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Explorations in Experimental Neuropsychology

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On April 19th, 1983, when boarding a plane travelling to Newark my eye was caught by the back page of the front section of the New York Times left on my seat: A full page advertisement had been placed by Omni Magazine. In part, the ad read as follows:

In a recent issue, OMNI Magazine discussed the problems of perception and memory with Dr. Karl Pribram, the neuropsychologist who developed the first holographic model of the brain. According to Pribram, the brain encodes information on a three-dimensional energy field that enfolds time and space, yet allows us to recall or reconstruct specific images from the countless millions stored in a space slightly smaller than a melon... The Pribram interview is a rich, provocative example of the journalism that has made OMNI the world's leading science magazine.

Provocative, it certainly is. I puzzled as to what it might have been that I had said that would make someone, anyone, even the current "media hype," attribute to me such a view of "the" brain. Ah, yes. The fields are the fluctuating polarizations that characterize the receptive fields of neurons, and quantum field theory provides one reasonable model of their functions. And true, a three-dimensional orthogonal (spectral) transform will enfold a four-dimensional space/time image. Storage capacity in the spectral domain is indeed prodigious. This domain is, of course, only one of several "languages of the brain," but, on the whole, someone had read me better than I had initially read them.

The *Omni* interview and other similar experiences have made me wonder how it is that my theoretical work has engaged so much popular interest, whereas discoveries made in the laboratory have often become part of the received wisdom in the neurosciences without popular fanfare or even acknowledgment within psychology or neurophysiology. The laboratory research takes up by far the greatest amount of my time and effort, and I therefore welcome this opportunity to show how this research led to theory.

The following report will outline the several phases of the research, the discoveries, and finally the theoretical work that has stemmed from these discoveries. But before this report must come the sources that motivated the initiation of the research program and a sketch of some of the earlier investigators on whose shoulders I have stood to look beyond the heritage they left.

Roots

The story begins in Chicago, which, at the time of my medical training in neurological surgery, was a major center for brain research. At the University of Chicago, where I received my undergraduate and medical degrees, were Heinrich Klüver and Paul Bucy, pioneers in investigations of the functions of the temporal lobe of the brain. I became Bucy's first resident when he moved to the nearby Chicago Memorial Hospital and wrote up our first one hundred brain operations in order to have the residency accredited. Bucy was editing a volume on the precentral motor cortex at the time, and I became privy to the controversies and details of explorations of this research, as well as learning the techniques of surgery from a master.

Stephen Polyak was working on the anatomy of the retina and visual system. I was intrigued by the work of Roaf on color afterimages and saw in Polyak's detailing of three sorts of retinal bipolar cells a mechanism for analyzing and further separating the Helmholtzian receptor process while accounting for the effects of color afterimages. I wrote up these suggestions with Polyak's help and submitted the result as a medical student thesis.

Paul Weiss was training Roger Sperry to transplant limbs of *Amblystoma*. We became well acquainted when Weiss appeared on my medical service during my internship. The friendship has lasted a lifetime and centered on the problem of "resonance": How could it be that a limb induces in the developing nervous system a code that allows the system to "recognize" the limb, irrespective of its innervation. Sperry's answer to this question invoked specific chemical codes; mine, suggested in *Languages of the Brain*, devolves on the finding of J. Z. Young of the induction of specific nerve fiber size spectra by each muscle. Most likely the specific chemistry induces specific fiber size spectra.

A. Earl Walker became chief neurological surgery when Paul Bucy left, and from Walker I learned the details of thalamic anatomy before joining Bucy. Over the years, together with Kao Liang Chow and with the help of Jerzy Rose at Johns Hopkins University, I extended Walker's anatomical research to complete a classification of thalamocortical connectivity. Also during this period, Ward Halstead introduced me to the procedures used to study the effects of brain injury in humans.

The University of Chicago was not the only center for neuroscience research in Chicago at the time. Magoun and Lindsley and their collaborators were beginning their research on the mesencephalic reticular formation at Northwestern University. I was to participate in this work in collaboration with Percival Bailey, in that I had received a fellowship to do so, but Bailey changed his plans and went overseas for that year. The proposed collaboration never took place, but my interest in the project had been piqued so that I kept abreast of developments as they occurred.

At the University of Illinois Neuropsychiatric Institute, Eric Olberg had gathered a stellar group that included Percival Bailey, Gerhardt von Bonin, and Warren McCulloch. After my year with Bucy, I became Oldberg's resident with privileged access to this group. Bailey took on another resident (John Green) and me and sat with us over a six-month period detailing the history of his tutelage with Hortega

del Rio, whose methods and neuroembryological approach led to Bailey's pioneering work on the classification of brain tumors. Each story was illustrated with microscopic material sectioned from brain tumors, which we examined together in great detail.

I occasionally participated in the then-ongoing strychninization experiments of chimpanzee cortex and listened attentively to Bailey, Bonin, and McCulloch discuss the results. Some years later, at Yale University, I was able to put to good use my surgical skills and the knowledge I had acquired from these discussions to complete the chemical stimulation experiments on cat and monkey by explorations of the medial and basal surfaces of the brain, which had remained inaccessible to the earlier research.

A most exciting part of the research going on at this time was the exploration of the lateral surface of the human brain for suppressor activity. Although the results obtained were highly controversial, the process of cortical stimulation in which Bucy also participated, the examination of the patient (sometimes left to me) while this stimulation was in progress, and the discussions that ensued were fascinating. I remember well the occasion during one of these procedures when a telegram arrived from Oxford University from Paul Glees stating that he had just found connections between the precentral cortex and the caudate nucleus, using his newly developed silver staining technique. McCulloch suggested that the term *negative feedback* be applied to explain the suppression of motor activity and that Glees had found the anatomical basis for such feedback.

