

International Review of

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Edited by

CARL C. PFEIFFER

JOHN R. SMYTHIES

# INTERNATIONAL REVIEW OF **Neurobiology**

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## PREFACE

Progress in neurobiological research must maintain a delicate balance between the fascination of basic explanation of clinical and physiological phenomena by means of chemical and physical concepts on the one hand and the pressing needs for the development of new and effective treatments of disease on the other. Advances in basic biochemistry and biophysics often give rise to developments in the clinical field, but mature judgment is required to select from the vast detail of biochemistry and biophysics, those parts which are likely to apply to human disease. The aim of this Review is to enable active workers in these fields of neurobiology, neurochemistry, neuroanatomy, neuropharmacology, neurophysiology, psychopharmacology, psychology, etc. as well as those in biological psychiatry and neurology to give an account of recent progress in their fields. The Review covers the whole field of neurobiology and includes work within a particular basic science as well as in neurology and psychiatry. Particular emphasis has been laid on the recent development of ideas of fundamental importance and general interest and also of ideas from these basic fields likely to further our understanding of nervous and mental disease. In the past the basic neurobiological sciences have played no little part in progress toward these ends. They are most active at present and they hold great promise for the future. The purpose of this Review is to contribute something to this objective.

CARL C. PFEIFFER  
JOHN R. SMYTHIES

*July 10, 1959*

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# RECENT STUDIES OF THE RHINENCEPHALON IN RELATION TO TEMPORAL LOBE EPILEPSY AND BEHAVIOR DISORDERS

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## I. Introduction

To tread once more the well-trodden paths of the reviewer of rhinencephalic functions, to seek amid the arches of the allocortex at least some aspect of its activities thrown into bold relief by recent research, may seem, indeed, a dubious field of endeavor, since in recent times many aspects of its functions have been comprehensively reviewed (Brodal, 1947; Pribram and Kruger, 1953; Maclean, 1955; Thomalske *et al.*, 1957; Adey, 1956, 1958). Nevertheless, within the limited scope of a review

directed mainly to some of the major contributions in the last three years, there would seem to be significant pointers which may yet lead to the unraveling of the tangled skein that binds the rhinencephalon to the diencephalon, the basal ganglia, and the rostral midbrain. It is proposed, therefore, to deal with this topic from four different aspects, including anatomical and physiological arrangements of neuronal systems, investigations of seizure discharges in the limbic system, behavior studies concerned with stimulation and ablation in these areas, and with metabolic and neuropharmacological investigations.

The classic contributions of Elliot Smith (1910), Herrick (1933), and Papez (1937) are too well known to need elaboration here, but they have indeed formed a valuable point of departure for many studies in the last twenty years. Papez' contention that the pathways between the hippocampus and the diencephalon provided an anatomical substrate for neuronal activity concerned with emotion has been shown to be substantially correct. The Papez "circuit" proposed that activity initiated in the hippocampus would pass through the fornix to the mammillary bodies, thence via the mammillothalamic tracts to the anterior thalamic nuclei. Thalamic radiations carry the activity to the cingulate cortex, and, thence, further relays, proceeding partly through the cingulum bundle, would ultimately reach the presubiculum and the entorhinal area around the caudal border of the corpus callosum. The temporoammonic tracts of Cajal would provide the final pathway for this activity to re-enter the hippocampus from the entorhinal area (Fig. 1).

Although the role of hippocampus and adjacent allocortical structures in emotional functions is generally conceded, their mode of interconnection is more complex than Papez envisaged, with important byways and even converse paths revealed by anatomical and physiological studies in recent years. We may now turn to these in more detail.

## II. Anatomical and Physiological Studies of Neuronal Systems

Attention has frequently been directed by Maclean (1955) to the participation of a ring of cortical structures at the medial border of the cerebral hemisphere forming the limbic lobe, as suggested by Broca (1878), and to which Maclean has applied the term "visceral brain." Evidence that the hippocampus does indeed receive visceral afferents has been supplied by Dunlop (1958). Stimulation of the stomach electrically, mechanically, and chemically modifies the hippocampal activity, with electrical stimulation eliciting the most striking results. A slow-wave response is evoked in the hippocampus 500 msec after stimulation. Where

a primary response with short latency occurred, no slow-wave ensued, and evidence is presented that the primary response may have resulted from stimulation of adjacent somatic structures. By contrast, no viscerosensory representation was seen in the amygdala, which is of interest in view of Dell and Olsen's findings (1951) of amygdaloid responses to stimulation of the cervical vagus.

