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Three Major Integrative Systems

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OVERVIEW OF THREE MAJOR INTEGRATIVE SYSTEMS

The amount of information in a system is a measure of its degree of organization.

(Wiener, 1948, p. 18)

Again addressing the oscillating, cause-and-effect relationship that has illuminated the development of knowledge of brain anatomy and physiology, we direct attention to three great systems on which the integrated behavior of higher animals depends: the ancient limbic system, the classical sensory or thalamocortical system, and the nonspecific ascending reticular system. Named in the order in which they were recognized and will be discussed, in each system an anatomic substrate was described before its “use,” or function, became apparent. The English-American neurophysiologist well known for her historical writings on the nervous system, M. A. B. Brazier, equated this triad of structures with the functions necessary to maintain the conscious state (1963, pp. 748–749). First, “transmission of the sense-labeled impulse bearing the message from the periphery to the brain” is achieved by “the classical afferent system, ascending laterally through the specific thalamic nuclei to specific cortical sites.” Second, “awareness that the message has arrived” occurs because “the ascending sensory systems in the midbrain core and medially placed thalamic nuclei are profoundly implicated.” Receiving and storing the message, the final requisite of the conscious state, “is served by the third of the three systems named: the limbic system, and in particular the hippocampal system.” This chapter considers the manner by which each of those integrated anatomic circuits was recognized as a functional entity. They cannot be envi-

sioned as neatly demarcated nor are they competitive; rather, they lack agreed-on boundaries and it is clear that they interact profusely, each feeding into and receiving information from the others.

THE LIMBIC SYSTEM AND MEMORY

“Modified by evolution, the structure plays an important part in man; this is the great limbic lobe of Broca.” (Schiller, 1979, p. 247.)

Much of the history of the limbic system consisted in demonstrating what it is not—a sensory system entirely engaged in olfactory functions. Its constituent parts were known and named by the early anatomists, but the idea that the elements functioned as a cohesive entity did not emerge until the last quarter of the nineteenth century. Initial recognition that such was the case came from that remarkable French neurologist-anthropologist-politician and superb comparative anatomist, Paul Broca, whose localization of speech in the left frontal lobe was described in Chapter 5. Broca was characterized by a modern biographer as “[b]old but not foolhardy, radical but not extreme, and fanatic only in his quasi-religious belief that facts were infallible” (Schiller, 1979, p. 234). Broca published a lengthy review of “Le grand lobe limbique . . . dans le série des mammifères” (1878a) in which he explained his choice of the term “limbic” for a group of structures surrounding

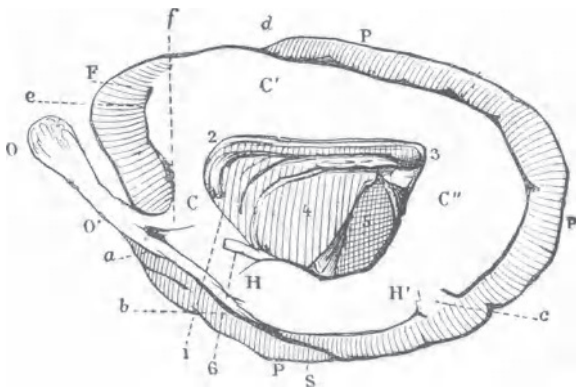


Fig. 12.2. Paul Broca chose “limbic lobe” to name the structures illustrated by Foville because the term “implied no theory” and “is applicable to all mammalian brains.” The otter’s brain (above) is one of many he dissected to demonstrate the ubiquity of the structure (C, C’, C’’) among mammals. (From Broca, 1878a, p. 399, $\times 1$.)

functions in two ways: first as a means of *investigation*, second as a means of *action*. . . .

The first function is called *sniffing*; it takes place in the sensory center to which the olfactory lobe transmits its impressions. . . . By contrast, what we might call *olfactory action* . . . has the simplicity of a reflex. . . . It is the direct transformation of sensation into movement without intervention of the will. . . . (ibid., p. 445, *passim*; translated in Schiller, 1979, p. 266).

Broca’s idea of an extended limbic lobe function received little attention during the six decades after he announced it, but his inferences (Broca, 1879) about its olfactory component persisted, and by the 1890s the entire limbic lobe was referred to as the rhinencephalon or “smell brain.” That restricted concept came apart under the virtually simultaneous impact of three proposals that were directly or indirectly concerned with the nature of emotion and its neural substrates. The psychologists especially were groping for a firm explanation of emotional responses, as witness the U.S. National Research Council’s organization in 1926 of the Committee on Experimental Study of Emotion with Margaret Floy Washburn (1871–1939) as chairman.

On a second front, the microanatomists had been constructing the foundations on which theories of emotion would rest by their diligent pursuit of tracts and nuclei; the contributions of Golgi, Ramón y



Fig. 12.3. James Papez and his artist wife, Pearl, collaborated on publications that dealt with the minutiae of the microscopic anatomy of fiber tracts and nuclei, thus building a solid base for his theory of emotion. (From MacLean, 1978, p. 10.)

Cajal, and Lorente de Nó are discussed elsewhere. The first important breakthrough came in 1937 when an American anatomist, James Wenceslas Papez (1883–1958; Fig. 12.3) from his isolated laboratory at Cornell University in Ithaca, New York, published a remarkable paper in which he described the circuit that later carried his name and cautiously suggested that it might constitute the neural substrate for emotion, thus substituting a circuit for a center. In that classic account of imaginatively related facts, Papez wrote that he presented

anatomic, clinical, and experimental data dealing with the hypothalamus, the gyrus cinguli, the hippocampus, and their interconnections. Taken as a whole, this ensemble of structures is proposed as representing theoretically the anatomic basis of the emotions. . . . The term “emotion” as commonly used implies two conditions: a way of acting and a way of feeling. The former is designated as emotional expression; the latter, as emotional experience or subjective feeling. The experiments of Bard (1928) have demonstrated that emotional expression depends on the integrative action of the hypothalamus. For subjective emotional experience, however, the participation of the cortex is essential (Papez, 1937, pp. 725, 726).

Papez believed that the substrate of emotion had evolved phylogenetically from mechanisms essential to nutrition and reproduction, that is, the taste and smell of food and products of the sex glands had formed the drives for feeding and mating, two essentials for survival of the species.

Immediate interest in Papez's proposal was minor, perhaps due to both his modesty in pushing his own ideas and the appearance the following year of two notable papers, in neither of which his work was cited; in all fairness, however, the timings were very close. In his paper, the experimental psychologist, Karl S. Lashley (1890–1958), later famous for his search for the engram of memory (1950), postulated the thalamus to be an important site of emotion, thus aligning himself with Cannon. The great value of Lashley's penetrating analysis of emotion (1938) was in its identification of two major areas of uncertainty in the then current concepts of the neural substrate of emotion. The first and more inscrutable concerned the affective aspects of emotional experience, in turn a feature of the more general problem of the basis of all consciousness and subjective experience. The second uncertainty had to do with the identity of forebrain mechanisms and processes that normally hold emotional behavior in check, the elimination of which in "decortication" releases diencephalic mechanisms, leading to an excessive expression of emotional behavior. This idea recalls the Jack-in-the-box analogy of Rhines and Magoun (*see* Fig. 9.20, *see* p. 197, this volume). As Lashley commented in his discussion of emotional states, "Although we may assume that the increased excitability of the motor centers is a result of withdrawal of inhibition, a survey of the evidence leaves some doubt as to the source of the inhibition" (*ibid.*, p. 46).

Additional support for the limbic circuit concept of emotion materialized with serendipity from a new quarter in an attempt to isolate the site of action of the psychomimetic drug, mescaline, by experimental psychologist Heinrich Klüver teamed with neurosurgeon Paul Bucy. A few months before Lashley's review appeared, they presented (1938) the results of a two-stage bilateral temporal lobectomy that included significant portions of the amygdaloid nuclei and hippocampi of the basal

forebrain, carried out initially in an unusually ferocious monkey.¹ The variety of abnormalities that followed the operation in this and subsequent subjects included a marked taming of this wild animal and its development of hypersexuality (*see* Chapter 5 for details of those studies and the priority of Sanger Brown and E. A. Schäfer).

A dramatic clinical confirmation of the findings of Klüver and Bucy was reported by Terzian and Ore in 1955 in a human subject. After bilateral temporal lobectomy, including most of the uncus and the anterior part of the hippocampus and amygdala, carried out for the relief of intractable psychomotor epilepsy, the postoperative syndrome reproduced all signs reported in monkeys except the oral tendencies and in addition there appeared a serious deficit in memory.

The changes in emotionality in "the temporal lobe syndrome" were supportive of Papez's proposal, replacing the earlier smell-bound thinking and even distracting some behavioral scientists from their preoccupation with the neocortex. A decade after the influential studies just described, a young neurologist, Paul D. MacLean (Fig. 12.4), organized and elaborated Papez's views in two publications: "Psychosomatic Disease and the Visceral Brain. . ." (1949), which enormously extended and enlivened its Papezian forebear and in the follow-up paper, "Some Psychiatric Implications. . ." (1952) revived Broca's term "limbic" and referred to the lobe and its brain stem connections as the "limbic system," the term that is current today. In essence, whereas Papez saw through binoculars, MacLean envisioned a wider scenario.

Based on his clinical research and comparative neurobehavioral studies, MacLean later proposed the "triune brain" (Fig. 12.4, right) to explain normal and pathologic human behavior. His concept of the evolutionary development of the human brain emphasized the key position of the limbic or paleomammalian brain (*see* p. 25, this volume), as evidenced by a relatively superior metabolic activity: the limbic cortex exceeds the neocortex in turnover of protein, a measure of the demand for new RNA in memory formation (Flanigan, Gabrieli, and MacLean, 1957; Hydén, 1969). That demand apparently occurs in spite of the fact that in phylogenetically higher mammals the neocortex, where

¹Information from interview of Paul Bucy by K. E. Klivington, titled "The Papez Memorabilia, Boston, April 8, 1981," with permission.



Fig. 12.4. As chief of the Laboratory of Brain, Evolution, and Behavior at the National Institute of Mental Health, Paul D. MacLean (left) directed studies on reptiles and squirrel monkeys that reinforced his concept of the “triune brain.” MacLean’s symbolic representation (right) of the successive overlay of neural tissue with new functions during evolutionary time was first published in 1967, p. 377, Fig. 2. Photograph ca. 1957.

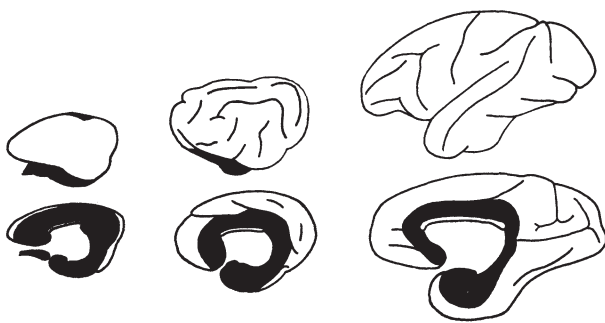


Fig. 12.5. The evolutionary old cortex (the limbic lobe) is a “common denominator” in mammalian brains with the neocortex mushrooming around it as the phylogenetic scale moved forward. (Adapted from MacLean, 1954, p. 106.)

“higher” nervous functions take place, has ballooned around the two older brains, as shown in Fig. 12.5.

MacLean gathered support from his own studies and those of others to conclude that the traits distinguishing mammalian from reptilian forms are three “cardinal” behaviors: caring for the young, audio-vocal communication, and play. From the “momentous significance” of the evolutionary acquisition of those behaviors, he extrapolated to write that “the history of the evolution of the limbic system is

the history of the evolution of mammals, while the history of the evolution of mammals is the history of the evolution of the family” (1990, p. 247).

The first association of memory with a specific part of the limbic system, the hippocampus, seems to have been made by Vladimir Mikhailovich Bekhterev (1857–1927; *see* Fig. 12.6, p. 254), the Russian neurologist–anatomist whose career was contemporaneous but not parallel with the work of Pavlov. Bekhterev described (1900) the brain of a patient with memory deficit and hippocampal degeneration, another example of a clinician leading the way to new insights, as was the case with the discovery of acromegaly (*see* Chapter 11) and Bright’s correlation of sensation with the thalamus (*see* Chapter 10). The hippocampus was targeted in memory deficit also by G. Elliot Smith in his Croonian Lectures (1919), a series presented by distinguished figures representing the contemporaneous accepted wisdom. Attempts at replicating human memory loss in the experimental animal (Orbach, Milner, and Rasmussen, 1960) did not clarify the problem of the exact site of memory deficit, however, nor had Lashley been able to find the site of the engram of memory in the rat brain in his dedicated, almost desperate search (1950). Rather, we turn from the experimental studies to

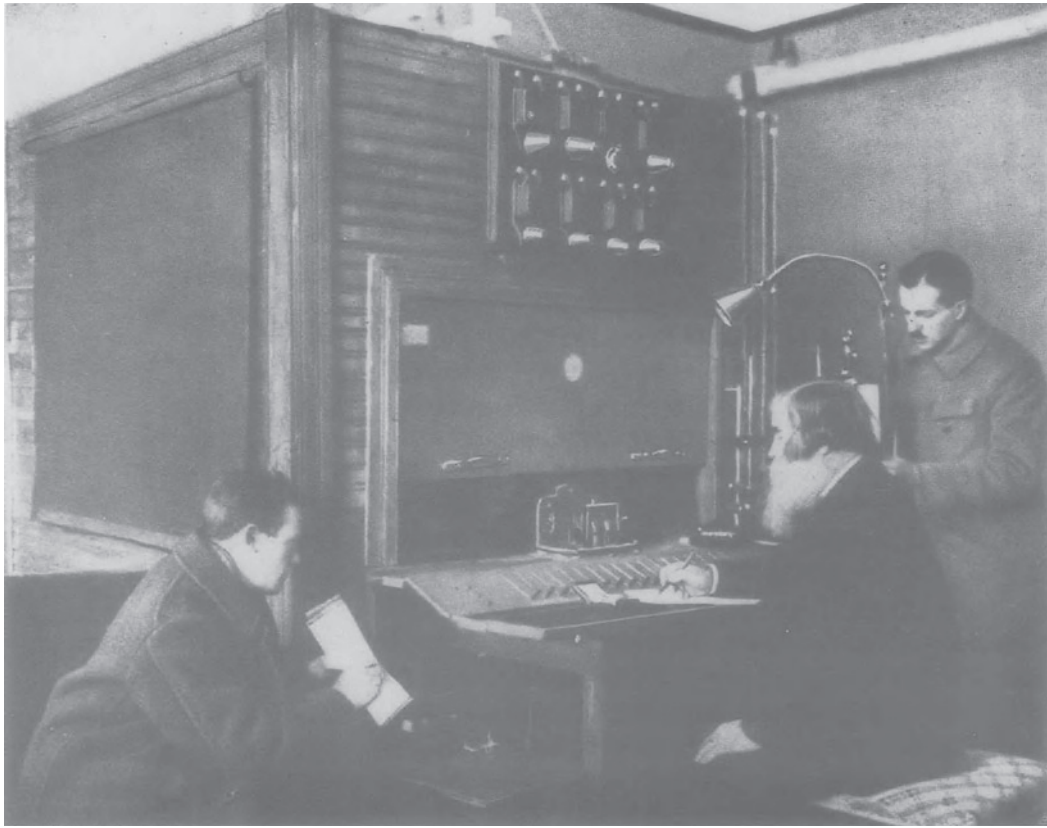


Fig. 12.6. The elderly Vladimir Bekhterev is shown with two assistants in the unheated Reflexology Laboratory at the State University in St. Petersburg. In his psychological work Bekhterev used muscular responses as an indicator, in contrast to Pavlov's more easily quantified drops of saliva.

the careful and persevering testing of a few human subjects for real insight into limbic functions.

