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PONTILE SYNCHRONIZATION OF THE HIPPOCAMPAL AND LATERAL HYPOTHALAMIC EEG: SPECTRAL CORRELATES OF AN EVOKED STATE

by

CRAIG E. TENKE

A dissertation submitted to the
Graduate Faculty in Psychology
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy, The City
University of New York.

1983

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

8/12/83
Date

Chairman of Examining Committee

August 16, 1983
Date

Executive Officer

Lloyd Gilden

Gad Hakerem

Mark Weiss
Supervisory Committee

The City University of New York

Abstract

PONTILE SYNCHRONIZATION OF THE HIPPOCAMPAL AND LATERAL HYPOTHALAMIC EEG: SPECTRAL CORRELATES OF AN EVOKED STATE

by

Craig E. Tenke

Adviser: Professor Lloyd Gilden

The anatomical pathways relating the hippocampus (HIP) and the lateral hypothalamus (LH) are well documented. Previous studies have not, however, established the degree to which they serve as a reliable transmission route for slow wave activity. The stability of the shared spectral properties of the EEGs of the dorsal HIP and the LH was therefore assessed using stimulation-induced θ as a spectrally distinct tracer.

Rats were restrained in a device incorporating a modified form of the Bellingham (1980) restraint bag. Data records were screened by means of a novel frequency domain artifacting procedure based on the defining characteristics of the power spectrum. In order to evaluate the differences between the stimulated and ambient EEGs, both the enhancement of power at the frequency of the emergent spectral peak and the suppression of the remaining (nonpeak) frequencies in the θ range were then tested by nonparametric methods.

Synchronous θ activity was varied by electrical stimulation of the dorsal pons. Maximal HIP rhythmicity was attained for sites in the diffuse subcoeruleus region. The frequency of the elicted peak was found to be significantly and positively correlated with ventral displacements of the stimulation site.

In the LH, gross θ activity was rarely sharply defined. Even so, changes in activity tended to be statistically predictable. For group data, peak enhancement and nonpeak suppression effects obtained significance in both HIP and LH power spectra, as well as in the coherence of the two signals. Individual data reproduced this pattern in a fashion that varied from measure to measure. The data suggest that the coherence of the two EEGs is directly related to the prominence of θ in the LH. A similar correspondence between the hippocampal EEG and coherent or total LH activity was not supported.

ACKNOWLEDGEMENTS

I would like to thank the members of my committee for their continued efforts related to the completion of this dissertation. I am indebted to Lloyd Gilden for helping me to achieve a greater degree of clarity in the presentation of this material, as well as for allowing me the freedom to adapt and develop the techniques required for this study. I am grateful to Mark Weiss for evaluating the spectral analysis procedures and bringing his experience to bear on this paradigm. Gad Hakerem deserves a special thanks for helping me survive Murphy's law. I would also like to thank Drs. Pedro Pasik and Barry Komisaruk for serving as outside readers. Their contributions greatly improved the intelligibility of this work.

It is important to acknowledge the technical resources and assistance required for the execution of this research. The Center Moriches Public Library, and in particular, Kathy Irish, are to be thanked for acquiring numerous, urgent technical publications. A considerable amount of time, both human and machine, was required of the Queens College Computer Center. Roger Chung and Karl Regnat are to be credited for the construction of numerous variations of the rigid restraint device. Marie Tucker did all of the required histology. I would also like to credit Michael Budek for his collaboration in the development of the restraint technique, as well as a number of hardware projects of importance for the recording procedure. Stanley Sham prepared the photographs used here and assisted in the repair of various pieces of lab equipment. He also supplied many years of moral support and good advice (not always taken).

I would finally like to acknowledge the support and encouragement offered me by my family throughout my graduate studies. My parents, Emery and Ruth, were always there when I needed them. In addition, my mother constructed the rat restraint bags described here. My aunt, Alice Schoener, was of incalculable value in accessing resources required for the synthesis of this dissertation into its final form. Most of all, I would like to thank my wife and "word processor", Jo-Ann, for transforming my scratch marks into intelligible, typewritten words. I would like to acknowledge my appreciation for the sacrifices made by her for all these years in allowing me to complete this work.

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CHAPTER I

INTRODUCTION

The gross electrical activity of the hippocampus is noted for the occurrence of rhythmic slow activity within the 4-8 Hz "θ" band. The hippocampal θ pattern was originally viewed as a correlate of sensory arousal or the orienting response (Green & Arduini, 1954; Grastyan, Lissak, Madaracz & Donhoffer, 1959). More recently, correlates in the motor domain have been reported (Vanderwolf, 1969; Coleman & Lindsley, 1975). The examination of the coherence and phase properties of this waveform with the EEG obtained from the nearby entorhinal cortex has led other investigators to suspect that it is directly involved in the learning process (Adey, Walter & Hendrix, 1961).

Vanderwolf (1969) has viewed hippocampal θ as a reflection of the activation of a more widespread system related to voluntary movement. The global cooperation suggested by this is reminiscent of the representational systems posited by John (1967). Such systems would require the cooperation of contributing structures in a self-stabilizing fashion. A reinforcement or sharing of characteristic modes of activity by participating structures may therefore be presumed.

The anatomical correlates of θ-related activity in the hippocampus are numerous. The local interneuronal organization, the strongly laminated structure and the properties of the cortical and subcortical afferents to the hippocampus all have properties related to rhythmicity at or near the frequency of θ. The origin, stability and predictability of hippocampal θ have been studied by many investigators. Intrinsic hippocampal (Winson, 1975; Green & Rawlins, 1979), cortical (Mitchell & Ranck, 1980) and septal (Apostal & Creutzfeldt, 1974) generating mechanisms have been examined in detail. Except for early reports in which the sensorimotor state of the organism was incompletely controlled (e.g., Adey et al., 1961), such studies have generally failed to include the investigation of loci below the level of the septal nuclei.

The descending transmission paths from the hippocampus include the classic postcommissural fornix bundle as well as a more diffuse precommissural route. The precommissural fornix distributes its influences to the hypothalamus and the midbrain through the medial forebrain bundle (MFB). The loosely organized nucleus of the lateral hypothalamus (LH) is traversed by the MFB, to which it also contributes fibers (Nauta, 1972). The precommissural fornix component of the MFB is therefore a likely conduit for the conduction and dissemination of tonic limbic influences related to the general sensorimotor and hormonal state of the organism.

The ambient gross electrical activity of the LH of the waking mammal is characterizedby the preponderence of slow, irregular activity with little rhythmicity evident (Oomura, Ooyama, Yamamoto & Naka, 1967; Gilden & Kozakiewicz, 1967). The episodic appearance of θ in the LH-MFB system of the rat has also been reported (Komisaruk, 1971). In the cat, slow wave activity in the midbrain has been found to exhibit a pattern of coherence with hippocampal activity that peaks in the θ range during the performance of a "T"-maze task (Adey et al., 1961). The synchronization between the hippocampus and MFB sites has been further supported at a unit level in the rat as well (Komisaruk & Olds, 1968).

The interconnections between the LH and the hippocampus are well documented. It is not clear, however, that they reflect a transmission route for slow wave activity. To address this problem, the existence of shared activity must first be verified in a concrete fashion. The manner in which such sharing might be expressed is therefore a problem that remains to be systematically explored.

If a well organized θ system exists, hippocampal θ should be able to serve as an endogenous tracer signal within it. While θ may at times appear in a discriminable form in the raw electroencephalogram (EEG) of the LH-MFB (Komisaruk, 1971), such regularity is not generally present under ambient conditions in motionless animals (Gilden & Kozakiewicz, 1976). The detection of stable θ in the hippocampal-MFB pathway is therefore unlikely in the time domain due to the presence of uncorrelated noise of relatively high amplitude. Spectral analysis procedures, however, allow properties related to sharing to be systematically explored without requiring that the EEG be clearly rhythmic. Since it is possible to formalize these signal properties in a strictly statistical form (Bendat & Piersol, 1971), statistical properties of potential importance (John, 1972) may be detected as well.

The rationale for the present study rests on the nature of the diffuse, ancient forebrain projection systems. In order to describe the known relationship between the gross EEGs of the hippocampus and the LH, a number of convergent sources must therefore be drawn upon. Anatomical descriptions provide a static view of these regions while defining the paths by which such influences may be induced and conducted. Evoked potential and unit studies introduce dynamic considerations into this framework. Finally, the properties of the free-running EEG may be incorporated into this substrate without the temporal constraint of the evoked response paradigm.

Anatomical Substrate

Hippocampal Anatomy

The relationship of the hippocampus to the basal telencephalon and hypothalamus is a phylogenetically old and stable one. These ancient properties are overlaid in mammals by those related to the growth of the neocortex. The increased corticalization that occurs in the progression from the reptilian to the mammalian brain is matched by an increase in the complexity of the hippocampus and its projection systems. The most obvious of these advanced projections is the postcommissural fornix system.

The LH is a prominent link in the polysynaptic MFB. By virtue of this participation, it is most clearly related

Fig. 1. Section through the telencephalon of Iguana iguana, as in Northcutt (1967). Cortical areas are as in Lohman and Mentink (1972). Other regions are based on Northcutt (1972). The density of cells throughout the mediodorsal cortex is particularly striking in this species. While true granule cells have been reported in its dorsomedial portions and true pyramids in its dorsal portions in some reptiles (Kappers, Huber & Crosby, 1960), Northcutt reported finding large double pyramids and small projection cells resp. ac = nucleus of anterior commissure; cx. d, l, md = dorsal ("general"), lateral ("pyriform"), and mediodorsal cortex; db = nucleus of the diagonal band; dls = dorsal limiting sulcus with underlying superpositio medialis; LFB = lateral forebrain bundle; MFB = medial forebrain bundle; par. l, m = lateral and medial parolfactory ("septal") nuclei; ph = primordial hippocampus; po = preoptic nucleus; str. hyp., pal., neo. = hyperstriatum, paleostriatum and neostriatum. v = ventricle.

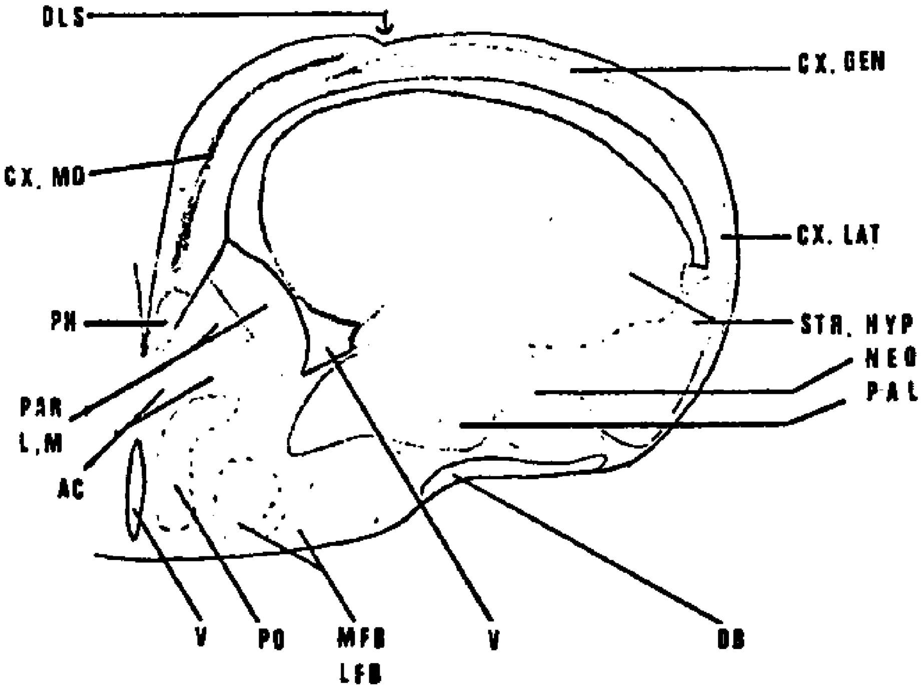
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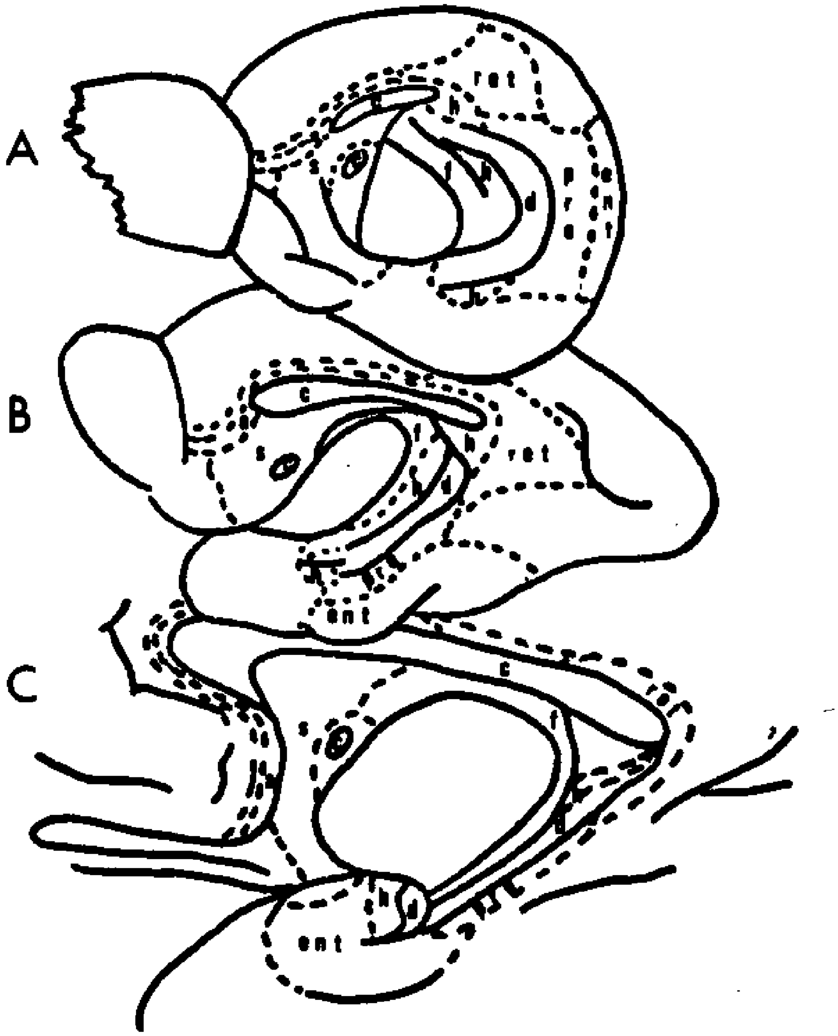
Fig. 2. Medial view of the telencephalon of (A) hedgehog, (B) galago, (C) man. Key figure illustrates gross features of relevance. Dotted lines indicate limits of adjacent cortical fields. Adapted from Stephan and Andy (1970). D, F and H = dentate gyrus, fimbria + fornix and hippocampal fields + subiculum; A, C and S = anterior extension of hippocampus, telencephalic commissures and septal region; PRE = presubiculum + parasubiculum; RET = retrosplenial cortex (Brodmann areas 26, 29 and 30); ENT = entorhinal + perirhinal cortex (Brodmann areas 28, 34 and 35).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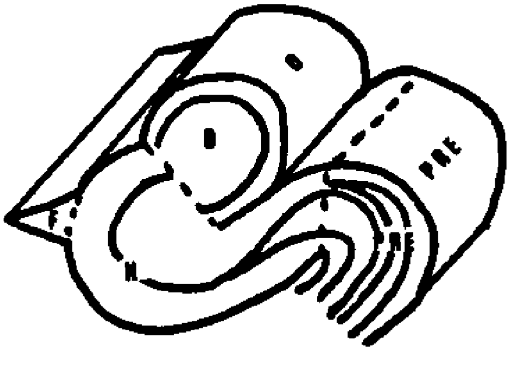
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to the hippocampus by means of the precommissural fornix. A brief description of the phylogenetic stability of the hippocampus and fornix systems in submammalian forms is therefore important for an adequate assessment of hippocampal-LH interactions.

Phylogenetic considerations. As archipallium, the hippocampus has a long phylogenetic history. While acraniotes (e.g., amphioxus) do not possess a differentiated telencephalon, in selachians (sharks and rays), a primordial archipallium already exists (Kappers, Huber & Crosby, 1960). In the amphibian brain the medially located archipallial cells do not appear to be very different from those of the brain stem (Herrick, 1948). Despite the scarcity of evidence for corticalization in the amphibian, a fornix projection descends to the diencephalon (Kappers et al., 1960). Ascending pallial projections also exists.

In the reptilian telencephalon, the archipallium is relatively well developed. As indicated in Figure 1, it consists of a cellular continuum along the medial surface of the telencephalon. Fibers of the corticoseptal path and the fornix originate from dorsomedial portions of this tissue (Lohman & Mentink, 1972). As illustrated in Figure 2, the fimbria-fornix system persists at the junction of the hippocampus and the septum in mammalian forms. It is elaborated from a component of the periventricular fiber system of the alveus, forming a major structural feature in placental mammals.

The gross anatomy of the hippocampal formation of mammals is quite consistent between species. While some reptiles show differences in cell differentiation within the hippocampus (see caption for Figure 1), no existing adult form bridges the gap between the smooth submammalian form and the convoluted structure typical of all mammals. The dentate gyrus is present in all mammals, forming a fissure (the hippocampal fissure) at its border with the higher cortical structures.

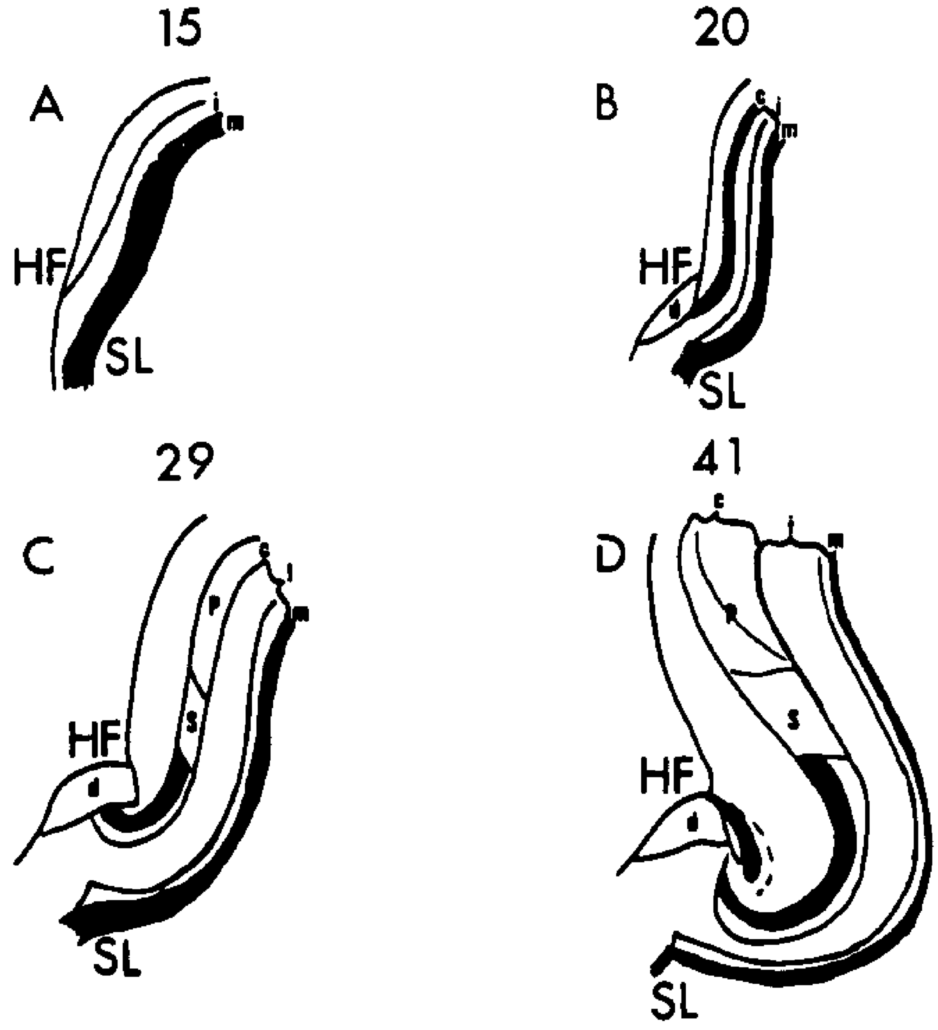
In marsupials, the hippocampus remains in its original medio-dorsal location. In placental mammals, the growth of the commissural system of the corpus callosum leads to a relative shift of Ammon's horn (hippocampal arch) into more temporal locations (Figure 2). Dorsal to the corpus callosum there remains, in a rudimentary form, an allocortical field with its associated white matter. These are the induseum griseum and the supracallosal stria. A compressed variant of the subiculum and the adjacent juxtallocortex is present as well (Sanides, 1970). This rudiment can be followed rostrally to a region adjoining the anterior limits of the septum.

As the corpus callosum grows, the main body of the hippocampus is displaced from its septal pole and pivots about the more stationary temporal pole. As this displacement occurs, the "splintering off" of the induseum griseum from the body of the horn does not necessarily occur in step with the rotation process. As shown in

Figure 2b, a component of the main body of the horn generally remains below the splenium. This component, the dorsal hippocampus, is quite large in rodents and carnivores but grossly absent from the highest primates (Figure 2c). A final trend of note is the enfolding of the granule cell fields of the dentate gyrus into the temporal end of the hippocampal pyramidal cell array to form the prominent bulge of the uncus (Figure 2c).

