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CHAPTER 5

The Case for a Brain Electrodiagnostic in "Functional" Disorders

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Let me first share with you a problem that has deeply concerned me. I think the problem pertinent to this group, and my response to it has been shaped in part by the transactions of the Manfred Sakel Institute. The problem arises from the attempts to perform brain research on man or to apply the results of animal research to man. In my laboratory we do primarily animal work, although our main interest is the human scene. The question is, of course, why not just barge in and do psychosurgical experiments on man? And the answer, equally obvious, is that ethical and moral considerations prevent it. I've puzzled for a number of years now as to just how to bring the moral issue into focus. As a former neurosurgeon, I feel that intervention into the functions of the human brain can indeed be therapeutic. Futher, I feel that sometimes we must work in partial ignorance simply to relieve suffering. But, the suggestion has been seriously proffered that psychosurgery ought to be considered to control violent behavior of unknown etiology; specifically, that amygdalectomy might be "offered" to prisoners as a way out of their incarceration. And other technical advances in biology have been put forward for the solution of human problems. Some of this technology is beautifully demonstrated by Dr. Delgado's experiments which we've been fortunate to have presented to us in such detail over the years of our meetings. Such experiments have led a number of people (e.g., Kenneth Clark (1971), a former president of the American Psychological Association, in his presidential address) to suggest that we begin to use these advances in psychobiological technology to control human behavior by chemical and electrical means.

I have been, up to now, somewhat unclear as to just how to proceed in this difficult field. Nonetheless, I was able to formulate some overall guidelines within which specific procedures could be worked out. I suggested that we legislate a modification of our Bill of Rights: suggesting that the right to territory augment the right to property; the pursuit of humanity replace the pursuit of happiness; and the right to integrity to supplement the mere right to life. (See Pribram, A Biological Bill of Rights, in press).

But, today, I want to talk about a more specific procedural ethic that can guide decision when specific psychosurgical and psychochemical interventions are imminent. I suggest that we limit direct therapeutic brain manipulation to those patients whose *brain* has been shown to be abnormal in function and that we resort to behavioral means to treat those people for whom we have been able to demonstrate only behavioral abnormalities. This ethic would be in keeping with current practice such as that of Dr. Bechtereva, Dr. Dongier, and the Bristol Group under Dr. Walter. These clinicians demonstrate specific brain conditions which are then specifically treated by brain manipulations. Such procedures fall readily within the ethical standards that I am proposing here. What I do suggest, however, is that we draw the line here: that whenever we *cannot* demonstrate something pathological going on in the brain, we desist from entry except for explicitly stated diagnostic reasons. It thus behooves us to provide more sensitive tools for demonstrating abnormalities in brain function.

There is, of course, an intermediate form of therapy available in the form of pills, pharmacological manipulation. This form of therapy does fall in between the extremes of psychosurgery and behavioral therapy because the patient himself has considerably easier control over the procedure than he would if he had to, say, devise electrical ways of stimulating his brain. But even the pharmacological path has its pitfalls. We become socially conscious of an ethical problem when therapy leads to addiction, i.e., when flexible control of the chemotherapeutic effect breaks down.

Given this procedural ethic, I turn to my own work. What I've been groping toward is to take what I have been doing in the laboratory and bring it to the human scene in an ethical way. As I hope to make clear, I believe I can do this by providing better *diagnostic tools* to show that, in fact, when certain behavior disorders become obvious, brain pathology *can* be demonstrated. I am going to take only one example of how to make an animal model of the human pathological condition with the aim of experimenting to accumulate knowledge which can then be reflected back to improving the treatment of the condition. The condition I will talk about today is agnosia, the inability to identify objects. This difficulty is of great basic, as well as therapeutic, interest since it leads to an exploration of the issues of epistomology, the problems of how it is that we know, of the brain mechanisms involved in "knowing".

