et au dispositif lecteur.

3. Les mémoires statiques sont, dans les solides, représentées par des éléments présents ou absents (carte et bandes perforées, émulsions photographiques) par des éléments orientés (bandes et cylindres magnétiques) par des passages ouverts ou fermés (valves électriques ou mécaniques). L'ensemble de ces éléments orientables, éliminables, transformables, préexiste à l'inscription et correspond aux dispositions également préexistantes du système inscripteur.

4. L'inscription se fait en général en série linéaire dans le temps, élément par élément. La structure spatiale et même spatio-temporelle du scripteur et de ses commandes doit donc correspondre à la structure de la mémoire. Dans le cas où l'inscription se fait par groupes simultanés d'éléments, comme dans le cas de la photographie ,la disposition des éléments récepteurs de la mémoire correspond d'avance à la disposition du scripteur : plaque à grains d'émulsion, réseau de récepteurs photo-électriques, faisceau de fibres optiques. Chacun des éléments inscrits correspond à un des éléments scripteurs.

5. L'inscription terminée, l'information a disparu du système inscripteur et ne subsiste que dans la mémoire, sous forme dormante. Pour la réutiliser.

par exemple pour un message, il faut la lire et donc la trouver, ce qui peut se faire de deux manières :

1°) par adresses. Dans ce cas les groupes d'éléments qui contiennent l'information recherchée sont situés en des lieux définis par un système de coordonnées qui permet de les retrouver lorsque ces coordonnées (adresse) sont connues. C'est le cas des cylindres et disques magnétiques.

2°) par étiquettes. Dans ce cas les groupes d'éléments porteurs de l'information comportent une partie qui les désigne et permet de les découvrir lors d'une exploration systématique. C'est le cas des titres d'articles, des noms d'auteurs, des résumés analytiques, etc...

6. La lecture se fait ensuite élément par élément, ou bien par groupes d'éléments inclus dans une structure qui a son correspondant dans le système lecteur. La consultation de la mémoire peut ramener celle-ci à zéro, ou bien la laisser subsister pour d'autres consultations suivant le principe physique de cette mémoire.

7. L'échelle dimensionnelle et aussi les paramètres temporels de ces mémoires physiques sont sujets à des changements fréquents dans les techniques, l'espace occupé par un élément binaire devenant de plus en plus petit. On peut actuellement inscrire quelques millions d'éléments sur un centimètre carré, et les consulter en moins d'un cent millionième de seconde chacun. Il doit subsister une séparation d'une dizaine de microns entre éléments. La question peut se poser de savoir si les moyens physiques permettront d'atteindre l'échelle moléculaire. Il n'y a rien qui s'oppose à ce que un jour les éléments d'information soient portés par un atome dans un réseau cristallin, par exemple, à condition que la séparation entre éléments soit suffisante pour permettre de les atteindre individuellement. Mais de toute manière cette inscription se fera élément par élément, et par un dispositif dont la structure correspond à celle du système de stockage, réseau cristallin ou longues macromolécules orientées.

8. Dans l'établissement d'hypothèses précises sur le mode de stockage de l'information dans la mémoire neurophysiologique il pourra utilement être fait appel à la comparaison avec les caractères du stockage physique de l'information. En particulier la distinction entre la structure des dispositifs d'inscription et de lecture, c'est-à-dire la machinerie (hardware) de la mémoire et le support qui pourrait être chimique (software). La machinerie, anatomique, serait basée essentiellement sur la mémoire génétique et en partie sur le conditionnement au cours de la croissance. Le support occasionnel (chimique) de l'information ouvrant et fermant les synapses par exemple, étant gouverné par les perceptions, l'idéation, et pouvant permettre le stockage à court ou à long terme.

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DISCUSSIONS

P. AUGER : Messieurs, il se trouve par les circonstances que je suis le dernier à parler dans cette partie du colloque qui correspond à des communications et des discussions puisque demain il s'agira de tables rondes. Par conséquent les dernières remarques que je fais ont un peu la qualité de remarques finales pour ce congrès.C'est dans ce sens que je voudrais parler.