A relationship of limbic structures to memory and learning was made clear by a Canadian neurophysiologist and student of Donald Hebb's, Brenda Milner, in her repeated study of H. M., whom she first saw in 1955 (B. Milner, 1992). Two years previously, H. M. had been operated bilaterally with a medial temporal lobe resection which included the radical removal of limbic structures: the amygdala, hippocampus, and parahippocampal gyrus. Milner found initially that her subject's limits of retention were dependent on the absence of attention-distracting intervening elements. Then in experiments carried out on the same patient in 1960 and with a series of complicated psychological tests, Milner uncovered what she described as a

"diencephalic memory system," and supposed that there might be many different memory systems in the brain.

In spite of statements in two influential textbooks, Obersteiner's (1890) and Schäfer's (1898), that some mammals have no sense of smell, yet possess a limbic system, the early notion that the hippocampal part of the system is "an important olfactory 'centre' " was one of those "conceptions [that] survive almost like proverbs. However, some general suspicion of the truth of this credendum seems to be just about to dawn" (Brodal, 1947, p. 179). Opening his review with those prescient words, the Swedish neuroanatomist, Alf Brodal, presented anatomic evidence that olfactory fibers had not been traced to the hippocampus proper and concluded that "[r]ecent physiological experiments

have yielded no support for the conception that the hippocampus has important relations to the sense of smell in mammals, nor does clinical evidence seem to favour this view" (ibid., p. 218).

The hippocampus, according to Frederick Tilney (1938), who could see no resemblance to the sea horse, had been named "with too loose a rein" by the Renaissance anatomist, Arantius (1587, pp. 44–45), yet it became the most thoroughly investigated part of the limbic system for good reason. That its major component offered great advantages for electrophysiological studies because of its simple and highly oriented structure compared with other cortical areas was recognized by Renshaw, Forbes, and Morison (1940, p. 75) who stated, "Our results demonstrate that particularly interesting deductions may be made from . . . data obtained in regions of the nervous system where the spatial arrangement of cells is particularly simple, as it is in the hippocampus." Thirty-five years later, and for the same reason—two completely separate cell populations, pyramidal and granular—it was proposed as a model system for research on neuronal plasticity (Lynch and Cotman, 1975). Additional advantages are that the surgical approach to the hippocampus is relatively free of damage to its blood supply and easy to isolate from other structures, thus facilitating excision or investigation *in vitro*. Those factors were especially conducive to single-unit research undertaken to probe for the source of complex action potentials displayed in the patterns recorded on the electroencephalogram (EEG). The question had been a recurring challenge to the "brain wavers" made by the "axonologists" who were working at the periphery of the nervous system and announcing exciting discoveries about the compound action potential and conductance in the axon. The axonologists, strutting on the boardwalk at annual meetings in Atlantic City (see L. H. Marshall, 1983a, p. 631, fn 23), delighted in taunting their peers about a perceived lack of progress in interpretation of the complex brain wave patterns and what they reveal of how the central nervous system works. On their part, the "EEGers" were searching for answers in several directions. Gibbs and Gibbs (1936) had already shown that, of the brain regions they tested electrically in cats, the hippocampus had the lowest threshold for seizure. The findings of J. D. Green and his associates (summarized in Green, 1959; Fig. 12.7), elicited a proposal that the

origin of the slow hippocampal (theta) wave in the rat is dual, "generated by the hippocampal pyramids between the distal part of the cell body layer and a level near, but not at, the termination of the apical dendrites" (ibid., p. 270). In Japan, somewhat similar studies in rabbits targeted the sites more precisely: "the somata and apical dendrites of the hippocampal pyramids are activated in a seizure discharge" (Taira, 1961, p. 198; see Fig. 12.8, p. 257).

In another direction, B. R. Kaada (1951) at the University of Oslo focused on the behavior-modulating effects of the limbic system. He found that electrical stimulation produced opposite effects depending on the region that was stimulated: from septal sites the effect was inhibitory for motor, reflex, and autonomic responses, whereas from the cingulate gyrus it facilitated those same responses. With that research as a background, the next step was to more closely identify an excitatory dendritic locus on the hippocampal pyramidal cells and to postulate that "a dendritic location of excitatory and a somatic location of inhibitory synapses may well hold true for other cortical pyramidal cells" (Andersen, Blackstad, and Lømo, 1966, p. 247). The Scandinavian group proposed a new model of the phenomenon, reproduced in Fig. 12.9 (p. 257), which suggests the possibility that fibers carrying impulses from thalamus en route to cortex send collaterals to inhibitory neurons. Acknowledged as "somewhat at variance with previously formulated theories," Andersen and Andersson (1968) stressed that there may be many facultative pacemakers governing cortical phasic activity. A decade later Winson and Abzug (1977) reported that the behavioral state of the subject influenced transmission of impulses in the hippocampus.

By the middle of the twentieth century, it was clear that the key to limbic system function must be sought from combined anatomic, physiologic, and behavioral sources. Some of the pioneers in the application of the multidisciplinary approach were concerned that reliable experimentation in integrated research is subject to certain hazards when scientists cross disciplinary lines to work in an unfamiliar field. Robert A. McCleary at the University of Chicago, a physiological psychologist, enunciated a strong caveat in the first issue of a published series, *Progress in Physiological Psychology* (Academic Press, 1967), dedicated to fos-

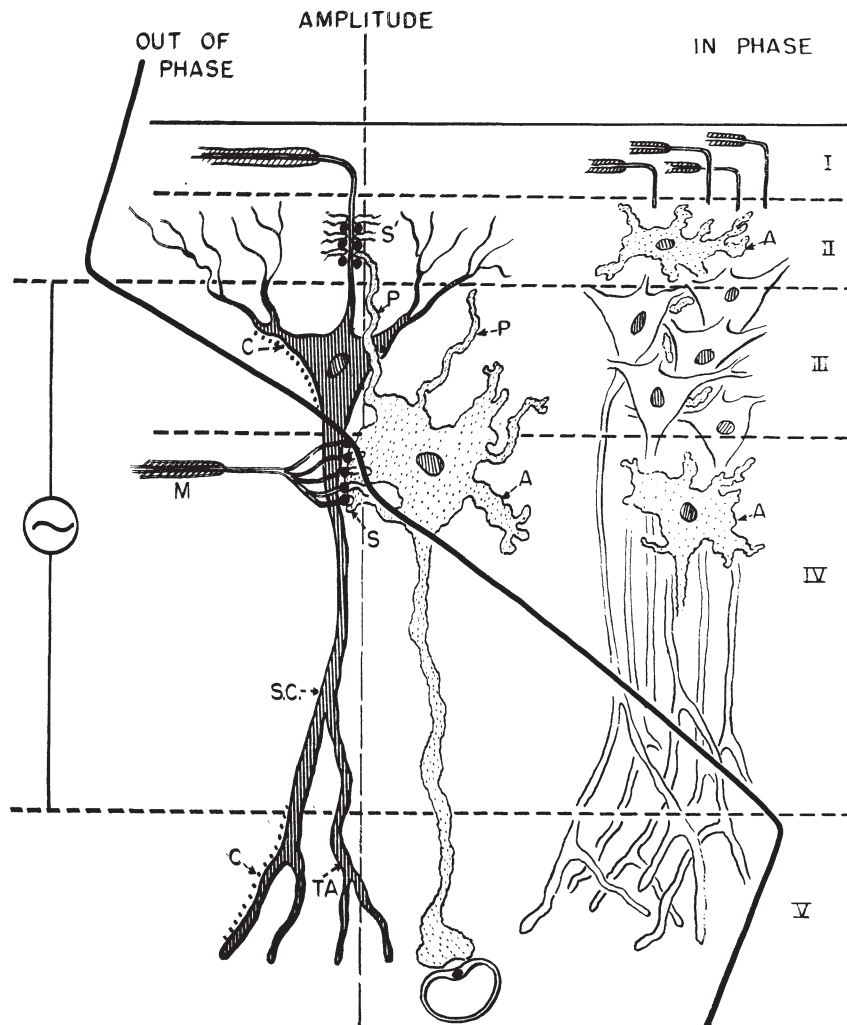


Fig. 12.7. John Green's diagram showing the single-unit potential superimposed on a pyramidal cell with a nearby astrocyte (A), to illustrate his theory of a dual source of the hippocampal theta wave (*see text*). (From Green, 1959, p. 268, $\times 1$.)

tering the momentum which that discipline was then experiencing as it struggled to catch up with neurophysiology and neuroanatomy in studies of brain and behavior. Concluding his review of the response-modulating functions of the limbic system, McCleary wrote:

[T]he general importance of considering the possibility of multiple deficits resulting from a particular lesion . . . is related to the obvious fact that experimental lesions most commonly are gross compared to the intricacy of the structures ablated. . . . [T]he remedy is the same in any case: the use of batteries of behavioral tests in evaluating the effects of lesions. The 'one lesion,

one test' study is certainly no longer justifiable, if indeed it ever was (1967, p. 266).

This statement is one of many examples of the experimental psychologists' endeavor to ensure that neuroscientists from other disciplines adhere to rigorous testing and interpretation of behavioral data.

As MacLean pointed out (1990, p. 412), probably there is no clinical condition that provides more windows for viewing the neural substrate of the human psyche than psychomotor epilepsy. It has produced "crucial evidence" that the limbic system is fundamentally involved in emotion, as in the aura occurring at the beginning of a seizure

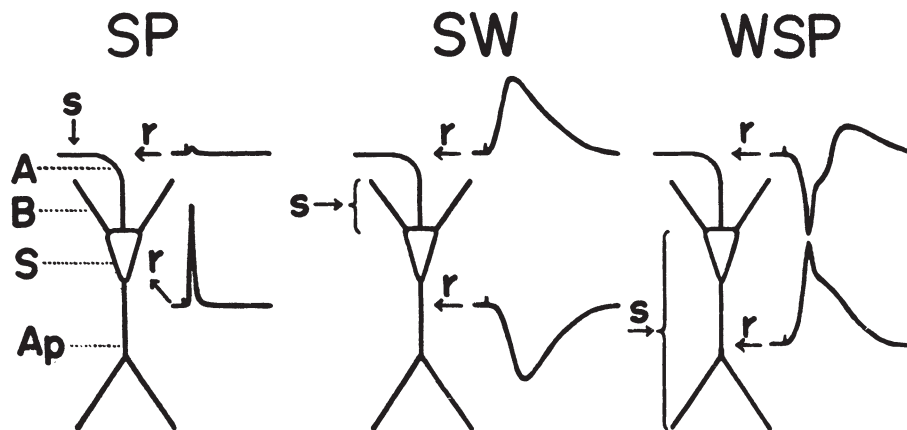


Fig. 12.8. Schema of types of evoked potentials (SP—spike; SW—slow wave; WSP—wave-and-spike) elicited by stimulation of different levels of hippocampal cells in rabbit brain. A—axon; B—basal dendrite; Ap—apical dendrite; S—soma. (From Taira, 1961, p. 193, Fig. 2. $\times 1$.)

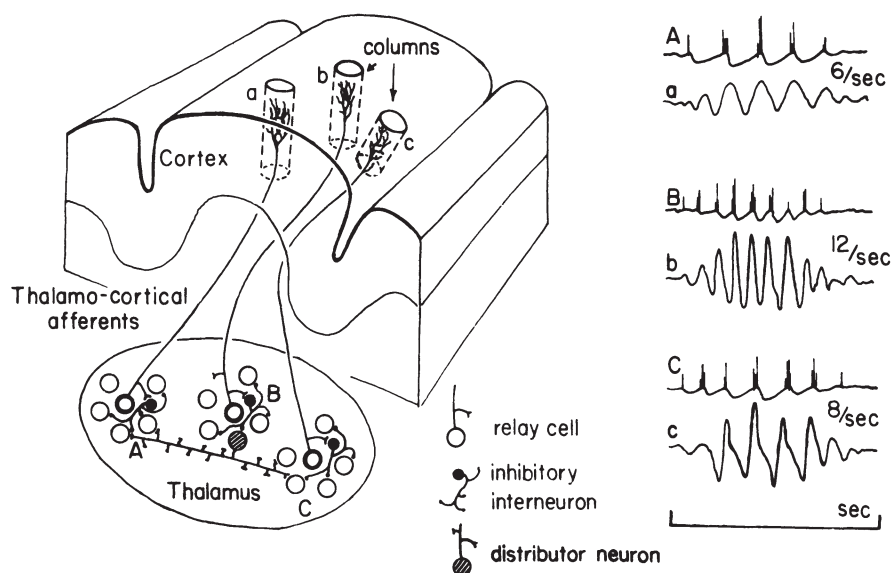


Fig. 12.9. A sophisticated model of cortical phasic activity showing different intraspindle frequencies and times of onset and stopping. Left—A, B, C: Thalamic nuclei send axons to cortex (a, b, c) and collaterals to interneuronal cells some of which are inhibitory (black). Right—imaginary spindles at thalamus (A, B, C), at cortex (a, b, c). (From Andersen and Andersson, 1968, p. 59, Fig. 5.9. $\times 4/5$.)

when patients may experience a variety of subjective states ranging from intense fear to ecstasy. Those emotions were reported by patients of one of the earliest active groups working on the EEG in America, at Massachusetts General Hospital (Gibbs, Gibbs, and Lennox, 1938). Termed “temporal lobe epilepsy” (Lennox, 1951), a more fitting name is “limbic lobe epilepsy” because it involves structures beyond the temporal lobe (Fulton, 1953,

p. 77; Glaser, 1967). By means of stimulation through depth electrodes chronically implanted at several sites, Pagni (1963) in Milan produced clinical signs of spontaneous seizures in human subjects and evidence that the hippocampus, Ammon’s horn, and the amygdaloid nucleus constitute a functional unit.