Microstructure. The emergence of the hippocampus as a cortical structure may be best appreciated by viewing its ontogeny. Stensaas (1967 a-e; 1968) studied the ontogenesis of the rabbit hippocampus in some detail. Stensaas reported that by the time the embryo is 15 mm long (Figure 3a), an intermediate lamina has already differentiated from the underlying matrix lamina. By 20 mm, not only has the intermediate lamina divided into an upper and lower portion, but a cortical plate has been formed as well. As shown in Figure 3b, an embryonic dentate region has also been formed (compare with Figure 2). Further differentiation of the cortical plate leads to the formation of an embryonic pyramidal and polymorphic layer (Figure 3c). These are the two major cellular layers of the mature region. At 41 mm (Figure 3d) the dentate region differentiates to form both a granule layer and an underlying polymorph layer, starting deep in the developing hippocampal fissure. This differentiation continues toward the surface, exhausting its embryonic supply in the process. The cortical plate of the hippocampus, itself

Fig. 3. The laminar structure of the hippocampus of the fetal rabbit. From Stensaas (1967a, b, c, d). Fetal length in mm is indicated for each stage. Beyond 15 mm, the intermediate lamina is divided into an upper and lower component. The formation of projection cell lamina and an underlying polymorphic lamina in the cortical plate at 29 mm and 41 mm is also apparent. c = cortical plate; d = embryonic dentate; HF = hippocampal fissure; i = intermediate lamina; m = matrix lamina; P, S = embryonic presubiculum and subiculum; SL = sulcus limitans hippocampi.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continuously growing, is overlapped by the newer dentate layers. It therefore arches to form the grossly defined structure called Ammon's horn.

The basic microstructure of the adult mammalian hippocampal formation has been known since the latter part of the 19th century. It consists of a single layer of pyramidal cells that merges with the adjacent periallocortex of the presubiculum (Broadmann area 27) through the subicular transition zone. This relatively simple microstructure is not reflected in the various nomenclatures used in its study. Table 1 illustrates the correspondence between the cell field limits described by Blackstad and Lorente de No. These fundamental terminologies are themselves subject to distortion in the experimental literature.

The term "hippocampal formation" is often used to refer to the entire allocortical continuum inclusive of the dentate fascia and subiculum. Likewise, the term "subicular fields" may be used to refer to the periallocortical pre and parasubiculum in conjunction with the allocortical subiculum. The practical considerations related to lesion and injection procedures give a degree of pragmatic credibility to such a loose useage, despite the obvious lack of precision. The interested reader is referred to Chronister and White (1975) for a more complete discussion of the different hippocampal cell field classifications.

TABLE 1

Hippocampal Cell Field Nomenclature[1]

	Lorente de No	Blackstad	Brodmann
allocortex	dentate fascia	dentate fascia	
	CA4	hilus of dentate fascia	
	CA3	regio inferior	
	CA2		
	CA1	regio superior	
	prosubiculum	subiculum	
	subiculum		
periallocortex	presubiculum	presubiculum	area 27
	parasubiculum	parasubiculum	area 49
	entorhinal fields	entorhinal fields	area 28

[1] After Chronister and White (1975)

In 1893, Ramon y Cajal delimited seven layers in the hippocampus, starting with the ependymal zone lining the lateral ventricle (while the terminology is clearest with a description of the regio inferior of the dorsal hippocampus, the relationship to the ventricle is constant even in the regio superior and in temporal sites). The white matter of the alveus comprises the second layer. The next layer, the stratum oriens, is a polymorphic layer consisting of two subzones. The inferior subzone, bordering the alveus, contains fusiform and triangular cells. The superior subzone, adjoining the pyramidal cell layer, is that region occupied by the basal dendrites and axon collaterals of these pyramids. Most characteristic of the polymorphic cells are those forming plexuses about the somata of the pyramids (basket cells).

The molecular region of the hippocampus is divisible into three layers: The strata radiatum, lacunosum and moleculare (Ramon y Cajal, 1893). The stratum radiatum contains displaced pyramids, stellate and triangular cells. Pyramidal cells of the stratum pyramidale, which tend to be elongated in a fusiform or ovoid fashion, send their apical dendritic shafts through the stratum radiatum to the other molecular layers. Along its course, secondary branches of the apical dendrites are emitted in this stratum, but not in the stratum pyramidale.

The pyramids nearest the subiculum (regio superior or CA1) are much smaller than those adjoining the dentate gyrus (regio inferior or CA3). Golgi stains indicate that the apical dendrites of the CA1 pyramids do not bifurcate until the second molecular layer is approached. In this layer, the stratum lacunosum, many myelinated fibers course parallel to the surface (Ramon y Cajal, 1893). Some irregularly spaced cells can also be found here. The most superficial layer, the stratum moleculare, contains stellate and fusiform cells as well as the most peripheral tufts of the apical dendrites.

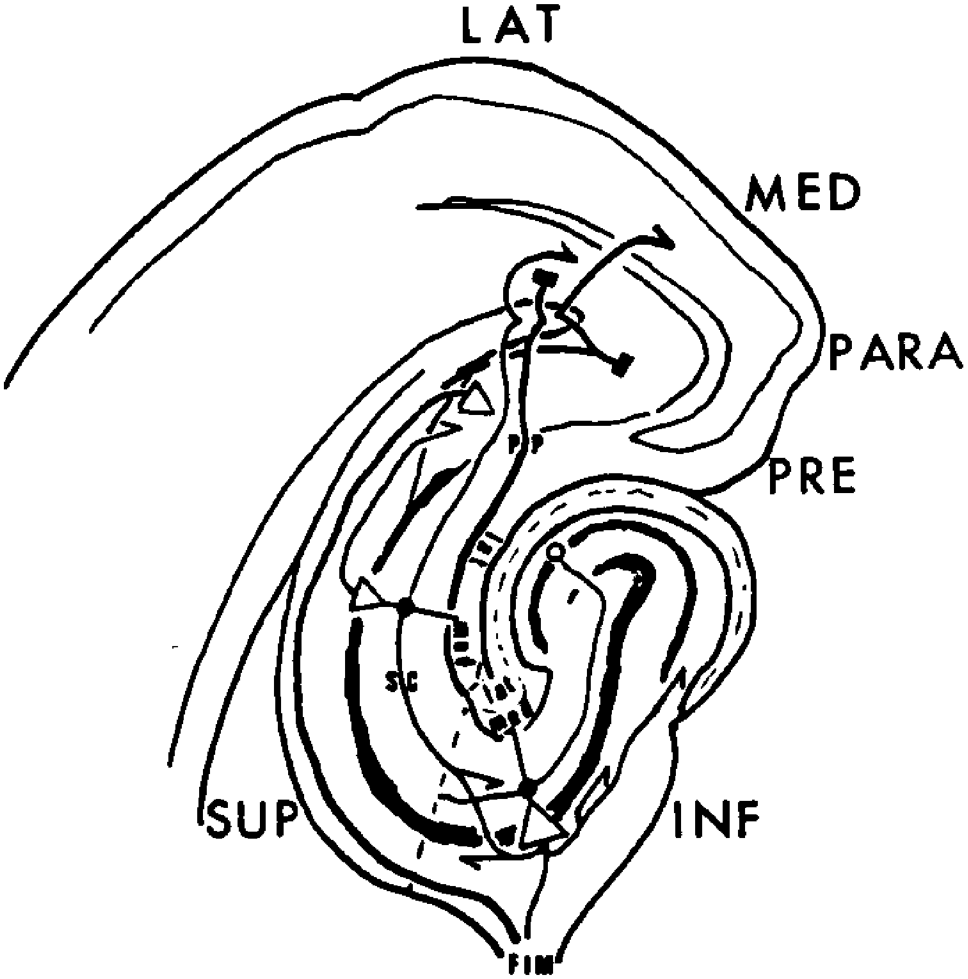
As shown in Figure 3, the dentate fascia consists of a peculiar elaboration of the basic structure of Ammon's horn. Before its characteristic arch is completed (e.g., Figure 3d), it overlies the molecular zone of the hippocampus. The projection cells of the dentate gyrus generally lack basal dendrites and, except for those deepest in the layer, they lack a singular apical dendrite. Spiny dendritic processes thus typically arise directly from the granule cell bodies. The bodies of these cells are so densely packed and have so little cytoplasm in small mammals that carmine stains reveal only the nuclei (Ramon y Cajal, 1893).

The molecular region of the dentate gyrus contains triangular cells and short axon cells of pyriform, ovoid and fusiform morphology (Ramon y Cajal, 1893). A supragranular plexus (toward the hippocampal fissure in the adjacent blade ofthe dentate gyrus) arises from axons of basket cells from the deeper polymorphic layer (away from the fissure). This polymorphic layer is continuous with the stratum oriens of Ammon's horn (Chronister & White, 1975).

The dentate fascia caps one end of the hippocampus. The other end of the hippocampus merges with the periallocortex through a transition region (the subiculum) that varies in spatial extent and relative location depending on the species and angle of section used. In the transition from the pattern of the horn to that of the subiculum, Ramon y Cajal (1893) observed that the thick rows of pyramids characteristic of the horn become scattered and invade the stratum oriens. The three molecular layers converge to the smaller width of the molecular layer of the subicular eminence.

In Ramon y Cajal's early work, the eminence of the subiculum was viewed as being composed of "typical cortex" with a superfcial small pyramidal cell layer, a deeper large pyramidal cell layer and a polymorphic layer atop its white matter. Despite this, a prominent cell free zone, the lamina dissecans, is quite obvious in this region with Nissl stains. This is a distinctive characteristic across the periallocortical fields (Chronister & White, 1975; Stephan & Andy, 1970). Also, although the parasubiculum (Broadmann area 49) contains a superficial pyramidal cell layer, the presubiculum (area 27) contains granular cells in its external cell layer (Chronister & White, 1975). These cells tend to cluster at certain levels. The tendency of cells of the superficial cellular layer to form clusters is a characteristic that becomes most marked in the ventral levels of the lateral entorhinal

Fig. 4. A somewhat schematized view of the intrinsic relations of the hippocampal formation and the related periallocortical fields of the rodent. The entorhinal fields collectively give rise to the perforant pathway. This projection is reciprocated by the large pyramidal cells of the regio inferior (CA3). Communication between the hippocampus and the entorhinal cortex courses through a sharply arched bundle of fibers that is continuous with the alveus and the commissural system (the angular bundle). Typical projections of cells from the dentate gyrus, the regio superior and the subiculum are also shown. Axons from higher subicular zones are also indicated. Arrows indicate termination zones. Axons shown arising from "bars" represent a generalized or unspecified projection from that field. LAT, MED lat, med = lateral and medial entorhinal fields and their terminal fields; PARA, PRE = parasubicular and presubicular; INF, SUP, FIM = regio inferior, regio superior and fimbria; pp = perforant path; sc = Schaffer collateral.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cortex (Brodmann area 28b).

The entorhinal-hippocampal loop. Electrical activation of the entorhinal cortex has been found to be capable of sequentially activating cells in the dentate fascia, the regio inferior and the regio superior (Andersen, 1975). The efferents of the pyramids of the regio superior continue this progression by entering the subiculum. The frequency specificity of this progression is consistent with the characteristics of the normal EEG. The nature of the hippocampus as a cortical structure and as a source of θ-rhythmicity may therefore be related to the circulation of information through this functional loop. Not surprisingly, this loop reflects the organization of the intrinsic fiber systems of the hippocampus. A summary of these pathways, irrespective of the axial dimension, has been presented in Figure 4.

The entorhinal cortex is as yet the only generally accepted cortical input field to the hippocampal formation. As Figure 2 illustrates, this field becomes displaced from the bulk of Ammon's horn through phylogeny so that in the primate the parahippocampal gyrus (e.g., TH of Von Bonin & Bailey, 1947) is in closer physical proximity. While it is conceivable that activity might be locally transmitted in a "cell by cell" fashion, it appears that even this region relays to the entorhinal cortex (Rosene & Van Hoesen, 1977).

The perforant path is the route followed by most, if not all, projections from the entorhinal cortex onto the hippocampus. The predominant origin of this path has been shown to be the superficial cell layer of the entorhinal cortex (Segal & Landis, 1974a). The perforant path of the rat has been studied in detail by Hjorth-Simonsen and Jeune (1972) with Nauta and Fink-Heimer techniques after entorhinal damage. As shown in Figure 4, entorhinal projections course through the parasubiculum into the medial aspects of the white matter of the angular bundle. The presubiculum and subiculum are then penetrated by these fibers as they collect into the stratum lacunosum-moleculare of CA1. At the transition to CA2, where this portion of the molecular layer grows, degenerating terminals become particularly apparent. The projection is continuous through CA3 in its molecular zone and into the middle portions of the molecular layer of the dentate gyrus. This continuity is not obvious in all horizontal sections, since, at dorsal levels, the dentate gyrus can appear "isolated" from the rest of the formation (see Figure 2a, b for an illustration of this geometric problem).

The relative size and location of the entorhinal cortex shifts through phylogeny (Figure 2). Even in the rat, however, the perforant path projection must spread out through its course to include all portions of the hippocampus (Hjorth-Simonsen & Jeune, 1972). These fibers collectively form a continuous sheet, coursing from the molecular zone of the subiculum through the superficial layers of CA1 or, at dorsal levels, along the obliterated hippocampal fissure. Regardless of spreading, the perforant path projection is topographically organized. This topography is overlaid by a medial-lateral entorhinal topography (Hjorth-Simonsen, 1972; Steward, 1976).

The granules of the dentate gyrus send efferent processes across the regio inferior in the deepest portions of the molecular region (often called the stratum lucidum or suprapyramidale). In Golgi material, these axons can be seen to be endowed with numerous synaptic swellings and appendages (e.g., Ramon y Cajal, 1893; Blackstad & Kjaerheim, 1961), leading to their identification as the mossy fiber system.

The course of the mossy fiber projection of the rat was explored by Blackstad, Brink, Hem and Jeune (1970). In cross sections through the hippocampal formation, degeneration in the mossy fiber system could be followed to the precise limit between the regio superior and the regio inferior (the CA1-CA2 border). Along the axial extent of the horn, the degeneration following lesions of the dentate fascia was found to follow an essentially transverse course in the horn, having only a slight temporal deviation. These sharply delimited bands of degeneration thus mimic the strict topography of the medial perforant path.

The mammalian hippocampus is apparently unique in its distribution pattern for zinc (Friede, 1966). In the rabbit, Timm's silver stain, indicating the presence of "heavy" metal, clearly outlines the dentate granular layer and courses primarily in the stratum radiatum of the regio inferior. Staining of the regio superior, however, is only at "background" levels. Numerous other mammals (but not the turtle, frog or fish) share these staining patterns as well.

In the postnatal development of the rat, zinc content of the hippocampal formation clearly reflects the development of the mossy fiber system. Using autoradiographic techniques (labelled zinc localization), Crawford and Connor (1972) showed zinc to concentrate in the granule cell layer of 10-18 day old rats. After 20 days, when the postnatal neurogenesis of the dentate granules is essentially complete (Angevine, 1975), more zinc was localized in the mossy fiber layer than in the dentate gyrus itself. The adult Timm's staining pattern included a degree of staining along the basal dendrites of the regio superior as well.

The pyramids of the regio inferior are the cells of origin of the classic Schaffer collateral system. This system strongly influences the pyramids of CA1. Its course is classically described as being in the stratum lacunosum of the CA1 field, with only secondary collaterals reaching the strata oriens and radiatum.

Hjorth-Simonsen (1973) found no evidence of terminal degeneration in the stratum lacunosum of the rat after damage to the regio inferior. While terminals were found in the stratum oriens, those that were detected in the molecular layers were clearly in the stratum radiatum.

In fact, this investigator compared evoked potential depth profiles for the Schaffer collateral system with measurements of the dimensions of the lamina of the horn in those species (and regions) previously examined physiologically (by e.g., Andersen's group) and found that here, too, the projection was confined to the stratum radiatum.

The pyramids of the regio inferior project bilaterally to the lower portions of the molecular layer of the dentate gyrus. After early section of the commissures to eliminate the commissural projection, Hjorth-Simonsen (1973) studied the ipsilateral projections of the regio inferior. This investigator suggested that the longitudinal associative connections may have the same origin as the Schaffer collateral system.

Of those fibers remaining in the regio inferior, Hjorth-Simonsen (1973) reported a dorsal course throughout the regio inferior in the stratum oriens and the superficial (away from the alveus) portions of the stratum radiatum beyond the mossy fiber termination. Ventrally, the predominant projection to the stratum oriens was found to disappear within a few hundred microns except for those aspects of CA3 nearest the alveus. The stratum radiatum projection continued, however, disappearing first in its most superficial portions. Both the Schaffer collateral system and the "local" association path here described have contralateral projections of the same type (Gottlieb & Cowan, 1973).

Another important projection of the CA3 field, one that was not classically acknowledged, completes the perforant path loop in the temporal third of the hippocampus. This projection was reported by Hjorth-Simonsen (1971) in the rat using the Fink-Heimer technique. Axons were found to run caudally throughout the molecular layers of the horn to terminate throughout the fourth layer of the medial entorhinal cortex (immediately below the lamina dissecans). This termination zone is identical with an acetylcholinesterase positive band in this region. The organization is a topographic one in which fibers from the CA3 field course via parallel paths to end in adjacent regions of the medial entorhinal cortex. This pattern does not appear to include the more dorsal (septal) regions of the horn. Despite the judicious use of control lesions, the possibility of a contribution from transient axons cannot, of course, be completely dismissed.

The regio superior of the horn appears to have no recurrent projection to the regio inferior (Hjorth-Simonsen, 1973). It does, however, project to the entire (mediolateral) extent of the subiculum, particularly to that portion near the presubicular border (Hjorth-Simonsen, 1973). The route travelled is in the alveus. At the V-shaped presubicular border, the termination abruptly ceases. Degeneration may be traced to the deep portions of the ipsilateral subiculum and is topographically organized. This pattern can be seen at dorsal levels, where the subiculum reaches the medial surface of the hemisphere, as well as at ventral levels, where degeneration immediately abuts the entorhinal cortex.

Andersen (1975) has reported a topography in the organization of the evoked response of the hippocampal formation to perforant path stimulation. In view of the projections from the horn to subicular and, probably, entorhinal fields, Andersen's physiologically defined "lamella" are thus probably closed loops. There are, however, shifts in the "usual" topography for projections to the entorhinal cortex (Hjorth-Simonsen, 1971; Shipley, 1975). The partial topographies to this area may supplement each other to produce a complete pattern.

Although the cortical afference of the hippocampus proper (CA1-4) is predominantly via the entorhinal cortex, the role of the subicular regions as a projection field complicates matters somewhat. Van Hoesen, Rosene and Mesulam (1979) have reported direct afferents to the subicular fields that arise in areas TH, TF and TE of Von Bonin and Bailey in the monkey. Field TG was reported to project to the entire extent of the parasubiculum. A projection from the dorsal convexity of the frontal cortex has been followed in the cingulum bundle as far as the presubiculum (Nauta, 1972).

In the vicinity of the uncus, the subiculum is in close proximity to the amygdala. The cellular continuum of the ventral subiculum merges indistinctly with the amygdala through an interposed confluence zone. It is not surprising, then, to find that the ventral subiculum also receives from the periamygdaloid cortex and the basolateral amygdala (Kretteck & Price, 1977).

The ascending projections of the primate subiculum were studied by Rosene and Van Hoesen (1977) using both autoradiographic and horseradish peroxidase techniques. A projection was demonstrated to regions of the frontal cortex adjacent to the genu and rostrum of the corpus callosum, within the gyrus rectus and into the orbitofrontal region. Projections to caudal portions of the cingulate gyrus were detected in the granular layer of the retrosplenial cortex, but not the induseum griseum. Subicular projections within the temporal lobe terminated in the deep pyramidal cell layer of the entorhinal cortex. Presubicular projections included the superficial cell layer of this region as well. The projection proceeded across the rhinal sulcus to perirhinal regions, as well as to caudal regions beyond the entorhinal field. A final projection was followed to mediobasal regions of the amygdaloid complex.

The Fornix Systems and the Hypothalamus

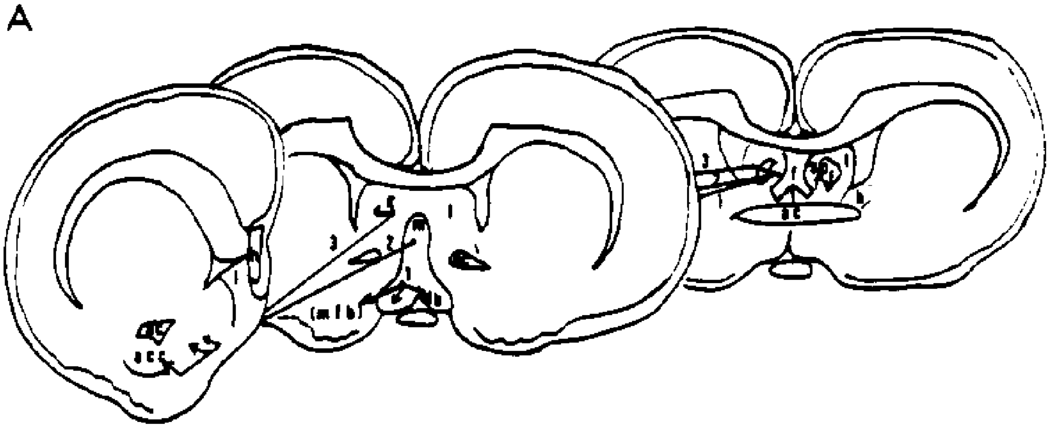
The most obvious output pathway of the hippocampal formation is the fornix. A rudimentary form of this pathway can be identified in the amphibian (Herrick, 1948) and the reptile (Lohman & Mentink, 1972). In the mammal, certain classical connections of the fornix bundle suggest themselves upon viewing normal, fiber-stained brain sections. The fornix columns descend to septal levels, where a division occurs. One contingent travels in a caudal direction through the hypothalamus as the clearly delimited postcommissural fornix. The mammillary bodies receive these bundles and in turn project via the mammillothalamic tract to the anterior thalamic nuclei. The second fornix component passes through the septum and rostral to the anterior commissure, where it joins the MFB in its course through lateral regions of the preoptic and hypothalamic fields.

Raisman, Cowan and Powell (1966) presented an excellent description of the efferent fornix system of the rat. They noted three projection routes from the hippocampal formation (Nauta method) after unilateral destruction of virtually the entire hippocampus and dentate gyrus. These projections are a commissural one, crossing in the ventral component of the hippocampal commissure, the precommissural fornix, and the postcommissural fornix.

The precommissural fornix is itself apparently composed of three components (Raisman, Cowan & Powell, 1966). One component travels rostral to the septofimbrial nucleus, then turns back to course laterally, ending in the horizontal limb of the nucleus of the diagonal band. Some fibers course medially to produce a contralatral diagonal band projection. The first component also contributes to the medial forebrain bundle, where fibers have been followed as far as the optic chiasm.