L'homme dans sa civilisation se trouvait confronté avec un certain nombre de problèmes, il a voulu faire un certain nombre de choses; comme se mouvoir rapidement sur la surface du sol ou voler dans l'air ou bien trouver de la nourriture pour beaucoup de monde ou faire fonctionner les grandes villes et les habitations à grande densité et il a pour cela utilisé toutes sortes de ressources de son intelligence et de sa technique et de ses possibilités théoriques et mathématiques. Il a trouvé des solutions. D'un autre côté, les êtres vivants se sont trouvés en face de difficultés du même ordre et ils les ont résolus de leur propre manière. Il se trouve que quelque fois la solution qui a été trouvée, qui a été mise en pratique par l'homme avec sa technique, ses capacités et son intelligence, et les solutions qui ont été élaborées par l'évolution des animaux et des plantes sont convergentes et dans d'autres cas elles ne sont pas convergentes; elles sont divergentes. Je crois qu'il est interessant de voir clairement dans quel cas il y a convergence, dans quel cas il y a divergence, et pourquoi. Cela peut aider à la formation d'une compréhension en somme intégrée de notre monde vivant ou non-vivant.

Par exemple, en ce qui concerne le déplacement sur le sol nous avons inventé la roue que les animaux pour différentes raisons assez claires ne pouvaient pas employer et par conséquent les solutions sont divergentes. De même pour se déplacer en l'air il y a une partie convergente c'est l'utilisation de la sustentation par des ailes, mais il y a une partie divergente que l'utilisation d'une hélice ou du réacteur qui n'a vraiment aucun rapport avec la manière dont les oiseaux ou les autres animaux se déplacent dans l'air. Par contre le réacteur, la navigation par réaction dans l'air est très analogue à un dispositif employé par les céphalopodes pour leur navigation dans l'eau. Il y a là, par conséquent, une convergence. On peut dire aussi que lorsque nous construisons des grandes maisons ou des villes nous les remplissons de tuyauteries d'une part et d'autre part d'une quantité de fils pour la communication — la tuyauterie pour l'alimenter en eau par exemple ou pour éliminer les déchets et les fils pour communiquer — et bien c'est exactement convergent avec ce que l'on rencontre chez les animaux où il y a plein de tuyaux et plein de fils,

pour des raisons tout à fait analogues. Lorsque nous voulons construire des machines qui reproduisaient une certaine partie au moins de l'intelligence humaine — les calculatrices électroniques — nous avons employé aussi des systèmes de circuits avec des commutateurs, avec des connections diverses, et il se trouve que dans le système nerveux, le système nerveux central en particulier, il y a convergence. Les mécanismes, les arrangements sont très semblables. On peut penser que cette convergence va beaucoup plus loin et on peut se demander si par exemple la mémoire n'est pas stockée dans le système nerveux central de la même manière que la mémoire est stockée dans nos calculateurs. Elle est stockée comme vous savez de plusieurs manières différentes, soit avec des adresses, soit avec des étiquettes. C'est-à-dire que pour rechercher un souvenir on peut soit aller le chercher à un endroit déterminé parce qu'on connait l'adresse ou bien on peut le retrouver par balayage, en recherchant systématiquement quelques caractères qui font partie de son étiquette et qui permettent de mettre la main dessus. Très simplement, lorsque vous consultez un dictionnaire alphabétique, vous avez l'adresse d'un mot, vous le trouvez tout de suite et vous avez le renseignement que vous voulez. Si vous consultez une encyclopédie thématique, rationnelle à classification rationnelle, vous ne pouvez pas aller tout de suite là, où vous voulez trouvez le renseignement mais vous faites un petit balayage. Vous avez une étiquette, vous feuilletez, vous recherchez les différents chapitres où il y a des chances que soit le renseignement et vous finissez par le trouver. Je me demande s'il n'y a pas aussi dans le système nerveux central deux dispositifs de mémoire — les uns par localisation, les autres par balayage ou un ensembles des deux. Peut-être le fait qu'il y a deux mémoires — une mémoire à courte durée et une mémoire à longue durée — a-t-il quelque chose à voir avec ces deux systèmes de stockage de l'information.

