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RESEARCH OBJECTIVES

The aims of this group are fourfold.

1. We are attempting to relate the coding of various sensory modalities in firstand second-order neurons to the categories of perception as subjectively experienced and as inferred from behavior.

2. We are trying to extract the transfer functions of reflexive apparatus involved in voluntary movement at axial joints under conditions of voluntary control. This is done with the intent of using the methods diagnostically and as a guide to a rational therapeutic in neurology.

3. We are concerned with developing analog devices for several aspects of nervous physiology, from the physiochemical systems discovered in excitable membranes to the nets of irritable units required for some schemes in artificial intelligence.

4. We are essaying a synthetic approach to the problem of chemoreception.

A. EFFECT OF TOUCH STIMULI ON PAIN AND TEMPERATURE SENSATIONS

In the course of experiments on the cat, measurements were made of the area of skin subserved by single peripheral nerve fibers and by single cells in the spinal cord on which peripheral nerve fibers end. It was found that each cell or fiber could be stimulated by touching a particular skin area. The size of these areas was larger for the cells within the spinal cord than for the peripheral nerve fibers, as shown by the following data.

In contrast to these cells which responded to touch in a fairly limited area of skin, another type of cell was encountered which required very heavy pressure or a pinch to the skin before a response was observed. These cells would respond equally well from very large skin areas that frequently extend all the way from foot to pelvis. It has been traditional practice to assume separate transmission pathways for touch and $pain(1, 2)$, and yet it appeared from these experiments as though the cells that responded

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to painful stimuli had such a wide peripheral area of representation that they could not transmit the location of the peripheral stimulus. It was therefore suggested that the "pain and touch" systems might be collaborating so that the incidental stimulus of the touch system by a painful stimulus might provide the information on the location of the stimulus while the other cells signaled the extreme intensity of the stimulus. This would lead to the suggestion that, if both the high and low threshold systems combined to produce the sensation of pain, there should be a change in this sensation if the touch pathways were "jammed."

This "jamming" was carried out by placing on the skin a rapidly vibrating annulus. In the cat it was found that this vibrating stimulus drove the low-threshold fibers at a high frequency, so that additional touch stimuli to the skin failed to produce any further augmentation of the frequency of nerve impulses in these fibers. When the stimulus is applied to man, the area that is being vibrated is completely insensitive to light touch. Using this method of jamming the touch system, we proceeded to test in man its effect on his ability to detect and localize heat and painful stimuli. Since suggestion can play a considerable role in experiments of this kind, care was taken to select subjects who knew nothing of the hypotheses that were being tested or of the results obtained on other subjects.

1. Method: Series A

In this series the investigators were concerned with examining the effects of mechanical vibration of the skin on sensory thresholds. The paradigm for all three experiments in this series was as follows.

a. Control condition. The sensory threshold was determined in each case by obtaining a number of values for the threshold and averaging over this range. For each determination of the threshold the experimenter increased the intensity of the stimulus until the subject reported a sensation.

b. Experimental condition. The threshold for each subject was again determined; this time, the surface of the skin was being stimulated with a mechanical vibrator. The vibrator consisted of a rectangular brass plate whose center had been cut out. The power was supplied by a small electric motor that caused the plate to vibrate on an axis perpendicular to its flat surface at a frequency of 60 cps with a peak-to-peak amplitude of vibration of $3/16$ inch. In each trial for the experimental condition, the stimulus was always placed in the center of the hole in the plate so that it was always circumscribed by the vibrating surface of the vibrator.

i. Effect of vibration on the threshold for "warmth."

Ten naive subjects were employed in this study. The stimulus in this case consisted of the light from a standard projection lamp with a modified lens system that focused

a spot of light 0.5 by 0.5 inch on the upper surface of the subject's right hand. The intensity of the light stimulus could be varied. In order to cut down the amount of reflected light from the skin surface, the subject's hand was blackened with burnt cork. A single trial consisted of having the experimenter set the light intensity at a particular value and then expose the skin for a period of 4 sec. The subject was told to close his eyes or to look away from the stimulating light, so that the only indication he had that the light was switched on was when he felt the stimulus. An interval of 45 sec was allowed between consecutive trials in order to reduce interference from heating effects from trial to trial. The stimuli were always given in an ascending order of magnitude, and a particular series of trials was terminated when the subject reported that he could feel a sensation of warmth from the light. The series of trials was repeated a number of times under each condition, so that in each case a range of threshold readings was obtained. Since the investigators were interested mainly in determining whether or not a difference existed between control and experimental conditions, and not in the value of the absolute threshold for each subject, they supposed that any effect attributable to expectation would cancel itself out. The design for the experimental condition was identical except that the light stimulus was focused on an area of the skin that was circumscribed by the vibrating surface of the vibrator.

