DISCONNEXION SYNDROMES IN ANIMALS AND MAN[1]

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PART I

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INTRODUCTION

THE early successes of the views of Broca and Wernicke led the classical neurologists to a mode of analysis of the disturbances of the higher neurological functions subsequently to be labelled with the derisive term "diagram-making." Starting from the picture of the brain as a collection of sets of more or less specialized groups of cells connected by relatively discrete fibre pathways, these classical neurologists deduced a series of symptom complexes. On the basis of this model clinical syndromes could be divided into those resulting from lesions of grey matter and those which resulted from lesions of the white matter interconnecting specialized regions. Thus, cortical syndromes were distinguished from "conduction" syndromes. Basically it was this mode of analysis which dominated the literature until the First World War.

An interest in the connexions between different parts of the speech region and between the speech region and the remainder of the brain dated back to almost the earliest of the classical writings. Wernicke (1874) had already predicted the existence of a particular aphasic syndrome resulting from disconnexion of the sensory speech zone from the motor speech area by a single lesion in the left hemisphere. Subsequent developments showed him correct in principle although probably at least partially incorrect in his assumption as to the location of the pathway between these regions. These earliest studies concentrated on lesions of white matter separating regions within a single hemisphere. Dejerine (1892) in describing the pathology of pure alexia without agraphia probably was the first to show definite clinical symptomatology as the result of a lesion of the corpus callosum. Hugo Liepmann carried the analysis of syndromes resulting from the disconnexion of specialized regions of grey matter to its most important development. He published the first post-mortem of a case of pure word-deafness from a unilateral lesion (Liepmann, 1898; Liepmann and Storch, 1902) consistent with if not fully establishing the hypothesis that this syndrome resulted from isolation of the speech area from auditory inputs into both the left and right hemispheres. He described the famous case of the Regierungsrat (Liepmann, 1900) in which he carefully analysed this patient's behaviour and explained it on the basis of a series of disconnexions. In this paper he predicted the sites of the lesions. The post-mortem findings (Liepmann, 1906) amply confirmed these published ante-mortem predictions. One year later he published with Maas the famous case, Ochs (Liepmann and Maas, 1907), which showed the effects of callosal disconnexion on motor function.

In the immediately following years Liepmann's results were repeatedly confirmed by such workers as Kurt Goldstein (1908), Bonhoeffer (1914) and a host of other authors. As Liepmann (1914) himself pointed out, those who were apparently his severest critics, such as von Monakow, had indeed fundamentally accepted his point of view; in fact, no really

important criticism was ever directed against his analysis. Goldstein's (1927) monograph on cortical localization showed his continuing acceptance of much of Liepmann's approach.[1]

That Liepmann's analysis of apraxia from the point of view of disconnexions continued to be part of the accepted doctrine of German neurology is evidenced by the article of Lange (1936) in the Bumke-Foerster Handbuch. By contrast, English-speaking neurology showed relatively little interest in this approach. Wilson (1908) summarized Liepmann's classical papers on apraxia accurately, but there was no rush of papers intimately describing cases similar to Liepmann's; Head's (1926) account of apraxia is cursory and, at least in part, incorrect.

On the whole the period between the wars seems to have led to a loss of interest in analyses in terms of disconnexion. The criticisms of the holistically oriented neurologists, Head, Marie, von Monakow, and Goldstein probably contributed heavily to this decline of interest. The growth of holistic psychology under the Gestalt school and Karl Lashley and the rapid development of holistic schools of psychiatry probably all played a role, perhaps more by their effects on the general atmosphere of thought than by their specific critiques of the classical school. The disappearance from the active scene of Dejerine and Liepmann removed two of the greatest contributors and defenders of the older school. When the papers by Akelaitis and his co-workers (Akelaitis, 1941*a*, 1941*b*, 1941*c*, 1942*a*, 1942*b*, 1943, 1944, 1945; Akelaitis *et al.*, 1942; Smith and Akelaitis, 1942) on the negative results of callosal section in epileptics appeared, most neurologists, at least in England and the United States, were prepared to reject for good the classical teaching on the importance of commissural and intra-hemispheric association pathways, a doctrine which had, after all, been losing ground for the previous twenty years. Only occasional papers such as those by Trescher and Ford (1937) and a later one by Maspes (1948) reasserted the importance of the corpus callosum but these were generally neglected.

The tide of interest in the callosum began to turn when Myers and Sperry (1953) showed that the callosally sectioned animal did show dramatic changes in behaviour if appropriately examined. Their work led

[1]It will perhaps strike the reader as curious that Goldstein should have embraced so classical an approach. I have discussed more fully elsewhere Goldstein's position in the history of aphasia (Geschwind, 1964*a*) but can only comment here that he was in fact much more of a localizationist than is generally appreciated. His theoretical writings with their criticisms of classical ideas contain so many qualifications that they are often compatible with even the most extreme localizationist views. The reader who goes carefully through the "Special Part" of Goldstein's 1927 monograph will repeatedly find in it an active defence of many classical ideas; indeed, many of Goldstein's disagreements with other authors are primarily on details of localization. His later book on language (Goldstein, 1948) continues to show his acceptance of many classical ideas, especially in his discussion of particular syndromes.

my colleagues and myself in 1961 to re-examine the older clinical literature and to reassess our patients with disturbances of the higher functions. We were gratified to find that within a few weeks we were able to find two patients whose symptomatology could be attributed to involvement of the corpus callosum. One of these patients showed the syndrome of pure alexia without agraphia (Geschwind, 1962; Howes, 1962). The second showed a much more extensive syndrome which my co-worker, Mrs. Edith Kaplan, and I attributed to an infarction of the corpus callosum. In late 1961 we presented our findings on this patient at the annual research meeting of the Veterans Administration and at a meeting of the Boston Society for Neurology and Psychiatry (Geschwind and Kaplan, 1962*a*). A more complete study of this patient was published later (Geschwind and Kaplan, 1962*b*) and we were able to point out in a last-minute footnote that the post-mortem findings had confirmed our ante-mortem prediction of a callosal infarction sparing the splenium. These cases have stimulated us to look further into our clinical material and to delve still further into the literature.

In the pages which follow I hope to give an account of the implications of thinking in terms of disconnexions for both clinical practice and research. The synthesis presented here was developed piecemeal out of study of the literature and clinical observation. I will not, however, present it in the order of its development but rather will try to organize the facts and theories along simple anatomical lines. There is, I believe, a unity in the theory which justifies this approach, and I hope that it will significantly contribute to clarification of the presentation. There are many facts recorded in the following pages; there is also much speculation which is, however, nearly all subject to the checks of future experiment and clinical observation.

While the material of this paper is fundamentally organized phylogenetically and in an order that is, hopefully, logical, I would like to stress that the individual sections may be considered separately as to the validity of the ideas contained in them.

Acknowledgments

It is customary to leave acknowledgments to the end of most papers. I feel, however, that the ideas presented here have been developed so much out of the stimulation of the work of others and out of so many hours of fruitful discussion with patient listeners that it is only appropriate to state my gratitude at this point.

I would like to thank first my colleagues of the Aphasia Research Section of the Boston Veterans Administration Hospital without whose clinical observations and close criticism this paper would not have been possible, in particular, Dr. Harold Goodglass and Mrs. Edith Kaplan. I

would like to express my thanks to two neurologists who grew up under the great German classical tradition, Dr. F. A. Quadfasel, formerly Chief of the Neurology Service of the Boston Veterans Administration Hospital, who (together with Dr. Samuel Tartakoff) first provided the author with the opportunity to study a large aphasic population and who constantly provided able criticism and the benefit of profound knowledge of classical writings on aphasia; Dr. Paul Jossmann, trained in Bonhoeffer's clinic, who provided the author with many invaluable German publications. I owe a special debt of gratitude to Dr. Paul Yakovlev who has read the many drafts of this paper. He has given many hours extending in many cases well beyond midnight to discussing with me the anatomical and broader philosophical aspects of this paper on the basis of his profound knowledge of human and comparative neuroanatomy. In addition, his suggestions as to the organization of this paper have been invaluable; the final arrangement of the material was, in fact, suggested by Dr. Yakovlev and the reader may well attribute much of whatever is lucid to this suggested reorganization.

I would like also to express my gratitude to those of my colleagues, too numerous to mention here, who have given me the benefit of their criticisms of the ideas expressed here; to Professor Oliver Zangwill who urged me to develop these ideas methodically in print; and to Professor Davis Howes who was the principal investigator of the research project under which this work was done and with whom I have had the privilege of working for several years.

I also owe a considerable debt to the work of others, which I hope is adequately expressed in the following pages. The remarkable set of papers by McCulloch, Bailey, Bonin and their many collaborators were indispensable in providing an anatomical basis for many of the ideas discussed here; the writings of Hugo Liepmann, a surprisingly neglected figure in the history of neurology, provided the outstanding clinical models for thinking in terms of disconnexion. The writings of Dr. Edwin Weinstein were a major influence in directing me to the importance of confabulatory responses.

Finally, I should like to express my appreciation for the opportunity of spending several hours with Professor Jerzy Konorski to whom goes the credit for having been the first to return in recent years to an analysis of aphasia from the point of view of intrahemispheric disconnexion; I hope we will soon have the opportunity to see an extensive presentation of his ideas in English.

I. Anatomical Background: Flechsig's Rule

The term "disconnexion syndrome" is applied to the effects of lesions of association pathways, either those which lie exclusively within a single

cerebral hemisphere or those which join the two halves of the brain. These syndromes are equivalent to the "transcortical" or "conduction" syndromes of older authors. It is appropriate to consider first the anatomical arrangements of such connecting pathways. Flechsig's principle (Flechsig, 1901; Bailey and Bonin, 1951) states that the primary receptive areas (the koniocortices) have no direct neocortical connexions except with immediately adjacent, "parasensory" areas, the "association areas" of common neurological usage. As Bailey and Bonin (1951) state this doctrine, "The primary sensory areas do not send messages very far into the surrounding cortex and receive cortical impulses almost exclusively from the parasensory areas; the parasensory areas, on the other hand, receive afferents from several other cortical areas and send their cortico-cortical efferents much farther away." As stated by Flechsig (1901), ". . . no long association system is known which connects two primordial zones that are to be regarded as sensory centres. . . ." (By the term "primordial zones" Flechsig meant regions of very early myelination.)

This doctrine applies not only to connexions within a single hemisphere but also to those between the hemispheres. Thus, the primary visual cortex has no callosal connexions (Myers, 1962*a*) nor does it have any long connexions to other parts of neocortex within the same hemisphere in the higher primates (Bailey, Bonin and McCulloch, 1950; Krieg, 1963). It has neocortical connexions only with the adjacent concentric association areas 18 and 19. Similarly, although the evidence is less clear, it is probable that the primary auditory and somesthetic cortices project only to immediately adjacent association areas. The limitation expressed in this rule applies only to neocortical connexions. The primordial sensory centres receive fibres from the thalamus and may in turn send long fibres to subcortical regions. The primary visual cortex has, according to some authors, direct connexions to the collicular region but not to neocortex. Crosby *et al.* (1962) express the opinion that even the connexions to the brain-stem in man come exclusively from area 18 while in the monkey these fibres arise from areas 17 and 18, whose borders are, however, harder to distinguish than they are in the human. The visual cortex can thus communicate with other areas of *neocortex* either in the same or the opposite hemisphere only by way of the concentric association cortex.

It is probable that the principle of Flechsig does not hold so strongly for subprimate forms. In the cat Curtis's experiments (Curtis, 1940) showed the presence of direct callosal connexions of the visual cortex while the same author showed their absence in the monkey. Similarly, Yakovlev and Locke (1961) have interpreted some of Cajal's findings in

the rabbit as meaning that there is a direct pathway from the visual cortex to the hippocampus in this animal.[1]

These data on the cat and rabbit suggest the general possibility that in subprimate forms association fibres may arise from primary projection areas. With increasing phylogenetic complexity these connexions would be transferred to the newly developed association areas. This would also suggest that the association areas do not appear *de novo* but are elaborations of parts of the projection cortex. It would be interesting to know whether particular elements of the primary sensory cortex migrate out to develop into more highly elaborated regions, and if so, which elements these might be. This possibility of the differentiation of association cortex out of projection zones is supported by the fact that in man the visual cortex is relatively more condensed than it is in the monkey and lower forms and also by the fact that in the monkey areas 17 and 18 are said by some authors to merge into each other indistinctly (Crosby *et al.*, 1962) while in man the border is sharp. It is not inconceivable that some of the more primitive connexions which directly join primordial zones may continue to persist in the higher forms but if so they are probably vestigial and functionally of minor importance. This gradual process of separation of association areas from primary projection areas is probably only the later stage of a process in which the primary motor and projection areas become individuated out of a less specialized brain. Thus, Lende (1963) has recently shown that in marsupials such as the opossum and wallaby, the primary motor and somesthetic areas overlap almost completely, a situation clearly different from the marked if not complete separation in the higher primates and man.

These anatomical facts imply that a large lesion of the association areas around a primary sensory area will act to disconnect it from other parts of the neocortex. Thus, a "disconnexion lesion" will be a large lesion either of association cortex or of the white matter leading from this association cortex. The specification of the association areas as way-stations between different parts of neocortex is certainly too narrow, but it is at least not incorrect. This view, as we shall see, simplifies considerably the analysis of effects of lesions of these regions. Since a primary sensory

[1]In the monkey there appears to be a bundle which is homologous to this structure in the rabbit and which perforates the splenium of the corpus callosum. There is, however, some question as to whether the bundle even in the rabbit does indeed rise in the visual cortex; for the monkey the site of origin of the corresponding tract is unknown, and it is certainly possible that it arises from retrosplenial cortex or from areas 18 or 19 on the medial surface. It is conceivable that this bundle may run directly from the visual cortex to the hippocampus in the rabbit while in higher forms these connexions must be made by way of association cortex. The analysis by Pribram and MacLean (1953) of the connexions of the mediobasal cortex of the monkey presents ample evidence for *indirect* pathways which could lead along the medial surface of the hemisphere from visual cortex to visual association cortex, hippocampal gyrus and hippocampus.

region has no callosal connexions, a lesion of association cortex may serve both to disconnect such an area from other regions in the same hemisphere and also to act in effect as a lesion of the callosal pathway from this primary sensory area.

Connexions of the Visual Association Areas

If the connexions of primordial projection areas are limited to adjacent concentric association areas, we find in turn that the connexions of the association areas are not distributed as widely as one might expect to the remainder of the neocortical mantle. Bonin and Bailey (1947) point out that in the macaque OB (equivalent roughly to area 18) projects most heavily to OB of the opposite side and to areas OA, FC (on the anterior convexity of the frontal lobe) and TE (lateral and basal temporal lobe) on the same side. Similarly, OB receives afferents from TE on the same side, from the opposite OB, and as we noted earlier from the primary visual cortex (OC). The preoccipital region (OA) has similarly restricted connexions, receiving fibres from OB, TE, and PG (posterior inferior parietal region), with a few fibres from PE (posterior superior parietal region). In a later review of the connexions of the macaque Bailey, Bonin and McCulloch (1950) record that OA projects essentially to the same regions as OB. The results for OA are probably less clear than for OB since its borders are more difficult to define by cytoarchitectural criteria.