Quand nous avons fait marcher les calculateurs, nous avons employé le système numérique binaire. Il se trouve que c'est aussi quelque chose comme cela qu'utilise le système nerveux central. Ce sont des dispositifs par tout ou rien du type binaire. Par contre l'information génétique est stockée par un dispositif quaternaire à quatre signes et tous ceux, physiciens ou mathématiciens qui ont lu des livres de génétique ont été frappés par cette extraordinaire convergence de retrouver dans les codages génétiques quelque chose que l'on connaissait très bien depuis longtemps qui était le codage que nous employons nous pour écrire nos mots, pour écrire des chiffres; il y a là une convergence extraordinaire qui est forcément la source de très grand progrès dans le rapprochement entre la physique, la chimie et la biologie. Mais, si l'on veut aller plus loin encore, on peut risquer de tomber sur une divergence au lieu d'une convergence. Et certains ont pensé que, étant donné la très grande complexité de nos souvenirs et la possibilité de stocker une information considérable par un codage linéaire, que c'était comme ça que l'information devait être stockée dans la mémoire et que c'était peut-être un codage linéaire sur des

molécules du genre RNA ou DNA que devait effectivement se trouver inscrite cette mémoire. Il ne semble pas que ça soit le cas — je crois qu'il n'y a pas la preuve que ça soit le cas — je pense qu'il y a des raisons profondes pour que ce ne soit pas le cas. De la même manière que l'hérédité des caractères acquis n'existe pas, c'est-à-dire que les conditions macroscopiques de vie d'un animal ne s'inscrivent pas dans la microscopique de son stock génétique, de même, je pense que les caractères macroscopiques des événements qui peuvent s'inscrire dans la mémoire ne s'inscrivent pas non plus directement dans un codage microscopique, à l'échelle atomique. Par contre c'est le microscopique qui commande la macroscopique. Le microscopique génétique commande la macroscopique du génome et aussi du comportement des animaux. Par conséquent le microscopique commande la macroscopique normalement et le macroscopique ne commande pas, au moins directement, le microscopique. Je crois qu'il y a des raisons profondes pour cela et que s'il y a une inscription microscopique, elle n'est probablement pas vraiment du microscopique — c'est-à-dire atomique — à l'intérieur d'un molecule, mais elle est simplement petite, à l'échelle moléculaire, mais non pas à l'échelle du codage intérieur des molecules. Ces convergences par conséquent et ces divergences doivent je crois attirer très fortement l'attention et des biologistes et des physiciens. Cela d'ailleurs doit donner le courage que vous avez eu tous ici — physiciens comme biologistes — d'écouter avec une certaine patience : du côté des physiciens d'écouter des biologistes parler des chats et des poissons rouges et du côté des biologistes d'entendre les mathématiciens leur parler longuement des machines de Turing dont ils ne voient pas peut-être immédiatement comment elles sont directement applicables à leur problème. Peut-être n'est-ce pas direct. Mais il y a certainement un rapprochement de plus en plus étroit entre les calculs et les théories des physiciens et aussi leur technologie et les expériences et les hypothèses faites par les biologistes. Pour qu'un congrès comme celui-ci soit bien réussi — et nous avons vraiment je crois la preuve que l'on peut réussir un colloque de ce genre — je crois qu'il faut faire un effort persistant de la part des physiciens et des mathématiciens d'une part, de la part des biologistes d'autres part, pour choisir parmi leurs problèmes ou parmi leurs solutions celles qui ont des chances d'avoir des convergences; celles qui ne s'éloignent pas vraiment trop évidemment des préoccupations de l'autre parti mais qui ont des chances d'être convergents. Par exemple, je ne pense pas qu'il soit très utile — pourtant c'est très amusant et très intéressant — de présenter ici des théories sur la fusion atomique, sur la cosmologie, sur l'évolution des étoiles. C'est passionnant. Mais je ne pense pas que cela ait des rapports suffisamment convergents avec la biologie. Dans le même sens pour les biologistes il y a des choses, des expériences de biochimie qui sont passionnantes et qui intéressent tout le monde, mais qui ne sont peut-être pas celles qui vont donner lieu à une convergence. Alors, si nous voulons avancer dans la voie qui a été ainsi très largement ouverte, je crois

qu'il faut que nous fassions un effort, chacun de notre côté pour choisir dans nos problèmes et dans nos voies d'accès, dans nos solutions, celles qui vraiment promettent quelque chose et pour lesquelles nous sentons que l'autre camp (c'est-à-dire les biologistes pour les physiciens et les physiciens pour les biologistes) soit qu'il va répondre à nos questions ou bien qu'il s'intéressera à ce que nous donnerons parce que ça répondra à quelques unes de leurs questions. Alors nous poserons les questions auxquelles nous pensons que l'on pourra probablement répondre, et nous répondrons à des questions qui nous ont été posées parce qu'il y a des chances que nous puissions donner une réponse. Quoiqu'un effort de ce genre doive être fait d'une façon très systématique pour que le congrès soit pas seulement une réunion d'amis qui aiment la science, et qui sont passionemment interessés par ce que chacun de nous dit, ce qui est toujours très très intéressant mais pour qu'il y ait effectivement un résultat, un outcome aussi concret que possible. Je crois que si cet effort est fait nous pouvons penser que d'autres congrès comme celui-ci, puisque peut-être nous continuerons à nous réunir, avanceront de plus en plus vers une constitution plus unifiée de notre science à la fois physique et biologique — c'est-à-dire en somme d'avancer notre compréhension du monde à tout les points de vue. Je vous remercie.