ii. Effect of vibration on the threshold for "painful heat." Twelve naive subjects were employed in this study. The procedure for this experiment was identical in design to that described for warmth, except that in this case the subject was asked to report when the stimulus first started to feel painful.

iii. Effect of vibration on the threshold to painful electrical stimuli. Eleven naive subjects were employed in this study. The subject was given an electric shock (60 cycle ac) through a silver electrode that was attached to the upper surface of the right forearm. The grounded electrode consisted of a sponge soaked in saturated sodium chloride solution, which the subject held in the hand of the arm that was receiving the shock. The circuit was interrupted by a knife switch that enabled the experimenter to administer brief shocks to the subject by closing the switch momentarily. The magnitude of the current given to the subject could be varied by the experimenter by means of a variac. A single trial consisted of having the experimenter set the intensity at a certain value and close the switch momentarily. The subject was told to report when he first felt a stab of pain that could be described as a pinprick. As in the preceding experiments, the stimuli were given in ascending order of intensity, and a range of values was obtained for the threshold under each condition. Again, as in the preceding experiments, the experimental series consisted in determining the threshold with the electrode circumscribed by the vibrating surface of the vibrator.

2. Results: Series A

The data for the experiments in series A are presented in terms of the mean voltage required to elicit the criterion response in the subject. The investigators realize that perhaps it would have been more meaningful in the first two experiments to have presented the data in terms of the amount of light energy falling upon a particular area of skin or of the rise of skin temperature. However, since the main interest was only in revealing a difference between control and experimental conditions, such procedures were deemed unnecessary. The thresholds in Tables XXII-1, 2, and 3 are given in terms of the voltage applied to the lamp. It was determined in separate experiments that there was a direct relationship between this voltage and the light energy falling on the skin in the range of intensities used.

a. Statistical procedure. The means and variances of the distributions of threshold values for the control and experimental conditions were computed for each individual subject, and the significance of the difference between the means of the two distributions was assessed for each subject by using Student's t-distribution. The proportion of subjects who showed a significant difference between control and experimental conditions was computed, and the x^2 distribution was used to determine whether such a proportion was significantly different from that which would be expected on the basis of chance alone.

b. Symbolism

 \bar{x}_c = mean of the distribution of thresholds in control condition \bar{x}_e = mean of the distribution of thresholds in experimental condition **nc =** number of threshold values recorded in control sample n_{α} = number of threshold values recorded in experimental sample $\sigma_{\rm c}^2$ = variance of distribution of threshold values in control condition σ_e^2 = variance of distribution of threshold values in experimental condition 2 = variance of the combined control and experimental distributions $t = Student's t-distribution computed for each subject$

3. Method: Series B

In this series the investigators were concerned with examining the effects of mechanical vibration of the skin on the subject's ability to localize a cutaneous sensory stimulus.

i. Effect of vibration on the ability to localize an electrical stimulus. Twelve naive subjects were employed in this study. Two standard galvanic skin response (GSR) electrodes were attached longitudinally, 1. 5 inches apart, on the upper surface of the subject's right forearm. A two-way knife switch allowed the experimenter to

Note: Vibration produces a significant increase of the threshold for detecting a rise of skin temperature $(p < 0.1)$.

Table XXII-2. Painful Heat

Note: Vibration produces a significant increase of the threshold for a painful rise of skin temperature (p < 0.05).

Table XXII-3. Pain Threshold for Electrical Stimuli.

Note: Vibration produces a significant increase of the threshold for a painful electrical stimulus ($p < 0.01$).