Limbic structures other than the hippocampus were also subjected to careful investigation and one

of the most interesting was the septal region. Psychiatrists at Tulane University reported some patients who experienced sensations of pleasure when the septal region was stimulated (Monroe and Heath, 1954, pp. 348, 560). The phenomenon was replicated by two Canadian psychologists, working in the laboratory of Donald O. Hebb at McGill University in Montreal. James Olds and Peter Milner taught rats to self-stimulate their septal regions electrically in positive reinforcement experiments. The bar pressing for a pleasurable reinforcement became addictive to the point of exhaustion, and Olds and Milner wrote: "[W]e have perhaps located a system within the brain whose peculiar function is to produce a rewarding effect on behavior. . . . In septal area preparations, the control exercised over the animal's behavior . . . is extreme, possibly exceeding that exercised by any other reward system previously used in animal experimentation" (1954, p. 426).

In the opinion of some members of the distinguished group of neuroscientists assembled by David McKenzie Rioch (1900–1985) American neuropsychiatrist, at the Walter Reed Army Institute of Research during and after the Second World War, the plethora of studies that followed the discovery of the apparent "pleasures" of self-stimulation did not adequately analyze "the interrelationships between the physiological events associated with self-stimulation and the behavior of the self-stimulated animal" (Porter, Conrad, and Brady, 1959, p. 43). Such an analysis revealed that in some chronically implanted monkeys, self-stimulation of the hippocampus produced seizure activity and "the maintenance of high lever-pressing rates appeared to be positively correlated with . . . seizure patterns. In contrast, seizure discharges following self-stimulation of the amygdala produced suppression of the lever-pressing rate" (*ibid.*, pp. 53–54), findings in the behaving animal which reinforced the physiologic events that had been found in single units of the hippocampus mentioned above.

A potentially important insight on limbic system function was provided in work of a group of Canadian neuropsychologists (Goddard, 1967; Goddard, McIntyre, and Leech, 1969). Describing a process which was later felicitously named "kindling," they reported that in experimental animals seizures can be induced by repeated application of subthreshold brain stimulation. They found the amygdaloid bodies are the most easily kindled

regions, that no demonstrable histologic damage is sustained, the effect is transsynaptic, and the epileptogenic changes are permanent; Goddard related the permanence to the mechanisms of learning. Later evidence suggested that alterations are localized at the synapses (Racine, Newberry, and Burnham, 1975). Eventually it was suggested that

we should seriously consider the possibility that the underlying mechanisms of learning and synaptic enhancement are one and the same. . . .

The machinery by which this happens need not be pathological at each synapse. The pathology may lie only in the number of synapses involved, and the number of neurons brought into synchronous activity (Goddard, McNaughton, Douglas, and Barnes, 1976, p. 363).

The report of kindling had been preceded by somewhat similar observations of Watanabe (1936, cited by Alonzo-de-Florida, 1994, p. 206) in Japan on dogs subjected to subthreshold cortical stimuli, and by a series of experiments carried out in the laboratory of José Delgado at Yale. Alonzo-de-Florida and Delgado (1955) used chronically implanted electrodes stereotaxically placed in cat amygdala to produce a state of electrical activity characterized by spontaneous seizures.

As a tribute to the high priority accorded research on the limbic system, the University of Toronto mounted a conference on "The Continuing Evolution of the Limbic System Concept" in 1976. One-third of the presentations concerned kindling, led off by Graham Goddard's review, "From Iconoclasm to Orthodoxy." When the papers were published two years later, Goddard's interesting title had become: "Synaptic Change in the Limbic System," and the monograph simply *Limbic Mechanisms*. In 1975 the editors of a two-volume collection of papers starkly titled *The Hippocampus*, wrote: "Thus the enigma of hippocampal function, although slowly yielding its wrappings, as yet has lost none of its appeal or challenge" (Isaacson and Pribram, 1975, p. 439).

CORTICOTHALAMIC CONNECTIONS AND CYBERNETICS

"[M]inute anatomy—those deserts of detail without a living functional watercourse, only a mirage from unverified speculation." (Rushton, 1977, p. 85.)

A distinctive feature of another major system of neural circuitry in the human brain was noted as early as 1839 by Carpenter in his textbook. He believed (*see* Chapter 10, this volume) that the impulse traffic between thalamus and cortex was in both directions, a concept not soon proven experimentally but one which generated speculation and search for the anatomic pathways. A century later, the imagery of a return loop was considerably broadened by British investigators: “[T]he conception of a thalamocortical circulation of neural impulse will in the future come to be found as fundamental for the neurology of what we colloquially call ‘thought’ as the conception of a circulation of the blood is for modern physiology!” (Campion in Campion and Smith, 1934, p. 97). Campion’s coauthor, G. Elliot Smith, subscribed to the same idea: “The circulation of the thalamic and cortical currents maintains this constant state of readiness and is a vital and essential part of consciousness and mind” (*ibid.*, p. 24). They were writing about the neural basis of thought, but the state of readiness referred to was muscle tone, again an illustration of the historical fact that entrée to the physiology of the nervous system was by way of the experimental study of muscular action.

Two decades later, however, it was not necessary to call on consciousness, mind, and the neuromuscular junction to explain the nervous system, for the experimental evidence of two-way circuits had become abundant. In Walker’s words (1949, p. 250), “It is . . . evident that as well as receiving a spatially well-organized system of fibers from the thalamus, the cerebral cortex sends to that ganglion a system having, if not quite as precise, at least a certain organization.” He recalled that Head and Holmes in England had labeled this centrifugal system the basis of inhibition, and the Germans concurred, whereas the French said the concept was not compatible with the clinical findings. To others, (Wallenberg, Brouwer, D’Hollander, for example), the corticothalamic pathways were a means by which the cerebral cortex “can modulate the sensitivity of the primary receptive centers to render them more susceptible to incoming impulses, in other words, it is a mechanism of sensory attention” (*ibid.*, p. 251).

As noted in Chapter 10, Luys knew as early as 1865 that the four then-recognized nuclei in each thalamus had representative cortical connections. He also depicted converging fibers from cortex to

the external thalamus (*see* Fig. 10.11, right, p. 212, this volume). Flechsig described a “descending efferent mechanism” as well as his “gateways” to the brain, ideas that were apparently based on the work of his associate, von Tschisch (1886), according to Mettler (1972, pp. 1, 2). Monakow, too, studied corticofugal projections (1895), coupling cortical ablations with degeneration in localized thalamic regions. At the turn of the century, a summary of views on information flow between cortex and thalamus in clinical material had been provided by Dejerine (1901), but at that time the polarity of the pathways was conjectural, especially in human material. With the continuing appearance of ever more reliable anatomic data, however, it became increasingly clear that Carpenter’s suggestion of an interactive relation between thalamus and cortex was correct.

The strongest evidence was seen through the microscope lenses of one of the period’s master histologists, Ramón y Cajal (*see* Chapter 7, this volume), who found (1903) a corticothalamic tract and asserted that it carried impulses in both directions (*see* Fig. 12.10, p. 260). Mention has already been made (*see* Chapter 10, this volume) of Sachs’s report (1909) of fibers between frontal cortex and thalamus, based on anatomic and physiologic data obtained with the first stereotaxic instrument constructed by Horsley and Clarke. Head and Holmes were believers, too: “The functions of this organ [thalamus] are influenced by the coincident activity of the cortical centres, and this control is effected by means of paths from the cortex to the thalamus which probably end in the lateral nucleus” (1911, p. 151).

Santiago Ramón y Cajal’s last and perhaps most eminent student, Rafael Lorente de Nó (1902–1990; *see* Fig. 12.11, p. 260), followed the master’s example in expert manipulation of the staining techniques for nerve tissue that had become available and brilliantly continued the investigation of the auditory system. When he emigrated to America he added expertise in electrophysiology to his competence in otolaryngology and during his tenure at Rockefeller Institute for Medical Research, he published a comprehensive study of nerve physiology (1947) that demonstrated his “extraordinary versatility, breadth of interest, and diligence” (Kruger and Woolsey, 1990, p. 2). In his section on nerve activity in Fulton’s *Textbook of Neurophysiology* (1938), Lorente reemphasized the physiologic rightness of a two-way communication between thalamus and cortex:

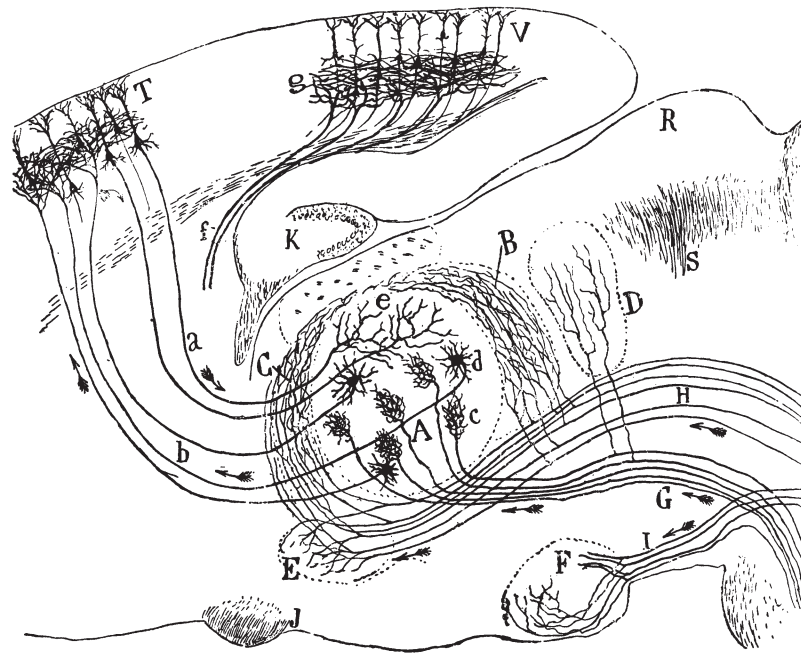
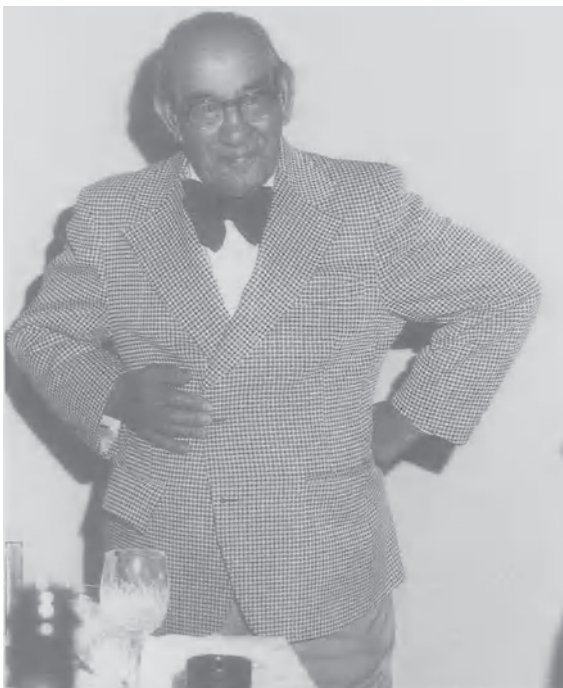


Fig. 12.10. This composite drawing of a thalamic nucleus by Santiago Ramón y Cajal was published in 1903, p. 339, Fig. 3. He repeated it in 1911, first to illustrate sensory paths to thalamus and again with a different caption to show corticofugal thalamic connections. A—Sensory nucleus of thalamus; T—sensory motor center; V—visual cortex; a—corticothalamic fibers; b—thalamocortical fibers; B, C—accessory nuclei of trigeminal nerve; D—post. nucleus of thalamus; E—nucleus zona incerta; F—ext. mammillary nucleus; G—medial ribbon of Reil; H—central path of 5th nucleus; I—pedicle of mammillary body; J—optic chiasa; K—Ammon's horn; f—sup. optic path. (From *Histologie . . .*, vol. 2, 1911, p. 876, Fig. 548; p. 501, Fig. 323, $\times 1$.)



Since the impulse conducted by a fibre necessarily passes into its collaterals and [since] branches of the descending axons are distributed in the same territories as the cortical afferents, there can be no doubt that the effect of the impulses entering the cortex depends largely upon the impulses at that moment circulating through the descending axons as a result of the existing cortical activity. The intracortical distribution of the axonal branches is as systematic as that of the dendrites (Lorente de Nó, 1938, pp. 307–308).

The earliest experimental study of corticothalamic projections that were both carefully timed

Fig. 12.11. Rafael Lorente de Nó was distinguished by his ebullient red bow tie, gracious Spanish manner, and relentless pursuit of his beliefs: “I want to make it stronger!.” (Photograph by Dr. Emilio Decima in early 1980s.)

(staining) and systematically controlled (lesions) were carried out by F. d'Hollander. His work was initiated at Louvain under the tutelage of van Gehuchten, but the records and slides were destroyed by the guns of August, 1914, and only in 1922 were the studies repeated and the results published. The author lamented the complexity of the thalamic structure—"c'est un encéphale miniature"—and divided the corticothalamic paths into two groups, superficial and deep with short and long fibers, respectively. D'Hollander decorticated adult rabbits serially from frontal to occipital poles and 15 days later determined the effect on the thalamus as revealed by careful Marchi staining. Although he admitted this was not yet direct proof, he believed his results showed that the judgment of there being few such fibers needed revision; Lorente confirmed those findings and made the revision.

During the 1930s, voluminous evidence accumulated for what came to be termed "feedback" of information passing between cortex and thalamus. In a presentation to the Boston Society of Psychiatry and Neurology, B. Brouwer from Amsterdam embellished his talk with slides, drawings, and glass models, then much in vogue, depicting centrifugal and centripetal brain systems. The neuronography of Dusser de Barenne had been used in his laboratory, and he reported: "A very remarkable fact is this, that many fibers descending from various parts of the cerebral cortex, go back to all their [thalamic] nuclei" (Brouwer, 1933, p. 624).

Dusser de Barenne argued that the bilateral "thalamic syndrome" of acute cutaneous hypersensitivity after application of strychnine to a small area of sensory cortex, in spite of decortication (with novocain) of the surrounding areas, must be due to setting "on fire the cortex of the whole sensory arm area and . . . those [representational] portions of the optic thalamus" (Dusser, 1924, p. 284). In the assumption of a close functional relationship between cortex and thalamus (Fig. 12.12), Dusser joined the company of those clinical investigators, among them Head and Holmes, Monakow, and Dejerine, who entertained the idea of an interactive information flow between cortex and thalamus.