Let us consider area OB for the moment since this can be regarded as clearly a visual association area. It has a very restricted afferent and efferent distribution, essentially receiving and sending fibres only to immediately adjacent regions of cortex and establishing major long cortical connexions with a limited number of regions. We may presume that the connexions to area FC relate to motor responses to visual stimulation which we will discuss more fully later on. What then of the only other long connexion of OB, the one to the lateral and basal temporal cortex? This connexion is of course by way of the classical inferior longitudinal fasciculus, a structure well recognized for many years although violent arguments about it went on at the turn of the century. Some authors doubted the existence of this pathway and assumed that all the fibres attributed to it actually were part of the geniculo-calcarine fasciculus. In the monkey it is probably the largest transcortical connexion of the visual association areas. The significance of this connexion of the visual association cortex becomes clearer when we look in turn at the connexions of area TE.

> Akert *et al.* (1961) found that when lateral and basal temporal neocortex (TE) and temporal polar neocortex (TG) were ablated in macaque monkeys, secondary degeneration appeared in the white matter of adjacent parts of the parietal, temporal, and occipital lobes; there was also degeneration of a large bundle going to posterior cingulate cortex and heavy degeneration in the uncinate fasciculus.

Degeneration was seen in the white matter entering the prepyriform cortex and the amygdala.

Since Akert *et al.* removed both TE and TG, it is important to separate the connexions of each of these regions in primates. Certain earlier studies cited by Akert *et al.* do make these distinctions. Studies on subprimate species probably cannot be considered for reasons already given. Bailey, Bonin, Garol, and McCulloch (1943*a*, 1943*b*) found that area 38 (temporal pole, equivalent to TG) when strychninized fired only locally. The pole did *receive* afferents from orbital frontal cortex. Petr, Holden and Jirout (1949) working in Bailey's laboratory were able to extend these fragmentary earlier observations by better technique. They now showed that temporal pole sent fibres to orbital cortex and also fired what they called "the anterior part of the fusiform gyrus (TH)" and the uncus (H). Other authors would probably name this region part of the hippocampal gyrus.[1] Pribram, Lennox, and Dunsmore (1950) found that strychninization of the temporal pole fired orbital cortex, anterior insula, amygdala and hippocampus. The first three regions are considered very well established connexions of the temporal pole. Segundo, Naquet and Arana (1955) using a variety of techniques confirmed connexions from temporal pole to amygdala and hippocampus, as well as hippocampal gyrus. It seems likely that we can accept these connexions of temporal pole as being well validated.

We may now turn to the connexions of lateral and basal temporal neocortex (area TE, comprising the middle and inferior temporal gyri). The strychninized middle temporal gyrus was found by Petr, Holden and Jirout to fire hippocampal gyrus but only weakly; the inferior temporal gyrus, however, produced significant firing in the hippocampal gyrus. Whitlock and Nauta (1956) found that a lesion of inferior temporal gyrus led to degeneration in basolateral amygdala and in the hippocampal gyrus. In addition, a large connexion was found from the middle and inferior temporal gyri to the dorsomedial nucleus of the thalamus. (Other connexions such as those to the basal ganglia were also found but will not be discussed here.) Poblete, Ruben and Walker (1959) found that after-discharges from TE spread readily to the homolateral amygdala and hippocampus in the macaque.

[1]Petr *et al.* use the term "fusiform gyrus" for areas TF and even TH in the macaque. Bonin and Bailey (1947) note the great similarities of TF and TH. Papez (1929) uses the term "fusiform-hippocampal gyrus" and "pyriform area" for these two regions. It is likely that the fusiform gyrus in the human sense is not present in the monkey and that these two areas are probably most reasonably considered as hippocampal gyrus (now called parahippocampal gyrus by some authors). Whitlock and Nauta (1956) in reporting the results of Petr *et al.* substitute the term "hippocampal gyrus" for "fusiform gyrus" and we will follow their usage.

Area TE thus projects to the hippocampal gyrus, basolateral amygdala and dorsomedial nucleus of thalamus. The hippocampal gyrus in turn is strongly connected to the hippocampus (Adey and Meyer, 1952). The amygdala has important hypothalamic connexions, as well as connexions to hippocampus via a multisynaptic route (Gloor, 1960) and a large projection to the dorsomedial nucleus of the thalamus (Nauta, 1962). The dorsomedial nucleus of the thalamus in turn has important hypothalamic connexions (Crosby *et al.*, 1962).

In none of these studies has there been any mention of connexions to the posterior cingulate region as mentioned by Akert *et al.* (1961) and Bucy and Klüver (1955). At present it would not be possible with assurance to assign this to the lesion of TG or to that of TE. It would appear likely that the temporal polar lesion is most likely the responsible one since the temporal pole may well make up part of the ring formed by the cingulate and hippocampal gyri and anterior insula (Kaada, 1960).

Let us summarize the conclusions from these studies. In order to understand better the reason for the large projection from the visual association cortex to area TE, consisting in the monkey of the middle and inferior temporal gyri, we have looked at the projections which in turn leave TE. The data support the notion that the connexions of TE are to limbic structures which in turn have important connexions with hippocampus and hypothalamus, i.e. with parts of the central core intimately involved in learning and in emotional responses. Thus TE (particularly the third temporal gyrus) projects (1) to hippocampal gyrus which in turn projects strongly to the hippocampus; (2) to amygdala which has important direct connexions to the hypothalamus and to the dorsomedial nucleus of the thalamus, and important indirect connexions to the hippocampus; and (3) directly to the dorsomedial nucleus of the thalamus which in turn has important hypothalamic connexions. Akert *et al.* (1961) in the conclusion of their paper on the effects of the removal of temporal neocortex in the macaque stated, "The significance of this study seems to lie in the further demonstration of close functional and anatomical relationship between rostral association cortex of the temporal lobe and the rhinencephalon." I would agree with this conclusion but with the important addition that this is true even if one confines one's attention to area TE alone without taking the temporal pole into consideration.

We have thus far described the pathway which proceeds from visual cortex to visual association areas 18 and 19, thence to lateral and basal temporal lobe and from there to limbic structures. Let us consider briefly the pathways in the reverse direction.

Votaw (1960) studied the degeneration which followed hippocampal lesions in the monkey; in addition to the expected changes in the fornix, he found "a definite and important hippocampotemporal

path, discharging from the hippocampus to the hippocampal gyrus and to other gyri of the temporal lobe. . . ." Votaw explains the functional significance of this projection by suggesting that "the hippocampus projects to the temporal lobe where it is known that motor responses of an extrapyramidal nature can be obtained. . . ." While not disagreeing with this interpretation, I will propose later that these connexions may be part of a pathway from hippocampus to visual association areas having functions other than, and perhaps in addition to, those suggested by Votaw. Gloor (1960) has reviewed the connexions of the amygdala very extensively. He notes that its cortical projection field is very limited in being restricted to hippocampal gyrus (pyriform area), temporal pole and insular cortex. The hippocampal gyrus in turn probably has connexions to temporal neocortex. It has important connexions with the hippocampus but probably via a polysynaptic route. He also finds no evidence for efferent cortical connexions of this structure beyond the confines of the temporal lobe. While the uncinate fasciculus is often mentioned as a connexion of the amygdala, it is likely that it actually connects basal and medial cortex of the temporal pole to the frontal orbital region. The amygdala receives an afferent connexion from dorsomedial thalamus although the connexion in this direction is not as large as that in the opposite sense (Nauta, 1962). The amygdala may thus act as a way-station from this part of the thalamus to the temporal lobe.

We may say in summary that although knowledge of projections *to* the temporal lobe *from* limbic structures is less complete than is our information about those projections going in the opposite direction, it appears that the hippocampal gyrus certainly receives afferents from limbic structures and that it may perhaps act as a relay from these structures to temporal neocortex. Further study of the connexions of the hippocampal gyrus may further elucidate this problem. We can probably regard portions of the temporal neocortex as perhaps representing association cortex for the limbic structures just as areas 18 and 19 represent visual association cortex. The concept that lateral and basal temporal neocortex and temporal pole are to be regarded as the association cortex of the limbic system is further strengthened by the fact that it is precisely these areas of the temporal lobe which utilize the anterior commissure rather than the callosum for their connexions to the opposite hemisphere. In fact Akert *et al.* (1961) summarize the regions ablated in their experiments as "noncallosal temporal cortex." They found no trace of callosal degeneration in their experiments. The fact that these parts of the temporal lobe utilize a commissure strongly associated with the limbic system is a further evidence of their close functional relationship to the limbic system and is at least compatible with the idea that they can be regarded as the association cortex of the limbic system. They are thus contrasted with the association

cortex concentric to the primary projection areas which makes use of the corpus callosum for connexions to the opposite side.

What is the significance of this two-way connexion from visual cortex to the limbic system? I will now present a theory of the functions of these pathways which I believe is supported by the published experimental investigations of animals with lesions in these connexions. The next section will, after a brief introduction, summarize some of these experiments and present a theoretical interpretation of the findings.

II. Agnosias in Animals

The study of lesions of the association cortex itself or of the connexions of this cortex leads naturally to a consideration of a group of disturbances in animals, at least in the primates, which may be reasonably described as *agnosias*; for the moment these may loosely be defined as disturbances of recognition in the presence of intact elementary sensation. As we shall see, the evidence is great that such disturbances do occur in animals; I will attempt to explain their mechanisms by reference to the anatomical arrangements of the association areas and their relations to limbic structures. In a later section I will discuss agnosias in man and will present the thesis that the mechanism for human agnosias is probably different from the mechanism of those seen in primates. Although the order of presentation of the data makes, I feel, evolutionary sense, I would like to stress again that the interpretation of the human syndromes can be considered independently of the animal material.

Removals of Temporal Neocortex: the Visual-limbic Disconnexion Syndrome

Klüver and Bucy (1938) showed that removal of the temporal lobe (neocortical and limbic structures) led to a characteristic syndrome which prominently included loss of the ability to make correct choices under visual control.[1] This disturbance occurs in the presence of many evidences of excellent retention of vision (Klüver and Bucy, 1938; Pribram, 1962), which led Klüver and Bucy to speak of the disturbance as a visual agnosia. Later investigators found that such disturbances in visual choice could be reproduced by lesions involving the temporal neocortex, in particular the middle and inferior temporal gyri, i.e. area TE. I will not cite here the many studies which have contributed to the clarification of this problem but would refer the reader to the paper by Chow (1961) where much of the relevant literature is reviewed by one of the major contributors to the investigation of this problem. The general conclusion of these studies has been that excisions of area TE bilaterally lead to a loss of previously acquired learning to choose one of two complex visual stimuli. These monkeys can relearn these tasks and can learn new visual

[1] I use this term advisedly rather than "loss of visual discriminations." The subsequent theoretical discussion will make the reason for this choice of words clear.

choices but usually more slowly than normals. Furthermore, these delimited temporal lesions do not produce defects in learning in other modalities, nor do cortical lesions elsewhere in the brain produce such disturbances with visual tasks.

Why should the lesion of TE produce such a disturbance? Looking at exactly how the monkey learns to make the choice will help to make the reason clear. In order to highlight the mechanism, I will first present a procedure that is slightly different from that generally employed. Assume the monkey to be presented visually with a cross and a circle. If he presses on either figure a small pellet comes out of a chute beneath that figure. The pellets are identical in external appearance. The one beneath the cross turns out, however, to consist of a food that is normally fed to monkeys, while the pellet released on pressing the circle is inedible, perhaps through admixture of some bitter component. We would find that the monkey will soon learn to press the cross and receive the edible pellet and to avoid pressing the circle which would lead to his receiving an inedible pellet. He must somehow learn to associate "cross" to "edible," "circle" to "inedible," i.e. to make a visual-gustatory or visual-olfactory association, or more generally a visual-rhinencephalic association (where "rhinencephalon" is used in the narrow sense). These olfactory or gustatory structures lie in the central core of the brain. I have suggested earlier that the pathway from the visual cortex to these rhinencephalic structures is via the lateral temporal neocortex whose destruction leads, therefore, to a disconnexion between the visual and rhinencephalic regions.

We may widen our view somewhat by noting that most of the stimuli which act as positive reinforcements in learning experiments, whether food, water or sexual objects, seem to depend on systems to which the structures of the medial temporal region have rich connexions. We may thus look at the lesion of lateral and basal temporal lobe as leading to a "disconnexion from reinforcement" without specifying the modality of the reinforcement.[1]

We can consider the data from still another point of view that is probably not fundamentally different but rather complementary. Konorski (1961) regards lesions of association areas as producing modality-specific deficits in recent memory, basing his conclusions on experiments performed

[1]These elementary results have an important bearing on the question of cross-modal associations. Recent studies, e.g. those of Ettlinger and different co-workers have clearly demonstrated difficulties of tactile-visual or visual-auditory transfers in monkeys (Burton and Ettlinger, 1960; Ettlinger, 1961). The conclusion should, however, not be drawn that monkeys form no cross-modal associations. It is abundantly clear, in fact, that the majority of classical learning experiments with most organisms do in fact demonstrate formation of cross-modal associations, as long as the modality to which the association is made is a "limbic" modality, i.e. a reinforcer, such as food, water, etc. I will return to the question of the difficulty of transfer between "non-limbic" modalities at a later point.

by himself and others. I will not comment on his interesting studies on frontal association cortex but will confine myself to his discussion of lesions of the visual and auditory association areas. His interpretation is that the projection areas and association areas form a reverberating circuit which is destroyed by lesions of the association areas. He ends his paper by briefly mentioning the effects of hippocampal lesions which produce defects of both auditory and visual recent memory in monkeys. He concludes "The physiological mechanism of these deficits (i.e. those resulting from hippocampal lesions) seems to us so far not clear and they require more detailed investigation."

I believe that the view which I have advanced above fills in the gap in Konorski's system by providing the nexus between the effects of lesions of association areas and lesions of the hippocampal region: the important fact is that the sensory association cortex projects to the medial temporal structures and receives projections from them. The hippocampal region thus probably communicates with all sensory modalities. The appropriate association area lesion may specifically disconnect the hippocampal region from a single modality and produce a recent memory defect in that modality alone. Konorski's theory of a reverberating circuit should therefore be amplified to include the hippocampal region.

I have not discussed here Dr. Konorski's interesting theory of the functions of the frontal association cortex. In later sections of this paper where the role of the motor cortex is discussed I will revert to the question of the functions of the association cortex lying immediately anterior to the classical motor cortex. The problem of frontal lobe associative functions is made more difficult by the fact that some portions of the human frontal lobe are extremely advanced phylogenetically and may represent new evolutionary developments. Comparisons may be difficult even between lower primates and carnivores. It is, of course, likely that the frontal lobe contains several association regions of differing function.

