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The Isocortex

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THE ISOCORTEX

The important role of neocortical mechanisms in cognitive behavior has been a focus of scientific interest for the past century and a half. In the early 1800s, arguments raged between physiologists (e.g., Flourens) and phrenologists, many of whom were good anatomists (e.g., Gall and Spurzheim as to whether the cerebral mantle functions as a unit or whether a mosaic of cerebral sub-organs determines complex psychological events. During the intervening period data have been subsumed under one or the other of these two views—almost always with the effect of strengthening one at the expense of the other. In the recent past, the accumulation of data has so markedly accelerated that a reevaluation of the problem promises to prove fruitful. Specifically, the data obtained by the use of electronic amplifying devices to study neural events has raised questions concerning the validity of concepts generated by neuroanatomical techniques; the adaptation to subhuman primates of measures of choice behavior has stimulated discussion of the validity of concepts derived from clinical neurological material.

Problems of Neural Organization

First, let us take a look at some *neural* data and see how they fit current conceptualizations of cerebral organization. Explicitly or implicitly, most of us tend to think of the brain as being composed of receiving areas (sensory

cortex) that function in some fairly simple fashion to transmit receptor events to adjacent areas of "association" cortex. Here, these neural events are "elaborated" and associated with other neural events before being transmitted to the motor areas of the brain; these motor areas are said to serve as the principal effector mechanism for all cerebral activity. This model was proposed some seventy-five years ago by Flechsig on the basis of the then available anatomical information. As we shall see, the neural data available today make it necessary to modify this model considerably.

But, before we can come to grips with a new conception of brain organization, it is necessary to clarify some definitions. Over the years many of the terms used in neurology have been imbued with multiple designations. Neocortex is such a term. Comparative anatomists use this word to describe the dorsolateral portions of the cerebral mantle since these portions show a *differentially* maximum development in microsmatic mammals (such as primates) as compared with macrosmatic mammals (such as cats). In other branches of the neurological sciences (see Grossman) the term neocortex has come to cover *all* the cortical formations that reach maximum development in primates. The definition as used in these sciences subsumes portions of the cortex on the medial and basal surface of the cerebral hemisphere, which, though well developed in macrosmatic mammals, do show *some* additional development in primates. Since this mediobasal limbic cortex has been related' to behavior rather different from that which concerns us in this

paper, it seems worthwhile to find an unambiguous term that delimits the dorsolateral cortex. As reviewed in an early publication, the cerebral cortex may be classified according to whether or not it passes through a six-layered embryonic stage. The medial and basal limbic structures do not pass through such a stage and are called allo- or juxtallocortex; the dorsolateral portions of the cerebral cortex do pass through such a stage and are called isocortex.

It has been fashionable to subdivide isocortex according to cytoarchitectonic differences; difficulties in classification have been pointed out' that question the immediate usefulness of distinctions based solely on the histological picture of the cortex. I should prefer, therefore, to subdivide isocortex on the basis of thalamocortical relationships since these relationships are determined by the most reliable neurohistological technique available to us: namely, retrograde degeneration of neurons in the thalamus following cortical resection. But, if we are to use this criterion of subdivision of cortex because it is a reliable one, we are forced into looking at the organization of the thalamus as the key to the organization of the cortex. Rose and Woolsey have divided thalamic nuclei into two classes: (l) those receiving large tracts of extrathalamic afferents and (2) those receiving the major portions of their direct afferents from within the thalamus. The former they called extrinsic (primary projection) and the latter, intrinsic (association) nuclei. Thalamocortical connections, demonstrated by retrograde degeneration studies' make possible the differentiation of

isocortical sectors on the basis of their connections with extrinsic (primary projection) or with intrinsic (association) thalamic nuclei.

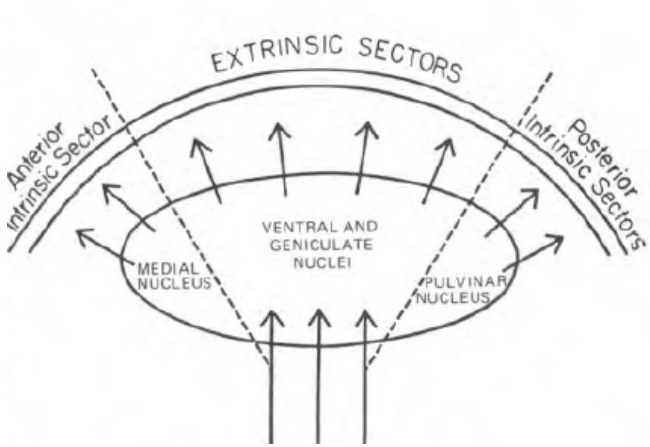

Figure 7-1.
Diagrammatic scheme illustrating the division of isocortex into extrinsic (primary projection) and intrinsic (assocoation) sectors on the basis of thalamic afferent connections. The ventral and geniculate thalamic nuclei which receive major direct afferents from extracerebral structures project to the extrinsic sectors; the medial and pulvinar thalamic nuclei do not receive such afferents and project to the intrinsic sectors.

It can be seen from Figure 7-1 that the portions of the cortex labeled as "extrinsic sectors" correspond essentially to those usually referred to as "primary projection areas," while those labeled "intrinsic sectors" correspond essentially to those usually referred to as "association areas." However, the terms association cortex and primary projection areas have their drawbacks: (1) Association cortex implies that in these portions of the cortex convergent tracts bring together excitations from the "receiving areas" of the brain. As we

shall see, this implication is unsupported by fact. (2) Electrophysiological experiments, which will be discussed below, have demonstrated a topographical complexity of organization that necessitated labels such as Areas I and II. Should the term primary projection areas be used to denote the Areas I only or should it cover such areas as II as well? Additional confusion arises since the intrinsic (association) sectors *do* receive a thalamic projection, so that the term "secondary projection areas" has been suggested for these sectors.67 These considerations have led me to substitute the currently less loaded terms, "extrinsic" and "intrinsic."

Can the subdivision of cerebral isocortex into extrinsic (primary projection) and intrinsic (association) sectors be validated when techniques other than retrograde thalamic degeneration are used? Figure 7-3 shows the extent of the cortical connections when myelinated fibers are traced by the Marchi (osmic-acid) staining technique from peripheral structures, such as optic tract and dorsal spinal roots, through the thalamus to the cortex. As can be seen by comparing Figures 7-2 and 7-3, there are, thus, at least two anatomical techniques that permit approximately the same subdivision of isocortex: one derived from cell body stains; the second, from nerve fiber stains. Further support for the classification comes from electrophysiological data. When receptors are mechanically or electrically stimulated or when peripheral nerves are electrically stimulated, an abrupt change in electrical potential can be recorded from portions of the brain that are connected to

these peripheral structures. Under appropriate conditions of anesthesia, maps may be constructed on the basis of size of the potential changes evoked and the latency that intervenes between the time of stimulation and the recording of the potential change (Figure 7-4). As can be seen from the comparison of the maps made by the histological and electrophysiological techniques, there is considerable, though by no means complete, correspondence between various delineations of the extrinsic (primary projection) from the intrinsic (association) sectors of the isocortex.

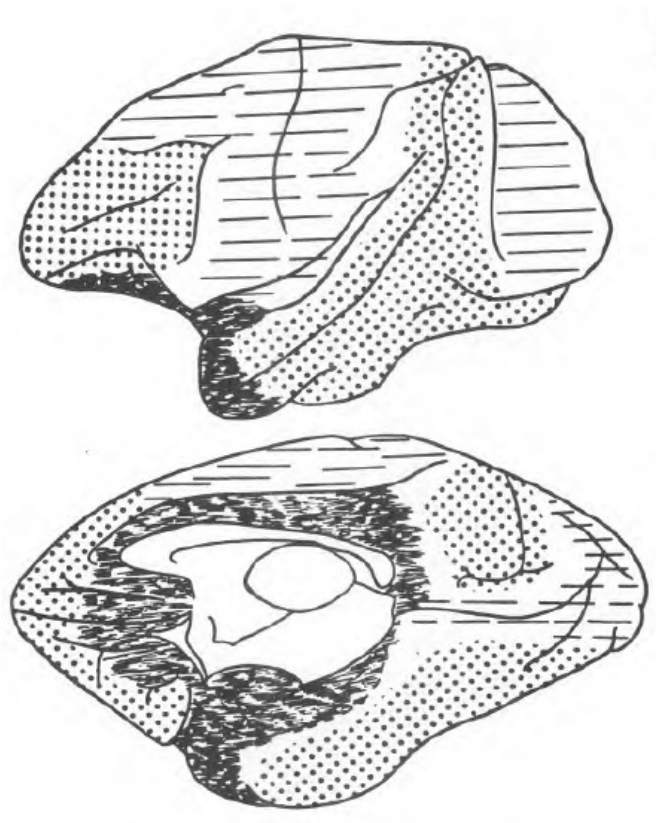

Figure 7-2.
Diagrams of the lateral (above) and mediobasal (below) surfaces of the monkey's cerbral hemisphere showing the divisions discussed in the text. Shaded indicates allo-juxtallocortex; lined indicates extrinsic (primary projection) isocortex; dotted indicates intrinsic (association) isocortex. Boundaries are not sharply delimited; this is, in part, due to minor discrepancies which result when different techniques are used and, in part, to difficulties in classification due to borderline instances and inadequate data (e.g., how should the projections of *n. ventralis anterior* and of *lateralis posterior* be classified?)