#### A. THE HIPPOCAMPAL-FORNIX SYSTEM

The neuronal circuit proposed by Papez envisaged the fornix as carrying activity from the hippocampus to the mammillary bodies. It is only recently that the complexities of the fornix bundles have been re-examined. Cajal (1911) had described it as the only efferent pathway from the hippocampus. There is evidence that many of its fibers terminate before reaching the hypothalamus, and that others enter the precommissural fornix to end in the septum. T. P. S. Powell and co-workers (1957) have counted the fibers in the postcommissural fornix and the number of cells in the medial mammillary and anterior thalamic nuclei in rabbit, cat, monkey, and man. The absolute number of fibers in rabbit, cat, and monkey is of the same order (200,000). In the rat they number 50-60,000 and in man, 1-2 million. In primates, the number of fibers in the precommissural fornix approximately equals that in the postcommissural fornix. One-half to one-third of the postcommissural fibers fail to reach the mammillary body in all species. The majority are lost in the rostral third of the hypothalamus and probably form a direct hippocampothalamic pathway. The anterior thalamic nuclei appear to receive the same number of afferent fibers directly from the fornix as by way of the mammillary nuclei.

Extension of the connections of the postcommissural fornix beyond the immediate confines of the mammillary bodies has also been seen in the rat by Guillery (1956) and Nauta (1956). They have detected in experimental anatomical material terminations of fornix fibers in the anterior thalamus, periventricular system and rostral midbrain. Many fibers leave the dorsal aspect of the postcommissural fornix and enter the anteromedial and anteroventral thalamic nuclei. Few, if any, enter the anterodorsal nuclei. In the hypothalamus, fibers terminate in the dorsal hypothalamic area, preoptic region, and nucleus of the diagonal band. Nauta describes a separate projection from the caudal third of the hippocampus to the periventricular zone of the hypothalamus, and particularly to the arcuate nuclei of the tuberal region. It is of interest that some of the fornix fibers terminate in the periaqueductal gray matter of the midbrain, since major pathways to this region have been found from the entorhinal area (Adey *et al.*, 1956), following lesions which spared

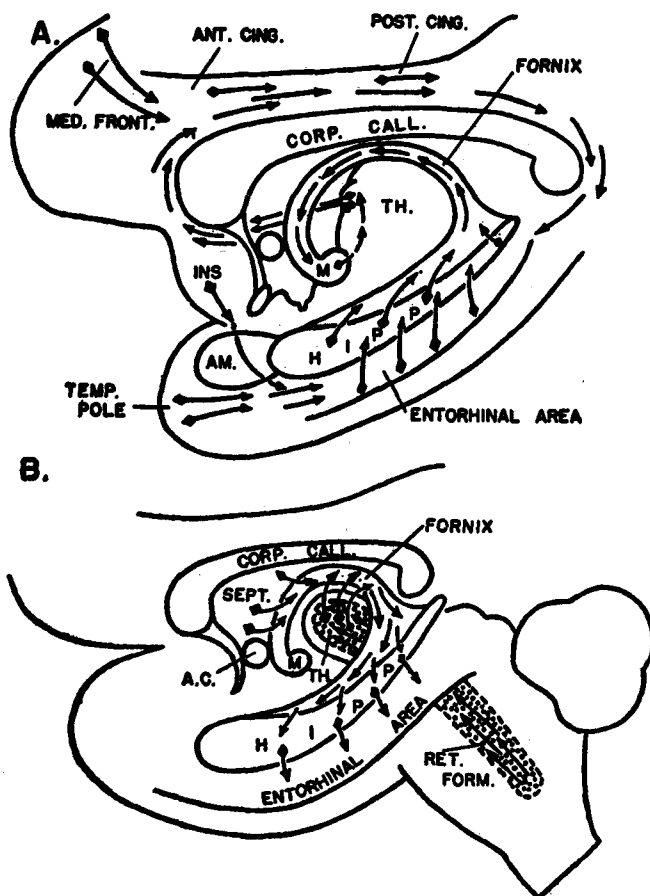


FIG. 1. A. A mechanism of emotion (after Papez). Activity from the entorhinal area passes via the hippocampus to the fornix bundles and thence to the mammillary body. The mamillothalamic tract then conveys activity to the anterior thalamic nuclei which project to the cingulate cortex. Activity returns to the hippocampal formation once again via the cingulum bundles running posteriorly in the cingulate gyrus.

B. A scheme suggested by recent investigations, with activity in the fornix running in the converse direction to the paths in A. Here, hippocampal activation is induced from the reticular thalamic nuclei and passes in turn to the entorhinal area. Pathways exist between the entorhinal area and the reticular formation (see Fig. 2).