Dr. Konorski has stressed the role of the frontal lobe in inhibitory conditioned responses. It is possible that the orbital cortex with its extensive connexions to limbic structures via the uncinate fasciculus and the temporal pole may be exerting a predominantly inhibitory influence on limbic reactions. Egger and Flynn (1963) have shown that some portions of the amygdala (in cats) inhibit hypothalamic attack behaviour while others facilitate it. It would be interesting to study the cortical connexions of the inhibitory and facilitatory regions. It would be most interesting to see whether the inhibitory regions are receiving their main connexions from the orbital cortex via uncinate fasciculus and temporal pole. Other parts of the frontal lobe have important connexions to the cingulate gyrus as has been stressed by such workers as Showers (1959) and Nauta. The signi-

ficance of these connexions is still to be determined. The role of connexions to the hippocampal region from the frontal lobe in motor learning and particularly in inhibitory learning also deserves further study.

Certain other aspects of the syndrome produced by lateral and basal temporal neocortical ablations are worthy of comment here. At one time the view was common that the Klüver-Bucy syndrome was the effect of a mixture of independent temporal neocortical and rhinencephalic disturbances. I have already suggested that the visual learning disturbances are the result of disconnexion of the pathways between the visual cortex and the rhinencephalon. A bilateral lesion of the hippocampal region produces a learning deficit as Scoville and Milner (1957) showed in humans. Stepien, Cordeau and Rasmussen (1960) have shown that bilateral ablations of the uncus, amygdala, hippocampus and hippocampal gyrus in monkeys led to a recent memory deficit for both vision and audition. It seems reasonable to interpret the isolated visual recent memory deficit that many investigators have shown as a sequel to removals of area TE as the effect of destroying the connexions of a specific modality to these medial structures. Can other aspects of the Klüver-Bucy syndrome also appear in animals with neocortical ablations as a result of disconnexion of a single modality from limbic structures?

Most investigators have not recorded finding many of the other disturbances found by Klüver and Bucy. However, Akert, Gruesen, Woolsey and Meyer (1961) have found some of these disturbances in their monkeys with neocortical temporal ablations. These investigators removed temporal pole (TG) as well as lateral and basal temporal cortex so that the final interpretation of their results must await further study. It may be instructive, however, to look at their experiments from the point of view being expressed here.

The monkeys operated on by Akert *et al.* showed marked diminution in emotional responsiveness in certain situations. They showed a markedly diminished fear response to brooms, nets, hoses and toy snakes. It would seem reasonable to explain this by the fact the lesion had effectively cut much of the pathway between the visual cortex and the limbic system, so that arousal of limbic responses by visual stimuli no longer occurred. A piece of evidence that is in support of this idea is the observation of the authors that "The monkeys, throughout their post-operative career, reacted violently only to physical restraint; they would bite if held down firmly but would do so with substantially less vigour than the normal animals." It would thus appear possible that the tameness was most marked to visual stimuli; this would be in keeping with the idea that the lesion was effecting primarily a disconnexion between visual cortex and limbic system.

The possibility of the existence of modality-specific tameness or loss of fear is supported by the findings of Downer (1962). He destroyed the amygdala unilaterally in monkeys combining this operation with section of the optic chiasm, corpus callosum, and anterior commissure. These monkeys were tame in response to visual stimulation when it was confined to the amygdalectomized hemisphere but were normally aggressive in response to visual stimuli confined to the normal hemisphere. These animals, however, responded with aggressiveness to tactile stimulation of either hemisphere. Their tameness was therefore confined to visual stimulation of the amygdalectomized hemisphere. It should be added, parenthetically, that this experiment also confirmed other views that amygdalectomy generally leads to tameness (e.g. Pribram, 1961). We would assume that the tameness of the animals of Akert *et al.* to visual stimulation may have been due to disconnexion of complex visual stimuli from the amygdala. Whether all the changes in emotional responsiveness depended on this disconnexion or on disconnexion from other limbic structures remains a subject for further study.

Akert *et al.* observed no changes in sexual behaviour. Their monkeys, however, were juveniles. The possibility must be considered that in more mature monkeys with similar temporal neocortical lesions the pattern seen by Klüver and Bucy of indiscriminate mounting of other monkeys, regardless of sex, and even of inanimate objects, might occur. The hypothesis in this case would state that since the limbic system is disconnected from visual cortex, the monkey might not be able to use the visual system to control the patterned sexual activities which arise from limbic activity. One can think of this situation as one in which, as far as the limbic system is concerned, the monkey is blind and he selects possible sexual objects randomly as might a blind monkey who (for other reasons) cannot use his visual learning to guide appropriate sexual activity.

The monkeys of Akert *et al.* did not eat ground meat, unlike the Klüver-Bucy monkeys. One possibility is that this behaviour resulted not from visual-limbic disconnexion but was the result in Klüver and Bucy's experiments of direct damage to rhinencephalic connexions so that there was a diminution of olfactory or gustatory sensitivity. This problem deserves further investigation.

Klüver and Bucy pointed out that a normal monkey will place an inedible pellet in his mouth but rapidly learns not to pick it up; by contrast their temporal lobectomized monkeys would repeatedly pick up such pellets, place them in their mouths and then reject them. Although the description is not given in detail, it appears that the animals of Akert *et al.* showed this behaviour in attenuated form. The explanation for this phenomenon would also follow from the fact that the visual cortex is disconnected from the olfactory and gustatory cortex and that therefore the visual cortex can never "learn" that an object it sees is inedible.

The behaviour described as release of oral tendencies, i.e. the exaggerated tendency of the animal to take objects in his mouth is another feature that the animals of Akert *et al.* shared with Klüver and Bucy's animals. It appears possible that this also results from the failure to acquire visual-rhinencephalic associations. The animal now uses the retained pathway via oral sensation for ascertaining whether the objects are edible. This behaviour might therefore be analogous to the tendency of the blind to palpate objects and might free us from the need of assuming a regression to an "oral" stage of behaviour.

I have dwelt at some length on these experiments on neocortical temporal lesions and their interpretation since I feel they illustrate the principles underlying the anatomical organization of the association areas in sub-human primates. It will be useful to discuss here some aspects of this problem and then go on to some possible objections to the theory,

The Effects of the Extent of the Lesion

I would like to lay stress first on the importance of the extent of the lesion. Thus Meyer (1958) points out that in the study by Akert *et al.* certain aspects of the Klüver-Bucy syndrome were seen which were not observed by Chow who had performed comparable but less extensive ablations of temporal neocortex. Meyer comments, "This (*sc.* difference in results) may be due to a difference in the size of the lesions for smaller ones characteristically are not sufficient." The importance of the size of the lesion is probably the same for all disconnecting lesions, i.e. for lesions of association cortex or of fibre connexions of association cortex. There is little evidence to suggest that very discrete lesions of association cortex or of highly delimited fibre pathways of limited extent have major behavioural effects. There is thus at least a definite quantitative difference between lesions of association areas and of primary projection areas, where even small lesions tend to produce definite effects. This may well be a qualitative difference and suggests a fundamental difference in organization.

The importance of size suggests that there is an important degree of equipotentiality in the association cortex and its connexions. Several experiments point to this conclusion. Thus, Ades and Raab (1949) point out that extensive destruction of the visual association cortex[1] in the macaque led to loss of a previously learned visual discrimination. But, if the operation was done in stages with practice between the serial ablations the task was retained. Similarly the task was relearned after bilateral

[1]The authors state that they ablated "areas 18 and 19," but it is possible from their diagram that part of the association cortex posterior to the lunate sulcus was preserved. Bonin and Bailey (1947) place OB behind the lunate sulcus and Crosby *et al.* (1962) show area 18 as behind the lunate sulcus. It is not unlikely that some of area 18 was spared in the Ades and Raab experiments.

simultaneous extirpation of these pre- and para-striate regions but lost again after an excision of the lateral and inferior temporal region which spared the temporal pole.

Another characteristic of these lesions which suggests equipotentiality is the sensitivity of the test procedures to complexity. Ades and Raab's monkeys who failed to learn a form-discrimination could learn a black-white discrimination. Similarly, as Meyer (1958) points out, in the experiments of Akert *et al.* monkeys who eventually were able to relearn form discriminations could not learn a more complex visual task involving the formation of discrimination learning sets. A related experimental result is that of Orbach and Fantz (1958) who found that overlearning before operation prevented loss of form-discrimination after ablations of the temporal neocortex.

The above experiments all seem to support the picture of the visual association cortex proper and area TE as forming an equipotential area with learning being diffusely represented. Overlearning leads to high redundancy and consequently little loss after partial ablation. Simple tasks can be learned after partial ablation but not more complex ones which require a greater expanse of cortex. The possibility is certainly raised that even in relation to simple tasks certain defects might be shown with appropriate testing, e.g. slowness in learning to reverse a discrimination, or the presence of marked interference effects (i.e. poorer retention of a task when similar tasks are interposed between testing sessions) which would appear to be reasonable consequences of cutting down the total amount of cortex involved. Riopelle and Churukian (1958) have, in fact, made a careful study of the problem of interference effects in monkeys including a group with extensive bilateral ablations of the lateral surfaces of the temporal lobes. While this group did very poorly in learning to make visual choices, they showed no evidence of such interference effects as I have postulated. I believe, however, that it might still be useful to press further the study of the relationship between extent of lesion and the magnitude of interference effects.

This very question of equipotentiality raises certain problems. We have implicitly assumed that the connexions from visual cortex via visual association areas to lateral-basal temporal neocortex and thence to limbic structures are exclusively devoted to visual-limbic associations. We have thus implicitly excluded the possibility that some components of this system are in fact not modality-specific and thus could make up part of the pathway from other primary sensory areas to rhinencephalic structures. Further experiments to be presented shortly in more detail point clearly to the fact that there is at least a gross separation of the pathways by modality. The possibility of significant overlap is not entirely excluded by these results but complete equipotentiality of all association systems can be rejected.

Non-limbic Associations

A second implication of the above discussion follows from the fact that the major connexions of the visual region feed eventually into limbic structures. It would appear therefore that non-rhinencephalic associations should not be of much importance in the monkey. Therefore, while visual-limbic associations are readily formed, bonds between vision and other modalities should be weak. This conclusion is compatible with many results particularly in conditioning theory on the weakness of sensory-sensory links and on the difficulty of chaining conditioned stimuli. Reinforcement cannot be too remote and reinforcement depends on rhinencephalic activity. As I have noted earlier, it is probably not correct to make the general statement that sub-human forms have difficulty in forming cross-modal associations since they, in fact, readily form associations to "limbic" modalities, such as, pain or olfactory-gustatory sensation; by contrast they perform poorly in establishing links exclusively between the non-limbic modalities (audition, vision, and somesthesis). Such purely "non-limbic" associations seem to be formed readily and stably only in man under certain conditions. Burton and Ettlinger (1960) suggest "that language may serve as a cross-modal bridge under these . . . conditions"; in other terms they are suggesting that "verbal mediation" is the means by which humans achieve cross-modal transfers. This theory, however, in my opinion, evades the fundamental point, to which we will return again, *that the development of speech itself depends on the ability readily to form stable intermodal associations*, particularly visual-auditory and tactile-auditory bonds. I have thus, as it were, inverted Burton and Ettlinger's statement: I would argue that because man can form certain intermodal associations, he can develop speech; once he has developed speech, he can succeed in turn in forming other intermodal associations.

Wilson and Wilson (1962) have pointed out that prior experience with 75 tactual object-choice situations facilitated visual-learning set acquisition when their test group of normal monkeys was presented subsequently with 75 different visual discriminations. However, as the authors themselves comment, "The present results do not throw any light upon the question of whether intermodality transfer of specific discriminations is possible. . . . However, the existence of general transfer of the kind here demonstrated must be borne in mind in planning experiments on specific transfer." I would agree with their view that these general effects may well depend on such factors as the elimination of error tendencies rather than on those factors involved in the transfer of information about a specific problem between modalities.

The problem of cross-modal learning deserves further study and the recent interest in this area is most welcome. It should be pointed out that experimental design is of vital importance here. Many experiments in the

literature are really tests of the ability of the animal to respond to multimodal stimuli and not necessarily of his ability to form intermodal associations. Thus, the ability to respond to both a sound and a light but not to a sound alone need not depend on visual-auditory connexions but might require only parallel visual-limbic and auditory-limbic associations. It would seem to me that the most reasonable type of experimental design in which cross-modal transfer was obligatory would be that using sensory preconditioning (Hilgard and Marquis, 1961). Here the animal is first exposed without reinforcement to, let us say, a visual stimulus followed by an auditory one. Later on he would receive reinforcement following the auditory stimulus presented alone. Finally, he would be presented with the visual stimulus alone. Appropriate response to the visual stimulus (proper controls having been instituted to rule out non-specific generalization) could then result only from the previous establishment of a visual-auditory bond.

Do the anatomical findings show no basis for cross-modal response? Unfortunately the exact anatomy of the interconnexions between association areas has hardly been worked out in detail. The experiments of Sugar, French, and Chusid (1948) provide some answer. They found (as we would expect from Flechsig's principle) no connexions between primary visual and primary auditory cortex. They found, however, connexions from auditory association cortex in the supratemporal plane to the anterior wall of the lunate sulcus (i.e. part of area 18) as well as some connexions to the exposed surface near this sulcus. Connexions in the reverse direction from visual association cortex to auditory association cortex are much less powerful. Sugar *et al.* state that their results confirm earlier results of Mettler's based on anatomical findings.

These results suggest that there is apparently some basis for auditory visual associations, and probably for much weaker associations in the reverse direction. The connexions present are probably not extensive (they are certainly far less massive than those from pre- and para-striate regions to the lateral and basal temporal lobe), but it certainly would be desirable to explore further their physiological significance. They probably constitute the basis for weak non-limbic intermodal associations. As I will point out in a later section, it is likely that cross-modal associations involving vision, audition, or somesthesis (in contrast to, let us say, the visual-limbic, tactile-limbic, and auditory-limbic associations of sub-human primates) become prominent only in man, and that it is probably associations involving the auditory system which are most significant in the development of language. As I shall also suggest later, there is some evidence for the existence of an extensive anatomical substrate which can subserve a much larger number of such associations in man than in sub-human primates.

"*Motor*" *Learning*

Another aspect deserving some comment here is that of the motor responses involved in learning. Thus, if the monkey reaches out and presses a cross under which there is a peanut it can be argued, as we have done, that he has learned a visual-gustatory association. But does not his motor response also suggest that he has learned a visual-motor connexion? I will discuss the problem of visual-motor learning in more detail in the section on the apraxias but some clarification appears reasonable here. In the first place many motor responses under visual control may not depend at all on connexions between visual and motor cortex. Thus, rage responses to visual stimulation probably depend on a pathway proceeding from visual cortex to visual association cortex, thence to lateral and basal temporal lobe and finally reaching the limbic system and here triggering off highly patterned behavioural sequences, mostly probably innate. Thus MacLean (1960) points out that Hess and Hunsperger obtained "full-blown angry behaviour" in the intact animal by stimulation of appropriate regions either in the hypothalamus or the central grey of the mid-brain. Other experimenters such as Bard had shown that highly patterned rage reactions were dependent on the intactness of connexions of the hypothalamus. It is thus not necessary to depend on connexions to motor cortex from visual cortex for such behaviours.

