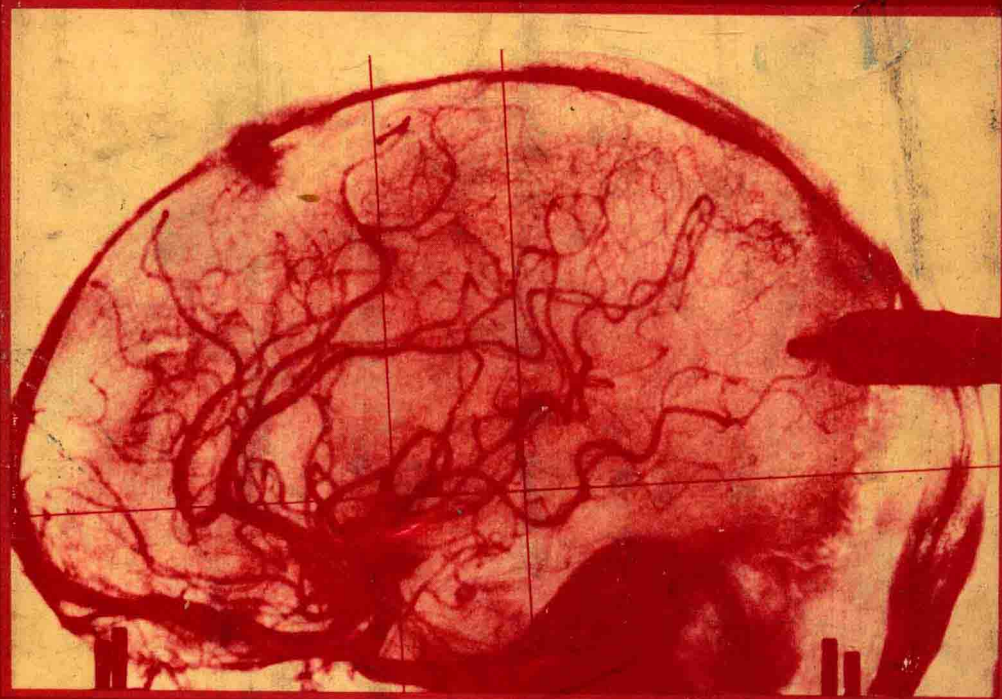


Functional Neurosurgery



Edited by

Theodore Rasmussen / Raul Marino, Jr.

Raven Press

Functional Neurosurgery

Edited by

Theodore Rasmussen, M.D.,
M.S., F.R.C.S.

Senior Neurosurgical Consultant and Former Director

Montreal Neurological Institute and Hospital

Professor, Department of Neurology and Neurosurgery

McGill University

Montreal, Quebec, Canada

Raul Marino, Jr., M.D.

Professor and Director

Division of Functional Neurosurgery

Hospital das Clinicas

University of São Paulo Medical School

São Paulo, Brazil

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

© 1979 by Raven Press Books, Ltd. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

Made in the United States of America

Library of Congress Cataloging in Publication Data

Main entry under title:

Functional neurosurgery.

Includes index.

1. Nervous system--Surgery. I. Rasmussen, Theodore. II. Marino, Raul. [DNLM: 1. Nervous system--Surgery. WL368 F979]

RD593.F86 617'.48 77-85871

ISBN 0-89004-228-4

Contents

- 1 Introduction: Functional Neurosurgery as a Specialty
Raul Marino, Jr.
- 7 Expanding Borders of the Limbic System Concept
Walle J. H. Nauta
- 25 Neurology of Brain Functional Disorders
P. Molina-Negro
- 45 Frontiers of Functional Neurosurgery in Biomedical Research
Ayub K. Ommaya
- 59 The Use of Pacemakers (Electrical Stimulation) in Functional Neurological Disorders
Philip L. Gildenberg
- 75 Computers in Functional Neurosurgery
Gilles Bertrand
- 89 Functional Surgery of Abnormal Movements
P. Molina-Negro
- 123 Neurosurgical Treatment of Spasticity
Jean Siegfried
- 129 Functional Surgery of the Trigeminal Nerve: Treatment of Trigeminal Neuralgia
John M. Tew, Jr., Jeffrey T. Keller, and David S. Williams
- 143 Functional Neurosurgery of Neuroendocrine Disorders
J. Hardy
- 155 Advances in Psychiatric Surgery
H. Thomas Ballantine, Jr., and Ida E. Giriunas
- 165 Psychological Assessment of Neurosurgical Patients
Laughlin B. Taylor