These are only some of the highlights of the Chicago period. There are many, many stories of fascinating encounters, but one will suffice. My first public address was made to the Chicago Neurological Society. I presented a case of an oligodendroglioma in the motor cortex that had produced localized seizures of contralateral facial sweating. The tumor was of considerable size but was successfully removed with no aftereffects. There were no more seizures. Two conclusions were reached; Careful resections of cortical tissue that did not deeply invade white matter did not result in any irreversible paralysis; the precentral motor cortex is involved in the regulation of visceroautonomic functions. At the time, these functions were thought to be autonomous with respect to cortex. The highest level of such control was believed to be hypothalamic.

The other person on the Chicago Neurological Society program was Warren McCulloch. I did not understand a single idea he was presenting, and I am afraid most of the others attending the meeting were in similar straits. It took me another thirty years of close interaction with McCulloch before I began to appreciate fully what he had to say, and one of my fondest memories is the week McCulloch spent with us many years later at Stanford discussing his insights and ours just before his death.

Exciting as all of these Chicago experiences were, they did not furnish me with some of the basic tools I needed to accomplish my goals, which were to explore the relationship between brain function and mental processes, such as emotion, cognition, and conation. In my search for a hay fever-free location where I might earn my living as a neurosurgeon and at the same time pursue these goals, I heard of

the Yerkes Laboratories of Primate Biology near Jacksonville, Florida, where Karl
Lashley was director. Fortunately, there was a position open in Jacksonville with
J. G. Lyerly. Lyerly (as well as Poppen in Boston) devised a superior incision for
frontal lobotomy that was safer than the classical (lateral) Freeman-Watts proce-
dure and left fewer unwanted side effects. The lateral incision was shown by Mettler
and Rowland to invade Broca's speech area. Although no language disturbances
followed the lateral incision, fibers from the medial orbital cortex were more apt to
be severed than when Lyerly's superior incision was used. Because of his innovative
bent, I felt that Lyerly would be sympathetic to my desire to work at Yerkes. I
took my Florida State Board Examinations and began practice.

Lyerly did agree to my working two half-days per week, plus any free time, for
my research at Yerkes. I called Lashley and he responded favorably, stating that
he had been looking for a neurosurgeon to assist him in his primate research. Thus
began a collaboration that was to prove most influential in shaping my subsequent
research program.

Lashley taught me the techniques of experimental psychology, a field of inquiry
that I did not know existed. Paradoxically, although Lashley was almost solipsistic
in his approach and interpretations, he provided many of the insights that led to
the discoveries that make up the substance of this report. Some of the discoveries
I made while he was still alive, such as the unique relationship between the frontal
cortex and the limbic forebrain and the sensory specificity of various sectors of the
posterior "association" cortex, he tried to ignore because they were contrary to his
belief that the mechanisms involved in organizing complex psychological processes
were distributed in the brain. But always, his critical wit sharpened my interpreta-
tions and provided the basis for further observation and experiment.

The opportunity to work full-time in research came when I was asked by John
Fulton to join him in the Department of Physiology at Yale University. My
association with Yale lasted for a decade, during which time I also directed the
research laboratories of the Institute of Living, a mental hospital in nearby
Hartford, Connecticut. The facilities at Yale and in Hartford provided ample space
for a group of young investigators dedicated to exploring the power of combining
the techniques of experimental psychology with those of neurophysiology and
experimental neurosurgery. Doctoral students from Yale (e.g., Martha Helson
Wilson), Harvard (e.g., Lawrence Weiskranz), McGill (e.g., Mortimer Mishkin),
University of California at Berkeley (e.g., William Wilson), and Stanford (e.g.,
Jerome Schwartzbaum) formed a nucleus of a most productive team, all of whom
received their degrees while working on the program.

During this period I spent a month a year at the Yerkes Laboratory, and Kao
Liang Chow, an early collaborator, spent a month with me in the North, reestablish-
ing at least in part Yerkes's original vision, a university related primate research
laboratory. This continuing collaboration led to an invitation to succeed Lashley
as director of the laboratories, and I filled this post until the president of Yale
University sold the laboratories to Emory University in Atlanta.

Also during this period, I began an intimate association with psychologists at
Harvard University. I taught summer school there one year, built operant equip-
ment in the Harvard shops, and learned a great deal from S. S. Stevens, Gary

Boring, and Georg von Bekesy. Once a month, Bert Rosner and I drove up to Harvard (and later MIT) to perform experiments with Walter Rosenblith on monkeys in which we evoked electrical potentials in the cortex by auditory stimulation. Somewhat later, these sessions were extended to explore with Wolfgang Kohler the evocation of DC (direct current) shifts under similar conditions.

My interactions with B. F. Skinner were especially memorable and led to a decade of primate operant conditioning experiments that developed into subsequent research in cognitive neuropsychology. Ultimately, I was able to automate and extend the operant equipment to record (including reaction time) the results of individual choices among a dozen possible panel presses. Over three decades, these responses were recorded in a large variety of problem solving situations. The computer-controlled testing apparatus was dubbed: "Discrimination Apparatus for Discrete Trial Analysis" (DADTA).

At one point in our interaction, Skinner and I came to an impasse over the possible mechanism involved in the chaining of responses. Chaining was disrupted by resections of the far frontal cortex. Skinner suggested that proprioceptive feedback might have been disrupted, but this hypothesis was not supported by my experiments. Furthermore, as I indicated to Skinner, he as a biologist could propose such an hypothesis, but I, as a loyal Skinnerian, had to search elsewhere than the "black box" for an answer to our question. George Miller overheard some of our discussions and pointed out to us that he had available an apparatus that made chaining of responses easy: a computer. Miller explained to me the principles of list programming, which he had just learned from Herbert Simon and Alan Newell. The culmination of the collaboration begun by that chance encounter in the halls of Harvard was *Plans and the Structure of Behavior*, a book influenced also by interactions with Jerome Bruner. The book was written in 1960 at the Center for Advanced Studies in the Behavioral Sciences, adjacent to the campus of Stanford University.