Furthermore, other motor reactions may also depend on pathways descending to the brain-stem from association areas. Large movements particularly will result from stimulation of supplementary motor areas projecting directly to brain-stem structures (Crosby *et al.*, 1962). It is true that even single limb movements are obtainable from these areas but these are usually much grosser than the delicate movements obtainable from the classical motor cortex. The important studies of Voneida (personal communication) strongly suggest that some visual-motor tasks are performed via pathways going from the cortex to the brain-stem.

It would seem quite likely that for either highly patterned emotional behaviour or for gross movements in response to, let us say, a visual stimulus, no connexions are needed from visual association areas to the frontal motor cortex. It would seem likely that involvement of motor cortex becomes necessary in relation to the learning of fine movements (e.g. finger movements particularly, precise reaching, or those movements of large muscles involving a very small number of motor units). Another possibility, suggested by the necessity of some parts of the frontal region for delayed-response learning, is that visual-frontal connexions might be brought into play when the motor response to a visual stimulus must be delayed. The recent work of Glickstein, Arora and Sperry (1963) is consistent with this view. In any case the term "visual-motor" may well correspond anatomically to a variety of different mechanisms, of which

only one or two involve cortico-cortical connexions. Presumably in man cortico-cortical connexions are more important in motor learning, a point to which I will return in the discussion of the apraxias. Even in man some responses to stimulation probably depend on pathways descending directly to the brain-stem, as I will point out in discussing the preservation of whole-body movements in some patients who show apraxic difficulties with individual limb or face movements.

In all cases of visual-motor learning except the one where the motor response is a "limbic" motor response, it is necessary to ask what the exact relationship is of the limbic structures to the learning. Thus, when a delayed motor response is carried out with a visual stimulus, are both visual-limbic and frontal-limbic connexions involved? Or can this learning take place with retention only of frontal-limbic connexions? As Riopelle and Churukian (1958) point out most experimenters have concluded that temporal lesions did not lead to difficulties in delayed response. More complex experiments could, however, be devised to study the question of whether multiple paths to limbic structures are involved in some types of learning.

Objections to the Theory

One objection that warrants brief consideration is the one that lesions of lateral and basal temporal neocortex lead to simple "perceptual" disturbances and that to treat them as "associative" or "memory" disturbances is incorrect. Many lines of evidence militate against this view. Thus, Klüver and Bucy (1938) point out that their animal (which, of course, had a temporal lobectomy, a procedure more extensive than the lateral and basal decortication which I have been discussing) promptly picked up fragments of white peppermint, some as small as a fraction of a millimetre from a black table or very small pieces of banana from a white background. Bucy and Klüver (1955) mentioned the expertness of their operated monkeys in catching cockroaches. As Pribram (1962) has indicated, these animals are capable of catching flying insects.

Some authors have concluded that infero-temporal lesions may have effects on visual acuity (Pasik, Pasik, Battersby and Bender, 1960). Animals with such lesions may show difficulty in discriminating small differences in size. It is, however, clear that animals with subtotal striate cortex lesions, which produce a much greater increase in the size discrimination threshold, have much less difficulty in discriminating painted patterns than do the infero-temporal monkeys (Wilson and Mishkin, 1959). These authors believe, however, that the striate lesion produces some deficit of learning and that the infero-temporal lesion produces some "sensory" deficit since the first group did show some impairment in painted pattern discrimination while the infero-temporal group did show some loss in visual acuity. I would feel, however, that the dissociation is

more complete than these authors are willing to concede. They themselves point out that the learning deficits of the striate lesion group may well be simply related to sensory deficit, particularly in colour vision. Secondly, the fact that the infero-temporal operates showed a more rapid diminution in performance on a size discrimination test as the difference in size between the test objects diminished does not prove that they had acuity defects. Any difficulty in learning is multiplied by increasing the difficulty of discrimination. A native English speaker who understands normally spoken English and French will almost certainly show a more rapid rate of decline in his comprehension of French as the rate of speech goes up than he will show in his comprehension of English. Viewed from the anatomical point of view a severe enough lesion of the striate cortex must eventually limit the information reaching the association cortex; a large enough lesion of association cortex may eventually limit accurate handling of what comes from the striate cortex. In this sense Wilson and Mishkin are correct in expecting some overlap of impairment. This view is, however, compatible with markedly different organizations of primary visual and associative cortex.

Negative Experiments

The most serious problem of all for the theory is posed by certain negative experiments. According to the view proposed here the outflow from the visual cortex is by way of the visual association areas to the lateral and basal temporal neocortex. This implies that lesions of the visual association areas 18 and 19 should themselves produce the same picture. Ades and Raab (1949) showed that monkeys lost a visual form discrimination after extirpation of the visual association areas but could later reacquire it. Chow (1961) has made a long and careful study of the visual association cortex. In his latest studies he found that in one monkey ablation of parastriate cortex (to which a pulvinar lesion was also added) led to loss of a visual choice learned pre-operatively although the animal reacquired the task in as few trials as before ablation; the second animal with the same lesion showed considerable savings in relearning this task. Both animals showed savings in relearning a choice of vertical versus horizontal striations (although the second animal showed more savings than the first). But these effects were less marked than those of removing temporal neocortex or of cross-hatching the temporal cortex.

These experiments raise two problems. Why are the effects of removing the para- and peri-striate regions not as profound as those of removing temporal neocortex and why in all the experiments we have cited is there so much ability to reacquire form discriminations? I suspect that the answer lies at least partly in incompleteness of lesions. Chow (1961) himself pointed out that he had never succeeded completely in removing the parastriate areas. This difficulty is increased by the fact that in the monkey the

borders of areas 17 and 18 are perhaps less clearly demarcated than they are in man (Crosby *et al.*, 1962). In addition there is particularly great difficulty in removing the association cortex on the medial surface. Ades and Raab (1949) specifically point out that "the medial and postero-ventral parts of areas 18 and 19 usually escaped serious invasion because of their inaccessibility." Their lesions also did not extend farther posteriorly than the posterior bank of the lunate sulcus and therefore some association cortex was almost certainly spared. Is there any way of ensuring complete removal of association cortex? It is possible that physiological criteria may be the most useful means of determining the appropriate extent of surgery. Thus, one could remove all that pre- and parastriate cortex which when strychninized gives responses in the lateral and basal temporal lobes.

There is yet another possibility to consider in the attempt to reconcile the general lack of marked results of pre-striate ablation with the known anatomical facts. Is it conceivable that certain connexions which are not active in the normal animal and hence do not respond to strychninization become active as the result of prestriate ablations? Is there, as it were, an unused reservoir of connexions proceeding directly from the striate cortex to the lateral temporal neocortex? This need not be merely a speculation but could be studied experimentally. After determining the pattern of response to strychninization of a normal macaque brain, one could perform pre-occipital removals and at a later date study the pattern of responses to strychninization to see if there is evidence of the opening up of previously unused pathways.

Could the important pathways from striate cortex to temporal lobe involve synapses in subcortical structures? Chow (1961) concludes from his own experiments (in which cross-hatching the temporal lobe led to effects similar to those of temporal ablations) that probably cortico-cortical connexions must be implicated and not connexions via the thalamus. Jasper, Ajmone-Marsan and Stoll (1952), however, found that after-discharges spread from the striate cortex to the pulvinar and superior colliculus (possibly by way of area 18) but not to parastriate cortex (area 19). Parastriate cortex itself also projected strongly to the thalamus. It would appear that the problem of the negative results of most studies on pre- and parastriate ablation deserves extensive further study both physiologically and anatomically.

Other Reward Systems

In the experiments I have so far cited the monkeys were rewarded with food. Since I have laid great stress on the interpretation of these disturbances as disconnexions between visual and rhinencephalic systems, the question must naturally arise as to whether the temporal neocortical lesions effectively disconnect the visual system from all reinforcements. I suspect that this is the case; there are, however, important reasons for

investigating this problem. Could learning in response to pain be preserved in animals who have undergone resection of lateral and basal temporal neocortex, despite the loss of learning in response to positive reinforcers? Furthermore, would such a discrepancy reflect only the greater effectiveness of pain as a reinforcer or might it reflect anatomical differences in the pathways involved?

Of even greater interest would be the use of less obviously "limbic" reinforcers. Thus, Butler (1953) has shown that monkeys will learn in order to have the opportunity to view briefly the environment outside the cage. He points out that this cannot be regarded as a "secondary" reinforcement since second-order conditioned responses extinguish rapidly, while the criteria of learning in these experiments remain stable over long periods of time. Does this type of learning also depend on connexions between the primary sensory areas and the limbic system mediated by way of the association areas? Or is this type of learning "self-reinforcing," in the sense that it does not need limbic connexions? The fact that animals with the Külver-Bucy syndrome still show a high degree of curiosity in examining objects visually suggests the possibility that this type of reinforcer might still be effective after removal of temporal neocortex. The possibility even exists that some of the recovery in animals with these ablations depends on the preservation of this variety of reinforcement. It is evident that the results of an investigation of this problem would be of importance.

Lesions of Somesthetic Association Areas

Blum (1951) demonstrated disturbances of somatosensory discriminative behaviour with lesions involving the parieto-temporo-preoccipital region. Pribram and Barry (1956) were able to demonstrate that monkeys with similar ablations (extended, however, to involve the medial surface of the superior parietal lobule) showed a decrement of retention of a somesthetic task, with no impairment in a visual task. More recently Ettlinger (1962) and Ettlinger and Kalsbeck (1962) have demonstrated the effects of unilateral posterior parietal ablations in monkeys. They found three effects of this procedure which I will attempt to interpret. These consisted of impairment in acquiring a tactile discrimination with the contralateral hand, a failure of transfer of learning from the ipsilateral to the contralateral hand, and a disturbance of visual reaching with the contralateral hand. I will try to show that the type of analysis given in detail for the visual system applies equally well to the somesthetic system.

It is important to specify the extent of the ablations in these animals. In one report Ettlinger and Kalsbeck (1961) describe the regions involved as "what used to be called areas 5 and 7." However, the lesions clearly extend beyond these regions and are more accurately described in the paper by Bates and Ettlinger (1960) as "superior parieto-occipital ablations." An even more complex description would be preferable since the

removals involved areas PE and PG posteriorly in the parietal lobe, area OA and the most posterior portion of the superior temporal gyrus (TA). Thus, in addition to areas 5 and 7, area 19 was extensively involved and perhaps part of area 22.

In these experiments Ettlinger and Kalsbeck rewarded the monkey with food if he made the correct choice in a shape-discrimination test. We may apply to this problem the same type of analysis used in the discussion of visual choice experiments. What is demanded of the animal is to make a somesthetic-rhinencephalic association, i.e. to associate a particular shape to the food reward. We must therefore concern ourselves with the pathways from the primary somesthetic cortex to the rhinencephalon.

We would not be able to exclude the existence of a pathway descending from the parietal lobe via the external capsule. Most of the evidence, however, is against this (Crosby *et al.*, 1962). Thus, we find that the external capsule carries fibres running to the basal ganglia from cortical motor areas other than the precentral gyrus. The only large group of cortico-cortical fibres in this system consists of connexions passing in an antero-posterior direction. We must therefore look for another path from the somesthetic cortex to the medial temporal region. Sugar, Amador and Gripponissiotis (1950) studied the connexions of PB (area 3 of Brodmann) forming the posterior wall of the central sulcus. They found that this area except for some weak connexions shares a common pattern of relationships with PC (area 1) which forms the exposed surface of the post-central gyrus. Both regions respond to peripheral sensory stimuli and receive afferents from the nucleus ventralis posterior of the thalamus. Neither area has significant callosal connexions. Both project most heavily to immediately post-jacent parietal regions PE and PG. Both send connexions anterior to the central sulcus, but these connexions, at least for PB, are weaker than those just mentioned to the posterior parietal region. These two regions therefore appear to have no significant long connexions either within or between the hemispheres and must therefore depend for their long connexions on adjacent regions of association cortex in the posterior parietal region.

According to Bonin and Bailey (1947), PE in turn projects to PC, PG, and FA. The posterior part of TE receives fibres from PG, the posterior inferior parietal region. It would thus appear that while there are no direct connexions from somesthetic association cortex to temporal lobe, there is an indirect pathway to temporal neocortex which travels around the posterior end of the Sylvian fissure. As we have noted earlier, there are connexions from temporal neocortex into the limbic structures lying along the medial surface of the temporal lobe. It would be most useful, however, to have a more detailed knowledge of the pathway from somesthetic cortex to these limbic structures and to see to what extent this is separable from the corresponding pathway of the visual system.

It would therefore be my speculation that the lesions in Ettlinger and Kalsbeck's experiments acted to disconnect the somesthetic cortex from the limbic system and thus led to much the same series of learning and retention difficulties as were caused by a similar disconnexion involving the visual system. The difficulty in making tactile choices may be regarded as resulting from failure to form tactile-gustatory associations; more broadly we can regard it as a disconnexion from reinforcement. In still other but essentially equivalent terms, we may, following Konorski (1961) speak of a recent memory defect specific to the tactile system; we would regard this as resulting from isolating somesthetic cortex alone from the hippocampal region.

The second finding of interest to us in these experiments is the failure of transfer of tactile learning between the hands. Ettlinger (1962) points out that unilateral posterior parietal ablations on either side prevent transfer of a tactile discrimination learned with the left hand to the right hand. The interpretation of this result follows from the same anatomical principles I have already discussed. As I have already pointed out in discussing the results of Sugar, Amador, and Griponissiotis (1950) there are few or no callosal fibres from either PB or PC in the macaque; Bailey, Bonin, and McCulloch (1950) found no callosal fibres from PC in the chimpanzee (they did not study PB). It is evident that callosal connexions of the somesthetic cortex must be by way of the somesthetic association cortex which was largely removed by Ettlinger and his colleagues in their experiments. The posterior parietal ablation is thus equivalent to a callosal ablation. This equivalence is based on the fact that the callosal fibres involved in transfer between the somesthetic association cortex of the two sides originate and terminate in the posterior parietal regions. It is highly likely that many of the effects of posterior parietal lesions in man depend similarly on the destruction of the origin and termination of callosal fibres. This will be discussed in a later section of the paper.

The third effect of unilateral posterior parietal ablations in Ettlinger and Kalsbeck's experiments was a disturbance of reaching with the contralateral hand. This disturbance was both visual and nonvisual. Nonvisual reaching was tested by having the monkey reach with one hand for a pellet held in the other restrained hand. This difficulty is readily explained on the basis that the posterior parietal ablation has destroyed the callosal connexions between the two somesthetic association areas. Hence it might be difficult for one hand to reach an object held in the other. This disturbance is comparable to the effects seen in the patient of Geschwind and Kaplan (1962*b*) to be discussed later in the paper who could not draw with one hand an object held in the other.