- 181 Depth Recordings and Stimulation of the Human Brain: A Twenty Year Experience
Blaine S. Nashold, Jr., William P. Wilson, and Elizabeth Boone
- 197 Stereotactic Neuroradiology and Functional Neurosurgery: Localization of Cortical Structures by Three-Dimensional Angiography
Gabor Szikla
- 219 Stereotactic Neuroradiological Concepts Applied to Surgical Removal of Cortical Epileptogenic Areas
Jean Talairach and Gabor Szikla
- 243 Long-Range Results of Medial Amygdalotomy on Epileptic Traits in Adult Patients
H. Narabayashi
- 253 Cortical Resection for Medically Refractory Focal Epilepsy: Results, Lessons, and Questions
Theodore Rasmussen
- 271 *Subject Index*

Introduction: Functional Neurosurgery as a Specialty

Raul Marino, Jr.

*Division of Functional Neurosurgery, Hospital das Clinicas, University of Sao Paulo
Medical School, Sao Paulo, Brazil*

The drop is a small ocean . . .

—R. W. Emerson

Neurological surgery, as a modern specialty, had its birth as a consequence of important acquisitions of knowledge in the anatomy, physiology, and clinical semeiology of the nervous system. This knowledge was acquired during the nineteenth century. The introduction of neuropathology, the discovery of anesthesia, the control of sepsis, and the development of antisepsis each were important landmarks in the establishment and growth of the specialty. The discovery of X-rays by Röntgen in 1891, followed by the development of other diagnostic procedures, paved the way for the continuing succession of technical advances that gave great impetus to the specialty of neurosurgery, particularly to the modern facets now described as functional neurosurgery.

Major therapeutic progress has sometimes preceded or led to the acquisition of new knowledge on the physiopathologic mechanisms of nervous diseases. The growing field of functional neurosurgery stands out today as one of the more philosophical approaches to medicine. It deals with the awake brain and with the human person who is usually fully conscious on the operating table. Talking to their examiners, the patients themselves guide the hands of the neurosurgeon during his therapeutic maneuvers on the nervous system as he endeavors to alleviate epilepsy, abnormal movements, pain, suffering, and sometimes behavior disorders.

Functional neurosurgery procedures have increased neurological knowledge concerning mechanisms of a variety of cortical functions such as speech, somatomotor, somatosensory, vision, and hearing,—and they have contributed to our knowledge of the function of the deep cerebral structures that modulate abnormal movements, pain, and behavior. Recording, stimulation, and ablation of a variety of areas of the brain in the process of carrying out therapeutic procedures for the relief of functional neurological disorders have enabled neurosurgeons and applied neurophysiologists to study a variety of structures and regions of the human brain. Functional neurosurgery has, then, become not only a productive

aspect of classic neurosurgery, but also an important instrument and an indispensable tool for the study of and research on the functioning of the human brain.

This instrument has enabled the neurosurgeon and his team to "listen" to the language of the brain, which is also the language and the music of life itself. Our means of study are still gross and rough, compared to the delicate functions of this organ, but in using them we are learning what epilepsy, pain, abnormal movements, and "emotions" have to tell us regarding certain functions of the brain. It is true that all we know represents only a drop in the ocean, but we also know that sometimes a simple drop of dew may reflect the whole sky.

There is no question in our minds that the study of the brain is the study of man's place in nature. This is the philosophical truth that motivated most of us to study the human brain, the temple and shrine of our thoughts, the most complex, the most perfect, and certainly the most important living structure in our universe.

The brain of man is the map of his destiny, the most beautiful instrument ever created by divine hands. On the dissecting table it is a bare mass of cells and nervous centers perfused with blood, but on the operating table, joined to the body, the awake brain is, in normal life, the only instrument through which man reveals himself and plays the concert of life, conducting the body, and being conducted by the soul. Our nervous cells constitute the link that connects our physical brain with the world in which our consciousness has its roots. Our knowledge of this organ is still meager, but it is already enough for us to understand that the brain may be the seat of our thought, but never its origin. How could a mass of protoplasm compose a sermon?