Thanks to Jack Hilgard and Robert Sears of the Psychology Department and to Tom Gonda in Psychiatry, I was given an appointment at Stanford. During the thirty years that elapsed after my departure from Yale and Harvard, the research was carried out at Stanford University aided by a lifetime research career award from the United States National Institutes of Health.

At Stanford another group of associates, both doctoral and postdoctoral, joined the program. (Altogether, some fifty theses have been completed under its aegis.) Robert Anderson, Muriel Bagshaw, Bruce Bridgeman, James Dewson, Robert Douglas, Daniel Kimball, Abraham Spevak, and Leslie Ungerleider were among those who made major contributions. Nico Spinelli became an integral and almost indispensable collaborator.

When I became emeritus at Stanford at age 70, I was offered the opportunity to continue work at Radford University in Virginia, where I am now organizing a Center for Brain Research and Informational Sciences with the help of Alastair Harris, who chairs the Psychology Department. The appointment is supported by the eminent scholars fund of the Commonwealth of Virginia and an endowment from the James P. and Anna King Foundation.

The results of the research completed thus far can be organized into overlapping

phases, each phase representing a problem area and the application of techniques appropriate to that problem area. A description of the phases follows.

Research Phases

Phase I

At the time my research program began, large areas of the primate cortex remained silent to experimental investigation. In humans, damage to these areas resulted in agnosias and aphasia and in changes in interpersonal emotional interactions. But it was not known whether these changes in competence and behavior were the result of additional damage to primary sensory-motor systems, or whether the changes could occur without such damage. Furthermore, it was not known whether the changes were specific to one or another location within the silent cortex.

By using a battery of behavioral tests and resecting large extents of the then silent cortex of monkeys without invading the primary sensory-motor systems, answers to these questions were achieved relatively rapidly. I devised a method that used superimpositions of reconstructions. The extent of the resections that produced a particular behavioral deficit were summed. From this, the sum of the extent of the resections that produced no deficit was subtracted. This "intercept of sums" technique allowed me to make multiple dissociations among the various deficits produced by the resections and to localize the brain system involved in the behavior represented by each task.

The results were unequivocal. One type of deficit was produced when the far frontal and the medial and basal limbic cortex were resected. Another type of deficit followed resections of the posterior cortical convexity, and this type could be further subdivided into sensory specific components, each of which was related to its own portion of the convexal cortex. In no instance was invasion of the adjacent primary sensory-motor systems critical to producing the deficit or even in enhancing it.

Phase II

Having identified specific behavioral indicators for the functions of specific areas of the cortex, the next problem was to discover what the indicators meant. Much as a Babinski sign serves as an indicator of improper functioning of the spinal pyramidal motor system, signs of malfunction of brain cognitive systems were now available to us.

In order to define the meaning of the behavioral indicators, we had to explore the effects of each brain resection with a wide range of behavioral tasks related in one way or another to the indicator. Limits were established by showing which tasks related to the indicators could actually be performed without any deficit. For instance, the visual deficit produced by resections of the inferotemporal cortex were observed during discriminations of color, brightness, size, and two- and three-dimensional shapes, but not when the animal was tracking even minute objects. Further, limits to the deficit on luminance or size discrimination were obtained when the difference between the luminance or size of the cues was either very large or very small. (In the latter case, normal controls had as much difficulty as did the

monkeys with brain damage.) Response operator characteristic curves (ROC) were used to check whether the deficiency in discrimination was a function of changes in detection threshold or in response bias.

Interpretation was seldom straightforward, despite the wealth of data accumulated. This was in large part due to the lack of agreement about the constructs used in experimental psychology. Just how does one compare the results obtained in a fixed-interval operant conditioning study with a result obtained in an ROC decisional experiment? How does one compare either of these with results obtained in a delayed alternation situation tested in a Yerkes box or the DADTA machine? Interpretation had to be made after much cross-validation of techniques, often using the same subjects and, of course, comparable resections. But in most cases some conceptual leaps were necessary in making the interpretations, and these leaps were guided on the one hand by findings on human neuropsychological patients and on the other by knowledge obtained about the anatomy and physiology of the neural systems being investigated.

Phase III

Another line of research made possible by the initial finding of Phase I was an analysis of the anatomy and of the physiological processes of the neural systems, of which the critical cortical areas were a part. Chemical and electrical stimulations in anesthetized or problem-solving monkeys were performed. The effects of such stimulations on electrical recordings of event-related potentials (ERP) were assessed while monkeys performed in the DADTA. Also, such effects on the microstructure of receptive fields of single units in the visual system were assayed.

Once again the results of these experiments yielded a good deal of data that are interesting in their own right. However, as in Phase II, interpretation and, in some instances, controversial interpretation became necessary. One major controversy centers on whether the sensory specificity of the convexal "association" cortex is due to its transcortical *input* via connections from the related primary sensory cortex, or whether the specificity is to be ascribed to an *output* that operates downstream on the primary sensory systems. I was able to make massive disconnections, some of which appear to be complete, between the primary sensory systems (at both the thalamic and cortical levels) and the inferotemporal cortex involved in visual discriminations. None of these disconnections produced lasting deficits in sensory discriminations, and this led me to propose the output hypothesis. The controversy hinges solely on whether the disconnections are in fact total; even a small remnant of connectivity could be sufficient to mediate an input.

