CHAPTER 17

Cerebral Cortex: Cytoarchitecture, Physiology and Overview of Functional Localization

PART I. ANATOMICAL CONSIDERATIONS

A firm knowledge of the structure and function of the cerebral cortex and the relationship of the cerebral cortex to the subcortical centers is of crucial importance for all who wish to understand the behavior and accomplishments of man as opposed to other animal forms. The use of the thumb and fingers for fine manipulations with tools, the use of linguistic and mathematical symbols for communication in the auditory and visual spheres, and the capacity for postponement of gratification all reflect the evolution of the cerebral cortex. This development of the cerebral cortex has led to a laminar arrangement of 16 billion nerve cells with an almost infinite number of synapses. Beaulieu and Colonnier have estimated that in a cubic millimeter of neocortex there are 2.78 times 10\8 synapses 84% of which are type I (excitatory) and 16% type II (inhibitory).

The almost infinite number and variety of circuits present not only has provided the anatomical substrate for the recording of an infinite number of past experiences but has also allowed for a plasticity of future function projected both in time and in space.

The attempt to relate functional differences to the differences in structure of the various areas of the cerebral cortex was a scientific outgrowth of the earlier philosophical arguments concerning the relationship of mind and body. We may indicate at the onset that to a certain degree cytoarchitectural differences do reflect functional differences. This is never, however, a one-to-one relationship. Moreover, at times, architectural differences are not sharp; strict borders may not be present.

The various areas of cerebral cortex differ as regards several parameters:

1. Thickness, evident on simple visual inspection (average thickness is 2.5 mm., motor cortex: 4.5 mm., visual cortex 1.45 to 2.0 mm.). In addition to differences in overall thickness, some areas differ in the thickness of the various layers that constitute the laminar pattern.

2. Relative density of the various cell types (evident in Nissl stains for cells or Golgi silver stains) to be discussed below e.g.: pyramidal, vs stellate, It must also be noted that within a given area of cortex, the various layers of cortex differ as regards the relative distribution of these various types of cells *(Fig.17-1)*

3. Density of horizontal fiber plexuses (stripes) (evident on myelin and silver stains) and density of axodendritic and other synapses (evident on Golgi stain and Fink-Heimer stains).

4. Degree of myelination of intracortical fiber systems (evident on myelin stain). To some extent the various myelinated bands may be seen with the naked eye in freshly cut sections of the cerebral cortex. For example, Gennari in 1782 and Vicq d'Azyr in 1786 independently had noted a white line in the cortex near the calcarine fissure. The various features to be noted in the several types of stains are demonstrated in *Figure 17-1.*

CYTOLOGY

From the standpoint of cytology the neurons within the cerebral cortex may be classified into two major categories pyramidal and stellate *(Fig.17-2)*. The axons of pyramidal cells (Type I cells/neurons with long axons) form the majority of association, callosal and subcortical projections while the stellate cells (type II/ neurons with short axons) form the local circuits (Refer to chapter 3 for additional discussion).

Neurons may also be classified on the basis of whether the dendrites have spines or an

E. M. Marcus et al., *Integrated Neuroscience*
© Kluwer Academic Publishers 2003

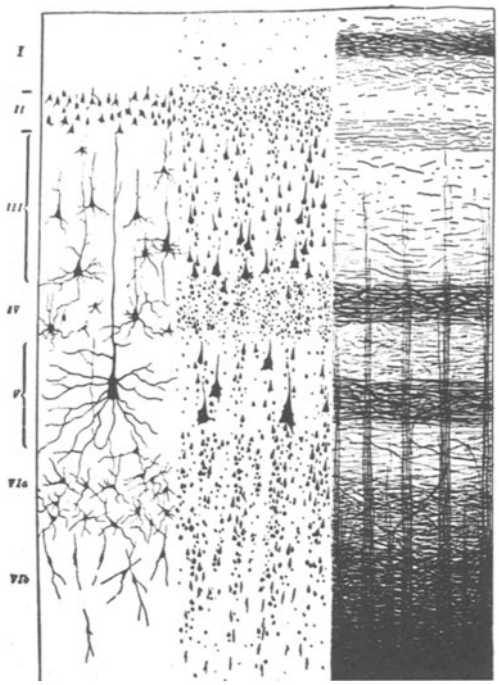


Figure 17-1. Diagram of the structure of the cerebral cortex. The results obtained with (a) a Golgi stain, (b) a Nissl stain or other cellular stain, and (c) a myelin stain are contrasted. I = molecular layer; II = external granular layer; III = external pyramidal layer; IV = internal granular layer; V = large or giant pyramidal layer (ganglionic layer); VI = fusiform layer. The following features should be noted in the myelin stain: 1a = molecular layer 3a1 = band of Kaes Bechterew; 4 = outer band of Baillarger; 5b = inner band of Baillarger. (After Brodmann, from Ranson, S. W., and Clark, S. L.: The Anatomy of the Nervous System, Philadelphia, W. B. Saunders, 1959, p. 350).

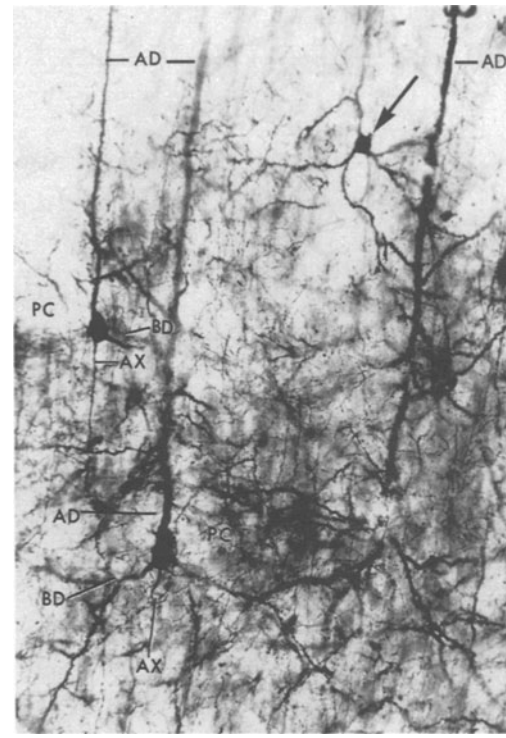


Figure 17-2. Pyramidal and stellate cells as demonstrated in Golgi stain of cat cerebral cortex. PC = pyramidal cells; arrow = stellate cell; AD = apical dendrite of pyramidal cell; BD = basal dendrite of pyramidal cells; AX = axons of pyramidal cell.

absence of spines.

From the standpoint of electrophysiology the neurons may be classified as fast spiking, regular spiking or bursting (repetitive discharge).

I. Neurons whose dendrites have spines (spiny neurons) account for the majority of the neurons in cerebral cortex. These are excitatory and are of two types:

a. Pyramidal cells: constitute 2/3 of all neurons in the neocortex. These cells are defined by a prominent apical dendrite extending through all layers of the cortex to layer 1.Pyramidal neurons have cell bodies of variable height--small 1u to 12 u; medium 20 to 25 u; large 45 to 50 u, and giant 70 to 100 u. The giant pyramidal cells are characteristic of the motor cortex. The upper end of the pyramidal cell continues on toward the surface as the apical dendrite. Numerous spines are found on the dendrite providing sites for synaptic contact. The pyramidal neurons have the largest dendritic trees and also contain axons that form associational, callosal and projectional connections. In general, the larger the cell body, the larger the apical dendrite and the wider the spread in terms of ramifications of the terminal horizontal branches. The wider the spread of the apical dendrite, the greater the number of possible axodendritic synapses. The larger the cell body, the greater the number of possible axosomatic synapses. In addition to the apical dendrite, shorter basal dendrites arise from the base of the cell body and arborize in the vicinity of the cell body. The axon emerges from the base of the cell body

and descends toward the deeper white matter. In general the axons of small- and medium-sized pyramidal cells terminate as association fascicles within the cortex. The axons of large and giant pyramidal cells enter the deeper white matter as (a) association fibers to other cortical areas, (b) commissural fibers to the contralateral hemisphere, or (c) projection (efferent) fibers to subcortical, brain stem, and spinal cord areas. In addition, recurrent collateral association fibers may branch off from these axons within the cortex. In addition to functioning as the main efferent outflow of the cerebral cortex to subcortical areas (thalamus, basal ganglia, brain stem and spinal cord), and to other cerebral cortical areas (ipsilateral, and contralateral hemispheres), the pyramidal cells also provide a massive collateral net work to other neurons with in the local area. Each pyramidal cell also receives multiple inputs on to its dendritic spines .The Betz cells, the giant pyramidal neuron of the motor cortex have at least 10,000 spines each with a type I excitatory synapse.

b. Spiny stellate neurons: the prominent apical dendrite is not present. Instead dendrites of almost equal length radiate out from the cell body (soma). These neurons are found primarily in layer 4 of sensory cortex. Their axons project locally within the area and not to distant sites.

Physiology: Most spiny neurons/pyramidal cells utilize glutamate as a synaptic transmitter and demonstrate "regular" spiking that is an adapting pattern of discharge in response to a constant current injection. These cells generally demonstrate a significant after hyperpolarization (AHP). Some of the pyramidal cells located in deeper layers, primarily layer 5 may demonstrate a bursting pattern at low threshold. These neurons respond to depolarization by generating repetitive spikes, usually 3 in sequence. The regular firing pyramidal cells are characterized by thin apical dendrites that do not branch extensively in layer 1. In contrast, the burst firing pyramidal cells have thick apical dendrites and extensive branching in layer 1. As we will discuss below, this may have considerable significance for the difference in excitability of the various cortical areas for example motor cortex compared to visual cortex.

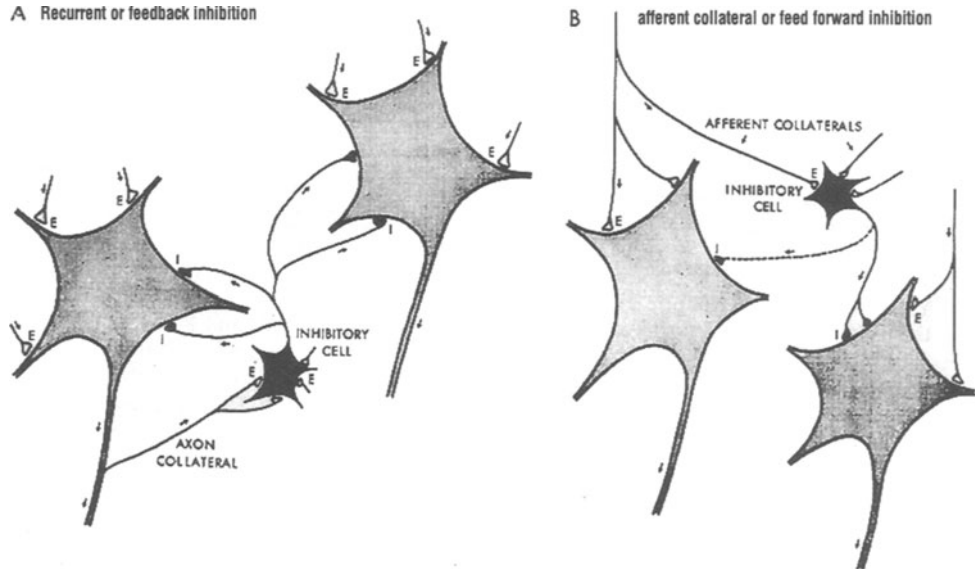


Figure 17-3 Diagram indicating possible function of stellate cells as inhibitory interneurons. Two mechanisms are demonstrated. A) Recurrent or feedback inhibition and B) afferent collateral or feed forward inhibition. Modified from Eccles, J.C. in Jasper, H.et al Basic Mechanisms of the Epilepsies Boston, Little Brown p.249, 1969.

II. Smooth neurons without spines formerly referred to as smooth stellate cells. Multiple types have been described. The most common

is the basket cell that has axons that form baskets around the soma of the pyramidal cells. The Retzius-Cajal neurons are horizontally oriented cells found in layer 1. The Martinotti cell, the double bouquet cell of Cajal and the chandelier cell have a vertical orientation.

Physiology: The smooth cells are generally fast spiking and make type II inhibitory connections utilizing gamma aminobutyric acid (GABA) as the transmitter. In contrast to pyramidal neurons, the action potentials of these fast-spiking cells are brief; the repolarization phase is rapid and followed by a significant under shoot. This has been correlated with very large, fast repolarizing potassium current.

The inter-relationship of neurons within the neocortex is demonstrated in *Figure 17-3.*

BASIC DESIGN AND FUNCTIONAL ORGANIZATION OF CEREBRAL CORTEX:

The cerebral cortex is characterized by two essential design principles: 1) the neurons have a horizontal laminar arrangement, 2) connections occur in a vertical columnar manner. These vertical columns extend from pial surface to white matter. A specific region, a specific stimulus, or a specific stimulus orientation activates each cylindrical column. Activation of a specific column also activates inhibition in adjacent columns, the concept of inhibitory surround. (See Angevine and Smith 1982). In the primary sensory each column is concerned with a particular modality of sensation for a particular representation of the body or specific sector of a field of stimulation. This columnar organization first was described by Mountcastle for somatosensory cortex and has been subsequently found in other sensory and associational cortex. As discussed by Rakic (1988) this columnar or radial organization maybe a reflection of the ontogenetic ingrowth of neurons from the ependymal surface via glial guide to the cortical surface to be discussed in chapter 4. A similar columnar organization of the callosal system has also been demonstrated (See Jones -1985).