Table XXII-4. Localization of Electrical Stimuli,

Note: Vibration decreases the ability to localize a painful electrical stimulus (p $<0,02\}$

Table XXII-5. Localization of Pinprick.

Note: Vibration decreases the ability to localize a pinprick (p $< 0, 01$).

select the electrode through which the shock was to be administered to the subject. Two variable resistors were introduced into the circuit to allow for fine adjustments in matching the shocks given through the two electrodes. The intensity of the shock was adjusted for each subject to that value at which he could feel it as a pinprick with the vibrator placed against the skin surface. A single trial consisted of having the subject receive a shock through one of the two electrodes and be asked to identify the electrode through which he felt the shock. In the experimental series the vibrator was held against the skin surface while the shock was being administered. The order of stimulation through the two electrodes was determined from a table of random numbers.

ii. Effect of vibration on the ability to localize a pinprick. Twelve naive subjects were employed in this study. A four-celled grid $(2.5 \times 2.5 \text{ inches})$ was inked on the upper surface of the subject's left forearm. The cells were numbered and the order of stimulation determined from a table of random numbers. A single trial consisted of having the experimenter prick the subject with a pin in the center of one of the four cells. The subject was then required to localize the stimulated point by pointing with his finger to the cell in which he thought he had received the prick. Each subject was given twenty trials under both control and experimental conditions. The only difference in these conditions was that in the experimental condition the subject received the prick in an area of the skin that was being vibrated.

4. Results: Series B

The data for each of the experiments in this series are presented in terms of the number of errors in localization made by the subjects in twenty trials. See Tables XXII-4 and **5.**

a. Statistical procedure. The Wilcoxon method for paired replicates was used to determine the significance of the difference between the control and the experimental data.

5. Discussion

It is evident from the tabulated results that a vibratory stimulus applied to the skin raises the thresholds of pain and temperature and decreases ability to localize the stimulus. The first explanation of this phenomenon that might be offered is that the effect is the result of distraction. This has been the common explanation of the many effects of "counterirritation." Many of the oldest methods of treating pain have used counterirritation, which has been usually assumed to work by distraction or by the patient's inability to pay attention to more than one pain at a time. In these experiments, however, the effect is localized to the area that is being vibrated and, furthermore,

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other sensory systems, such as hearing, are quite unaffected. This removes distraction, in the ordinary sense, as an explanation. A second explanation might be that the vibration of the skin produces some local changes, such as vasodilatation, which might change the threshold of all elements in the region. This explanation is unlikely because the effect is immediately apparent after the beginning of the vibration, whereas local vascular or intracellular changes would be expected to develop slowly, as in the case of the Lewis triple response (3).

It is clear that the fertile mind of psychologists could invent an ark containing many highly complex "explanations" of this phenomenon based on assumed central mechanisms. However, the simplest explanation need only consider the known facts on the peripheral nervous system. The classical work of Head (4) and the recent work of Weddell and his colleagues (5) suggest that a pathological disturbance of the pattern of peripheral innervation produces a marked disturbance of the sensations evoked from these regions. It is no longer possible to hold the ideas of those who followed Müller that the sensation evoked from a region of skin depends only on the activity in single specialized fibers which innervates the point of skin tested. It now seems much more likely that the sensation evoked by skin stimulation results from the combined activity of all of the fibers in the skin area. This is supported by the findings reported here and by the peculiar changes in skin sensation seen in leprosy or in the partial denevation of a skin area which follows peripheral nerve lesions.

6. Summary

a. Light vibration of the skin in man, which "jams" touch sensations, reduces ability to detect temperature changes.

b. The threshold for pain is considerably increased by vibrating the skin, no matter how the pain is produced. The methods used have included heat, pinprick, and electrical stimulation.

c. The ability to localize a painful stimulus is decreased by skin vibration.

d. These results are discussed and the change in pattern of activity in peripheral nerve fibers is suggested as the simplest explanation for the observed phenomena. It is further suggested that it is no longer useful to consider separate peripheral projection pathways for touch, pain, and temperature because it is evident that changing the activity in one of these hypothetical pathways seriously interferes with the ability of the subject to analyze information transmitted over the other systems.