Phase IV

The research program began with the aim to clarify the brain mechanisms involved in cognitive, conative, and emotional processors in humans. The final research phase of the program therefore must address the relevance of the results of the nonhuman primate research, in which some 1,500 monkeys were used, to human neuropsychological findings. Since my early days in the neurosurgical clinic, electrical recordings of event related scalp potentials, computerized tomography, and nuclear

magnetic resonance techniques have been developed to aid in the localization of brain pathological conditions. Another recent innovation are batteries of clinical tests based on reliable research developed by experimental psychologists. Several members of the Neuropsychological Laboratories at Stanford and the Brain Research Laboratories at Radford are using these tools to provide a basis for comparison of nonhuman and human neuropsychological data.

Phase V

The laboratory research has yielded many unexpected results. These results have dramatically changed my views from time to time and posed, as critical to further research, problems that I had thought I could ignore. Much of the theoretical work that has engaged me has stemmed from these surprises.

Discoveries

Karl Popper has claimed that science is based on conjecture and refutation, and Karl Lashley was always comfortable when he operated in this mode. My own research appears to have proceeded in a somewhat more haphazard fashion. Despite the planning that is represented in the phases described previously, the actual research was more truly a search that stemmed from problems and paradoxes (such as unexpectedly finding relatively direct sensory inputs to the motor cortex) rather than from well formulated conjectures or hypotheses.

Theses there were, but only rarely did I derive single, testable hypotheses with experiments designed to confirm or disconfirm. Rather, the rule was that several more or less clearly defined alternatives presented themselves once the thesis, the reason(s) for performing the research, became clear. Experiments were designed to find out which of the alternatives fit the data obtained. Sometimes the data fit none of the alternatives, the thesis itself was found wanting, and new directions had to be taken. Often these new directions stemmed from attempts to systematize the data already obtained and to develop an appropriate frame for sorting and classifying them.

Whatever the merits or deficiencies of this approach, it is shared by many biologists. Claude Bernard, when asked how he proceeded in the laboratory, answered that he simply asked nature some questions. By adopting this perspective, the yield of the program has been substantial, and many discoveries were made that might not have been uncovered by a more rigid approach. Some of these discoveries are detailed next.

The Functions of the Frontolimbic Forebrain

The limbic forebrain   Early research results led me to redefine the boundaries of the limbic forebrain by establishing the relationship between limbic cortex and visceroautonomic activity.

Based on the earlier work of McCulloch, Bailey, and von Bonin, I established by strychnine neuronography, electrical stimulation, and histological examination the

interrelationship between the amygdaloid complex and the surrounding orbito-frontal, anterior insular, and temporal polar cortex and the direct connections of all of these to the hypothalamus.

The work of Arthur Ward and Robert Livingston had shown that viscero-autonomic responses were obtained from electrical stimulation of the cingulate gyrus and orbitofrontal cortex. With Kaada and Epstein, I extended these results to the anterior insula, temporal pole, and amygdala.

Thus the amygdala and its surrounding cortex were shown to be part of the limbic forebrain, which had previously included only the hippocampal and cingulate systems. Further, an entire extent of mediobasal motor cortex was discovered whose primary function is to regulate peripheral visceroautonomic functions.

The far frontal cortex and limbic forebrain   Next I established the fact that the far frontal cortex is the "association" cortex for the limbic forebrain. This accounted for the psychosurgical effects of frontal lobotomy. Using the delayed response and delayed alternation techniques, I extended the work of Jacobsen and Nissen, who had shown that resections of far frontal cortex disrupted performance on these tasks. I found that resections of the various structures composing the limbic forebrain (hippocampus, amygdala, cingulate cortex) and lesions of the head of the caudate nucleus also disrupted performance of delayed alternation. By contrast, resections of the cortex of the posterior cerebral convexity failed to disrupt performance on these tasks; if anything, monkeys with such resections tended to perform better than their unoperated control subjects.

These findings, as well as results of anatomical experiments that showed that the organization of the projections from the dorsal thalamus to the far frontal cortex and cingulate gyrus differed substantially from the organization of the projections to cortex of the posterior cerebral convexity, indicated that the far frontal cortex can be considered to be intimately related both in structure and function to the limbic forebrain. This relationship between the far frontal cortex and the limbic forebrain was quickly recognized to account for many of the changes produced by frontal lobotomy in humans.

Neurobehavioral and psychophysiological analyses of the functions of the frontolimbic forebrain   In addition to the effects on the performance of delayed alternation, we showed that amygdalectomy affected a set of behaviors I labeled the four Fs: fighting, fleeing, feeding, and sex. Aggression and fighting were assayed in a dominance hierarchy and shown to be dependent on the immediate (48 hours) interaction between the amygdalectomized monkey and his next-dominant neigh-bor. It is as if the familiarization process during which relative dominance becomes established had to be repeated anew.

Fleeing was examined in a conditioned avoidance procedure. Not only amygda-lectomy but all limbic and far frontal resections markedly altered avoidances, despite the fact that the escape (pain) threshold was unaffected. It is the memory of the familiarity with pain that is affected, not sensitivity.

A large number of experiments were done measuring the effect of food deprivation

on the amount eaten, the effect of the amount of food used as reinforcer (size and number of food pellets) in determining the rate of lever pressing, and the amount of food ingested when the animal had unlimited access. Amygdalectomized animals (monkeys, dogs, rats) ate more than their controls, but deprivation had very little effect on the amount eaten, nor did changes in the quantity of reinforcer. The increase in the amount eaten proved to be the result of eating long after control subjects were satiated. Satiation proved to be akin to familiarization.