The disturbance of visual reaching is at first apparently susceptible to a similar explanation but certain difficulties arise which make it uncertain whether this explanation is in fact correct. There are at least two mechan-

isms by which we could conceive that visual reaching might take place. There are almost certainly no significant direct connexions from the visual to the motor cortex. Chusid, Sugar, and French (1948) have shown that there are important connexions in the macaque from the depths of the lunate sulcus (i.e. visual association area) to the arcuate sulcus (area 6), from which there are connexions to the motor cortex proper (Bonin and Bailey, 1947). This would thus constitute a pathway for carrying out motor activities under visual control. Alternatively there is a path from the visual cortex to brain-stem motor mechanisms. These subcortical motor connexions do not arise from the visual cortex proper but rather from the parieto-occipital junction; this region thereby becomes a supplementary motor area (Crosby *et al.*, 1962). The pathway may then descend to the pons and after relay in the pontine nuclei reach the cerebellar hemisphere of the opposite side (Jansen and Brodal, 1954). Whether the cortico-cortical and cortico-subcortical pathways are equivalent or whether one might not subserve more precise reaching remains to be determined. A large unilateral parieto-preoccipital lesion such as that produced by Ettlinger and his colleagues should destroy both these visual-motor pathways in the involved hemisphere. One might therefore expect that following such a unilateral ablation there should be a defect of reaching by the hand contralateral to the ablation in the visual field contralateral to the ablation. By contrast reaching by the hand ipsilateral to the ablation in the visual field ipsilateral to the ablation should be normal. Both these effects were seen in the animals of Ettlinger and his co-workers.

The problem becomes, however, more complex when we consider "crossed" reaching, e.g. reaching by the right hand in the left visual field. That this type of activity depends on callosal connexions is made likely by the experiments of Downer (1959), in which the callosum and chiasm had been sectioned. When one eye was covered in these animals, control of the hand ipsilateral to the uncovered eye was very poor while control of the contralateral hand was normal.[1] It appears not unlikely from Downer's descriptions that his monkey showed a defect of visual reaching such as Ettlinger *et al.* described. There appear to be two reasonably possible pathways for this transcallosal visual reaching. Let us assume for simplicity that what is required is reaching with the left hand in the right visual field. One pathway would go from the left visual cortex to the left visual association area; from there it would proceed to the region of the arcuate sulcus (i.e. "motor association area" or area 6) of the same side, then to the arcuate sulcus region of the opposite side and finally to the motor cortex of the opposite side. If this were the pathway the effect of a large parieto-preoccipital region should be to produce difficulties in visual reaching with

[1] Since the writing of this section it has been called to the author's attention that other experimenters have had results different from those of Downer. It will be important to ascertain the reasons for these discrepancies.

both hands in the *right* visual field but with neither hand in the left. This pathway may well be the correct one for visual reaching in man. The difficulty in reaching with either hand in one visual field is a sign of what some authors have called "visual disorientation" in a half-field (Brain, 1941; Ettlinger and Kalsbeck, 1962). In the experiments by Ettlinger and his colleagues the animal made errors in reaching with the contralateral hand in either visual field, which is not in accord with this anatomical route.

An alternative pathway for crossed movements would be one that proceeded from the visual cortex to the visual association areas of one side, then crossed the callosum to the opposite visual association area and then ran forward to the motor association region in the vicinity of the arcuate sulcus, and finally reached the motor cortex. The effects of a parieto-preoccipital lesion might depend on exactly where the callosal fibres crossed. If they crossed posterior to such a lesion then the animal would show (1) a defect of visual reaching on the contralateral side with the contralateral hand, since the lesion would effect a visuo-motor disconnexion in the operated hemisphere; (2) a defect of visual reaching with the contralateral hand in the field ipsilateral to the ablation. This pathway would proceed via the right visual association area to left visual association area and then forward via the posterior parietal region to the motor region; (3) visual reaching with the ipsilateral hand would be preserved in both visual fields.

This pattern of defect and preservation outlined under the headings 1–3 is in fact what Ettlinger and Kalsbeck found. This pathway is therefore a possible one.

There is of course one further and very likely possibility. This is that both of the pathways listed above are actually used in the intact animal in carrying out crossed reaching and that disruption of either will lead to difficulties in crossed reaching which may, however, not be permanent since restitution may occur via the spared pathway. More stable difficulties should follow disruption of both pathways.

In any event the views expressed here are susceptible of further experimental test. One simple test of the theory would involve extending the unilateral lesions produced by Ettlinger and Kalsbeck a short distance posterior to the lunate sulcus. This should probably lead to a disruption of the callosal pathway between the right and left area 18; the animal should then show normal reaching only with the hand ipsilateral to the ablation in the ipsilateral field.

A third alternative is to assume that visual reaching in one field in the *monkey* depends on a subcortical pathway from visual association cortex which projects bilaterally, thus excluding callosal participation. This would not, however, be consistent with Ettlinger and Kalsbeck's results.

It is very likely that in man certain effects of parietal lesions are based on visual-motor disconnexions, a view which in part goes back to Liepmann

(1900, 1906). We have mentioned this briefly above in regard to disturbances of visual reaching in man but will return to it more extensively in our discussion of the apraxias.

In summary I would hypothesize that posterior parietal ablations such as those described by Ettlinger produce a triple disconnexion (1) between somesthetic cortex and limbic structures, (2) between the somesthetic cortex on the two sides, (3) between visual and motor regions. Of these three mechanisms probably that listed under heading (3), i.e. the visuomotor disconnexion, presents the greatest difficulties of interpretation.

The Auditory System

I will not discuss the auditory system in detail. Its precise corticocortical connexions in primates are poorly known as a result of the poorly accessible location of the primary auditory cortex in the Sylvian fissure of these animals. As Bailey *et al.* (1950) point out, it was difficult, on the basis of their experiments, to separate the connexions of the primary auditory cortex (TC) from those of the para-auditory cortex TB in the chimpanzee since both of these lie on the supratemporal plane in the Sylvian fissure. The studies on the macaque suggested that TC fired TB, and TB fired TA (the posterior end of the superior temporal gyrus). In neither monkey nor chimpanzee did they find any callosal connexions between TA of one side and that of the other. We would expect if Flechsig's rule holds here that the callosal connexions which do in fact exist between the two auditory regions on the supratemporal plane would proceed from area TB on one side to the same area on the other side rather than between the two areas TC (the primary auditory cortex). This, however, remains to be precisely confirmed.

Stepien *et al.* (1960) removed the first and second temporal convolutions anterior to the primary auditory area bilaterally in African green monkeys. These monkeys failed on a task involving auditory recent memory. Their experiments are similar to those reported by Goldberg, Diamond, and Neff (as summarized by Ades, 1959) who showed that removal of the so-called insular and temporal cortex of a cat (i.e. the cortex ventral to the para-auditory areas AII and EP) led to loss of simple tone discrimination and tonal pattern discrimination with subsequent failure to reacquire tonal pattern discrimination. Stepien *et al.* point out that the lesions they produced in monkeys were probably homologous to those produced by Goldberg *et al.* in cats. It should be pointed out, however, that such homologies may not be precise. As I have pointed out earlier for the visual system, there is some suggestion that the distinction between primary receptive areas and association cortex is less sharp in animals lower on the phylogenetic scale. It is therefore possible that the auditory receptive area and association cortex are also more sharply distinguished in the primates

than they are in lower forms. Further research on the auditory system of primates should help to clarify these questions further. Important steps in overcoming the technical difficulties in this field were made by Pribram *et al.* (1954); further advances in knowledge may be expected to result from such improvements in technique.

In interpreting the effects of the removal of auditory association areas, Stepien *et al.* (1960) noted that removing the rhinencephalic portions of the temporal lobe led to recent memory defect in all modalities. They comment, "The mechanism whereby these rhinencephalic portions interact with neocortical functions . . . is unknown." They go on to quote from a recent paper by Jasper and Rasmussen: ". . . We may assume that separate projections of neocortical and rhinencephalic structures to common centrencephalic systems . . . are of critical importance. . . . On the other hand, rhinencephalic formations may act as an intermediate way station in the conduction of impulse patterns from neocortex to brain-stem or conversely for impulses arriving to the cortex from subcortical structures . . .". I would tend to stress the latter of these hypotheses and to state further that the association areas in turn act as way stations between primary receiving areas and rhinencephalic structures.

The Problem of Mirror Foci

The concept of disconnexion from the rhinencephalon may be useful in explaining certain aspects of the physiology of mirror foci. Morrell has speculated that the development of a mirror focus on the side opposite a primary epileptogenic lesion may represent a "learning" situation by the uninvolved side. He has shown (Morrell, 1960) that an area of cortex in the rabbit isolated from all connexions except the callosal ones can develop a *dependent* mirror focus but will not develop an independent epileptic focus. Morrell sees this result as showing the importance of subcortical connexions in the establishment of an independent focus. I would agree with Morrell that this result is highly suggestive that the establishment of an independent mirror focus may be a "learning" activity. While he stressed the importance of thalamic connexions, an alternative hypothesis is that the significant factor in his experiments was the isolation of the cortical slab from the hippocampal region, i.e. that he had produced a disconnexion from the limbic system. I have already stressed the importance of such disconnexions in animal learning. The hypothesis that the development of mirror foci at a particular site is a learning process dependent on the intactness of connexions from that site to limbic system leads to some interesting possibilities for research. The study of sites of development of secondary epileptic foci in higher animals may be a useful adjunct in tracing association systems.

It should be noted that theoretically there is no reason why independent secondary foci should not develop as readily within the same hemisphere

as the primary focus as within the opposite hemisphere. Furthermore mirror foci should be rare when commissural connexions are lacking, as is true of the classical receptive and motor areas.

Disconnexions from the Limbic System in Man

This paper has so far considered disturbances of the higher functions in animals and has placed emphasis on lesions disconnecting primary receptive centres from rhinencephalic structures. In a later section I will discuss disturbances of the higher functions in man and will present the thesis that those which have been observed generally do *not* depend on disconnexions from the rhinencephalon but on other mechanisms not extensively present in subhuman forms. The question at issue in this section is therefore a much more limited one: Do there exist in man disconnexions from the limbic system and if so, what are the manifestations of these lesions? There is certainly very little good evidence to aid in answering these questions and this section must be regarded as highly speculative.

It might be argued that syndromes of disconnexion from the limbic system homologous to those seen in monkeys have rarely, if ever, been seen clinically because the appropriate lesions are highly unlikely ones. I suspect, however, that an even more important reason is that the types of sensory-rhinencephalic linkages seen in subhuman primates are less common in man, their role being taken to a great extent by more indirect associations by way of the speech areas. This newer type of indirect association will be discussed in greater detail in the next section.

Lesions in man comparable to those in the lateral and basal temporal lobes in monkeys might thus not produce the same effects. For although the phylogenetically less advanced visual-limbic pathway was destroyed, there would still remain a pathway going from the visual association cortex (probably via the angular gyrus) to the temporal speech area, i.e. part of the auditory association cortex and from there proceeding to the limbic system. This type of indirect pathway might be present in a monkey but as I have already commented only in much attenuated form.

There are, however, some clinical conditions which arouse speculations as to whether they might not be the result of disconnexions of cortical regions from the limbic system. One of these is the syndrome first described by Schilder and Stengel and called by them "asymbolia for pain" (Rubins and Friedman, 1948). In this condition the patient correctly distinguishes sharp from dull but shows no response to pain or even to threatening gestures. Some of the patients explicitly denied feeling pain. On the other hand, it was quite characteristic of these patients to respond appropriately to verbal threats. Schilder and Stengel (1928) pointed out that their original case also showed an indifference to loud noises.

A striking feature of this condition is the fact that it tends to be strongly associated with lesions of the dominant parietal lobe. Schilder and Stengel (1931) brought post-mortem evidence that the supramarginal gyrus was the structure involved. The clinical picture of Rubins and Friedman's cases was strongly compatible with the diagnosis of left parietal disease (e.g. the various components of Gerstmann's syndrome were frequently present).

In order to put these data together—speculatively—let us further note the fact that some observers have suggested that the cortical end-stage of the pain pathway lies in the supramarginal gyrus. This would correspond with the second sensory area (*see* discussion by Sweet, 1959). Biemond (1956) found evidence for this localization in three cases. Let us assume now that a patient develops a lesion not of the secondary sensory area but of the connexions between it and the limbic system. It is conceivable that while the patient could still distinguish the qualities of the stimulus, he would have no emotional response to it. This distinction between pain as a sensation and the emotional response to pain has long figured in the literature of research on pain. Denny-Brown (1962) has stated this distinction well, ". . . for such patients (i.e. those with asymbolia for pain) that we have seen can feel pain and can discuss it, though it is not of any biological importance to them." What I am suggesting here is that there may be an anatomical basis for this distinction.

My speculation would be that the connexions from the secondary sensory area to the limbic system would go by way of insular cortex. The lesion causing pain asymboly would in fact spare the secondary sensory area but involve perhaps parietal operculum and insula, cutting off the connexions to the limbic system. Schilder and Stengel's first case showed impairment of response to unpleasantly loud noises. It is possible that the secondary auditory area near the secondary somatic area may similarly be part of the pathway from auditory system to limbic system which was also cut off by the lesion. These explanations would also be consistent with the fact that these patients may respond to verbally expressed threats which presumably can still reach the limbic system by connexions from the posterior speech area on the lateral surface of the temporal lobe.

This mechanism might be approached profitably via animal experimentation. Conceivably it might even have practical usefulness since a reasonably discrete lesion might be available for the patient with intractable pain. As Sweet (1959) points out, the syndrome of asymboly for pain is quite unlike the syndrome resulting from lobotomy in which the patient's physical reactions to pain are, if anything, increased and who verbally readily admits to pain. The effectiveness of lobotomy is probably based on some other mechanism, perhaps decreased attentiveness to a chronic pain. Conceivably pain asymboly could be achieved without the serious emotional and judgmental effects of many lobotomies.

The same mechanism might possibly play a role in the syndrome of congenital indifference to pain which bears a definite resemblance to asymboly for pain. Patients with this congenital disturbance also appear to show excellent appreciation of painful stimuli as sensations but demonstrate little emotional arousal by such stimuli. Furthermore these patients differ from normals in another striking way. Normals appear to learn readily that certain stimuli will lead to pain and consequently can learn to develop almost automatic avoidance movements to such stimuli (e.g. the rapid withdrawal movements made on touching an unexpectedly warm kitchen utensil). Patients with congenital indifference seem to fail to acquire these and consequently often suffer considerable tissue damage. It is not unreasonable to speculate that the combination of inadequate emotional response to painful stimuli and the inability to learn appropriate responses to such stimuli may both perhaps be the result of failure to form the normal connexions between the cortical regions involved in pain perception and the limbic system. Whether the congenital lesion would involve a bilateral failure of development of those regions involved in acquired asymboly for pain remains of course to be determined.