To date, we are far removed from the mechanistic views of the eighteenth century when LaMettrie (3) concluded that thought was the result of mechanical processes in the brain and in the rest of the nervous system and also from the concepts of Cabanis (1), the so-called father of psychosomatic medicine, who stated that the brain was the organ of thought, "secreting thoughts and ideas as the liver secretes the bile"!

The proper study of the human brain requires that we should first understand its structure before we can ask intelligent questions about its organization and functioning. Only then will we be able to understand the relationship between brain, mind, and life itself.

The findings that to date relate sensation, movements, feelings, and emotions to the brain have not as yet permitted even the most sophisticated neurophysiologist or philosopher to use this knowledge of brain function to resynthesize the phenomenon of everyday life.

The contributions of neurosurgery and its subspecialties to knowledge of the brain and the nervous system are still meager in comparison to the vastness and the complexity of its capabilities; however, we should not forget that more progress has been made in the last few decades than in many previous centuries.

Functional neurosurgery is still a modest branch of the neurosciences, but it has made significant contributions to the discipline and promises to make many more as the discipline advances and is further refined.

Functional neurosurgery has emerged as a result of the need of neurosurgeons, neurologists, neurophysiologists, neuroanatomists, neuropathologists, and psychologists to study the higher functions of the human brain and nervous system in order to provide more effective treatment of a variety of nervous system disorders. More recently a variety of special talents have been recruited to this already complex team. Included in this group are electroencephalographers, biochemists, electronic engineers, and computer experts.

One of the precursors of the term functional neurosurgery was provided by René Lèriche (4,5) when he used the term "functional surgery" to describe some of his interventions on the sympathetic nerves for pain and circulatory disturbances. Lèriche removed the pejorative sense of the term "functional" which was used at that time to designate hysterical or conversion phenomena. He stated that this term should be used to denote function and that where function is present we are "plain pied" on normal and pathological physiology. Since Lèriche's time, there is general agreement that the functional is an important part of pathology and that it may precede or even create the anatomical.

As far as we know, it was one of Lèriche's disciples, P. Wertheimer, who for the first time assembled in a book (6) the present characteristics of functional neurosurgery, granting that name to this division of neurosurgery. In his book, Wertheimer included the physiopathology and treatment of involuntary movements and the surgery for epilepsy, pain, and relief of mental illness. He also included a chapter on the treatment of vascular pathology of the brain and a separate chapter on the treatment of brain edema and alterations of intracranial pressure. He recognized that this separation was, to a certain extent, artificial. He justified this as the need to associate, in his nosological conceptions, the anatomical lesion to the functional changes. According to Wertheimer, functional neurosurgery would be the part of neurosurgery taking advantage of the new neurophysiological acquisitions, and functional procedures would consist of "moderating" and "reformative" interventions, guided by neurophysiological information. Action would be taken toward excitatory and inhibitory phenomena with the aim being the suppression of irritative foci that produce convulsion and the neutralizing of other pathological effects by the interruption of motor paths and sensory paths of nuclei in the surgery for epilepsy, involuntary movements, pain, and mental disorders.

Hughlings Jackson was the first to stress the importance of the correct use of the term functional. He stated: "I have long urged that the term functional should be used as the adjective of the word function. [I remark, parenthetically, that such expressions as that "consciousness is a function of the brain," or any part of it, are illegitimate. Consciousness attends functioning of the brain, or of some parts of it.] "Function is a physiological term; it deals with the 'storing up' of nutritive materials having potential energy, with nervous dis-

charges (or liberation of energy by nerve cells); it has to do with the rates of those liberations, with the resistances encountered, and with different degrees of those resistances." [(2), Vol. 2, p. 472-473]

Jackson continues: "Physiology deals with the dynamics of the organism—that is, with its function. I use the term 'function' with regards to nervous diseases in a strict sense, and never in the way it or its adjective (functional) is used when applied to the symptoms of an hysterical woman, or to minute or transitory changes of structure." [(2), Vol. 1, p. 428]

Jackson emphasizes the correct use of the term *functional* in many other instances in his famous writings: ". . . it is desirable that the term functional should be used with exactness, and that the functional (physiological) changes should be distinguished from the pathological changes producing them." [(2), Vol. 2, p. 472-473]