My program started out with making brain lesions in monkeys, and we were able to show, using discrimination tests, that when lesioned in the appropriate sites

of the brain, monkeys do lose the ability to make discriminations very much the way people with similar brain lesions lose the ability to identify objects when you show them a particular object. Over the years, we have studied an area which we discovered some 20 years ago (Pribram, 1954) in the inferior part of the temporal lobe which, when lesioned, produces visual agnosia in monkeys. More recently we began to use electrical techniques to study the organization of the visual process to see how this temporal lobe area relates to visual processing. So these are the experiments I will present first, and then come back to the kind of diagnostic tools that might be developed from this research'

Figure 1 shows one procedure we have used (Pribram, 1969). There is a panel on which a projector flashes cues, either vertical stripes or a circle. The panel is split down the center into two halves. Each is movable so that a fully awake monkey can depress either half of the panel. In the initial procedure, the monkey pulls a lever which flashes one of the cues over the entire panel. The monkey was to push the left panel whenever he saw the stripes and the right panel whenever he saw a circle. The cues were flashed on the screen for 10 msec, a tenth of a millisecond, very brief flashes, which evoke transient potential changes in the brain, whose onset and amplitude is readily measurable. In addition, when the animal depresses one of the panels, a second brief pulse is generated. This pulse also serves as a time marker from which electrical brain activity can be measured. These two time markers are used to process the monkey's electrical brain response to the stimulus and to the response, respectively.

Figure 2 illustrates our first finding (Spinelli, 1967): we were immediately able to identify the difference between a potential evoked by the circle and one evoked by stripes. As shown in this diagram, the stripes evoked a rather long first leg of the W-shaped wave form, whereas the circle evoked a more symmetrical W-shaped potential. These records are made bipolarly with small electrodes with the tips about 1 mm apart, one tip at the base of the cortex and one on top.

Other events become encoded in the visual cortex as the animal learns to respond correctly in the task (Pribram et al., 1967). These difference in the pattern of electrical brain activity are response related. For instance, we can distinguish the brain wave evoked when the animal is being reinforced for a particular choice of cue and also whether he intends to push one or the other of the two panels. Both of these events become encoded only after the monkey reaches criterian performance. Again, the differences in evoked brain electrical activity are distributed over the extent of visual cortex rather randomly, and are not present at every electrode. Nor does one electrode encode all of the differences: one electrode may encode the stimulus evoked, others the response evoked wave forms.

Figure 3 shows a modification of the procedure used to probe the function of the temporal lobes of the brain (Rothblat and Pribram, 1972). Now, the monkey is faced with a red circle and green stripes presented simultaneously, each cue falling on one half of the panel. We thus can train an animal to respond to the differences in pattern, vertical stripes or circle, or we can differentially reinforce color, so that

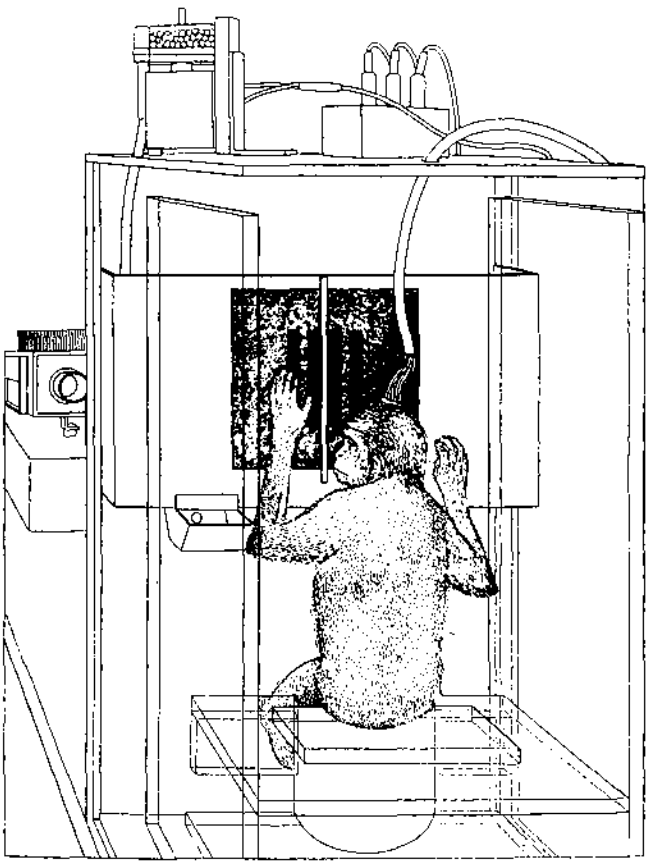

Fig. 1. Results of an experiment demonstrating the functions of the striate cortex. A monkey initiates a flashed stimulus display and responds by pressing either the right or left half of the display panel to receive a reward while electrical brain recordings are made on-line with a small general purpose computer (PDP-8). On the translucent panel in front of him the monkey sees either a circle or a series of vertical stripes, which have been projected for 0.1 msec from the rear. He is rewarded with a peanut, which drops into the receptacle at his left elbow, if he presses the right half of the panel when he sees the circle or the left half when he sees the stripes . . Electrodes record the wave forms that appear in the monkey's visual cortex as he develops skill at this task. Early in the experiments, the stimulus-locked waveforms show whether the monkey sees the circle or stripes. Eventually they reveal in advance which half of the panel the monkey will press. Each trace sums 300 trials of 500 msec of electrical activity following the stimulus flash.