I would like to stress again the speculative character of this discussion and the evident problems it raises. Why should asymboly result from a *unilateral* parietal lesion? Why do the patients show a lack of response to *visual* threat? Even more basic objections might be raised against the above discussion. On the one hand, the thesis that the cortical representation for pain is in the secondary somatic area is certainly not conclusively proven. On the other hand, certain authors such as Weinstein, Kahn, and Slote (1955) have cast doubt on the occurrence of pain asymboly as a localizable phenomenon. Sweet (1959) appears to be sympathetic to their view. The arguments of these authors, however, while cogent, are not conclusive. The whole problem of asymboly and its possible anatomical substrates needs new evaluation.

Another possibility to consider is that disconnexion from the limbic system may play a role in certain situations in man in which there is denial of illness. It has often been observed by clinicians that there is a marked difference in the emotional reaction to their illness of patients with aphasias resulting from frontal lesions and of those with temporal lesions. The frontal group are typically depressed and acutely aware of their disabilities. The patients with temporal lesions are frequently euphoric, often behave as if they are unaware of their aphasia and may even actively deny any disability. One possibility to account for the behaviour of the temporal group is that the temporal lesion may in damaging Wernicke's area also lead frequently to the cutting off of connexions to the limbic system from this part of the temporal lobe. This lesion might therefore lead to a failure of the disability to arouse emotional responses. Another effect of such a disconnexion of the speech area from the limbic structures might be to

cause difficulties in verbal learning[1] and thus make rehabilitation more difficult. I would like to stress that the mechanism here speculatively raised as a cause of denial of illness is certainly not the only one. I will discuss other possible mechanisms of denial later. I leave unsettled the issue as to whether the syndrome discussed in this section or any other syndromes in man are the result of disconnexions from the limbic system.

III. Disconnexion Syndromes in Man

The Anatomical Basis of Language

Man was the first species in whom disconnexion syndromes were clearly delineated. The writings of Dejerine and Liepmann mentioned in the introduction constitute the great landmarks of the early period of this type of investigation. I have placed the human material later in this paper because I feel it makes more sense to study it from the point of view of the evolution of the nervous system. As I have pointed out earlier, many of the discussions presented in this section can, in fact, be considered independently of the evolutionary hypotheses; despite this fact, I believe that these hypotheses may aid in bringing order into the material and in stimulating the design of specific experiments.

The preceding parts of this paper have cited the evidence that in lower mammals, the primary projection areas of the cortex subserve certain functions which tend subsequently to be separated in the primates. In keeping with this relatively minor degree of separation of functions, only a few regions of differing cytoarchitectonic structure are distinguishable. As we ascend the phylogenetic scale, the associative activities become separated to a great extent from the receptive. Large association areas more clearly separable from primary projection areas appear, and cytoarchitectonic differentiations increase. In accordance with the principle of Flechsig (which is applicable to man and the other primates but not to subprimate forms), the primary projection areas now send their connexions primarily to the immediately adjacent association cortex (parakoniocortex); the long connexions (either within a hemisphere or between hemispheres) between different cortical regions take place predominantly between parts of the association cortex. To a great extent the most important connexions of the association cortex are with the neocortex of the temporal lobe (and perhaps also of the insula) which in turn feeds into limbic structures. In keeping with this, connexions involving linkages between any one sensory modality and the limbic system tend to be powerful (these connexions sub-

[1]Meyer and Yates (1955) showed that patients with left temporal lobe lesions are likely to have verbal recall difficulties. Milner (1962) has confirmed their findings, showing that left anterior temporal lobectomy has a more profound effect on verbal memory than similar right temporal lobectomies. It is quite likely that the reason for this is that left temporal lobectomy cuts off connexions between the posterior speech area and the limbic system and thus leads to verbal learning deficit.

serve emotional and autonomic responses to sensory stimuli, associations between one sensory modality and gustatory or olfactory stimuli, etc.) while other non-limbic sensory-sensory connexions tend to be weak. I have, in the first part of this paper, discussed in detail the effects of lesions separating the primary sensory modalities from the limbic structures in the primate.

The situation in man is not simply a slightly more complex version of the situation present in the higher primates but depends on the introduction of a new anatomical structure, the human inferior parietal lobule, which includes the angular and supramarginal gyri, to a rough approximation areas 39 and 40 of Brodmann. In keeping with the views of many anatomists Crosby *et al.* (1962) comment that these areas have not been recognized in the macaque. Critchley (1953), in his review of the anatomy of this region, says that even in the higher apes these areas are present only in rudimentary form. In keeping with the late evolutionary development of this region are certain other findings. The gyral structure of this area tends to be highly variable. In addition this area is one of the late myelinating regions or "terminal zones" as Flechsig termed them. In fact, this region was, in Flechsig's map, one of the last three to myelinate. DeCrinis (cited by Bonin and Bailey, 1961) showed that part of this region is one of the last cortical areas in which dendrites appear. Yakovlev (personal communication) has pointed out that this region matures cytoarchitectonically very late, often in late childhood. In addition, he has pointed out that preliminary studies suggest that this region receives very few thalamic afferents. In this respect it is similar to part of the frontal association area which is also largely athalamic; this part of the frontal lobe is also phylogenetically new, myelinates late and forms dendrites late. The afferent connexions of this new parietal association area may therefore be predominantly from other cortical regions. As an association area, this region is also different from the older association areas in not being essentially concentric with one of the primary projection centres.

The newness of this region is also reflected in another anatomical feature probably unique to the human brain. G. Elliot Smith (1907) studied distinctions of cortical architecture based on naked-eye appearances of the freshly cut brain. He found that his inferior parietal area A (roughly corresponding to the region I have been discussing here) was bounded above and below by thin distinctive bands of cortex. The lower is the so-called "visuo-auditory band." As Elliot Smith comments, "This attenuated band is all that is left of the extensive bond of union between these two areas which in the lower mammals have co-extensive borders: in man and to a less extent in the apes the great development of the inferior parietal area above it and the temporal areas below it have pushed these two parts asunder, leaving this narrow connecting bridge. In support of this hypothesis of the primitive nature of the band, I might call attention to the fact

(which Flechsig has clearly established) of its early medullation. . . ." The upper band is the "visuo-sensory band," another thin band of cortex running along the superior lip of the intraparietal sulcus. Flechsig had shown that this strand also undergoes early myelination. Elliot Smith comments, "It is the attenuated fragment of that extensive connexion between the visual and sensory areas of the brain which has remained after these areas have been pushed apart by the great expansion of the parietal areas. . . ." Cytoarchitectural studies such as those of von Economo and Koskinas have confirmed the existence in this band of cortex of structure different from that of the cortex above and below the band.

Some authors (e.g. Konorski recently) have interpreted certain clinical syndromes as disconnexions between visual and other sensory spheres resulting from lesions of these bands. I believe, in fact, that the primitive character of the bands and their small size make these interpretations unlikely; more probable is that the observed phenomena resulted from lesions of the adjacent portions of the inferior parietal lobule.

We thus have this extensive, evolutionarily advanced, parietal association area developing not in apposition to the primary projection areas for vision, somesthetic sensibility, and hearing but rather at the point of junction of these areas as Critchley (1953) has indicated. This region possibly being one of few thalamic connexions may well receive most of its afferents from the adjacent association areas; it is thus an association area of association areas. In more classical terms, it would be called a secondary association area. The probable significance of this anatomical location is heightened by reference to our earlier discussion of subhuman forms. In these it appears as if association areas feed into temporal neocortex relaying in turn to limbic and rhinencephalic structures. As I pointed out in the earlier discussion, cross-connexions between primary nonlimbic sensory modalities are weak in subhuman forms. In man, with the introduction of the angular gyrus region, intermodal associations become powerful. In a sense the parietal association area frees man to some extent from the limbic system. This independence is only relative since ultimately learning still depends, even in man, on intact connections with limbic structures. The well-known permanent severe disturbance of new learning resulting from bilateral lesions of the hippocampal region attests to this fact (Scoville and Milner, 1957).

The development of language is probably heavily dependent on the emergence of the parietal association area since at least in what is perhaps its simplest aspect (object naming) language depends on associations between other modalities and audition. Early language experience, at least, most likely depends heavily on the forming of somesthetic-auditory and visual-auditory associations, as well as auditory-auditory associations. Whether this great association area is as powerfully involved in mediating other cross-modal associations (e.g. visual-tactile) is not clear. Situations

which demand these other types of cross-modal association appear to be less important than those involving audition, probably because language depends on this latter type of association. Perhaps in the deaf person learning written language tactile-visual associations become important. Critchley (1953) comments that it is tempting to associate the growth of the postparietal region with the development of speech. I would think that the parietal region is involved in the development of speech because of its importance in enhancing cross-modal associations. As I have noted earlier, *it cannot be argued that the ability to form cross-modal associations depends on already having speech;* rather we must say that *the ability to acquire speech has as a prerequisite the ability to form cross-modal associations.* An important area of research which remains to be studied extensively is that of the course of acquisition of cross-modal learning in childhood before speech is fully developed.

The objection might be raised that in some congenitally deaf people language is learned entirely in the form of visual-visual associations. If we restate the principle stated above in somewhat more precise form it will be seen that this objection is readily met. *In sub-human forms the only readily established sensory-sensory associations are those between a non-limbic (i.e. visual, tactile or auditory) stimulus and a limbic stimulus. It is only in man that associations between two non-limbic stimuli are readily formed and it is this ability which underlies the learning of names of objects* (Geschwind, 1964*b*).

It is also not unlikely that the development of cerebral dominance is related to greater development of this new parietal association area. Bonin (1962) has discussed this problem and stressed the smallness of the differences between hemispheres. However, the results which he himself quotes as well as those cited by Connolly (1950) do, in fact, tend to support the view that the left hemisphere is the more developed, at least as far as fissural pattern is concerned, and it is quite possible that Bonin's assessment of the data is much too conservative. I would speculate that left cerebral dominance is based on (or indeed perhaps equivalent to) the ability of the left hemisphere more readily to make cross-modal associations, an ability perhaps based on greater development of the left posterior parietal region. A detailed discussion of dominance would, however, lead us too afar afield.

We will simply assume from here on that the left hemisphere is dominant for speech functions and that this dominance depends on enhanced activity of the left speech area. The most important part of this area is the middle and posterior portions of the superior temporal gyrus which are, of course, part of the auditory association area and form the classical Wernicke's area. Connexions from other sensory modalities, at least vision and somesthetic sensation, are assumed to come to this speech zone by way of the angular gyrus region. Connexions from the speech area to other

sensory parts of brain (i.e. connexions which subserve the arousing of tactile and visual associations by auditory stimuli in general and speech in particular) are presumed to go in the reverse direction by way of the angular gyrus region. An important area of research is suggested by these briefly stated assumptions: the detailed pattern of connexions between the angular gyrus and the specified regions of the superior temporal gyrus (roughly area 22 of Brodmann) deserves careful elucidation.

I would like to point out here that although the predominance of the human parietal association areas is generally admitted not all authors would give them as much prominence as I have. Thus Bonin and Bailey (1947) state, "We cannot agree . . . that the homologues of Brodmann's areas 39 and 40 in man exist in the macaque only as very small patches. . . ." These same authors, however (Bonin and Bailey, 1961), stress that the part of the brain which increases in man most strikingly is not the frontal lobe but "the parietal and temporal lobe in the widest meaning of that term, and it is here that we should look for the substrate of certain functions which are supposed to be characteristic of man." They quote with approval Weidenreich's statement that the growth of the brain in man affects primarily the parietal lobes and the posterior region of the inferior part of the temporal lobe. At any rate, if these authors deny the marked parietal predominance that I have stressed they at least admit a relative predominance of this region in man. The exact degree of the uniqueness of the inferior parietal region in man remains to be determined.

In the preceding paragraphs I have outlined some of the new elements that must be considered in evaluating disturbances of the higher functions in man. In animals I have stressed disconnexions from the limbic system. In man with the development of speech, Wernicke's area becomes of major importance. Disconnexion syndromes will result from lesions which cut off Wernicke's area from primary sensory areas. Some of these lesions will lie in the white matter of the hemispheres while others will involve the cortex of the angular gyrus which probably acts as a way station between the primary sensory modalities and the speech area. In addition lesions which cut off connexions from Wernicke's area to motor portions of the hemispheres will lead to profound effects on behaviour.

In the following sections I will specify in greater depth some of the clinical and anatomical evidence which supports the model I have sketched. I will first consider lesions which lead to modality-specific disturbances by isolating specific sensory projection regions from the speech area. The lesions producing these disconnecting effects may be either in white matter systems such as the corpus callosum or in the association cortex giving rise to these fibre tracts. This discussion of highly specific receptive aphasic disturbances will lead us into a discussion of a related group of impairments, the agnosias. Similarly, I will consider disconnexions of this posterior temporal speech area from the motor systems, which will lead

us into a discussion of the apraxias. Finally, I will consider disconnexions of the posterior speech area from the anterior (frontal) speech region.

Pure Word-blindness Without Agraphia

This condition must be regarded as of special importance since it is probably the first example of a callosal disconnexion syndrome for which clear anatomical evidence was forthcoming. I have discussed Dejerine's (1891, 1892) classic papers elsewhere in detail (Geschwind, 1962) and will only summarize here. Dejerine developed his analysis of word-blindness on the basis of the findings of two patients reported in consecutive years. The first patient (Dejerine, 1891) showed the clinical picture of pure alexia *with* agraphia in the absence of other significant aphasic disturbances. The second patient had by contrast the syndrome of pure alexia *without* agraphia. The information from the two cases combines to form a simple picture of the mechanisms of disturbances of reading. Before discussing pure word-blindness without agraphia, I will present first the findings in alexia with agraphia.

The first paper (Dejerine, 1891) described a 63-year-old man who developed the sudden onset of inability to read and write in the absence of other significant neurological disabilities except for a right hemianopia. At post mortem (eight months after the onset) the brain was entirely normal except for a lesion involving the inferior three-quarters of the angular gyrus and penetrating inwards to the occipital horn of the lateral ventricle. The inward extent of the lesion had, of course, involved the optic radiations. Dejerine concluded that the lesion had destroyed a "visual memory centre for words" with resultant loss of the ability to comprehend written language or to write. Within a year Berkhan and Serieux (cited by Dejerine, 1892) had published similar cases with similar localization.

The second paper (Dejerine, 1892), longer and more detailed than the first, describes a patient followed by Dejerine over a period of more than four years. This patient suffered from the acute loss of the ability to read letters, words or musical notation in association with a right hemianopia. He could copy words correctly but could not transcribe print into script; he could write correctly (in script) either spontaneously or to dictation but could not read what he had written a short time previously. Although he could not read "visually," he could "read" by tracing the outlines of letters with his hand and could recognize the letters formed by having the examiner move his hand passively through the air. Although he could not read, he was able to name even extremely complex objects such as pictures of scientific instruments in a catalogue. There was no evidence of any general intellectual disturbance since the patient continued during his illness to operate a highly successful business, to gamble at cards successfully, and to learn vocal and instrumental parts of operas by ear since he

could no longer read music. Ten days before death he suddenly developed an agraphia. At post-mortem the brain showed an infarct of the left occipital lobe and of the splenium of the corpus callosum. The occipital infarct was shrunken and yellow and adherent to the overlying meninges, all of which indicated a lesion of considerable age. By contrast the patient showed a fresh infarct of the left angular gyrus which must have led to the new symptomatology ten days before death.