Although this line of inquiry was not immediately pursued during the decade of the 1940s because of competition from the more compelling concepts of diffuse and specific projections of the thalamic nuclei, as described in Chapter 10 and below, nonetheless, the ground was ready for an

entirely new approach to understanding neural networks and needed only the cultivation by scientists with different mind-sets to come to fruition. The recognition of neural nets as aggregates of Cajal's discrete structures making nonconnecting contact with each other through Sherrington's synapses opened the door to computational theory and intelligent control technology. Because neural networks are flexible, capable of analyzing problems with many variables, and self-propagating with feedback and feedforward loops (J. R. Zweig, personal communication, 1989), they lent themselves to the symbiosis of elements from mathematical and physiological sciences from which cybernetics evolved.

The union was nowhere more productive than in the collaboration of a few people around Warren Sturgis McCulloch (1898–1968; *see* Chapter 5, this volume), first at Yale, then the University of Illinois, Chicago, and finally at the Massachusetts Institute of Technology. From an early interest in philosophy, McCulloch trained as a psychiatrist; his attainments eventually gained him memberships in an unusually broad array of professional societies representing the fields of neurology, anatomy, physiology, mathematics, biological psychiatry, and arts and sciences. Such diversity was lodged in a man who was dubbed a "rebel genius" (Gerard, 1970) and whose intense eyes, unfashionable beard, and abrupt manner did not inspire confidence. Nonetheless, he was a magnet to those neuroscientists who could conceptualize beyond impulse conduction and the neuromuscular junction.

The first modeling of the functional possibilities of neural networks was perhaps that of Sigmund Exner (1846–1926), Austrian physiologist, published in 1894 (Fig. 12.13). Crystallization of the neural network concept into cybernetics came much later, but there were clues scattered, albeit sparsely, throughout the work of neurophysiologists, some of whom have been mentioned. Recall, for example, that Gall had cast "a long shadow" on networks (*see* p. 55, this volume); Forbes (1922) suggested feedback in mammalian spinal recruitment responses; Lorente de Nó (1938) was convinced that feed-back loops accounted for afterdischarge; and Zed Young (1938) found in squid giant nerves "self-reexcitatory" circuits that he proposed might be involved in memory. When McCulloch moved to Chicago in 1941, he soon took under his wing a child prodigy, Walter H. Pitts Jr.,

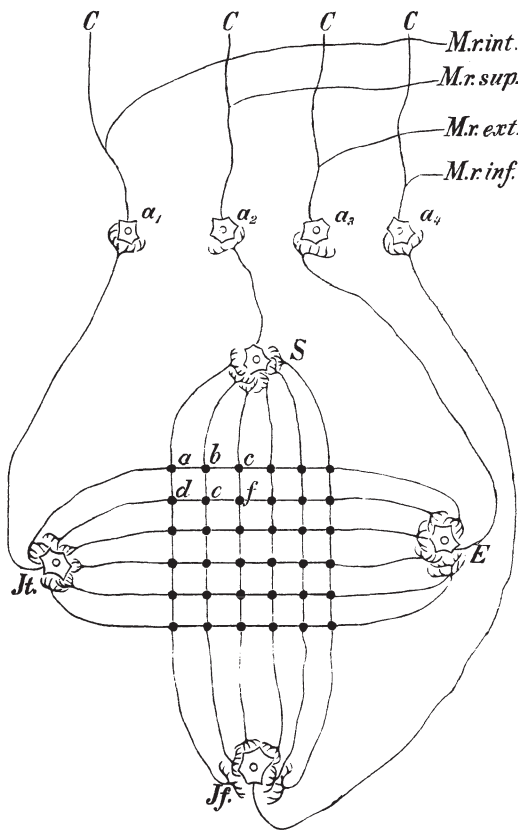


Fig. 12.13. The earliest diagram of a neural network, representing a center for visual perception of movements. a–f—Points where fibers from the retina enter the network. S, E, Jt, Jf—Cells representing terminals from any stimulus point. a₁–a₄—Centers closely associated with the nuclei of four external eye muscles (M. rectus inf., sup., ext., int.). C—Fibers to cortex as the organ of consciousness. (From Exner, 1894, p. 193, Fig. 53, $\times 4/5$.)

temporaries in other disciplines. For example, he sent an early version of Wiener's *Cybernetics* to Wolfgang Köhler, the "Granddaddy of Gestalt psychology" (McCulloch, quoted by Heims, 1991, p. 236) to nourish Köhler's interest in carrying out some neurophysiological measurements of steady currents in the brain's visual apparatus. Probing the ancient problem of perception was in full swing, with the Pitts–McCulloch group endeavoring to "mechanize" perception using the individual neuron as the unit of activity (see Lettvin et al., 1959, "What the frog's eye tells the frog's brain"), whereas the Köhler school was promoting perception as an isoelectric phenomenon encompassing the entire cortex.

Looking over the enormous volume of research stimulated by the ideas of feedback mechanisms and loop circuits, it is apparent that the interest in the return pathways from cortex to thalamus and the educated guessing about possible routes was conducive to a resurgence of illustrative artistry in neuroscience. Attractive model diagrams flourished and became so useful a method of depicting ideas that no one decried their abundance as had been the case in the late nineteenth century in trying to explain the aphasias (Fig. 5.7). Perhaps the diagrams were inspired subliminally by the cyberneticists' "loopy" models, and again illuminated presumed pathways for information exchange between brain stem, cortex, and the interposed thalamus. Pitts and McCulloch (1947) updated Exner's prototype, thus documenting the progress in theory and knowledge achieved in the intervening half-century (see Fig. 12.14, p. 264). We note two other examples from the proceedings of a major conference convened explicitly to redeem the neglect of the corticothalamic thoroughfare while attention had been largely on the neural traffic in the reverse direction. In 1972, the Parkinson's Disease Research Center at Columbia University's College of Physicians and Surgeons brought together neuroscientists interested in corticothalamic projections and sensorimotor processes. At that conference, the report from Scheibel's laboratory emphasized the key role of nucleus reticularis thalami in the cortical influence on thalamic neurons (see Fig. 12.15, p. 265). Another vivacious diagram embodied the ideas from a laboratory at the University of Oslo, Norway, showing three major paths between cortex and thalamus (see Fig. 12.16, p. 265). With degeneration studies and silver impregnation of brain tissue, axons from areas S I and S II and M I and M II in cat were traced and a substrate established for the cortical influence on sensory input (Rinvik, 1972).

Rinvik's summarizing diagram above is misleadingly simple compared with the confusing array of discoveries of the organization of systems that are so vital to the quality of life. In John Eccles's many writings he has consistently emphasized the interconnectedness of the systems that maintain the organism's contact with its environment. This legacy from Sherringtonian integration was expressed in a confusingly crowded yet curvy diagram of the interconnections of thalamus and cortex with the limbic system (Fig. 12.17), presented

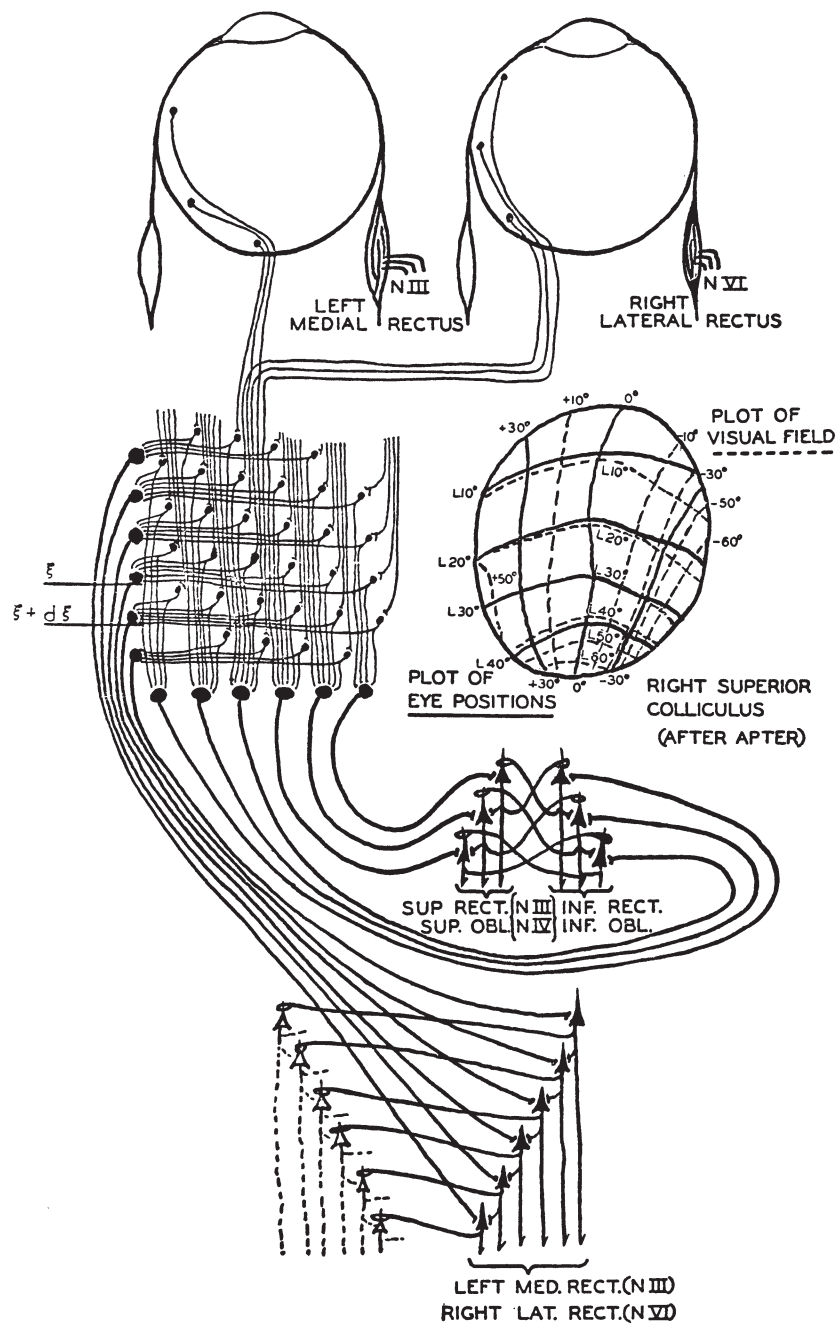


Fig. 12.14. Diagram reproduced for comparison with the previous figure shows ocular afferents to left superior colliculus whence they are relayed to the motor nuclei of the eyes. An inhibiting synapse is indicated as a loop about the apical dendrites. (From Pitts and McCulloch, 1947, p. 141, Fig. 6, $\times 1$.)

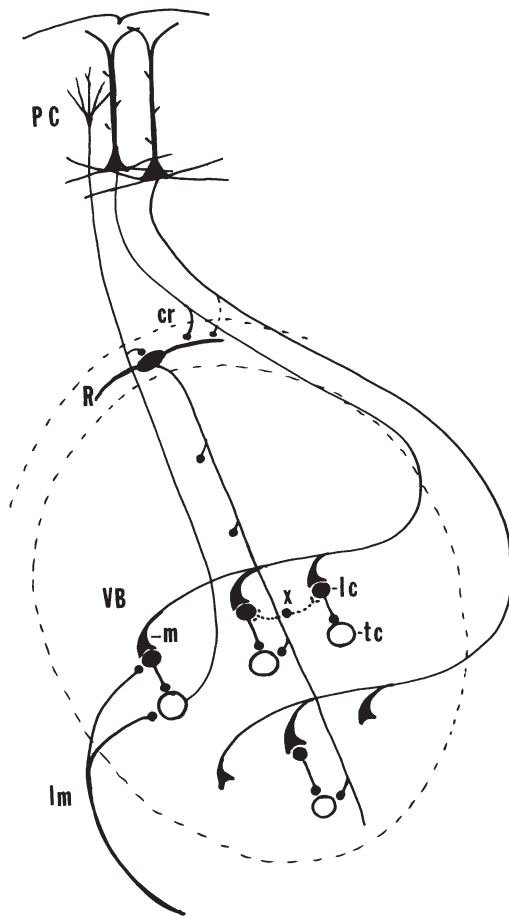


Fig. 12.15. A simplified view of the relation between corticofugal systems and sensory thalamus that shows axonal projections from pericruciate cortex (PC) and nucleus reticularis thalami (R) establishing contacts with linear arrays of thalamocortical circuit (tc) and local circuit (lc) interneurons arranged in rostral-caudal sequence. VB—ventrobasal complex; lm—medial lemniscus fibers; cr—input from cerebral cortex; x—cells without axons. (From Scheibel, Scheibel, and Davis, 1972, p. 152, Fig. 15, $\times 4/5$.)

in one of Sir John's more recent philosophical-physiological series of lectures, *The Human Mystery* (1979).

THE BRAIN-STEM RETICULAR FORMATION AND AROUSAL

"There is no better description than Sherrington's '... functions for which the words neither motor nor sensory are fitting'." (G. Jefferson, 1958, p. 731.)

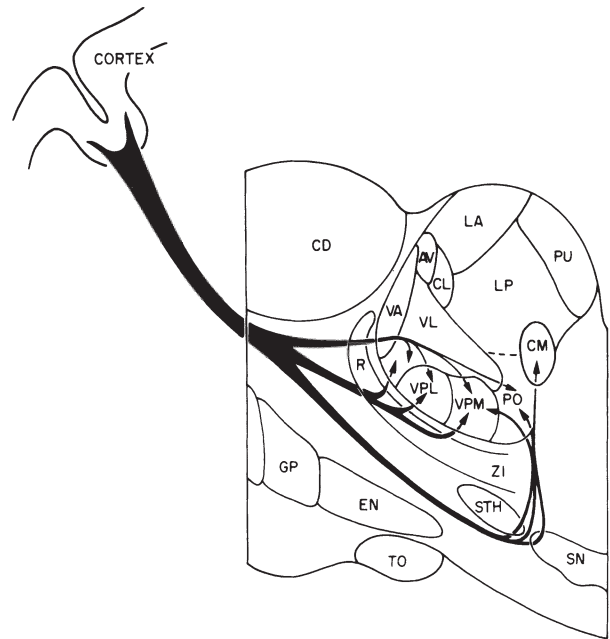


Fig. 12.16. The three major pathways of fibers from sensory and motor areas of the cerebral cortex to thalamus. AV—nuc. ant. ventralis thalamii; CD—caudate; CM—centrum medianum; EN—entopeduncularis; GP—globus pallidus; LA, LP—nuc. ant., post. lateralis thalamii; PO—post. group thalamic nuclei; PV—pulvinar; R—nuc. reticularis thalamii; SN—substantia nigra; STH—nuc. subthalamicus; TO—tractus opticus; VA, VL—nuc. ventralis ant., lat. thalamii; VPL, VPM—nuc. ventralis post. lateralis, medialis thalamii; ZI—zona incerta. (From Rinvik, 1972, p. 71, Fig. 5, $\times 4/5$.)