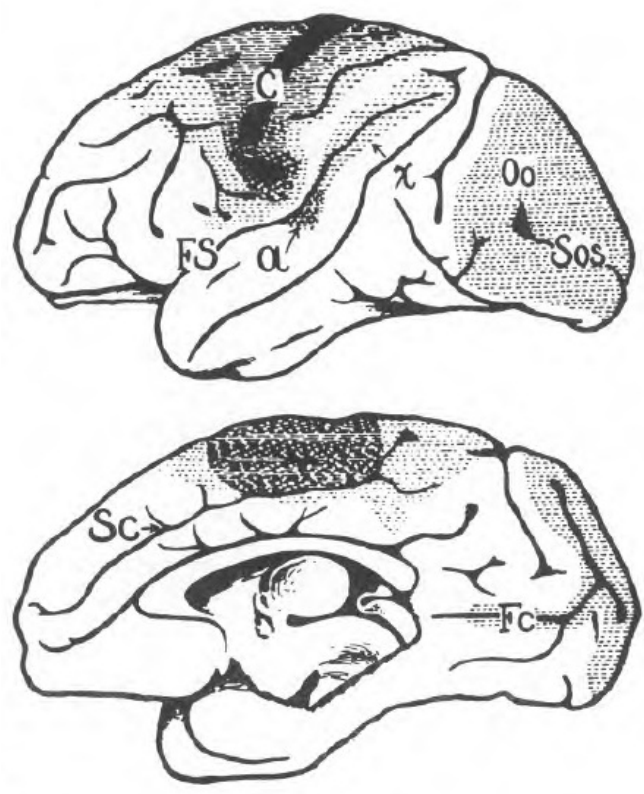

Figure 7-3.
Extrinsic (primary projection) sectors as mapped by staining degenerating axons following thalamic lesions.

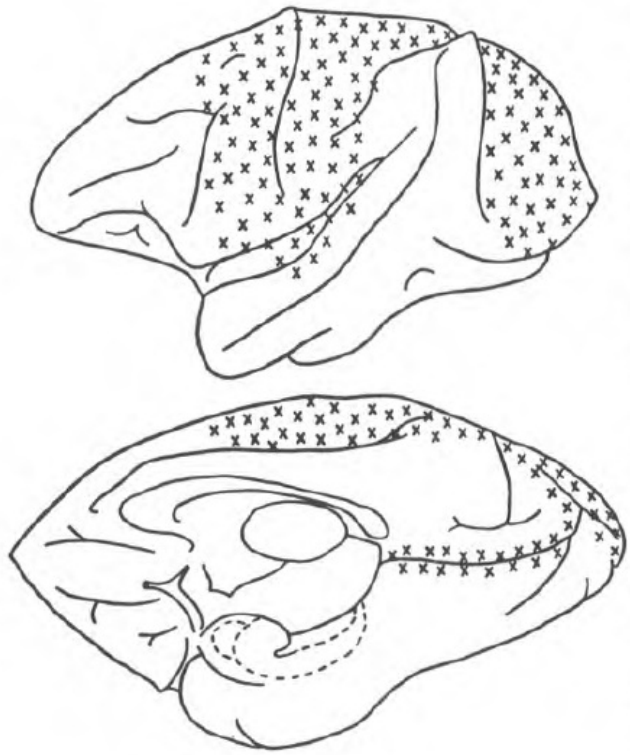

Figure 7-4.
Diagrams of the monkey cerebral hemisphere as in Figures 2 and 3. This map of the abrupt electrical changes induced in cortex by peripheral stimulation was compiled from studies using animals sufficiently anesthetized with barbiturates to practically abolish the normally present spontaneous rhythms of potential changes recorded from the brain. Those potential changes were counted which were larger than 50μv and showed a latency within 3 milisec of the minimum latency of any abrupt potential change evoked in the particular afferent system investigated. These criteria were chosen as the most likely to indicate major direct afferents from periphery to cortex. The correspondences and minor discrepancies between this figure and Figure 3 indicate the approximate range of such similarities when different techniques and brain diagrams are used.

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Input—Output Relationships

Enough of definitions. I am sure you are convinced by now that the cerebral isocortex may usefully be divided according to whether its major input derives, via the thalamus, directly from the periphery or whether that input is largely intracerebral. But have you noticed that, according to all of the techniques mentioned, input from extra-cerebral structures reaches the portions of the cortex usually referred to as motor as well as those known as sensory areas? Electrophysiological experiments demonstrate that somatic afferents are distributed to both sides of the central fissure of primates. Since

the *afferents* reaching the precentral motor areas as well as those reaching postcentral sensory areas originate in both skin and muscle nerves, the critical differences between the input to the precentral and to the postcentral cortex must yet be determined if the differences in effect of resection of the pre- and postcentral cortex on behavior are to be explained in terms of input. What is important for us today is the fact that afferents from the periphery reach motor cortex relatively directly through the thalamus, a fact that becomes more meaningful on consideration of the efferents leaving the isocortex.

It has been commonly held for the past half century that the pyramidal tract originates in the motor cortex, especially that portion close to the central fissure. A monograph by Lassek thoroughly documents the evidence for a more extensive origin of the pyramidal tract from the entire extent of the precentral as well as from the postcentral cortex of primates: a return to an earlier held anatomical position that had become submerged during the first half of this century. Another conception held during this latter period, the distinction between pyramidal and extrapyramidal, has repeatedly been questioned in the light of these and other data. Woolsey has shown that the differences in movement brought about by electrical stimulation of the various parts of the precentral cortex may be ascribed to differences in somatotopic relationships rather than to differences in the complexity of organization of the movement. Thus, Woolsey finds that stimulations in the

more forward portions of the precentral region, which had formerly been called premotor, activate the axial musculature, while those close to the central fissure activate appendicular musculature. Since axial muscles are larger, the movements they produce appear grosser than those produced by such discrete appendicular muscular units as those found in the hand—one need not invoke different orders of coordination or complexity to distinguish between the posterior and anterior portions of the motor cortex. Thus, the distinction between motor and premotor cortex fades and, as a result, makes unnecessary the classical distinction between the locus of origin of the pyramidal and extrapyramidal systems, which has already been called into question by anatomical data.

On the other hand, evidence from ablation and stimulation experiments in both man and monkey indicates the continued necessity for differentiating precentral motor from postcentral sensory mechanisms. Certainly the distinction cannot be thought of simply in terms of afferents reaching the postcentral and efferents leaving the precentral cortex. Thus, with these data in mind, a thorough reinvestigation is needed of the organization of the input-output relationships of the extrinsic (primary projection) system related to somatic structures.

The marked overlap of input-output is not limited to the somatic extrinsic (primary projection) system. With respect to vision, eye movements

can be elicited from stimulation of practically all the striate cortex; these eye movements can be elicited after ablation of the other cortical areas from which eye movements are obtained. With respect to audition, ear movements have been elicited;- respiratory effects follow stimulation of the olfactory receiving areas. Thus, an overlap of afferents and efferents is evident not only in the neural mechanisms related to somatic function but also in those related to the special senses. The overgeneralization to the brain of the law of (Bell and) Magendie, which defines sensory in terms of afferents in the dorsal-spinal and motor in terms of efferents in the ventral-spinal roots, must, therefore, give way to a more precise investigation of the differences in internal organization of the afferent-efferent relationship between periphery and cortex in order to explain differences such as those between sensory and motor mechanisms. As yet only a few experiments toward this end have been undertaken.