FUNDAMENTAL TYPES OF CEREBRAL CORTEX:

Brodmann in 1903 distinguished 2 fundamental types of cerebral cortex: Homogenetic or Heterogenetic.

1. *Homogenetic.* This type as already illustrated in Figure 17-1 has a 6-layer pattern at some time during development recognizable by the end of the 3rd fetal month. This type of cortex is also called neocortex or isocortex, or neopallium, or supra limbic.

2. *Heterogenetic:* This type of cortex does not have 6 layers at any time during development or during adult life. This type of cortex is also called allocortex and has 3 layers. There is a transitional zone between allocortex and the neocortex: the mesocortex that corresponds to the cingulate gyrus, the parahippocampal gyrus, the piriform area and the anterior perforated substance (*Fig.17-4).*

SUMMARY OF THE FUNDAMENTAL 6 LAYERED SCHEME OF NEOCORTEX (refer to Figure 17-1):

Layer I: The molecular or plexiform layers. This layer primarily consists of dendrites and axons from other cortical area, deeper layers and nonspecific thalamic input. A tangential plexus of fibers composed of the apical dendrites, ascending axons and axon collaterals provides a dense collection of axodendritic synapses.

Layer II: The external granular layer. This layer is a relatively densely packed layer of small stellate granule cells and small pyramidal cells whose apical dendrites terminate in the molecular layer and whose axons are sent to lower cortical layers.

Layer III: The external pyramidal layer. This layer is composed of medium and large pyramidal cells whose apical dendrites extend to layer I. The axons of these cells may function as association, commissural or intra cortical association fibers.

Layer IV: The internal granular layer. This layer is densely packed with granular/stellate

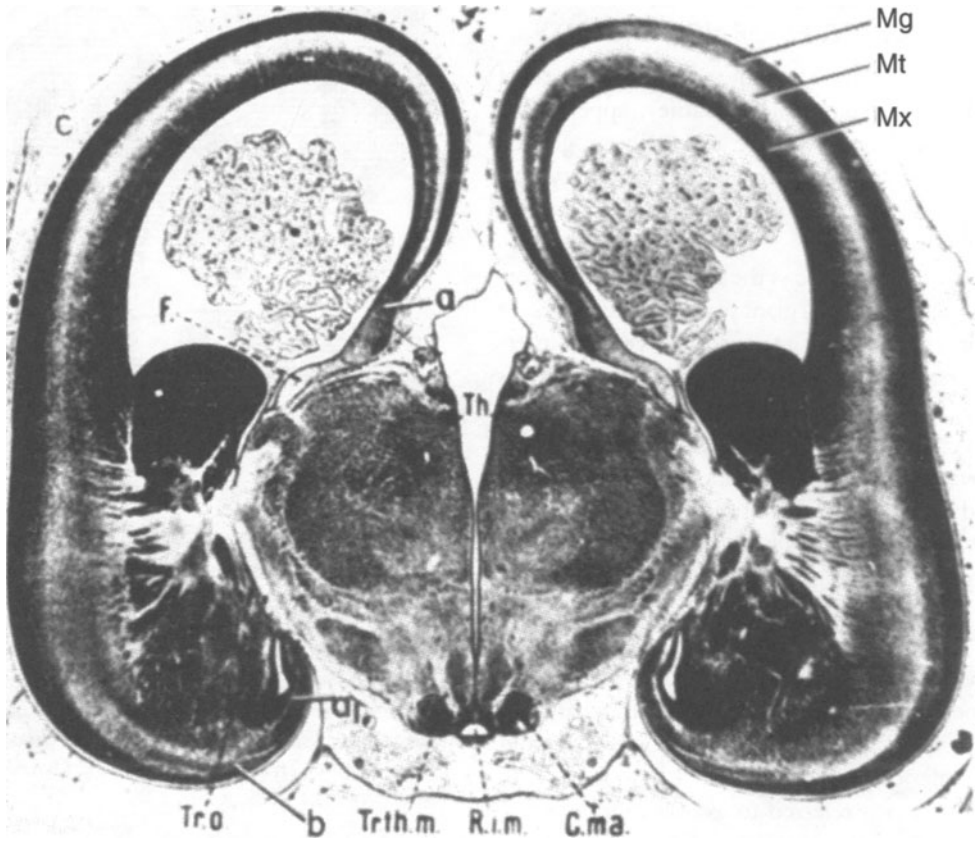


Figure 17-4. Frontal section through the diencephalic part of the prosencephalon of an 87 mm. (crown to rump), 3-1/2-month embryo. a and al = anlage of the hippocampus (heterogenetic or rhinal allocortex); b = anlage of the parahippocampal cortex (limbic mesocortex); c = supra limbic isocortex (or homogenetic). Mg = marginal layer; Mt = mantle layer; Mx = matrix layer. From Yakovlev, P.I.: Res. Publ. Assn. nerv. ment. Dis., 39:3-46, 1962 (Wiliams and Wilkins).

cells. A dense a horizontal plexus of myelinated fibers, the external band of Baillarger is also present composed of the branches of the specific thalamo-cortical projection system. These fibers synapse with the stellate cells of this layer or the basilar dendrites of the pyramidal cells of layer III or with the apical dendrites of the pyramidal cells of layers V and VI.

Layer V: Internal or large and giant pyramidal cell layer also called the ganglionic layer This layer serves as the major source of outflow fibers particularly to motor areas of the basal ganglia, brain stem, and spinal cord and possibly to the projection nuclei of the thalamus. Although cortico- cortical out put arises primarily from the more superficial pyramidal cells of layer 3, layers 5 and 6 also provide such an output. Note that there is some overlap of the functions of pyramidal cell of layers 5 and 6. Collaterals of the axons also function as intra cortical association fibers. In the deeper portion of this layer a dense horizontal plexus of fibers is present the internal band of Baillarger.

Layer VI: The fusiform or spindle cell multiform layer. This layer is composed of a mixture of spindle shaped cells, pyramidal and stellate cells. Dendrites ascend to various cortical levels. The axons enter the white matter as short association fibers or ascend to other cortical layers. However the corticothalamic outflow usually occurs from pyramidal cells in this layer.

CLASSIFICATION OF THE VARIOUS TYPES OF NEOCORTEX:

It is evident that in the adult not all areas of neocortex have the same appearance. Brodmann termed those areas of homogenetic neocortex that demonstrated the typical 6-layered pattern seen in Figure 17-1 as homotypical.

At one extreme is the agranular motor cortex. This has many giant pyramidal cells present in layer 5 but with a virtual absence of an internal granular layer 4. At the opposite extreme is the granular primary sensory projection cortex. Layers 2, 3, and 4 appear as an almost continuous granular layer. Layers of 5 and 6 are thin and few large pyramidal cells are present.

Von Economo divided the cerebral cortex into 5 basic categories (Fig.17-5):

Type 1 is the agranular motor cortex.

Type 2 is referred to as homotypical or frontal granular cortex and is found in the superior frontal gyrus of the prefrontal area.

Type 3 is the midpoint and is best seen in the inferior parietal lobule.

Type 4 is referred to as polar and is represented by the non striate visual association cortex of area 18 close to the occipital pole

Type 5 is the granular striate occipital visual projection cortex. Because the large number of granule cells in this type of cortex resembles- - a cloud of dust, - the Greek word konios is employed –thus the term koniocortex.

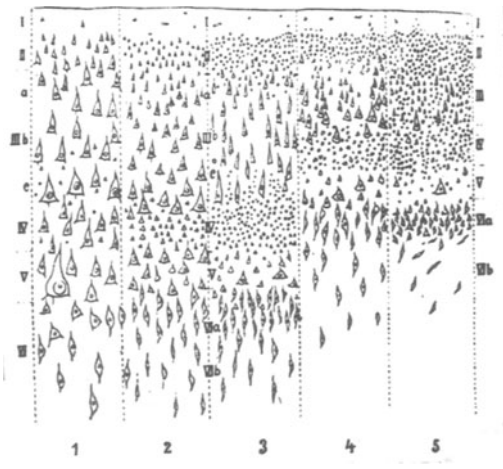


Figure 17-5. The five fundamental types of cortical structure: Type I = agranular motor cortex. Type 2 = frontal homotypical (frontal granular). Type 3 = parietal homotypical. Type 4 = polar, e.g., area 18. Type 5 = granular koniocortex. (From Von Economo, C.: The Cytoarchitectonics of the Human Cerebral Cortex. London, Oxford University Press, 1929, p. 16).

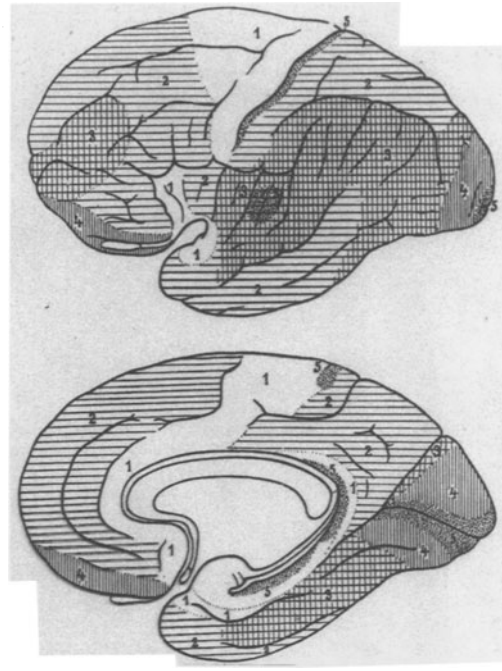


Figure 17-6. Distribution of the five cortical types of Figure 17-5 over the lateral and medial surfaces of the cerebral surface. The Sylvian fissure has been laid open. (From Von Economo, C.: The Cytoarchitectonics of the Human Cerebral Cortex. London, Oxford University Press, 1929, p. 18).

Figure 17-6 demonstrates the distribution of these various cortical types. Von Economo and Koskinis (1925) then developed a classification that dealt in a logical manner with the variations of cytoarchitecture in terms of definable histologic gradations using a letter terminology. Thus motor cortex received the designation FA, premotor cortex FB, and the frontal eye field, FC etc. In this textbook we will follow the classification of Brodmann that has been most commonly employed *(Fig.17-7)**. Numbers were initially assigned as histologically distinct areas were identified in successive horizontal slices moving in anterior and posterior directions from the central sulcus. The crest of the postcentral gyrus would then

** For a comparison of the 2 systems in the monkey see fig. 17-8.*

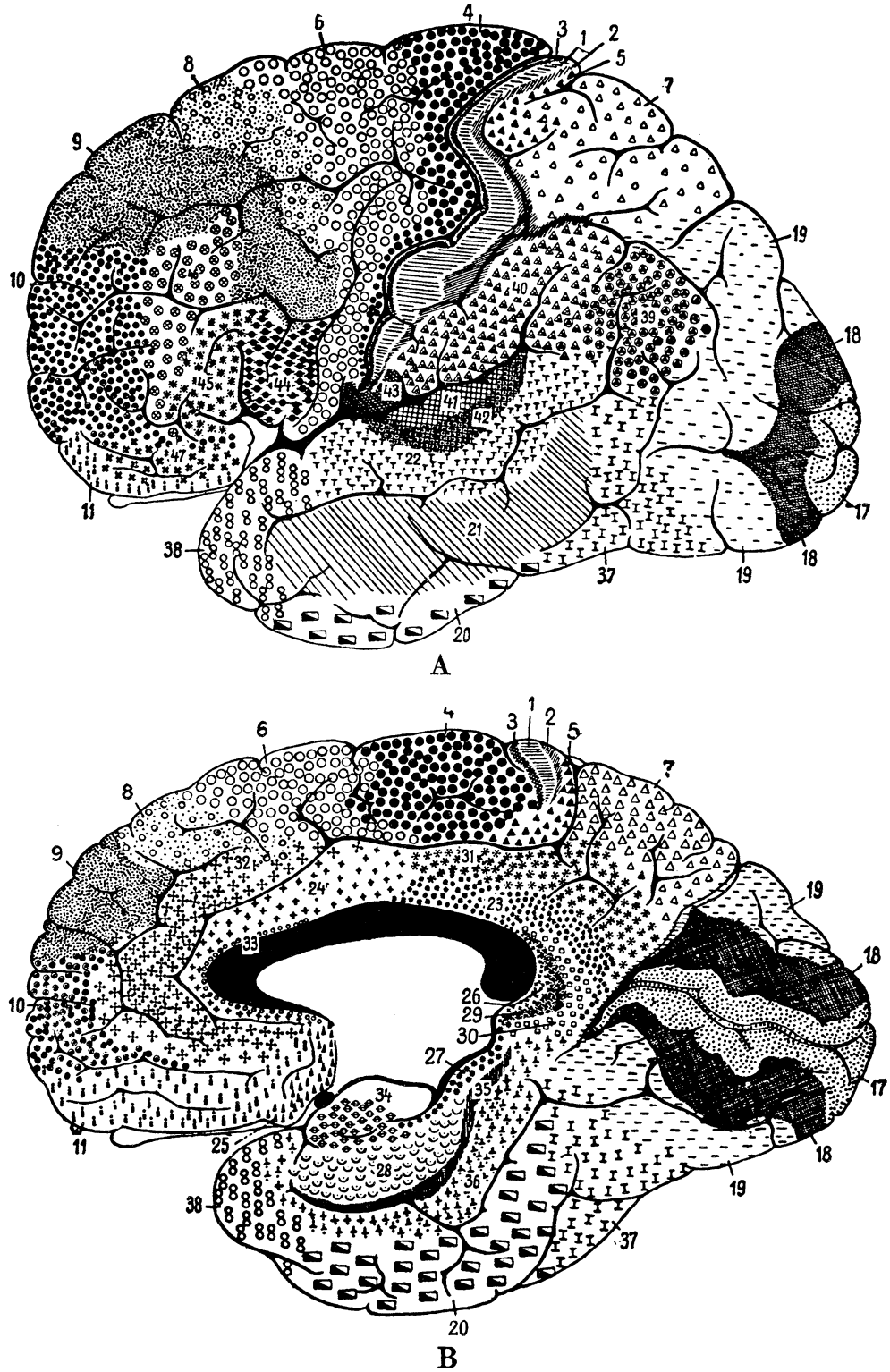


Figure 17-7. Cytoarchitectural areas of cerebral cortex as designated by Brodmann. (From Ranson and Clark: The Anatomy of the Nervous System. Philadelphia, W. B. Saunders, 1959, p. 356).

appear in the 1st horizontal section and would be assigned the number 1 .The primary motor cortex is assigned 4,the premotor cortex 6 and the frontal eye field 8. Thus there is no logical reason why the numbers 6 and 8 are assigned to areas of the frontal lobe and 5 and 7 to areas in the parietal lobes. Nevertheless, some of the numbers are used with sufficient frequency in everyday neurological language that the student should commit these to memory. Before we review these areas with their correlated function, it is necessary to consider the methods employed in the study of functional localization.