The most ancient of the three major functional systems considered here has roots in a primitive neuropil which is, in C. J. Herrick's words, "the mother tissue from which the specialized central functional systems have been derived in vertebrate phylogeny. . . . [A]n intricate tangle of thin unmyelinated fibers from various sources . . . representing no specific modality. . . ." (1961, pp. 628, 629). The mass of neuronal processes and somata that constitute the major part of the central nervous systems of early vertebrate species evolved into ever more complex structures in parallel with the species' ascents along the phylogenetic scale. The evolutionary growth of the reticular formation of the brain stem pushed the established motor and sensory neural structures laterally, surrounded some thalamic and hypothalamic nuclei, and encompassed clusters of neurons such as the red

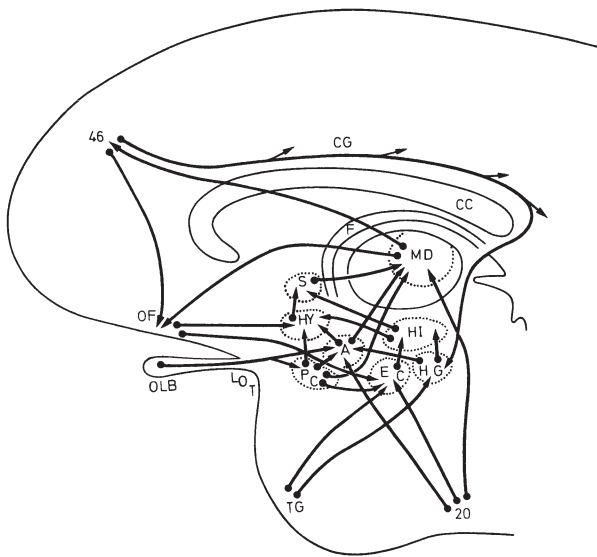


Fig. 12.17. The schematic drawing of interconnections between neocortex, the mediodorsal thalamus (MD), and the limbic system is an attempt on the part of one of neuroscience's great synthesizers to summarize on one schema what was known at the time. OF—Orbital prefrontal cortex; TG—temporal gyrus; HG—hippocampal gyrus; HI—hippocampus; S—septum; F—fornix; CC—corpus callosum; OLB, LOT—olfactory bulb, tract; PC, EC—piriform, entorhinal cortex; A—amygdala; HY—hypothalamus; CG—cingulate gyrus. (From Eccles, 1979, p. 175, Fig. 8–14, $\times 1$.)

nucleus, substantia nigra, the subthalamus, and other brain stem elements, more than 100 in all (Olszewski, 1954). The process of cephalization involved groups of cells that developed

parallel to the elaboration of sensory inputs which became successively important in the animal's economy. Such a picture of central nervous system major levels linked to one another by ascending and descending fiber paths serves as the primitive apparatus of integration. . . . This way of looking at a reticular system as a main component of the nervous system is supported by . . . currently derived information (Bishop, 1958a, p. 416).

The brain-stem reticular formation in higher mammals extends from the lower medulla oblongata (bulb) forward to the interface of the mesencephalon with the diencephalon, although, like the regions essential to consciousness (see Chapter 10,

this volume), its boundaries and functional components have never been sharply defined. This deep region of the brain was usually neglected by early anatomists who found it difficult to see or dissect. During the late nineteenth and early twentieth centuries, while anatomic and physiologic investigations focused on spinal reflexes below (Sherrington) and cerebral localization above (Broca, Ferrier), the intervening brain stem was largely unattended (see Magoun, 1958a, p. 11). The situation quickly changed, however, in midcentury: As was facetiously commented by a participant in the heyday of reticular system discoveries: "It was not too absurd to say that wherever any really interesting fun was going on in brain research, that part was immediately claimed as part of the reticular system" (G. Jefferson, 1958, p. 729). The inadequacy of the early anatomic definitions was highlighted when neurotransmitters and their related enzymes were found in different nuclei of the reticular formation and were correlated with sleep states and EEG changes (Jouvet and Michel, 1958). Those findings suggested that a neurochemical "map" would more meaningfully collate the reticular formation's anatomy and physiology (see A. B. Scheibel, 1987, pp. 1057–1058).

The existence of motor and sensory pathways, centrifugal and centripetal respectively, between the spinal cord and neocortex, only hinted at by the early French ablation studies, was made factual with Hitzig and Fritsch's crude physiological experiments and the detailed cell and fiber tracings of Golgi and of Ramón y Cajal with their new stains. The pyramidal tracts seemed to fulfil the needs of the organism for a prompt reaction to rapid transfer of information from the external environment. The first idea of extrapyramidal connections between spinal cord and brain-stem reticular formation sprang largely from work of O. Kohnstamm and F. Quesnel, during the first decade of the twentieth century and were summarized in a short notice in the *Neurologische Centralblatt* (Quesnel, 1907). Working with puppies and using degenerative techniques, on the basis of Marchi-stained preparations and the work of others, they hypothesized a "centrum receptorium medullae oblongatae" for converging sensory impulses, which were then conveyed by the *formatio reticularis* to thalamus and thence to cortex. "The notion of a multineuronal pathway of pain and temperature conduction involving the brain-stem reticular formation was

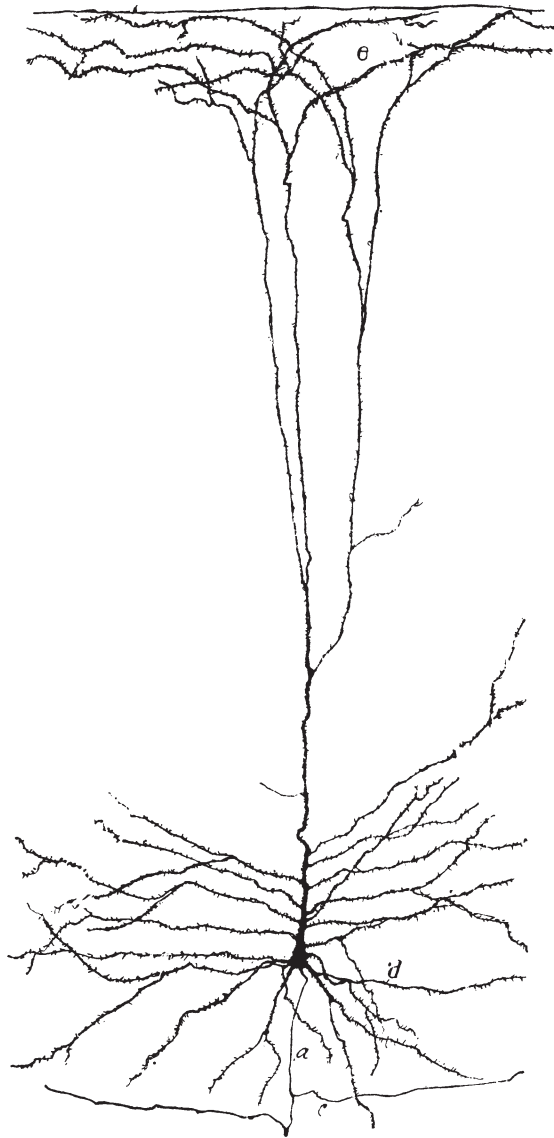


Fig. 12.18. Ramón y Cajal's depiction of an axon (a) with collateral processes (c) allowing spread of impulses at preterminal levels contributed importantly to the development of ideas about reverberating circuits. This drawing shows a Betz cell in the parietal convolution of 30-day-old infant. Golgi method. d—Long basal dendrites, e—terminal protoplasmic bouquet. (From Ramón y Cajal, 1909–1911, vol. 2, p. 566, Fig. 369, $\times 1$.)

thus explicitly formulated, apparently for the first time" (Nauta and Kuypers, 1958, pp. 3–4).

The reticular formation was a minor interest of Ramón y Cajal, who devoted to it only 10 pages of his almost 1000-page *Histologie* (1909, pp. 949–959). He traced two groups of fibers coursing between brain stem and thalamus and noted the

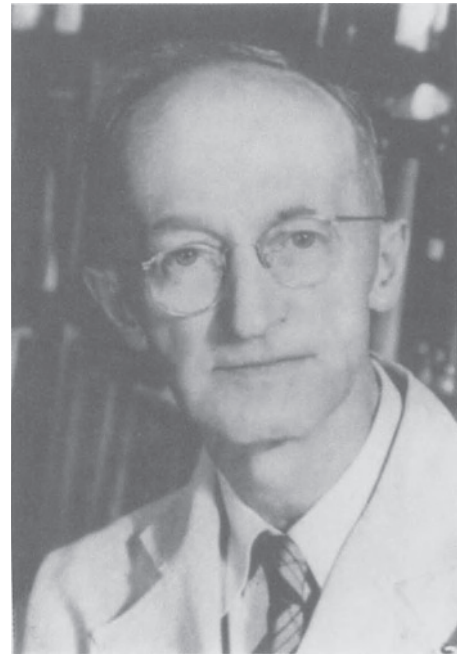


Fig. 12.19. William F. Allen was 40 years old when he received his Ph.D. from the University of Minnesota in 1915. By then he had been assistant to E. P. Allis in France and Jacques Loeb in California and was an authority on the vascular and lymphatic systems of fishes.

abundance of collaterals (Fig. 12.18) from axons in the corticospinal tracts that projected to the reticular formation of the pons and medulla. No significant study of the reticular formation was carried out in the United States until that of William Finch Allen (1875–1951; Fig. 12.19) at the University of Oregon. Allen regarded the *formatio reticularis* as consisting of the “left over cells of the brain stem and spinal cord which are not concerned in the formation of motor root nuclei and purely sensory relay nuclei” (Allen, 1932, p. 498), and described its efferent and afferent fibers. He “presumed” that all sensory fibers communicated “in one way or another” with the reticular formation, concluding that it contained visceral centers as important to the organism as the hypothalamic nuclei at lower levels. From his studies of cerebellar stimulations he made an interesting and prescient speculation: “It may be that there are separate areas [of cerebellar cortex] for inhibition as well as for augmentation” (*ibid.*, p. 494). Unfortunately, because it was published in an obscure local journal, Allen’s work had low visibility beyond the Pacific Coast.

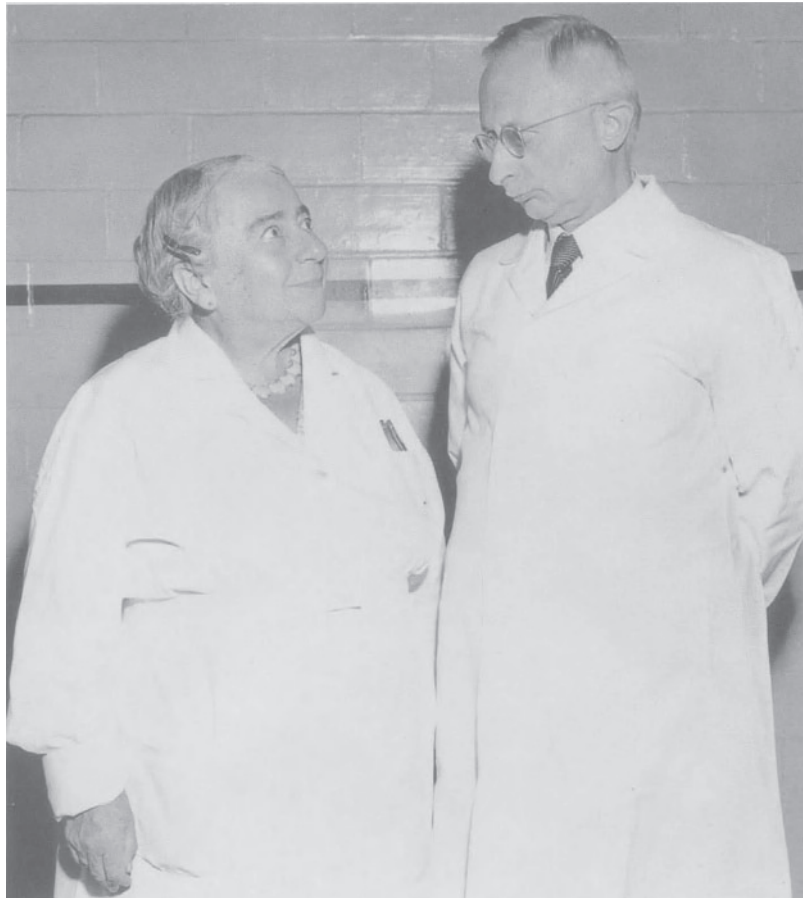


Fig. 12.20. Ernest A. Spiegel and his wife, Mona Spiegel-Adolf, photographed in 1982 at Temple University, Philadelphia, where they had long scientific careers. Spiegel, Wycis, Marks, and Lee (1947) collaborated on the first human stereotaxic apparatus.