I did not perform any formal experiments on the effects of amygdalectomy on sexual behavior. However, informal observation and a careful review and personal observation of the work of the Baltimore, Washington, and UCLA groups led to the conclusion that familiarization with the situation in which sexual behavior takes place as well as familiarization between the sexual partners is a potent variable in determining the change in sexual behavior that results from amygdalectomy.

It took a quarter of a century of experimental analysis to reach the conclusion that "familiarization" is the common denominator of the disturbance produced by amygdalectomy. Early on, it became clear that the four *F*s were related to each other in some special way. In lay terms, fight and flight, food and sex were instincts. But the term *instinct* had become suspect in experimental psychology because of a lack of agreed-upon definition, as demonstrated by Frank Beach's presidential address, "De-Scent of Instinct," to Division 3 of the American Psychological Association. Instead, ethologists had substituted *species-specific behaviors*. But this concept somehow failed to capture the spirit of what is meant by instinct. Human language is species-specific but does not qualify as an instinct.

What makes the four *F*s so interesting to us—whether they are exhibited by birds, bees, or nonhuman mammals—is not only the fact that we all "do it" but also that we all do it in a somewhat similar fashion. Rather than being species-specific, instincts such as the four *F*s are species-shared behaviors. The question therefore arose as to just what is the property that is disturbed by amygdalectomy and shared by the four *F*s? In order to answer this question experimentally, I decided to take a long chance and first ask another: What might it be that is *not* shared, that is, what are the limits of the impairment produced by amygdalectomy?

I chose to examine monkeys' responses on a set of stimulus equivalence problems. Behaviors exhibited in such situations could not be labeled instinctive. Still, equivalences characterize the reinforcing properties of various food and sex objects. In a similar vein, equivalences characterize the deterrent properties of various agonists to be aggressed against or avoided.

Over a decade, with different collaborators (Jerome Schwartzbaum, Eliot Hearst, Muriel Bagshaw, and Robert Douglas), I undertook four sets of experiments on amygdalectomized monkeys. The results of these experiments demonstrated, first, that indeed equivalence was disrupted by amygdalectomy, whereas stimulus generalization remained intact (generalization is disruapted by resections of the posterior cortical convexity). Second, the disruption of equivalence is due to the fact that amygdalectomized monkeys treat as novel what control monkeys respond to as equivalent.

Equivalence thus depends on not treating a situation as novel but as familiar.

The results of the experimental analysis were consonant with observations made in the clinic where patients with epileptogenic lesions of the amygdala experience "dejavu" and "jamais vu" phenomena.

The changes in dominance and in avoidance produced by amygdalectomy can be understood as deficiencies in familiarization: the monkey's position in the dominance hierarchy is no longer familiar after the resection, and reestablishing a position is impaired by failures in the familiarization process. The effects of deprivation and of changes in the amounts of food used as reinforcer depend on previous experience, that is, with being familiar with the sensations produced by deprivation and "recalling" the ordinary, familiar amount of food used as a baseline reinforcer. The effects of amygdalectomy on sex in the UCLA study turned out to be dependent on territoriality: sexual behavior that is ordinarily restricted to certain familiar places and times is now displayed over a much larger range of situations.

At first glance, these results regarding familiarization appear to be too cognitive, too devoid of the gut feeling that is imparted by the concept "instinct." But while I was engaged in the series of experiments on equivalence, I was fortunate enough to be introduced to Eugene Sokolov by Alexander Romanovich Luria. Sokolov and Luria came to my newly established laboratory at Stanford and stayed for two weeks. Sokolov had demonstrated that an orienting reaction would occur when a stimulus was omitted from a regular series and even when the intensity of a repetitive stimulus was suddenly reduced. This demonstrated that a representation, a neuronal model of the series, had been constructed against which the change was perceived as novel.

Aside from the importance of demonstrating that neural representations of stimulus events exist, to me the intriguing aspect of Sokolov's experiments was that he used visceroautonomic indicators in his experiments. What we needed to do was replicate his experiments, both with humans and with amygdalectomized and control monkeys.

Muriel Bagshaw helped implement the execution of such experiments. On the basis of my earlier experiments, which showed the amygdala to be the focus of a forebrain system controlling visceroautonomic responses, we predicted a change to occur in the rate of habituation of visceroautonomic responses in the Sokolov paradigm. Much to our surprise, we found that visceroautonomic responses were almost totally wiped out, and habituation of the orienting reaction failed to occur. Together, these results indicated that the familiarization process underlying behavioral habituation is dependent on the occurrence of visceroautonomic responses to the stimulus. I concluded that the visceroautonomic components of orienting were important in rapidly familiarizing novel events. Without these visceroautonomic responses, rapid familiarization did not occur.

The experiments using visceroautonomic indicators to track the habituation of the orienting reaction were extended to monkeys and human patients with far frontal lesions with results essentially the same as those obtained with amygdalectomized subjects. We also extended the inquiry to the effect of frontolimbic resections on classical conditioning to show its dependence on this occurrence of visceroautonomic responses. Similar results were obtained by James McGaugh in a long

series of conditional avoidance experiments. His aim was to identify the variables critical to consolidation of the memory trace.

The protocritic aspects of sensation and the frontolimbic forebrain   Having demonstrated frontolimbic regulation of visceroautonomic activity and its importance to the familiarization process, I wondered whether regulation was limited to the interoceptive "world within." After all, it is exteroceptive stimuli that, in our experiments, induce habituation. I therefore set up a new series of experiments addressed to answering the question, Which class of exteroceptive stimuli and what sorts of sensory input are processed by the systems of the frontolimbic forebrain?

Because of its relation to food intake, taste threshold discrimination (using bitters) was examined and shown to be disrupted by resections localized to the anterior portion of the planum temporale, just forward of the primary auditory input area. After resections of the temporal pole, monkeys would repeatedly eat meat (hot dogs), something that control monkeys do not do. Thus the anterior portion of the planum temporale was shown to serve as the primary receiving cortex for taste, whereas the temporal polar cortex, so close to the olfactory input, serves a higher level of gustatory processing.