The second precommissural projection courses through the medial septum. This projection lies dorsal to the first one and is the larger of the two. Along its rostral

Fig. 5. The projection of the fornix as described by Raisman, Cowan and Powell (1966). A. A schematic representation of the three components of the precommissural fornix. B. The postcommissural fornix system. fim, d. fx, f and pf = fimbria, dorsal fornix, fornix columns and precommissural fornix bundles; ac = anterior commissure (division point); Acc, B, L, M, Sf and T = nucleus accumbens, bed nucleus of the stria terminals, and the lateral, medial, septofimbrial and triangular nuclei of the septum; db = diagonal band; LM, MM and X = lateral and medial mammillary nuclei and the supramammillary decussation; AM, AV and ret = anteromedial, anteroventral nuclei of the thalamus and the thalamic reticular, parataenial, and reuniens nuclei; SUP = supraoptic nucleus; LH, MFB = lateral hypothalamus and medial forebrain bundle. Other structures include: h = hippocampal rudiment; st. hab. = stria habenularis; C.Aq. = cerebral aqueduct.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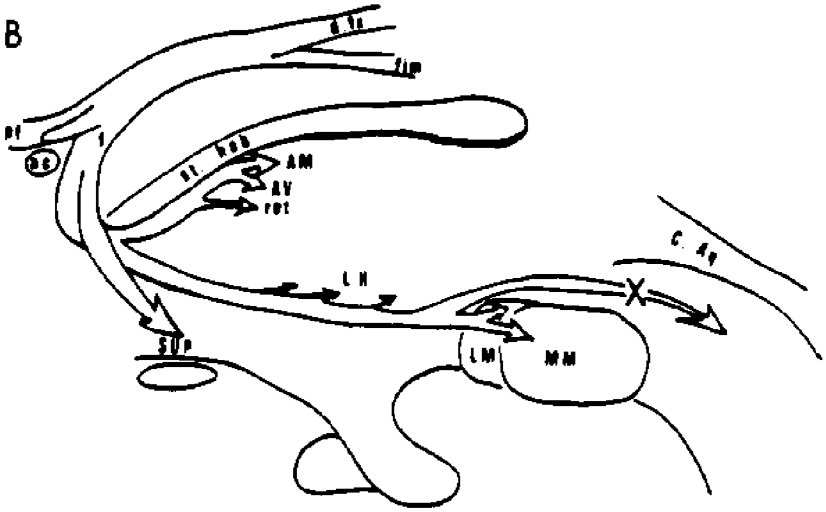
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course, it is displaced laterally at levels beyond the corpus callosum, whereupon it ends in the medial aspects of the nucleus accumbens. The third component of the precommissural fornix travels caudally in the septofimbrial nucleus and widens rapidly as the lateral septal nucleus is reached. The later nucleus becomes filled with fibers from this contingent. This projection continues rostrally to invade the medial portion of the nucleus accumbens and fill its rostral pole. Figure 5a illustrates the termination of the three components.

The postcommissural fornix is also heterogeneous in its composition (Raisman, Cowan & Powell, 1966). One component gives rise to the medial cortico-hypothalamic tract. This tract forms a separate mediodorsal cap of fibers of the postcommissural bundle and extends to the dorsal border of the suprachiasmatic nucleus. Its existence has been substantiated by autoradiographic techniques (Swanson & Cowan, 1975; 1977). Immediately caudal to the level at which the medial cortico-hypothalamic tract emerges, a posterolateral group separates to lie within the arch of the stria medullaris. This contingent travels to the thalamic nuclei anterior medialis and ventralis, but not to anterior dorsalis. Some of these fibers also project to the reticular, parataenial and reuniens nuclei, and a small number cross to the opposite anterior nuclei.

The primary postcommissural fornix bundle at hypothalamic levels proceeds largely to the mammillary bodies, although some fibers leave its dorsal aspect to terminate locally. A small number of fibers bypass the mammillary bodies. Some of these fibers cross in the supramammillary decussation and terminate near the periaqueductal gray of the midbrain. The postcommissural fornix projection system is illustrated in Figure 5b.

Valenstein and Nauta (1959) conducted an early cross-species study of the fornix system using a degeneration technique. The long projections were found to follow the route of the dorsal fornix. One component of the postmammillary fornix projection of the guinea pig spread dorsally to the rostral portions of the central gray and the posterior hypothalamic nucleus. In the monkey and cat, the central gray projection of the fornix was also reported to be pronounced. In the rat, however, such projections are apparently sparse.

The second, larger bundle of the postmammillary fornix of the guinea pig contained the greatest proportion of crossed fibers. This projection coursed medial to the fasciculus retroflexus and then dorsal to the interpeduncular nucleus to find the lateral portions of the superior central nucleus of Bechterew (median raphe) and the adjoining tegmentum. Both of these projections were also reported to exist in the rat, but in smaller numbers. A third group was found to distribute bilaterally to the central regions of the midbrain tegmentum and field H of Forel. This projection was not seen in the rat.

The fornix projections to the diencephalon may also be subject to a degree of interspecies variability.

Precommissural fornix projections through the medial forebrain bundle proceed only to the lateral preoptic region in rodents, but reportedly continue throughout its course in the monkey and rat (Valenstein & Nauta, 1959). Furthermore, discrete fascicles branch off from the postcommissural fornix into the lateral hypothalamic region in the cat, a projection that is quite sparse in the rodents. Conversely, the medial hypothalamic projection via the corticohypothalamic tract in the rodent may have no representation in the cat or monkey. A fornix projection to nucleus lateralis dorsalis of the thalamus was more pronounced for the monkey than for other species. Valenstein and Nauta did not view these projection differences as being a demonstration of any functional differences between species, since secondary projections (e.g., via the lateral preoptic area to the lateral hypothalamus; via the mammillary bodies to the subthalamic region) could produce similar effects.

The efferent projections of the hippocampus via the fornix have been studied using other techniques in recent years. Using the rat as a subject, Swanson and Cowan (1975) made the interesting discovery that autoradiographic techniques (using tritiated proline) reveal direct projections from the hippocampus only by a precommissural route and only as far distal as the septal nuclei. Although the lateral septal projection was reported to be a topographic one, no postcommissural fibers could be detected. Rosene and Van Hoesen (1977) have replicated these findings in the primate brain.

According to Swanson and Cowan, rostral portions of field CA1 project ipsilaterally to medial portions of the lateral septum, while caudal CA1 projections occupy more lateral loci. Fields CA2 and CA3 have similar, but bilateral, projection patterns. Earlier reports of a sizeable CA1 field projection upon the medial septum (the degeneration study by Raisman, 1966) could not be substantiated.

A study of the subicular regions, from the allocortical transitional region to the periallocortical parasubiculum, has revealed that these are the fields contributing to the classically defined postcommissural fornix (Swanson & Cowan, 1975; 1977). The bilateral projection to the medial mammillary nucleus was found to arise only from the dorsal subicular regions. The medial corticohypothalamic tract projection was traced to the medial preoptic-anterior hypothalamic region, as well as ventromedial and arcuate nuclei. This tract was labelled after ventral subicular injections, proceeding in lateral portions of the fimbria. Ventral injections also labelled precommissural fornix fibers to septofimbrial, lateral septal and accumbens nuclei, the bed nucleus of the stria terminalis, and neighboring basal cortical areas. In one case, in which the injection only involved the pre and parasubiculum, projections were found to the anterior thalamus (especially anterior ventralis), the mammillary nuclei (particularly the medial nucleus) and the contralateral subiculum and entorhinal fields.

Long ascending projections. A projection to the hippocampus from the mammillary complex has been discovered. This projection originates in a cell group in and lateral to the supramammillary nucleus at levels just rostral to the ventral tegmentum and caudal to the posterior lateral hypothalamus (Segal & Landis, 1974a). The supramammillary nucleus has been found to project to the dorsal posterior hippocampus, and, to a lesser degree, to the ventral hippocampus (Pasquier & Reinoso-Suarez, 1976). Another group, located below the mammillothalamic tract (to anterior thalamic nuclei), was found to project only to the dorsal posterior hippocampus (Pasquier & Reinoso-Suarez, 1976). Thus, the classic postcommissural fornix pathway itself reflects a bidirectional projection system.

The hypothalamus is not the only diencephalic site to maintain reciprocal relations with the hippocampal formation. In a study of the connections of the nucleus reuniens of the rat (horseradish peroxidase and autoradiographic techniques) Herkenham (1978) reported a projection to molecular layers of the retrosplenial and entorhinal fields, as well as the lamina dissecans of the latter. This projection was found to proceed unbroken through portions of the molecular layer of the ventral subiculum and the stratum lacunosum-moleculare of the regio superior of both the dorsal and ventral aspects of the hippocampus. No labelling could be detected in the regio inferior or the dentate gyrus. Reciprocating projections from this region arise from the ventral subiculum.

The longest descending projections of the fornix system are reciprocated by direct ascending projections. Horseradish peroxidase stains have shown that the locus coeruleus and raphe nuclei of the rat's brainstem both project to the septum and the dorsal and ventral hippocampus (Segal & Landis, 1974a, b).

The locus coeruleus is known to be the origin of a large noradrenergic projection to the diencephalon and telencephalon. After hippocampal injections of horseradish peroxidase (HRP), Segal and Landis (1974a) reported that the locus coeruleus stained throughout its extent, particularly in its anterior pole. Pickel, Segal and Bloom (1974) traced locus coeruleus fibers through the MFB to precommissural levels in the rat (autoradiography). This MFB route has been refuted by investigators using histofluorescent (Ungerstedt, 1971) and microassay techniques (Palkovits, Brownstein, Saavedra & Axelrod, 1974; Kobayashi, Palkovits, Kopin & Jacobowitz, 1974).

Pickel, Segal and Bloom (1974) reported that at precommissural levels, some fibers followed the route of the supracallosal stria and the cingulum to terminate in the cingulate gyrus, the subiculum and the hippocampus. Using an immunofluorescent technique, Swanson and Hartman (1975) followed other corticopetal fibers through a ventral route, between the olfactory tubercle and the striatum.

According to the neurochemical study of Storm-Mathisen and Guldberg (1974), the ventral route provides over half of this class of afferentation. Within the hippocampus, the distribution of norepinephrine-containing fibers and terminals follows a perforant path trajectory (Moore, 1975). A fornix contingent appears to penetrate the stratum oriens of field CA3, but not CA1. A subgranular plexus is found in the dentate gyrus as well.

Conrad, Leonard and Pfaff (1974) found the ascending course taken by fibers of the dorsal and median raphe nuclei of the midbrain of the rat to be similarly represented in studies using autoradiographic and reduced silver approaches. Ascending fibers were found to course largely through the ventral tegmentum into the MFB. From this branch, fibers were followed into the hypothalamus and the preoptic region, the fornix and the stria terminalis, as well as the olfactory tubercle and the anterior amygdala. Other fibers continued into the diagonal band to the septal nuclei and through the cingulum bundle. Based on the effects of the disruption of these pathways, Storm-Mathisen and Guldberg (1974) estimated that the dorsal route (fimbria, dorsal fornix and cingulum) contributes about 75% of the serotonergic fibers to the hippocampus, the rest arriving via the ventral route.

The distribution of the raphe projection within the hippocampus has been described by Moore (1975). Using an autoradiographic technique, a moderately dense labelling was found in the molecular layers with a fairly dense course detectable along the route of the perforant path in CA1. In CA2 and CA3, this branch disperses, filling the stratum radiatum uniformly. This pattern proceeds into the molecular layer of the dentate fascia. A smaller contingent follows an alvear route, sparsely innervating the stratum oriens of CA1. From the fornix, fibers distributes along the stratum oriens into the hilar zone, where a dense subgranular plexus is formed.

Another long ascending projection to the hippocampus arises in the cerebellum. Heath and Harper (1974) used both electrophysiological and anatomical (Nauta-Gygax and Fink-Heimer) techniques to study this projection in the cat and the monkey. After lesions of the nucleus fastigius, degeneration could be traced through both the dorsal fornix and (fimbrial) fornix from an access ventrocaudal to the anterior commissure (Heath & Harper, 1974). These fibers were found to ramify in the polymorphic layer of the dentate gyrus, where terminal degeneration was also found. Granular and molecular layers of the dentate fascia were apparently spared. The stratum oriens of the horn was also found to receive fibers and terminals. This projection was heaviest in CA3, disappearing in CA1. Some fibers were followed through the layer of pyramids without terminating. The latter contingent was found to terminate primarily in the strata radiatum and lacunosum of CA2, CA3 and CA4. Fibers contributed via the dorsal fornix were followed to a terminal field in the deeper cellular portion of the subiculum and presubiculum, but not in the region of transition adjacent to CA1.

The nucleus of the LH and the MFB. The MFB is a mixed projection system originating rostrally in the olfactory tubercle (Papez, 1929). From early degeneration studies, it was viewed as a largely reentrant bundle linking septal and midbrain loci via interposed synapses within the LH (Raisman, 1966; Nauta, 1972; Nauta & Kuypers, 1958). Autoradiographic studies have verified the descending projection of both medial and lateral septal nuclei to the mammillary complex through medial preoptic and LH fields (Swanson & Cowan, 1975; 1976). The preoptic region reinforces and extends the diencephalic projections of the septum. Hypothalamic projections of the preoptic field include the periventricular, ventromedial, posterior and lateral nuclei, as well as the median eminence (Swanson, 1976).

Scattered, large multipolar cells with deeply staining cell bodies characterize the nucleus of the LH (e.g., Truex & Carpenter, 1969). The application of autoradiographic techniques has supported the inference that all portions of the LH contribute to both septal and midbrain trajectories of the MFB. The projections of the most rostral portions of the LH contribute direct afferents to the medial septum, as well as to the lateral habenula (Troiano & Siegel, 1975; Saper, Swanson & Cowan, 1979).

The septal projection has been further supported by the retrograde transport of horseradish peroxidase (Segal & Landis, 1974b). In the rat, the LH appears to project to the ventromedial nucleus of the hypothalamus (VMH) (Saper, Swanson & Cowan, 1979), although a horseradish peroxidase study has failed to reveal this projection in the cat (McBride & Sutin, 1977). The nucleus reuniens of the thalamus also maintains reciprocal relations with the LH (Troiano & Siegel, 1975).

The rostral limit of the projection of the LH may well exceed the septal nuclei. In the primate, the frontal neocortex has been reported to maintain reciprocal relations with the LH by way of the fornix (Leichnetz & Astruc, 1976; Kievit & Kuypers, 1975). After medial "prefrontal" lesions, Leichnetz and Astruc (1976) found terminal degeneration in the entorhinal cortex and in the hippocampus itself by way of an alvear route. A possible contribution to the body of the fornix was suggested. Fibers were followed out of the postcommissural fornix to terminate locally in the LH, while others continued to the mammillary bodies. The LH contingent was reinforced by fibers descending in the internal capsule. A large number of fibers continued to the midbrain tegmentum at the dorsolateral margin of the periqueductal gray.

At tuberal levels, the LH is adjacent to the VMH. The VMH has been reported to extensively innervate the surrounding hypothalamic nuclei, including the LH and the anterior hypothalamus (Saper, Swanson & Cowan, 1970).

While this large nucleus may make a meager contribution to the MFB, the most prominent path followed by VMH fibers is apparently the periventricular system. A rostral projection was found to course by this route to the ventral portion of the lateral septum and the bed nucleus of the stria terminalis. The innervation of the midbrain central gray and the locus coeruleus is also achieved by this system. The contribution of the VMH to the LH-MFB may therefore be typified as internuclear, rather than transient.

A number of similarities may be discerned in the organization of the hypothalamus and the brainstem reticular formation. Both are characterized by a nonspecific, multimodal afference, with cellular groupings interspersed along and within fiber bundles in a manner that appears to favor polysynaptic modes of transmission. By these criteria, Nauta viewed the hypothalamus as a rostral continuation of the reticular formation that proceeds to basal forebrain levels (Nauta, 1972). The hypothalamus is, of course, quite unique in its close relationship to the pituitary, and therefore, to the endocrine system in general. In a parsimonious observation related to both domains, Zaborszky (1982) has described the organization of the medial hypothalamus as being quasi-segmental. Overlaying a local modular arrangement, long periventricular and local MFB fibers were viewed as likely participants in the intersegmental spread of information between these transverse units.

Ascending brainstem projections and the MFB. The ascending component of the MFB has a diffuse origin in the central gray and throughout the lateral tegmental regions of the midbrain and pons (Zaborszky, 1982). It includes both aminergic and nonaminergic projections. The MFB gains access to the diencephalon via the ventral tegmentum and the ventrolateral portions of the central tegmental field. At hypothalamic levels, it retains its mixed composition, while successively reinforcing and extending its range via the interspersed projections of the LH itself.

The MFB is not completely separable from other ascending fiber systems of importance. The mammillary peduncle is a compact fiber system which connects the dorsal and ventral tegmental nuclei with the mammillary bodies. This bundle also receives fibers from other tegmental regions as well. It courses in the ventral tegmentum adjacent to the interpeduncular nucleus, where it abruptly turns toward the mammillary bodies. The trajectory of the mammillary peduncle leads its fibers through and around the mammillary bodies to ventral and medial portions of the MFB (Zaborszky, 1982). Some of its fibers proceed into the ventromedial and premammillary nuclei.

Adjacent to the MFB at hypothalamic levels is a contingent of fibers contributing to the supraoptic commissural system. This system is noteable for its subthalamic access to the diencephalon. The hypothalamic component courses adjacent to the optic tract and within the dorsal portions of the MFB itself. The origin of the fibers of the supraoptic commissural system include the spinal cord, the pontine reticular formation and the tegmentum of the midbrain (Zaborszky, 1982). These fibers are joined by others from the superior colliculus, the peripeduncular nucleus and the globus pallidus as it courses into the forebrain.

The sense of taste is of obvious importance to the performance of food-motivated behaviors. The limbic hypothalamic components of the gustatory projection systems may therefore be relevant to activity at hypothalamic and/or hippocampal levels. Norgren and Leonard (1973) traced brainstem gustatory projections in the rats (cerebelli and inferior colliculi had been removed neonatally to avoid confusion with cerebellar efferents). A secondary path was followed from its origin in the rostral pole of the solitary nucleus ipsilaterally to a region surrounding the brachium conjunctivum (lateral to the locus coeruleus). At this level, the projection did not include the medial lemniscus. The sensory properties of these tertiary gustatory units was verified by electrophysiological recordings during the application of gustatory stimuli to the tongue. A lesion was then placed at this level in a site where units responded "exclusively" to gustatory stimuli.

The projection of the "pontine taste area" followed a course just ventral to the central gray and lateral to the medial longitudinal fasciculus. At midbrain levels, the projection moved dorsally to ascend lateral to the central gray, without entering either dorsal or ventral tegmental nuclei. In the thalamus, the usual termination in nucleus ventralis posteromedialis (the arcuate nucleus) was found. Fibers were found to continue rostrally in the subthalamus. These fibers began to ramify in the anterior subthalamus and dorsolateral hypothalamus. Many continued through the medial edge of the internal capsule to distribute over a large area ventral to the globus pallidus.

A further study of the limbic component of the gustatory projection was conducted with autoradiographic techniques (Norgren, 1976). The projection was again followed along the dorsomedial corner of the internal capsule, terminating in a zone from the subthalamic nucleus down into the far-lateral hypothalamus. Other fibers continued rostrally to ramify in the substantia innominata and laterally into the central nucleus of the amygdala. The amygdaloid termination was noted to be dense.

Using horseradish peroxidase techniques, McBride and Sutin (1976; 1977) explored the afferents to the LH from brain stem sites. Labelled regions included the median and dorsal raphe, the locus coeruleus and the subcoeruleus group. McBride and Sutin also reported an

LH projection from the lateral parabrachial nucleus and a cell group continuous with the subcoeruleus region and among the fibers of the brachium conjunctivum. These investigators found a continuum of dorsal pontine cells to project to the LH, VMH and the preoptic region. Within the continuous projection zone, distinctive loci of origin were observed for each field of termination.

Septohippocampal projections. The existence of projections from the septal region to the hippocampus is now well established. It is now generally accepted that the medial septal nucleus (and the vertical limb of the diagonal band) projects to the CA3-CA4 region of the hippocampus, particularly in its most septal portions. Raisman (1966) studied the septal projections in rats using the Nauto-Gygax degenerating axon technique. Degeneration in the hippocampus was only found when medial septal regions were involved and was strictly ipsilateral.

Raisman found that degeneration from effective septal lesions coursed laterally through the septofimbrial nucleus to lie in the ventral hippocampal commissure, ultimately finding the ventral portions of the fimbria. Throughout the axial extent of the hippocampus, fine degenerated fibers traversed the alveus to ramify in the strata oriens and radiatum, but not the upper molecular strata, of CA3. Degeneration in the stratum pyramidale was attributed solely to fibers of passage. Degeneration continued to the hilus of the dentate gyrus, where a subgranular plexus was formed. While at least some of field CA2 contained degenerating fibers, field CA1 was free of degeneration along its entire extent. A sparse bilateral projection was followed into the dorsal fornix to mid-hippocampal levels, but Raisman suggested a presubicular termination for these fibers. Preoptic lesions were also found to lead to degeneration in this path.

Hjorth-Simonsen (1973) found that large septal-fornix lesions led to terminal degeneration primarily in the hilus and the strata oriens and radiatum of the regio inferior. A smaller number of terminals were also found in the regio superior and only a few were found in the subiculum and the molecular layer of the dentate gyrus. Retrograde transport of horseradish peroxidase centered at CA3-4 has been observed in the medial septal nucleus and both vertical and horizontal limbs of the diagonal band in the rat (Segal & Landis, 1974a). Within these regions, dorsal hippocampal injection sites led to staining in their most medial aspects, while ventral injections led to cell staining displaced laterally.

Using light and electron microscopic autoradiography, Rose, Hattori and Fibiger (1976) substantiated the relative confinement of the medial septal projection to field CA4 and the strata oriens and radiatum of CA3. Other investigators (Mosko, Lynch & Cotman, 1973) have reported terminal degeneration after medial septal lesions in a supragranular band that parallels the localization of acetylcholinesterase. The supragranular projection has not been supported by comparabale autoradiographic studies (Swanson & Cowan, 1976).