The afferent-efferent overlap in the *extrinsic* (primary projection) system suggests the possibility that the intrinsic (association) systems need not be considered as association centers upon which pathways from the extrinsic sensory sectors converge to bring together neural events anticipatory to spewing them out via the motor pathways. Unfortunately, there are few reliable anatomical data concerning the connections of the intrinsic sectors so that our analysis of the organization of these systems relies largely on neuropsychological data. Let us turn, therefore, to

experiments that manipulate cerebral isocortex either by stimulation or resection, and observe the effects of such manipulations on behavior.

Classification of the Amnestic Syndromes

I want to take this opportunity to dispel the myth that experimentally produced local brain lesions (especially ablations) do not affect memory functions, that is, learning and remembering. This conception, like so many in neuromythology, derives its strength from the fact that it is a half-truth. In this instance, the idea rests largely on Lashley's contribution, *Brain Mechanisms and Intelligence,* and derives support from his later publication, "In Search of the Engram." Lashley presented evidence and made interpretations. I shall show here that his data have been superseded -—thus the fanciful aspect of the current myth —but that his interpretations were extremely shrewd—thus the myth's persistence. To make the counterargument I will describe data from experiments made over the past twenty-five years. In my laboratories alone some twelve hundred behaviorally tested rhesus monkeys have been subjected to selective brain operations during this period. These studies provide evidence that makes me think that the impairments in memory functions produced by local experimental lesions are best subsumed as deficiencies in input processing, and I will describe the evidence that demonstrates that memory traces become distributed widely within a sensory projection system. I will then

argue that the mechanism of remembering critically involves input coding, both during storage and retrieval.

As noted earlier, the experimental analysis of subhuman primate, psychosurgical preparations has, contrary to popular opinion, uncovered a host of memory disturbances. The initial technique by which these brain-behavior relationships were established is called the method of the "intersect of sums," an extension of what Teuber named the method of "double dissociation" of signs of brain trauma. The intersect-of-sums method depends on classifying the behavioral deficit produced by cortical ablations into *yes* and *no* instances on the basis of some arbitrarily chosen criterion; then plotting on a brain map the total extent of tissue associated with each of the categories —*ablated:deficit; not ablated:no deficit*—and finally finding the intersect of those two areas (essentially subtracting the *noes* from the *yeses-plus-noes).* This procedure is repeated for each type of behavior under quantitative consideration. The resulting map of localization of disturbances is then validated by making lesions restricted to the site determined by the intersect method and showing that the maximal behavioral deficit is obtained by the restricted lesion (see Table 7-1 and Figure 7-5).

Once the neurobehavioral correlation has been established by the intersect-of-sums technique, two additional experimental steps are undertaken. First, holding the lesion constant, a series of variations is made of

the task on which performance was found defective. These experimental manipulations determine the limits over which the brain-behavior disturbance correlations hold and thus allow reasonable constructions of models of the psychological processes impaired by the various surgical procedures.

Second, neuroanatomical and electrophysiological techniques are engaged to work out the relationships between the brain areas under examination and the rest of the nervous system. These experimental procedures allow the construction of reasonable models of the functions of the areas and of the mechanisms of impairment.

Two major classes of memory disturbance have been delineated by these operations: *specific* and *contextual* amnesias.

*Table 7-1. Simultaneous Visual Choice Reaction**

Operates without deficit			Operates with deficit			Nonoperate controls		
	Pre	Post		Pre	Post		Pre	Post
OP 1	200	0	PTO 1	120	272	Cl	790	80
OP 2	220	0	PTO 2	325	F	C 2	230	20
OP 3	380	0	PTO 3	180	F	C 3	750	20
LT 1	390	190	PTO 4	120	450	C 4	440	0
LT 2	300	150	T 1	940	F			
H 1	210	220	T 2	330	F			

HA	350	240	VTH 1	320	F
FT 1	580	50	VTH 2	370	F
FT 3	50	0	VTH 3	280	F
FT 4	205	0	VTH 4	440	F
FT 5	300	200	VT 1	240	F
FT 6	250	100	VT2	200	F
DL 1	160	140	VT 3	200	890
DL 2	540	150	VT 4	410	F
DL 3	300	240	VT 5	210	F
DL 4	120	100			
MV 1	110	0			
MV 2	150	10			
MV 3	290	130			
MV 4	230	10			
MV 5	280	120			
CIN 1	120	80			
C1N 2	400	60			
CIN 3	115	74			
CIN 4	240	140			

*Pre- and postoperative scores on a simultaneous visual choice reaction of the animals whose brains are diagrammed in Fig. 5, indicating the number of trials taken to reach a criterion of 90% correct on 100 consecutive trials. Deficit is defined as a larger number of trials taken in the "retention" test than in original learning. (The misplacement of the score H 1 does not change the overall results as given in the text.)

The Specific Amnesias

Between the sensory projection areas of the primate cerebral mantle lies a vast expanse of parieto-temporo-preoccipital cortex. Clinical observation has assigned disturbance of many gnostic and language functions to lesions of this expanse. Experimental psychosurgical analysis in subhuman primates, of course, is limited to nonverbal behavior; within this limitation, however, a set of sensory-specific agnosias (discrimination disabilities and losses in the capacity to identify cues) have been produced. Distinct regions of primate cortex have been shown to be involved in each of the modality-specific mnemonic functions: anterior temporal in gustation, inferior temporal in vision, mid-temporal in audition,' and occipitoparietal in somesthesis. In each instance, discriminations learned prior to surgical interference are lost to the subject post-operatively and great difficulty (using a "savings" criterion) in re-acquisition is experienced, if task solution is possible at all.

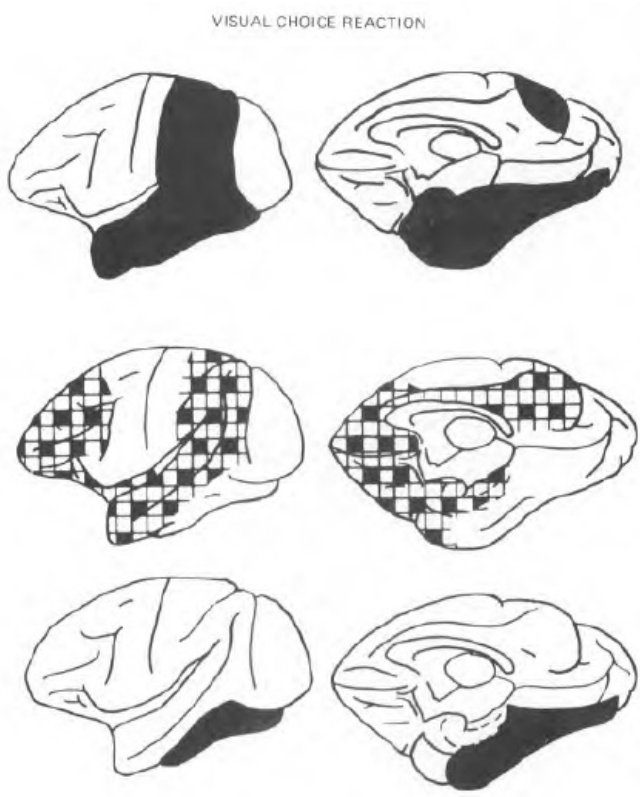

Figure 7-5.
The upper diagram represents the sum of the areas of resection of all the animals grouped as showing deficit. The middle diagram represents the sum of the areas of resection of all of the animals grouped as showing no deficit. The lower diagram represents the intersect of the area shown in black in the upper diagram and that not checkerboarded in the middle diagram. This intersect represents the area invariably implicated in visual choice behavior in these experiments.

The behavioral analysis of these "specific" amnesias is still underway, but an outline of the psychological process involved can be discussed.

Perhaps the easiest way to communicate this outline is to detail the observations, thinking, and experiments that led to our present view of the function of the inferior temporal cortex in vision.

Search and Sampling

All sorts of differences in the physical dimensions of the stimulus—for example, size (Figure 7-6)—are distinguished less after the lesion, but there is more to the disability than this as illustrated in the following story.

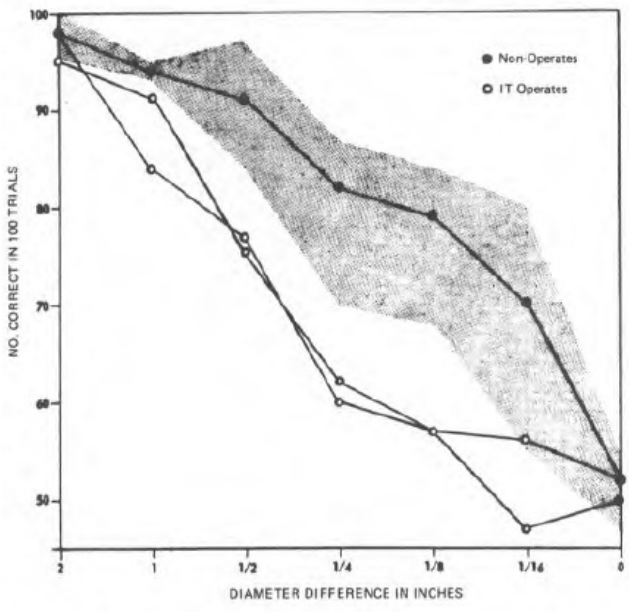

Figure 7-6.
Scores for two operates and four controls on the first run of size discrimination. Shaded area indicates the range of performance of the four nonoperate controls. IT operates monkeys with resections of inferior temporal cortex.