As already noted, pain threshold was shown unaffected, but avoidance conditioning was disrupted by all resections that invaded the far frontal or limbic formations, including amygdala, hippocampus, and cingulate cortex.

In the spinal cord, tracts conveying pain and temperature run together. It seemed reasonable to ask, therefore, whether these strange bedfellows continue to travel together in the forebrain. Experiments were undertaken to investigate whether the structures found to be critical in the maintenance of avoidance behavior were also critically involved in temperature discrimination. Tests of temperature discrimination were performed and found to be disrupted by resections and electrical stimulations of the orbitofrontal cortex and the amygdala. No such disruption was seen after resections or electrical stimulations of parietal cortex.

I summarized these findings with a proposal, derived from a distinction made by Henry Head, that the frontolimbic forebrain processes the "protocritic" aspects of sensation, whereas the systems of the cortical convexity process the "epicritic" aspects. Epicritic sensations display local sign (i.e., can be accurately localized in time and space). The protocritic aspects of sensation are devoid of local sign and are suggested to define familiarity in terms of the bandwidth of tolerance (not threshold) for an *intensive* dimension of sensations.

The Functions of the Posterior Cortical Convexity

Sensory specificity in cognition and the posterior cortical convexity   In another part of the research program, I was able to show that the cognitive aspects of epicritic processes were dependent on the sensory specificity of restricted regions within the posterior "association" cortex of the cortical convexity. The cortical terminations of epicritic sensory input were well known when this program of research was initiated. However, at that time it was thought that the expanse of cortex lying

between the primary sensory receiving areas served an "associative" function. Thus the sensory specificity of agnosias found in human patients was thought to result from lesions of the association cortex that invaded the adjacent primary sensory cortex as well.

The experiments using the multiple dissociation technique demonstrated that, in the monkey, no such invasion of primary sensory cortex was necessary to produce the sensory deficits. In addition to the cortical systems involved in taste already described, a nonprimary area specific to the tactile sense, another specific to hearing, and a third, specific to vision, were identified.

An extensive series of experiments centered on the functions of the inferotemporal cortex, the area shown to be specific to vision. The results of this series showed that, although visual sensory functions such as threshold and detection remained essentially intact, resections produced marked deficits whenever selections among visual inputs are demanded.

Electrical recording of event-related potential led, by way of multidimensional analyses, to similar conclusions. Recordings made from the primary visual cortex were sensitive to changes in number and kinds of features that characterized the input. Recordings made from the inferotemporal cortex were sensitive to variables that influenced selection or "choice," especially when this was difficult.

Selection was interpreted to be the rudiment of the cognitive process underlying development of prototypes and thus categorizing and comprehension. (The steps leading to this interpretation are detailed in *Brain and Perception* Lecture 7.) When comprehension is disturbed by a brain lesion in humans, the identification of objects (e.g. their use) is impaired, which results in an agnosia.

Perceptual constancy Experimental evidence was provided to show that, in vision, size constancy is a function of the perisensory system that immediately surrounds the sensory receiving cortex. In an initial experiment, together with Anderson, I showed that object constancy was not related to the functions of the frontolimbic forebrain. In the complementary study, carried out by Ungerleider and myself, size constancy was shown to be disrupted by a combined lesion of the pulvinar of the thalamus and the peristriate cortex. Following such lesions, monkeys responded to the size of the retinal image and did not take distance cues into account.

The results of these experiments indicate that at least one form of constancy is dependent on the perisensory visual system. Electrical stimulation of this system produces eye movements. Object constancy is likely, therefore, to depend on eye movements that group the invariants occurring in a series of related sensory images.

Reciprocity between the functions of the frontolimbic systems and those of the cortical convexity A Jacksonian reciprocity was demonstrated to exist between the functions of the frontolimbic formations and those of the cortex of cortical convexity. Resections of the frontolimbic cortex actually speeded learning of sensory discriminations while making the learning of delayed alternation well-nigh impossible. Resections of the cortex of the posterior convexity actually speeded learning

of delayed alternation while making the learning of difficult sensory discriminations well-nigh impossible.

This reciprocity was also demonstrated with electrophysiological techniques. Recovery cycles in the visual system were shortened by electrical stimulations of the convexal system and lengthened by electrical stimulations of structures within the frontolimbic forebrain. Receptive fields of neurons in the lateral geniculate nucleus and in the primary visual cortex were made smaller by electrical stimulations of the systems of the posterior convexity and made larger by stimulations of frontolimbic systems.

Feature encoding by neurons in the visual cortex   Having utilized plots of receptive fields in the studies on reciprocity, I became interested in classifying the properties of visual receptive fields. Initially with Spinelli and Bridgeman, and later with Ptito and Lassonde, I attempted to classify "cells" in the visual cortex. This proved to be impossible because each cortical cell responded to several features of the input such as orientation, velocity, and the spatial and temporal frequency of drifted gratings. Furthermore, different cells displayed different conjunctions of selectivities that included: (1) tuning to auditory frequency, (2) whether a stimulus property had been reinforced, and (3) even whether a particular response had been made. I concluded that receptive field properties could be classified but not the cells, per se.

The possibility remains, however, that the temporal pattern of the spike train of a neurons shows specificity that allows classification. Currently, I am therefore investigating whether the spike train output of a cell encodes a specific feature, or whether an ensemble of neurons is required to encode it. Should an ensemble be necessary (as indicated by Vernon Mountcastle's work on the parietal cortex), the common assumption that single neurons serve as feature detectors or channels must be abandoned. Classification of receptive field (network) properties rather than of cells would be demanded.