Abbreviations: A.C., anterior commissure; AM., amygdaloid complex; ANT. CING., anterior cingulate area; CORP. CALL., corpus callosum; HIPP, hippocampal formation; INS, insular cortex; M, mammillary body; MED. FRONT., medial frontal cortex; POST. CING., posterior cingulate area; RET. FORM., reticular formation; SEPT., septal area; TEMP. POLE, cortex of temporal pole; TH., thalamus (from Adey, 1956).

the hippocampus. The size of the fornix contribution to these midbrain zones appears much less than from the entorhinal area, at least in our electrophysiological studies described below.

There remains the much more intriguing aspect of fornix functions concerned with its septal connections. It has become clear that fornix fibers form, in part, an afferent pathway to the septum, but much less is known of possible septofugal pathways coursing caudally in the fornix and perhaps terminating in the hippocampus. Such pathways would offer a channel of entry to the hippocampus for activity ascending from the brain stem and thalamus to the septum. Behavioral and electrophysiological evidence supports the notion that the septum may be a way-station on diencephalic paths from the brain stem. Green and Arduini (1954) found that septal lesions block the slow-wave response in the hippocampus to an alerting stimulus, and, in a systematic survey of stimulus thresholds in diencephalic areas yielding hippocampal responses, Green and Adey (1956) found the most sensitive zones in the septum, fornix, and anterior thalamus. Precautions taken in these experiments could not entirely preclude the possibility of either antidromic activation of pyramidal cells, or orthodromic activation of some cells through axon collaterals running a recurrent course in the alveus. These problems have to some extent yielded to histological and further electrophysiological investigations.

A septofugal component ascending in the fornix of the guinea pig was described by Morin (1950), but he was unable to detect its termination. McLardy (1955a, b) found, after fornix section in the monkey, finely myelinated fibers running to or through the opposite lateral septal nucleus, but considered that there might also be some decussating septofugal fibers coursing caudally from the medial septal nucleus. Fibers of the medial fifth of the body of the fornix, when followed caudally, curved dorsally and posteriorly through the corpus callosum to emerge into the cingulum, and thence fanned deeply into the parietotemporal white matter. Such an arrangement would provide an additional path for septal activity to reach the hippocampus through relays in the cingulate gyrus. White *et al.* (1958) have recently re-examined caudally directed activity in the cingulate gyrus, reaching the presubiculum and entorhinal area along pathways as proposed by Papez (1937). Certain difficulties are attached to histological investigations following fornix section, due to the well-known resistance of hippocampal cells to retrograde degeneration in these circumstances. McLardy could detect no cellular changes in hippocampus, dentate gyrus, subiculum, or entorhinal cortex. He ascribes the absence of change to persistence of collateral axons which pyramidal hippocampal cells are known to distribute within the ipsilateral hippo-

campus. By contrast, in 8 of 25 hemispheres following fornix section or temporopolar lesions, nerve cells in the medial septal nucleus were degenerated widely or focally, suggesting that there may be a septofugal system coursing between the septal region and isocortex of the temporal lobe, although it would seem that septo-hippocampal connections are not thereby excluded.

Since section of the fimbria rostral to the hippocampal recording site does not abolish the large response to fornix stimulation (Green and Adey, 1956), the question arises as to the course which such afferent fibers might follow within the hippocampus. It has been noted that during exploration in depth radially through the hippocampus, "turnovers" occur in the responses to fornix stimulation (Green and Adey, 1956), and that various components of the response are differentially susceptible to anesthesia and asphyxia. There is an early response which may be construed as "presynaptic" to the later "cellular" potential. This presynaptic component displays a greater resistance to asphyxia and anesthesia than the later cellular component. Exploration of the hippocampus with a bipolar electrode arranged to pass radially through the hippocampus (and, thus, to be oriented at first in the long axis of the hippocampal pyramidal cells in region CA2 of Lorente de N6 (1934), and at greater depths to pass through region CA4, between dentate and hippocampal pyramidal cell layers, before finally penetrating the dentate pyramidal cell layer), indicates a "turnover" in the region CA4, which may be interpreted as a synaptic activation at this level (Adey *et al.*, 1957b). On the basis of this evidence, it may be suggested that this hippocampal afferent pathway runs deeply within the hippocampus to synapse on the dentate granule cells. Here activity is relayed to the arc of hippocampal pyramidal cells situated more peripherally in the Ammon's horn. Convergence of different sensory modalities on the cells of the dentate gyrus has been described (Green and Machne, 1955). Further anatomical and physiological evidence supports this hypothesis (Fig. 2).

In histological investigations of hippocampal commissural and septal connections in the rabbit, Cragg and Hamlyn (1956) sectioned the fimbria on one side and found degenerating fibers in the posterior half of the fimbria of the opposite side, extending into fields CA3 and CA4 of the hippocampus. In the ipsilateral hemisphere additional degeneration was seen in the fimbria extending back over the dorsal alveus to all layers of the presubiculum. The authors consider that these fibers could have come from the septal nuclei. Lesions of the angular tract of Cajal produced degeneration sharply delimited to the upper part of the entorhinal cortex bilaterally and present in all layers of the cortex. Black-

stad (1956), however, has undertaken a more extensive survey of the hippocampal commissural connections in the rat, in the belief that the terminal ramifications from interhemispheric fibers end at definite cortical levels, exclusively different for each area studied.

