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Regional Physiology of the Central Nervous System

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Reprinted from PROGRESS IN NEUROLOGY AND PSYCHIATRY, Vol. XVI

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CHAPTER 3

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THE SEARCH FOR THE ENGRAM—DECADE OF DECISION

IN 1950 KARL LASHLEY HAD TO CONFESS THAT: "In experiments extending over the past 30 years, I have been trying to trace conditioned reflex paths through the brain or to find the locus of specific memory traces. The results for different types of learning have been inconsistent and often mutually contradictory in spite of confirmation of repeated tests. I shall summarize today a number of experimental findings. Perhaps they obscure rather than illuminate the nature of the engram, but they may serve at least to illustrate the complexity of the problem and to reveal the superficial nature of many of the physiological theories of memory that have been proposed." In this article entitled "In Search of the Engram," Lashley reviews his own work as well as that of others interested in the problem of brain function in learning. Much has been done in the decade since this publication, and a good deal of this work owes its impetus to Lashley's statement of the problem.

The work of the past decade can be considered under two major and five sub-headings, each development based on ingenious extensions of tried techniques, sometimes in combination with newly available ones. The two major headings are Neuroelectric and Neurochemical Concomitants of Behavior; Hemispheric Isolation, Hemispheric Dominance, and Behavior.

NEUROELECTRIC AND NEUROCHEMICAL CONCOMITANTS OF BEHAVIOR

Initiation of Engrams

Two concurrent reviews by E. Roy John[19] and by Killam and Loeser[21] cover in detail the studies that have involved the measurement of electrical activity in the brains of behaving animals. Of immediate interest here are those studies that have explored the neurophysiological concomitants of the learning process. John and Killam[20] used electrical tracers in

the cat brain to establish that one or another portion of the brain is processing the trace stimulus. These investigators flashed light at certain frequencies (e.g. 30/sec.) and recorded from various locations in the brain. Their interest focussed on the electrical activity that had become locked with the frequency of stimulation. Their experiments demonstrate that during learning of a conditioned avoidance problem there is a progressive restriction of the locus of such areas. At the beginning of training the electrical activity of a wide variety of brain structures appears synchronous with the tracer stimulus. After learning has occurred and performance is at criterion the electrical activity synchronous with the tracer can be recorded only from the appropriate projection system. In the earlier phases of learning the electrical activity of many of the core areas of the brain stem and forebrain show a rhythm synchronous with the tracer: reticular formation, hippocampus, amygdala, to name only a few of the structures involved. The synchronous rhythms drop out progressively and the dropping out is correlated with progressively better performance on the part of the animal.

One interpretation of these experiments could be that during the initial phases of learning the organism is reacting on a grosser, more "emotional" level and therefore a larger portion of his brain mass is involved in the experience. Another, not necessarily contradictory, interpretation, however, holds that the core structures (especially the reticular formation and the limbic systems of the forebrain) are integrally necessary to the initiation of a memory record during learning. The latter interpretation is supported by the results of an experiment by Ross Adey[1] who has shown, after performance of a task has reached a certain level of competence, recrudescence of bursts of 6/sec. electrical activity in the hippocampus whenever the organism makes an error. Such bursts are typical of the initial phases of learning. Freeman[12] has further correlated specific electrical concomitants recorded from the region of the amygdala with the anticipatory and various active phases of performance during a trial of food-getting behavior.

Doty's[7] experimental approach takes this multiple initiation of the engram seriously. He maps the variety of neural mechanisms that contribute to the formation of a single conditioned response. To date this mapping procedure has not proceeded sufficiently far to allow many generalizations to be made. However, Doty argues effectively that the best explanation for the fact that a multitude of neural systems is involved in the establishment of any conditioned response is that the final neuron alteration which accounts for the response must be located someplace in the *effector* system. He thus supports the position of Sperry[46] who has argued that a change in the level of excitability in the motor mechanism would render it prone to be triggered by slight additional sensory input. What

remains then of the functions usually assigned to the motor cortex? It might be, as Lashley[28] has suggested, and as his and other experimental results have indicated[42,43] that the motor cortex is just one other of the several facilitatory mechanisms that preset the final common path, so that it can be more readily triggered either by sensory input or by intrinsic neural activity.