The aim and objective of functional neurosurgery are to treat, correct, or balance the functions of the brain that are altered toward either hyperfunctional or hypofunctional states. Functional neurosurgical procedures often involve circuits or structures of the nervous system that may frequently be normal except for transient states of altered function. Those circuits are not necessarily the same as those involved in the primary derangement of function. Equilibrium will be reestablished through lesions or stimulation of nervous centers or pathways, as dictated by the origin of the disturbance: biochemical changes, lesions of centers or paths, and so forth, trying to compensate for them through procedures that will reestablish the original balance in the system. The origin of disequilibrium may be vascular, tumoral, degenerative, or infectious, and it may or may not require specific treatment. Main emphasis is given, however, to the correction of the disordered function responsible for convulsions, abnormal movements, pain, mental change, neuroendocrine disturbance, and the like.

Jackson again throws much light on the subject of the normal and abnormal functions of the brain and their pathological bases (2):

. . . . There are two diametrically opposite kinds of functional changes: 1. degrees from slight defect to loss of function; 2. degrees from slight to excessive exaltation of function. The former, negative state of function, exists in cases of paralysis, the latter, positive state of function, in cases of epilepsy, chorea, tetanus, etc. I never use the expression 'disorder of function,' but speak of degrees of negative functional states, and of degrees of states of over-function. The two may coexist. Some elements of the set of motor arrangements, representing a muscular region may have lost function. Whilst other elements of the same set may be in over-function. For example, we find not rarely persisting hemiplegia and occasional convulsion of the muscular region paralyzed.

One advantage of the scheme of investigation by the triple division is that we learn by it where our knowledge is deficient. Indeed, of some cases of nervous diseases it would be commonly said that we know symptoms only. The scheme enables us to separate definitely what we know from what we only suppose. In chorea we know there is the second kind of functional lesion; at any rate, it is an irresistible inference that the movements depend on unduly high instability of nerve cells. But we do not know the site of that lesion, nor the pathological process leading to it. On the anatomy and pathology of chorea all of us have hypotheses only.

We may thus infer that normal function is an interplay between inhibitory and facilitatory functions. The loss of one function may result in a decrease in function of certain other structures and an increase in function in still others.

A *positive symptom* is the result of an exaggerated activity of a certain structure that has been liberated from an inhibitory control that is normally exerted by another structure that has suffered a lesion. Function in this case is exalted, as in the cells of a discharging lesion, hypertonus, tremor, abnormal movements, and central pain. These are, according to Jackson, "hyperphysiological" states. Functional neurosurgery endeavors to correct this abnormal excess of function. It aims primarily to reestablish a broken equilibrium, since the lesion of origin often requires no treatment. For instance, in labyrinthine irritation producing spasmodic torticollis, we will treat structures anatomically intact but functionally out of control (interrupting impulses on nucleus ventralis intermedius of the thalamus).

In a case with epilepsy of the supplementary motor area, it is implied that neurons in this area are intact and thus able to produce the epileptic seizures. So, the epilepsy is a functional change consequent to the exaggerated function of neuronal mechanisms of this area—the lesion may be in other neurons that act to influence the former. A scar or a calcification is not all epileptogenous zone, but it may result in hyperfunction of neurons and circuits that are adjacent or at a distance.

A *negative symptom* is the result of decrease or loss of function of a certain structure such as hemianopia, hemiplegia, anesthesia, akinesia, or facial palsy. Positive and negative symptoms may exist together, as in the case of a meningioma, causing hemiplegia and epilepsy. When the tumor has been removed, epilepsy may continue, since the surrounding brain tissue is lesioned, or uninhibited, resulting in epilepsy as a functional symptom.

In conclusion, general neurosurgery tends to concentrate on the lesion, rather than on the symptoms, negative or positive. Functional neurosurgery tends to focus on the symptoms, that is, on the abnormal functions which are often positive or hyperfunctional states and which appear at a distance as a consequence of the primary lesion.

Many specialties deal with the human brain, as many insects alight on the prairie flowers. However, only the bees know how to extract the honey. The bees alone are able to do that job and leave the flowers intact without hurting them or making them lose their freshness, allowing the flowers to remain exactly as they were before. This is the hope and aim of functional neurosurgery.