Acetylcholinesterase (AChE) is a functionally defined enzyme responsible for the degradation of acetylcholine (ACh). The hippocampus of the rat has a distinct pattern of staining for AChE (Storm-Mathisen, 1970). In the regio inferior, staining is most dense in subpyramidal and suprapyramidal laminae. In the regio superior, the suprapyramidal stain shrinks in magnitude and becomes diffuse as the subiculum is reached. While neocortical regions stain relatively lightly, the cellular layers of the periallocortical fields are heavily stained.

In the dentate gyrus, as in the horn, a thin supragranular lamina stains deeply, as does the entire hilus. This latter region extends to the horn, forming a continuous, arrow-shaped pattern. Another regiment, with light to moderate staining properties, approximates the course of the perforant path. The activity of choline acetyltransferase (ChAc; responsible for acetylcholine synthesis) is distributed in a consistent fashion (Fonnum, 1970).

The cholinergic afferents to the hippocampal formation appear to arise from the diagonal band and medial septal nuclei, travelling to their destinations via the medial supracallosal stria, dorsal fornix and fimbria (Lewis & Shute, 1967). After section of the (combined) dorsal pathways to the hippocampus, a decrease of 90% or more has been reported for the activity of ChAc (Storm-Mathisen & Guldberg, 1974). Since bilateral lesions of the cingulum only slightly descreased ChAc activity, this pathway seems to be a relatively unimportant cholinergic route.

Hippocampal Rhythmicity

The synchronization of hippocampal cellular activity into the grossly detectable wave processes recorded in the EEG of this structure is derivative of concurrent, yet distinct, processes. It is in part a property of the afference of this structure. The local structural and physiological properties of the hippocampal tissue are themselves, however, of unquestionable importance in enabling and maintaining the dynamic substrate of rhythmic responsivity.

Local Processes

Excitatory-inhibitory balance. The most important local synchronizing influence in the hippocampus is the physiological property of inhibition. After the electrical stimulation of the fornix, prolonged inhibitory postsynaptic potentials (IPSPs) lasting over 100 msec can be recorded from hippocampal pyramidal cells (Spencer & Kandel, 1969). Andersen, Eccles and Løyning (1964), using extracellular procedures, reported an inhibitory response in CA3 units after the electrical activation of septal or commissural pathways. A similar response was found after direct local stimulation. The depth profile of the positive extracellular response exhibited a clear maximum at the pyramidal cell layer. This response was presumed to arise from the basket cells of the stratum oriens, whose axons extensively ramify about the pyramidal cell layer (Andersen, 1966).

The loss of inhibition is functionally equivalent to an excitatory process. As a region noted for its high suceptibility to seizures (e.g., Green, 1960; Pampiglione & Falconer, 1960), the nature of the dynamic balance of the normal hippocampus may be clarified by a consideration of these pathological states.

Neurochemistry and seizure suceptibility. In both neocortex and archicortex epileptic foci induced by the topical application of penicillin or strychnine produce interictal EEG spikes that have been reported to be correlated with the depolarization and later hyperpolarization of intracellularly recorded pyramidal units (Spencer & Kandel, 1969). At the periphery of the focus lies a region in which only the inhibitory influences may be detected. In the hippocampus of the cat, an intermediate zone has also been found in which the depolarization and subsequent hyperpolarization occur only after an initial period of hyperpolarization (Dichter, 1968). The transition from interictal spiking to true seizure activity in the hippocampus is accompanied by the elimination of the late hyperpolarization. Afterdischarges then appear as depolarization shifts arising from a flat baseline.

Stimulation of either an intact or a deafferented fornix has been shown to be capabale of triggering interictal penicillin spikes in the hippocampus (Spencer & Kandel, 1969). In the normal hippocampus, a rebound from the hyperpolarization induced by the stimulation of the deafferented fornix may result in a situation quite similar to the paroxysmal depolarization shifts seen in epileptic foci. After an initial discharge, intracellular records have revealed a monotonic relationship between the amplitude of the stimulus and both the magnitude of the resulting inhibition and the later rebound excitation (Spencer & Kandel, 1969). Rebound discharges vary from single spikes to spike trains sychronized by means of the preceding IPSP to bursts of spikes.

The paroxysmal origin of the burst is evident from the within-burst spike structure. As the excitatory rebound period progresses, spike discharges may be seen to ride on a continuously depolarizing potential shift, their amplitudes diminishing in a manner consistent with the general deactivation of the spike generator (Spencer & Kadel, 1969). When strips of hippocampal tissue are examined in vitro, CA1 pyramidal cells may be induced to burst, while CA3 cells burst spontaneously (Schwartzkroin & Stafstrom, 1980).

The most likely candidate for the inhibitory transmitter in the hippocampus is γ-aminobutyric acid (GABA). Bicuculline has been used as a relatively specific and reversible antagonist of GABA (Curtis, Duggan, Felix & Johnston, 1970). The systemic administration of bicuculline to rhesus monkeys and light sensitive baboons produces seizures that tend to be quite prolonged and severe (Meldrum & Horton, 1971). In the hippocampus, iontophoretic bicuculline reduces the period of inhibition following fimbrial stimulation (Curtis, Felix & McLennan, 1970).

Hippocampal GABA is apparently intrinsic to this structure. The activity of glutamic acid decarboxylase, the enzyme responsible for the conversion of glutamate to GABA, is virtually unaffected by perforant path or mossy fiber system lesions and reduced by only 16% after fimbrial lesions (Storm-Mathisen & Fonnum, 1972). The small magnitude of this reduction may be contrasted to the approximately 90% reduction of ChAc under comparable circumstances (Storm-Mathisen & Guldberg, 1974).

The topical application of .15% GABA to the exposed hippocampus prior to local electrical stimulation has been reported to decrease the amplitude and intensity of an elicited seizure within 1-2 min. (Killam, Dasgupta & Killam, 1960). Electrographic spikes were also eliminated by this method. When 5-15 mg GABA was administered intraventricularly, the threshold for limbic seizures could also be increased. After cortical stimulation, topical GABA (1-2%) was also reported to alter the form of seizure activity but not to prevent it. To abolish seizure activity a 4-5% solution was required. Intraventricular administration of 10 mg GABA could also block both electrically elicited and spontaneous (after thiosemicarbazide) seizure activity. In contrast to these findings, the effect of GABA on an ongoing (electrically induced) seizure was only a prolongation of its duration.

The ability of the opioids to generate hippocampal seizures, even when the tissue is maintained in oculo (Taylor, Hoffer, Zieglgansberger, Siggins, Ling, Seiger & Olson, 1979) may be directly related to the intrinsic inhibitory system. An acute, in vivo study (Zieglgansberger, French, Siggins & Bloom, 1979) has shown that the biphasic response of CA1 units to stimulation of the commissural system loses its inhibitory component after the iontophoretic application of metenkephalin. The excitatory effect on spontaneous activity was capable of blockade by iontophoretically administered bicuculline. Magnesium was also capabale of preventing this effect, presumeably by blocking ongoing synaptic transmission. Since a smaller, distinct population of units exhibited inhibition after metenkephalin, it appears that these seizures are specifically caused by the disinhibition of the pyramidal cells by means of a direct inhibitory effect on the inhibitory interneuron.

While a deficiency in the inhibitory system of the hippocampus is capabale of producing seizure disturbances, an excess in the excitatory side of the balance may produce a similar effect. In this case, the cholinergic system is most clearly implicated. Cholinesterase inhibitors such as diisopropylfluorophosphate (DFP) and tetraethylpyrophosphate (TEPP) lead to an accumulation of acetylcholine as well as seizures in intact animals (Stone, 1957). These seizures may be blocked by large doses of atropine. Microinjection of 30 mg DFP into the cat hippocampus can lead to paroxysmal discharges that may be antagonized by scopolamine or the cholinesterase activator pyridine-2-aldoximine methoidide (Baker & Benedict, 1968). When the effects have begun to subside, seizures can be reinstated by injection of normally ineffective doses of ACh (1-5 mg).

Although cholinergic influences may be presumed to be an important excitatory input to the hippocampus, there is evidence that the pyramidal cells themselves may be the origin of the spike bursts that are so apparent under pathological conditions. Wong and Prince (1979) examined the in vitro activity of cells in transverse slices of hippocampal tissue. Pyramidal cell dendrites of field CA1 were impaled in the stratum radiatum. These dendrites were found to generate slow depolarization shifts (about 50-100 msec duration) with associated spontaneous bursts of action potentials whenever their membrane potentials dropped below -60 mV. Cells with higher potentials could be forced into a burst pattern by applying a depolarizing current pulse. Conversely, a hyperpolarizing pulse was capable of aborting a burst in progress and resetting the membrane to the resting level.

The orthodromic activation of CA1 cells by radiatum stimulation at intensities below the threshold for spike initiation evoked a depolarization-hyperpolarization sequence. The overlap of the excitatory and inhibitory potentials gave rise to an abbreviated depolarization. After the application of penicillin to the tissue, resting potentials and thresholds were unaltered. Instead, the excitatory phase was prolonged to take the form of a simple, exponentially decaying process. It is therefore likely that bursting is a property of hippocampal pyramidal cells and that the suppression and synchronization of such bursts is under the control of the local network.

MacVicar and Dudek (1980; 1981) have examined the physiological relationship between CA3 units on a local scale with in vitro intracellular techniques. After the presentation of an effective current pulse, 11% of the 88 pairs impaled (tip separation less than 200 μm) showed inhibition in the second unit. Such inhibition usually occurred without a detectabale IPSP. In about 6% of the pairs, action potential were also detected in the second unit after .5-22 msec.

The reason for the relatively low frequency of linked inputs is not clear, considering the generality and magnitude of inhibition reported with other procedures. A later study, in which horseradish peroxidase was used to identify the impaled cells, has demonstrated the existence of electrotonic coupling in cell pairs separated by less than 100 μm (MacVicar & Dudek, 1981). It is therefore possible that synchronous influences may be enhanced by the direct spread of activity at the local level.

Frequency potentiation in the perforant path system. The physiological influence of the perforant pathway on cellular activity in the hippocampal formation has been found to be related to the temporal recurrence rate and persistence of a stimulus. Andersen studied these influences with the use of extracellular techniques in a series of studies in which anesthetized rabbits served as subjects (reviewed in Andersen & Lømo, 1970; Andersen, 1975).

Due to the rigid lamination of the molecular layers and the simplicity of the composition of the cellular layers, the activation of the pyramidal cells and their dendritic shafts may be inferred from the comparison of the depth profile of the gross response with corresponding intracellular responses after the excitation of known anatomical inputs. The generation of spikes in the apical dendrites of field CA1 after entorhinal stimulation has thus been reported (Andersen, Holmquist & Voorhoeve, 1966). In extracellular records, these spikes appear as a population spike with an amplitude peak in the pyramidal cell layer. At the level of the Schaffer collaterals, a negative wave with a slow propagation rate attains its peak. The dendritic origin of the population spike is suggested by the relatively constant speed with which it travels toward the cell layer (about .5 m/sec). In subpyramidal zones, into which the basal dendrites project, the propagation rate is markedly slowed (about .2 m/sec).

Studies in Andersen's lab have physiologically verified the topographic mapping of the entorhinal cortex onto the dentate gyrus, as well as to secondary and tertiary projections into the horn itself. A particularly significant finding is the temporal specificity of this system. In both unit and gross records, the frequency and duration of a tetanizing stimulus has been found to determine the degree to which the intrahippocampal system is affected. Data presented by Andersen and Lømo (1970) indicate that while stimulation at 10 /sec may penetrate as far as the CA1 pyramids, at interstimulus intervals above about 2 sec, only the dentate granules may discharge.

As a recording electrode descends through the overlying CA1, very little electrical activity may be detected at low stimulation rates. Upon crossing the hippocampal fissure into the dentate gyrus, however, a negative wave appears (Andersen, 1975). This wave reaches its maximum in middle parts of the molecular layer and is temporally coincident with the appearance of excitatory postsynaptic potentials (EPSPs) in intracellular records. The negative wave is followed by a large positive wave in the granule cell layer corresponding to an intracellular hyperpolarization (Andersen, 1975).

With prolonged, repetitive stimulation of the entorhinal cortex, it is possible to activate the CA3 field via the mossy fiber system. Thus, the stimulation of the entorhinal cortex with pulses of sufficient amplitude at an interstimulus interval of 1.5, 1.4 or 1.0 sec has been reported to lead to a small population spike in field CA3 after 13, 8 and 2 sec trains of stimuli, respectively (Andersen & Lømo, 1970). Further increments in train length lead to increases in the amplitude of the response until a stable maximum is recorded.

The capacity for frequency potentiation extends into field CA1 via the Schaffer collateral system. With interstimulis intervals of 1.5 sec or greater, no extracellular signs of activation may appear in this field. At 1.4 sec, a response may be discerned with 30 sec stimulation trains. At 1.0 sec intervals, CA1 activation begins within 10 sec of onset (Andersen & Lømo, 1970).

Andersen (1975) has noted that the optimal frequency for the generation of the largest potentials throughout the trisynaptic intrahippocampal system is about 10-15 Hz. Frequency potentiation may also give rise to posttetanic potentiation effects, since the enhancement of the amplitude and rising slope of the population response may persist for many hours after the administration of several series. The maximal response for a rate of 10 stimuli/sec appears after 10-30 stimuli. At rates of 5-8 /sec, the frequency potentiation effect in the dentate gyrus and field CA3 may be well-developed despite a negligible or weak effect on CA1. At rates above 40 Hz, the potentiation is maintained for only a few stimuli, after which a depression occurs. This depressed state may last as long as 2 min after termination of the stimulus. Unless afterdischarges occur, a complete recovery will occur within 5 min.

Frequency potentiation in the mossy fiber system has been found to depend on the availability of zinc (Hesse, 1979). In anesthetized, adult rats, the potentiation after dentate gyrus stimulation with .33-4.0 /sec stimuli reverses in sign when dietary zinc is eliminated. Thus, the usual increase in response amplitude over stimuli in a train is replaced by a depression. This effect is greatest at the highest rate tested. The decay rate of the response amplitude, derived for a given latency (pulse number) from the onset of the train, was related to stimulation rate in a roughly exponential fashion. In one animal, potentiation of normal form was reportedly restored after only 48 hr of zinc supplementation. In contrast to the mossy fiber response, frequency potentiation after commissural stimulation was not reversed.

It is evident that the physiology of the hippocampus is one in which a stable system is enforced through inhibition. The unleashed activity of the pyramids themselves, particularly those of field CA3, is somewhat less stable and prone to bursts of action potentials. Although local inhibitory influences tend to predominate, the effective influence of one cell field on its successor is an excitatory one. Based on the frequency potentiation studies, it appears that the classic perforant path and intrahippocampal projection systems are quite responsive to the frequency-specific properties of a signal in a range that is at least loosely related to the normal composition of the EEG.

Distal Processes

Before describing the physiology of the ascending afferent projections to the hippocampal formation, it may be instructive to examine the properties of the descending efferent systems. In this way, the influence of the hippocampus on the hypothalamus and brain stem may be viewed in the simplistic sense of a descending forebrain control system. Since the reciprocating influences have certain strongly rhythmic characteristics, this approach postpones questions related to bidirectional and feedback properties until the time domain correlates of the system have been described. Considerations of rhythmicity at both gross and unit levels will then find themselves fused with those derived from the ascending anatomical substrate.

Descending systems and responses. The fimbria and dorsal fornix projections to the septum have been studied in the rat by stimulation-recording techniques. McLennan and Miller (1974) reported that (dorsal) fornix stimulation led to a predominatly negative biphasic or triphasic evoked potential of short (2-4 msec) latency in a restricted zone of the medial septum. This response was capable of following 60-80 Hz stimulation with little or no attenuation and was accompanied by the excitation of medial septal units. An even shorter latency response (.9-1.5 msec) capable of following 100 Hz stimulation was detected in medial septum after fimbrial stimulation and was presumed to be antidromic in origin.

Fimbrial stimulation was found to lead to two distinct evoked potentials in the lateral septum. Stimulation of the anteromedial fimbria caused a 4-7 msec latency response capable of following up to 60 Hz before attenuating. This response was centered at mid-anterior-posterior regions of the lateral septum. Posterior fimbrial stimulation led to another response with a latency of 12-16 msec capable of following rates of stimulation of only 30 Hz before attenuating. Within the lateral septum, the short and long latency components could be most readily recorded in dorsal and ventral portions, respectively.

At a unit level, fimbrial stimulation led to an excitation of lateral septal units followed by a period of inhibition ranging from 100 to 800 msec (220 msec mean duration). Medial septal units showed effects depending on their ongoing spontaneous activity. During periods of irregular firing, fimbrial stimulation was followed by a period of silence, the duration of which was related to the amplitude of the stimulus. If the unit was engaged in rhythmic bursting activity, the (truncated) inhibitory period acted to affect the synchrony of the discharge. Furthermore, lateral septal units responded to medial septal stimulation with an antidromic discharge followed by a period of silence.

McLennan and Miller viewed their data as indicative of a fimbrial projection directly onto lateral septal neurons and indirectly, via both excitatory and inhibitory interneurons, onto medial septal cells. The lateral septal units were then seen as being autoinhibited via an interposed interneuron. The correspondence with the descending projections of the hippocampal formation is apparent.

Vinogradova offered independent support of the influence of the fornix system on units of the lateral septum of the rabbit, reporting that these influences are necessary for the habituation of sensory responsivity in this nucleus (Vinogradova, 1975). Since field CA3, in both its dorsal and ventral portions, was the only hippocampal field characterized by the habituation of tonic, multimodal responses, this field may well be the source of the response decrement. Vinogradova also corroborated the predominantly inhibitory effect of hippocampal stimulation on units of the medial septum, reporting a disorganization of θ bursts or a gradual decrease in burst frequency from 4-6 /sec to 3-3.5 /sec. Such stimulation was also found to render medial septal units unresponsive to sensory stimuli, the opposite effect to that observed after stimulation of the midbrain reticular formation.

Radioactive deoxyglucose may be used in a metabolic version of the stimulation-recording paradigm. In this procedure, the labelled variant of glucose is taken up by cells in proportion to their utilization of glucose. The spread of metabolic activity due to localized activation may then be followed.

Kliot and Poletti (1979) used the uptake of labelled deoxyglucose as a means of visualizing the effects of hippocampal afterdischarges elicited by direct electrical stimulation. When only the hippocampus proper was involved, increased activity could be detected throughout the hippocampus and the subicular fields. This effect was bilateral for dorsal afterdischarges, with a variable involvement of the ventral subiculum. Perirhinal sites were also activated. Afterdischarges in ventral sites led to effects that involved the dorsal regions less extensively. Variable increases were also found in the entorhinal cortex, the basal, medial and cortical nuclei of the amygdala, the confluence zone, and the nucleus accumbens. For both dorsal and ventral cases, the effect on basal forebrain regions was confined to the dorsal aspect of the lateral septum, with ventral hippocampal discharges labelling more ventral sites.

The most extensive uptake pattern was found in cases in which the ventral subiculum was the origin of the afterdischarge pattern. The amygdala, entorhinal cortex, the deep layers of the perirhinal cortex and the claustrum were all ipsilaterally labelled. Bilateral increases appeared throughout the hippocampal formation, being most marked in ventral regions. The entire extent of the lateral septum was also labelled, continuing into the diagonal band, the nucleus of the lateral olfactory tract, the bed nucleus of the stria terminalis and the nucleus accumbens. Both medial and lateral preoptic regions were markedly labelled, continuing caudally to include anterior, lateral, ventromedial, dorsal, posterior and premammillary nuclei of the hypothalamus.

Under conditions in which the ventral subiculum is not involved, this study corroborates the anatomical studies in which no true hippocampal contribution have been found to the long descending projection systems. It is curious that even in the wake of electrographic afterdischarges, the activation pattern is quite localized. The widespread domain of subicular influence contrasts sharply with this pattern.

Poletti, Kinnard and MacLean (1973) electrically stimulated the hippocampus of the monkey with brief pulses and recorded the response of hypothalamic and basal forebrain units. When combined, a total of 22% of all units were responsive. In the LH, 3 of 29 recorded units were responsive (10%). Of 99 VMH units, only 4 changed firing patterns (4%). In the lateral septum, diagonal band and perifornical hypothalamus, however, 33%, 54% and 29% of all units recorded were responsive, respectively.

More than 85% of all hypothalamic and basal forebrain units responsive to hippocampal stimuli showed an initial excitation. Afterdischarges recorded in the hippocampal record likewise elicited excitatory effects more often than suppression of firing, although the latter effect did occur in about a quarter of all responsive units. Over 25% of all units responsive to stimulation showed alternating phases of excitation and inhibition. Thus, patterned responses are not uncommon even under the simplified physiological conditions of this study.

Miller and Morgenson (1971) used a stimulation-recording paradigm to examine the descending influence of the septum on the LH of anesthetized rats. The evoked potentials so produced were typically characterized by two components of opposite polarity. The two components were at least partially separable by the appropriate selection of the stimulation site. At dorsal and midline stimulation loci, the shorter latency (10-14 msec) response was predominant, while in the region of the bed nucleus of the stria terminalis and the nucleus accumbens, the longer latency component (18-23 msec) was maximal. It was suggested that precommissural fornix and stria terminalis influences accounted for the short and long latency responses respectively.

As a test of the origin of the short latency components of the LH evoked potential, the hippocampus was stimulated (Miller & Morgensen, 1972). The obtained response was consistent with this hypothesis. Its peak latency was slightly longer than that after septal stimulation (11-17 msec). After lesioning the medial septum and a portion of the ipsilateral lateral septum, the amplitude of the response was markedly attenuated. A comparable verification of the stria terminalis component was also conducted.

The correlates of the LH evoked potential at the unit level have also been examined (Miller, 1972). In a group of 27 units showing an excitation-inhibition sequence after intermediate stimulation loci, the early and late components closely overlapped temporal plots of the number of units excited or inhibited, respectively. When dorsomedial septal stimuli were applied, half of the units showed this biphasic response pattern. Of the remaining responsive units, about 60% showed a pure facilitation. Since about 70% of all units detected were responsive to stimulation of either the dorsomedial or the bed nucleus site, it appears that the descending precommissural fornix is capable of a great deal of control over the activity of the lateral hypothalamus.