One day while testing monkeys with such lesions at the Yerkes Laboratories in Orange Park, Florida, I sat down to rest from the chore of carrying a monkey the considerable distance between home cage and laboratory. The monkeys, including this one, were failing miserably at the visual discrimination task being administered. It was a hot muggy, typical Florida summer afternoon and the air was swarming with gnats. My monkey reached out

and caught a gnat. Without thinking I also reached for a gnat—and missed. The monkey reached out again, caught a gnat, and put it in his mouth. I reached out—missed! Finally, the paradox of the situation forced itself on me. I took the beast back to the testing room: He was as deficient in making visual choice as ever. But when no choice was involved, the monkey's visually guided behavior appeared to be intact. This gave rise to the following experiment (Figure 7-7), which Ettlinger carried out. On the basis of this particular observation, we made the hypothesis that choice was the crucial variable responsible for the deficient discrimination following inferotemporal lesions. As long as a monkey does not have to make a choice, his visual performance should remain intact. To test this hypothesis, monkeys were trained in a Gantzfeld made of a translucent light fixture large enough so the animal could be physically inserted into it. The animal could press a lever throughout the procedure but was rewarded only during the period when illumination was markedly increased for several seconds at a time. Soon response frequency became maximal during this "bright" period. Under such conditions no differences in performance were obtained between inferotemporally lesioned and control animals. The result tended to support the view that if an inferotemporally lesioned monkey did not have to make a choice he would show no deficit in behavior, since in another experiment the monkeys failed to respond differentially to differences in brightness.

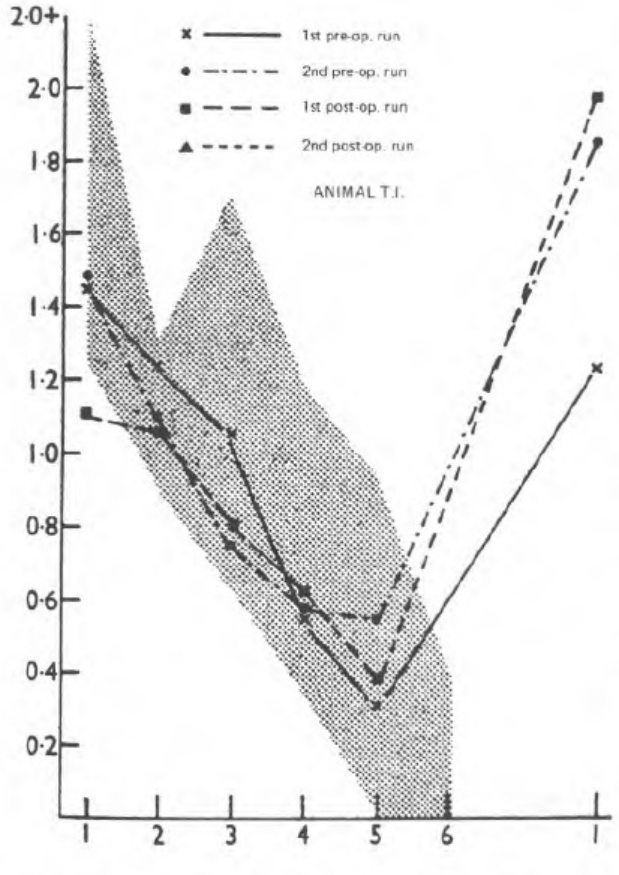

Figure 7-7.
Single manipulandum performance curves of a single animal in a varying brightness situation. Shaded area indicates variability among groups of four animals.

In another instance we trained the monkeys on a very simple object discrimination test: an ashtray versus tobacco tin (Figure 7-8). These animals

had been trained for two or three years before they were operated on and were therefore sophisticated problem-solvers; this, plus ease of task, accounts for the minimal deficit in the simultaneous choice task. (There are two types of successive discrimination: In one the animal has either to go or not to go, and in the other he has to go left or right.) When given the same cues successively, the monkeys showed a deficit when compared with their controls, despite this demonstrated ability to differentiate the cues in the simultaneous situation.

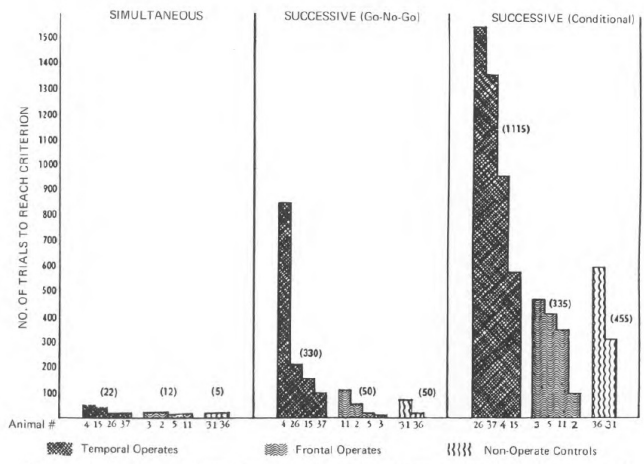

Figure 7-8.
Comparison of learning scores on three types of object discrimination by three groups of monkeys. Note that though the cues remain the same, changing the response which was demanded increased the deficit of the inferotemporal groups.

This result further supported the idea that the problem for the operated

monkeys was not so much in “seeing” but in usefully manipulating what they saw. Not only the stimulus conditions per se but the whole range of response determinants appear involved in specifying the deficit. To test this idea in a quantitative fashion we next asked whether the deficit would vary as a function of the *number* of alternatives in the situation. The hope was that an informational measure of the deficit could be obtained. Actually something very different appeared when the number of errors was plotted against the number of alternatives (see Figure 7-9).

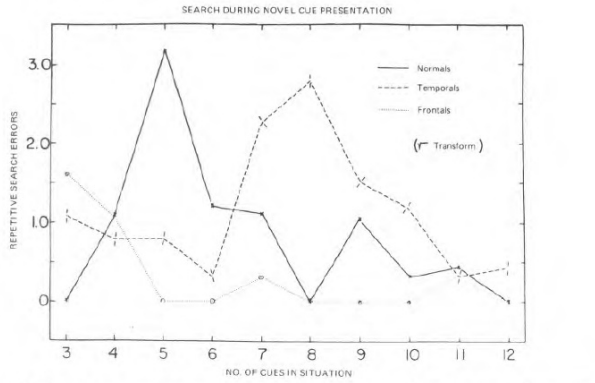

Figure 7-9.
Graph of the average number of repetitive errors made in the multiple object experiment during those search trials in each situation when the additional, that is, the novel, cue is first added.

If one plots repetitive errors made before the subject finds a peanut—that is, the number of times a monkey searches the same cue—versus the number of alternatives in the situation, one finds there is a hump in the curve,

a stage where control subjects make many repetitive errors. The monkeys do learn the appropriate strategy, however, and go on to complete the task with facility. What intrigued me was that during this stage the monkeys with inferotemporal lesions were doing better than the controls! This seemed a paradox. As the test continued, however, after the controls no longer made so many errors, the lesioned subjects began to accumulate an error hump even greater than that shown earlier by the controls.

When a stimulus sampling model was applied to the analysis of the data, a difference in sampling was found (Figure 7-10). The monkeys with inferotemporal lesions showed a lowered sampling ratio; they sampled fewer cues during the first half of the experiment. Their defect can be characterized as a restriction in the visual field; however, the limitation is not in the visual-spatial field but in the information-processing field. That is, in the number of alternatives they can sample or handle at any one time.

In short, the modality-specific defect that results from a posterior "association" system lesion appears to produce an information-processing defect best described as a restriction on the number of alternatives searched and sampled.