REFERENCES

1. Cabanis, P. J. G. (1802): *Rapports du Physique et du Moral de L'homme*.
2. Jackson, J. H. (1958): In: *Selected Writings of John Hughlings Jackson*, edited by J. Taylor, Vol. 2., p. 376–377. Basic Books, New York.
3. LaMettrie, J. D. de. (1747): *L'homme-Machine*.
4. Leriche, R. (1949): *La Chirurgie de la Douleur*. Masson, Paris.
5. Leriche, R. (1951): *La Philosophie de la Chirurgie*. Flammarion, Paris.
6. Wertheimer, P. (1956): *Neurochirurgie Fonctionnelle*. Masson, Paris.

Expanding Borders of the Limbic System Concept

Walle J. H. Nauta

*Department of Psychology, Massachusetts Institute of Technology, Cambridge,
Massachusetts 02139, and Mailman Research Center, McLean Hospital,
Belmont, Massachusetts 02178*

In recent years, concepts of the limbic system have undergone a notable amplification, especially as a result of intensive anatomical studies that have drawn the afferent and efferent relationships of the limbic system into sharper focus. Before these more recent developments can be reviewed, it is necessary to deal briefly with the connotation of the term limbic system.

As used here, the term broadly denotes the hippocampal formation and amygdala together with some medial and basal cortical regions connected with these structures either directly or by way of the thalamus (gyrus cinguli, retrosplenial cortex, and parahippocampal gyrus). From these medial regions outward, the border of the limbic system becomes indistinct, and it is particularly difficult to decide whether and to what extent certain parts of the neocortex of the basal frontotemporal region should be considered part of it. Much as the gyrus cinguli is associated especially with the hippocampus by way of direct and indirect fornix projections to the anterior thalamic nucleus, the posterior orbito-frontal cortex is associated with the amygdala by way of a prominent amygdalofugal projection to the medial subdivision of the mediodorsal thalamic nucleus (20,25). The inferior temporal neocortex even receives a direct projection from the amygdala (20,25).

This vagueness presents a fundamental problem in defining the limbic system: unlike the wholly subcortical corpus striatum, much of its expanse forms part of the pallial mantle, and hence gradates into the surrounding neocortex. Despite this difficulty, however, the term, limbic system, has a certain utility, as it denotes an assembly of structures that not only are related by common peculiarities of neural circuitry, but also appear collectively to form part of the neural mechanism determining the organism's internal and overt behavioral responses to its environments. Put in other words, as currently used, the term, limbic system, is based in part at least on a morphophysiological correlation.

It is a matter of preference whether one chooses to extend the term to those diencephalic and mesencephalic structures with which the limbic region of the cerebral hemisphere is known to be associated by largely reciprocal fiber connections. Together, these structures form a subcortical continuum that extends from the septum caudally over the preoptic region, substantia innominata, and

hypothalamus and, beyond the latter, throughout a paramedian zone of the midbrain that includes, among other structures, the ventral tegmental area of Tsai and the mesencephalic raphe nuclei. Direct projections leading into this continuum from the cerebral hemisphere originate not only from the hippocampus and amygdala but also from the posterior orbitofrontal cortex.

Anatomical studies of the past 15 years have cleared up at least one long-standing problem: that of the afferent connections of the limbic system with the neocortex. Other studies of recent date have expanded our knowledge of the subcortical ramifications of the limbic circuitry and, more particularly, these studies have brought out previously unknown links with the corpus striatum. The remainder of this chapter will deal with such more recent developments in the anatomical definition of the limbic system.

NEOCORTICAL AFFERENTS OF THE LIMBIC SYSTEM

After the general concept of the limbic system had been explicitly formulated (22,23), it seemed logical to assume that a neural organization of such great behavioral importance would receive substantial projections from the sensory mechanisms of the neocortex. This assumption ultimately proved to be correct, but it is remarkable that the neocortico-limbic connection for a long time remained conjectural. As late as 1958 it was possible to state: "In spite of much speculation, the anatomical substratum for such neocortico-limbic interaction is almost entirely obscure; it would seem to hold a lively challenge for future investigation." (24).