Further electrophysiological studies have revealed that the earliest component of the hippocampal response to fornix stimulation, a sharp diphasic potential with a latency of less than 1 msec, probably represents a fiber response in the fimbria and alveus, and that if it is partly antidromic, it nevertheless fails to invade the hippocampal pyramidal cell somata (von Euler *et al.*, 1958). A second small deflection with a latency of 1.5 msec is seen in area CA4 at the level of the dentate granule cells. The main deflection has a latency of 4-5 msec, and is a negative potential only at the level of the hippocampal pyramidal cell bodies. Above and below the layer of hippocampal pyramidal cells, the deflection normally has a positive sign, suggesting that these cells are synaptically activated close to the cells and, also, that propagation is blocked in the dendritic layer.

This apparent block of somatofugal conduction along the pyramidal cell dendrites would seem a point of major interest in relation to current theories of cellular excitation concerned with the role of dendritic excitability. Green and his colleagues have further elaborated their data to display latency shifts and current flows in progressive penetration of the hippocampus. At 1.8 msec a negative peak occurs at the level of the granule cells, and disappears at 2.7 msec. At 3.6 msec there is very little sign of any gradient along the tract, but at 5.4 msec a negative peak appears at the pyramidal cell level and grows progressively. A marked voltage gradient between the cell layer and the dendrites persists up to 21 msec. In the period 9-20 msec, the synaptic zone between dentate axonal terminals and pyramidal cell apical dendrites becomes isopotential and may represent the point where outward current of the pyramids ceases and outward current of the granule cells begins. Other aspects of dendritic functions in the cerebral cortex have been discussed by von Euler and Ricci (1958).

### 1. *Summary of Hippocampal-Fornix System*

Recent investigations have shown that a large part of the postcommissural fornix terminates in the anterior thalamus, dorsal hypothalamic, and preoptic areas. A few descend in the periventricular system as far as the central gray of the midbrain. Only about one-half of the postcommissural fibers reach the mammillary body in all mammals. The precommissural fornix in man is about the same size as the postcommissural.



Evidence is presented concerning a septofugal pathway running in the fornix to enter the hippocampus. Its suggested intrahippocampal course is from the dentate granule cells to hippocampal pyramids.

#### B. RELATIONS OF THE HIPPOCAMPUS WITH THE ENTORRHINAL AREA

Classic accounts of the hippocampus have emphasized the afferent paths reaching it from the entorhinal area. Cajal (1911) and Lorente de Nó (1934) have described in elegant detail the course of the temporoammonic tracts arising in the entorhinal area and passing, as the perforant and alvear paths, to terminate in relation to the arch of the hippocampal pyramidal cells. These pathways have formed the basis of Papez' proposal that activation of the hippocampus occurred largely from the entorhinal area and this activity in turn passed to the hypothalamus through the fornix. The existence of the temporoammonic pathways has been confirmed histologically (Adey and Meyer, 1952a), and potentials can be evoked in the hippocampus from entorhinal stimulation (Adey *et al.*, 1957b).

The functional continuity of the series of pathways from the entorhinal area to the fornix appears less certain. In the marsupial (Adey *et al.*, 1957b) and the cat (Adey, Killam, and Killam, unpublished observations), despite the appearance of evoked potentials in the hippocampus from the entorhinal stimulation, only small and irregular responses occur in the fornix and septum. This confirms the earlier observations of Renshaw *et al.* (1940) that, following entorhinal stimulation, they were unable to discern a response with microelectrodes in the fimbria and fornix which could be satisfactorily separated from the cellular response in the hippocampus itself. These effects of entorhinal stimulation contrast sharply with the results of fornix stimulation, where impulses clearly pass freely in the opposite direction through the hippocampus to reach the entorhinal area. Indeed, unit activity in the entorhinal cortex, concurrently with a slow-wave train, is readily evoked from fornix stimulation (Adey, 1958).

Some importance may be attached to these connections passing caudally from the hippocampus to the entorhinal area in a direction opposite to the course of the temporoammonic tracts. Lorente de Nó (1934) has described these fibers as a major afferent pathway to the entorhinal area. In his Golgi preparations, he observed bifurcation of axons of pyramidal cells as they entered the alveus, and noted that the collateral branches ran a recurrent course to enter the subiculum. Some of these branches could be traced still further into the entorhinal cortex.