he will be responding either to red or to green. There are four possible combinations of cues: these are indicated in the figure. What we do with all of these records is to sum (or average) by computer, *all* of the records that are made when the monkey reaches criterion on a particular problem, which means that he is performing at 90 or better for three consecutive days (300 trials). When we do this, we find

that in the records made from the temporal lobe we can see differences related only to the response. When we take as our marker the stimulus presentation, we find essentially flat lines. But if we take as our marker the response which occurs right in the center of the figure and average forward for 250 msec and backward for 250 msec we can see definite potential changes evoked in the record. We see that when the monkey is making the color discrimination (either the red or the green being rewarded) the first and fourth record are alike. When we change to a pattern discrimination (either circle or stripes being rewarded) then the first and third records look alike. These differences are not related to position of the cue or of the response *per se*: if we average all of the records that have to do with position, we again get a flat line.

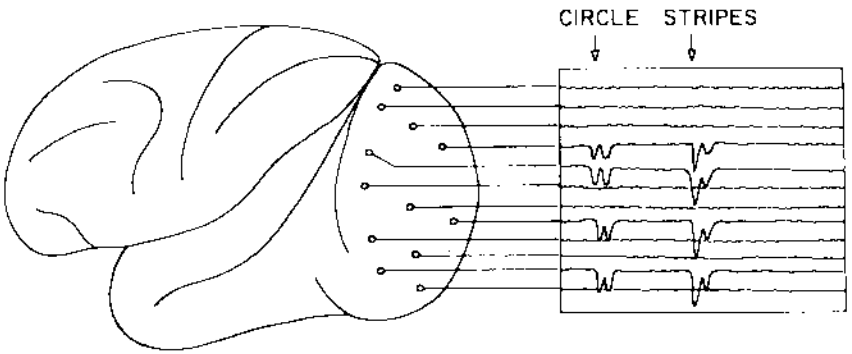

Fig. 2. Diagramatic representation of the finding that the differences in the potentials evoked by circles and stripes are distributed over the striate cortex. Note that not every lead shows the differences.

Figure 4 shows the same result in another monkey (Pribram and Johnston, in preparation). Look only at the bottom records to begin with. On the left, he is doing a color discrimination so the first and fourth records are similar; when he switches to a pattern discrimination, shown on the right, the first and third records are similar. But this figure shows more: we now examine what happens when the animal shifts from a color discrimination to a pattern discrimination. Note that in the second record from the left, while the monkey is performing at chance level, there is no reliable difference between any of the recordings. When, in the second record from the right, the animal is in a late transition period performing at about 70-75 correct on the pattern discrimination, the first and third records begin to look alike, as do the second and fourth. This difference later becomes enhanced when the monkey performs at criterion.

Now examine the top set of records. These show that the same sort of differences occur in the visual cortex. But note that in the late transition period, one sees absolutely nothing of the differences that are already evident in the recording made from temporal cortex. Only when criterion is achieved does one see anything