It is true that by that time some fragments of the connection had already been glimpsed. In 1952, Adey and Meyer (1), from a study by the Glee's method in the monkey, reported evidence of a projection from the medial frontal cortex through the fasciculus cinguli to the parahippocampal gyrus. Furthermore, a direct projection from the inferior temporal cortex to the amygdala had been reported in 1956 by Whitlock and Nauta (45), likewise in the monkey. Almost 10 years earlier, neurophysiological studies by the method of strychnine neuronography had provided evidence of direct projections from the orbitofrontal cortex to posterior parts of the hypothalamus (34,42), evidence that had soon thereafter been confirmed by anatomical findings (7,41). However, these early observations hardly seemed to satisfy the original expectation of finding substantial projections from all of the sensory areas of the neocortex to the limbic structures at the medial margin of the cerebral mantle. For several years, neuroanatomists, working with fiber-degeneration methods, found themselves frustrated in their attempts to demonstrate such variegated projections to the entorhinal area, the region on the parahippocampal gyrus that since the time of Cajal was known to be the origin of the largest single afferent fiber system of the hippocampus, the temporoammonic bundle. It was not until 1965 that the general pattern of organization of the neocortico-limbic relationship began to be revealed. In that year, Cragg (11) published an important study in the cat, in which he

demonstrated a projection from the parietal association cortex (suprasylvian gyrus) to the cingulate cortex, as well as projections from the frontal cortex and temporal cortex to the entorhinal area. This report provided Jones and Powell with a valuable clue (32) when they (14) found that not only the somatic sensory cortex but also the auditory cortex in the cat projects to the suprasylvian gyrus. The question raised by this finding was: could it be that projections from the sensory regions of the cortex converge upon particular association areas that in turn project into the limbic system? Turning to the larger monkey brain, Jones and Powell (18), in a monumental study, were able to show that, indeed, cortico-cortical pathways leading out of all the primary sensory areas of the neocortex, by way of a variable number of intercalated association areas in the parietal, frontal, and temporal lobes, ultimately converge in three places. One of these is the anterior cingulate cortex (areas 24 and 25); a second one is the convexity of the frontal lobe; and the third one is the temporal pole (area TG of v. Bonin and Bailey) and a contiguous strip of medial temporal cortex at the border between the neocortex and the allocortex of the parahippocampal gyrus (area 35). Most recently, Van Hoesen and Pandya (38-40), in a series of important papers, provided a detailed description of the complex pattern of cortico-cortical connections leading from the anteromedial temporal cortex and basal frontal cortex to the entorhinal area, the cortical gateway to the hippocampus.

In hindsight, it does not seem surprising that the neocortico-limbic connection long remained obscure. Quite unlike the neocortical projection to the striatum (caudate nucleus and putamen), which is organized as a system of parallel direct lines originating independently from apparently all cortical areas, the neocortico-limbic connection is characterized by a convergence of concatenated cortico-cortical pathways upon the lower frontotemporal region. The ultimate link to the hippocampus and amygdala thus originates from a limited region of the cortex. It can be inferred from this arrangement that information from the neocortex must reach the limbic system in a highly sequentially processed form. Moreover, the strongly convergent nature of the connection suggests that the information conveyed by it undergoes considerable intermodal integration. It seems likely that the integral contains not only exteroceptive but also viscerosensitive elements (27), and thus represents both the organism's external and its internal milieu.

CROSSROADS OF LIMBIC AND STRIATAL CIRCUITRY

Despite their invariable coexistence in the mammalian brain, limbic system (hippocampus and amygdala) and corpus striatum (striatum or caudatoputamen, and pallidum or globus pallidus) have long given the impression of being two mutually isolated neural mechanisms. Until about 25 years ago, these two major components of the forebrain seemed to lack any direct interconnection; for an even longer time, they appeared to have no common sources of afferent supply,