The notion of an excitatory influence from higher levels on the motor outflow of the spinal cord had been put forward to explain decerebrate rigidity, which Sherrington (1898), in the Pavlovian tradition, attributed to a release phenomenon due to interruption of inhibitory impulses to the contracting muscles. That time-honored explanation did not satisfy everyone; among the contrarians, Ernest Adolf Spiegel (1895–1985, Fig. 12.20), a Viennese neurologist and neurosurgeon known chiefly for his later work in human stereotaxy, found that decerebrate rigidity was abolished completely only when the reticular formation was transected (Spiegel and Bernis, 1925), implicating its involvement in tonic posture control. That finding and Allen's speculative suggestion were apparently unknown to Magoun

and Rhines (and to Ranson) when they continued the investigation of antigravity muscle control begun by Ranson and for which he had reintroduced the stereotaxic instrument, as described in Chapter 11. Magoun and Rhines studied postural and movement behaviors after stimulation of extrapyramidal spinoreticular pathways in cat and monkey *encéphale isolé* preparations and discovered that the regulatory (in contrast to the initiating) influence was inhibitory or facilitatory according to which part of the brain-stem reticular core was stimulated (Fig. 12.21). The senior author later explained the relation of those findings to spasticity as follows:

The inhibitory or facilitatory effects of reticular stimulation are exerted as markedly upon pos-

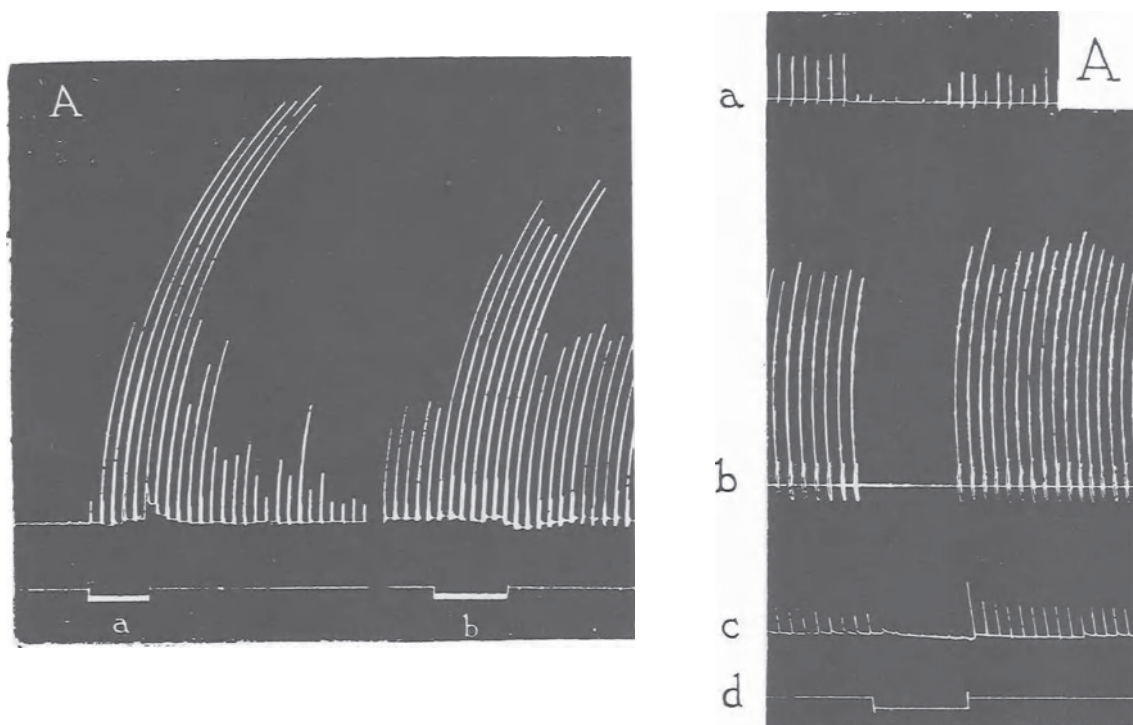


Fig. 12.21. Kymograph smoked-paper records of reflexes evoked by electrical shocks at two-second intervals. Right—*inhibition in cat by bulbar stimulation.* a—Flexor, b—patellar, c—blink, d—signal; $\times 1$. (From Magoun and Rhines, 1946, p. 166, Fig. 1A.) Left: *Facilitation by midbrain stimulation (signal).* a—monkey hind leg response to cortical stimulation, b—patellar reflex. (From Rhines and Magoun, 1946, p. 220, Fig. 1A; $\times 1\frac{1}{2}$.)

tural or stretch reflexes as upon phasic motor activity and, following chronic ablation of cerebellar and cortical regions which project to the reticular region, a pronounced exaggeration of stretch reflexes ensues. . . . Excitability of the inhibitory component of the reticulo-spinal mechanism may be dependent upon bombardment by those cerebellar and cortical regions whose ablation is followed by spasticity and become deficient in their absence (Magoun, 1963, pp. 24,25).

Their series of papers (summarized in Magoun and Rhines, 1947; Magoun, 1950) constituted an in-depth analysis that validated the switch from an inhibitory to an excitatory view of postural control and provided a background for the later interpretation of the “chance observation” of an arousal pattern in the EEG on stimulation of the brain-stem reticular formation that initiated “one of the greatest booms in the history of neurology” (French, 1958, p. 97).

With the advantage of hindsight, it was possible to detect other early evidence of reticular-core function. In a pointed search for antecedents, Brazier (1980, p. 48) claimed as an unrecognized clue a report from Bremer’s laboratory of cortical “arousal” in response to stimulation of the vestibular cortical projection area (Gerebtzoff, 1940b). More relevant to the concept of an ascending reticular system was the earlier identification on the cortex of a slow “secondary response” to sensory stimulation made by Forbes and his associates at Harvard. Although Forbes (1936) thought it was due to unit discharges, he later suggested that the secondary response was delayed by indirect passage over intervening synapses (Forbes, Renshaw, and Rempel, 1937), in contrast to the classical, monosynaptic pathway to cortex.

The observations of Caton in 1875 and of Beck in 1905 (*see* Chapter 5), that electrocorticogram oscillations cease when any afferent nerve is strongly stimulated, was confirmed by Neminsky in 1913 and found in the human EEG by Berger

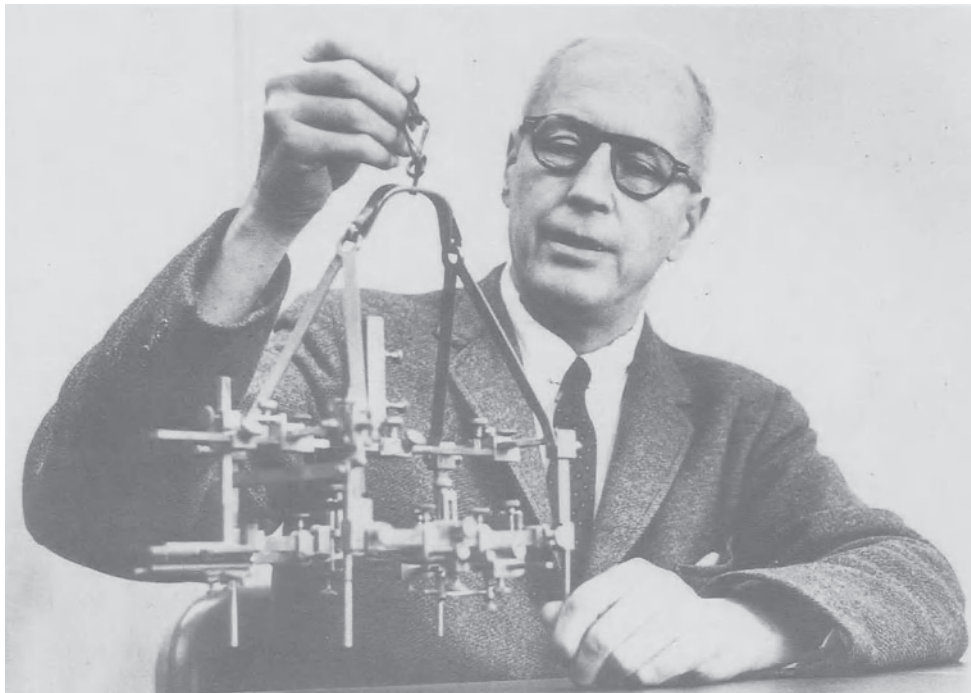


Fig. 12.22. Horace Winchell Magoun shown ca. 1957 holding the second unit of the Horsley-Clarke stereotaxic instrument, built in London for Ernest Sachs in 1908. The instrument was in use at Washington University while Ranson and Hinsey were there and was presented by Dr. Sachs to Magoun as “the next torchbearer.”

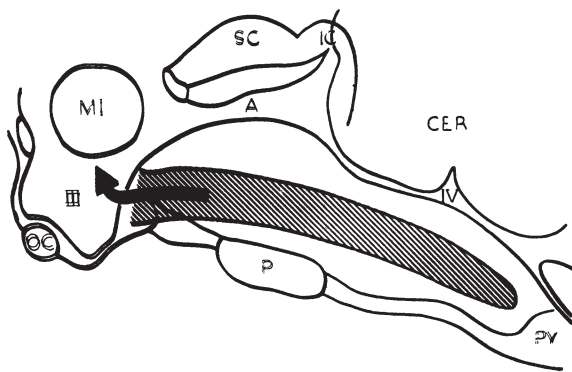


Fig. 12.23. Reconstruction of midsagittal plane of cat's brain showing (crosshatching) the ascending reticular activating system. A—Aqueduct; CER—cerebellum; IC—inferior colliculus; MI—massa intermedia; OC—optic chiasma; P—pons; PY—pyramidal crossing; SC—superior colliculus; III and IV—ventricles. (From Moruzzi and Magoun, 1949, p. 457, Fig. 3, $\times 3/4$.)

(1929). Additional evidence of a diffuse effect of peripheral stimulation was provided by the work of Bremer, whose findings from *encéphale isolé* preparations (see Fig. 9.18, p. 196) prompted him to recognize some global influence of the brain-stem

reticular core in mediating a change in state: “Modification of the cortical oscillogram during passage from a state of sleep to one of wakefulness does not represent a local sensory effect of the stimulus. . . . It can be observed identically, whatever the localization of the recording electrode, or the mode of stimulation. . . . One is dealing here with a general modification of cortical activity” (Bremer, 1936, pp. 466–467). Relatedly, in unanesthetized cats with electrodes on the dura, Rheinberger and Jasper (1937) found patterns of activity recorded from motor, sensory, auditory, and visual areas were related to behavioral state: “The electrogram from all regions was characterized by low amplitude higher frequency potentials when the animal showed behavioral indications of being generally aroused or activated. . . .” (*ibid.*, p. 195).

The confluence of two new techniques—stereotaxis as a means of precise localization in the deep brain (and spinal cord) and electroencephalography in the service of an objective “end point” in probes of the systems’s electrical activity—coupled with classic histological verification, facilitated a flood of new work on the interior regions of the brain, as

noted. When Horace Winchell Magoun (1907–1991; Fig. 12.22) at Northwestern University Medical School was joined in late 1948 by Giuseppe Moruzzi (*see* Chapter 9), an Italian neurophysiologist intent on improving his technical skills, they combined their respective interests in brain stem and cerebellum and looked for corticopetal effects of stimulation of those two regions in their anesthetized cats; they found that with low-frequency stimulation the EEG was flattened to resemble that of an alerted animal (Moruzzi and Magoun, 1949). Initially they thought they were seeing either an artifact or inhibition, but careful elimination of technical errors and with sufficient amplification, they identified the low-voltage, fast waves characteristic of arousal.² The lead paragraph of the paper's discussion section stated:

The evidence given above points to the presence in the brain stem of a system of ascending reticular relays, whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity. This effect is exerted generally upon the cortex and is mediated, in part at least, by the diffuse thalamic projection system. Portions of this activating system, . . . have previously been identified (Moruzzi and Magoun, 1949, p. 468).

In addition to numerous electroencephalograms, the authors illustrated their results with a schematic reconstruction of the stimulated points (Fig. 12.23). The initial findings were corroborated by the effects of lesions: the arousal response was absent in animals in which the region of stimulation was electrocoagulated (Lindsley, Bowden, and Magoun, 1949) and the sleep pattern appeared in the EEG after damage to the midbrain reticular formation (Lindsley, Schreiner, Knowles, and Magoun, 1950).

Intuitively, the presence of two afferent pathways conveying sensory information to the neocortex would seem to be redundant, but each has its role:

As [afferent] signals ascend [the classical] paths, they contribute polysensory excitation to parallel ascending nonspecific connections, distributed through the central core of the brain. The

functions served by these specific and nonspecific cortical input channels are supplementary. The specific one conveys the informational content of the afferent message, for its signals are both modality- and locality-related. The core system, lacking these features, provides instead for behavioral and EEG arousal underlying an orientation and attention to the message (Magoun, 1969, p. 179).

The concept of diffuse projections from thalamus and brain-stem reticular formation, although backed by clear physiologic evidence, did not enjoy easy acceptance. Challenged by that evidence, W. J. H. Nauta, the consummate neuroanatomist, and his associates at MIT set out to definitively locate the possible pathways and inaugurated a rigorous series of "true" Wallerian degeneration studies (not retrograde or transneuronal). First investigating the specific thalamic fibers, they classified them into three neat groups: intrathalamic, subcortical, and cortical (Nauta and Whitlock, 1954). As for the diffuse projections, Nauta and Kuypers (1958) confirmed many of the earlier histologic findings using the Nauta-Gygax stain and added details of reticular interconnections at all levels of the brain stem. As they wrote: "knowledge of the pathways was in place waiting for a function. . . . [The] notion of an ascending reticular activating system was novel only in its striking function" (*ibid.*, p. 3). Acceptance of the notion of a functioning system with an anatomic base, however, was dishearteningly slow: none of the ascending sensory collaterals which disperse widely in the reticular formation

can offer an obvious explanation for the phenomenon of diffuse cortical arousal so clearly demonstrated by physiologic experimentation. Indeed, it may be logical to ask; Do any of the pathways here traced actually ascend beyond the confines of the "reticular formation"? . . . It must . . . be emphasized that at the present time no structures outside the "specific" thalamic nuclei of the thalamus have been definitively demonstrated to project significantly to the neocortex (*ibid.*, pp. 26,27).

Papez, on the other hand, was not hesitant to identify pathways from brain stem to thalamus taken by

²For Moruzzi's recollection of the discovery, *see* L. H. Marshall (1987; an account by Magoun was published in 1985).