The question remains to be answered as to the path of convergence of these various neural mechanisms since Sperry made multiple incisions into sensory (striate) and motor cortex without finding any effect on discrimination or on motor behavior. These results make it improbable (though not impossible since *postoperative* learning was not studied) that convergence takes place transcortically. Limbic forebrain-subcortical-cortical interdependencies are suggested by the studies mentioned above as well as those of Olds[41] who has made stimulations on those portions of the brain from which he has obtained self-stimulating behavior in rats. He records with microelectrodes from cerebral cortex and finds that he can condition the activity of the neural units under his microelectrodes by such stimulations. The results of these experiments would suggest therefore that the core structures, such as the central region from which Olds obtained self-stimulating behavior, act as tuning mechanisms that allow conditioning to take place by virtue of the increased local excitability that follows convergence of "reinforcing" and "external" stimulations.

Thus the initiation of engramatic structures apparently involves a *host* of neurological loci. It is not yet clear which loci are invariably involved. Are there some, such as the core and motor systems, that are always essential while others are more specific to particular situations? Finally, the pathways of this convergence of excitation remain to be spelled out.

Consolidation of Engrams

After exploring more than 100 substances with which to make epileptogenic lesions of the brain cortex, Kopeloff, Kopeloff and Pacella[23] finally hit upon aluminum hydroxide cream as an ideal irritant, although they were never able to determine the chemical or histological mechanism in the epileptogenesis. An alternate method which has been found successful in producing cortical foci from which electrical disturbance will spread has been the temporary freezing of a portion of the brain cortex. Early studies established that an irritative focus made in the precentral region of one hemisphere would in due time establish a mirror focus in the opposite hemisphere and that the mirror focus was persistent in the face of excision of the original irritative lesion. Section of the corpus callosum prevented the formation of the mirror focus. Recently Morrell[37, 38] has used this finding to make histochemical analysis of the mirror focus and has shown

that chemical changes do indeed occur in the mirror region. This is perhaps the first demonstration that repeated neural bombardment will leave a chemical residue in its wake.

In another series of experiments[25, 48, 49] the technique of making epileptogenic lesions has served usefully to distinguish between the effects of brain lesions on the performance of a learned task and on the learning of that same task. Cortical lesions made with aluminum hydroxide cream impair the learning some five fold. Yet when epileptogenic lesions are made after the task has been learned, performance remains essentially intact. The decrement in learning is associated with the initiation of the abnormal electrical activity. Should the monkey learn the task in the interim between placement of alumina cream and the onset of abnormal electrical activity, no defect in learning is noted.

Similar effects are obtained from electrical stimulation of the brain cortex made during acquisition of a learned response.[47] The effect of this procedure depends on the intensity of the electrical stimulus. Mild stimulation interferes with learning, greater stimulation leads to a decrement in the performance of a previously learned response. The results obtained with electrical stimulation raise the question whether those obtained with aluminum hydroxide cream are not simply due to a partial involvement of the system studied, since partial lesions of a particular cortical system impair the capacity to acquire and leave intact the capacity to perform. Such an interpretation would imply that learning and remembering were on some continuum and that Lashley's law of mass action was in effect.

An alternative interpretation would hold that the epileptogenic lesions interfere with some process of consolidation of the neural memory trace necessary before learning can take place. That consolidation is an important aspect of this problem has been suspected for a long time on the basis of the retrograde amnesias that follow head injuries and electroconvulsive shock to the brain. More direct evidence of the importance of a consolidation mechanism has been recently gathered in a series of detailed experiments performed by McGaugh and his collaborators[3, 31, 32, 33, 34, 53] who became interested in the problem as a result of the experiments of Krech and Rozenzweig[26] that correlated chemical differences between the brains of strains of rats with differences in learning rates in specific tasks. In McGaugh's experiments the attempt has been made to speed up the consolidation process by the injection of appropriate substances such as strychnine. The experiments were successful in demonstrating the range over which facilitation of learning can occur; the period of from 15 minutes to a half hour after exposure to a problem situation seems to be the critical one during which consolidation is effected.

The clear cut issue is, therefore, whether learning and performance of a

task are mediated by the same brain mechanism. Learning can be hindered without effect on performance; learning can also be speeded up without any noticeable effect on performance. But so far no experiment has been accomplished that shows interference with performance—based on memory—without at the same time impairing the animal's ability to learn this same task. The results of such an experiment are now crucially awaited. If performance can be affected without concomitant impairment or acceleration of learning, then the demonstration would be complete that at some level the mechanism of learning and that of performance are independent of one another. If on the other hand, such a demonstration cannot be made, then the suspicion must be held that the neural locus of setting down the memory trace and the storage of that memory are so intricately interwoven that separation is not feasible.