Murphy, Driefuss and Gloor (1968) examined the responsiveness of hypothalamic units to septal and amygdaloid stimulation in the cat. Electrocoagulation lesions of the midbrain reticular formation were used in place of anesthetic approaches to maintaining a somnolent state.

Basal amygdaloid stimulation led to responses in VMH units that were often tightly driven by the stimulus. The modal activation latency was 12 msec and was clearly defined. Activation of LH units occurred at a less sharply delimited mode of 27 msec. Septal stimulation had similar effects on hypothalamic units, although latencies were often slightly longer and less well defined. An increase in the intensity of the septal stimulus often resulted in the appearance of a secondary activation period of longer latency.

Of all hypothalamic units recorded, 79% were influenced by the stimulation of amygdaloid or septal sites. Of those responsive units, half showed some form of inhibition. While about 60% of these exhibited a simple inhibition, 40% were characterized by an excitatory-inhibitory sequence. Spike firing was typically suppressed for 100-250 msec. Inhibitory effects were more constant in their appearance than the excitatory effects. Since units of the LH tended to have high rates of spontaneous activity, the inhibitory effects were most readily discerned in this region.

The descending influences of the LH and the preoptic region onto units of the ventral tegmentum of the midbrain was examined by Edinger, Kramer and Siegel (1977). Using a stimulation-recording paradigm, about half of the responsive units were found to react by a short latency suppression of the ambient discharge rate. Presumed orthodromic activation of midbrain units was also reported after either long or short latencies, as was the antidromic activation of some units.

Grantyn, Margnelli, Mancia and Grantyn (1973) explored the descending influences of the hippocampus in encephale isole cats by using a stimulation-recording paradigm. The dorsal hippocampus, entorhinal cortex, medial septum and LH were stimulated with brief rectangular pulses, either in short bursts (2-10 pulses at 100-333/sec) or at .5-30 /sec. Units of the midbrain reticular formation and the bulbopontine reticular core were recorded intracellularly. Responses were found to be predominantly excitatory.

In bulbopontine cells, EPSPs after limbic volleys tended to be time locked with a rapid rise and decay. In the midbrain, depolarizations occurred after a long, shifting latency (means of 21-32 msec for stimulation of different limbic forebrain loci) and were characterized by slow rise times and long durations. It was concluded that while an oligosynaptic route is responsible for the bulbopontine influence, the midbrain response is via a polysynaptic pathway.

In the mean, bulbopontine spikes appeared 13 msec and 16 msec after stimulation of the entorhinal cortex or hippocampus, with standard deviations of 6.4 msec and 8.5 msec, respectively. Latencies after septal and LH stimulation were 10±5.9 msec and 5±4.5 msec. Thus, as would be expected, those sites that are most widely separated anatomically tend to exhibit the largest response latencies.

Repetetive responses to brief stimulus trains were rare for bulbopontine units, but were common in the midbrain. Mean response duration varied inversely with distance from the midbrain recording site. Thus, while the mean duration after entorhinal and hippocampal stimulation was 57 and 61 msec, respectively, after septal and LH stimuli spike discharges persisted for 88 msec and 129 msec.

Grantyn et al. (1973) further catergorized units as "ascending" or "descending" by antidromic invasion properties after stimulation of the subthalamic-hypothalamic region or the anterior funiculus of the spinal cord. A few units were found to have both ascending and descending projections. Antidromic invasion was occasionally observed after limbic stimulation. Units that could be identified by these procedures were found to be significantly less responsive to hippocampal or entorhinal stimulation than those that could not be so identified. The mode of the response did not differ between the two classes of units.

Vinogradova (1975) made use of 5-30 /sec stimulation of the CA3 region of the unanesthetized, slightly restrained rabbit. While most brainstem units showed only tonic changes to such stimulation, phasic responses with mean latencies of 15-25 msec were often recorded in the raphe. Units of the more lateral reticular formation responded with mean latencies of 20-40 msec. In these lateral placements, tonic effects usually followed the phasic influence. The effect of CA3 stimulation on the spontaneous activity of raphe units was typically an enhancement of activity, while the reticular formation placements usually showed a decrement.

Important functional relations were also uncovered. In 83% of the reticular formation units, the usual response to sensory stimulation was found to weaken or disappear after CA3 stimulation. A similar, but less pronounced tendency was seen in raphe units as well. Consistently, electrolytic lesions of the fornix system at the level of the septofimbrial nucleus of the septum had no effect on either the spontaneous activity of the septum (except for a possible increase in the number of units exhibiting θ bursts) or the responsiveness of medial septal units to sensory or direct reticular formation stimulation. Such lesions were capable of totally eliminating the ability of lateral septal units to habituate to repetitive sensory stimuli.

Ascending systems and rhythmicity. The descending influences of the hippocampus on the reticular core of the brainstem are clearly capable of modulating or directly controlling the sensorimotor state of the organism. From the anatomical information that exists to date, it appears that a respectable proportion of these influences proceed through the hypothalamus in the descending fiber paths of the medial forebrain bundle. Through this route, numerous patterns of control over mesencephalic and diencephalic activity are possible. Yet the reciprocating influences are at least as important when one considers the many projections previously described anatomically.

Grantyn and Grantyn (1972) found midbrain stimulation to be effective in eliciting CA2-3 field (dorsal hippocampus; anesthetized cats) activity at a unit level (intracellular records) in 84% of those sampled. Most responses were composed of a hyperpolarization-depolarization sequence. The most common initial effect was a slow hyperpolarization, with depolarization or a mixed pattern primarily occurring later. When stimulation of the midbrain reticular formation or central gray elicited any response at all within 50 msec, it was almost invariably a hyperpolarization. In 22% of these units, the initial IPSP was followed by a sequence of secondary hyperpolarizations with successively shorter durations. The IPSP latencies usually encountered were 10-20 msec. While they were quite stable in some units responsive before 15 msec, in other units latency shifts of 2-6 msec, and sometimes as much as 10 msec, were seen.

Although brief tetanic bursts were usually required to elicit a response, early IPSPs that could be recorded after a single stimulus pulse were usually 2-5 mV in amplitude with a 12-37 msec rise time. The durations ranged from 70 to 220 msec and were not correlated with the amplitude of the IPSP. When brief tetanic trains were used, IPSPs increased in both amplitude and rise time, saturating with trains of 30-50 msec duration. After accounting for secondary depolarizations, the investigators concluded that the uncontaminated initial IPSPs evoked by tetanic stimulation of the midbrain have typical durations of 160-220 msec (sometimes as long as 300 msec).

In about a quarter of the units responsive to midbrain stimulation, IPSPs with extremely long durations were found. While these hyperpolarizations generally lasted 400-700 msec, some lasted 1500 msec. About a quarter of these "sustained" IPSPs had latencies exceeding 50 msec (sometimes as much as 150-180 msec). Half of the "sustained" IPSPs had rise times that exceeded 40 msec or eluded definition due to a slow, irregular buildup.

Despite the generality of hyperpolarization after midbrain stimulation, Grantyn and Grantyn (1973) have found that 62% of those hippocampal units recorded exhibit long latency depolarizations. Membrane potential oscillations were usually 2-10 /sec with the earliest oscillations occurring at higher frequencies (5-16 /sec). The total duration of the oscillatory response reached 300-1200 msec. Action potentials were generally produced with a latency of 40-140 msec, with latency shifts of less than 40 msec. Discharge rate was increased over prestimulus values in 80% of those units showing IPSPs, especially during earlier depolarization shifts. It appears, then, that the response of the hippocampus to midbrain stimulation is a patterned one.

The role of inhibition in the response of the hippocampus to afferent stimulation is beyond question. Likewise, the existence of patterned responses in both ascending and descending pathways has been well established. The existing evidence strongly suggests that the complexity of the temporally defined unit data has a simplified correlate in the frequency composition of the gross EEG.

The traditionally defined activation pattern of the hippocampus is marked by the appearance of the θ rhythm in its EEG. This electrographic pattern is composed of a continuum of activity that is, by physiological standards, highly synchronized in the 4-8 Hz range. The θ pattern is quite well developed in the rodent.

The medial septum is presumed to be the pacemaker of the θ rhythm of the hippocampus. Units of the medial septum-diagonal band complex fire in bursts with an interburst timing that closely coincides with that of the θ wave (e.g., Petsche, Stumpf & Gogolak, 1962). In the curarized cat, θ induced by midbrain stimulation can be reversibly blocked by septal cooling, causing a shift of EEG power toward lower frequencies (Eddy, Bremner & Thomas, 1971).

Apostal and Creutzfeldt (1974) used time series techniques to study the relationship between the hippocampal and septal EEG of the curarized rabbit. After stimulation of the midbrain reticular formation, the autocorrelation functions for the two EEGs were virtually identical, exhibiting a clear rhythmicity with a period of 200-300 msec (4.3-5 Hz). Crosscorrelations showed that the septal site consistently led the hippocampal record by 1-2 msec.

When the binary record of septal unit activity was crosscorrelated with the ongoing spontaneous hippocampal EEG, it was determined that bursting units fired with a constant phase relationship. These phase properties varied from cell to cell. Nonbursting units of the medial septum at times exhibited a moderate rhythmicity in such crosscorrelograms, but the phase properties so derived were not stable.

From anatomical considerations, the medial septum may be viewed as an ascending linkage between the brain stem reticular core and the hippocampus. Likewise, the lateral septum appears to be the primary locus from which descending hippocampal (CA1-CA3) influences are disseminated to lower sites. Since these descending influences also affect the activity of the medial septum (McLennan & Miller, 1974), the degree of autonomy of the septal pacemaker is not intuitively obvious. In fact, whereas descending modulation of septal activity may be inferred, it is at least possible that the θ pattern is exclusively derived from a septo-hippocampal feedback loop.

In an effort to explore the nature of ascending, descending and intrinsic mechanisms in the control of septal unit discharge patterns, Vinogradova, Brazhoick, Karanov and Khadina (1980) examined septal units after section of hippocampal and hypothalamic projection paths (chronic rabbit preparations). Septal undercutting was found to lower θ burst mean frequency from 5.2 Hz to 3.3 Hz without affecting the prevalence of this response mode. Rhythmicity was noted to be extremely regular, with 21% of the neurons tested exhibiting a non-bursting, clocklike form. This kind of pacemaker activity is rare in the intact septum. In general, the rate of spontaneous firing for medial septal units doubled over that in intact subjects.

After the removal of descending hippocampal influences, the composition of the different response modes changed in the septum. The proportion of θ bursting units detected increased markedly (from 28% to 42%) while burst frequency remained intact (increased .2 Hz). Non-bursting pacemaker activity appeared in 26% of the units recorded. Lateral septal units as a whole doubled in their response rates.

Vinogradova et al. (1980) also examined the activity of units recorded from guinea pig septal slices in vitro. Unit discharges tended to be highly regular in 64% of the cases. The proportion of units exhibiting bursts was roughly normal. Burst frequencies ranged from 2.0-5.1 Hz. Spontaneous activity generally tended to be high.

These findings support the hypothesis that an intrinsic septal θ pacemaker is driven by the ascending barrage from brainstem sites. They also suggest that hippocampal influences compete for control of θ burst units in all-or-none fashion, potentially blocking bursts without otherwise affecting burst frequency. It is interesting to note that both ascending and descending routes have, in general, a resultant inhibitory effect on septal activity. The linkage between these two structures is clearly suceptible to disruption. At times, such as after the administration of hallucinogenic drugs, the hippocampal EEG may become markedly dysrhythmic, while septal records remain largely unaffected (Stumpf, Petsche & Gogolak, 1962).

Anchel and Lindsley (1972) described a dual hypothalamic role in the generation of hippocampal EEG patterns in the flaxedil-paralyzed cat. Stimulation (25 msec pulses at 100 /sec) of medial regions led to hippocampal synchronization in the form of a clearly defined θ pattern. Lateral stimulation, however, led to a desynchronized state in which low amplitude fast activity appeared.

The frequency of the θ pattern elicited by medial hypothalamic stimulation was found to vary with the stimulus voltage. Thus, in one animal, 1 V stimulation led to an initial synchronization at 3.5 Hz. The synchrony strayed a bit during the record, becoming somewhat irregular at times. At 3 V, a steady, regular θ at 4.3 Hz appeared, while at 5V the frequency was further elevated to 5.5 Hz. At the highest intensities, the elicited θ persisted after removal of the stimulus by 3-4 sec at a reduced frequency. Stimulation of lateral regions of the hypothalamus at low voltages was capable of disorganizing ongoing hippocampal θ. At higher voltages, a low voltage fast pattern occupied the hippocampal record in a manner that was sharply delimited by the onset and offset of the stimulus.

The route by which these hypothalamic influences are distributed to the hippocampus has been tested by lesions and reversible cryogenic blocade of sites rostral to the stimulation zone (Anchel & Lindsley, 1972). The synchronizing effect of stimulation of the medial hypothalamus has been found to require the integrity of rostral medial, but not lateral, fields. Conversely, the desynchronizing effect of lateral stimuli requires the integrity of lateral, but not medial, loci rostral to the stimulus. Lesions of the fimbria fornix system indicate that the synchronizing system ascends in this bundle, while desynchronizing effects must utilize an alternate route.

Not all sites in the LH could be simply categorized in terms of a synchronizing-desynchronizing dichotomy. While loci in the vicinity of the densest concentration of MFB fibers were typically good desynchronizing sites, mixed responses were reported from a number of posterior regions in the vicinity of the postcommissural fornix. Mixed responses were characterized by hippocampal synchronization after low intensity stimulation, but desynchronization at higher voltages.

Paiva, Lopes Da Silva and Mollevanger (1976) have examined the influence of hypothalamic and midbrain stimulation parameters on the hippocampal EEG of the halothane anesthetized cat. Rather than simply using direct observation to categorize the EEG, these investigators compared pre and poststimulation power spectrum measures (derived from notch filters) as a means of quantifying synchrony. Stimuli consisted of 10 sec trains of .15 msec pulses of variable amplitude (0-8 V) and rate (0-100 /sec). It should be noted that this technique confounds stimulation rate and root mean square (RMS) stimulation voltage. Even so, differences between the effects produced by changes along these dimensions allow at least a partial separability of these influences.

Paiva et al. (1976) used stimuli at or near threshold voltage for the production of a detectable EEG effect at 100 /sec (approximately mid-range in voltage). An increase in pulse rate was found to shift the spectral peak to higher frequencies for both midbrain and LH stimulation sites. In contrast, all spectral components of the response to VMH stimulation were significantly depressed with the exception of that at about 5 Hz. Despite this loss of power, a sizeable peak appeared in the digitally analyzed power spectrum after such stimulation.

When stimulus repetition rate was held constant at 100 /sec, increases in stimulation voltage at medial and posterior regions of the hypothalamus led to an increase in the amplitude of all frequency components of the EEG with a corresponding increase in peak frequency. Stimulation of lateral and anterior regions led to a shift in peak frequency with a decrease in power in the lowest portions of the θ range (4 Hz) and, at times, others as well. With midbrain sites, stimulation voltage increments also led to peak frequency increases and a corresponding suppression at 4 Hz.

It should be noted that of 9 cats stimulated in the LH, only two showed "desynchronization" (statistically significant suppression of all θ components) with low intensity stimuli. Of these, one electrode placement overlapped the postcommissural fornix. The other was in the region of the greatest concentration of fibers of the MFB. It must be emphasized that these investigators found no evidence of separate synchronizing and desynchronizing systems in the hypothalamus.

The response of septal units to hypothalamic stimuli has been reported by Wilson, Motter and Lindsley (1976). As would be expected, synchronization of the hippocampal EEG was closely associated with the activity of θ bursting units. Of all rhythmic bursting cells, 73% responded with 1.7-4.5 msec latencies after LH stimulation. Medial stimuli were never found to affect these units at a fixed latency. Bursting cells accelerated in firing rate and fired continuously in 59% of all cases after LH stimuli. A complete suppression of firing or a marked reduction in rate occurred in 33% of those observed.

Based on anatomical considerations, the effect of hypothalamic stimulation on septal neurons is not particularly obvious. While the suggestion of periventricular and MFB systems does appear to have some anatomical credibility, it is also clear that these influences do not act in vacuo. If a physiological system is to be posited, it is more parsimonious to suppose a dual influence in which synchrony takes the form of a continuous, rather than a dichotomous, variable. An alternative possibility that is also consistent with the data is that one route affects a synchronicity synaptically, while the alternate route disorganize it via the utilization of a pathway in violation of normal information flow. Two such abnormal modes are antidromic activation and orthodromic activation far beyond the normal dynamic range of the system.

Intrahypothalamic rhythmicity. The relationship between the electrical activity of medial and lateral divisions of the hypothalamus has been studied in detail by Oomura et al. (1967). In the quiet, waking cat, a desynchronized EEG pattern is present in the VMH, while the LH record is characterized by large amplitude slow waves. Under pentobarbital anesthesia, these patterns are reversed. This reciprocal relationship applies at the unit level as well. Under light ether anesthesia, LH units discharge slowly, while VMH units fire rapidly. As the anesthesia is deepened, VMH activity slows as LH activity increases.

Autocorrelation functions, expressed in standardized form as product-moment correlation coefficients, were calculated over 100 msec epochs with a resolution of 10 msec under light (N=900) and deep (N=907) ether anesthesia (Oomura et al., 1967). These results also support the proposed reciprocity between VMH and LH unit activity. Both LH units under light anesthesia and VMH units under deep anesthesia showed a lack of correlation between discharges. Over the entire (non-contiguous) record, values tended to be reasonably stable at about -.02. Under the opposite conditons, a suppression to about -.14 appeared within a 10 msec lag period. This suppression declined to approximately zero within 50 msec.

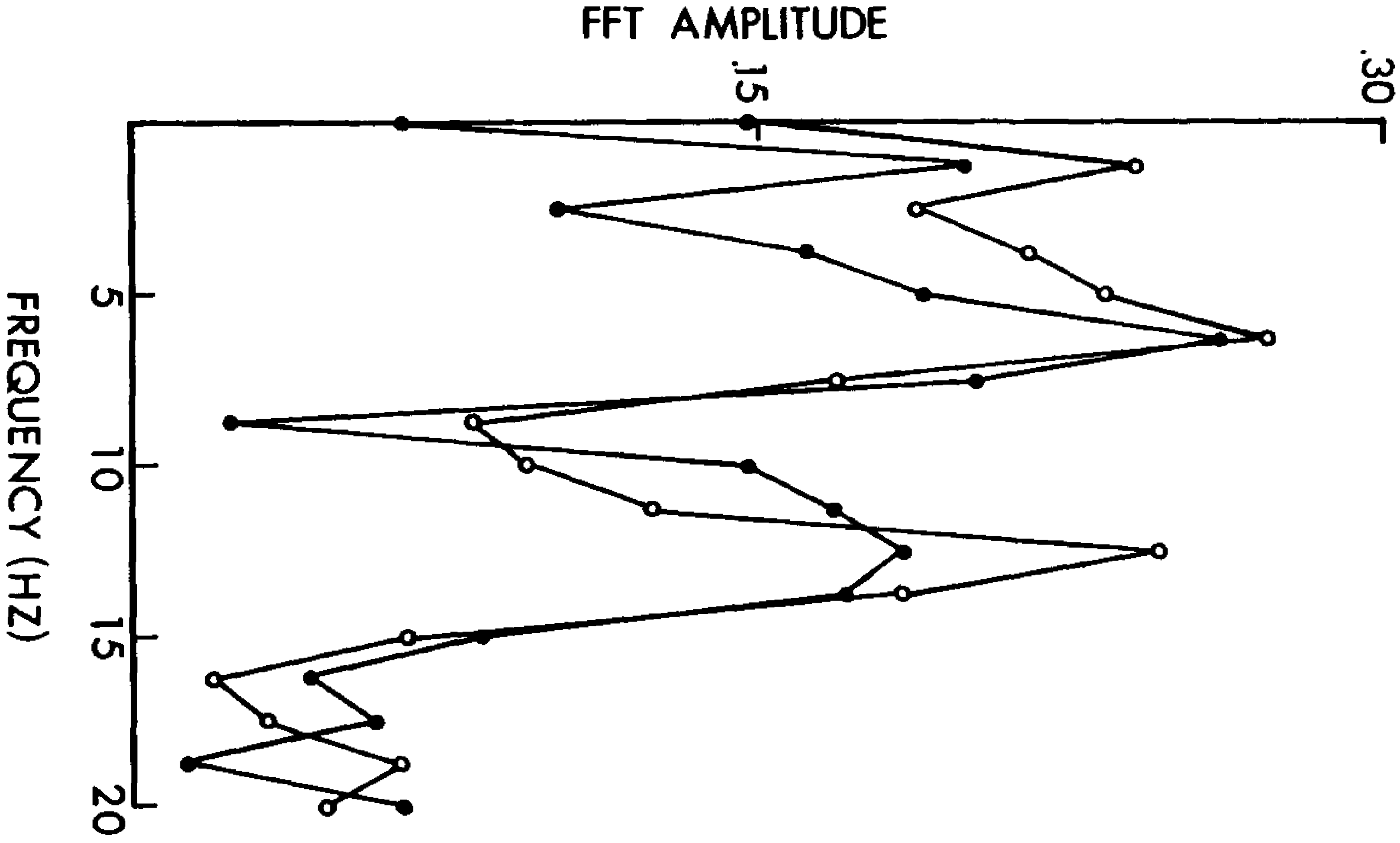
Although the differences in the autocorrelation derived from spontaneous unit activity are small, further support for their validity may be found in stimulation-recording data (Oomura et al., 1967). In the course of stimulation of the VMH with .1 msec pulse trains, 24 LH units were recorded. Of these, 63% showed a decrease in firing rate. This effect was more pronounced with high voltage stimuli. A quarter of the units recorded were unresponsive, while the three remaining units tended to increase somewhat with more intense stimuli. The response of VMH units to LH volleys was likewise generally a suppression of firing. Inhibition of firing was found in 68% of 44 units recorded. One fifth were unchanged, while 11% (5 units) increased in discharge rate.