The Contextual Amnesias

The second major division of the cerebral mantle to which mnestic

functions have been assigned by clinical observation lies on the medial and basal surface of the brain and extends forward to include the poles of the frontal and temporal lobes. This frontolimbic portion of the hemisphere is cytoarchitecturally diverse. The expectation that different parts might be shown to subserve different functions therefore is even greater than that entertained for the apparently uniform posterior cortex. In the case of the posterior cortex, the diversity of lesion effects nonetheless allowed classification: differential discriminations were always involved, and the defects turned out to be sensory-mode specific. In the same manner, lesions of the frontolimbic region, irrespective of location (dorsolateral frontal, cingulate-medial frontal, orbitofrontal-caudate, temporal polar-amygdala, and hippocampal) have been shown to produce disruption of "delayed alternation" behavior. The alternation task demands that the subject alternate his responses between two cues (for example, between two places or between two objects) on successive trials. On any trial the correct response is dependent on the outcome of the previous response. This suggests that the critical variable that characterizes the task is its temporal organization. In turn, this leads to the supposition that the disruption of alternation behavior produced by frontolimbic lesions results from an impairment of the process by which the brain achieves its temporal organization. This supposition is in part confirmed by further analysis, but severe restrictions on what is meant by temporal organization arise. For instance, skills are not affected by

frontolimbic lesions, nor are discriminations of melodies. Retrieval of long-held memories also is little affected. Rather, shorter term mnestic processes are singularly involved. In animal experiments these are demonstrated especially clearly when tasks demand matching from memory a cue (as in the delayed response problem) or outcome (as in the alternation task) that in the past has shown some complexity in the regularity of its recurrence. Rather than identify an item, the organism must fit the present event into a context of prior occurrences, only some of which relate directly to the situation at hand.

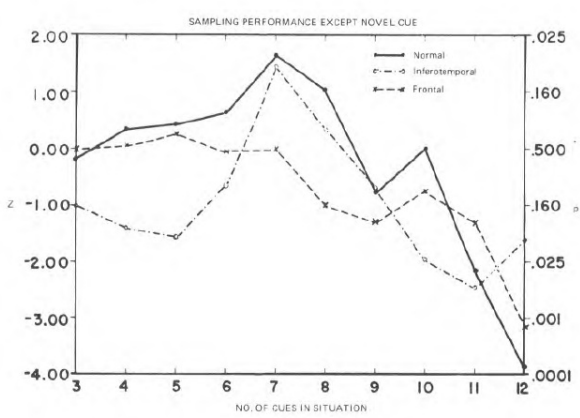

Figure 7-10.
Graph of the average proportion of objects (cues) that are sampled (except novel cue) by each of the groups in each of the situations. To sample, a monkey had to move an object until the content or lack of content of the food well was clearly visible to the experimenter. As was predicted, during the first half of the experiment the curve representing the sampling ratio of the posteriorly lesioned group differs significantly from the others at the 0.024 level (according to the nonparametric Mann-Whitney U Test).

As noted, different parts of the frontolimbic complex would, on the basis of their different structures, be expected to function somewhat differently within the category of short-term mnestic processes. Indeed, different forms of contextual amnesia are produced by different lesions. But these relationships between the structures of the limbic forebrain and behavior are beyond the scope of this paper. Let us therefore examine more closely the effects of frontal isocortical resection on problem solving.

The Parsing Problem

Classically, disturbance of immediate memory has been ascribed to lesions of the frontal pole. Anterior and medial frontal resections were the first to be shown to produce impairment on delayed response and delayed alternation problems. In other tests, frontal lesions also take their toll: Impairment of the orienting galvanic skin response (GSR) is found, and of conditioned avoidance behavior, as well as of classical conditioning. Furthermore, error sensitivity was tested in an operant conditioning situation (Figure 7-11). After several years of training on mixed and multiple schedules, four hours of extinction were run, that is, the reinforcement (peanuts) was no longer delivered, although everything else in the situation remained the same. Note that the frontally lesioned animals failed to extinguish in the four-hour period, whereas the control monkeys did.

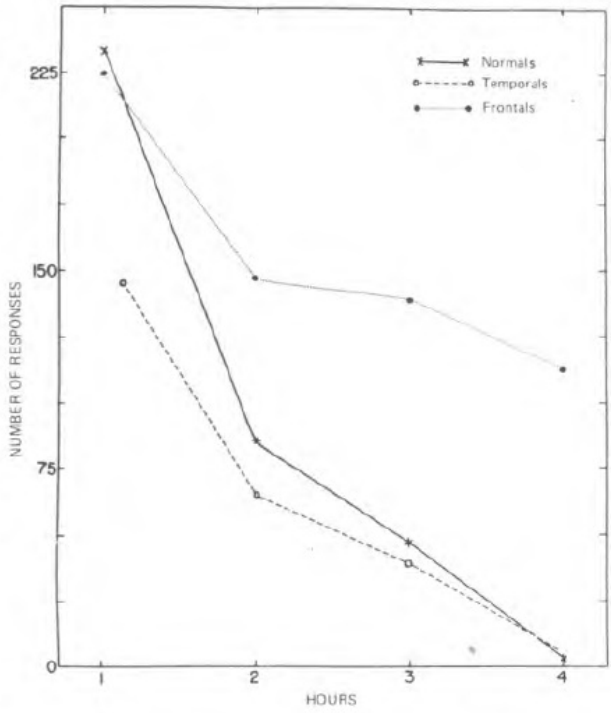

Figure 7-11.
Graph of performance of three groups of monkeys under conditions of extinction in a mixed schedule operant conditioning situation. Note the slower extinction of the frontally lesioned monkeys.

This failure in extinction accounts in part for poor performance in the alternation already described (Figure 7-12): the frontally lesioned animals make many more repetitive errors. Even though they do not find a peanut, they go right back and keep looking.

This result was confirmed and amplified in a study by Wilson. He analyzed the occasions for error: did errors follow alternation or non-reinforcement? To determine which, he devised a situation in which both lids over the food well opened simultaneously, but the monkey could obtain the peanut only if he had opened the baited well. Thus the monkey was given "complete" information on every trial and the usual correction technique could be circumvented. With this apparatus the procedure was followed with four variations: correction-contingent, correction-noncontingent, noncorrection-contingent, and noncorrection-noncontingent. The contingency referred to is whether the position of the peanut depended on the prior correct or incorrect response of the monkey or whether its position was alternated independently of the monkey's behavior. Wilson then analyzed the relationship between an error and the trial preceding that error. Notice (Table 7-2) that for the normal monkey the condition of reinforcement and non-reinforcement of the previous trial makes a difference, whereas for the frontally lesioned monkey this is not the case. Alternation affects both normal and frontal subjects about equally. In this situation, frontal subjects are simply uninfluenced by rewarding or non-rewarding consequences of their behavior.

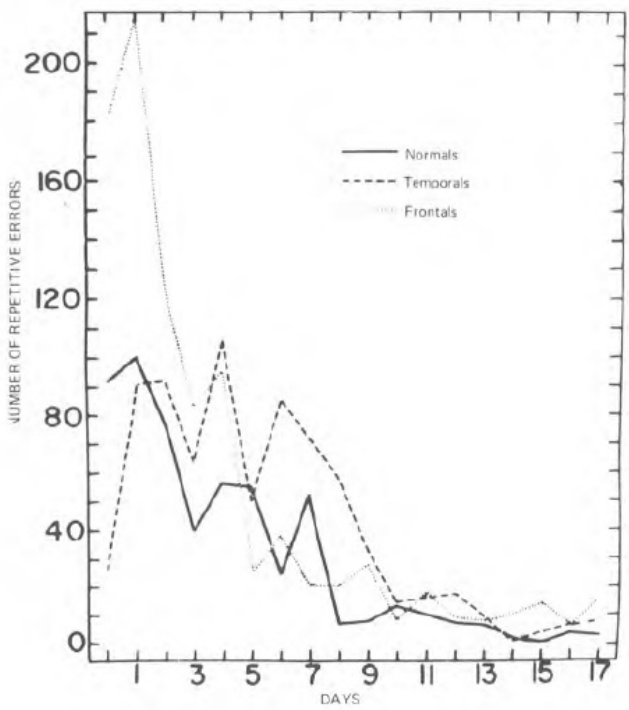

Figure 7-12.
Graph showing the differences in the number of repetitive errors made by groups of monkeys in a go, no-go type of delayed reaction experiment. Especially during the initial trials, frontally operated animals repeatedly return to the food well after exposure to the "nonrewarded" predelay cue. Note, however, that this variation of the delay problem is mastered easily by the frontally operated group.