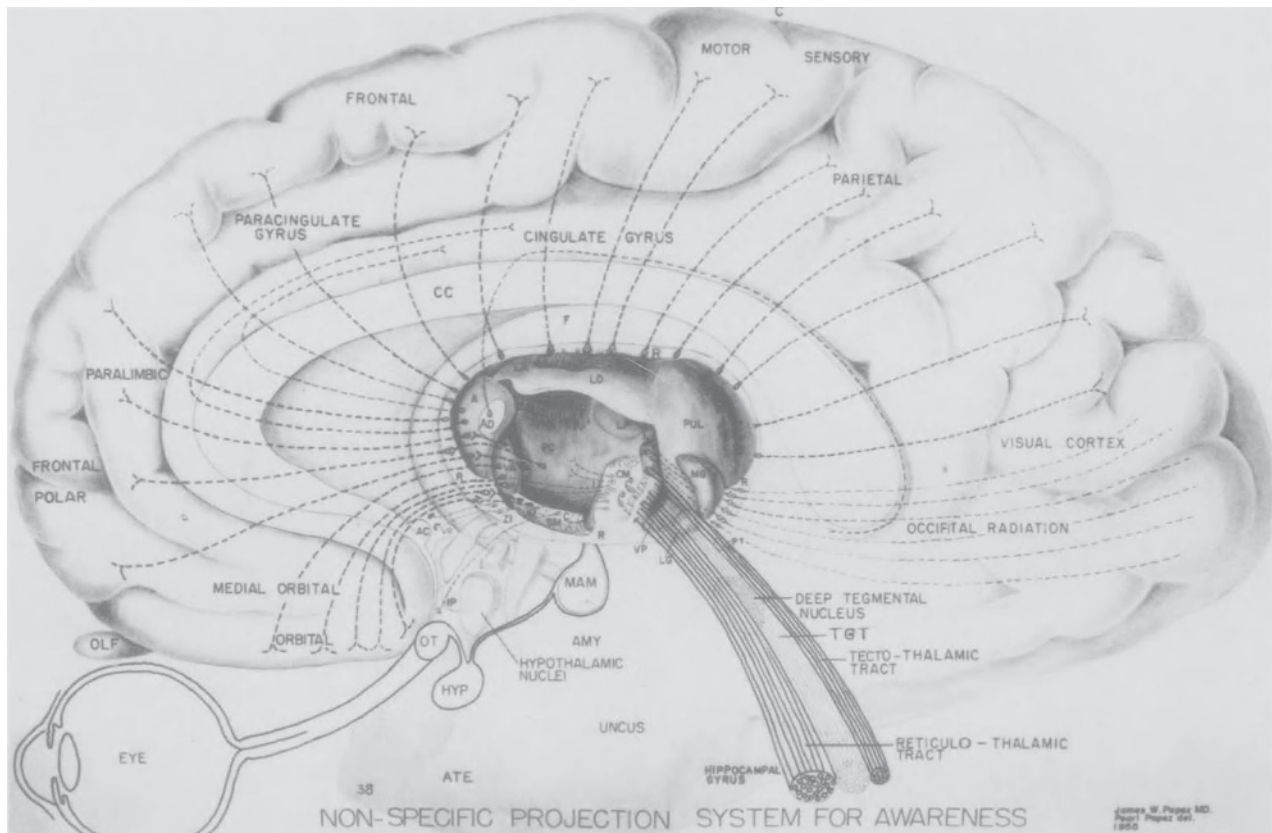


Fig. 12.24. Semidiagram of projections to the right thalamus and cerebrum of nonspecific impulses related to the EEG and consciousness. RTT, TGT—reticulo- and tegmentothalamic tracts; CM—centrum medianum; PF, L—parafascicular, limitans fibers; R—reticular nuc.; I—intralaminar bundle; SM—submedial nuc.; PC—paracentral nuc.; CL—central lateral nuc.; IP—inf. thalamic peduncle; NB—ant. perforated substance; A—anterior nuc.; VM—ventral medial nuc.; VA—ventral ant. nuc. (From Papez, 1956, p. 118, Fig. 1, $\times 3/4$.)

nonspecific impulses and to diagram their abundant projections to the cortex. Compulsive for neuronal detail, he supervised his wife's drawing of the "Non-specific Projection System for Awareness" (Fig. 12.24).

Efforts to extend knowledge of the diffuse system were of course pursued most vigorously by the principals themselves, at the temporary Long Beach laboratories of the group assembled by Magoun when he moved to the University of California, Los Angeles in 1950, and at the Instituto Fisiologia of the University of Pisa, in what was "a magic period of research and study" (Zanchetti, 1981, p. xiv) initiated by Moruzzi's energy and vision on his return to Italy after two years in Chicago. In a summary of the unitary studies carried out with colleagues, Moruzzi (1954) described,

among other findings, two responses of the bulbar reticular system to stimulation: the phasic, mediating EEG arousal, and the tonic, for maintenance of wakefulness. Although supportive data continued from many laboratories, an American neurophysiologist visiting the laboratory in Pisa reported informally:

As Moruzzi puts it, the reticular story is going through a period of "crisis." The original concept . . . is being seriously challenged by many different kinds of evidence, particularly by the work of Adametz, Sprague, Huttenlocher, Bot[e]s, and by the work in low-voltage fast sleep. I think it is greatly to Moruzzi's credit that he recognizes this and is trying to come to terms with these new data (Spencer, 1961).

In addition to the skeptics, another major obstacle to advance of the arguments was the recurring annoyance of nomenclature, due largely to superimposing terms from structural and functional domains. As Brodal (1969, p. 306) later emphasized with italics, "*It should be made perfectly clear that the 'activating system' is a functional concept, the 'reticular system' a morphological one, and it has been obvious for many years these do not correspond.*" This thorough Swedish investigator, whose Golgi preparations revealed that the short-axon and long-axon reticular cells are aggregated in clusters, argued that the organization of the reticular formation was not diffuse nor did it lack order.

The implications of an ascending reticular system, formulated from laboratory animal experimentation, for the human domains of such phenomena as sleep and wakefulness, epilepsy, and consciousness, were of great interest to investigators in many branches of biomedicine. Bremer's fundamental observations after transection of the upper brain stem (see Chapter 9, this volume) had signaled the beginning of attention to the problem of sleep and arousal (Magoun, 1954a, p. 6) even though the new data undermined his widely held theory of "deafferentation" of the specific paths as the cause of sleep. The ascending reticular system filled a gap in neurosurgical theorizing, as Hugh Cairns (1952, p. 142) suggested in a lecture on consciousness, because with its far-reaching collateral connections it resolved the seeming paradox of unconsciousness resulting from too little or too much afferent stimulation from the periphery. In psychiatry, "The functions of the brain stem . . . are related to the integration of the organism in three-dimensional space in one or another pattern of interaction. . . . These highly complex differential functions can be carried out only if the brain stem integrative functions are stable. . . ." (Rioch, 1954, p. 477).

Colleagues and visitors at Magoun's laboratory knew they were on to something big and pursued it accordingly. With the equipment in use around the clock, the ever-changing groups working on various aspects of the brain stem diffuse system added to the mass of data from that and other laboratories in such volume that attention to the specific thalamic tracts was refocused as collaterals from them to the diffuse system threatened to become more important than the "direct corticopetal paths in EEG arousal induced by afferent stimulation" (Magoun, 1954a, p. 6). Deep pathways were found anatomi-

cally and physiologically between the limbic and activating systems (Adey, 1958). Figure 12.25 recapitulates the known effects of reticular core activity, effects that were elegantly summarized in *The Waking Brain* (Magoun, 1963).

The pervasive interest in the concept of an ascending reticular system and the accumulation of knowledge of its role in the problem of how the brain works can be traced between 1954 and 1980 through a series of major conferences centered on that topic. The proceedings of the first conference, dubbed "the Laurentian" for its Canadian locale, were published as *Brain Mechanisms and Consciousness* (Delafresnaye et al., eds., 1954), a title linking the aroused cortex with neuronal activity. Magoun's paper was on wakefulness, and Jasper set the adversary tone of the discussion: "We are now afforded a rare opportunity to put Dr. Magoun on the carpet. . . ." (Magoun, 1954a, p. 15). And the audience did just that—the published discussion is lengthier than the text of the talk; there were comments about definitions, e.g., behavioral arousal versus EEG flattening; about experimental methods; and anatomic pathways—queries pertinent to a just-emerging concept. The second paper read at the Laurentian conference was by Moruzzi, who discoursed on the physiologic properties of the puzzling reticular system as revealed by work from his laboratory in Pisa. His concluding words attested to the still uncertain state of knowledge at the time: "The microphysiology of the central nervous system is just beginning and it is about one century younger than microscopic anatomy. There is no reason to be surprised, therefore, that many basic problems have not been approached experimentally and that the meaning of much of our data remains unclear (Moruzzi, 1954, p. 48).

During a discussion period (notorious for generating some of the most significant ideas at any meeting) the question of where do specific and nonspecific systems interact was posed by Magoun, who sensed a "merging attitude" on the part of investigators to recognize that interaction between the systems takes place at the diencephalic level in addition to that shown at a cortical level (Jasper and Ajmone-Marsan, 1952). From studies already noted, Nauta contributed the opinion that "we have anatomical evidence of such connections between the diffuse and specific parts of the thalamus as well as of connections of both parts with the reticular nucleus" (Nauta and Whitlock, 1954, p. 113).

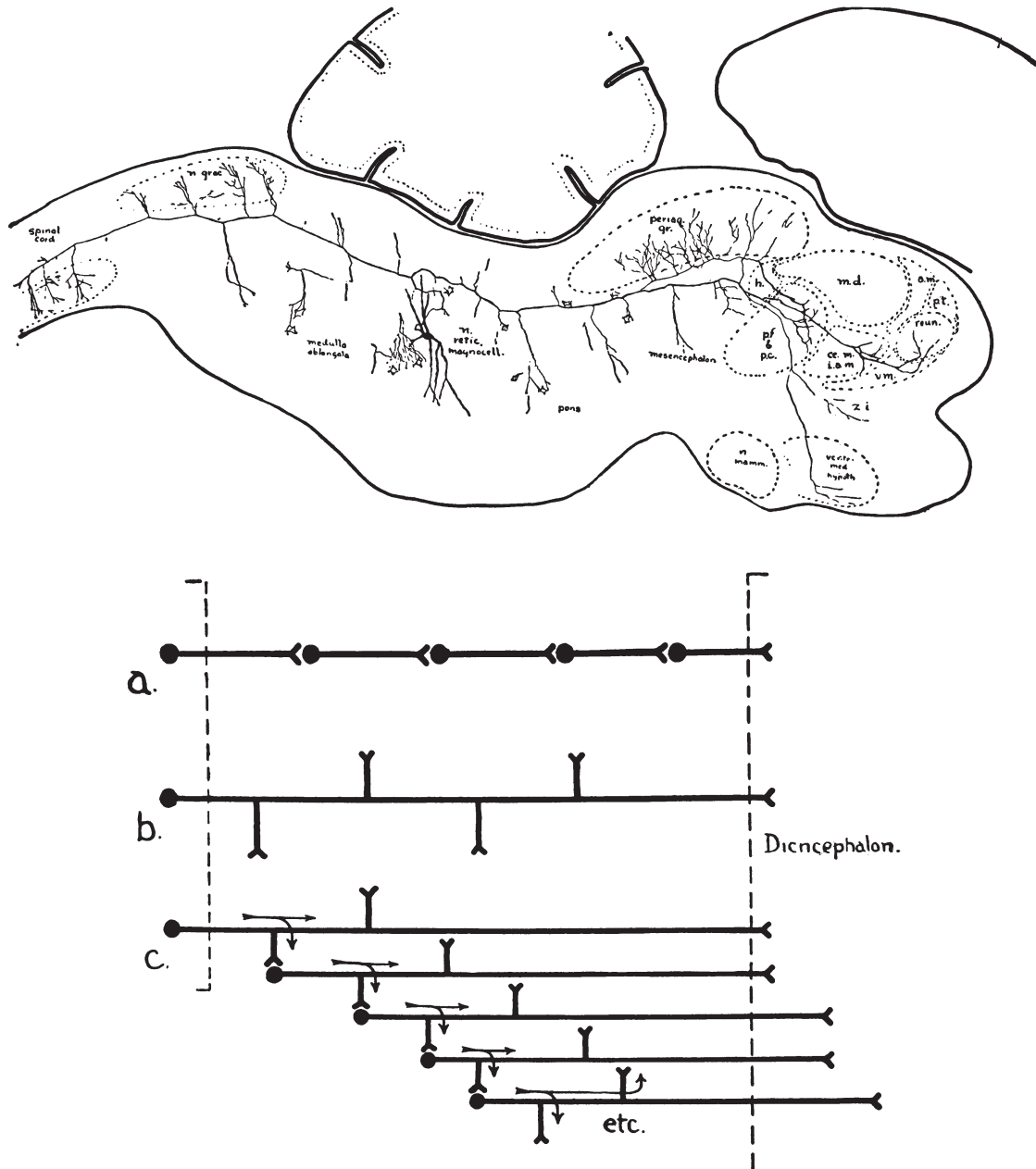


Fig. 12.25. Above—Drawing of a single, large reticular cell of the magnocellular nucleus in a two-day-old rat. The axon bifurcates, the caudal segment giving off collaterals to the reticular formation, nucleus gracilis, and spinal cord; the rostral segment gives off collaterals to the reticular formation and periaqueductal gray and appears to supply nuclei of the thalamus and hypothalamus. (From Scheibel and Scheibel, 1958, p. 46, Fig. 12, $\times 1$.) Below—Diagram of possible conduction circuits through the reticular core of the brain stem. a—Short-axon cells hypothesized by Moruzzi and Magoun, b—single, long-axon cell from bulb (left) to diencephalon found predominantly, c—branching of collaterals in b forming circuitous paths through the reticular core producing longer latencies and conduction times. (From *ibid.*, p. 44, Fig. 10, $\times 4/5$.)

Four years after the Laurentian conference, a second major meeting was aimed directly at the morphology and function of the reticular system; it was held at the Henry Ford Hospital in Detroit and

was published as *Reticular Formation of the Brain* (Jasper, Proctor, Knighton, Noshay, and Costello, eds., 1958). The papers reveal not only the focal interests of the active investigators and their accep-

tance of the concept, but also demonstrate the enormity and potential scope of reticular formation influence. As Brodal (1957, p. 23) had noted elsewhere, the early descriptions of long ascending connections from the reticular formation had been “largely forgotten” until their stimulation was shown to influence cortical electrical activity, and thus a reinvestigation of the microstructure of the region was not surprising. In addition to the anatomical studies of Nauta and Kuypers (1958) already described, the Scheibels offered both histologic and physiologic data that showed convergence of “heterogenous afferents on single elements of the brain stem reticular core” (Scheibel and Scheibel, 1958, p. 32; Fig. 12.25, above). Those authors also postulated various circuits to account for latency, conduction times, and lateral dispersion of impulses traversing the reticular core (Fig. 12.25, below). Amassian and Waller described (1958) clear evidence from individual brain-stem reticular neurons of the relation of different firing patterns (“coding”) to their receptive fields. Magoun (1958, p. 109) related those findings to Sharpless and Jasper’s (1956) report of brain stem components at distinct levels and activities. From microelectrode studies of the cortical arousal system in behaving monkeys, Jasper suggested “that the rapid switching of local activation or inhibition may occur not primarily through unspecific thalamocortical circuitry, but by effects upon specific thalamocortical projection systems at a subcortical level” (Jasper, 1958, p. 328).

Other reports of research-in-progress at the Detroit symposium included, but were not limited to, drug actions, stress, gonadotrophin release, motor activity and muscle spindles, cortical circulation, vision and perception, conditioned and visceral reactions, and learning. That wide array, a measure of the clarifying and interpretative potential of the notion of the ascending arousal system, was summarized eloquently from a broad perspective:

A quotation from Claude Bernard [says]: “The stability of the milieu intérieur is the condition of a free life”. . . . This freedom to act, to play, to carry out intellectual work, one of the main achievements of evolution, is precarious. . . . That is to say, to be active or to sleep, to preserve and protect the integrity of our internal organi-

zation. Even more, the way in which we apprehend the outside world depends on the actual balance of our internal milieu and its repercussion on the brain stem reticular activity (Dell, 1958, pp. 377-378).