PART II. METHODS FOR THE STUDY OF FUNCTIONAL LOCALIZATION IN CEREBRAL CORTEX

A. HOW DO WE STUDY FUNCTION?

In considering functional localization, and the correlation with cytoarchitecture, it has been customary to consider the effects of two general categories: stimulation and ablation.

Stimulation: Various disease processes in man involving the cerebral cortex may produce a local area of excessive discharge, in a sense, a local area of stimulation resulting in focal seizures

Actually our first understanding of cortical function was derived from the systematic study of such cases of focal discharge *(termed focal seizures, or focal convulsions, or focal epilepsy, or epileptiform seizures)* by Hughlings Jackson in 1863 and 1870. Jackson was able to predict that an area existed in the cerebral cortex that governed isolated movements of the contralateral extremities. *Such focal seizures are also referred to as partial seizures in the International Classification (see Commission, 1981, 1989).* These partial seizures are subdivided into *simple partial* (simple motor or sensory or psychic symptoms) as contrasted to *complex partial* (complex motor sequences of automatic behavior and/or alterations in mental function as regards perception, memory and affect) accompanied by impairment of consciousness, confusion and amnesia.

Partial seizures or partial epilepsy must be distinguished from those seizures which are nonfocal that is bilateral or generalized in their onset *(generalized or idiopathic epilepsy in the International Classifications).*

Other methods of stimulation:

Electrical stimulation, of the cerebral cortex may be carried out, in the human patient undergoing operative procedures on the cerebral cortex to identify specific cortical areas or may be employed on animal preparations in the experimental laboratory. Transcranial electrical and magnetic stimulation of cerebral cortex has been developed as a clinical technique.

Evoked potentials: stimulation of afferent pathways may be utilized to identify short latency responses evoked from specific cortical areas. When stimulating the lower extremity (or sciatic nerve) response is limited to that specific area of the contralateral postcentral gyrus devoted to the representation of the lower extremity. Stimulation of the upper extremity will elicit a similar response from a different portion of the contralateral postcentral gyrus: that devoted to representation of the upper extremity. Eventually it is possible to prepare a map of the somatosensory projection cortex of the postcentral gyrus. It is possible to refine this technique at the response end by using microelectrode recordings from within or just outside neurons at particular depths of the cortex. It is also possible to define more carefully the parameters of stimulation as Hubel and Wiesel have done in their analysis of responses in the visual cortex to specific types of visual stimuli (see Chapter 23). The evoked potential method has been subsequently developed as a practical noninvasive method to study conduction in the visual, auditory and somatosensory systems.

By stimulating particular thalamic nuclei, one may map out specific thalamocortical relationships.

A modification of the technique is that of antidromic stimulation of an efferent pathway, such as the pyramidal tract, to map out the cortical nerve cells of origin of fibers in this tract.

Chemical agents locally applied to the pial surface of cerebral cortex may be employed in the laboratory preparation to produce an acute or chronic focus of discharge. The most common agent employed for the acute focus penicillin. Chronic foci are produced by cobalt, or alumina cream.

Interpretation of results: The results obtained by the method of stimulation are subject to several possible interpretations from the standpoint of functional localization:

1. The effect observed may be clearly related to the actual function of the area stimulated, e.g., stimulation of the motor cortex results in discrete movements.

2. The effect observed may be in part related to the spread of discharge to other cortical areas via corpus callosum to the opposite hemisphere or association pathways, within the same hemisphere.

The effects observed may in part reflect the spread of discharge to various subcortical and brain stem centers. The generalized convulsive seizure that may develop secondary to the focal seizure represents such a spread.

At times, the secondary spread to other cortical and subcortical areas may be so rapid that the focal origin of the seizure discharge may be difficult to ascertain and it may be difficult on clinical grounds to separate such seizures from non-focal (primary, generalized) epilepsy.

3. The effects observed may indicate that the remainder of the central nervous system is functioning without the participation of the area stimulated. Thus, if all the neurons of a given cortical area are involved in a seizure discharge, they may be unable to participate in their usual activities, be they of an afferent, integrative, or efferent nature. Thus, the effects of seizure discharges involving prefrontal or hippocampal areas may be in some aspects quite similar to the effect of ablation of these areas as regards intellectual functions, personality, and memory or learning. This concept also implies, in a sense, to release of function in other areas (cortical and subcortical). Therefore, certain of the emotional responses of the patient with seizure discharges involving the prefrontal or temporal lobe areas are also similar to the effects obtained on ablation of these areas and suggest release of other centers.

4. In the interpretation of the relationship of location of the pathology to the seizure manifestation, the threshold for discharge of the underlying cortex must be considered. Thus, in the large series of parasagittal meningiomas reported by Cushing and Eisenhardt (1938), seizure invariably accompanied those overlying the Rolandic cortex ("middle third parasagittal") at a relatively early point in the clinical history, whereas, anterior or posterior one-third parasagittal lesions, had seizure manifestation at a much later point corresponding to a larger size of tumor. Motor cortex has a much lower threshold for seizure discharge than other areas of cerebral cortex.

Ablation: This method involves destruction of a specific area by operative resection, coagulation, or freezing to the point of tissue death. In man, the method of clinical pathological correlation has produced considerable information. The destructive lesions have been the result of a local area of tissue destruction due to blood vessel occlusion, hemorrhage, solitary metastatic tumor, or intrinsic tumor. In the laboratory transient focal depression may be produced by focal cooling or by application of KCl.

Interpretation of results:

1. The observed effects may indicate deficits directly related to a failure of a positive function normally sub-served by the area destroyed. For example, after destruction of parietal somatosensory projection areas, deficits in stereognosis and position sense occur.

2. The effects may reflect the release of centers in other cortical areas or at other levels of the neural axis. This presumes that the area ablated usually inhibits certain functions of these other centers. The end result then is an enhancement of certain functions. Spasticity several days' weeks or months after ablation of the motor cortex is an example.

3. A temporary loss of function of a lower center may follow acute ablation of higher centers. For example, following acute unilateral ablation of all motor cortex in man, there will be observed a temporary loss or depression of deep tendon reflexes and of other stretch reflexes in the contralateral extremities. There will be initially a flaccid paralysis. This state (referred to as the "diaschisis of Von Monakow") is analogous to spinal shock or pyramidal shock. As recovery from this state occurs, deep tendon reflexes return and become progressively more active. The flaccid paralysis is replaced by a spastic paresis. Trans hemispheric effects also occur as discussed by Andres (1991).

B. HOW DO WE CONFIRM THE LOCATION OF THE PATHOLOGY?

Initially, data as to the actual location of the disease process and its nature (old scar from traumatic injury, old area of tissue damage due to ischemia, infection, local compression, or invasive brain tumor) were dependent on final examination of the brain at autopsy. One may then speak of the method of clinical pathological correlation. With the development of neurosurgery it became possible to define and to confirm during life the anatomical boundaries of some disease process, often allowing for treatment or cure of the basic disease process.

The specialized techniques of electroencephalography, arteriography, pneumoencephalography, and radioactive brain scan were developed during the 1930s, 1940s, 1950s, to provide some information about localization prior to surgery.

The subsequent development of the more precise noninvasive imaging techniques of computerized axial tomography, (CT scan), magnetic resonance imaging (MRI scan) and positron emission tomography (PET scan) during the 1970s and 1980s now provide the closest correlation of clinical findings and anatomical location of the lesion in the living patient, supplanting the earlier radiological techniques of arteriography, pneumoencephalography and radioactive brain scans. The techniques of CT scan, MRI, PET and SPECT have been discussed previously (Chapter 2).

Concept of representation and re representation of function: In considering functional localization, one must keep in mind that a given function may be represented and re represented at the various levels of the neural axis.

Ontogenetic factor. In considering the effects of ablation, one must also consider the ontogenetic factor. Bilateral ablation of the prefrontal cortex in the adult monkey produces impairment in the capacity to delay responses. Bilateral prefrontal ablation at one week of age in the infant monkey does not have this effect. Such a monkey when tested at 4 months, the usual age when delay response appears, is able to manifest this capacity. Similar observations may be made with regard to somatosensory and visual pattern discrimination in the infant cat as compared to adult cats following the appropriate resection of the somatosensory or visual projection cortex. Similar observations may be made in man. Thus, extensive destruction in most adults of the speech areas in the left hemisphere will result in a marked and lasting deficit in linguistic expression (so-called Broca's expressive aphasia). Destruction of this same area in the infant or young child does not produce an enduring defect.

C. CORRELATION OF NEOCORTICAL CYTOARCHITECTURE AND FUNCTION

General observation: Those neocortical areas with specialized cytoarchitecture deviating from the classical 6-layered cortex have very specialized function for example primary motor or sensory cortex. In contrast the classical 6-layered pattern tends to occur in association areas such as prefrontal, which have more complex and not such limited highly specialized functions.

The more commonly used Brodmann numbers are listed in the following outline with a brief note as to function. The corresponding terminology of Von Economo and Koskinis is

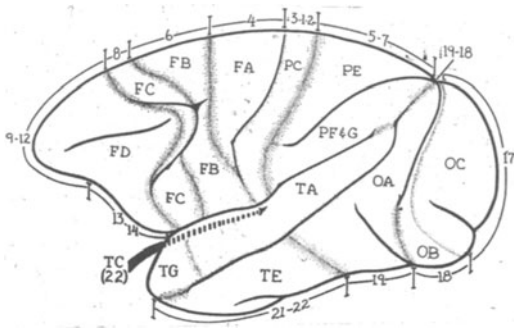


Figure 17-8. Reference diagrammatic cytoarchitectural map of monkey brain relating number system terminology of Brodmann to the letter system terminology of Von Bonin and Bailey (after Von Economo and Koskinis). The borders are only approximate. (From Ruch, T.C., and Patton, H.D.: Physiology and Biophysics. 19th Edition, Philadelphia, W.B.Saunders, 1965, p.156.)

indicated in parentheses. The list is not all inclusive and does not include the areas of mesial temporal lobe. Since many studies have been performed in the monkey a comparison guide for cytoarchitecture is provided in *Figure 17-8.*

Figure 17-9 demonstrates the lobes, gyri and major sulci visible on the lateral surface of the cerebral hemisphere. Figure 17-10 demonstrates the lobes, gyri and major sulci visible on the medial surface of the cerebral hemisphere. The orbital surface is illustrated in Figure 22-1.

FRONTAL LOBE

The following cortical areas according to Brodmann *(Fig 17-7)* are noted in the frontal lobe: Primary motor area - 4, Premotor - 6 & 8, inferior frontal (Broca's) 44, 45, 47; Frontal eye fields area 8, Prefrontal/Orbital - 46, 9, 10, 11, 12, 13, 14. It is customary to divide the frontal lobe into those more posterior areas devoted to motor functions and those more anterior areas devoted to non-motor functions.

TABLE 17-1. MAJOR GYRI IN THE FRONTAL LOBE.

Gyrus	Major Function
Precentral	Origin of volitional motor pathways, the corticospinal and corticonuclear pathways (upper motor neurons)
Superior frontal	Premotor and prefrontal regions
Middle frontal	Prefrontal and frontal eye fields
Inferior frontal	Broca's motor and speech area in the dominant hemisphere
Orbital	Limbic
Gyrus rectus	Limbic

MOTOR AREAS:

Area 4 (FA) corresponds in general to the precentral gyrus and functions as the primary motor cortex. It is continued onto the medial surface as the paracentral lobule (*Fig.17-10, 17-11).*

Stimulation: discrete repetitive focal movements are produced based on the area stimulated for example repetitive jerks of the thumb or of the foot. A march of focal movements may occur, for example starting in the thumb, then spreading to hand, then to arm, then to face and leg etc.

Ablation: an upper motor neuron type weakness occurs with a contralateral monoplegia or hemiparesis.

Area 6 (FB) located anterior to area 4 and thus referred to as premotor cortex, functions as motor association or elaboration area (Fig. 17-8, 18-6). This area also functions to inhibit certain functions of the primary motor cortex. The supplementary motor cortex represents the continuation of this area onto the medial aspect of the hemisphere *(Fig.17-11, 18-12).*

Stimulation: patterns of movement occur, for example tonic rotation of head eyes and trunk to the opposite side associated with tonic abduction of the arm at the shoulder and flexion of the arm at elbow. Stimulation of the supplementary motor cortex produces similar complex patterns of tonic movement .In addition there are bilateral movements of the trunk and lower extremities.