Irrespective of the possible separateness of learning and remembering, the results suggest the necessity for some kind of consolidation process before learning can take place. When consolidation is interfered with learning is retarded. When consolidation is speeded up learning is enhanced. Something of the nature of this consolidation process and some of the neurochemical and neural mechanisms have been studied. The chemical studies center on the production of RNA by neurons and may involve glia as well as neurons. Hydén[17, 18] has proposed the following model: Neurons have been found to be the tissue of the body most actively producing RNA throughout their lifetime. Neurons also do not divide. On the other hand, glial cells do divide. Hydén therefore has performed a series of experiments in which he has demonstrated that RNA is produced by neurons during excitation but that during quiescence the RNA fractions within the neuron remain constant or even diminish, while those of the adjacent glial cells increase markedly. This balance between the RNA production by the neuron under stimulation and in the glia cells at rest is used by Hydén as the basis for a consolidation mechanism, the consolidation taking place only during the rest periods when neurons are not stimulated. Galambos[13] also has focussed attention on the importance of glia cells—he reviews such recent literature as Windle's symposium[54] on the subject, Gless'[14] monograph, and Klüver's[22] statement of the issue, among others. An earlier statement by Kornmüller[24] serves as a key to the German literature. Since glial cells do divide it may well be that here is the mechanism that has hitherto been overlooked which allows for storage without impairment of the essential sensitivity of neurons to new inputs. The stored changes are assumed to be produced by a process somewhat akin to that which characterizes an immunization reaction. The stored changes are assumed effective by alterations of an optimal frequency of discharge of the neuron involved in the glial-neural complex.

Specification of Engrams

But it is not enough to state the problem in global terms of learning and remembering. One must also ask the learning of "what" and the remembering of "what?" The defects in learning that follow epileptogenic lesions are as specific as those obtained when the retention of some learned performance is tested. The defect of learning that follows a circumscribed cerebral lesion is not global. Rather, the same portions of the brain are involved in learning as in the remembering of a particular task. When visual discrimination learning is affected then learning of another kind of task such as alternation is not affected and the converse also holds. As in the case of ablation studies, visual discriminations are affected with temporal isocortical lesions,[49] whereas alternation and similar tasks are affected when the epileptogenic foci are located in the frontal eugranular isocortex[48]. Epileptogenic foci in the motor cortex affect the skilled performance of hasp box tasks.[43] Parietal epileptogenic lesions have a selective effect in the somesthetic mode.[51] These results show that consolidation may be as modality specific as capacity to perform; that "lesions of learning" are as specific to task as to the brain locus.

The initiation of the formation of the engram is thus seen as multiply determined. Consolidation on the other hand, though dependent on the continuing activities of the initiating mechanisms, is conceived to be a local chemical process that critically involves those projection and related "association" systems specific to the task situation to be remembered. The dilemma that neural tissue must at the same time be sensitive to new input and yet maintain some record of past excitation is in this fashion resolved *not* by invoking a separate locus for sensory-motor (the projection systems) and for memory processes (the "association" systems). Rather, the resolution of the dilemma is now proposed to be at a cytological level. Glial cells as well as neurons are declared important to the engram. Glial-neural couples involve the production of RNA by the neuron during excitation, the maintenance of prior configurations of molecular structure in glia during this period of excitation, and consolidation of the new RNA with pre-existing patterns in the neuron during subsequent periods of rest.

Hemispheric Isolation, Hemispheric Dominance, and Behavior

Utilization of Engrams

Another avenue of approach to the engram has been the use of the split brain technique in animals and the fact of cerebral dominance in man. Hemispheric isolation in animals consists of severing the corpus callosum, the anterior commissure, the optic chiasm, and more recently the upper portion of the brain stem. The current wide interest in this split brain

preparation was initiated by Myers and Sperry[40] who began their work on the interocular transfer of visual learning in the cat. Midline section of chiasm and callosum when performed prior to training prevented the right brain from knowing what the left brain had learned through the left eye. Sparing of either the chiasmal or callosal connections during the learning process was sufficient for the interhemispheric transfer to take place.

These experiments that used callosal section in the study of interhemispheric transfer of learning follow many years after the earlier studies of Bykov in Russia. Bykov[5, 6] in 1914 showed in the dog a blocking of the usual contralateral elaboration of conditioned inhibitory or excitatory foci when callosal fibers were transected. In the normal dog, conditioned salivation to cutaneous stimulation of one paw always leads to generalization of this conditioning so that stimulation of the homotopic point on the contralateral paw also elicits salivation. In the callosal sectioned dog, this interhemispheric transfer is absent.