J.Z. YOUNG : Would anyone like to ask Dr. Auger a question ? Dr. Bronowski, you're the expert in these matters. Some comments ?

J. BRONOWSKI : I was wondering whether it is appropriate (and polite) to ask Auger whether the fact that physics developed before biology is not, in some rough sense, synonymous with his thesis. The distinction that he has presented can, in that rough sense, be expressed in the form of a paradox : namely, that the brain is the agent that does our thinking, but we can only think about the brain with physical concepts.

P. AUGER : Il se développe depuis quelque temps une science que l'on appelle... la bionique, c'est une sorte de science où les physiciens, où les technologistes, cherchent à prendre leurs enseignements dans la biologie, pour tâcher de faire aussi bien que font les animaux, c'est-à-dire qu'ils ont reconnu que la sélection naturelle avait pourvu les êtres vivants d'une série de solutions à des problèmes; quoique évidemment, comme le dit André Gide, dans la nature il n'y a pas de problèmes, il n'y a que des solutions. Mais il y a des solutions qui ont, si l'on peut dire, précédé les problèmes. Par contre les hommes se sont posés des problèmes et alors ils ont vu qu'il y avait des solutions dans la nature. S'ils avaient observé les chauves-souris depuis longtemps, ils auraient découvert le radar, ou le sonar; en fait c'est le contraire qui s'est produit. Il est certain qu'une étude du cerveau si elle est vraiment poussée à fond comme

vous êtes en train de le faire pourrait et doit donner aux physiciens et à ceux qui construisent des machines électroniques des idées par la bionique que cela constitue, des idées nouvelles et donc la solution d'un certain nombre de leurs problèmes.

Pourquoi commençons-nous seulement à comprendre un peu le cerveau, alors que nous avons fait beaucoup de physique depuis longtemps, je pense que c'est probablement trop difficile et que nous n'allons peut-être jamais comprendre ce cerveau qui est tellement loin de nos machines. C'est peut-être une application du théorème de Gödel, d'après lequel, en restant à l'intérieur d'un système logique on ne peut pas prouver que ce système est bon ou mauvais, qu'il est self consistent ou pas : il faut le regarder de l'extérieur. Or il nous est difficile de regarder notre propre cerveau de l'extérieur. Nous le regardons avec notre cerveau...

En ce qui concerne la mémoire on a d'abord certainement des analogies, des voies d'accès. Mais à un moment on touchera la solution, parce qu'elle est bien quelque part, la mémoire, physiquement, chimiquement, nous en sommes convaincus; elle n'est pas dans les étoiles; elle n'est pas en l'air, elle est dans notre cerveau, et c'est là, qu'il faut la saisir.

Je saisis cette occasion aussi pour dire que, quoique je ne sois pas biologiste, j'ai souvent regardé dans le microscope, il y a une chose qui, en tant que physicien, m'étonne énormément, c'est que les chromosomes se promènent et vont d'un endroit bien déterminé à un autre à l'intérieur d'une cellule. Il y a même une circulation permanente dans certaines cellules végétales, des chloroplastes par exemple circulent dans un certain sens. Qu'est-ce qui les fait bouger ?

Les biologistes n'ont jamais pu me dire quelle était la force qui fait déplacer effectivement des organelles à l'intérieur d'une cellule.

Il y a une force, parce que nous physiciens nous savons que si un objet se meut, c'est qu'il y a une force qui s'y applique. Quel genre de force ? Nous n'en savons rien. Ce problème est simple, et il me semble que les physiciens, s'ils s'y attachaient vraiment, pourraient peut-être donner la solution aux biologistes. Il n'y a pas de réponse à l'heure actuelle, du moins je ne crois pas qu'il y en ait. Là il y a peut-être des problèmes très simples où le physicien pourrait suggérer des solutions.

Thank you very much.