Dejerine interpreted this case as a disconnexion of the visual cortex from the speech area. Since the left occipital cortex was destroyed, this patient could perceive words only in the left visual field, i.e. only in the right occipital cortex. It is, however, not possible to read with the right hemisphere alone since destruction of the left hemisphere produces an alexia as one part of a gross aphasic syndrome. The visual stimuli received in the right visual cortex must therefore be transmitted to some region of the left hemisphere. It would seem reasonable on the basis of the findings of the first case discussed to assume that the relevant region in the left hemisphere is in the angular gyrus. The extensive lesion of the white matter of the left occipital lobe and of the splenium of the corpus callosum, however, cut off the connexions between the right occipital lobe and the left angular gyrus. Dejerine therefore argued that pure word-blindness without agraphia resulted from disconnection of the intact right visual cortex from the left angular gyrus in a patient in whom the left visual cortex had been destroyed.

The preservation of the left angular gyrus explains several aspects of the syndrome of alexia without agraphia. Thus, the preserved ability to write suggested to Dejerine that the "visual word-centre" was intact. The ability to "read" tactilely clearly relies on the fact that the pathway to the angular gyrus via the somesthetic system is intact.

There is one further difference between pure alexia with agraphia and pure alexia without agraphia which supports the Dejerine interpretation of the former syndrome as the result of a lesion of a "memory centre" and of the latter as a disconnexion from this "memory centre." Dr. Davis Howes and I have had the opportunity to observe the spelling performance of a patient with pure alexia with agraphia. This patient had normal spontaneous speech. He was unable, however, to spell correctly even the simplest word. Similarly, although he understood complex spoken sentences, he could not understand even three- or four-letter words when they were spelled to him. By contrast the two patients with pure alexia without agraphia whom I have observed (one in collaboration with Dr. Howes and one with Dr. Michael Fusillo) have been able both to spell and to comprehend simple spelled words. The explanation of this phenomenon derives from the fact that spelling is learned only as part of learning to read and write. In order to comprehend a word spelled out loud, the listener must transform it into written form and then "read" it. Conversely, to spell orally one must transform the spoken word into its written form and then

"read" the letters one by one. One can state this argument more simply by noting that a loss of visual word-memory returns the patient to the state of being illiterate; lack of reading, writing, and spelling and incomprehension of spelled words are all components of this more primitive state.[1] The patient with pure alexia without agraphia preserves the ability to spell since he still preserves the "centre" which turns spoken into written language and also carries on the reverse operation.

Parenthetically it should be noted that this disturbance of spelling gives us a particularly useful clue as to the function of the part of the angular gyrus involved in "visual word memory." It is a region which turns written language into spoken language and vice versa. It is, in short, a region specifically designed for carrying on visual-auditory cross-modal associations in both directions and indeed for storing the memory of the "rules of translation" from written to spoken language. I will return to this point later on.

It should be pointed out that Dejerine's paper described only the gross findings in the brain of the patient with pure alexia without agraphia. Vialet (1893) published a year later the detailed description of the central nervous system which had been cut in whole brain sections.[2] The lesion described by Dejerine for pure alexia without agraphia was soon confirmed by other authors. Bastian (1898) only a few years after Dejerine's publication was able to cite several cases where the lesion had involved the left occipital cortex and the splenium of the corpus callosum.

Many facts can be marshalled to show the importance of the lesion of the splenium which acts to disconnect the right visual region from the angular gyrus. Foix and Hillemand (1925) pointed out that one patient who at post-mortem had an infarct of the left visual cortex without involvement of the splenium had had no alexia in life; another patient with an infarct of the left visual cortex and in addition destruction of the splenium had shown the syndrome of alexia without agraphia. As I have pointed out elsewhere (Geschwind, 1962), the lack of this syndrome after penetrating head trauma results from the fact that a missile is very unlikely to destroy the left visual cortex and the splenium of the corpus callosum. The study of Hécaen, Ajuriaguerra, and David (1952) showed that alexia invariably

[1]This mechanism for incomprehension of spelled words appears to Dr. Howes and myself to be more simply and more clearly based physiologically than the classical explanation, which simply invokes a new disturbance, "word-sound deafness," to account for incomprehension of spelled words. By any standard the term "word-sound deafness" is a poor one. "Letter-name deafness" would have been closer to being a correct description. "Inability to understand words spelled orally" is the best descriptive term.

[2]I am indebted to Sir Charles Symonds for having called Vialet's monograph to my attention. It was in fact his paper (Symonds, 1953) which alerted me to this interesting syndrome. I am also grateful to him for having read and criticized an earlier paper of mine on this topic.

occurred after left occipital lobectomy but was transient in all cases, clearing in a few months. The splenium, of course, was left intact so that there was a path from the right occipital cortex to the left angular gyrus. The case of Trescher and Ford (1937) and the cases of Maspes (1948) who had the splenium cut in the course of removal of a colloid cyst of the third ventricle all developed alexia in the left visual field. By contrast, the patient of Geschwind and Kaplan (1962*b*) in whom there was no alexia of the left visual field showed at post-mortem an intact splenium although the anterior four-fifths of the callosum was infarcted. The patient of Gazzaniga, Bogen and Sperry (1962) in whom the splenium was cut showed an alexia in the left visual field.

By contrast to the above results, Akelaitis (1941*b*, 1943, 1944) described six patients in whom the splenium had been cut and who showed no alexia in the left visual field. I will defer a critique of these discrepancies to a later section of the paper where all the Akelaitis results will be discussed.

A further anatomical point deserves discussion. The first is the exact path of the connexions between the right visual cortex and the angular gyrus. Since the visual cortex has no callosal fibres, this pathway must be by way of the association areas, i.e. the pathway goes from the right area 17 to the right-sided area 18 (Myers, 1962*a*) and from this it eventually crosses the callosum.

I can conceive of three possibilities for the course of this pathway: (1) The pathway proceeds from the right area 17 to the right visual association areas, from there to the right angular gyrus and finally across the corpus callosum to the left angular gyrus. (2) The pathway runs from the right area 17 to the right visual association areas, then crosses the callosum to the left visual association areas and finally runs forward to the left angular gyrus. (3) The third possibility is that both pathways are used. This possibility is the one that would appear most likely under the assumption that we are dealing with an equipotential system in which a part can take over some of the functions of the whole.

Possibility 2 is ruled out as the *exclusive* pathway by the fact that no permanent alexia results from left occipital lobectomies (Hécaen, Ajuriaguerra, and David, 1952). But that there is some participation of this pathway is made highly likely by the fact that the alexia from left occipital lobectomy does last for several months, too long for the effect to be due to post-operative œdema but long enough for pathway 1 to come to take over the role completely. There is probably some permanent effect of destroying pathway 2 since as Hécaen, Ajuriaguerra, and David (1952) point out, their patients with left occipital lobectomies disliked reading even after their ability to read had returned.

It is likely that pathway 1 also participates normally since patients with right parietal lesions may show a failure to read the left halves of words despite an intact left visual field (Kinsbourne and Warrington, 1962). The

localization of the lesions in this latter paper, however, is not certain and more studies will be needed. The conclusions are, however, in keeping with the clinical observations of others on alexias from right parietal lesions.[1] It would thus appear that both pathways are normally used, i.e. possibility 3 is the correct one.

If we refer back to our earlier discussion of the possible functions of the angular gyrus, we can speculate as to the mechanism of its function as a visual memory centre for words. The angular gyrus, as we have noted already, becomes a memory for written words by acting as an area for forming—and storing—cross-modal associations between vision and hearing. It seems likely that this store of cross-modal associations involves more than words. An analysis of what is lost and preserved in pure alexia without agraphia may help to clarify this point.

While the reading aloud and comprehension of written words is lost, the ability to name and recognize objects is preserved. We can expand a suggestion by Adolf Meyer (1905) to develop the explanation for this. Objects have rich associations in other modalities, e.g. we can recognize an apple by vision, touch, taste, smell, even by its texture on being bitten. The arousal of such associations permits the finding of an alternative pathway across an uninvolved more anterior portion of the corpus callosum. The reading of numbers is also frequently preserved in these cases—in Dejerine's case number reading was perfect. Other authors, e.g. Symonds (1953), have discussed this striking fact. The learning of numbers is also associated with heavy somesthetic reinforcement (counting on the fingers) which frequently persists for a long time in childhood because the child can use his own fingers for this purpose. By contrast, reading is learned, except in the very earliest stages, as a pure visual-auditory task.

A difficulty with colours is common in these cases. Dr. Michael Fusillo and I (Geschwind and Fusillo, 1964) have recently studied a case of pure word-blindness with persistent difficulty in colours. We were able to show that this was a pure difficulty in colour-*naming*. Thus the patient matched colours by hue without error despite large differences in brightness and saturation. He could without error identify the figures on two different pseudo-isochromatic tests of colour vision. It is obvious that a colour has no smell, taste, or feel—the only association unique to the colour is its name. The loss of colour-naming is thus another example of loss of visual-auditory associations. The loss of ability to read music, as in Dejerine's case, appears to be another example of loss of visual-auditory associations.

[1]It may be objected that the alexia in a half-field from a right parietal lesion is the result of "neglect" of that field. While I do not wish to discuss this problem extensively here, I would like to point out that what I am attempting to show is that one mechanism of "neglect" of a normal left visual field is disconnexion of the normal right occipital cortex from the speech area.

I would like to stress the fact that many combinations of lesions may lead to the same syndrome. I recently observed a patient who had suffered a cerebral vascular accident which seemed likely to have been in the left posterior parietal region. A year later he developed a *left* hemianopia and became alexic. I wondered whether his initial lesion had not destroyed the connexions between his *left* visual cortex and his left angular gyrus so that he was reading only with the right occipital cortex until this was destroyed by a subsequent infarct. Unfortunately a post-mortem was not obtained and the above must remain pure speculation. This case illustrates, however, that it is a serious error to reject a case with multiple lesions since some interesting syndromes may result in such situations which could not be the effect of any single lesion.

Another area of speculation is the applicability of these results to failures of acquisition of reading, so-called congenital dyslexia. One possibility is that this syndrome is due to delayed development of the angular gyrus region—probably bilaterally. The results cited earlier that the angular gyrus region typically matures late make it plausible that a significant group will not have achieved adequate development by the time of the usual age of learning to read. The tendency for this condition to disappear in many children with increasing age is compatible with the notion of slow maturation. The smaller proportion of girls showing this disturbance might be related to a more rapid maturation of the angular gyrus region in girls; this would be consistent with the more rapid attainment of most developmental milestones by girls. Study of an adequate number of anatomical specimens should make possible the verification or rejection of this developmental sex difference.

If the hypothesis of slow maturation is correct and if my views as to the possible functions of the angular gyrus region are correct, then certain predictions are possible. The child with congenital dyslexia should also show slower acquisition of colour-naming and music-reading. Reading of numbers should be more rapidly acquired. In fact, tests specifically designed to study cross-modal associations, particularly visual-auditory but also in the other modalities[1] might well be very rewarding. Birch (1962) has actually done preliminary studies on intersensory transfers in children and in particular in dyslexics. It will be most interesting to follow these pioneering studies.

It is probably necessary to study children as early as possible before language development has progressed very far and certainly before the

[1]In an illiterate society a lack of visual-auditory associations would not seriously inconvenience anyone except in unusual situations; literacy makes this ability highly important. Other cross-modal association deficits may exist but might never be detected because they cause so little disturbance. It is conceivable that direct visual-tactile associations may be as badly developed in many humans as they appear to be in monkeys (Ettlinger, 1960) but only specific testing will bring this out. It is important, of course, to study children as early as possible in the course of development.

learning of written language. I believe it would be possible to select a group in whom it could be predicted that the development of reading would be delayed on the basis of failures in learning other visual-auditory associations; it is conceivable that even the age of attainment of colour-naming might be a significant clue to the age at which reading can be acquired. Even casual observation among children shows a great variation in the age of acquisition of colour-naming among children in whom non-verbal testing shows colour-perception to be normal.

Pure Word-deafness

Pure word-deafness probably has a similar pathogenesis to that of pure word-blindness without agraphia. Liepmann (1898) in a very carefully studied patient in whom ordinary deafness was clearly excluded showed that this syndrome could be produced by a unilateral lesion. The pathology was described in fuller detail by Liepmann and Storch (1902). The lesion, located subcortically in the left temporal lobe, had destroyed the left auditory radiation as well as the callosal fibres from the opposite auditory region. The lesion therefore had the effect of preventing the speech area (i.e. that part of the auditory association cortex generally called Wernicke's area, which comprises the posterior portion of area 22 and occupies the posterior part of the superior temporal gyrus) from receiving auditory stimulation. The right primary auditory cortex could receive auditory stimuli but could not convey them to the speech area because the callosal connexions from the right side were destroyed in the left temporal lobe. This syndrome is rarer than pure word-blindness without agraphia for the obvious reason that a lesion which involves these structures usually extends into Wernicke's area and produces a more extensive aphasic picture. Some variation in the extent of the lesion causing pure word-blindness without agraphia would not lead to such obscuring symptoms.

The exact anatomy of the auditory cortex and of the callosal pathways between the two auditory regions is still uncertain in primates and man, in contrast to the more advanced state of knowledge of the anatomical arrangements in the cat (Ades, 1959). The primate data are less complete not only because of the smaller number of experiments but also because of the concealment of areas 41 and 42 in the supratemporal plane, i.e. within the depths of the Sylvian fissure. The crowding of structures in the supratemporal plane makes it particularly difficult to study the responses of TB (area 42) which is interspersed between the primary auditory cortex TC (area 41) and the rather extensive and on the whole readily accessible TA (area 22) on the lateral surface (occupying the first temporal gyrus in its middle and posterior regions). The cat data cannot be applied to the primate with confidence, not only because the anatomical homologies are not obvious but also because the danger would always exist that the distinction of primary receptive and association areas was more sharply

defined in the phylogenetically advanced primates. We have already remarked that such a discrepancy between primate and feline anatomy exists in the visual system; while the cat's visual cortex according to some authors gives rise to callosal fibres that of the primate does not (Curtis, 1940; McCulloch and Garol, 1941; Bailey, Bonin and McCulloch, 1950; Myers, 1962*a*; Krieg, 1963).