Ablation: Transient release of "primitive" automatic reflexes mediated by the primary motor cortex such as instinctive grasp, and suck occurs. A more persistent release of these instinctive reflexes follows the combined abla-

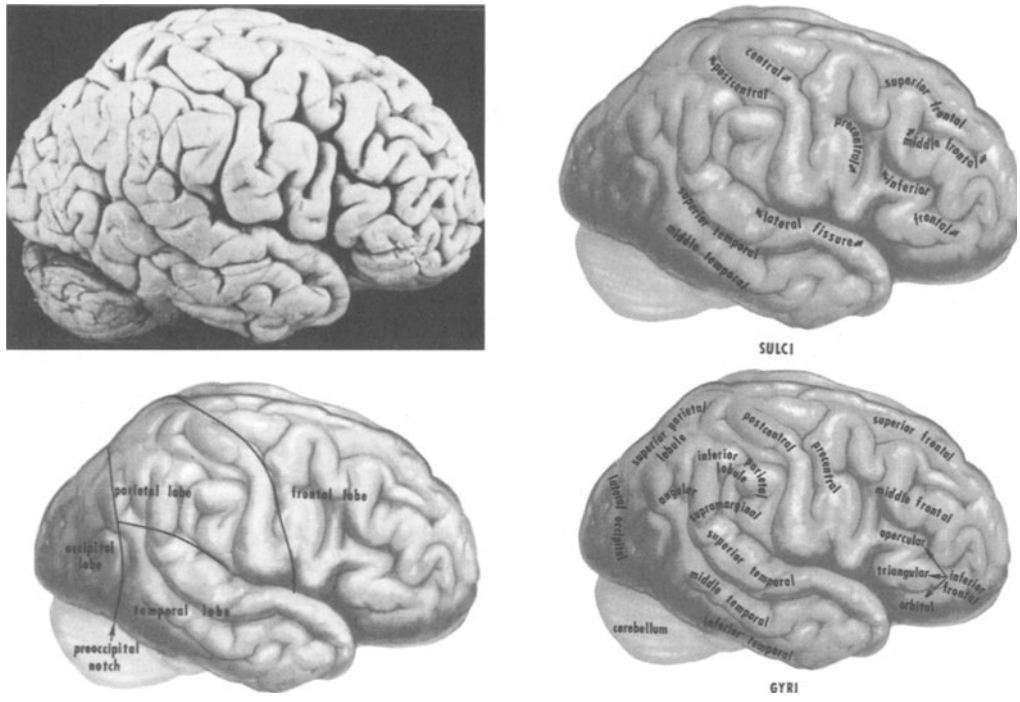


Figure 17-9. Lobes, gyri and major sulci. Lateral surface.

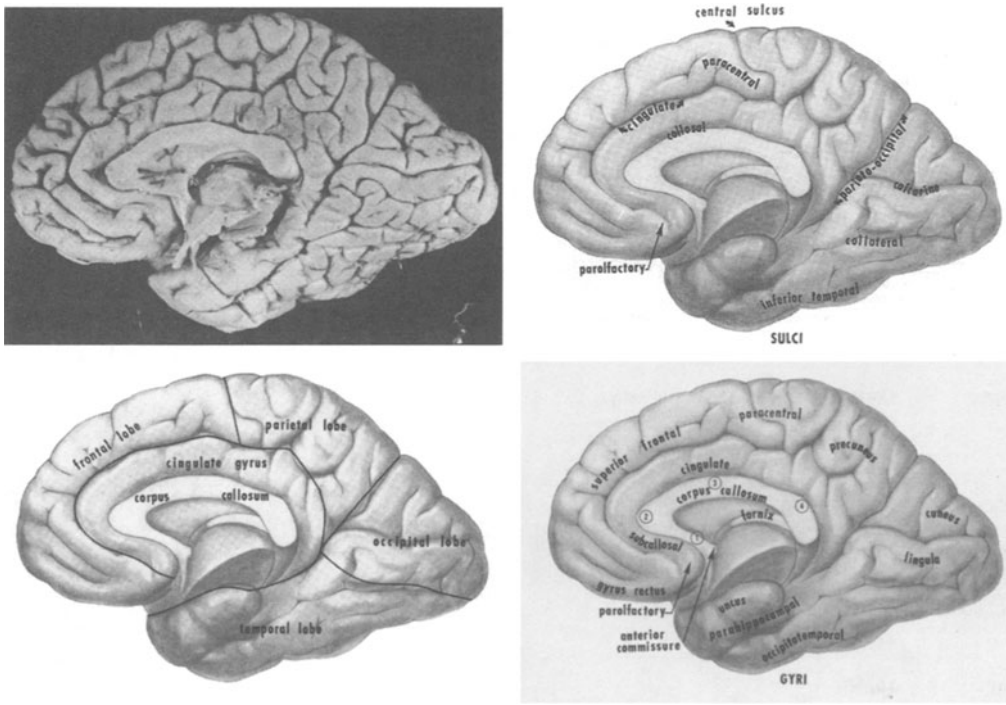


Figure 17-10. Lobes, gyri and major sulci. Medial surface

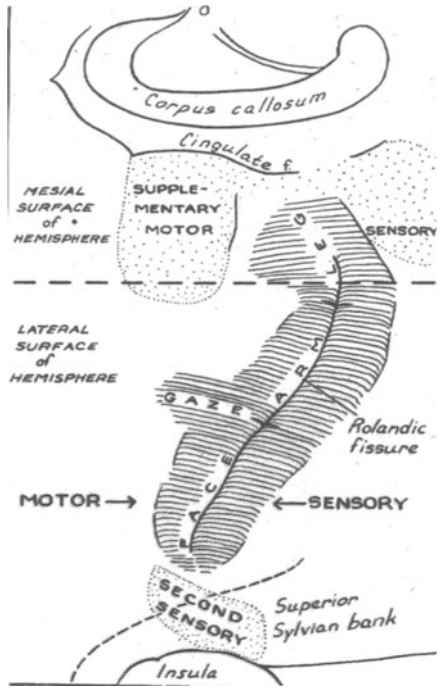


Figure 17-11. Map of somatic motor and sensory areas. Note that the primary motor and sensory areas extend into the depth of the rolandic fissure and extend onto the medial surface of the hemisphere. Note that the premotor cortex, area 6 also extends onto the medial surface of the hemisphere as the supplementary motor cortex. Note the location of the adversive gaze field in relation to motor cortex. (From Penfield, W., and Jasper, H.: Epilepsy and the Functional Anatomy of the Human Brain. Boston, Little, Brown and Company, 1954, p.103.)

tion of areas 6, 8 and supplementary motor cortex. Such lesions also produce a significant gait apraxia –an impairment of the ability to walk without actual weakness or sensory deficit. Other deficits in the initiation of patterns of movement in relationship to somatosensory or visual stimuli may also occur.

Area 8 (FC) (Fig.18-18) located anterior to area 6 in the middle frontal gyrus in the human is often grouped with area 6 as premotor cortex. This area functions in relation to conscious eye turning and is often referred to as the frontal eye field or frontal center for adversive or contraversive eye movement. This area is involved when the subject responds to the command "turn your eyes to the left (or right)" The effects are mediated by descending crossed connections to the pontine center for lateral gaze

Stimulation: (Fig.18-18) a conscious repetitive conjugate eye movement to the opposite field occurs. More specific effects can also be achieved by discrete stimulation within this area for example eyelid opening, repetitive eyelid movements' pupillary dilatation. (Fig.18-19). Bilateral stimulation will result in conjugate upward eye movements.

Ablation: transient paralysis of voluntary conjugate gaze to the contralateral visual field occurs. In general, in man, this paralysis of voluntary gaze does not occur in isolation but is associated with those processes such as infarction which have also produced a severe hemiparesis. The patient then lies in bed with the contralateral limbs in a hemiplegic posture and with the head and eyes deviated toward the intact arm and leg. This deviation most likely reflects the unbalanced effect of the adversive eye center of the opposite intact hemisphere. The effect is usually transient clearing in a matter of days or weeks. A transient neglect syndrome primarily involving the contralateral visual field occurs although contralateral tactile and auditory stimuli may also be neglected. Bilateral ablations within this area in the monkey, resulted in animals that had a bilateral neglect of the environment, remained apathetic and continued to have a "wooden expression". Similar findings may occur in the human patient with degenerative disorders involving these frontal areas.

Areas 44 and 45 (FCB) These areas correspond in general to the inferior frontal gyrus triangular and opercular portions. In the dominant (usually left) hemisphere this constitutes Broca's motor speech center or the anterior speech center (Fig.24-1).

Stimulation (Fig. 24-2): arrest of speech occurs. Occasionally, simple vocalization occurs. A similar arrest of speech may also occur on stimulation of the other speech centers –posterior and superior.

Ablation: a non-fluent aphasia occurs. The patient is mute. With limited lesions, considerable language may return. While isolated

lesions (for example embolic infarcts) involving this area may occur, more often this type of language defect is associated with a contralateral hemiparesis.

PREFRONTAL –NONMOTOR AREAS

Areas 9, 10, 11 and 12 (FD), the prefrontal areas, are concerned with emotional control and other aspects of cognitive function (Fig. 18-21). Areas 13,14 (FE, FF, FG, FH) are also often included in this group.

Stimulation: Complex partial seizures with alteration of personality, emotion, and behavior occur often accompanied by tonic motor components. Note that 25% of complex partial seizures originate in frontal lobe structures but 75% originate in temporal lobe.

Ablation: An alteration in personality, affect and control of emotion may occur and /or there may be an alteration in cognitive/executive function.

PARIETAL LOBE

Areas 3, 1, 2 (PA, PB, PC) These areas correspond to the *postcentral gyrus* and function as the somatosensory projection areas (continue into paracentral lobule).

Stimulation: Episodes of localized tingling paresthesias occur which may spread as with focal motor seizures.

Ablation: Deficits in cortical sensory (discriminative sensory) modalities will occur, for example stereognosis, position sense, graphesthesia, and tactile localization.

Areas 5, 7 plus in human 39, 40 (PD, PE, PF, PG): The Parietal Lobules About half way up the postcentral sulcus, the *intraparietal sulcus* extend posteriorly, dividing the parietal lobe into superior and inferior parietal lobules. The *inferior parietal lobule* consists of the supramarginal and angular gyri. The *supramarginal gyrus* surrounds the posterior ascending limb of the lateral sulcus. The *angular gyrus* is behind the supramarginal gyrus and surrounds the posterior end of the superior temporal sulcus *(Table 17-2).*

Areas 39, 40 (PG, PF) correspond to the inferior parietal lobule (the angular and supramarginal gyri). These areas in the dominant hemisphere function in relation to reading and writing as higher integrative areas for language. This area is part of the posterior speech area. In the nondominant hemisphere these areas relate to our concepts of visual space.

TABLE 17-2. MAJOR GYRI IN THE PARIETAL LOBE.

Gyrus	Major Functions
Postcentral	Sensory cortex
Superior parietal lobule	Sensory associational
Inferior parietal lobule: --Pars supramarginal --Pars angular	Sensory language areas in the dominant hemisphere
Precuneus	Sensory associational

Stimulation: In the dominant hemisphere, arrest of speech occurs.

Ablation: In the dominant hemisphere, defects in reading, writing and calculations occur. These deficits along with difficulty in finger identification and left/right confusion constitute aspects of the Gerstmann syndrome. A variety of fluent aphasia occurs. In the nondominant hemisphere, a denial or neglect syndrome occurs.

TEMPORAL LOBE:

The temporal lobe is a complex structure that includes neocortex, allocortex, mesocortex and a subcortical nucleus (the amygdala). At its posterior borders it merges into the parietal and occipital lobes.

Major areas in the Temporal Lobe from figure 17-7:

Auditory (Transverse Temporal) 41; Auditory associational 42 and 22; middle temporal 21; inferior temporal 20; posterior temporal 37; entorhinal 27, 28, 35.

The temporal lobe lies below the lateral sulcus and on its lateral surface has a sequence of three anterior to posterior arranged gyri: the superior, middle, and inferior temporal gyri.

The inferior temporal gyrus extends onto the ventral surface of the cerebrum. The supe-

TABLE 17-3 GYRI IN THE TEMPORAL LOBE

Gyrus	Major Functions
- Hippocampal formation - Amygdala	- Limbic and memory - Limbic
Parahippocampal	Limbic
Occipitotemporal	Limbic
Inferior temporal	Limbic
Middle temporal	Limbic and facial recognition
- Superior temporal - Transverse temporal gyri	- Sensory language area in the dominant hemisphere; - Auditory area

rior temporal gyrus forms the temporal operculum. Near its posterior end two gyri are seen running into the lateral fissure (Table 17-3). These are the transverse temporal gyri, consisting of the primary receptive auditory cortex, area 41.

One of the first conclusive bits of evidence on the significance of anatomic asymmetry in the cerebrum was noted by Geschwind and Levitsky (1968) in the temporal lobe. They made a horizontal section through the lateral sulcus and removed the overlying parietal and occipital cortex. They called this exposed region of the superior temporal gyrus, the *planum temporale.* They noted a larger planum temporale in the left temporal area than on the right side in right handed humans. In left-handed individuals the area was the same on both sides. Their observations on the anatomical basis of cerebral dominance have since been supported by radiological and other anatomical studies.