For single LH pulses, crosscorrelations between the binary records of the stimulation pulse and the unit record were also computed. A clear, statistically significant suppression was found for lag times of up to 75 msec, after which the curve reversed to a significant elevation. Rhythmic properties of this response were not examined, despite the existence of secondary inhibitory and excitatory peaks.

The crosscorrelation data presented by Oomura et al. (1967) for the tally of VMH unit discharges (N=1380) were computed with 25 msec lag increments. This means that frequency components of this response above 20 Hz will be aliased as activity in the 0-20 Hz range. Units of these nuclei appear to respond reciprocally through various anesthesia depths, with an expected maximum response of about 20 /sec. The persistence of the immediate inhibitory effect suggests that the patterning of the response may actually be much slower. It is therefore unlikely that the data are misrepresented due to aliasing.

Oomura et al. (1967) published data for lag times up to 500 msec after the LH stimulus. This approximation is appropriately one-sided, since the posited system

Fig. 6. Fast Fourier transform (FFT) of "cross-correlation" data of Oomura et al. (1967). Raw data sequence was extended to next power of 2 by adding zeros (Bendat & Piersol, 1971). First zero crossing for sample period boxcar function is at 2 Hz. Open circles = FFT of untreated data record; Solid circles = cosine tapered data record to reduce the contribution related to the sample period itself (Bendat & Piersol. 1971).


FFT AMPLITUDE
.15
.30
FREQUENCY (HZ)
5
10
15
20

is a causal one. For negative lag times, a constant zero correlation derived from ambient noise may be supposed. If one subjects the published crosscorrelation data to Fourier transformation, a variant of a (post-stimulus) cross spectrum may be obtained by virtue of the Fourier identity of these measures (e.g., Bendat & Piersol, 1971). Since a .1 msec stimulation pulse is brief enough to approximate an instantaneous impulse function in its 0-20 Hz composition, a true cross spectrum would be formally identical to a frequency response function for an LH-to-VMH system. While questions of linearity may be raised, such an experimental approach has a clear potential for increasing our understanding of the participation of local unit activity in such widespread patterns as those detected in the EEG.

The Fourier amplitude spectrum of the Oomura et al. (1967) crosscorrelation plot has been computed and is presented in Figure 6. Raw amplitudes are plotted for both raw data and data subjected to a cosine tapering procedure. The latter procedure reduces the spectral side lobes related to the sample period itself. The small number of complete (averaged) cycles available for the derivation of reliable amplitude estimates of the component sinusoids is somewhat problematical. Further, the lack of the corresponding autocorrelation data prevents a true standardization in the frequency domain. With these cautions in mind, the results may be tenatively examined.

The frequency response of the VMH unit record to LH stimulation is typified by a distinct peak in the θ band as well as a secondary peak at twice this frequency that exceeds the traditionally defined 8-12 Hz limits set for α activity. It is not clear whether the secondary peak represents an independent response mode or rather a simple harmonic of the primary θ peak. Its existence, however, is consistent with reports of a stable spectral peak in this range in data acquired from the hippocampus (Boudreau, 1966; Holsheimer & Feenstra, 1977). The low frequency peak at 1.2 Hz is delimited much more tenuously, since at this frequency only one half of a complete cycle exists in the (averaged) data sequence.

Oomura et al. (1967) reported that both the initial 75 msec suppression and two successive excitatory peaks attained statistical significance in their temporal plots. If wave periods are extrapolated from these points and from the initial suppression, θ range activity is suggested. Thus, the primary spectral peak is a frequency correlate of the statistically delimited temporal oscillations of the VMH unit response.

Theoretical considerations also support the validity of the θ peak. The synchronizing properties of hippocampal inhibition has already been detailed. The ubiquity of hippocampal inhibition after afferent bombardment, the activity of septal bursting units and the richness of the anatomical interconnections between limbic and hypothalamic sites make θ mode responses highly probable.

Finally, given the fact of rhythmicity in the nervous system, the suggestion of a single spectral peak to account for complicated temporal data has the advantage of being the least tortuous explanation. The statistical structure of patterned activity at a cellular level and the organization of the gross EEG are likely to at least partially converge when studied in this fashion.

Hippocampal Theta

The electrical activity of the mammalian hippocampus may be divided into two traditional categories according to its synchronized or desynchronized structure. The synchronized state of the hippocampus is characterized by its higher amplitude fluctuations and its relative confinement to the 4-8 Hz θ band. Although strongly synchronized activity often exceeds the frequency limits of θ, the term will be maintained here for historical purposes. Desynchronized hippocampal activity may appear as low voltage fast activity, as in the corresponding neocortical pattern. It also may take the form of large amplitude irregular activity with a predominance of activity well below the θ range (Vanderwolf, Kramis, Gillespie & Bloom, 1975).

The classically defined arousal response of the neocortex is desynchronization. In early studies performed with the rabbit, any novel sensory stimulus capable of producing neocortical desynchronization was also found to lead to hippocampal θ (Green & Arduini, 1954). For this reason, the θ rhythm became known as the activation pattern of the hippocampus. This linkage with neocortical activity was also found to occur in sleep. In paradoxical sleep, in which rapid eye movements (REMs) occur, these signs of activation reappear (Jouvet, 1969).

The existence of such obvious EEG modes suggests a functional correlate. Before such relationships may be explored, however, the electrographic phenomenon itself must be clearly delimited. The hippocampal θ pattern is derivative of its anatomical substrate. Its form is largely defined by the properties of the septal afference and the intrinsic response mechanisms of the hippocampus.

Generators of Theta

In delimiting the regional substrate of θ in the hippocampus, Winson (1976) made use of a particularly straight-forward approach. A single recording probe was incrementally plunged through the dorsal hippocampus while the EEG was recorded. The θ patterns recorded during such vertical penetrations through the dentate gyrus of the rabbit exhibited a single amplitude peak. This peak occurred at the hippocampal fissure near the most apical portions of the CA1 pyramids. The fissure itself was not clearly defined by this method. A null point within the stratum radiatum was also found, while a relatively constant amplitude θ was recorded from the alveus into the pyramidal cell layer. This profile has been found in REM sleep, during sensory stimulation or free movement (Winson, 1976), as well as after curarization (Green, Maxwell, Schindler & Stumpf, 1960).

Winson referred to it as a Type 1 θ profile.

Winson also explored the phase properties of the intrahippocampal θ pattern in the rabbit. Records of θ obtained simultaneously from fixed electrodes in the alveus and the dentate gyrus were 180° out of phase. The record from a small moveable probe was found to closely reflect the timing of the alvear reference at loci dorsal to the amplitude null. In the vicinity of the amplitude null, ventral movement of the probe was associated with a rapid shift in phase. After this narrow zone was crossed, the phase properties of the dentate reference were present.

In the curarized rat, θ is difficult to elicit. While visual and auditory stimulation are not generally effective, a θ pattern may be pharmacologically induced after treatment with the anticholinesterase eserine (physostigmine). A more "behavioral" approach is the use of rotary stimulation (Winson, 1976). A Type 1 profile is found under these circumstances.

In the undrugged, freely moving or REM sleeping rat, the θ profile differs from the Type 1 pattern (Winson, 1975; 1976). Instead of a null point, θ amplitude persists throughout the stratum radiatum phase shift zone. Instead of a single marked amplitude peak near the fissure, a pair of peaks is found. These peaks lie in close proximity to the projection cell layers of the two fields. This Type II profile suggests the existence of two phase inverted generators. While the linkage between these generators is generally a tight one, a partial separation may appear after seizures (Winson, 1975).

Feenstra and Holsheimer (1979) examined θ depth profiles in urethane anesthetized rats using spectral analysis techniques. At peak θ frequencies, high coherence values were found between the CA1 and dentate generators. Amplitude maxima were reported to occur near the CA1 projection cell layer and the hippocampal fissure. Phase reversals were detected in the stratum radiatum of CA1 and, in some cases, in the molecular layer of the dentate. At twice the peak θ frequency, coherence values were again high. Phase profiles for this harmonic were essentially identical to that for the θ peak. These investigators viewed their data as suggestive of the local generation of sychronous effects.

There is evidence that θ in at least some of the higher cortical fields of the limbic lobe may be of intrinsic origin. While Gerbrandt, Lawrence, Echardt and Lloyd (1978) reported evidence for a mere passive electrotonic spread of θ to the dorsal neocortex, Feenstra and Holsheimer (1979) reported θ amplitude peak and phase reversal point within the cingulate cortex. Mitchell and Ranck (1980) reported evidence for the local generation of θ in both superficial and deep lamina of the entorhinal cortex. It is of interest to note that a suggestive correspondence with anatomy again exists.

In the entorhinal cortex, the deep θ is similar in phase and shape to CA1 θ, while the phase relations of the superficial layer corresponds to those of the dentate generator.

There may be regional differences in the θ generating properties of the hippocampus. Green and Rawlins (1979) made use of urethane anesthetized rats in which the overlying neocortex had been ablated. Theta was elicited by the delivery of .1 msec pulses to the rostral reticular formation at 50 /sec. Data obtained from a stationary electrode placed on the middle of the exposed alvear surface of the dorsal hippocampus acted as a comparison record, against which data derived from a moving microelectrode probe could be assessed.

In general, superficial (CA1) θ could be readily detected unless the recording site was within 1 mm of the fimbria. In fimbrial loci, the amplitude of the EEG decreased while its frequency composition increased to well beyond the θ range. In the other regions, movement towards the subiculum generally led to a decrease in θ amplitude. Movement along the axis of the horn into more temporal locations caused an enhancement of θ. Activity in the deep (dentate) generator did not share these regional properties.

The crosscorrelation of surface probe EEG with that obtained from the reference showed a significant decrease with spatial displacement in any direction. This effect was most marked with movement along the fimbriosubicular dimension. Crosscorrelations of θ from deep stationary and moving probes were characterized by high magnitudes ($\geq$ .88). While no changes could be detected with fimbriosubicular displacements, a small, statistically significant drop occurred at both septal and temporal extremes.

Green and Rawlins (1979) also examined phase properties along these spatial dimensions. At rostral extremes, both generators were found to lag central regions by about 55°. In the deep generator, θ from medial sites was found to lead the reference. During penetrations for depth profiles, the phase inversion appeared to occur through a successive lead of depth over surface records. Despite the regularities of their phase characteristics, the two generators could be uncoupled. Mechanical stimulation of the alveus was capable of abolishing surface θ without affecting deep θ. In one case, the deep generator only produced a fully-developed θ after the surface generator had been operating for about 10-20 sec. After stimulus offset, the deep generator continued producing θ without reduction, despite an amplitude decrease in the surface record.

When one considers the powerful projection of the medial septum onto the CA3 field, it might be assumed that θ would be generated in this field in a consistent, reproduceable fashion. Unfortunately, in the Green and Rawlins study of the urethane anesthetized rat, clear θ in field CA3 could only be detected when cerebrospinal fluid was in contact with the electrode top. They viewed their data as having a better fit to the neuroanatomy of the perforant path system, rather than the septal projection system. Bland, Andersen and Ganes (1975) failed to detect θ in field CA3 of the urethane anesthetized rabbit. A weak θ was found in the stratum oriens of field CA3 in the urethane anesthetized rat by Bland and Whishaw (1976).

The existence of θ and its purity must be preserved as independent problems to be explored. The ability to record some form of θ activity from field CA3 in the unanesthetized rat has not been seriously disputed. While some investigators have noted that field CA1 placements are excellent for obtaining θ without appreciable fast activity (Kurtz & Adler, 1973), Winson has not mentioned any difficulty in determining phase properties in field CA3. With penetrations lateral to the dentate, the phase shift occurs more slowly and is complete only when the thalamus is reached. Vanderwolf (1969) also failed to recognize field CA3 as being an inadequate site for recording θ. Likewise, Ranck (1975) has published the corresponding unit and slow wave data from the same CA3 electrode. This record also shows a clear θ rhythmicity. In the curarized rabbit, Petsche and Stumpf(1960) noted that the θ rhythm reached its maximum amplitude in fields CA3-4.

Sleep Correlates

The states of sleep are known to affect hippocampal and neocortical electrical activity. In the early stages of sleep slow waves come to predominate the neocortical EEG. The hippocampal pattern at this stage is also dominated by high amplitude irregular activity (Winson, 1975). In REM sleep, hippocampal θ is strong and regular, while the neocortex exhibits a low voltage fast pattern (Jouvet, 1969). Because these clearly delimited EEG modes alternate spontaneously in relatively immobile subjects, the influence of the sleep-waking continuum on hippocampal activity has been examined by a number of investigators. These findings are relevant to hippocapal function, the origin and form of its EEG, and its relationship to lower structure.

The now classic "wet" physiological model for sleep as presented by Jouvet (1969) requires three keys for the induction of paradoxical sleep. Two of them are serotonin and norepinephrine, which have been linked with their presumed anatomical origins in the raphe nuclei and the locus coeruleus, respectively. The third key is acetylcholine. Even without acknowledging the likelihood of a cholinergic septal involvement, important changes in the activity of hippocampal neurons should be expected during sleep. Slow wave sleep has been reported to lead to an increase in serotonin metabolism and an increase in dopamine concentration in the hippocampus, but not the neocortex of the cat (Kovacevic & Radulovacki, 1976). Since the hippocampus has been found to be capable of influencing the responsivity of lower regions to sensory stimuli (e.g., Vinogradova, 1975), such activity changes may reveal the nature of its relationship to other portions of the brain.

Hippocampectomy in the cat has been found to decrease the total time and episodic duration of sleep, as well as both its slow and fast wave phases (Kim, Choi, Kim, Kim, Kim, Park & Ahn, 1975). Consistently, the rate of incidence of the fast wave stage (paradoxical sleep) was decreased as well, although the incidence of slow wave epochs was increased. Mays and Best (1975) reported that the activity of 75% of the units of the rat hippocampus was altered following the presentation of a tone stimulus that aroused the subject from sleep, as compared with 18% when the subject was already awake. While affected units of the dentate gyrus were all inhibited, 36% of the affected units in field CA1 increased their activity.

Unit studies. Olmstead, Best and Mays (1973) found that while units of the regio superior were at their lowest rates of activity during paradoxical sleep, units of the regio inferior and the dentate gyrus were at their most active level in this state. It is conceivable that the patterns of the aminergic innervation of the horn are related to these differences. While both amines terminate throughout field CA3 and most densely outline the lower border of the granular layer, serotoninergic terminals are also extremely dense in the region of the perforant path in CA1. The cholinergic-septal projection terminates in layers both above and below the projection cells of the regio inferior and dentate fascia, but primarily in the subpyramidal portions of CA1. This suggests that the cholinergic innervation may more readily account for this pattern of unit activity.

Ranck (1975) has examined the unit activity of the hippocampus of the rat in both sleeping and waking states. Two distinct categories of spontaneous activity were found to be of relevance. The first category defines "θ-cells" and are characterized by a burst pattern of discharge corresponding to the ongoing slow wave activity. These units were recorded in the layers of the projection cells as well as the surrounding layers. In the dentate gyrus, no θ-cells were detected in the molecular layers, and most were found in the hilus. In CA3, θ-cells were recorded only in pyramidal and suprapyramidal layers. In CA1, where the largest number of θ-cells were recorded, most were found in the strata oriens and virtually all were in or below the stratum pyramidale. Ranck noted that these concentration gradients reflect the prevalence of large interneurons in the laminae of these regions. While θ-cells accounted for only about 6.5% of the units encountered, their possible link to the septal projection system is obvious.

Non-θ cells accounted for the bulk of the units recorded in the rat hippocampal formation. Virtually all of these could be recorded only in the vicinity of the projection cell layers or in the hilus of the dentate fascia. The most characteristic non-θ cell was the complex spike cell, named for the generation of complex spikes, i. e., brief burst of action potentials in which subsequent spikes are of different amplitudes, generally taking the form of a decreasing series. In contrast to the regularity of firing in θ cells, complex spike cells were quite irregular, with extremely slow average firing rates.

During slow wave sleep or "non-θ" ("automatic" or consumatory) waking behaviors, θ-cells tended to fire at their lowest rates. Firing rates increased in paradoxical sleep, reaching a maximum in phasic episodes, during which gross θ activity was marked. During θ associated behaviors ("voluntary" or appetitive) in the waking state, activity was at a level between those attained in the two paradoxical sleep phases.

Except for the slow wave stage of sleep or specific behavioral situations in the waking state, Ranck found complex spike cells to be relatively quiet. Some of them fired at times during paradoxical sleep in an irregular, highly unpredictable fashion as well. During slow wave sleep, these units usually held clear phase relations with the ongoing (slow wave) activity. Thus, the activity of complex spike cells during sleep is essentially a slow wave phenomenon, while θ-cell activity is characteristic of the paradoxical phase. A possible correlate of this is the increased spiking at foci in mediotemporal structures reported in epileptic humans during slow wave sleep (Mayanagi, 1977).

Since the activity of complex spike cells tends to be "released" during slow wave sleep, the specific waking behaviors associated with their activity may be relevant to the study of the hippocampal relations with other sites. Ranck (1975) reported that some of these units, particularly those in the dentate fascia, fire in a consistent fashion during the execution of some orienting or approach behavior ("appetitive" cells). Other units, recorded most frequently in the CA3 field, were responsive during specific consummatory responses as well as during the associated (well-learned) appetitive behaviors ("approach-consummate" cells).

In field CA1, the absence of a specific goal object ("approach-consummate mismatch") was found to be the most characteristic stimulus for the generation of complex spikes. Such conditions include, for example, proximity to the location of an "expected" water bottle when the bottle is missing. It may be speculated that the localization of such "frustrative" (non-reward) units in more "cortical" aspects of the hippocampal allocortex are related to the subicular origin of the medial corticohypothalamic tract in the rat. Interestingly, in the pre and parasubiculum, complex spikes were not detected. Instead, highly specific θ-cells were found, e.g., units that fired for 1-3 sec if and only if the rat oriented to food ("specific orient" cells).

Cortical throughput. The trisynaptic efficiency of the perforant path system has been found to vary with changes of state. Winson and Abzug (1977) examined the response of field CA1, the dentate gyrus and the entorhinal cortex to stimulation of the perforant path system in the region of the angular bundle. Using rats as subjects, dentate recordings were made in both the molecular layer and in the vicinity of the granule cell layer, allowing estimates of the synaptic and action potential responses of cell populations.

For a given stimulating current, the dentate synaptic response was found to decrease in amplitude with sleep. The response recorded at the cell body layer was in the opposite direction, resulting in an increased transmission with sleep. This is presumeably due to a shift in the excitability balance toward excitation in the states of sleep.

The population response generated in the vicinity of the projection cell layer of CA1 shared the increased efficiency of the dentate gyrus in slow wave sleep. The response was clearly not a simple transfer of the already enhanced activity of the latter field, since the response in REM sleep was not enhanced. Thus, slow wave sleep appears to be the optimal state for the transmission of perforant path information to the CA1 field. This corresponds well with Ranck's finding of maximal complex spike activity in this stage of sleep.

The return response to the entorhinal field was also examined. This response, presumeably transmitted by the intercession of field CA3, showed no selectivity for sleep stage. The response for both stages was enhanced. Winson and Abzug therefore suggested that the differential effect noted for CA1 may have a local origin.

A recent study by Marczynski, Burns and Marczynski (1980), in which motionless, unrestrained cats were used, has indicated that the structure of the temporal patterning of unit discharges within the hippocampus is quite stable for any given unit. In slow wave sleep, these patterns are degraded to a form statistically indistinguishable from randomness. During REM sleep, there is a greater tendency for units to share a common pattern than during quiet wakefulness. Even in the human, the REM stage of sleep is characterized by an increased synchrony between EEG records obtained from widespread areas of the brain (Moiseeva, 1979). Other investigators, however, have reported that the crosscorrelation of hippocampal unit discharges is minimal in REM sleep or behavioral arousal, reaching its maximum in slow wave sleep (Noda, Manohar & Adey, 1969).

It is possible that enhanced activity and enhanced information processing are at least partially separable.

If a regulating system is operating in a state characterized by enhanced background noise, its signal processing characteristics may clearly be affected. Since the distinction between signal and noise in the normal activity of the hippocampus in any state is far from clear, we must merely note that hippocampal activity is peculiarly affected by the slow wave stage of sleep.

Serotonergic effects and the raphe nuclei. Brain serotonin levels are known to be subject to a diurnal pattern of variation. These levels appear to be inversely related to seizure susceptibility (Schreiber & Schleisinger, 1971). The evidence suggesting the importance of serotonin in the generation of slow wave sleep is quite strong, although largely correlational (Jouvet, 1969). The exact nature of this role is still not clear. Studies on the effects of direct microelectrophoretic application of serotonin to cells of the hippocampus have generally indicated an inhibitory influence on hippocampal unit activity, despite the occasional appearance of excitation (Straughn, 1975). The excitatory effect, when it appears, is capable of progressing to the extreme of a seizure discharge.

Lesions of the median raphe of the rat, but not the dorsal raphe, reportedly lead to behavioral effects that are similar to those obtained after the administration of parachlorophenylalanine (PCPA), a tryptophan hydroxylase block, or after large combined lesions of the raphe (Geyer, Puerto, Menkes, Segal & Mandell, 1976). These effects include hyperactivity in a novel environment and throughout the day/night cycle, an enhanced startle response, and perseveration of incorrect responses in a "Y"-maze. The locomotor hyperactivity after either PCPA or median raphe lesions has been prevented by prior aspiration of the dorsal hippocampus (Jacobs, Trimbach, Eubanks & Trulson, 1975). Curiously, Sheard and Aghajanian (1968) reported that stimulation of the caudal midbrain raphe can prevent the habituation of the startle response to sensory stimulation without leading to hyperactivity. This effect could be blocked by pretreatment with PCPA.

Hippocampal stimulation has been found to have a predominatly excitatory effect on units in the midbrain raphe (Vinogradova, 1975). These phasic excitatory effects appear with short latencies (15-25 msec), after which diffuse, tonic effects continue. Lateral regions of the midbrain reticular formation show predominantly inhibitory effects after a longer latency (20-40 msec). Tonic effects induced in midbrain sites may appear as an initiation or suppression of regular, high frequency (30-60 /sec) "pacemaker-like" activity of a non-bursting type. Such tonic activity changes often persist after the termination of the stimulus. Hippocampal volleys have further been reported to decrease the reactivity of most units of the midbrain reticular formation to sensory stimuli (Kitchigina & Vinogradova, 1974).