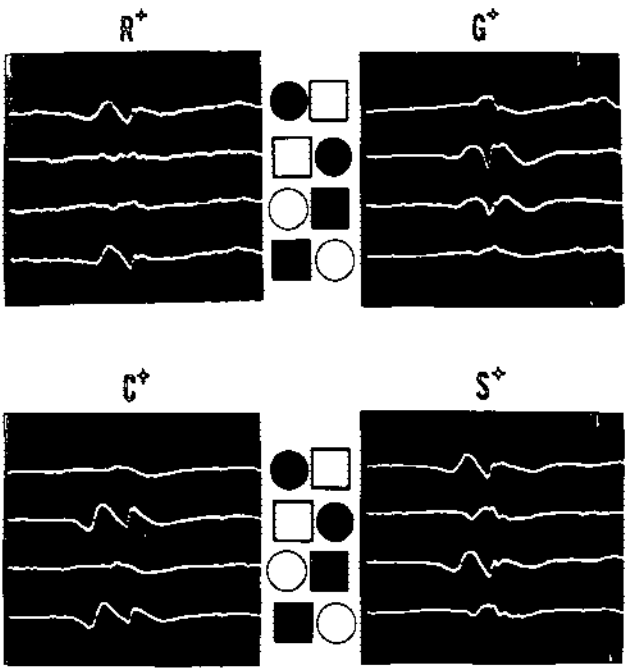

Fig. 3. Results of an experiment demonstrating the functions of the inferotemporal cortex by behavioral-electrophysiological techniques. Comparison of *response-locked* activity evoked in temporal cortex (IT) when monkeys are performing (90 correct) color (top panels) and pattern (bottom panels) discrimination. Each tracing sums, over 300 consecutive trials, the activity recorded when the stimulus configuration presented to the monkey appeared as in the diagrams between the panels. Each tracing includes 500 msec of electrical activity: 250 prior to and 250 just after each response. Note that during the color discriminations the 1st and 4th (and the 2nd and 3rd) traces are similar, while during the pattern discriminations the 1st and 3rd (and 2nd and 4th) traces are alike. These similarities reflect the position of the color cues in the color task and the position of the patterns in the pattern task. Position *per se*, however, is not encoded in these traces. Note that this difference occurs despite the fact that the retinal image formed by the flashed stimulus is identical in the pattern and color problems.

happening in the visual cortex and the difference is enhanced by overtraining the animals for two or three weeks. The suggestion is that by the time the difference becomes manifest in the visual cortex, the animal is doing the discriminations rather automatically and rapidly without even "thinking" about it.

Figure 5 shows the problem that must be faced in relating the functions of temporal cortex to those of the visual mechanism. As the text books would have it, the temporal cortex receives its visual input via the geniculo-striate system: retina to lateral geniculate nucleus, lateral geniculate nucleus to occipital cortex, occipital cortex by stages to the peristriate cortex from whence the temporal cortex receives its inout. There are no direct connections from occipital cortex to the temporal cortex so there must be an intermediate synapse in the peristriate belt —

in fact, there are probably at least two synapses as far as current neuroanatomical knowledge goes. Now in a series of experiments, some done by Chow (1952), some done by myself (Pribram et al., 1969), some done by my students (Mishkin, 1966), and their students (Gross et al., 1971) as much as possible of this prestriate tissue has been removed to see what the effects would be on visual discrimination by monkeys. The result is exemplified (Pribram et al., 1969) by one particular monkey in whom the lesion proved practically complete; that is, I was able to remove all of the peristriate cortex. This animal was totally blind immediately after surgery, probably because of the trauma to the optic radiations which lie right