A similarly ingenious study using the isolation of a hemisphere has been explored by Bureš and Burešová.[4] Repeated waves of Leão's spreading depression are induced by the local application of 25% KCl to the exposed cortex during avoidance conditioning and discrimination learning. Each hemisphere can thus be "trained"—even conflicting problems can be separately learned. The memory trace once formed can be utilized *only* by those parts of the brain that are *active* during the training procedure—in spite of anatomically intact callosal and other interhemispheric connections.

The recent surge of interest in the isolated hemisphere has ranged from fish to monkeys. In Sperry's, Myer's and Downer's laboratories especially, the work has gone far beyond the initial studies. Somesthetic tasks as well as visual ones are used. Frontal eugranular isocortical functions are explored as well as those of projection cortex. Taken together these experimental results show the following:

As already noted, there is a failure of interocular transfer in the split brain cat.[40] This failure is also reported for the split brain monkey.[9] Further, there is a failure of intermanual transfer of somesthetic discrimination in the split brain cat[50] and in the split brain monkey.[16] This lack of somesthetic transfer is somewhat unexpected in view of the bilaterally obtained potentials evoked in somatic cortex during electrical stimulation of peripheral nerves. This finding is consonant, however, with the primarily contralateral evokation of responses when "physiological" stimuli are applied. Are these results to be interpreted as evidence for a primitive type of hemispheric dominance in mammals?

As would be expected there has been some work to localize the important connections within the corpus callosum for some of these functions. For instance, the posterior portion of the corpus callosum is the important one

in the transfer of the visual engram from one hemisphere to another.[39] This would be expected from the known neuroanatomical relationships. Conversely, the importance of the behavioral measure used to study interhemispheric transfer has also been assayed. McCleary[30] used the fish to show that though sensory transfer may be present after callosal section, visual-motor transfer is absent.

In another series of related studies, the split brain technique has been used to trace the connections important to the utilization of the engram by making frontal and posterior eugranular isocortical lesions—the so-called association areas of the monkey cortex. For frontal isocortex these studies have just begun. Glickstein, Arora and Sperry[15] recently reported a deficit in visual delayed response performance that followed unilateral optic tract section and contralateral prefrontal ablation when the corpus callosum had been sectioned. In other words, a unilateral frontal lobectomy had the effect of a bilateral frontal lobe removal when the visual input is restricted to the side of the lobectomized and isolated hemisphere. For the posterior "association" areas, two studies, one by Mishkin[36] and another by Ettlinger,[10] have shown that removal of the inferotemporal cortex of an isolated hemisphere disrupts discrimination when visual input is restricted to that hemisphere. In Mishkin's study the visual input was restricted by the occipital lobectomy; in Ettlinger's study the optic tract was cut. The method is now being extended to trace the connections necessary for intact performance of visual discrimination in greater detail.

Finally, Sperry[45] has isolated a particular projection area rather than the whole hemisphere by removing all else in that hemisphere and examining learning, both before and after corpus callosum section. As a result of these studies, a remarkable autonomy of utilization of the engram, especially in the somatic sphere, can be ascribed to the projection areas. This experimental demonstration confirms the view that Lashley expressed during his later years after his many studies on visual learning.[28]

It thus appears that once an engramatic formation has been initiated and consolidated, its use depends on brain structures necessarily active during formation. The projection systems show a remarkable autonomy of function in this respect— an autonomy which again raises the question of the role of the so-called association systems in the process of remembering. The techniques of hemispheric isolation currently continue to be applied to the problem and some answers to the question should soon be available.

Evocation of Engrams

In man the story of engram utilization may be somewhat different, for here hemispheric dominance is a fact to be considered. Whether dominance is an immediate consequence or necessarily involves continued action of

both hemispheres for a period of time is, at present, unknown. What has become evident is that a large share of the everyday memory functions is carried by the hitherto silent *sub*dominant hemisphere. Studies by Milner[35] show that nonverbal visual performances are impaired when the subdominant (usually the right) hemisphere is injured. Verbal performances continue to be allocated to the dominant hemisphere. A detailed well-documented study of the somesthetic mode by Semmes, Weinstein, Ghent and Teuber[44] in a recent monograph, comes to a similar conclusion: The evidence of this study is that sensory discriminations made with the left hand involve the right hemisphere more diffusely than do those made with the right hand involve the left hemisphere. Furthermore, sensation of the left hand is frequently affected by lesions of the *ipsi*lateral sensory-motor region. Finally, the nature of the sensory impairment of the left hand is not the same as that of the right hand. Note that these are called differences in "*sensory*" function rather than in "agnosias" or "apraxias."