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B. OPTIC NERVE

We are now reasonably certain that most of the responses seen in the colliculus (Quarterly Progress Report, Jan. 15, 1958, p. 141) were not of receiving cells there but of afferent optic nerve fibers. Our present work on optic nerve has not only verified some of the coding as then reported but has provided us with several additional kinds of response. There seem to be at least five species of neurons:

1. Some have moderately low sensitivity but a wide receptive field. An object moving through the field generates a response whose frequency varies with the radial component of the movement away from the center of the field. The magnitude of this response also depends on a factor with a long time constant which signifies recent change of average light intensity over the whole retina. Darkening increases sensitivity.

a. Of these fibers some prefer responding to an object darker than the background.

b. Other fibers prefer an object lighter than the background. However, except for this qualitative preference, the response seems more or less independent of the relative intensities of the moving object and the background.

2. A second group of neurons is much like the first except for having narrow fields and high sensitivity.

3. A third group is much like the other two in quality of response except that the field has a large hole in the center. We have always found these fibers paired with their complementary fibers - that is, those responding to the hole. Two fibers would have fields with the same center, but when a target is moved the response of one would begin only when that of the other had left off, regardless of the direction in which the target is moving, and at whatever velocity.

4. The fourth group is much like the first except that the radial response is markedly weighted by a direction, almost always the forward or downward directions.

5. The fifth group is not particularly concerned with movement. It measures the degree of darkness of the field. In bright light it is silent, in absolute darkness it shows its maximum rate of firing.

Now, for all of these diverse types this general property holds: A sudden increase of light intensity over the whole field, if it produces a response at all, evokes a small response, delayed and meager with respect to a response to some change of the appropriate category in the first four listed above.

Anatomically, it seems that contiguity in the optic nerve has little to do with contiguity in the receptive fields. It is common experience to find three or four fibers within an area of 10 square micra that represent regions as far apart as one can get on the retina. This, of course, is consonant with the observation that myelinated and unmyelinated fibers in the optic nerve weave among themselves. They do shift relative positions frequently both in the retina and in the optic nerve itself. Also, if a partial section is made in the optic nerve, there is no gross scotoma that could be detected by the responses of the frog to a moving lure in the various parts of the optic field. In this way, as much as half of the optic nerve can be transected. Following such an operation, the responses of the animal may occur with a larger delay than usual, but no definite blind region can be detected. Similar results can be obtained by constricting the nerve with a ligature to half of its diameter, which presumably destroys at random a large proportion of the optic axons.

We have not yet been able to identify by signal the large and the small fibers. After a visual stimulus has been applied, the delay before any signal appears in the optic nerve is so long and variable that it is at least an order of magnitude greater than any effect from conduction time.

One somewhat shocking phenomenon that we have observed is that the response of a fiber to an appropriate stimulus occasionally seems to be dependent, in part, upon the history of the stimulus before it arrives at the receptive field. What it suggests is obvious.

A word about our preparation. The frog is not anesthetized during the study. A small flap of bone has been opened above the optic nerve, but there has been no other surgical damage, and the circulation in the pial sheath of the optic nerve has been completely preserved (for it is the only supply the nerve has). The best sign we have that our data may be relevant to normal operation is that during the experiment the frog will sometimes attempt to capture a target despite restraints.

Several instruments have been built for this work, but only one is of some slight interest, and that, possibly, only to a physiologist. It is a device that gives the logarithm of pulse interval between 1 msec and 1 sec. It is modular with the Tektronix 160 series and runs on the same power supply.

Our electrodes are simply $15 - \mu$ silver wire swaged down inside a thin glass sheath to a $3-\mu$ tip and sharpened.

Because of the extraordinary sensitivity to movement of any sort we finally had to devise an aluminum hemisphere (16 inches in diameter), silvered with matte finish inside and out and greyed by chloriding. This hemisphere is mounted concentric with the eye, and the targets are mounted on small magnets that are moved by a magnet which runs on the outside of the shell on a track that is always part of a great circle.