Now let me return to the multiple choice experiment discussed earlier. (p. 114). Here also this inefficacy of outcomes to influence behavior is

demonstrated; it is illustrated (Figure 7-13) by an increased number of trials to criterion after the monkeys have first found the peanut. The procedure calls for the strategy of return to the same object for five consecutive times, that is, to criterion. The frontally lesioned animals are markedly deficient in doing this. Again, we see that the conditions of reinforcement are relatively ineffective in shaping behavior once the frontal eugranular cortex has been removed, so that the monkeys' behavior is relatively random when compared to that of normal subjects.'' Behavior of the frontally lesioned monkeys thus appears to be minimally controlled by its (repeatedly experienced and therefore expected) consequences.

*Table 7-2. Percentage of Alternation as a Function of Response and Outcome of Preceding Trial**

	Preceding trial**			
S	A-R	A-NR	NA-R	NA-NR
Normal				
394	53	56	40	45
396	54	53	36	49
398	49	69	27	48
384	61	83	33	72
Total	55	68	34	52
Frontal				
381	49	51	41	43

437	42	46	27	26
361	49	48	38	35
433	43	39	31	32
Total	46	46	33	33

*Comparison of the performance of frontally ablated and normal monkeys on alternations made subsequent to reinforced (R) and non-reinforced (NR) and an alternated (A) and non-alternated (NA) response.

**A, alternated; NA, did not alternate; R, was rewarded; and NR, was not rewarded.

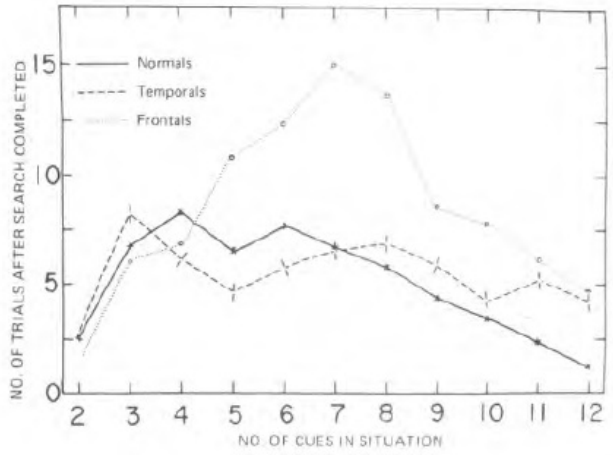

Figure 7-13.
Graph of the average number of trials to criterion taken in the multiple object experiment by each group in each of the situations after search was completed, that is, after the first correct response. Note the difference between the curves for the controls and for the frontally operated group, a difference that is significant at the .05 level by an analysis of variance (F = 8.19 for 2 and 6 df) according to McNemar's procedure performed on normalized (by square root transformation) raw scores.

Frontal lesions work their havoc on yet another contextual dimension. This is best demonstrated by manipulating the alternation task in a special way: Instead of interposing equal intervals between trials (Right-5"-Left-5"-Right-5"-Left-5"-Right-5"-Left-5" . . .) as in the classic task, couplets of RL were formed by extending the intertrial interval to 15 seconds before each R trial (R-5"-L-i5"-R-5”-L-i5”-R-5"-L-i5" . . .). Immediately the performance of the frontally lesioned monkeys improved and was indistinguishable from that of their controls. I interpret this result to mean that for the subject with a bilateral frontal ablation, the alternation task becomes something like what this page would seem were there no spaces between words. The spaces, and the holes in doughnuts, provide some of the structure, the parcellation, parsing of events (doughnuts, alternations, and words) by which they became codable and decipherable.

An Alternative to the Transcortical Reflex

Models of cerebral organization in cognitive processes have, heretofore, been based to a large extent on clinical neurological data and have been formulated with the reflex as prototype. Such models state that input is organized in the extrinsic sensory, elaborated in the intrinsic associative, and from there relayed to the extrinsic motor sectors. I have already pointed out that the afferent-efferent overlap in the extrinsic (primary projection) system makes such notions of cerebral organization suspect. A series of

neuropsychological studies by Lashley, Sperry, Chow, Evarts, and Wade in which the extrinsic (primary projection) sectors were surgically cross-hatched, circumsected, or isolated by large resections of their surround, with little apparent effects on behavior, has cast further doubt on the usefulness of such a transcortical model. Additional difficulties are posed by the negative electrophysiological and anatomical findings whenever direct connections are sought between the extrinsic (primary projection) and intrinsic (association) sectors. These data focus anew our attention on the problem faced repeatedly by those interested in cerebral functions in cognitive behavior. Experimentalists who followed Flourens in dealing with the hierarchical aspects of cerebral organization—e.g., Munk, Monakow, Goldstein, Loeb, and Lashley—have invariably come to emphasize the importance of the *extrinsic* (primary projection) sectors not only in "sensorimotor" behavior but also in the more complex "cognitive" processes. Each investigator has had a slightly different approach to the functions of the *intrinsic* (association) sectors, but the viewpoints share the proposition that the intrinsic sectors do not function independently of the extrinsic. The common difficulty has been the conceptualization of this interdependence between intrinsic (association) and extrinsic (primary projection) systems in terms other than the trans-cortical reflex model—a model that became less cogent with each new experiment.

Is there an alternative that meets the objections leveled against the transcortical reflex yet accounts for currently available data? I believe there

is. The hierarchical relationship between intrinsic (association) and extrinsic (primary projection) systems can be attributed to a convergence of the *output* of the two systems at a subcortical locus rather than to a specific input from the extrinsic cortex to the intrinsic. Some evidence supporting this notion is already available. Data obtained by Whitlock and Nauta, using silver staining techniques, show that *both* the intrinsic and extrinsic sectors implicated in vision by neuropsychological experiments are *efferently* connected with the superior colliculus. On the other hand, lesions of the intrinsic thalamic nuclei fail to interfere with discriminative behavior.' Thus, the specific effects in behavior of the intrinsic (association) systems are explained on the basis of output to a sub-cortically located neural mechanism that functions specifically (e.g., superior colliculus in vision). This output, in turn, affects input to the extrinsic (primary projection) systems either directly or through the efferent control of the receptor (e.g., in vision, mechanisms of eye movement, accommodation). According to this conception, the associative functions of the central nervous system are to be sought at convergence points throughout the central nervous system, especially in the brain stem and spinal axis, and not solely in the intrinsic (association) cerebral sectors.

How the Brain Controls Its Input

Recently much of our effort has been channeled into an attempt to increase the evidence for such efferent control mechanisms. To this end, a

series of experiments was undertaken to find out how the brain cortex might affect the processing of visual information. It is appropriate to begin with some facts—or rather lack of facts—about the neuroanatomical relationships of the inferotemporal cortex. There is a dearth of neurological evidence linking this cortex to the known visual system, the geniculostriate system. There are no definitive anatomical inputs specific to the inferotemporal cortex from the visual cortex or the geniculate nucleus. Of course, connections can be traced via fibers that synapse twice in the preoccipital region, but connections also exist between the visual cortex and the parietal lobe, the excision of which results in no change in visual behavior (as shown above). In addition, massive circumsection of the striate cortex does not impair visual discrimination. Further evidence that these "corticocortical" connections are not the important ones can be seen from the following experiment. I performed (Table 7-3) a crosshatch of the inferotemporal cortex, much as Sperry had done earlier for the striate cortex, and found no deficit either in visual learning or in performance. On the other hand, undercutting the inferotemporal cortex made a vast difference: it precluded both learning and performance in visual tasks. This suggests that the relationships essential to visual behavior must be cortico-subcortical.

Table 7-3. Comparison of the Effects of Undercutting and Crosshatching Inferotemporal Cortex of Monkeys on Their Performance in Several Discriminations

Animal	3 vs 8	R vs C	3 vs 8

Crosshatch	158	380	82	0
	159	180	100	0
	161	580	50	0
	166	130	0	0
Undercut	163	[1014]	100	300
	164	[1030]	200	[500]
	167	704	50	0
	168	[030]	150	[500]
Normal	160	280	100	0
	162	180	100	0
	165	280	100	0
	170	350	100	0

This proposal can be tested, viz that the essential relations of the posterior association cortex are centrifugal, or efferent. There is physiological evidence to suggest and support such a notion. In addition to an output to the superior colliculus (mentioned above), a large system of connections leads from the inferotemporal cortex to the ventral part of the putamen, a basal ganglion usually considered motor in function. How would an efferent mechanism of this sort work? To find out we performed the following experiment.

Instead of making ablations or implanting an epileptogenic lesion, we now chronically and continuously stimulate the brain. Dr. N. Spinelli in my laboratory designed the stimulator (Figure 7-14) and the recording equipment. The stimulator is sufficiently small so that it can be implanted under the scalp. It puts out a square-wave bidirectional pulse, 1 msec, in duration and about 3 v in amplitude. The frequency of stimulation is approximately 8 to 10 pulses/second. The batteries that drive the stimulator are rechargeable.