and their respective efferent fiber pathways until very recently seemed to have no points of convergence anywhere along their course. To be more specific, until about 20 years ago, known or suspected neocortical afferents to the limbic system were limited to the cingulo-hippocampal connection suggested by Cajal (5) and later by Papez (31), whereas cortical afferents to the corpus striatum were generally believed to originate largely or even entirely from the sensorimotor cortex; neither were any other sources of afferents known to be shared by limbic system and corpus striatum. As to the efferent connections of these two forebrain mechanisms, those of the corpus striatum until only a few years ago were thought to be distributed exclusively to the substantia nigra, subthalamic nucleus, centrum medianum, and VA-VL complex of the thalamus, and to certain mesencephalic regions; see Nauta and Mehler (29) for a review. In none of these distributions did the projections of the corpus striatum seem to overlap the efferents of the limbic system. The latter, instead, have been traced to the anterior and mediodorsal nuclei of the thalamus, as well as to the subcortical continuum formed by the septum, preoptic region, and hypothalamus. They extend caudally beyond the hypothalamus over the ventral tegmental area throughout the paramedian region of the midbrain, partly by way of the medial forebrain bundle and partly also by a more dorsal route composed of the stria medullaris, habenular nuclei, and fasciculus retroflexus. It is important to note that a substantial second component of the medial forebrain bundle deviates laterally from the main bundle and distributes itself largely to more lateral regions of the midbrain tegmentum (see below).

As could have been expected, this initial impression of separateness of the limbic system and the corpus striatum has faded over the past two decades, and at present several forms of association between the limbic system and the corpus striatum can be pointed out. The one detected earliest is a direct connection between these two major forebrain mechanisms: In 1943, Fox (16), from an experimental study by the Marchi method, reported precommissural fornix fibers distributed to the nucleus accumbens septi, a basal forebrain structure which, although in the past regarded by some as part of the septum, nonetheless by cytoarchitectural and histochemical criteria can be interpreted only as a ventromedial subdivision of the striatum. Confirmed in later years by Carman et al. (6) and Raisman et al. (33), this earliest evidence of a direct limbico-striatal connection was amplified more recently by the discovery of additional afferents of the nucleus accumbens originating from the amygdala (13). It is interesting to note that thus far no reciprocating direct striatal projection to the amygdala or hippocampus has been described.

The first evidence of a source of afferents common to the limbic system and corpus striatum appeared in 1956 in the monkey in the form of a projection from the inferior temporal cortex to both the amygdala and ventral regions of the striatum (45). In the two decades since, the cortical afferentation of the limbic system and corpus striatum has been analyzed in considerable detail, and it now seems possible to state that all or nearly all of the neocortex is

connected with both mechanisms, either, as in the case of the corpus striatum, by direct corticostriatal fibers originating throughout the expanse of the neocortex (6,19,43,44) and distributed to both caudate nucleus and putamen, or, in the case of the limbic system, by way of variously complex sequences of cortico-cortical connections.

Finally, only very recently has a point of convergence of limbic and striatal efferent systems been demonstrated. The locus in question is the lateral habenular nucleus, a subdivision of the habenular complex long known to receive stria-medullaris fibers originating from the lateral preoptico-hypothalamic region. An autoradiographic study in the cat (17,28) revealed that the nucleus also receives a quite massive projection from the entopeduncular nucleus, the homolog of the internal segment of the globus pallidus of primate forms. Since the globus pallidus is a major recipient of striatal (caudatoputamenal) efferents, and the lateral habenular nucleus appears to be a principal—if not indeed the principal—source of afferents to the paramedian zone of the midbrain (24; also Herkenham and Nauta, *manuscript in preparation*), this finding suggests the raphe region of the midbrain tegmentum as an ultimate destination of conduction pathways originating in both the limbic system and the striatum. At present, no other loci of confluence of striatal (or pallidal) efferents with limbic conduction pathways are known, but preliminary observations in this laboratory suggest that pallidal fibers may converge with the lateral component of the medial forebrain bundle in the ventrolateral tegmental region containing dopamine cell group A8 of Dahlström and Fuxe (12) (see below).

Outlying Nigral Cell Groups

In the foregoing overview, mention was made of direct projections from the hippocampal formation and amygdala to the nucleus accumbens. In the next section of this chapter, I shall report experimental evidence, obtained in the rat in collaboration with my colleagues Valerie Domesick and Richard Faull, of a second, more indirect but apparently also more widely distributed, conduction route by which the limbic system could be thought to affect the mechanisms of the corpus striatum. Since this route largely leads over the outlying nigral cell groups A10 and A8, a brief review of the anatomical data concerning these cell groups would seem appropriate.