Areas 41, 42 (TC, TB) the transverse gyri of Heschl function as primary auditory projection areas.

Stimulation: Episodic tinnitus (a ringing sensation) occurs. Usually such seizures are not limited to this symptom in isolation, since other aspects of temporal lobe are involved to produce the more complex phenomena of the temporal lobe seizure.

Ablation: limited unilateral lesions may produce a disturbance in the ability to localize sounds. Bilateral lesions of a limited nature would be rare but could produce "cortical deafness"

Area 22 (TA) corresponds to the superior temporal gyrus and surrounds areas 41-42. This is an auditory higher association center. In the dominant hemisphere, the posterior half of this area represents an auditory association area concerned with the reception and interpretation of spoken language. This is one component of the posterior speech area. The area is often referred to as Wernicke's receptive aphasia center. In the nondominant hemisphere this area is more concerned with visual aspects of space.

Stimulation: Stimulation of the posterior speech (Wernicke's) area (Fig.24-2) produces an arrest of speech. Seizures originating in the superior temporal gyrus are also characterized by "experiential "phenomena: distortions of auditory and visual perception alterations in the sense of time and in well formed visual and auditory hallucinations (psychical seizures). As will be discussed in chapter 22,complex partial seizures that may begin with these phenomena but subsequently proceed to impairment of awareness; amnesia and automatisms (unconscious stereotyped patterns of movement) reflect involvement of or spread to the mesial temporal areas of hippocampus and amygdala. Fear that may also accompany these seizures reflects involvement of the amygdala. Olfactory hallucinations that may also accompany these seizures reflects involvement of the mesial temporal structure, the uncus.

Ablation: Damage to Wernicke's area a part of the posterior speech area produces a deficit in the comprehension of speech, a type of fluent aphasia.

Additional information about more extensive unilateral or bilateral damage to the temporal lobe will be considered in chapters 22 and 30. Suffice it to say, that bilateral damage to the hippocampus will produce severe deficits in the ability to record new memories. Damage to the amygdala will alter emotional control

TABLE 17-4 MAJOR GYRI IN OCCIPITAL LOBE.

Gyrus	Functions
Lateral occipital	Visual associational
Lingula	Superior visual field
Cuneus	Inferior visual field

OCCIPITAL LOBE

The lateral occipital gyri consist of visual associative cortex. The visual receptive cortex (calcarine-cortex) is found on the medial surface of the hemisphere (Table 17-4).

Areas in the Occipital Lobe: visual (calcarine) 17; visual association 18 & 19.

Area 17 (OC) corresponds to the striate cortex bordering the calcarine fissure and functions as the primary visual projection area. In modern physiological terms the designation V1 is utilized.

Stimulation: Seizures originating in this area produce simple unformed visual hallucinations such as flashing lights, stars or jagged lines. The phenomena may be localized to the contralateral visual field or at times to the contralateral eye.

Ablation: Homonymous visual deficits are produced for example, a homonymous hemianopsia or quadrantanopsia.

Areas 18, 19 (OB, OA) form surrounding stripes around area 17. These areas function as visual association areas of varying complexity. The terms V2-V4 are utilized. These areas are also involved in the fixation and following of objects in the contralateral visual field. Note that visual areas V4 and V5 extend into the adjacent temporal-parietal cortex.

Stimulation: Some of the effects are similar to stimulation of area 17. In addition conjugate deviation of the eyes to the contralateral field will occur.

Ablation: Selective lesions may produce deficits in some of the more complex visual activities. In addition defects in visual fixation and following may occur.

III. DEVELOPMENTAL ASPECTS OF NEOCORTEX:

The topics of prenatal development, postnatal development and abnormalities of cortical neuronal migration are discussed in chapter 4 and on this chapter's CD ROM .

IV. SUBCORTICAL WHITE MATTER AFFERENTS AND EFFERENTS

Essentially three types of fiber systems occupy the subcortical white matter: (1) projection fibers, (2) commissural fibers, and (3) association fibers.

Projection fibers consist of the corticopetal afferent fibers, such as the thalamocortical radiations, and the corticofugal efferent fibers such as the corticospinal, corticoreticular, and corticorubral tracts *(Fig. 17-12)*.

The major commissural systems are the corpus callosum, anterior commissure, and hippocampal commissure. The corpus callosum is the major commissure for the neocortical areas (except the middle and inferior temporal gyri) *(Fig. 17-13)* and the rostral portions

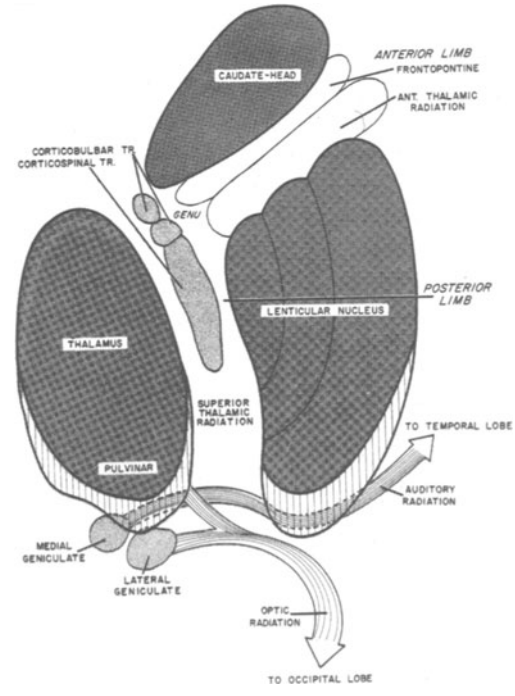


Figure 17-12. Projection fiber systems passing through the internal capsule. The superior thalamic radiation includes fibers projecting from ventral thalamus to sensory and motor cortex.

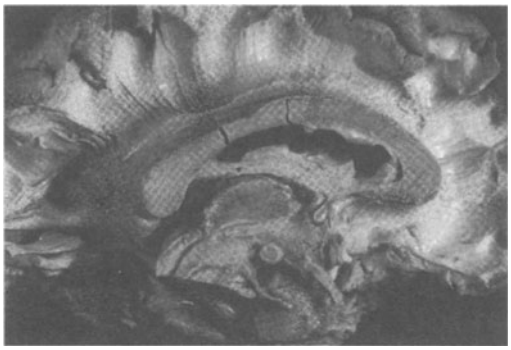


Figure 17-13. Radiation of fibers from corpus callosum as dissected in human brain.

of the superior and inferior temporal gyrus (see Pandya and Posene 1985- for a more detailed discussion). In general, homologous areas of the two hemispheres are interconnected. However, there are significant regional variations between homologous areas as regards fiber density *(Fig. 17-14)*. Thus, there is a high density of callosal fibers connecting the premotor areas of the two cerebral hemispheres. On

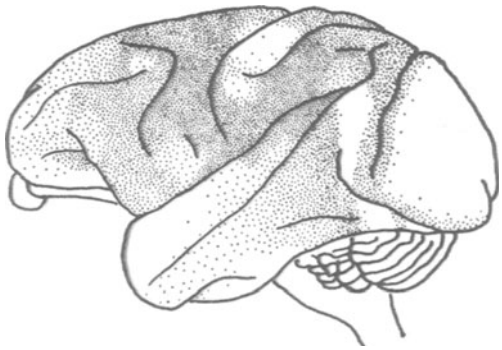


Figure 17-14. Pattern of distribution of commissural fibers over the cortical surface of the left hemisphere of the monkey (Macaca mulatta) as studied following section of major commissures. (From Myers, R. E.: In Ettlinger, E. G. (ed.): Functions of the Corpus Callosum. Boston, Little, Brown & Company, 1965, p. 142).

the other hand, a primary visual projection area - area 17 - has almost no direct callosal connection to the contralateral hemisphere. Area 17 transmits to the adjacent area 18 that has connection to contralateral area 18[1].

Cortical areas also differ as regards the spread of fibers to asymmetrical as well as to symmetrical points in the contralateral hemisphere. Thus area 6 has widespread connections in the contralateral hemisphere not only to area 6 but also to areas, 4, 5, 7, and 39, whereas area 4 has discrete contralateral connection only to the homotypic points.

The anterior commissure interconnects the rostral portions of the superior, middle and inferior temporal gyri, inferior-posterior orbital gyri and paleocortex (parahippocampal gyrus). The hippocampal commissure[2] interconnects the hippocampal formation and dentate gyri (archicortex) and the surrounding presubiculum, entorhinal and adjacent inferior temporal gyrus. These fibers are conveyed via the fimbria of the fornix and cross at the point beneath the splenium of the corpus callosum, where the posterior pillars of the fornix converge.

Two types of subcortical association fibers may be distinguished (excluding from this discussion, the intracortical association fibers): (a) short subcortical U or arcuate fibers which interconnect adjacent gyri and (b) long fiber bundles which reciprocally interconnect distant cortical areas. The following long fiber bun-

---

[1]*The organization of callosal projections is more complex than the picture provided by the early degeneration maps. Thus within somatosensory cortex callosal connections are most dense in areas 2, less dense in area 1 and least dense in areas 3B. Within each of those areas differences also occur. In area 3B, relatively dense connections are present for trunk and head but relatively sparse connections for hand and foot. In contrast within area 2 relatively dense connections are present for all parts of the body. Significant changes occur during development in part related to the overlap with thalamocortical afferent input. For a more complete discussion see Killackey 1985, Killackey and Chalupa 1986, Dehay et al 1988. The end result is in part a complementary relationship to the distribution of thalamocortical fibers.*

[2]*In the monkey two hippocampal commissures have been identified-based on relationship to the fornix. (For a more complete discussion of the topography of commissural fibers see Pandya and Rosene, 1985).*

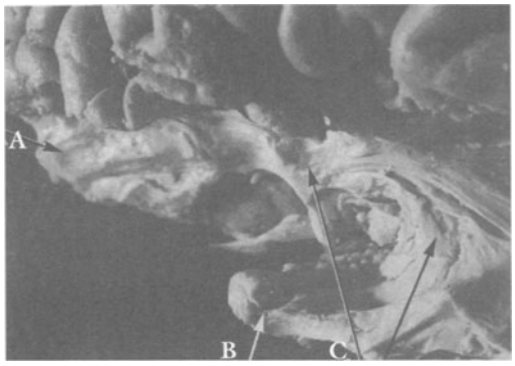


Figure 17-15. Dissection of long fiber systems; the uncinate fasciculus (C) passing from orbital frontal (A) to anterior temporal areas (B).

dles may be distinguished on blunt dissection of the cerebral hemisphere:

1. The *uncinate fasciculus* interconnects the orbital and medial prefrontal areas and the anterior temporal area *(Fig. 17-15)*.
2. The *superior longitudinal fasciculus* interconnects the superior and lateral frontal, parietal and temporal, and occipital areas (Fig. 24-5). The extension of this fiber system into the temporal area, passing through the subcortical white matter of supramarginal and angular gyri, is often distinguished as the arcuate fasciculus. This fasciculus has considerable importance because of its role in connecting the receptive language centers of the temporal lobe with the expressive motor speech centers of the inferior frontal gyrus. Such a connection must be made if a sentence that has been heard is to be repeated.
3. The *cingulum* passes within the subcortical white matter of the cingulate gyrus; it interconnects the subcallosal, medial-frontal, and orbital-frontal with the temporal lobe, occipital areas, and cingulate cortex.
4. The *inferior longitudinal fasciculus* interconnects the occipital and inferior temporal areas.
5. The *inferior frontal occipital fasciculus* interconnects the frontal and occipital areas. It is often difficult to clearly differentiate this fiber system from the uncinate fasciculus.

MAJOR AFFERENT INPUTS AND EFFERENT PROJECTIONS OF NEOCORTEX:

AFFERENT INPUTS:

THALAMUS:

The thalamus is the major source. The transmitter is glutamate. With the exception of the olfactory system, all sensory information passes through the thalamus`.

In many classifications, the thalamus has been divided into three major divisions: 1) the dorsal thalamus, 2) the ventral thalamus, and 3) the epithalamus.

The **dorsal thalamus** is by far the largest component and at times the term thalamus has been applied only to the dorsal thalamus. This structure is composed of a series of relay nuclei that connect in a reciprocal manner with the cerebral cortex and the striatum (Refer to chapter 15) these nuclei can be subdivided into specific projection (or relay) nuclei and nonspecific or diffuse projection (or relay) nuclei.

The *specific nuclei* have specific afferent inputs and project in a relatively precise topographic manner to specific areas of cerebral cortex. Experience, or functional disuse may modify the precise cortical areas devoted to the topographic representation of a given sensory area. Examples of specific nuclei and their cortical projections have been provided in chapter 15.

The densest input from the specific relay projection nuclei is to layer 4, but as indicated above, pyramidal cells in layers 3 and 5 many also receive direct or indirect inputs. There is a modality specific columnar arrangement.

The *nonspecific nuclei* have a more diffuse input and a more diffuse but not necessarily a generalized cortical interaction. Examples include the following: midline nuclei (massa intermedia), central-medial, intralaminar nuclei, and the medial dorsal (which is diffuse to frontal areas).

The nonspecific nuclei project mainly to layer 1.

The **ventral thalamus** is a thin shell nucleus that is external to the external medullary lamina. It does not project directly to cerebral

cortex, but receives innervation from cerebral cortex. The subnuclei grouped as the thalamic reticular nucleus have specific reciprocal relationships with projection (relay) nuclei in the dorsal thalamus. As we will see below in discussing the basis of the electroencephalogram these nuclei have a significant effect on thalamocortical interactions. These nuclei in the rodent (but not in the primate) have a high concentration of GABA-ergic neurons. The drive on the relay nuclei is therefore inhibitory.