Figure 7-14.
Stimulator and batteries for chronic brain stimulation. Batteries are rechargeable nickel-cadmium and are available in different sizes from the manufacturer.

Records were made in the awake monkey (Figure 7-15). Paired flashes

are presented and recordings are made from electrodes implanted in the occipital cortex. The response to fifty such paired flashes are accumulated on a computer for average transients. The flash-flash interval is varied from twenty-five to two hundred msec. All are records from striate (visual) cortex. The top traces were recorded prior to the onset of stimulation and the lower ones after stimulation of the inferotemporal region had begun. Note that with cortical stimulation the recovery function is depressed, that is, recovery is delayed.

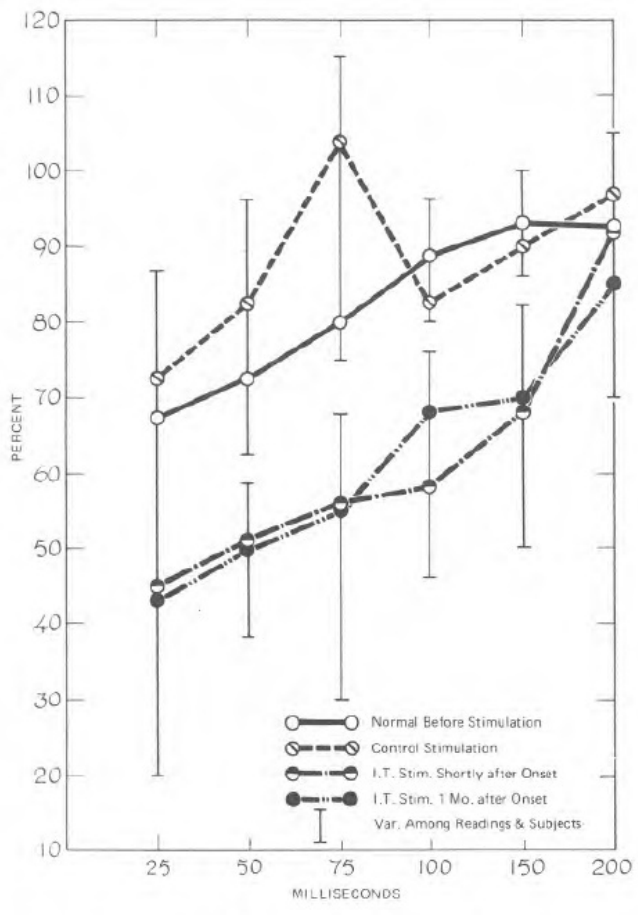

Figure 7-15.
A plot of the recovery functions obtained in five monkeys before and during chronic cortical stimulation: relative amplitude of the second response as a function of inter-flash interval.

Figure 7-16 shows the average of such effects in five subjects. Chronic stimulation of the inferotemporal cortex produces a marked increase in the

processing time taken by cells in the visual system.

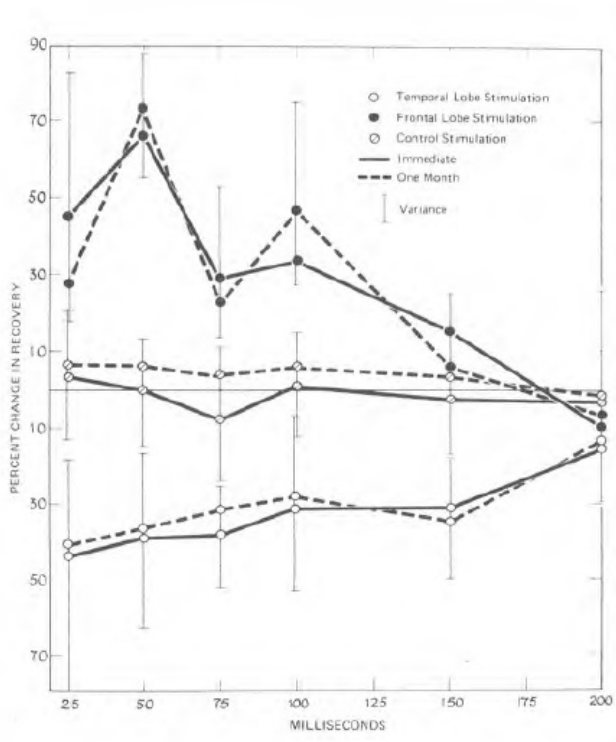

Figure 7-16.
This figure plots the percent change in recovery for all subjects in the various experiments. It is thus a summary statement of the findings.

A parallel experiment in the auditory system was done in collaboration with Dr. James Dewson. In this study, made with cats, removals of the auditory homologue of the inferotemporal cortex were performed. This homologue is the insular-temporal region of the cat. Dewson had shown that

its removal impairs complex auditory discrimination (speech sounds), leaving simple auditory discriminations (pitch and loudness) intact. Removal, in addition, alters paired-click recovery cycles recorded as far peripherally as the cochlear nucleus. Bilateral ablation shortens the recovery cycle markedly. Of course, control ablations of the primary auditory projection cortex and elsewhere have no such effect. Thus, we have evidence that chronic stimulation of the intrinsic (association) cortex selectively prolongs, while ablation selectively shortens, the recovery time of cells in the related primary sensory projection system.

These results have been extended in both the auditory and visual modes. Electrode studies have shown alterations of visual receptive fields recorded from units at the optic nerve, geniculate and cortical levels of the visual projection system produced by electrical stimulation of the inferotemporal cortex. The anatomy of the corticofugal pathways of these controls over sensory input also is under study. In the auditory system the fibers lead to the inferior colliculus and from there (in part via the superior olive) to the cochlear nucleus. Definitive results as yet have not been achieved in our studies of the visual pathways, but preliminary indications lead to the puta-men, as already noted, and to the pretectal-collicular region as the site of interaction between the corticofugal control mechanism and the visual input system.

The contextual amnesias only recently have become subject to neurophysiological analysis. Again, as in the case of the specific amnesias, corticofugal efferent control mechanisms have been demonstrated. Results obtained in my laboratory show that in many instances these controls are the reciprocals of those involved in the sensory-mode specific processes. Others *(Brain Res.1)* have shown that the most likely pathways of operation of the frontolimbic mechanisms involve the brainstem reticular formation. Here, however, as in the case of the specific amnesias, control can be exerted as far peripherally as the primary sensory neuron.

In general terms, the model derived from these experiments states that the operation of efferents from sensory-specific posterior intrinsic (association) systems tends to reduce and from the frontolimbic systems to enhance redundancy in the input channels, that is, the extrinsic (primary projection) systems. This presumably is accomplished by inhibition and disinhibition of the ongoing interneuronal regulatory processes within the afferent channels, both those by which neurons regulate the activities of their neighbors and those which decrease a neuron's own activity.

The Distribution of Information in the Brain

As noted, this is not the first time in the history of experimental brain research that data have led investigators of complex mnestic disorders to

focus on the primary projection systems. Munk, von Monakov, and Lashley pursued this course from an early emphasis on the "association" to a later recognition of the importance of the organization of the input systems. Of special interest in this pursuit are the experiments of Lashley that demonstrated that pattern vision remains intact after extensive resection—up to 85 percent—of the optic cortex. These results make it imperative to assume that input information becomes widely distributed within the visual system. Two types of mechanism have been proposed to account for such distribution.' Here I want to present evidence that it indeed does occur.

We trained monkeys to discriminate between a circle and a set of vertical stripes by pressing the right or left half of a plastic panel upon which the cues were briefly projected (for 0.01 msec.). Transient electrical responses were meanwhile recorded from small wire electrodes. The electrical responses were then related by computer analysis to the stimulus, response, and reinforcement contingency of the experiment. Thus we could distinguish from the record whether the monkey had looked at a circle or at the stripes, whether he had obtained a reward or made an error, and whether he was about to press the right or the left leaf of the panel. Interestingly enough, not all of these brain patterns were recorded from all of the electrode locations. From some input-related patterns were obtained best; from others the reinforcement-related patterns were derived; and still others gave us the patterns that were response-related. This was despite the fact that all

placements were within the primary visual system, which is characterized anatomically by being homotopic with the retina. It appears therefore not only that optic events are distributed widely over the system but that response and reinforcement-related events reliably reach the input systems. Such results surely further shake one's confidence in the ordinary view that input events must be transmitted to the "association" areas for associative learning to be effected.