Simultaneously with the physiological work, we have been making a systematic study

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of the dendritic distribution of the ganglion cells of the frog retina. In general, the ganglion cells with the largest cell bodies (15 to 20 μ in diameter) do have the largest dendritic expansion, which sometimes covers a circular area that is 0.5 mm in diameter. However, small cells (8 to 10 μ in diameter) need not have a very restricted dendritic field and some of them may have a dendritic expansion of 100 to 200 μ . The following cell types can be singled out at the moment:

1. Large cells with a circular dendritic field and the cell body in the center.

2. Large cells with a circular dendritic field and the cell body eccentrically placed (closer to the optic papilla).

3. Large cells with an elongated dendritic field and the cell body in the end closer to the optic papilla. The long axis of the field can be oriented at any angle with respect to the issuing axon that goes directly to the papilla.

4. Small ganglion cells with a circular dendritic field.

5. Small ganglion cells with an elongated dendritic field. In general, smaller cells do have fewer and more slender dendrites.

The most notable thing with respect to the general arrangement of the retinal ganglion cells is the extraordinary degree of overlapping of their dendritic areas. There are approximately 460, 000 ganglion cells in the retina of the frog. Most of these have small cell bodies (7 to 10 μ in diameter), and most of them are distributed on a single layer, side by side. In this circumstance, several hundred may be present in the dendritic field of a single large one. It cannot be concluded, however, that each ganglion cell will be connected with all the receptors present in its dendritic field.

C. NERVE MODELS

We have built two kinds of nerve model during the last three months. The first is an analog of nerve membrane which behaves according to the Hodgkin-Huxley equations, with separate nonlinear conductances for $Na⁺$, and $K⁺$. It is a very good analog, in that each conductance is a two-ended device, as supposed for nerve. With it we can already confound some of our friends and colleagues. However, its description would take too much space in this report, and besides it is only of parochial interest now. We have a thesis student working on it and his report will be given at a later date.

The other model is being worked out for 0. G. Selfridge of Lincoln Laboratory, M.I.T. It is essentially a dc amplifier coupled to a blocking oscillator in such a way that the frequency of the oscillator is a linear function of the signal on the amplifier over a very wide range. Thus several of these devices can be combined arithmetically by time-sharing, which is useful in coupling them. The circuit diagram is shown in Fig. XXII-1. This neuron was mentioned, but not illustrated, in the Quarterly Progress Report of July 15, 1958, page 162, and several people seem to be interested in the

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Fig. XXII-1. Neurolemma.

actual schematic diagram, which has been modified since the previous report was written.

D. AUTONOMIC CONDITIONING

Somewhat apart from the usual form of our work, and in response to a problem set by O. G. Selfridge, we devised a method for rapid conditioning of an autonomic function. It seems to work crudely, and although the method is trivially obvious, it may be of interest.

We chose to condition sweating. The galvanic skin response (GSR) is a secular change in voltage or resistance across the skin of the palm in response to a large number of personal events from the simple shifting of attention to the experiencing of pain. The change comes on slowly over several seconds and decays even more slowly. Since we cannot give a quantitative statement of the resistance or voltage as a variable in proper terms (because of unmeasurable shunts and contact potentials), we shall simply speak of increase or decrease of response and of saturation.

Ordinarily, small changes in sweating, particularly in a dry atmosphere, cannot be detected by direct sensation. By having a small portable unit with a meter that is clasped onto his hand, a man rapidly assures himself (or learns) that this meter reflects something related to his inner feelings. Such an instrumental sense he takes as quite reliable, as the Russians have shown.

If the experimenter then attaches a somewhat irritating stimulator somewhere else on a man, say to produce a small local electric shock, the man sees a fairly large sweat response to the shock and is not surprised. Thereupon, the electric shock is coupled to the rising phase of the sweat response, which becomes regenerative in step fashion and rapidly goes to the limit. From now on, any stimulus (of any sort) that sets off a sweat response sets it off regeneratively, and thus the nexus is magnified. The regenerative and saturating response does not seem, in the two people on whom we have tried it thus far, to be set off by arbitrary shocks uncoupled to sweat response, no matter how the shocks are spaced. The, sensation is curious under these conditions. The man gets quite wet rapidly but without feeling very anxious.

Finally, under these conditions, we have found what appears to be an active turn-off of the GSR. That is to say, a response falls more rapidly if shocks are coupled to the falling phase of GSR. These findings are tentative thus far, but exceedingly curious.