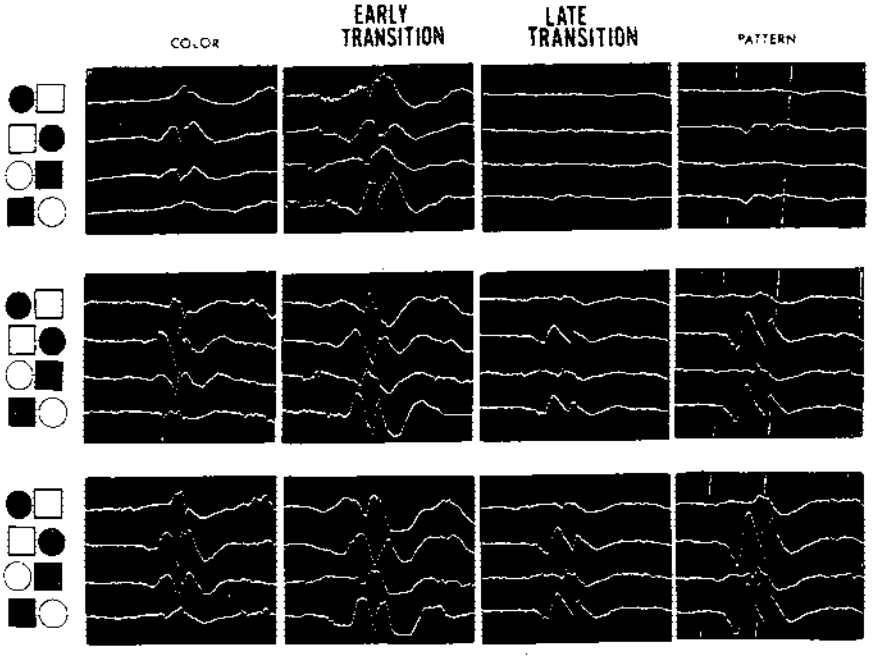

Fig. 4. Experiment shows the development of the response-locked activity. In this experiment the flashed stimulus again consisted of colored (red and green) stripes and circles, exactly as in Fig. 3. Reinforcing contingencies determined whether the monkeys were to attend and respond to the color (red vs. green) or pattern (circle vs. stripes) dimension of the stimulus. As in the earlier experiment, shown in Fig. 1, stimulus, response, and reinforcement variables were found to be encoded in the primary visual cortex. In addition, this experiment showed that the association between stimulus dimension (pattern or color) and response shown in Fig. 3 occurs first in the inferotemporal cortex. This is shown in the lower panels where the electrophysiological data averaged (summed) from the time of response (forward for 250 msec and backward 250 msec from center of record) again show clear differences in waveform depending on whether pattern or color is being reinforced. Note that in these tracings the response-locked difference in recorded activity can already be seen in the temporal lobe recording when the monkey is performing at 75 correct but does not appear in the striate cortex recording until criterion performance is attained. Overtraining enhances this difference in the striate cortex recording.

under the peristriate belt. But gradually his vision came back and by training him to seize a peanut which was hung on the end of a string and dangled in front of him, he relearned how to use his vision and reach for objects in space. We then put him in the automated testing apparatus (Pribram, 1969), retrained him to pushing panels and then tested him on the discrimination (a numberal 8 versus a numeral 3 pseudo-randomly occuring over 16 possible positions). The first day of formal testing, some two months after surgery, he did 76. All of his errors were in the ventral field, in which he was blind. The second day he did 86 and the third day he came to criterion (90 in 100 consecutive trials). This example shows that we are not able to interfere with visual discrimination permanently by making lesions in the perstriate cortex, which raises the question of how then the temporal lobe is connected to the visual mechanism, if not via the peristriate synapses?

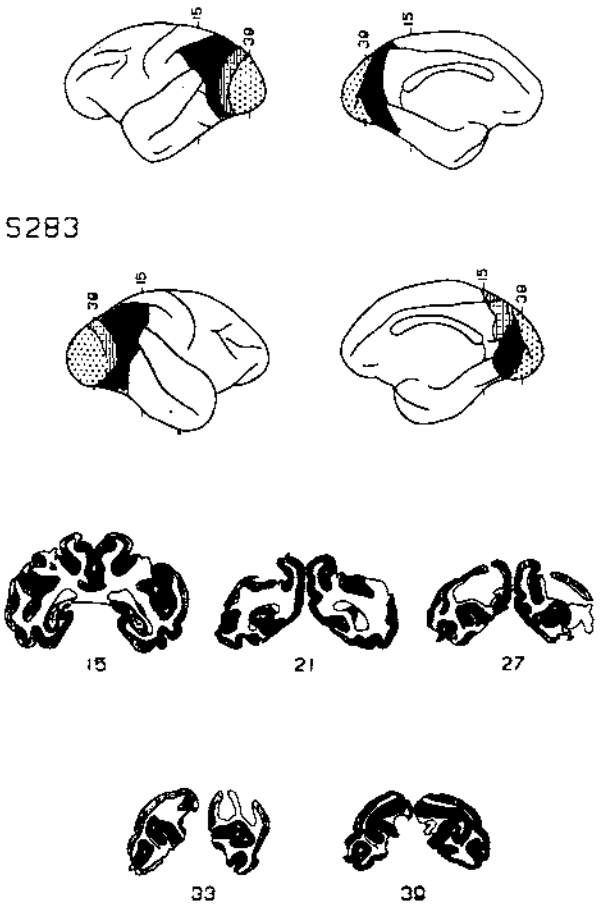

Fig. 5. Reconstruction of bilateral prestriate lesions after which monkey could still perform a visual discrimination (the numerals 3 vs. 8) at 90 criterion.

One possibility is, of course, that the visual input to the temporal cortex arrives through the pulvinar of the thalamus, which is the only known source of subcortical input to the temporal lobe cortex. However, this possibility has been eliminated by a former student and colleague (Mishkin and Rosvold, in preparation). In 35 animals, huge destructions of this portion of the thalamus (I have seen the lesions) produce *no* deficit in visual discrimination. Combined lesions of thalamus and peristriate cortex have never been done so totally, but there have been subtotal combined lesions of this sort and they also produce no deficit in visual discrimination (Chow, 1954).