The label, A10, was given by Dahlström and Fuxe (12) to a large, somewhat wedge-shaped group of dopamine cells protruding from the medial half of the pars compacta of the substantia nigra (dopamine cell group A9) in the mediodorsal direction. Most of the relatively large cells of the A10 group occupy the basomedial midbrain region labeled *ventral tegmental area* by Tsai (36), and their presence appears to have been the main characteristic by which Tsai demarcated this area from the rostrally adjacent lateral hypothalamic region. Not until 40 years later was the histochemical likeness of these cells to those of the substantia nigra's pars compacta established (12). Shortly thereafter Andén

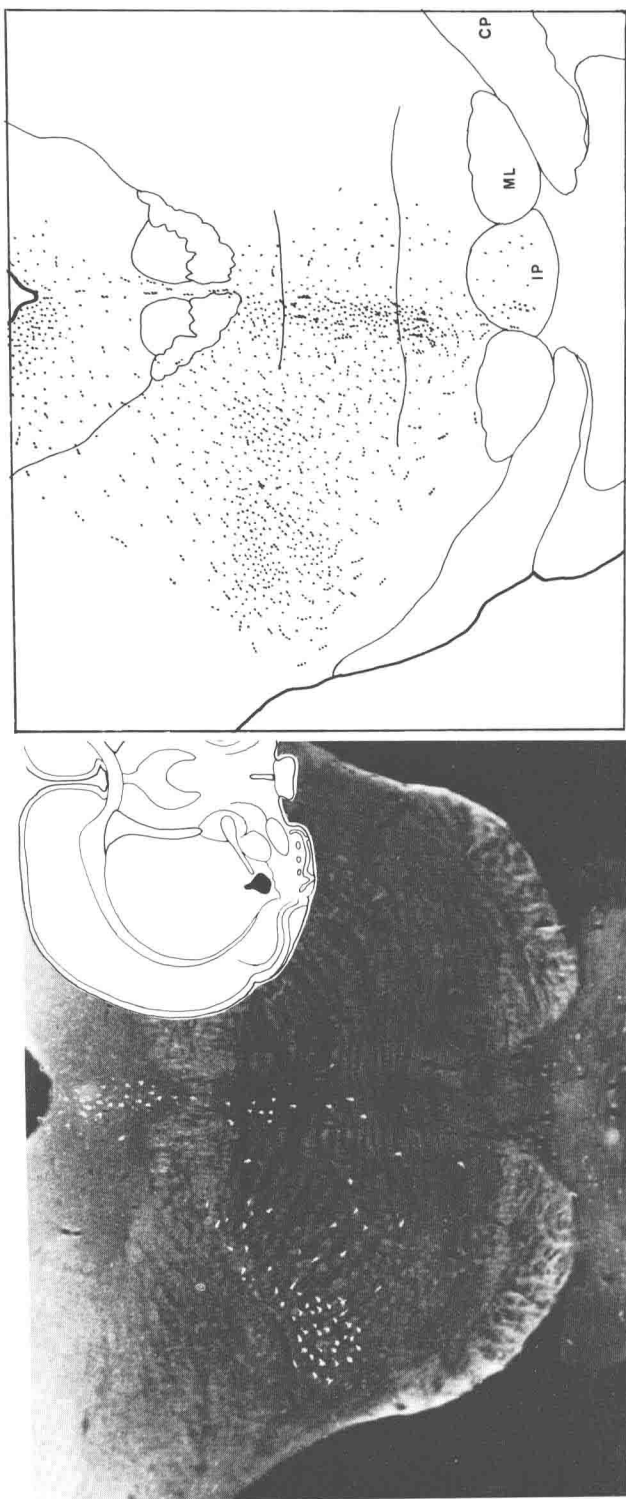


FIG. 1. Left: A section slightly caudal to the substantia nigra, showing retrograde cell labeling in the caudal region of dopamine cell group A8 in a case (RH 27) of HRP injection in the subcommissural striatal pocket (*inset*). Note trails of sparser labeled cells extending medially from the A8 region. Labeled cells in the tegmental midplane represent caudal part of A10; those in the central gray substance, the dorsal raphe nucleus. (Dark-field photograph, retouched.) **Right:** Charting of radioactive fiber labeling at corresponding level of the midbrain in case RR 89 (*inset* to Fig. 2, right column). IP, interpeduncular nucleus; ML, medial lemniscus; CP, cerebral peduncle.