So far, we have found that the long-range steady-state output of the neuron (after the first second of stimulus onset) reflects only whether a stimulus is present and not the specific features composing that stimulus. Barry Richmond at NIMH has examined the first 300 milliseconds of the response evoked by a multidimensional stimulus using harmonic component analysis. He found that each of the spike trains carries a part of the information (about one half bit) of the conjunction of features that characterizes the input.

The mechanism by which each feature differentially influences the temporal pattern was investigated in my laboratory. We found that different features are responsible for different factors that determine the initiation of a spike. One factor is a boundary condition or "barrier height" that reflects the amount of depolarization necessary for the spike to occur; the other is "drift rate," which reflects the rate at which depolarization proceeds. The orientation of a visual stimulus determines both the boundary condition and drift rate; spatial frequency determines only the drift rate.

Further investigations have been undertaken to relate the multidimensional character of the code carried in the spike train of a single neuron as described by

a Baro elementary function (see section on theory) to ensemble processing by the system network. Computer simulation in parallel distributed (PDP) "neural network" as well as multiple unit recordings are being explored.

The Functions of the Peri-Rolandic Central Cortex

The sensory nature of motor control   The finding of a mediobasal motor cortex and the involvement of motor control in the production of object constancy inspired a closer look at some aspects of the functions of the classical motor systems.

Quite by accident I discovered direct cutaneous and proprioceptive inputs to the precentral motor cortex. My student and neurosurgical colleague, Leonard Malis, had developed and perfected an apparatus to study the brain electrical potentials evoked by sensory stimulation. Together with Lawrence Kruger, he placed electrodes on the cortex of a monkey. I had earlier opened the skull to expose the central Rolandic area of the cortex but had left to test another group of monkeys with the delayed alternation procedure. Returning, I found Malis's oscilloscope displaying crisp, large electrical responses every time the sciatic nerve was stimulated. We were ecstatic. For almost two years we had waited for the oscilloscope, a DuMont, the first to be built for use in neurophysiology and designed by Harry Grundfest of Columbia University. Grundfest received the initial production model, we the second. Finally we were able to do the experiment we had planned.

Our joy was short-lived. I asked where the electrodes had been placed. Malis and Kruger replied in unison: "On the brain, you dummy." I asked, "But where on the brain?" When I looked, the electrode site was squarely in the upper middle part of the precentral gyrus. "Artifact!" I exclaimed.

It took a thesis by Kruger and consultations with Clinton Woolsey and Wade Marshall before we all were convinced that indeed the "motor" cortex received afferents directly from the periphery—not via the cerebellum or the postcentral gyrus. I resected these structures in various experiments without producing any change in the evoked response. Only the incitement of spreading depression diminished the response, attesting to the fact that it was not, after all, artifact.

With another student and neurosurgical colleague, Joseph Berman, I explored the effects on behavior of extensive resections of the precentral cortex using latch boxes and cinematographic recordings of the behavior of monkeys in a variety of situations. The results of these investigations showed (as had the resection of the oligodendroglioma noted earlier) that all *movements*, defined as sequences of muscle contractions, remained intact. The skill of opening latch boxes was, however, impaired; transition times *between* movements were markedly increased. This increase in transition time was specific to the latch box situation; it was not present in more ordinary circumstances, such as climbing the sides of cages and grabbing food.

On the basis of these experiments and the importance of the gamma motor system, I concluded that the precentral cortex exerted its effect by changing the set points of the muscle spindles involved. Behavioral *acts* were defined in terms of patterns of these set points, which thus resulted from particular *consequences* of movement.

Control over acts had in some way to encode and represent the input resulting from movements rather than controlling specific muscles or even muscle sequences per se. When encoding was impaired transition times became prolonged.

Spectral encoding of load in the motor system The nature of the encoding process remained opaque to me for almost a decade after completing the initial experiments. Then, a series of events occurred that allowed me to continue the explorations. First were data obtained by Edward Evarts that showed that the activity of neurons in the precentral motor cortex was proportional to the load placed on a lever manipulated by a monkey, and not the metric extension or contraction of the muscles used in the manipulation. Second, the results obtained in the 1930s by N. Bernstein in the Soviet Union were translated into English. Bernstein had shown that he could predict the course of a more-or-less repetitive series of actions by performing a Fourier analysis of the waveforms produced by spots placed over the joints involved in the action.

These data and analyses fed into the thesis I had by then developed, that certain aspects of cortical function could best be understood in terms of harmonic analysis. Orthogonal transforms of sensory inputs, such as the Fourier, were hypothesized to be the "code" used for cortical processing. Together with Sharafat, I therefore performed an experiment in which we inquired as to whether neurons in the cat motor cortex were tuned to certain bandwidths of frequencies of passive movements of their forelimbs. Here, for once, we were testing a specific hypothesis, and the hypothesis was supported by our results. Certain cells in the motor cortex are responsive to the frequency of the movement of a limb. Some of these cells are also selective of phase. The ensemble of cells are therefore performing a spectral analysis of changes produced by the movement. A set of values is computed that, when inversely transformed, represents the load imposed by the situation (the apparatus moving the limb) on the movement. It is this load, not the muscles or movement per se, to which the cells are responding.

Theory

1. The publication of *Plans and the Structure of Behavior* in 1960 had a major impact on moving psychology from a strictly behavioristic stimulus-response or response-reward stance to a more cognitive approach. In that publication, George Miller, Eugene Galanter, and I called ourselves "subjective behaviorists." I have already noted how I became involved with Miller after Skinner and I reached an impasse on the problem of the chaining of responses. Clinical considerations, set forth in my contribution to Sigmund Koch's *Psychology as a Science*, were also instrumental in taking more seriously the verbal reports of introspection than was the custom in mid-century. Thus came about a major divergence from Skinner, who abhors the use of subjective terminology because of the difficulty of extracting the exact meaning of a verbal communication. This topic was explored at great length at the Center for Advanced Study in the Behavioral Sciences with Ormond van Quine, who was writing *Word and Object* while we were engaged in writing *Plans*.