In response to these data, I suggested some fifteen years ago (Pribram, 1958) that the temporal cortex of the brain alters the functions of the visual system by means of an efferent pathway to that system rather than by abstracting visual information from the visual mechanism (and I have been testing this suggestion since). In computer terminology, the idea is that the temporal lobe generates a program tape which operates somewhat as an active filter that makes us see according to the program that is activated. For instance, when, during a lecture, I look out at the audience, I can either look at faces or I can be more aware of the colors that grace the dresses and suits. I can make either a pattern dicrimination or a color discrimination according to the set that I have taken. From the evidence I have presented here, visual set is produced by the function of the cortex of the temporal lobe.

Figure 6 shows one example (Spinelli and Pribram, 1967) of many experimental demonstrations of the existence of efferent connections from the temporal lobe that influence the visual mechanism. Such influences extend all the way to the retina: we can change optic nerve potentials generated by flashes. We can also change the receptive field characteristics as shown in this figure of such a field change at the lateral geniculate nucleus.

We do not yet know fully the pathways by which this influence from the temporal cortex on the visual system is exerted. But a beginning has been made. Figure 7 shows that when we stimulate the temporal lobe electrically (Reitz and Pribram, 1969) we find responses in the superior colliculus and in the putamen. Lesions in both of these regions have been shown to interfere with visual discrimination. Interestingly, these structures have heretofore been considered to be parts of the motor system, so that an effect on sensory discrimination would not have been attributed to their function.

But our ideas of how the motor system functions have been undergoing changes as well (Pribram, 1971, ch. 12 and 13). The motor system apparently does not work by contracting one or another muscle. What seems to be happening is that the system largely operates by altering the set points on the muscle spindles. Muscle spindles are receptors, so the motor systems are really influencing receptor mechanisms in their "motor" function. The question then arises "why cannot these same motor systems also influence set points in the special sensory systems?"

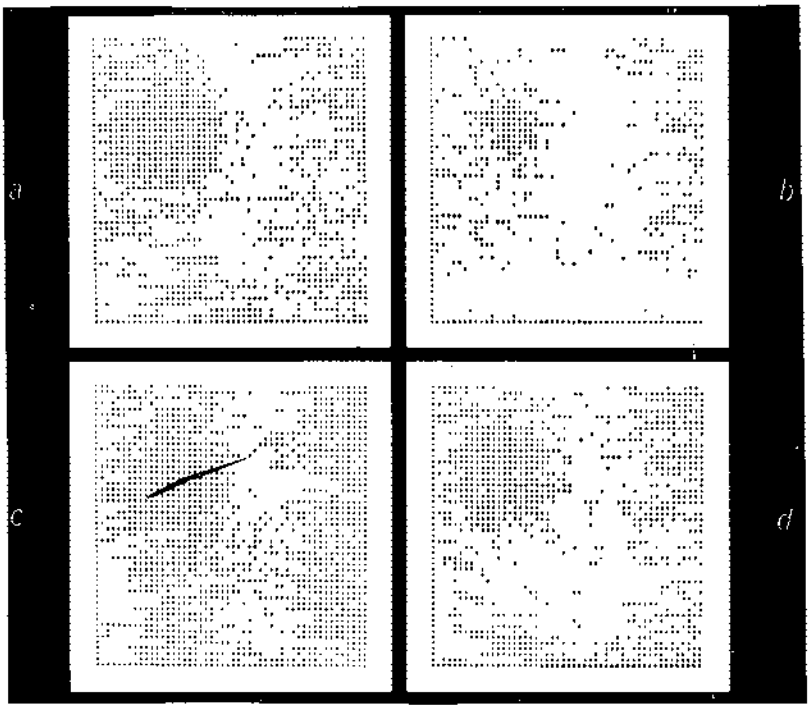

Fig. 6. Visual-receptive field maps show how information flowing through the primary visual pathway is altered by stimulation elsewhere in the brain. Map a is the normal response of a cell in the geniculate nucleus when a light source is moved through a raster-like pattern. Map b shows how the field is contracted by stimulation of the inferior temporal cortex. Map c shows the expansion produced by stimulation of the frontal cortex. Map d is a final control taken 55 min after recording a.