The **epithalamus** includes the pineal body, the stria medullaris and the habenular trigone. These structures relate primarily to the hypothalamus and are not relevant to a discussion of thalamocortical interactions.

NON-THALAMIC SOURCES OF INPUT:

There are multiple other subcortical sources of input including the following.

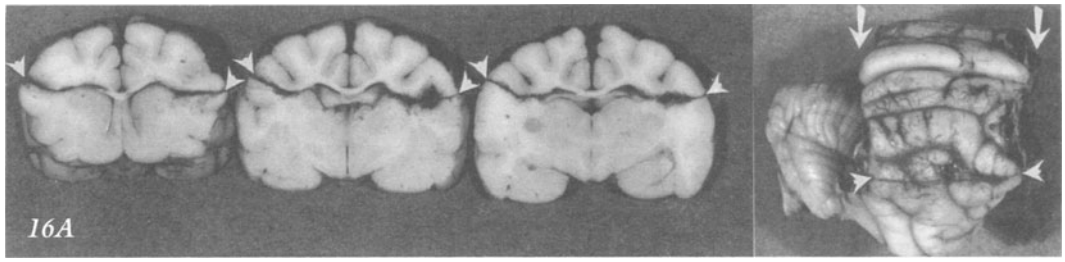
1. **noradrenergic (norepinephrine)** pathway from the locus ceruleus of the midbrain projecting in primates predominantly to layer 6 of the motor and somatosensory cortex and related frontal and parietal association cortex. This pathway functions in relationship to arousal responses induced by sensory stimuli and activity in this system is altered during the rapid eye movement stage of sleep
2. **serotoninergic pathway** from the raphe nuclei in the pons and medulla and the pontine reticular formation. Although these neurons project to all cortical areas, the predominant projection in the primate is to layer 4 of area 17, the primary visual cortex. This system may be involved in the onset of the slow wave stage of sleep. During rapid eye movement sleep there is decreased activity in this system. Damage to the system produces insomnia.
3. **dopaminergic pathways** from ventral tegmental – rostral mesencephalic nuclear groups. The strongest projection is to the prefrontal cortex, and limbic system. The fibers extend to all cortical layers except for IV. The projection is primarily inhibitory. This system is probably involved when psychotic behavior occurs in schizophrenia.
4. **cholinergic pathways** from the basal fore brain nucleus of Meynert project widely to cerebral cortex. In addition cholinergic neurons in the septum project to the hippocampus. In addition, cholinergic neurons in the brain stem tegmentum project to the thalamus and will be discussed in the chapter on sleep (chapter 29). Electrical stimulation of brain stem reticular formation (resulting in desynchronization /arousal of the EEG) results in an increase in rate of liberation of acetylcholine from the surface of cerebral cortex. This effect may be mediated through the reticular formation projection to the basal fore- brain.
5. **GABAergic pathways** from basal forebrain, ventral tegmental area and zona incerta to sensory and motor cortex.
6. **claustrum** projects to all sensory, limbic, and motor areas with an excitatory input.

EFFERENT PROJECTIONS:

Projections occur in a reciprocal manner with many subcortical areas (thalamus, basal ganglia, brain stem and spinal cord). However these projections are estimated to account for only 0.1 to 1% of all fibers in the white matter. Instead most fibers are involved in intra- hemispheric and interhemispheric connections, pyramidal neurons to pyramidal neurons and to interneurons.

Part V: Neurophysiology Of The Cerebral Cortex: Correlates Of Cortical Cytoarchitecture And The Basis Of The Electro-Encephalogram will be found on the CD ROM chapter 17

Part VI: Clinical And Physiological Correlates Of Cytoarchitectural Variation will be found on the CD ROM chapter 17



PART V: NEUROPHYSIOLOGY OF THE CEREBRAL CORTEX: CORRELATES OF CORTICAL CYTOARCHITECTURE AND THE BASIS OF THE ELECTRO-ENCEPHALOGRAM:

The cerebral cortex of man and of other mammals is characterized by continuous rhythmic sinusoidal electrical activity of variable frequency. This electrical activity may be recorded through the scalp of man in the form of the electroencephalogram (EEG) or directly from the cerebral cortex during surgery in the form of the electrocorticogram (ECG). The term EEG will be used during the subsequent discussion to refer to the activity found in either the EEG or the ECG. The electroencephalogram provides a physiologic correlate of the various states of consciousness.

The normal electroencephalogram (EEG) in the awake adult who is recorded while resting with eyes lightly closed is characterized by a dominant activity in the posterior (parietal-occipital) recording areas of continuous 8-13 Hz sinusoidal waves of 25-75uv (Fig.2-18). Amplitudes recorded directly from the cortex are higher. This pattern is referred to as the alpha rhythm since this was the first pattern discovered. The second described pattern the beta rhythm is found predominantly in the frontal recording areas and consists of low amplitude 14-30Hz activities. Many sedative medications will produce increased amounts of generalized beta activity and eventually generalized slow wave activity. The frequency of the basic background activity is also influenced by the age and level of consciousness of the patient. Any pattern slower than alpha is referred to as composed of slow waves (theta=4-7Hz; delta =0.5-3Hz) as illustrated in figures 2-24, 2-25. Many

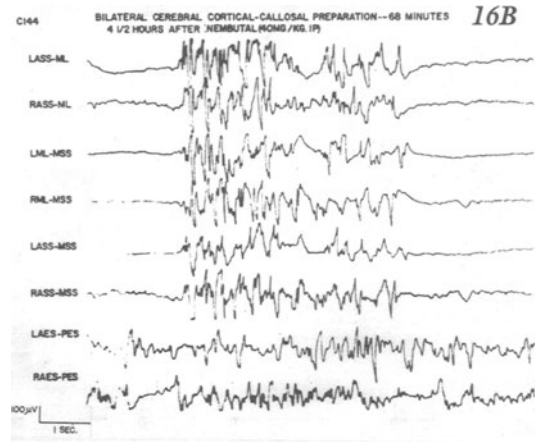


Figure 17-16. Isolated cerebral cortex. A) The anatomical bilateral cortical callosal preparation. B) The electrical activity of the preparation. The upper 6 channels are bipolar recordings from the isolated areas. The lower 2 channels are recorded from the non-isolated cortex. From Marcus, E. M. In Reeves, A. Epilepsy and the Corpus Callosum, New York Plenum Press, p.158. 1985.

sedative medications will produce increased amounts of generalized beta activity and eventually generalized slow wave activity. (Fig. 2-21). The frequency of the basic background activity is also influenced by the age and level of consciousness of the patient. (Fig. 2-19, 2-20) In general the activity of the two cerebral hemispheres is relatively symmetrical and synchronous.

The electrical activity recorded is not a result of axon potentials and does not represent the activity of individual neurons and synapses. Instead EEG rhythms represent the summated electrical activity of a large number of synapses located in the more superficial layers of the cerebral cortex. Seizure discharges do not originate in single neurons but instead are generated in a group of neurons that manifest increased excitability and synchronization (the

epileptic focus). Never the less certain mutations involving the neuronal membrane and the synaptic receptor provide the basis for several types of genetically determined seizure disorders (see chapter 29). The difference between axonal and synaptic activity has been discussed in chapter 5.

THE ACTIVITY OF ISOLATED CEREBRAL CORTEX:

In considering the basis of the electroencephalogram, it is of value to first consider the activity of large blocks of cerebral cortex isolated from all subcortical interactions, but retaining pial blood supply. The basic activity of such preparations in the cat, the monkey and in the human is characterized by bursts of electrical activity composed of mixed frequency sharp waves, spikes, slow waves and fast activity alternating with periods of relative electrical silence (Ingvar and Echlin). In the chronic studies of Kellaway et al (1966) the bursts of activity were correlated in large part with unit discharges in the depths of cortex at the level of the large pyramidal cell bodies. In a related preparation large homologous blocks of cerebral cortex were isolated in each hemisphere along with the interconnecting corpus callosum *(Fig.17-16A),* (Swank (1949, Marcus&Watson, 1966). The basic pattern is composed of bilateral relatively synchronous and symmetrical bursts of activity with intervening periods of relative electrical silence *(Fig.17-16B)*. Similar burst suppression type activity is obtained in preparations in which all thalamic, hypothalamic and rostral mesencephalic structures have been ablated. The burst suppression pattern may be seen in several clinical circumstances: 1) very deep anesthesia, 2) diffuse encephalopathies as in anoxic encephalopathy or encephalitis, 3) following intractable status epilepticus or 4) in the premature brain.

THE ACTIVITY OF ISOLATED THALAMUS

In contrast in the studies of Kellaway et al (1966), the electrical activity of isolated thalamus was characterized by continuous sinusoidal waves of 8Hz.The more recent studies of Steriade and Llinas (1988) have demonstrated that all thalamic reticular neurons can spontaneously generate rhythmic discharges at a rate of approximately 10 Hz. Groups of such cells even when deafferentate can generate synchronized oscillations. These neurons have a strong inhibitory input to the thalamic relay (projection) neurons and thus could entrain these neurons in a similar oscillation. This could then be reflected in a similar entrainment of cortical neurons and synapses in a 10 Hz oscillation. (See below).

In brief then the continuous rhythmic activity seen in the electroencephalogram must indicate the effects of thalamic neurons on the activity of cortical neurons and synapses. As we will see below, brain stem structures are also of importance in modifying cortical activity.

MODIFICATION OF CORTICAL ACTIVITY BY STIMULATION OF VARIOUS STRUCTURES: EVOKED POTENTIALS.

The background cortical electrical activity may be modified by stimulation at various levels. These evoked responses include the superficial cortical response, the direct response, the transcallosal response, the primary evoked response, the recruiting response and the generalized arousal response.

Primary evoked response. Stimulation of the sciatic nerve or of other specific sensory pathways produces a similar surface positive wave followed by a surface negative wave. *(Fig.17-17)* A similar response of much shorter latency (1-5msec) is produced by stimulation of the specific thalamic nucleus involved in the primary evoked response.

Augmenting response: With repetitive stimulation of the same nucleus at 6-12 Hz the amplitude and latency of each successive response increases *(Fig. 17-17).*

Recruiting response: In contrast, repetitive 6 to 12 Hz stimulation of the nonspecific thalamic nuclei such as the intralaminar, the medial or midline groups or the thalamic reticular

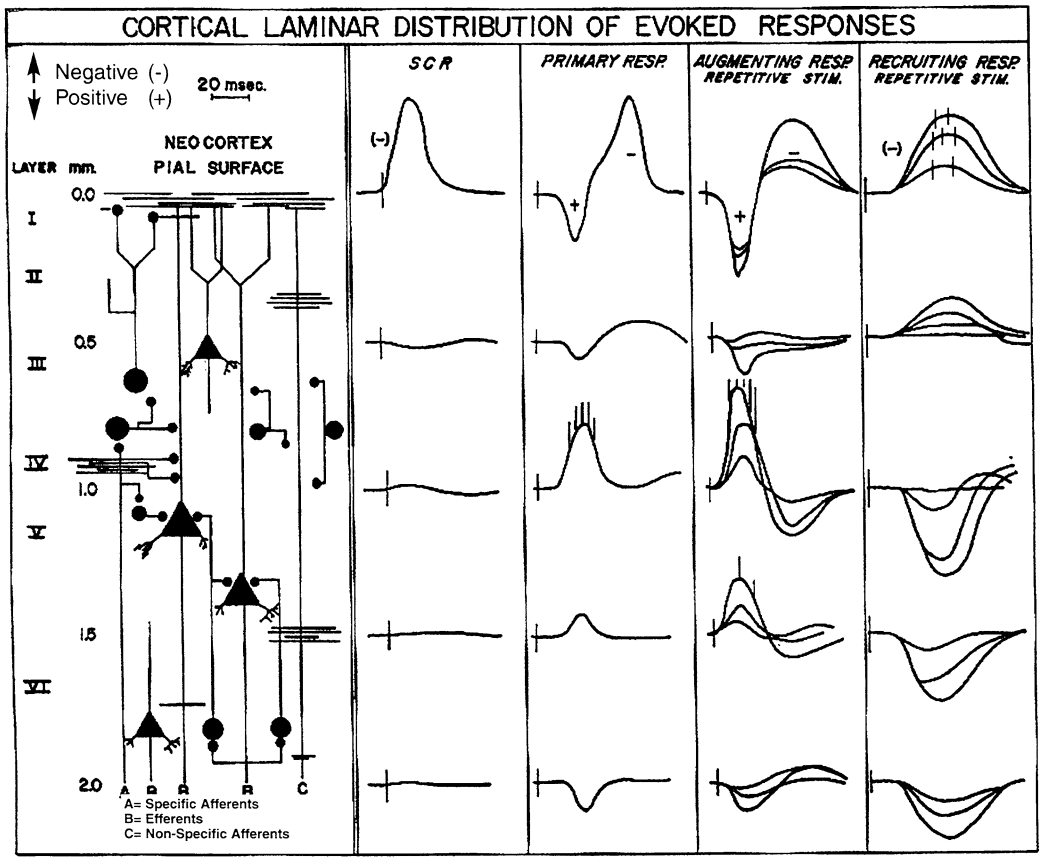


Figure 17-17. Laminar analysis of the various cortical evoked responses in terms of the type and magnitude of response recorded with an external microelectrode at various depths. Specific afferent fibers terminate in layer IV and are shown making synaptic contact with both granule cell interneurons and adjacent pyramidal cells. Nonspecific afferent fibers are shown terminating in many layers including layer I. The SCR (superficial cortical response) is limited to the superficial layers of cerebral cortex. The initial surface positive component of the primary evoked response (specific stimulus, recording from specific cortical projection) originates in the deeper cortical layers (the vertical lines represent cell discharges). The subsequent surface negative wave originates in superficial cortical layers. The transcallosal response would have a similar form and analysis. Specific thalamic nucleus stimulation results in the augmenting response. The origin of the recruiting response to stimulation of nonspecific thalamic nuclei is complex (see text). (Reproduced with modifications from an unpublished diagram by Purpura)

nucleus) produces a predominantly surface negative response of greater latency (15-60 msec) termed the recruiting response *(Fig.17-17, 17-18)*. The response waxes and wanes and is similar to the 8 to 12 Hz spindle response that characterizes light anesthesia in the cat .In the human, a similar spindle occurs at 14 - 15 Hz during stage 2 sleep. Although this system is referred to as the diffuse thalamocortical system, in the monkey, the response is obtained predominantly from the frontal and parietal association cortex. The recruiting response represents summated EPSPs (excitatory post synaptic potentials) generated in the more superficial layers of cerebral cortex and the waves are therefore surface negative. At times a small initial surface positivity may be present. Under particular conditions of anesthesia with stimulation of these same thalamic nuclei, a longer duration (100-200 msec) surface negative wave may follow the initial wave of the recruiting response. This is however correlated with a prolonged hyperpolarization in the deeper cortical layers .In the cat preparation