The thrust of *Plans* was that computer programs and computers can serve as

powerful metaphors for understanding cognitive processes and the brain mechanisms involved in them. That thrust has been realized in that conceptualization in the neuroscience community as well as in psychology is in terms of "information processing" and the implementation of "motor programs."

However, it has also become clear that brain mechanisms are considerably different, even in the fundamentals of their operation, from current serial processing computers. Brain mechanisms rely to a large extent on parallel processing, which suggests that addressing occurs by content rather than by location. Our mails are representative of location-addressable systems. Content-addressable systems are akin to those in which a broadcast is receivable by a properly tuned instrument, irrespective of location within the broadcast region.

2. These differences were highlighted in *Language of the Brain*, published a decade after *Plans. Languages* continued to explore the power of hierarchically arranged information-processing mechanisms but added the mechanisms of image processing, which, although they had been integral to the conceptions proposed in *Plans*, were not explored because no appropriate metaphor was available at that time. Such a metaphor became available in the early 1960s in the form of optical holograms. Image processing depends on parallel processing and thus is better fitted to some aspects of brain anatomy and function than is serial programming.

One of the consequences of considering parallel as well as serial processing was the introduction of a model for feedforward operations. In *Plans* we had made much of hierarchically organized feedback loops. As Roger Brown pointed out in his review of the volume, this left the mental apparatus almost as much at the mercy of input as did the earlier stimulus-response psychologies. In *Languages* this deficiency was remedied by showing that coactivation of two or more feedback loops by a parallel input would produce the kind of feedforward organization basic to voluntary control. This proposal was in consonance with similar suggestions put forward by Helmholtz, Ross Ashby, Roger Sperry, and Hans-Lukas Teuber, but was more specific in its design features than were the earlier suggestions.

3. Of the many languages described in *Languages of the Brain*, the language of the hologram has engendered the greatest lay interest and controversy—as noted in the introduction. This impact is due to the fact that the optical hologram displays vividly the operations of image processing. Image processing relies on orthogonal transformations such as the Fourier, which because of their linearity are readily invertible. This means that image and transform are reciprocals, that is, duals of one another, and that transformation in either direction is readily achieved.

The transform domain has properties that make it ideal for storage and for computation. Millions of megabytes of retrievable information can be encoded in a centimeter cube of holographic memory. IBM uses such storage devices in the machines that read the bar codes that identify grocery store items. Correlations are computed by simply convolving (multiplying) one input with the next. The ease with which such correlations can be computed in this fashion accounts for the value of the fast Fourier transform (FFT) in statistics.

There are other properties of the transform domain that are not so obviously useful but that have had a tremendous theoretical impact. Information becomes distributed in the transform domain so that essentially equivalent images can be reconstructed from any portion of the stored representation. Computer simulations of such parallel distributed processes (PDP) have become commonplace. Such simulations can "learn" language by going through stages very similar to those developed during language learning in human infants. The relations between such simulations and neurophysiological and neuropsychological data are reviewed in my recently published book, *Brain and Perception: Holonomy and Structure in Figural Processing.*

Holography was a mathematical invention designed by Dennis Gabor to enhance the resolution of electric microscopy. Optical realization of the mathematics came over a decade later. It is important to emphasize that other realizations of the mathematics such as those made by computer (as in the IBM example) are also holographic. To the extent that certain aspects of brain function realize Gabor's mathematics, to that extent they too can be thought of as holographic.

During the 1970s considerable evidence accumulated that one of the properties of receptive fields of cells in the primary visual cortex can be expressed in terms of Gabor elementary functions. In a 1946 paper, before his invention of holography, Gabor had developed a phase space for psychophysics that had as its coordinates not only space and time but the spectral properties of the process (later to be embodied in holography). Because he used Hilbert's mathematics, as had Heisenberg, in developing the formulation of quantum physics, Gabor recognized the elementary functions populating the phase space as "quanta of information." *Brain and Perception* further develops the implications for brain function of Gabor's quanta of information, their relation to Shannon's measure on the amount of information, to PDP theory, and to the data obtained in my investigations.

The characteristics of the spectral and phase space domains are very different from the familiar space-time dimensions that characterize the image domain. Consider for instance the dimensions of a spectral representation of an electroencephalographic record: its dimensions are frequency and power. Time is not represented as such; it has become enfolded into the representation of frequency.

In addition to the data and theory reviewed in *Brain and Perception*, the implications of this aspect of the spectral domain are detailed in a number of other theoretical essays. One of the most intriguing facets of this domain is that causality becomes a casualty. In a domain that enfolds space and time, causality in the sense of an efficient cause cannot obtain. Thus, ordinary Newtonian-Cartesian-Euclidian mechanics no longer holds. According to Gaborian mathematics, this applies not only to quantum physics but to psychophysics as well. My interpretation of these attributes of transformation has been that the spectral and quantal domains characterize a potential that becomes actualized to the extent that it becomes inversely transformed into a macroscopic space-time domain.

Exploring the brain potential as actualized in our experience and behavior has been a wonderful adventure. Discoveries in this world hidden within us are certainly equal to those experienced in expeditions of yore to polar and equatorial territories. As I continue to explore this frontier between the brain and behavioral sciences, I wonder what other vistas are poised on the horizon? More than likely, new surprises are in store for me, surprises that will once again intrigue the editors of *Omni*.

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