The difficulties resulting from anatomical crowding on the supratemporal plane are reflected in the studies on the macaque where a clear-cut correlation between electrical response and cytoarchitecture has not so far been possible. The chimpanzee would probably represent a more suitable subject for this study because of the larger size of the brain. Bailey, Bonin, Garol and McCulloch (1943*a*) found in both the monkey and chimpanzee that auditory stimuli caused a large response in area 41 (TC) followed by a small one in area 42 (TB). However, in a later publication on the chimpanzee Bailey, Bonin and McCulloch (1950) note, "It is impossible on the basis of our scanty data to separate surely the connexions of the auditory cortex (TC) from those of the para-auditory (TB). The efferent fibres seem to come mainly from the periphery, therefore, probably from TB." Sugar, French and Chusid (1948) studied the supratemporal plane in monkeys; they simply divided this region into five strips without regard to cytological differentiations between areas 41 and 42. They found the area of primary auditory response in the posterior third of the supratemporal plane. On strychninization this region fired the remainder of the supratemporal plane and also areas 22, 21 and 37; however, one cannot conclude with certainty that the primary auditory cortex itself fires these regions since the possibility must exist that the stimulated area may also have included part of area 42. These authors like McCulloch and Garol (1941) found a paucity of callosal fibres arising from area 22 or reaching area 22 from any part of the auditory system of the opposite side. Callosal fibres from one supratemporal plane to the other were plentiful but no distinction was made as to whether they arose from area 41 or 42. The data of Sugar and his co-workers suggest that there are more callosal fibres from the anterior portion of the supratemporal plane. This may correspond to the region in which Bailey *et al.* (1943*a*) saw small secondary responses and which they regarded as the anterior part of TB.

The suggestion that the main associative outflow of the auditory cortex is in the anterior part of the supratemporal plane receives some support in the work of Pribram, Rosner and Rosenblith (1954). They found in the macaque that the region of short-latency responses to click lay posteriorly in the supratemporal plane; there was an anterior strip in which responses of much longer latency were seen.

It would seem likely that these anterior regions are "secondary" areas which are fired by the primary areas.[1]

We have presented these data in some detail to emphasize the tenuous nature of our knowledge of auditory association areas in the primate, and, obviously, in man. We might summarize roughly by saying that there appears to be general agreement that the centre of the primary auditory cortex lies in the posterior part of the supratemporal plane. Area 22 on the lateral surface of the first temporal gyrus constitutes a large area of auditory association cortex but is probably not the source of the callosal fibres of the auditory system. Callosal fibres probably arise from the supratemporal plane somewhat anterior to the primary auditory cortex. However, more detailed physiological study is needed to confirm even this rough picture. In addition a more careful study of the correlation of the pattern of transmission of impulses with cytoarchitectural differentiations is badly needed.

Clinical data perhaps may aid us in thinking about this problem and in suggesting further experiments in primates. As we noted at the beginning of this section Liepmann (1898) first described pure word-deafness from a *unilateral lesion.* There are, however, many more cases recorded of this syndrome from *bilateral* lesions. In these cases the most common pattern has been that of bilateral often rather symmetrical cortico-subcortical lesions in the *anterior* Part of T_1, with Heschl's gyri intact. The subcortical penetration, particularly on the dominant side, is not very profound. These are the findings of Hoff (1961) but they generally coincide with those of other authors. Kurt Goldstein (1927) in his discussion of the localization of pure word-deafness places the lesion in the bilateral cases in the middle portion of T_1. I suspect that this is not a difference from Hoff's data since they were probably both emphasizing as the centre of the involved zone roughly the junction of the anterior and middle thirds of T_1. This zone is at the junction of area 42 with the anterior part of area 22. The precise mechanism of this lesion is not clear. One possibility is that the outflow from auditory cortex proper (area 41) goes to area 42, that the outflow path then continues from the region of junction of areas 42 and 22 posteriorly in area 22. The left-sided lesion would cut off the left auditory cortex from the left area 22; the right-sided lesion would cut off the origin of the callosal fibres (presumably coming from area 42) from the right auditory region. This interpretation would be in keeping with the findings in primates that area 22 gives rise itself to no callosal fibres. It would also be in keeping with our tentative

[1]These authors also found another group of parietal areas which responded to click with only slightly longer latency than the primary auditory region. They presented evidence that the response in these areas depended on collaterals from the medial geniculate body. These areas would not in my terms be "association" areas. I will not discuss their possible function here.

summary of the experimental data which suggests that the major outflow from the primary auditory cortex is to a region anterior to itself. The correspondence between the two sets of data is at best rough but is close enough to suggest that further research may clarify this problem.

I will close this section with the consideration of a hypothetical problem. Could one develop pure word-deafness in one ear? The extent of duplication in the auditory pathways would almost ensure that the lesions necessary to produce this in a patient could hardly occur as the result of natural causes. With more detailed knowledge of the anatomy of the system one could probably specify what the requirements of such an unlikely lesion would be. Hartmann (1907) thought that one of his patients showed this phenomenon. There are, however, so many difficulties in the interpretation of other data pertaining to this particular case that I prefer to suspend judgment on the possibility of such a unilateral word-deafness.

Lesions of Wernicke's Area

Pure word-deafness as the preceding discussion suggests probably results from the disconnexion of Wernicke's area from auditory stimulation. The normalcy of the patient's speech testifies to the intactness of Wernicke's area. With a lesion in Wernicke's area proper not merely is verbal comprehension impaired, but speech is also impaired. I will not present my conception of this type of aphasia extensively here but would only point out that the loss of Wernicke's area can be regarded as the destruction of a memory store—as it was in fact regarded classically. Presumably it functions importantly as the "storehouse" of auditory associations. I have already suggested the importance of the angular gyrus in acting as a region involved in cross-modal associations, particularly in cross-associations between either vision or touch and hearing. If the angular gyrus is important in the process of associating a heard name to a seen or felt object, it is probably also important for associations in the reverse direction. A "name" passes through Wernicke's area, then via the angular gyrus arouses associations in the other parts of the brain. It is probably thus that Wernicke's area attains its essential importance in "comprehension," i.e. the arousal of associations.

I have presented this only cursorily since a more extensive discussion would lead us to a consideration of topics lying beyond the range of our interest at this point. I would like to stress that what is here regarded speculatively as the function of Wernicke's area implies the existence of extensive connexions to the angular gyrus region. Since this latter region is probably so poorly developed in subhuman forms, the fuller knowledge of this aspect of the connexions of Wernicke's area depends on careful study of those rare human cases with small lesions in the first temporal

gyrus, particularly in its posterior portion. It is hoped that such studies will be made in the near future.[1]

Tactile Aphasia

This term describes a disturbance characterized by an inability to name objects tactilely with preservation of the ability to name on the basis of visual or auditory stimulation and in the presence of intact spontaneous speech. The existence of this condition has been disputed (*see* for example the discussion in Critchley, 1953). The case of Geschwind and Kaplan (1962*b*), however, established beyond doubt the existence of this entity and I will therefore present the relevant findings in this patient. I will confine myself to this aspect of the patient's problem and reserve discussion of the patient's "apraxic" disturbances until a later section of the paper.

This patient had had an excision of a left frontal glioma. We examined him about six weeks later. This patient, when blindfolded, incorrectly named objects placed in the left hand. That this defect was one of *naming* was proved by several facts: (1) the patient would handle the objects correctly in the left hand while he was giving an incorrect name; (2) if the object was taken away and the patient was then instructed to select the object he had held from a group, he always selected the correct object either visually or tactually with his left hand; (3) similarly he could, after holding an object, concealed from vision, draw it correctly with his left hand although he had misnamed it. By contrast, after holding the object while blindfolded in his *left* hand, he could not afterwards select it from a group or draw it with the *right* hand. He correctly named objects held in the right hand and could draw such objects or select them from a group with the *right* hand but failed if he attempted to use the *left* hand for these tasks. That the disturbance was not one of transfer between limbs but rather between hemispheres was shown by the fact that he could draw with the left foot a pattern drawn on his left hand but not one drawn on his right hand.

Testing of elementary somesthetic sensation was difficult to carry out in the left hand if verbal responses were demanded but not if nonverbal responses were used. Thus, he demonstrated correct position sense on the left when he was made to respond by pointing up or down with the left hand; verbally his answers were random in this situation. Two-point discrimination on the left was normal when tested by having the patient indicate with one or two fingers the number of points touched. By contrast

[1]It should be added that the second temporal gyrus of man appears to be a phylogenetically very late region of whose connexions we know very little. It may be a region of great importance and it is conceivable that the view of Wernicke's area presented above is too narrow. I would, however, disagree with those authors who include in Wernicke's area all the posterior regions involved in speech in both the temporal and parietal lobes.

his verbal responses were random; not only were replies of "one" and "two" given incorrectly, but such totally inappropriate responses as "four" or "eight." He could correctly point with his left hand to a place touched on the left side but gave incorrect verbal responses. Pain sensation similarly could be shown to be normal.

In brief this patient responded correctly to somesthetic stimulation if response was demanded from the same hemisphere as the stimulus but not if response was demanded from the opposite hemisphere. Thus, the patient responded correctly with his left hand to somesthetic stimulation of the left side of the body. By contrast his responses to such stimulation with the right hand were incorrect. In addition his verbal responses, which of course would have had to come from his left hemisphere, were incorrect when he was given somesthetic stimulation to the left side of the body. By contrast he responded correctly with the right hand to somesthetic stimulation of the right side of the body and gave correct verbal responses to such stimulation; in this testing situation he gave incorrect responses with the left hand.

We interpreted these disturbances as reflecting a failure of somesthetic stimulation to cross to the opposite hemisphere and thought that we would probably find a callosal lesion. The post-mortem confirmed the presence of a callosal infarction, probably secondary to ligation of the left anterior cerebral artery at the time of excision of the left frontal lobe. Tumour was entirely confined to the left hemisphere and did not involve either the callosum or the right hemisphere.

Had similar cases been observed before ours? Liepmann and others of the writers about the turn of the century had already commented on the inability of a patient to imitate with one hand the postures of the other as reflecting a callosal disconnexion. In addition, Liepmann (1900) called attention to the fact that the Regierungsrat who gave poor verbal responses on somesthetic stimulation must have had nearly intact sensation as evidenced by nonverbal manifestations. This disturbance was due to a disconnexion *within* the left hemisphere rather than to a callosal lesion. Goldstein (1908, 1927) on the basis of his own experience thought that a callosal lesion caused astereognosis on the left side of the body. Critchley (1953) mentions several other authors echoing the same opinion. Goldstein thought that this was the result of the fact that the left hemisphere was dominant for sensation. A more likely explanation is that Goldstein misinterpreted the incorrect verbal responses of his patient as representing sensory loss; he did not check whether sensation was intact when nonverbal criteria were used. The case of Trescher and Ford (1937) was regarded as having a "tactile agnosia" on the left. Their patient showed only an inability to identify letters but not objects placed in the left hand. This more limited disturbance may well have a somewhat different interpretation from the more extensive disturbance in our patient.

The findings and interpretation of Geschwind and Kaplan have been more recently confirmed by Gazzaniga *et al.* (1962) who were able to demonstrate similar disturbances in a patient with a surgical transection of the corpus callosum.

None of these cases permit a more precise delineation of the pathways involved; one can only conclude that they traverse the midcallosum, a result already likely on anatomical grounds and on the basis of experimental results (Myers, 1962*b*). My earlier discussion on the somesthetic system in animals makes it likely that Flechsig's principle is followed here and that there are no callosal fibres from the primary somesthetic cortex in primates; the same rule probably holds in man. Ettlinger's (1962) experiments involved so much of parietal lobe posterior to the postcentral gyrus that they do not help us in deciding whether a more or less circumscribed part of the parietal lobe comprises the association cortex from which the callosal fibres which transfer somesthetic stimulation to the opposite side originate. After synapse at the corresponding locus in the left hemisphere the "message" presumably can be shunted to the speech area (i.e. the auditory association cortex of area 22) or to other parts of the hemisphere.

This simple model which is concordant with the known anatomical facts has certain interesting implications. A lesion of the right parietal lobe which involves the association cortex might produce the same effect as a callosal lesion, i.e. a defect in naming objects held in the left hand and a failure of the right hand to select or draw correctly objects held in the left hand. It is possible that this syndrome exists although the lesion producing it probably must be a large one. It is also likely that such cases have been incorrectly recognized as cases of astereognosis rather than cases of tactile aphasia because of failure of correct examination technique. The problem of the locus of the lesion producing astereognosis has long been a moot one and many authors have suggested a posterior parietal localization (*see* discussion in Critchley, 1953). Perhaps those with posterior parietal lesions were in fact cases of tactile naming defect based on the disconnexion of somesthetic regions from the speech area.

A lesion of the somesthetic association cortex on the left might have a more extensive effect. By destroying the connexion between left somesthetic cortex and speech area it should lead to a failure of tactile naming in the right hand. The lesion could also destroy the terminus of callosal fibres from the right hemispheric somesthetic association cortex and could therefore also produce tactile naming defect on the left. The net result should be a bilateral tactile naming defect. There is some evidence for the existence of this condition. My colleague, Mrs. Edith Kaplan, has recently called my attention to a patient who showed a marked difficulty of tactile naming in both hands while naming *visually* was nearly

normal. That the disturbance was one of naming was shown by the fact that the patient could handle the object correctly or could select it afterwards from a group without error. This patient showed a further additional feature; he could correctly select from a group with one hand an object held with the other hand. This suggests that the callosal connexions between the two somesthetic association cortices were intact and that the lesion must lie between left somesthetic association cortex and speech area.

This patient exhibited no aphasia in speaking and an occasional mild visual naming difficulty. His chief finding, other than the tactile naming disorder, was pure alexia with agraphia. The evidence appeared good that the lesion was in the left posterior parietal region but in the absence of confirmatory evidence, we must restrict ourselves to the fact that this case illustrates the possibility of a bilateral disturbance of tactile naming in the presence of a much milder visual naming difficulty.

Other cases described in the literature are almost certainly cases of the same disturbance although again comparison is made difficult by the failure of most authors to have tested for evidence of retained stereognostic function by nonverbal means. Cases such as those of Foix (1922) in which a unilateral lesion is said to have led to bilateral astereognosis might well have turned out to be cases of bilateral tactile aphasia had tests for nonverbal recognition been employed. Some others have preferred the term "tactile agnosia" for such cases as those of Raymond and Egger (1906). I feel, however, unconvinced by Claparède's highly philosophical critique of the use by these authors of the term "tactile aphasia." The broader question of the position of the agnosias will be dealt with in the next section of this paper.

Summary

The first part of this paper has been devoted to a consideration of some of the anatomical features of the organization of the cerebral cortex which play a major role in determining some of the features of disturbances of the higher functions in animals as well as men. Stress was laid on the pattern of corticortical connexions in the brains of primates, including man. It was pointed out that disconnexion of cortical regions can be achieved by lesions involving either white matter connexions or by damage to association areas which constitute obligatory way stations between the primary sensory, motor, and limbic regions of the brain in primates. This analysis was applied to a discussion of the agnosias in the subhuman primates. In the last portions of this paper attention was turned to the human brain and to those anatomical features which underlie the development of language. Examples were given of specific syndromes which could best be interpreted as resulting from disconnexion.

Part II of the paper will be devoted primarily to a discussion of further applications of the concept of disconnexion to disturbances of the higher functions in man, including the agnosias, the apraxias, and certain aphasic syndromes. A more complete summary of the entire discussion will be found at the end of Part II.

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