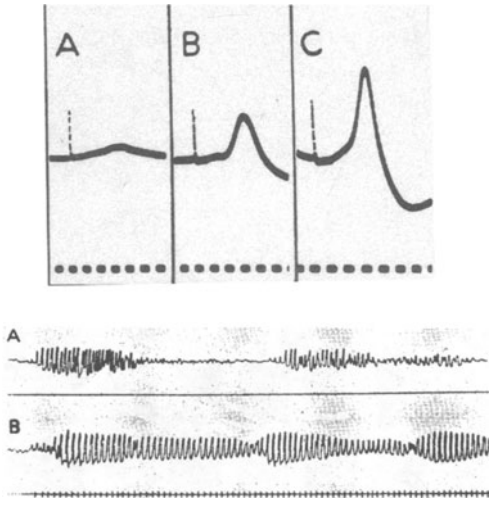


Figure 17-18. The recruiting response. Cortical responses in anterior sigmoid gyrus of cat to successive stimulation of intralaminar nuclei of thalamus (A, B, C) at 8 Hz characterized by long latency and a progressive increase in amplitude of the surface negative response. The time marks indicate 10 msec. (From Morison, R.S., and Dempsey, E.W.: Amer. J. Physiol., 135:288, 1942) II. The similarity of the waxing and waning amplitude of the recruiting response to the spontaneous 8-12 cps spindles, which characterize sedation or anesthesia with Nembutal or other barbiturates, is also demonstrated. Recordings from middle suprasylvian gyrus of cat. A) Spontaneous spindle bursts. B) Recruiting response to stimulation (stimulus marker) or intralaminar areas of thalamus. From Dempsey, E. W., and Morison, R. S.: Amer. J. Physiol., 135:297, 1942 (Amer. Physiol. Soc.)

this combination of the initial recruiting wave (the spike) and the subsequent slow wave provides a model of the thalamic induced spike wave complex and has been correlated with behavioral changes (arrest of activity, myoclonus) similar to the absence seizures of idiopathic epilepsy (see chapter 29).

Arousal or activation or desynchronization response: Stimulation of the sciatic nerve or other sensory pathways or eye opening or intense mental activity will also have a significant generalized effect on the background activity of the EEG. The alpha rhythm is replaced by a low-voltage fast activity (Fig. 2-18C). This response can be reproduced by high frequency (50-300Hz) stimulation of the brain stem ascending reticular activating system. The response occurs with a latency of approximately 40 milliseconds and outlasts the period of stimulation. The long latency suggests a pathway involving several synapses as opposed to the classic short latency lemniscal sensory pathway. This system has diffuse effects on the cerebral cortex via 2 systems: the nonspecific thalamic nuclei and the pathway from basal diencephalon to the basal forebrain. The intralaminar nuclei of the thalamus represent an upward continuation of the ascending reticular formation. Stimulation of these thalamic nuclei, e.g., centrum medianum, at high frequency (300 Hz) produces the same effects on cortical electrical activity as stimulation of ascending reticular formation at a brain stem level Thus sciatic stimulation produces not only the short latency, localized, primary evoked response but also the long latency, generalized, arousal response. This reflects the fact that sensory data enters the reticular formation via collaterals from the specific sensory pathways, particularly the spinothalamic system. Moreover, multiple sensory modalities may synapse on the same neuron in the reticular formation. The system then is in a sense nonspecific as to the modality identity of the incoming stimulus.

The role of the reticular formation and

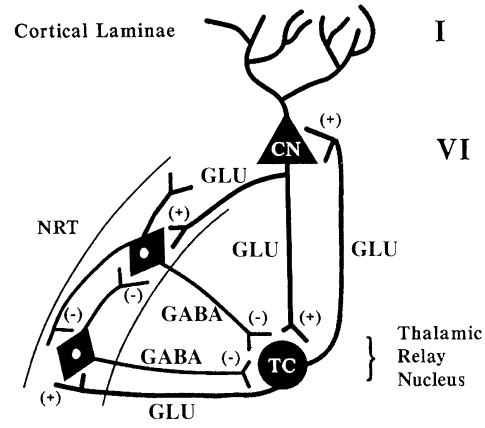


Figure 17-19. The interaction of cortical pyramidal cell (CN), thalamic relay nucleus (TC) and thalamic reticular nucleus (NRT), GLU=Glutamate, GABA= Gamma amino butyric acid. Modified from Snead, O.C. III, In Malafossa, A. Idiopathic Generalized Epilepsies: Clinical, Experimental and Genetic Aspects. London John Libbey

other brain stem areas in sleep, consciousness, and attention will be considered in greater detail in chapter 29.

THE INTERACTION OF CORTICAL NEURONS AND THALAMIC RELAY NUCLEI:

The interaction is complex. Thalamic relay nuclei function in two possible states: (1) a transmission mode when the neuron is near firing threshold in which the discharge reflects the sensory input. (2) A burst mode when the neuron is hyperpolarized by inhibitory input. The thalamic relay neurons have a special voltage gated calcium channel (transient or T type) that is inactive when the membrane potential is near threshold. However when the cell is hyperpolarized, incoming excitatory synaptic potentials trigger transient opening of this calcium channel. The resulting calcium current then brings the neuron potential above threshold. The neuron then fires a burst of action potential until the calcium that has entered the cell activates potassium current that again produces a hyperpolarized state. During burst firing the thalamic relay neurons cannot transmit sensory information to the cerebral cortex. The source of the hyper polarization of the thalamic relay neurons is the reticular thalamic nucleus that is composed of GABA-ergic inhibitory neurons. In turn the neurons of the reticular nucleus receiving collateral input from cortical thalamic and thalamocortical relay neurons (Fig.17-19). The thalamic reticular nucleus also has the property of the burst mode of discharge when hyperpolarized. The burst firing of the thalamic relay cells is reflected in rhythmic waves of excitatory postsynaptic potentials in the dendrites of cortical neurons and is expressed in the surface EEG as rhythmic slow waves. This pattern of slow wave activity may be seen in sleep or in diffuse encephalopathies

During states of wakefulness, the thalamus remains in the transmission mode because of cholinergic input from rostral pons to the thalamic relay and thalamic reticular neurons. There are also cholinergic inputs to the thalamic reticular nucleus from the basal forebrain.

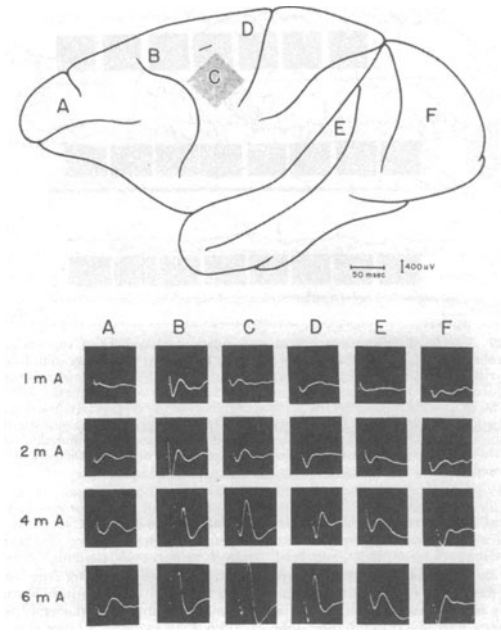


Figure 17-20. Variations in thresholds and amplitude of superficial cortical response (local cortical response) as a function of locus of stimulation in the monkey. Note the low threshold and relatively higher amplitude of the premotor and motor cortex responses (B, C, D) compared to those obtained in area 17 (F) posterior temporal (E) and prefrontal areas (A). The stimulation intensities were the same in all areas (0.10 msec. single shocks). From Eidelberg, E., Konigsmark, B., and French, J.D.: Electroenceph. clin. Neurophysiol. 11:123, 1959 (Elsevier).

PART VI: CLINICAL AND PHYSIOLOGICAL CORRELATES OF CYTOARCHITECTURAL VARIATION

1) The capacity for focal seizure discharge:

Anatomical Observation: In the monkey as in man the motor cortex (area 4) of the precentral gyrus is characterized by the presence of giant and large pyramidal cells. These giant and large pyramidal cells are characterized by a long apical dendrite. Associated with these pyramidal cells, there is noted in the Golgi stain, the presence of a massive tangential plexus in the molecular layer with the presence of many axodendritic synapses. In contrast, the striate occipital cortex (area 17) has a dense external line of Baillarger in layer IV but only a thin tangential plexus in the molecular layer.

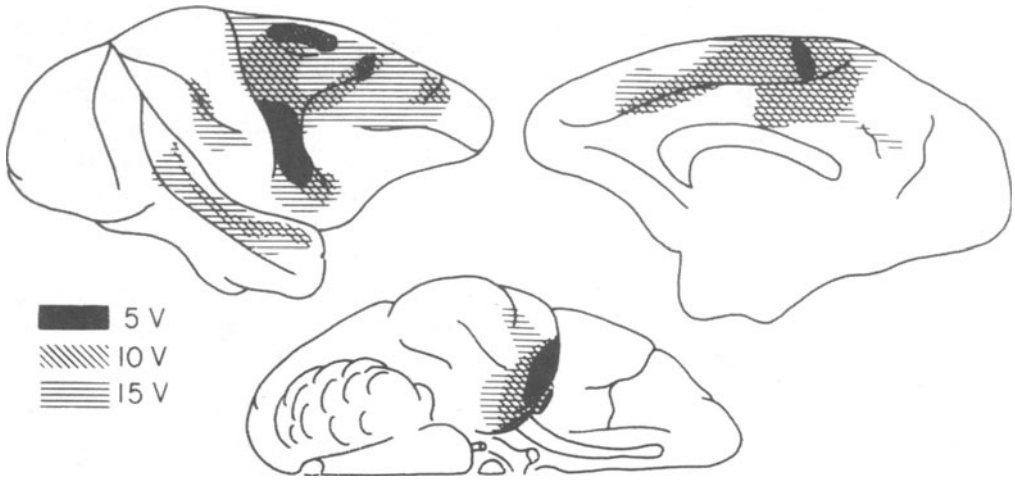


Figure 17-21. Regional Differences in Seizure Susceptibility in Monkey Cortex. The thresholds for electrical seizure after discharge in response to direct stimulation of cerebral cortex are shown. Note the low threshold of motor cortex of sectors in premotor cortex and of anterior medial temporal area as contrasted to striate occipital, (area 17) prefrontal posterior temporal, and parietal areas. Compare to Figure 17-30, note the similarity as regards pattern of regional variation. From French, J.D., Gernandt, B.E., and Livingston, R. B.: Arch. Neurol. Psychiat., 75:270, 1956 [American Medical Association (AMA)].

Giant pyramidal cells are absent and large pyramidal cells are sparse.

Physiological Observations: The superficial cortical response represents the summated postsynaptic potentials generated at superficial axodendritic synapses. In the studies of Eitelberg et al. (1959) this response could be easily obtained at low threshold in the motor cortex. On the other hand, only a feeble response was produced in the striate occipital cortex *(Fig. 17-20)*.

French et al. (1956) studied the threshold for generation of propagated seizure after discharge following electrical stimulation of monkey cerebral cortex. Low thresholds were found in the motor cortex with the ready development of generalized seizure discharge. On the other hand, high thresholds were present in the striate occipital cortex *(Fig. 17-21)*.

Clinical Correlation: The capacity for a clinical seizure is directly related to the capacity for generation of repetitive discharge and of after-discharge. Thus whether a tumor involving the cerebral cortex announces its location with a seizure will be related to its location. There is, then, an extremely high incidence of focal or generalized seizures in patients with parasagittal meningiomas overlying the motor cortex. On the other hand, tumors in the prefrontal, posterior-temporal parietal, or occipital areas may grow to a large size without producing focal seizures. When focal seizures occur they may indicate a compromise of low threshold motor cortex with discharge originating at that area rather than at the primary site of involvement.