And so, strangely, these investigations have uncovered another important aspect of the engram—the mechanism for its evokation. The focus of attention turns here, as in the animal experiments, to the projection areas—another monograph by Teuber's group[52] details studies of visual performances as a function of visual field defects. The direction taken by this work on man as well as that reported on the basis of animal experiments raises again the question posed by Lashley and before him by von Monakov and still earlier by Munk, each of whom after a lifetime of work came to the conclusion that disturbances of the more complicated aspects of behavior invariably involve a malfunctioning of the projection systems of the brain. Though other neural mechanisms are necessary to the initiation, and perhaps the consolidation of engrams, their utilization and certainly their evokation is not only dependent on, but interdependent with, the more classically conceived functions of the projection systems.

What then is a summary view of the engram as it emerges from this decade of activity? First, neural bombardment of neural structures can give rise to chemically detectable differences in brain tissue so that the long maintained search for the way in which neurological function can be permanently recorded is considerably closer to realization than a decade ago. A histochemical picture emerges that involves RNA production by neurons and includes *glia* as essential elements. Second, this recording process takes time. Disturbance of the neural process which is manifested as altered electrical activity retards the recording process even when insufficient to interfere with the engram once it has been laid down. Third, the neurological systems that provide this period of time include the limbic systems and probably the reticular activating mechanisms of the brain stem core. Interference with the functions of these systems during the

recording process either prevents the initiation of engramatic structures or distorts them so that later utilization is impossible. Fourth, engrams are specific to the task (i.e., the situation) in which they are formed, thus the consolidation process must be critically located in the sensory-motor (and probably the related "association") systems active during engram initiation. Different portions of the brain become involved in the laying down of memory traces in different situations. Visual cortex is involved in the visual problems, auditory cortex in auditory problems. Inferotemporal cortex is involved in the learning of visual choices, parietal cortex in the learning of somesthetic choices, the frontal isocortex in the acquisition of the capacity to alternate. Fifth, in the intact subhuman mammal the utilization of the engram involves the activity of not only a considerable portion of a particular hemisphere, but most likely the respective counterparts of the opposite hemisphere are used as well. At least for subhuman mammals there is, therefore, a considerable duplication of the engramatic structure throughout a series of systems bilaterally distributed. For man, the situation seems different. Although it is not as yet determined whether both hemispheres are important to the laying down of engrams, it is clear that dominant and subdominant hemispheres each become specialized in their own way: e.g. the dominant temporal lobe is essential to verbal activity, the subdominant one for visual performances. These differences in specialization between hemispheres are not simply at the "higher levels" of behavioral complexity; they are differences in functions more usually called "primary" sensory. Attention is therefore again focused on the functions of the projection systems of the brain, as at least necessary to the evocation of engrams and possibly to their utilization and consolidation as well.

Engrams so conceived have a look about them reminiscent of Bartlett's schemata[2]—they must be extended networks of neurological and neuroglial structures (perhaps in the projection and related "association" systems) rather than encapsulated pieces of tissue; they must be continually changeable representations of excitation rather than forever frozen images isomorphic with a particular moment of experience. Change is dependent on diverse neural processes such as those mediated by the core limbic and reticular formations of the brain and convergent excitations from these to the isocortical tissues where consolidation may be in progress. These networks appear to be indistinguishable from those that process directly the inputs to and outputs from the brain: reconstruction of remembrances evoked by current input appears, from these studies, to predominate over the retrieval of stored bits of information. Should the trend of the results of these experiments continue in the direction that has been charted in the past decade, we will very likely come to conclude that a considerable por-

tion of the engram is carried not in the neuron alone but in the glia as well; not in the head alone but in the environment with which the owner of that head interacts—for the book as well as the brain, words as well as neurons and neuroglia, ABC as well as RNA, are an integral part of the memory process.

ACKNOWLEDGMENTS

My thanks to Dr. Mitchell Glickstein for his help with the review of the split-brain data; to Drs. Glickstein and Muriel Bagshaw for editorial comments, and to Phyllis Ellis and Jeanette Hogan for the preparation of the manuscript.

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