Although not centered on the brain stem reticular formation, the timing of the Moscow Colloquium on the EEG of higher nervous activity—in 1958 and only a year after the conference in Detroit and a meeting of the World Federation of Neurology in London—ensured that the topic was a major item of earnest discussion. Not surprisingly, the full weight of Pavlovian conditioning was brought to bear on “higher” nervous activity in the first sentence of the presentation by the eminent Russian physiologist, Petr Kuzmich Anokhin (1898–1984): “An analysis of the present-day situation in the physiology of the nervous system shows that the conditioned reflex is the nodal point at which the different trends in the physiology of the nervous system meet” (Anokhin, 1960, p. 257). Establishment of the International Brain Research Organization (IBRO)³ was a permanent outcome of the successful Moscow meeting of 1958. A large part of the enthusiasm of the participants lay in the frank and open exchanges and Magoun praised Moruzzi’s paper (Moruzzi, 1960) on a bulbar mechanism for synchronization of cortical activity as “the second major contribution to reticular physiology presented at this colloquium” (Magoun, 1960, p. 253). In Magoun’s opinion, the first major paper was by Bremer, followed by Dell who gave a detailed discussion of his own and Bremer’s simultaneous and independent demonstrations of facilitation of sensory evoked potentials by reticular activation (Dumont and Dell, 1958; Bremer and Stoupel, 1959). And yet another “landmark” singled out by Magoun was the “pronounced modification” of unit discharges in the reticular formation and elsewhere during spreading depression, demonstrated in the presentation by Bureš and Burésová (1960). With so much of the discussion centering on the reticular formation, this confluence of electroencephalography and behavioral conditioning was a waysign pointing the direction into the new terrain of neuroscience.

Another gathering of neuroscientists, this time organized specifically to consider the brain-stem

³See Jasper (1991) and L. H. Marshall (1996).

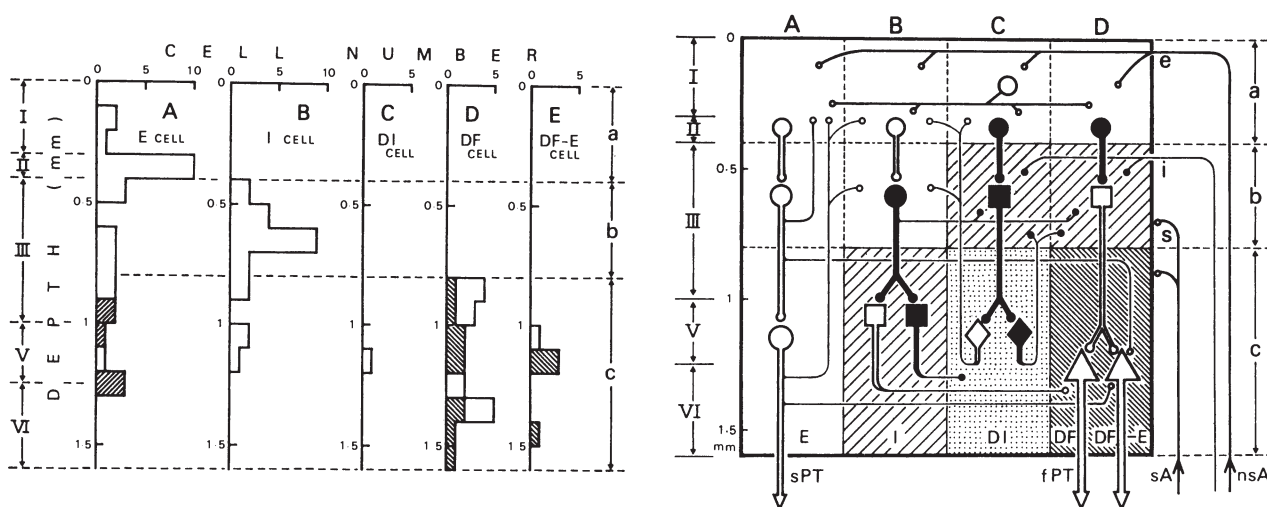


Fig. 12.26. Left—Distribution chart of four different types of action plus a mixed type found in cortical cells of laminae I through VI. The data were obtained on cats in an attempt to elucidate the electrical events of EEG arousal. Hatched columns—pyramidal cells; blank columns—nonpyramidal cells; E—excitatory; I—inhibitory; DI—disinhibition; DF—disfacilitation. (From Inubushi, Kobayashi, Oshima, and Torii, 1978, p. 701, Fig. 8.) Right—Summary diagram of an “arousal” circuit model based on data shown in the previous figure. The parallel three-neuron relays represent four different mechanisms for membrane stabilization in EEG arousal. Large, small open circles—excitatory neurons, synapses; large, small filled circles—inhibitory neurons, synapses; nSA—nonspecific afferents; sPT—specific pyramidal tract. (From *ibid.*, p. 703, Fig. 9.)

reticular core, took place three decades after the 1949 papers. Sponsored by the Society for Neuroscience and IBRO, in *The Reticular Formation Revisited* (Hobson and Brazier, eds., 1980) the amorphous issue of who first formulated the concept was submerged by the rich array of new supportive evidence. As the Canadian neurophysiologist Mircea Steriade declared elsewhere, “It is a pleasure to reread [Moruzzi and Magoun’s] 1949 communication and see how later developments not only confirmed the data but fully justified some of the major theoretical issues” (Steriade, 1981, p. 327). After reviewing the main conclusions of 1949, Steriade recalled subsequent work showing the psychophysiologic correlates of experimental reticular activation: improved accuracy and reduced reaction time in tachistoscopic tasks carried out by monkeys (Fuster and Uyeda, 1962), and single-cell experiments which demonstrated that

the original concept “is alive and well” (Steriade, 1981, p. 371).

The mechanisms of the brain-stem reticular formation remained a prominent neuroscience research area for many years and are not yet exhausted.⁴ The use of intracellular recording and stimulation in interpreting the EEG arousal response was elevated to a rarified altitude by elegant studies from Japan which constitute the first systematic study of the responses at the cellular level, according to the authors, and attest to the tremendous progress since Jasper reported cellular studies in 1958. Inubushi, Kobayashi, Oshima, and Torii (1978) minutely analyzed the activity of cortical neurons during arousal by reticular stimulation. Laminar II neurons in motor cortex are excited initially, then activity spreads to excitation or inhibition of deeper neurons. They found desynchronization of the EEG to consist of a

⁴A recent report of dramatic results of brain imaging studies implies activation of the midbrain reticular formation by sensory stimulation in man (Kinomura, Larsson, Gulyás, and Roland, 1996).

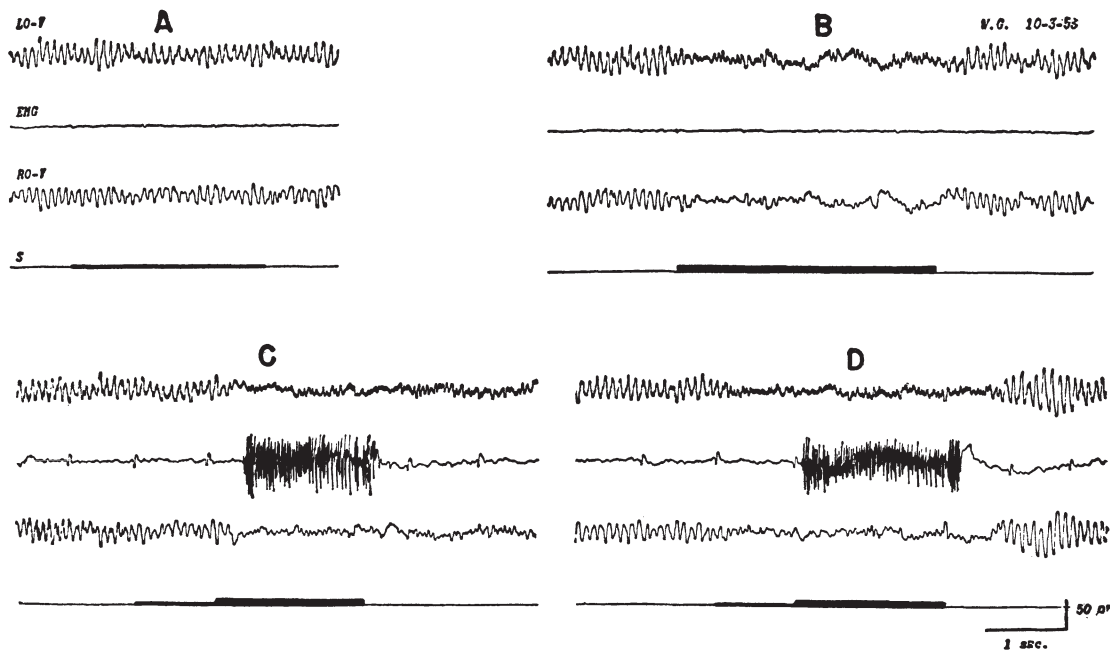


Fig. 12.27. Blocking of the alpha rhythm by conditioning (first, third traces) in normal human subject. A—No change with tone stimulus of 1024 c/s (thin signal line). B—Change with bright light (thick signal line). C—First paired trial showing no change until bright light is on. D—Ninth trial showing alpha desynchronization with tone before light stimulus. Second trace is right forearm EMG with an EKG artifact; fourth trace is signal. (From Morrell, 1958, p. 547, Fig. 1.)

sequential flow of information among five types of cortical cells characterized by the nature of their responses; Fig. 12.26, left, pictures a distribution chart of cell types among the cortical laminae. The authors offered a model “arousal” circuit (Fig. 12.26, right) and noted its relevance to the afferent nonspecific projection to lamina I and II demonstrated by Scheibel and Scheibel in 1958.

One of the most interesting derivatives of the ascending reticular system concept was its involvement in conditioning. It had been shown at the Collège de France, by the fundamental work of Fessard, one of the earliest neurophysiologists to make experimental use of the EEG, that in human subjects the click of the camera shutter became the conditioned stimulus for the “arrest reaction” to visual stimuli shown in the EEG (Durup and Fessard, 1935); that finding was immediately confirmed in the United States (Loomis, Harvey, and Hobart, 1936; Travis and Egan, 1938). Twenty years later the work was reinvestigated (Morrell and Ross, 1953) and extended, again in human subjects, to show that alpha-rhythm blocking could be conditioned by pairing a light with low-intensity

sound, the latter being ineffective as an unconditioned stimulus. This implied that there are specific inhibitory and excitatory processes, seen by comparing rates of conduction between the striatal and precentral regions: there was a lengthening of conduction time whenever the inhibitory process was induced (Fig. 12.27). The authors concluded that “these results lend further support to the concept that the discrete, local activation pattern requires the participation of topographically organized diencephalic reticular formation” (Morrell, 1958, p. 558). Other conditioning experiments from the Bureš laboratory were mentioned above.

The findings on laboratory animals suggesting the usefulness of the diffuse reticular concept in the study of conditioning also opened the possibility that the formation of temporary connections fundamental to learning could be explained through the mediation of the brain-stem reticular formation.

Involvement of the cephalic brain stem may make it easier to account for the important role which emotion and reward or punishment can play in the learning process. Exten-

sion of these studies . . . which are directly exploring changes in the activity of the brain associated with learning are likely to form a major development interrelating neurophysiology and behavior (Magoun, 1958a, pp. 113-114).

It would be difficult to estimate the extent of the role played by the reticular system concept in furthering the emergence of neuroscience from a confluence of neural and behavioral disciplines, as though aroused to a new consciousness. Not so difficult to recognize, however, is a novel hypothesis stemming from the multiple circuits available in the reticular formation. "[O]ne of the very fundamental bases of species differences in animal behaviors" may lie in the number of relays and organization of pathways which all species nonetheless share (Nauta, 1958, p. 667). It remains for future developments to quantify that imaginative combination of form and function.

OVERVIEW OF THREE MAJOR INTEGRATIVE SYSTEMS

In the attempt to designate specific parts of the brain as constituting a "system," there is the risk of implying that boundaries and circuits are precise and neat. No implication could be more misleading. The three systems selected for historical description are characterized by many connections and functions that are in a state of continuing discovery and even obsolescence, already the fate of the limbic system (Swanson, 1987). Looking as though drawn up with a purse-string (Broca), the system was suggested as having something to do with emotion (Papez), an idea boosted by the Klüver-Bucy syndrome and expanded by its description as the paleomammalian brain (MacLean). The limbic involvement in learning and memory (Bekhterev) was demonstrated by careful testing in human patients (B. Milner). Ease of manipulation stimulated research on the hippocampal region, and, with single-unit recording, the seizure-active sites on dendrites were explored (Andersen et al.). The septal region was found to be the site of a reward center (Olds and P. Milner) and the amygdaloid body came to attention as being the most susceptible brain region tested to "kindling" by subthreshold stimulation (Goddard et al.). With varying boundaries and functions, the limbic

system's strong connections to other parts of the brain, particularly to the hypothalamus, confer on it a basic role in behavior.

The presence of corticothalamic connections was projected in 1839 (Carpenter) and their topographic specificity noted soon after (Luys). By the end of the century, histologic and ablation studies had demonstrated the presence of two-way thalamocortical-corticothalamic circuits. The concept of feed-back and feed-forward mechanisms was a natural outcome (McCulloch and Pitts) and the application of biomathematics to create a novel subdiscipline, cybernetics (Wiener), was the result, opening the field of neural networks to research that did not hesitate to extend to artificial intelligence.

The best historical overview of the brain-stem reticular system and its myriad effects is framed in the words of one of its promulgators:

Full attention did not return to the brain stem until recently, however, for it will be recalled that Edwardian contributions to the physiology of the central nervous system were focused largely upon reflex functions of the spinal cord below and upon activities of the sensorimotor cortex above, leaving the intervening stem of the brain unattended.

Recent study has once more stressed the importance of this neural part, however, in identification of centrally placed, nonspecific mechanisms, which parallel the more lateral, specific systems of classical neurology and are richly interconnected with them. These nonspecific mechanisms are distributed widely through the central core of the brain stem and, as spokes radiate from the hub of a wheel to its peripheral working rim, so functional influences of these central systems can be exerted in a number of directions: caudally upon spinal levels which influence postural and other activity; rostrally and ventrally upon hypothalamic and pituitary mechanisms, concerned with visceral and endocrine functions; . . . and more cephalically and dorsally still, upon the cortex of the cerebral hemispheres. . . .

. . . Just as all spokes move together in the turning of a wheel, though they may bear weight sequentially, so the variously directed influences of these nonspecific reticular systems are closely interrelated in normal function (Magoun, 1963, pp. 18, 20).