Enhancement and suppression of responsivity are both observed in raphe units.

Paradoxical sleep correlates. The phase of sleep known as paradoxical sleep is associated with the initiation of tonic processes that lead to forebrain activation and the elimination of muscle tone (Jouvet, 1969). The most characteristic phasic event of paradoxical sleep is the ponto-geniculo-occipital (PGO) wave, which occurs in close temporal relation to REMs. Although cats have generally been used in sleep experiments, waves similar in form and onset to PGO waves have been reported in the rat from the locus coeruleus and the dorsal parabrachial nucleus (Farber, Marks & Roffway, 1980). Electrode placements in the reticular formation underlying the locus coeruleus show no such waves.

Chu and Bloom (1973) reported that units of the locus coeruleus of the cat tend to fire slowly during periods of slow wave sleep or quiet wakefulness. In the mean, firing rates increase in paradoxical sleep. Discharge patterns become organized into bursts in over half of the units and are associated with PGO spikes or REMs. Units of the pontine gigantocellular tegmental field of the cat have been found to increase their discharge rate hundreds of msec before the onset of PGO waves (Pivik, McCarley & Hobson, 1977). The specificity and time locking of this effect was not indicative of a PGO generator. Another class of unit of interest has been recorded in a zone from the posterior border of the brachium conjunctivum to the dorsal portions of the central tegmental field (McCarley, Nelson & Hobson, 1978). More lateral portions of this zone maintain the same spatial relationship to the brachium conjunctivum. These units exhibit the timing and specificity required for a generator of the PGO waves.

The behavioral correlates of the units of the pontine gigantocellular field are of interest in relation to questions of descending limbic control. In the unrestrained cat (Siegel & McGinty, 1977), these units have been found to respond at short latency to somatic, auditory or vestibular stimulation. Many units are multimodal and exhibit a rapid habituation to repeated stimulation. Despite these sensory properties, the closest correlations are in the motor domain. Motor correlates were found to be adequate for the description of sensory properties as well, since unit responses were produced only when movement occurred. These effects suggest the possible significance of the motor substrate to REM sleep, at which time the voluntary musculature is functionally blocked.

The effect of the application of norepinephrine to the hippocampus on unit activity has been reported to be a slow, weak depression of firing (Straughan, 1975). The administration of d-amphetamine and the electrical stimulation of the locus coeruleus of the rat have both been found to lead to a similar inhibition of spontaneous activity (Segal & Bloom, 1976a). The effect of locus coeruleus stimulation has been found to be suceptible to antagonism by α-methyltyrosine (blocks DOPA synthesis from tyrosine) as well as 6-hydroxydopamine (a selective neurotoxin).

At a neurobehavioral level, the inhibition of hippocampal units by loud auditory stimuli has also been demonstrated (Segal & Bloom, 1976b). This inhibition has been found to be suceptible to adrenergic antagonists as well. When such sensory responses are allowed to habituate, stimulation of the locus coeruleus leads to their dishabituation.

The noradrenergic projections of the locus coeruleus have been implicated in the generation of the REM phase of sleep (Jouvet, 1969). A rebound of this stage of sleep after its (relatively) selective disruption reportedly leads to an increase in the turnover of norepinephrine (Pujol, Mouret, Jouvet & Glowinski, 1968). Seizures, such as those arising from electroconvulsive shock, have a similar effect (Kety, Javoy, Thierry, Julou & Glowinski, 1967). Since locus coeruleus stimulation has reinforcing properties (supports self-stimulation behavior; e.g., Segal & Bloom, 1976b), a relationship of the noradrenergic system to mood and motivational states is likely.

Brainstem stimulation and hippocampal theta. Macadar, Chalupa and Lindsley (1974) probed the brainstem of acute (flaxedil) cats with electrodes delivering a 100 Hz, 5-7 V stimulus. The effect of this stimulation on the EEG pattern of the dorsal hippocampus was then observed. Theta rhythm could be evoked from sites in the ventrolateral periaqueductal gray and the tegmentum of the midbrain, as well as the locus coeruleus and the nuclei reticularis pontis oralis and gigantocellularis. The only sites from which desynchronization could be evoked were the raphe nuclei and the nucleus reticularis pontis caudalis. The influences were bilateral.

The θ rhythm induced by the stimulation of effective sites apparently differs from site to site. Thus, while the ventral periaqueductal gray and midbrain tegmental sites led to regular 3.2 Hz and 3.5 Hz patterns, respectively, the nucleus reticularis pontis oralis site led to a 4.2 Hz pattern (Macadar et al., 1974). Locus coeruleus stimulation led to a 5.5 Hz θ rhythm. The only one of these regions leading to a continued rhythmic pattern after the termination of the electrical stimulus was the nucleus reticularis pontis oralis. There, post-stimulus activity declined to 3.2 Hz. In the medial hypothalamus, a less intense stimulus was capable of eliciting a lower frequency pattern than that generated by stimuli of 5 V or more (Anchel & Lindsley, 1972). This rhythmicity was followed by somewhat slower regular activity after the termination of the stimulus.

In a similar experiment in which anesthetized rats were examined, Vertes (1980) reported a somewhat different brainstem distribution of θ generating sites. Theta was found to be generated within approximately the medial third of pontile tegmentum, including both the oral and caudal reticular zones. Dorsal stimulation sites in the vicinity of the locus coeruleus were not capable of synchronizing the electrographic record. In contrast, pontis caudalis stimulation led to a distinct θ rhythm. In general, medial sites were more effective than lateral ones. Stimulation of the medial longitudinal fasciculus was quite effective in generating high frequency θ. At midbrain levels, θ generation occurred with stimulation of most of the tegmentum. Desynchronization occurred after stimulation of the median, but not dorsal, nucleus of the raphe.

Glucocorticoids and Hippocampal Function

Due to the moderative influences of the hippocampal formation on the reticular formation (e.g., Vinogradova, 1975), the presence in the regio superior of units selectively responsive to the lack of reinforcement (Ranck, 1975) and the evidence of a direct (ventral) subicular projection in rodents to the medial preoptic-anterior hypothalamic region and the ventromedial and arcuate nuclei of the hypothalamus (Swanson & Cowan, 1975), one might expect the hippocampus to be related in some relatively direct manner to the stress response of the organism.

It has been reported (Kim, Choi, Kim, Kim, Park, Ahn & Kang, 1976) that hippocampectomy increases the susceptibility of rats to gastric ulcers, whether they are subjected to restraint stress or merely housed under usual conditions. An effect on the pituitary-adrenal axis is therefore quite likely. This finding is in contrast to the suppression of restraint-induced ulcers after damage to medial amygdaloid regions or the ventral amygdalofugal system (Henke, 1980). Stria terminalis lesions, however, also led to an increased severity of stomach pathology.

The hippocampus has been shown to have a remarkably specific capacity to take up and bind labelled corticosteroids. The corticosteroid uptake potential of the hippocampus is demonstrable in adrenalectomized rats, but it is masked by its limited capacity in unaltered subjects (McEwen, Zigmond, Azimitia & Weiss, 1970). This potential is much greater in the hippocampal formation than in the amygdala, other parts of the cerebral cortex, or the hypothalamus. In keeping with the close relationship of the septum with the hippocampus, septal uptake is moderately high, although less than that of the hippocampus itself. This binding potential was reported to be more pronounced and more specific for corticosterone in the subcellular fraction containing cell nuclei than in the cytosol fraction. Muhlen and Ockenfels (1969) reported an increase in the size of pyramidal cell nuclei and nucleoli after gluococorticoid administration in the guina pig hippocampus. Curiously, after either glucocorticord administration or environmental stress, a number of pyconotic cells were found as well.

Within the hippocampus of the adrenalectomized rat, systemic (tritiated) corticosterone accumulates primarily in the stratum pyramidale of the horn and in the granular layer of the dentate fascia (McEwen, Gerlach & Micco, 1975). The boundaries of this uptake capacity are so sharp that the projection cell laminae are clearly delimited in autoradiograms. The most marked labelling occurs in the dentate gyrus and the regio superior. Labelling density in the stratum pyramidale of CA2, CA3 and CA4 is somewhat less marked. Although dorsal portions of the hippocampal formation have been reported to take up somewhat more label than middle or ventral portions, no statistically significant differences have been found along this axis (McEwen, Weiss & Schwartz, 1969).

The influence of the reticular formation on adrenocorticotropic hormone (ACTH) released by the pituitary appears to depend on circulating steroid levels. Taylor (1969) reported that stimulation of the physiologically defined reticular activating system facilitated ACTH release when steroid levels were low, but either inhibited or had no effect on release when levels were high. Dorsal hippocampal units have been reported to decrease their discharge rates after the systemic administration of corticosterone (10-40 min latency; 2 hr duration) in both urethane anesthetized and awake, freely moving female rats (Pfaff, Silva & Weiss, 1971). These effects were found in both intact and hypophysectomized subjects. Behaviorally, both cortisol and environmental stress have been reported to inhibit alternation behavior in the rat, with permanent effects being noted after early exposure (Douglas, 1975).

The administration of ACTH apparently affects the activity of hippocampal units in a manner opposite that of corticosterone (Pfaff, Silva & Weiss, 1971). These effects have a shorter latency (3-10 min) and a shorter duration (25-50 min) than those reported after corticosterone. Kawakami, Koshino and Hattori (1966) have reported an increase in fast wave activity in the hippocampal EEG after ACTH.

The effect of hippocampal stimulation and ablation on the pituitary-adrenal axis has been reviewed by Van Hartesveldt (1975). Influences on the diurnal variations of this hormonal system suggest that the hippocampus is not essential for its rhythmicity, although a number of studies suggest at least temporary changes in the amplitude and/or phase of the rhythm may accompany hippocampal manipulations. In general, the only condition in which a predictabale effect has been elicited by stimulation was in response to stress. Basal level studies have shown variable effects. Thus, stimulation at low rates (e.g., 10-40 Hz), but not high rates (e.g., 120 Hz), have been found to decrease the stress induced rise of activity in the hormonal axis. Hippocampal ablation or fornix section, however, have led to conflicting results. A moderative role, rather than a strictly facilitative or inhibitory one, probably typifies the hippocampal influence on neuroendocrine processes.

Hippocampal EEG and Behavior

The activity of the hippocampus of the waking, behaving subject reflects its anatomical substrate. The domain of its influence is a dual one, reflecting both cortical and subcortical processes. Even at its simplest level, such processes may be expected to overlap sensory, motor and motivational domains. Learning is related to these functions in the most obvious incidental fashion, although a more essential contribution is at very least a possibility. These domains must be simultaneously kept in mind when the hippocampus of the waking subject is examined.

Evoked potential correlates. The averaged evoked potential recorded at the molecular layer of the dentate gyrus in response to an auditory stimulus has been explored in the rat by Deadwyler, West and Robinson (1981). The two negative waves composing this response were found to be separable on the basis of both their localization and their informational significanace. The early component (N_1) has a 20 msec latency. Its maximum amplitude may be recorded in the outer molecular layer and a sign reversal appears within the hilus. This component is present in naive subjects, but diminishes or disappears during the learning of a single cued operant. It reappears in an enhanced form during extinction. Its correlate may therefore be tenatively described as an unexpected or unpredictable feature of the stimulus. Since bilateral lesions of the entorhinal cortex eliminate this response, it presumeably reflects a response of the perforant path system.

The N_2 response occurs after a latency of roughly 50 msec. It persists after lesions of the entorhinal cortex and is maximal in amplitude at deep portions of the molecular layer, a pattern consistent with the commissural projection system. The N_2 response does not occur in a naive subject. It develops only with conditioning, and diminishes during extinction. Its correlate may be tenatively described as the behavioral significance attached to the stimulus. After medial septal lesions, N_2 appears with a particularly large amplitude even in untrained animals. Extinction also fails to substantially diminish this component in septal subjects. It may therefore be assumed that the septal projection is responsible for the normal suppression of N_2. This influence is normally overridden by learning.

In the epileptic human, high voltage, long latency hippocampal potentials have been reported to increase in amplitude with infrequently delivered stimuli (Halgren, Squires, Wilson, Rohrbaugh, Babb & Crandall, 1980). The amplitude of these responses, their occasional polarity inversion and their correspondence with unit records suggest a local origin. A possible contribution to the late potentials of the response obtained from cortical and scalp derivations has also been suggested. This conclusion has recently received support from a magnetic field study by Okada, Kaufman and Williamson (1983). It appears that similar information may be represented in the EEG of human and rat hippocampi.

Behavioral correlates of hippocampal function. If the EEG of the hippocampus were a simple inverse of that obtained from the neocortex, a rudimentary hypothesis related to the reciprocity of these regions might be suggested. Unfortunately, the θ response of the hippocampus has been found to vary in its correlates depending on the experimental paradigm and the species under investigation. Green (1960) reported that it was virtually impossible to record θ from the monkey hippocampus unless the animal was emotionally agitated. Vanderwolf (Vanderwolf & Heron, 1964; Vanderwolf, 1975) studied hippocampal rhythmicity extensively in the free-moving rat. The general conclusion to be derived from these investigators is that the appearance and magnitude of θ is distinctly linked to the performance of virtually any nonautomatic ("voluntary") behavior by the rat. The reliable generation of θ in the waking cat may be even more selective, requiring scanning eye movements (Coleman & Lindsley, 1975).

The search for neurobehavioral correlates of the θ pattern has generated a volume of studies and a proportionate number of hypotheses. The domains in which hippocampal claims have been laid likewise scan the neuroscience subfields, from sensory to motor realms. An overview of the hippocampal literature leaves one with the impression of either a ubiquity of function or a vestigial correlation with behavior that is largely under the control of other regions. It is not unlikely that both of these extremes are equally valid in some cases.

If the medial septum supplies a cholinergic input to the hippocampus and is responsible for the generation of its θ rhythm, an effect of cholinergic agonists and antagonists on the hippocampal EEG would be expected. Vanderwolf has divided the rhythmic slow activity of the hippocampal EEG of the rat into an atropine resistant (7-12 Hz) and an atropine sensitive (5-7 Hz) component Vanderwolf et al., 1975). The resistant, faster activity was found to be suceptible to suppression during ether anesthesia and occurred when and only when "voluntary" (appetitive) behavior occurred. The atropine sensitive component was found to be released during ether anesthesia and was not as reliably linked with behavioral measures.

The slower vs. faster dichotomy may have some generality. Eddy, Bremner and Thomas (1971) suggested that the 4-5 Hz component of the hippocampal EEG of the cat was related to a reticuloseptal input. The 6-7 Hz activity was not found to be related to this route and therefore was presumed to reflect other, probably cortical, influences. Their techniques made use of spectral analysis of the hippocampal EEG as affected by stimulation of the midbrain reticular formation (100 HZ stimulation of the nucleus of Bechterev at a point 2 mm lateral to the midline) and cryogenic lesions of the medial septum of acute cats.

Coleman and Lindsley (1975) reported a shift from 3.5 HZ to 4.5 Hz θ when an alert cat orients and "looks attentively". An even higher frequency (6.5 Hz) was found to accompany continuous slow scanning behavior. Rhythmic, 5 Hz activity accompanied the REM phase of sleep. Lindsley's group (Macadar et al., 1974) has also reported a 5.5 Hz θ after stimulation of the locus coeruleus. In the rat, Vertes (1980) was capable of evoking θ of widely varying frequency and regularity from the stimulation of adjoining pontine sites. The θ activity so elicited spanned both of Vanderwolf's frequency categories. Thus, while θ may spontaneously vary in a bimodal fashion under certain conditions, it is by no means clear that a qualitative shift in its anatomical substrate is essential for the production of these patterns.

A cholinergic mechanism has been implicated in a number of behaviors of relevance to hippocampal function. The habituation of exploratory behavior in the rat appears to be susceptible to attenuation by the anticholinergic, scopolamine (Williams, Hamilton & Carlton, 1975). At the time a rat is 15 days old (prior to the completion of dentate neurogenesis) exploratory activity has been reported to have a lower incidence than in adults (36 days old) and not to be subject to habituation at all (Williams et at., 1975). Hippocampal rhythmic slow activity induced by forced running or systemic physostigmine has itself been found to be susceptible to elimination by means of either systemic scopolamine or lesions of the medial septal nucleus (Teitelbaum, Lee & Johnnessen, 1975).

Spontaneous alternation behavior in the rat has been linked correlationally to the postnatal development of the hippocampal mossy fiber system (Douglas, 1975). It was described by Douglas as being "as specifically cholinergic as it is hippocampal". The approximate age at maturation of the "hippocampal-cholinergic inhibitory system" was estimated by Douglas to be 25-30 days in the rat.

Grastyan (Grastyan et al., 1959) reported studies in which cats were allowed free movement both within and without a learning paradigm. The hippocampal slow wave response was quite reliably linked with overt attentional or orienting responses. While θ could be recorded during the early stages of learning, overlearning led to its elimination. Bennett (1970; 1975) has confirmed the decay of this pattern with learning and maintained an attentional correlate for the θ state.

It was noted quite early that sensory stimulation alone is not enough to guarantee the generation of θ, even in the curarized rabbit. Green and Machne (1955) reported that an interstimulus interval of about a half a minute was required to maintain the responsivity of hippocampal units. In the case of the macroelectrode record, a delay of more than 10 sec was often required for responsivity to return.

Vinogradova (1975) reported a series of studies of hippocampal unit activity conducted with unanesthetized rabbits. In field CA3, habituation to sensory stimulation was reported to be quite rapid. Any change in the timing or intensity of the stimulus could lead to a reappearance of the response (dishabituation). Units of the dentate fascia did not show complete habituation, while units of the lateral septum lost their ability to habituate when the fornix system was sectioned. It was therefore concluded that habituation is a property of the CA3 field itself.

Douglas and Pribram (1966) conducted a lesion experiment in which either amygdaloid or hippocampal tissue was damaged. They viewed their data on learning in the monkey as suggestive of a shift in the functional balance of a paired limbic control system. The moderative or evaluative function of the hippocampus was interpreted as an "error-evaluate" system. The function of the amygdala proposed was a "reinforce-register" process.

Adey's group examined the EEG of the dorsal hippocampus and entorhinal cortex of the cat during performance in a visually guided "T"-maze (Adey, Dunlop & Hendrix, 1960; Adey, Walter & Hendrix, 1961). The hippocampal EEG during waiting records varied widely, with a 3-4 Hz dominant frequency. During approach to the goal box, a narrowly banded 6 Hz activity became dominant. In contrast to Grastyan's findings, these investigators failed to note a response decrement with learning. Through the examination of both the crosscorrelation and the coherence function (standardized cross spectrum) derived from the EEGs of two regions, they observed a shift in an otherwise stable phase pattern between correct and incorrect responses. It was suggested that "integration of information at the cellular level may occur on the basis of these ubiquitous and pervasive wave processes" (Adey, Walter & Hendrix, 1961). A role in the learning process itself was therefore suggested.

It should be noted that Bennett (1971) repeated this experiment in an effort to determine if θ is necessary for correct "T"-maze performance. After the cats had reached a 90% performance criterion, they were injected with scopolamine hydrobromide. Scopolamine severely attenuated the θ response without appreciably affecting performance. In another study (Bennett, 1973), the delivery of this drug directly to the medial septum prior to either original learning or retention trials produced no effect on learning, despite a blocade of θ.

Crowne, Konow, Drake and Pribram (1972) examined the hippocampal EEG of monkeys during learning of go/no-go and delayed alternation tasks. Spectral analysis revealed a tendency to peak or plateau in the 3-5 Hz band. The θ peak increased on no-go trials and during the alternation task, while tending to decrease during go trials. Active hippocampal involvement in the anticipatory organization of response inhibition was therefore suggested.

While the spectral analysis of the hippocampal EEG of monkeys may indicate the level of refinement required for a truly comparative study of this phenomenon, the appearance of θ in rodents is so clearly defined that valuable research is still being conducted using the direct observation of the EEG. By viewing the EEG record, Vanderwolf (1969) correlated the presence or absence of obvious θ activity with the behavior of freely moving rats. Whenever the animal walked, regular 6-12 Hz activity was present from hippocampal records. If "freezing" occurred, in which a rat would abruptly cease movement, irregular slow waves replaced the strongly synchronous θ despite the maintenance of a low voltage, fast pattern of activity in cortical records. If a motionless rat made a slight movement of the head, a brief run of θ usually occurred (about 90% of 1500 cases cited), as well as during isolated limb movements. Vanderwolf plotted the observed probability of activity as categorized by its frequency during the occurrence of walking, rearing, head movement and the handling of food. These plots show that regular θ is almost universal during such behaviors, exhibiting a band limiting between about 6-12 Hz and a marked concentration about specific peak values.

Movement itself is not sufficient for θ to occur. Repetitive movements of the head, limb, jaws or tongue such as occurs during grooming are only accompanied by θ when postural shifts occur as well. While the handling of food was accompanied by a short run of θ, chewing was not. When such behaviors were stopped by exposure to a mild sensory stimulus, slow, irregular activity would generally persist (75% of 282 cases) unless visible movement occurred as well. When restrained, θ only appeared if the rat was struggling, at which time θ of high frequency and large amplitude occurred.

Vanderwolf reported one case in which his waking subjects generated θ without movement (Vanderwolf, 1969). During the performance of an active avoidance response, the intertrial interval was characterized by low voltage, fast activity in the neocortex and an irregular hippocampal pattern. Prior to the performance of the jump response, a period of immobility occurred in which only slight head movements and a tensing of the body were executed. Continuous θ at 6-7 Hz appeared during this time, increasing in frequency to 8-12 Hz by the onset of the jump. After the jump, θ frequency rapidly declined.

The general conclusion drawn by Vanderwolf from his observations is direct, if lacking in restraint. Vanderwolf concludes that those behaviors which may be labelled as voluntary are linked with hippocampal θ. Indeed, the general activity pattern associated with θ may even be necessary for the production of voluntary movement. The hippocampus itself is not, however, the source of some vague homunculus of the will. Records from some thalamic sites also show θ with identical properties despite a markedly smaller amplitude (Vanderwolf, 1969). One might intuit a generalized volitional system, with θ merely existing as a convenient marker for its activity.