The Mechanism of Remembering

The experimental findings detailed here allow one to specify a possible mechanism to account for the lesion-produced amnesias. On the basis of the neurobehavioral and neuro-anatomical data, I had suggested earlier that the posterior association cortex by way of efferent tracts leading to the brain stem (most likely to the colliculi or surrounding reticular formation) partitions the events that occur in the sensory-specific system and classifies these events. During the course of our joint work, Dr. Spinelli would repeatedly ask: "What do you mean by 'partitioning'? What is partitioning in neurological terms?" Until we had accomplished our electrophysiological experiments, I really had no idea just how to answer. But once we saw the results of these experiments, the neurophysiological explanation became evident: partitioning must work something like a multiplexing circuit. In neurophysiological terms, when the recovery time of neurons in the sensory-

projection system is increased by posterior intrinsic (association) cortex stimulation, fewer cells are available at any given moment to receive the concurrent input. Each of a successive series of inputs thus will find a different set of cells in the system available to excitation. There is a good deal of evidence that, in the visual system at least, plenty of reserve capacity—redundancy—exists so that information transmission is not, under ordinary circumstances, hampered by such "narrowing" of the channel. Ordinarily, a particular input excites a great number of fibers in the channel, ensuring replication of transmitted information. Just as lateral inhibition in the retina has the effect of reducing redundancy, so the operation of the sensory-specific posterior intrinsic (association) cortex increases the density of information within the input channel.

Conversely, the functions of the frontolimbic mechanism enhance redundancy, making more cells available at any given moment to concurrent input. This diminishes the density of information processed at any moment and enhances temporal resolution.

The model has several important implications. First, the nonrecovered cells, the ones that are still occupied by excitation initiated by prior inputs, will act as a context or short-term memory buffer against which the current input is matched. A match-mismatch operation of this sort is demanded by models of the process of recognition and selective attention spelled out on

other occasions.® These “occupied” cells thus form the matrix of “uncertainty” that shapes the pattern of potential information, that is, the “expectancy” that determines the selection of input signals that might or might not occur. The normal functions of the posterior cortex are assumed to increase the complexity of this context while those of the frontolimbic systems would simplify and thus allow readier registration and parsing.

Second, in a system of fixed size, reduction of redundancy increases the degree of correlation possible with the set of external inputs to the system, while enhancement of redundancy has the opposite effect. The number of alternatives or the complexity of the item to which an organism can attend is thereby controlled. This internal alteration in the functional structure of the classic sensory—projection system thus allows attention to vary as a function of the spatial and temporal resolution that excitations can achieve, with the result that events of greater or lesser complexity can be attended to. The sharper the spatial resolution, the greater the uncertainty and, thus, the more likely that any set of inputs will be sampled for information. Conversely, the greater the temporal resolution, the more likely that attention is focused and that events become grouped, memorable, and certain. In the extreme, the sharpening of the appetite for information becomes what the clinical neurologist calls stimulus-binding. Its opposite is agnosia, the inability to identify events because they fail to fit the oversimplified context of the moment.

Third, this corticofugal model of the functions of the intrinsic (association) systems relieves us of the problem of infinite regress-—an association area "homunculus" that synthesizes and abstracts from inputs, only to pass on these abstractions to a still higher homunculus, perhaps the one that makes decisions, etc. Former ways of looking at the input-output relationships of the brain invariably have come up against this problem (implicit or explicit) of little men inside little men.

According to the model presented here, there is no need for this type of infinite regress. The important functions of perception, decision, etc., are going on within the extrinsic (primary-sensory and motor-projection) systems. Other brain regions such as the posterior sensory-specific intrinsic ("associated") systems and the frontolimbic systems exert their effects by altering the functional organization of the primary systems. Thus these *associated* intrinsic systems are not association systems; they simply alter the configuration of input-output relationships processed by the projection systems. In computer language, the associated intrinsic systems function by supplying *subroutines* in a hierarchy of programs, subroutines contained within and not superimposed from above on the more fundamental processes. In this fashion the infinite higher order abstractive regress is avoided. One could argue that in its place a downward regress of sub- and subsub-subroutines is substituted. I would answer that this type of regress, through progressive differentiation, is the more understandable and

manipulable of the two.

A final advantage of the model is that the signal itself is not altered: the invariant properties of a signal are unaffected unless channel capacity is overreached. It is only the organization of the channel itself—the matrix within which the signal is transmitted—that is altered. Thus the same signal carries more or less information, depending on the width of the channel. I am here tempted to extrapolate and say that the signal carries different meanings, depending on the particular structure or organization of the redundancy of the channel.

Concretely, the intrinsic (association) cortex is conceived to program, or to structure, an input channel. This is tantamount to saying that the input must be coded by the operation of this cortex. In its more fundamental aspects, computer programming is in large part a coding operation: The change from direct machine operation through assembler to one of the more manipulable computer languages involves a progression from the setting of binary switches to conceptualizing combinations of such switch settings in "octal" code and then assembling the numerical octals into alphabetized words and phrases and finally parceling and parsing of phrases into sentences, routines, and subroutines. In essence, these progressive coding operations minimize interference among like events by identifying and registering unique structures among the configurations of occurrence and

recurrence of the events.

The evidence presented here makes it not unlikely that one function of the posterior and frontolimbic formations of the forebrain is to code events occurring within the input systems. As already noted, the distribution of information (dismembering) implies an encoding process that can reduplicate events without recourse to widespread random neural connections. Regrouping the distributed events (remembering) also implies some sort of coding operation—one similar to that used in decoding binary switch settings into an octal format.

An impaired coding process therefore would be expected to produce grave memory disturbances. The question is thus raised whether lesion-produced amnesias, specific and contextual, primarily reflect malfunctions of the mechanism of coding and not the destruction of localized engrams. (See Pribram.)

Conclusion

Conceptions concerning neocortical mechanisms in cognitive behavior have been reevaluated in terms of recently accumulated data. Since the designation neocortex has become ambiguous, isocortex is substituted; relations to cognitive processes are inferred from discriminative and problem-solving behavior.

Isocortex has been classified according to the input it receives from the thalamus. When a sector of isocortex receives fibers from a thalamic "relay" nucleus that, in turn, receives its major afferents from outside the thalamus, the sector is called extrinsic. When a sector of isocortex receives fibers from a thalamic nucleus that receives no such extrathalamic afferents, that cortex is classified as intrinsic.

Neurally distinct portions of the *extrinsic* (primary projection) isocortex are known to serve distinct classes of behavior. The distinctions are in part related to differences in input from different peripheral receptor mechanisms (e.g., sense organs). Other distinctions such as between motor and sensory cortex *cannot* be attributed to such gross anatomical differences (e.g., that only afferents reach sensory and efferents leave motor cortex). Rather, differences in detail of the organization of the overlapping input to and output from *each* of the extrinsic (primary projection) sectors must be investigated.

Intrinsic (association) isocortex can also be divided according to demonstrated relationships to one or another class of behavior. Discriminative behavior (response to invariants) in specific modalities is affected when particular subdivisions of the posterior intrinsic cortex are removed. When the anterior intrinsic (frontolimbic) cortex is ablated, those discriminations are affected which are based primarily on recurring variable events which are not contemporaneous with the choice, irrespective of

modality.

In several instances, intrinsic (association) and extrinsic (primary projection) systems are related to the *same* class of behavior. In these instances, the organism is limited in the possible complexity of cognitive behavior when the intrinsic cortex is resected—a limitation that is, however, not as severe as that resulting from extensive damage to the extrinsic system nor as that resulting from gross interference with receptor mechanisms. The hierarchical relationship described by these data has, heretofore, been attributed to specific afferents originating in subdivisions of extrinsic, and connecting to subdivisions of intrinsic, isocortex. Experiments have been quoted that make it unlikely that such *specific afferents* exist. Instead, the specificity of function of subdivisions of the intrinsic (association) isocortex is, in this analysis, attributed to *convergence* on a common subcortical mechanism of *efferents* from hierarchically related intrinsic (association) and extrinsic (primary projection) systems. The output from the intrinsic systems has been shown to influence, via regulation of the peripheral sensory mechanism, the input to the extrinsic systems.

Thus, experimentally produced local brain damage does demonstrably impair memory function. However, the impairment apparently is not so much a removal of localized engrams as an interference with the mechanisms that code neural events so as to allow facile storage and retrieval. The evidence

shows that anatomically the memory trace is distributed within a neural system by means of an encoding process, while as a function of decoding the engram is reassembled, that is, re-membered. What and whether something is remembered is in large part dependent on how it is—and that it is—adequately coded.

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