2) The capacity for contralateral spread of discharge as related to callosal fiber system density:

Anatomical Observation: Using the Nauta method to study degeneration of axons, Ebner and Myers (Myers, 1965) have evaluated the density of callosal projection approximately 10 days after section of the major interhemispheric commissures. A dense callosal projection was found in the precentral, premotor and inferior parietal areas. Only a sparse callosal projection was present in striate occipital and superior temporal areas *(Fig. 17-14)*.

Physiological Observations: The original studies of Curtis (1940) on the transcallosal response in the monkey indicated significant regional differences in the capacity for generation of this response. The response was easily obtained on stimulation of the premotor, precentral, and parietal areas but could not be

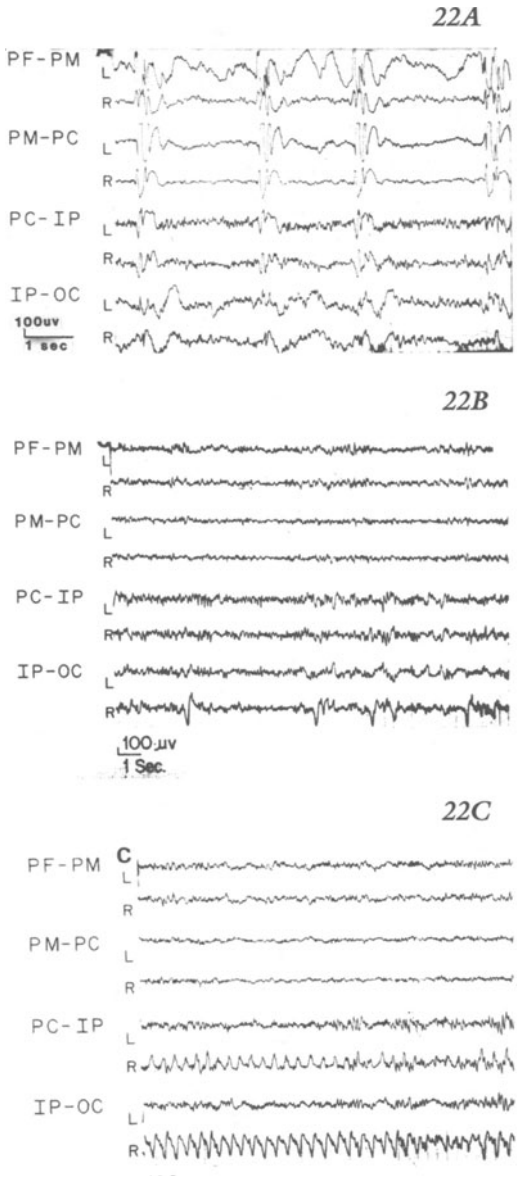


Figure 17-22. Capacity for spread of an experimental focal discharge. A) Unilateral focus in the left premotor area 6 of the monkey results in a wide intra and inter hemispheric spread. B) Production of the same unilateral focus in area17 of the right occipital area results in a restricted unilateral discharge which even when prolonged as in C) fails to spread. PF=prefrontal, PM= premotor, PC= precentral, IP= intraparietal, OC=Occipital.

obtained on stimulation of the striate occipital cortex. In general, similar differences were found in studies of McCulloch and his associates (1944) employing a local area of seizure discharge (strychnine neuronography) rather than direct electrical stimulation. Both series of studies also indicated that significant regional differences existed as regards the diffuseness of callosal projection. Thus, certain cortical areas (e.g., motor cortex) had projection only to the symmetrical area of the contralateral hemisphere. Other areas, such as the premotor area

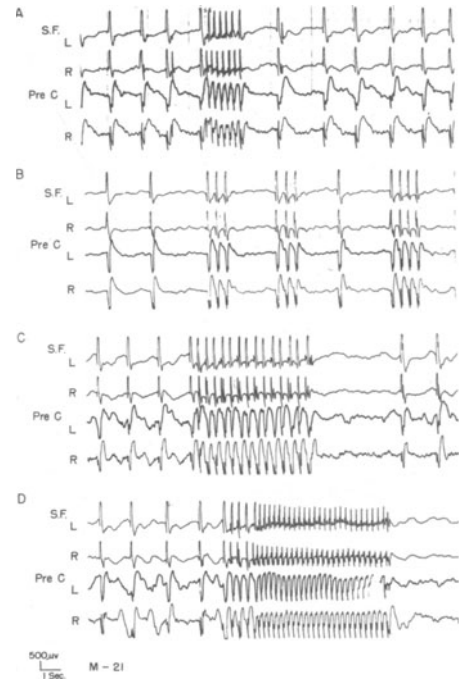


Figure 17-23. Capacity for bilateral synchrony in premotor area of monkey cerebral cortex. Experimental design of bilateral symmetrical discharging premotor foci (1% conjugated estrogen). Recordings from superior frontal (S.F.) and precentral gyri (Pre C). Note the repetitive bilaterally synchronous discharges of spikes and spike slow wave complexes. Compare to Figure 17-24. From Marcus, E. M., and Watson, C. W.: Arch. Neurol., 19:102, 1968 (AMA). See also chapter 29.

(area 6) had widespread projection to many points in the contralateral hemisphere (areas 6, 4, 1, 5, and 39 as regards area 6).

Clinical correlation: Experimental or clinical seizures originating from the premotor cortex will have widespread bilateral effects where-

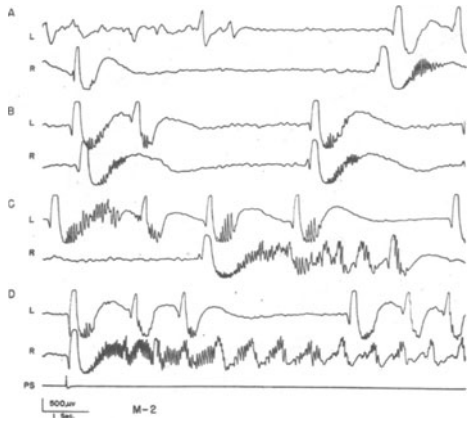
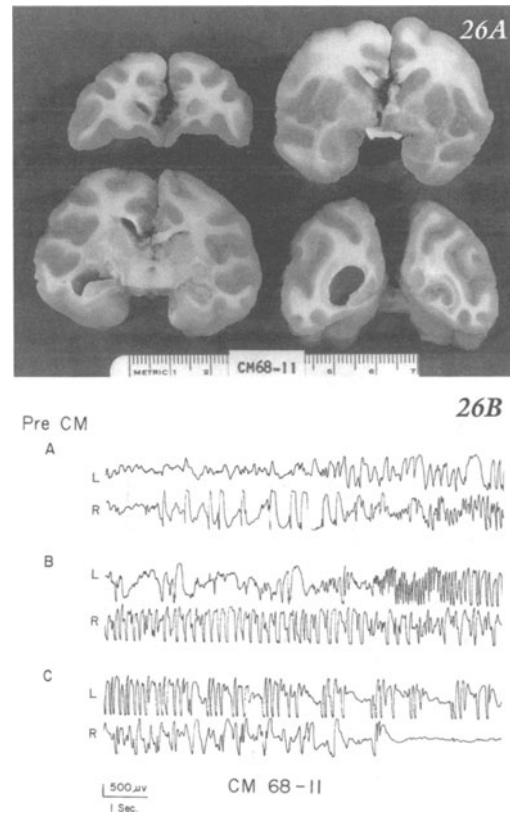


Figure 17-24. Lack of capacity for bilateral synchrony in area 17 of monkey cerebral cortex. Experimental design of bilateral symmetrical discharging foci as in figure 17-23. Recordings from left and right occipital area. Note independence of discharge particularly when prolonged (A and C). Occasional bilateral discharges relatively synchronous at onset could occur (B), particularly discharges when triggered as in D) by an extrinsic source, e.g., photic stimulation (PS). From Marcus, E. M., and Watson, C. W.: Arch. Neurol., 19:107, 1968 (AMA).



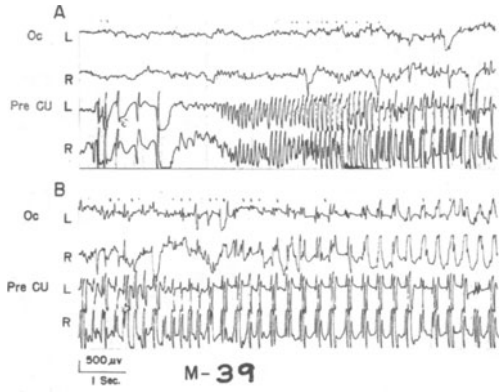


Figure 17-25.Regional variations in capacity for discharge and bilateral synchrony following administration of a threshold dosage of an intravenous convulsant agent (15mg/kg) in a monkey. Discharges begin in a bilateral synchronous manner in the precentral areas (Pre C U). Only later do discharges begin in the occipital area (Oc) and these are not synchronous or symmetrical. From Marcus, E. M. in Reeves, A. G. Epilepsy and the Corpus Callosum. New York Plenum Press p.169. 1985.

Figure 17-26: Intravenous pentylenetetrazol at threshold dosage 6 days after complete section of major commissures in the monkey. Bipolar recordings from upper –middle precentral gyrus. All bilateral synchrony is lost. A) Anatomy. B) EEG recording. From Marcus, E.M. in Reeves, A.G. Epilepsy and the Corpus Callosum New York Plenum Press. P183.

as seizures originating from the striate occipital cortex will have limited focal effects. The wide spread intra- and interhemispheric spread of discharge from a unilateral experimental focus in area 6 is demonstrated in Figure *17-22A*. Compare this to the limited spread of discharge from a similar focus in areas 17 of occipital cortex *(Figure 17-22 BC)*.

3) The capacity for bilateral synchronous discharges: *Anatomical and Physiological observations: see above*

Experimental epilepsy correlation:

A) Bilateral foci of epileptic discharge in symmetrical cortical areas of the two hemi-

spheres: an interaction soon occurs, resulting in the synchronization of the seizure discharges in the two hemispheres. However in the monkey there are significant regional variations in the capacity for this interaction. In the premotor and precentral areas a close and well-developed interhemispheric synchrony is evident *(Fig. 17-23)*; in striate occipital and superior temporal areas, bilateral synchrony is poorly sustained *(Fig.17-24)*. Section of major commissures markedly disrupts the synchrony of discharge. Refer to Marcus (1985).

B) Intravenous injection of a threshold amount of pentylenetetrazol (Metrazol) provides an example of a diffuse toxic disease (Marcus- 1985): Following injection in the monkey, bilateral synchronous discharges developed first in the premotor and precentral areas. Discharges in the temporal and striate occipital areas develop later and are independent and multifocal *(Fig 17-25)*. Synchrony is lost following section of the corpus callosum (Fig 17-26), but is maintained in the cortical callosal preparation *(Fig. 17-27)*.

The role of the corpus callosum in other generalized models of epilepsy is discussed in chapter 28.

Clinical Correlation: Seizure discharges, as recorded in the human electroencephalogram, may be focal, multifocal, or generalized with bilateral symmetry and synchrony of discharge. When the latter category of bilateral discharges is examined it is evident that the bilateral synchrony is usually best developed in the frontal and central and parietal parasagittal recording areas. On the other hand, bilateral discharges in the temporal and occipital areas often appear to be independent, that is, multifocal. Section of the corpus callosum has been employed to limit spread of seizure discharge or to prevent the interaction of multiple foci of epileptic seizure discharge when seizures could not otherwise be controlled (See Reeves, 1985).

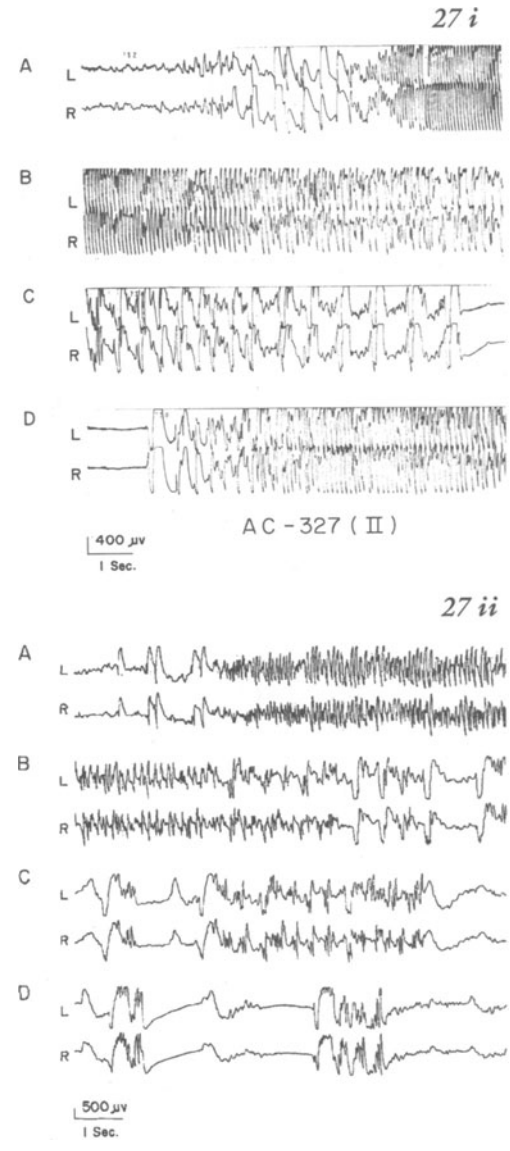


Figure 17-27. Intravenous pentylenetetrazol at threshold dosage (20 mg/Kg) I) Intact cat II) Bilateral cortical callosal isolation. The apparent amplitude differences between the intact and the isolate reflect differences in the degree of amplification.