The beauty of this result is that such a "motor" mechanism can operate on the distributed encoding that I demonstrated in Figure 1. I am suggesting that a program generated in the temporal cortex simultaneously addresses in parallel all of the "distributed" locations, in striate cortex that have encoded in them the relevant "characteristics of input" (Pribram, 1973).

That is a brief of the animal work as far as it has gone. There's much more to do and one of the directions I want to develop is the use of multiple microelectrodes to perform the kind of analysis that Dr. Bechtereva has been doing on humans, and that Verzeano has been doing in animals for the last 15 or 20 years (Verzeano and Laufer, 1970).

But for our present concern at this conference a more pertinent aspect of this work is to take it to the human level. Over the past year one of our students (Roberta Day) has been working with children, trying simply to replicate the finding in monkeys, not by putting electrodes in the brain, of course, but by using scalp electrodes. We use three electrode locations; one over the temporal lobe, one

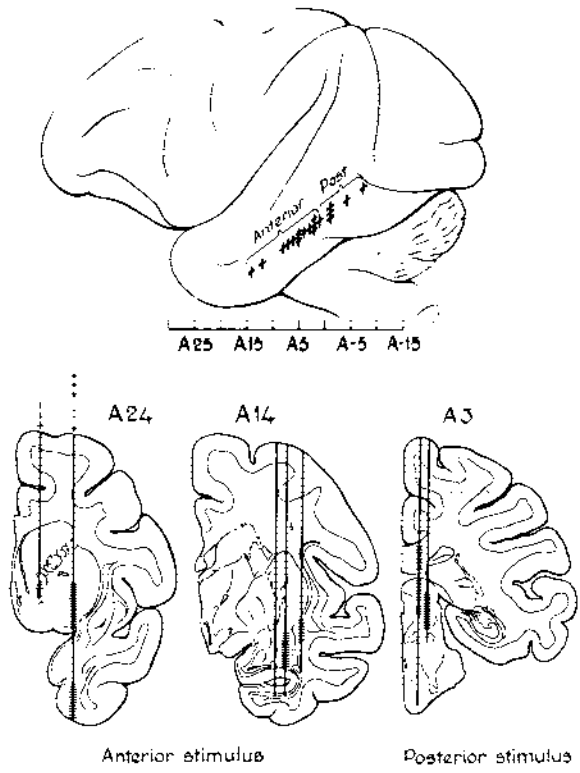

Fig. 7. (a) Side view of the brain showing stimulation sites in experiment that traced the subcortical connections of the inferotemporal cortex. (b) Selected cross section showing sites ( ) where response was evoked by inferotemporal cortex stimulation. Note especially the responses in putamen and superior colliculus.

over the motor cortex, and one over the occipital lobe. Initially, we found that we couldn't tell much from these scalp recordings. But in a previous study this young lady had been using more subtle analyses for distinguishing changes in rhythmic electrical activity recorded from the hippocampus. She reasoned that if we perform such analyses on hippocampal activity, the same techniques might work on the analyses of the evoked activity recorded from human children. And so she first applied some filters and then performed a fast Fourier transform to obtain power spectra. She then analyzed the variables that contributed to a particular spectral shape; such variables as stimulus, recording location, and the response performed. When she plotted this analysis, she found that she could obtain a profile of the task performed from the electrical scalp recordings. So far she has been able to test only three children. What we need, of course, is to shorten the time of analysis. It now takes six months to analyze, even in this simple form, the records from one child performing the color and pattern discriminations. Once this speed-up is accomp-

lished we can have the children perform other tasks; e.g., an expectancy task, pressing a key down at a ready signal, and then letting up at the onset of a second signal, as it is performed in the Bristol and Montreal laboratories. A small selection of maybe half a dozen tasks already shown to be of diagnostic value, among them the expectancy and discrimination tasks, matching from sample, both spatial and go, no-go alternation tasks have already proved themselves in animal experiments. Now we are ready to use them to show up differences in the way individual human brains solve problems. First we would have to define the normal population of problem solving patterns, then, when our subjects fall outside of that population, we can reliably state that we have demonstrated brain pathology to exist. We thus increase our diagnostic power to relate brain abnormality to behavioral abnormality and so come to meet the criterion I set in the initial part of this article for an ethical therapeutic intervention in brain function. The techniques demonstrated here by Delgado, Grey Walter, and Bechtereva, could then be exploited to their full power with a clear conscience.

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