While voluntary movement as a potential correlate of hippocampal θ appears to give a reasonable fit to the data derived from the rodent, a closely aligned distinction may overlap this measure. Kurtz and Adler (1973) studied the hippocampal EEG of the male rat during sexual behavior. The distinction that they suggested was between appetitive and consummatory response modes.

During orienting or approach to a female in estrus, 7-10 Hz θ appears. Sniffing of the female by the male is accompanied by θ and occurs in a manner synchronous with this wave form. The EEG becomes irregular upon cessation of the pursuit. High frequency θ slows during the mount, becoming irregular after penetration and withdrawal. While motivational variables are obscured in Vanderwolf's conceptualization, in this form of behavior the linkage is clear.

Neuroendocrinological and anatomical evidence indicates a dual organization of limbic influences in the domain of sexual behavior. The microstructure of the preoptic region has revealed a higher incidence of projections from nonamygdaloid sources onto the dendritic spines of male rats than females (Raisman & Field, 1973). Early castration of males or treatment of females with testosterone propionate has been reported to reverse this pattern. In view of the joint stria terminalis and fornix contribution to the descending physiological projection of the septal region (Miller & Morgenson, 1972), an effective differential suceptibility to hippocampal control is likely.

While the hippocampus appears to be the site of maximal corticosterone binding, estradiol binding in the amygdala markedly exceeds that in the hippocampus (McEwen et al., 1970). Maximal estradiol is concentrated in the hypothalamic-preoptic zone (McEwen et al., 1970). Systemic administration of tritiated estradiol labels cells in the cortical and medial amygdala, the bed nucleus of the stria terminalis, and premammillary and ventromedial hypothalamus, as well as the medial portions of the preoptic area and anterior hypothalamus (Pfaff & Keiner, 1973). Estradiol-concentrating regions related to the hippocampus include the lateral septum, and the diagonal band. Cortical loci include the prepiriform and entorhinal cortices, as well as the most ventral aspects of the hippocampal formation itself.

Stimulation of the vaginal cervix of the rat is capable of blocking ongoing θ recorded from the MFB during exploratory behavior (Komisaruk, 1971). At such times, both exploration and vibrassae movement cease. The relevance of these findings in the domain of sexual behavior to both dual process models of limbic function and movement related θ is obvious.

When the electrographic record of the hippocampus of the rat is locally transformed by an experimentally enhanced suceptibility to seizures, the corresponding behavioral correlates may be compared with those suggested by models of hippocampal function. Taber, McNamara and Zornetzer (1977) reported that while foci in the more cortical regio superior were associated with generalized seizures, those in the regio inferior led to a state in which only simple, automatic and repetitive behavior such as grooming and chewing were produced. These investigations suggest this as an animal model for the human condition of psychomotor epilipsy.

Stimulation and lesion paradigms are common tools for the study of the function of brain structures. A correlate of the lesion technique that directly applies to electrographic measures is the technique of spreading depression. The blocade of hippocampal function in the rat by means of KCl-induced spreading depression has been reported to impair a number of behaviors known to be suceptable to hippocampal lesion. Thus, both spontaneous and learned alternation, spatial reversal and extinction have been impaired by this procedure (Green, 1971). At times, these subjects would stop running for 30 sec or more, at which time breathing would become heavy and shaking might occur. The EEG records at such times exhibited an alternation between seizure and depression patterns.

Spatial correlates of hippocampal function are present throughout the phylogenetic history of this tissue. Bitterman (1965) categorized learning in terms of its similarity to the performance of a normal rat or fish on a number of tasks. Turtles and pigeons, in which a clearly delimited dorsomedial archicortex exists, can perform spatial reversal tasks and will tend to maximize their reinforcement under partial schedules of reinforcement. This is similar to the pattern used by the rat. Fish fail to improve in the reversal of an acquired position preference and distribute their responses to match the probability of reinforcement for a given task.

Neodecorticate rats learn as normal rats in spatial problems, but as fish in visual tasks (Gonzalez, Roberts & Bitterman, 1964). This corresponds well with the results obtained from the normal turtle. The pigeon is capable of reversal learning, but probability matches in visual tasks. Since the ablation of dorsomedial regions of the telencephalon of the chick has been reported to impair reversal learning on a visual problem, the involvement of the hippocampus is again suggested (Benowitz & Teng, 1973). In mammals, spontaneous alternation and spatial reversal learning deficits generally follow hippocampal damage (Douglas, 1975; O'Keefe & Nadal, 1978).

The hippocampus is not merely a primitive transitional field. The persistence and relative growth of the septum and hippocampus with phylogeny (Stephan & Andy, 1970; Andy & Stephan, 1976), the continued origin of dentate granules in ontogeny (Angevine, 1975) and the unique projections comprising the perforant path system all speak for its importance and uniqueness. In the human, the profound disturbances of recent memory and the spatial disorientation attributed to bilateral hippocampal lesions have underscored its importance for decades (Scoville & Milner, 1957; Milner, 1966).

Based on a volume of anatomical and physiological data, O'Keefe and Nadel (1978) have suggested that the convergent influences impinging upon the hippocampus are built into cognitive maps. This mapping function operates by building up "cartoons" of the simultaneous stimuli encountered in the environment (Nadel & O'Keefe, 1974). The proposed mechanism follows the perforant path system in much the same way as Olds (1970) scheme for a temporary memory register. They further proposed that the θ rhythm has a synchronizing function, timing behavior against experience.

In support of their model, O'Keefe and Nadel reported the existence of "place" units in field CA1 of the rat hippocampus which fire maximally when the animal is in a specific location in the maze. While some investigators have reported a close relationship between hippocampal θ and the timing of motor patterns (Semba & Komisaruk, 1978) and sniffing (Komisaruk, 1970; Macrides, 1975), it may well be argued that the generality and regularity of hippocampal θ is inadequate for the timing of all access operations required for such a map. It may be relevant that Winson (1978) reported that while lesions of the medial septum capable of eliminating hippocampal θ in rats also disrupt the performance of a learned spatial task, they do not prevent the later learning of the same task.

Behavioral Correlates of Lateral Hypothalamic Function

The importance of the LH and MFB as a link in the limbic-midbrain circuit is undeniabale from anatomical considerations alone. There are, however, properties of this region that suggest an importance to behavior apart from its role as a transmission line from the limbic forebrain. The best documented of these properties are in the motivational domain.

Possibly the best studied behavioral correlate of LH function is feeding behavior. Electrical stimulation of the LH leads to an increase in eating (Delgado & Anand, 1953), while LH lesions lead to an anorexic state (Anand & Brobeck, 1951; Anand, Dua & Schoenberg, 1955). The MFB system has been found to support high rates of electrical self-stimulation in rats (Olds, 1962), suggesting an important role in the domain of reinforcement. A reciprocity between the rate of such self-stimulation at LH sites and eating after food deprivation has been reported (Hoebel & Teitelbaum, 1962). Electrical stimulation of the LH is itself capable of driving food motivated behavior, even in sated animals (Mendelson, 1966).

Miller and Morgenson (1971) implanted rats with both septal and LH electrodes. With LH stimuli at threshold intensities for self-stimulation, prior septal stimulation significantly facilitated self-stimulation in 11 out of 12 animals. A lead of 5 msec was more effective than 15 msec. With suprathreshold stimuli, self-stimulation was decreased by prior septal stimulation in 5 of 10 subjects, the rest showing no effective change. Of those showing an effect, a 15 msec lead was more effective than 5 msec. Another behavioral relationship between the septum and the LH is exerted by way of two descending limbic projection systems. Stimulation of the dorsomedial septum, associated with the fimbia-fornix system, was found to increase drinking induced by the stimulation of appropriate LH sites (Morgenson, 1973). Ventrolateral stimulation led to a reduction of the induced consumption of water.

The ventromedial hypothalamus is reputed to be related to satiety, since lesions of this region lead to obesity (Hetherington & Ranson, 1942). Its electrical activity, both at gross and unit levels, maintains a reciprocal relationship with that of the LH under varying anesthetic depth and in response to the administration of glucose (Oomura et al., 1967). Even a strong reciprocity in an organized system does not, however, necessarily suggest that separability into component "centers" is possible across all behavioral conditions. From anatomical and electrophysiological considerations, it is clear that medial and lateral hypothalamic zones are themselves components of a diffuse integration and projection system. Since rebound eating can follow periods of electrical stimulation of both the LH (Huston, Ornstein & Siegfried, 1975) and the dorsal hippocampus (Milgram, 1975), feeding mechanisms are apparently accessible from other regions as well. In reviewing the hippocampal literature, Jarrard (1973) has emphasized the motivational character of presumed hippocampal functions.

The controversy over the nature of LH involvement in motivated behavior has been widespread, addressing numerous aspects of the problem. Stomach lesions have been reported after LH damage (Grijalva, Lindholm

Schallert & Bicknell, 1976). The existence of such lesions suggest a possible sensory origin for the aphagia typical in these animals. Turner (1973) has reported the existence of a sensorimotor syndrome after lesions of the LH or amydgala. This syndrome is associated with an inability to orient to or localize contralateral sensory stimuli. As such, it may be similar in form and possibly origin, to that induced by lesions of the substantia nigra in the ventral midbrain (Feeney & Wier, 1979).

Leibowitz (1974) has reported that feeding and drinking behavior may be differentially enhanced or inhibited in hypothalamic zones immediately surrounding the postcommissural fornix by the administration of α or β -adrenergic substances. Self-stimulation at MFB sites has also been shown to have an adrenergic correlate (Stein & Wise, 1969). Gold (1973) suggested that the obesity derived from VMH lesions may be an artifact caused by the incidental damage of noradrenergic pathways. Damage to these pathways has since been reported to cause overeating only at night, rather than throughout the circadian cycle (Ahlskog, Randall & Hoebel, 1975). In contrast, lesions of the VMH increased eating throughout the cycle. The two effects were further found to be additive.

Zeigler & Karten (1974) have suggested that the lateral hypothalamic syndrome may be at least partially caused by the incidental damage to more lateral fibers of passage from the trigeminal system. The aphagia and adipsia after damage of these nearby projections might therefore be considered to be a sensory deficit rather than a motivational one. The meandering of the taste projection system into the far lateral hypothalamus (Norgren, 1976) may also be recalled.

To counter the suggestions of a non-hypothalamic origin of the feeding deficit after LH lesions, Grossman, Dacey, Halaris, Collier and Routtenberg (1978) preferentially produced cell body damage in the LH of the rat by injections of Kainic acid. In this study, histological and neurochemical techniques failed to indicate an appreciable damage to fibers of passage. Degeneration patterns in the lateral septum were consistent with autoradiographic findings after LH injections (Troiano & Siegel, 1975). These animals exhibited an aphagia and adipsia that lasted up to 10 days. Although startle responses were exaggerated, no sensory, arousal, or motor dysfunctions were apparent.

Enhanced behavioral activity due to food deprivation has been found to be related to an increased reactivity to external cues (Sheffield & Campbell, 1954). Food deprivation has been reported to increase hippocampal θ activity in the rat (Ford, Bremner & Richie, 1970). The degraded habituation to stimulus change that occurs in hippocampectomized rats reportedly equates the response patterns of satiated animals with that of food deprived controls (Kamback, 1967). Operated subjects who were also food deprived showed a considerable exaggeration of this pattern. Hyperactivity induced in rats by lesion of the median raphe or the administration of p-cholorphenylalanine, which interferes with the synthesis of serotonin, has been found to be blocked by prior aspiration of the anterodorsal hippocampus (Jacobs et al., 1975).

Within the hippocampus of the rat, field CA3 is the field most clearly linked to the septal interface (Raisman, 1966; Andersen, 1975). Vinogradova's studies have suggested that habituation may occur within this field and as such regulate activity at septal levels. Lesions of the fimbria which primarily sever the septal projections of CA3 replicate a number of the deficiencies of total hippocampectomy (Jarrard, 1976). Specifically, improved shuttle box avoidance has been reported, as has an increase in activity. The enhancement of activity occurs, among other conditions, in response to food deprivation. It is likely that these effects reflect motor predispositions directly accessible from the LH as well.

The resting EEG of the LH has been described qualitatively in the cat (Oomura et al., 1967). It is typified by an abundance of irregular activity of very low frequency. When a 12 hr food deprived cat is exposed to the odor of food, the EEG is changed to a low voltage fast pattern, while reciprocal effects appear in the VMH. When searching for food, the LH again shows this mode of activity, but VMH activity exhibits slow waves only rarely. During feeding, LH activity again tends to be a low voltage fast pattern, while in the VMH a short-lived slow wave pattern appears.

In the rat, the resting EEG pattern recorded from the LH-MFB is also dominated by slow waves (Gilden & Kozakiewicz, 1976). During exploratory locomotion, this activity is replaced by a strong θ (Komisaruk, 1971). A link between limbic and hypothalamic θ rhythmicity and sniffing has also been reported (Komisaruk, 1970). Physiological evidence exists suggesting a direct conduction of olfactory information to the midbrain by way of the MFB (Motokizawa, 1974). Despite this, other investigators have not found the relationship between hippocampal θ and vibrissae movement to be generalizeable (Whishaw & Schallert, 1977; Vanderwolf, 1975). The participation of the LH in limbic θ rhythmicity apparently varies with the behavioral state of the organism.

In general, hypotheses about the influence of the LH on behavior are all flawed by the lack of a comprehensive overview of this region. This does not indicate a lack of progress in the formalization of its functions, but rather a problem related to its complex anatomy. It is by now clear that numerous behavioral functions (hormonal, attentional and motivational) have in common a bidirectional access to the MFB system. As a bed nucleus of the MFB, it appears unlikely that the LH would have functional correlates simpler than the multiplicity of the MFB itself.

Rationale for the Present Study

Anatomical rationale. A number of anatomical pathways exist for the transmission of information between the hippocampus and the LH. Both ascending and descending pathways rely heavily upon septal intercession (Saper, Swanson & Cowan, 1975; 1976). The rhythmicity of the hippocampal EEG is clearly influenced by some of them as well (Anchel & Lindsley, 1972; Paiva et al., 1976).

The descending fornix pathways have been shown to be physiologically active in the rat by evoked potential procedures (Miller & Morgenson, 1972). They are capable of modifying drinking and self-stimulation behavior arising from LH stimulation as well (Miller & Morgenson, 1971). Miller (1972) has reported a close correspondence between the form of the evoked potential and the unit response of the LH after fornix stimulation.

The pathways ascending through the hypothalamus have been shown to be capable of modifying the rhythmicity of the hippocampal EEG. Upon examining the raw EEG of the hippocampus during hypothalamic stimulation in the cat, Anchel and Lindsley (1972) reported that the LH is part of a θ-desynchronizing system. Stimulation of medial sites were reported to lead to an induction of rhythmicity. Paiva et al. (1976) found no evidence of this simple dichotomy after comparing pre and post-stimulus power spectra. Stimulation of the LH led to an increase in peak frequency. The response to VMH stimulation was generally a suppression across all frequencies, despite the appearance of a decisive peak in the power spectrum.

The close relationship between hippocampal rhythmicity and septal unit activity has been clearly demonstrated by time series techniques (Apostal & Creutzfeldt, 1974). Evoked potential (McLennan & Miller, 1974) and lesion (Vinogradova et al., 1980) studies suggest that the hippocampus may itself modulate septal activity as well. Caudal to the septum, units of the LH-MFB system have been shown to discharge in synchrony with the hippocampal EEG (Komisaruk & Olds, 1968). The extent to which this pathway participates in the spread of grossly defined θ-rhythmicity has yet to be systematically explored.

The possibility of a direct sharing of hippocampal θ activity by the LH-MFB is of general interest in view of the important motivational (Anand & Brobeck, 1951; Hoebel & Teitelbaum, 1962), reward (Olds, 1962) and sensorimotor (Turner, 1973) properties attributable to the latter continuum. Within the hippocampus, the regio inferior is the field that most unambiguously (Andersen, 1975; Raisman, 1966) maintains reciprocal relations with the septum, and thereby the MFB system (Swan & Cowan, 1975; 1976). Since the regio inferior of the hippocampus is related to the LH in an anatomically close, but electrophysiologically ambiguous fashion, the appearance of shared θ in the LH is an essential and nontrival test of the proposed θ-distribution system. The current study was therefore conducted to investigate the distribution of θ by this path through an analysis and comparison of the characteristics of θ-activity in the two regions.

Characterization as a study of an endogenous state. In the evoked potential paradigm, averaging procedures are applied to the gross response of a physiological system to a transient stimulus. This generates a measure that is formally identical to a crosscorrelation function when the stimulus is represented as instantaneous and of unit amplitude. While transient stimuli are useful for this purpose, any arbitrary stimulus might be applied in theory. The contribution of any signal to the ongoing EEG pattern may thereby be extracted from the ongoing noise. Such stimuli may serve as tracers whereby signal transmission and processing may be followed.

John and Killam (1960) reported that widespread areas of the brain may be labelled by their frequency-following responses to informationally distinct stimulus repetition rates. These response patterns were found to be assimilated by the brain and spontaneously released with ambiguous stimulation rates in a manner consistent with the observed behavioral response. While such extrinsic rhythms may be imposed and used as tracers, a spontaneous EEG pattern might also serve as a tracer in its own distinct physiological state.

The possible anatomical generality of the θ mode (Komisaruk & Olds, 1968; Vanderwolf, 1969) is reminiscent of a similar generality inherent in two recent models of memory-related processes. In John's (1972) model of the storage and retrieval characteristics of the brain, the statistical properties of groups of cells are of importance rather than the activity of individual cells. Functional interactions between regions are therefore a result of the cooperation of groups of cells in a particular nonrandom pattern. The average activity of a neural ensemble is the basic unit of activity in this model. In contrast to the marked individual variability of the activity of a single cell, the ensemble is capable of the stability of a distribution mean. Representational systems composed of large numbers of cells in different parts of the brain are therefore presumed to be built upon a coherent pattern of activity organized around the characteristics of the stimuli at the time of initial learning.

The second model of memory of relevance to an anatomically widespread θ pattern is based upon the optical hologram (see Pribram, 1971). The logic and methodology underlying the optical hologram are those of linear systems in which space, rather than time, is the domain of the raw data (see Stroke, 1969 for a reasonably comprehensive discussion of holography). From the holographic model of brain function, the widespread distribution of stored information may, in effect, by regarded as statistical in any physically realizable system. The unification of the storage and retrieval context by means of a coherent reference beam in an optical hologram suggests that an analagous generalized, persistent signal by the brain may itself become informationally relevant by acting as a context in which learning may occur. While the holographic model may be most directly applied and appreciated in the domain of space, where its physical correlate resides, the same processes may readily be generalized to the domain of time as well. The underlying Fourier transforms of the hologram may therefore be applied to effects in the temporal frequency domain.

The activity of any specific brain region is only relevant in either of these models as a component in the more globally distributed pattern. Both models also require a shared or reference pattern upon which the mnemonic process may act. In the holographic model, the effective reference must be recreated and stabilized to produce its effect. In John's model, a rhythmic sensory stimulus may occupy this role. It is not difficult to envision a similar capacity for a stable internal rhythmic state such as θ.

In view of the identifiability of the hippocampal θ rhythm, it is proposed that the precommissural fornix-LH system may be studied through the use of this EEG pattern as a physiological tracer. The structure of this activity is such that analysis in the frequency domain is indicated. The current study of the spectral correlates of θ in the hippocampus and the LH may therefore be viewed as an application of the tracer technique to an endogenous state.

Experimental control of θ. Two distinct approaches have generally been used in the investigation of brain rhythmicity. The first approach, used extensively by Vanderwolf, makes use of free-moving animals. The technique allows the discovery of the EEG correlates of behavior at the expense of an increased variability of the data base itself.

For the shared properties of θ-rhythmicity to be adequately studied, the nature of the transition from nonrhythmic to rhythmic states must itself be clearly and precisely described under simplified conditions. In unrestrained animals, the variation of the hippocampal EEG with behavior (Bennett, 1975; Vanderwolf, 1969) will produce an ambient condition that is quite variable over time (nonstationary or nonergodic). The confound may be reduced, but not eliminated, in various learning paradigms (e.g., Adey et al., 1961; Crowne et al., 1972).

To produce stabilized data, some investigators have resorted to the use of drugged animals (e.g., Apostal & Creutzfeldt, 1974; Macadar, Chalupa & Lindsley, 1974; Vertes, 1980). Because of the reduction in the variability of the EEG, this approach allows a more conclusive assessment of the properties of the rhythmicity. The improvement is particularly important when higher order correlations, such as signal coherence or crosscorrelation functions, are required. The problem with such studies is that their applicability is certain only in the state in which they were conducted. Unfortunately, the properties of hippocampal θ have been shown to vary with the administration of various drugs (Vanderwolf, 1975; Winson, 1975; 1976).

The present study was conducted to describe the spectral changes underlying the induction of θ-rhythmicity in the hippocampus and their relation to shared (correlated) EEG activity in the LH. In order to assure the validity of the changes observed, it was important to limit the study to the investigation of a simplified subset of those EEG patterns generally typified by the presence or absence of θ. In contrast to most studies of θ conducted with awake, undrugged animals, great care was therefore taken to assure that distinct, reproduceable EEG states could be evoked experimentally. For this reason, θ was studied in restrained rats.

Hippocampal θ, itself a correlate of natural behavioral states, may be artificially induced. This induction leads to an enforced rhythmicity that may be varied experimentally to study its properties and the degree to which it is shared by other regions. The selection of a brainstem stimulation site which receives a substantial projection from the LH-MFB would be expected to disorganize such coherent activity due to the antidromic invasion of the participating cell groups. The activation of θ by electrically stimulating sites in the dorsal pons of the rat largely avoids this problem and may therefore serve as an appropriate model for the investigation of the θ mode.

The frequency and purity of hippocampal θ might be expected to vary with the site to which the stimulus is applied. Using usual stereotaxic techniques, variability of this form will therefore occur. As an ancillary problem, it should therefore be possible to assess the conflicting results obtained by Macadar et al. (1974) and Vertes (1980) for the generation of θ from this region.

Spectral characterization of the study. The LH is not merely a communication link in the precommissural fornix system. Much of its activity must reflect its participation in other systems as well. The role of the LH in the transfer of slow wave information within the hippocampal-midbrain circuit may also selectively vary depending on the stimulation-induced state of the organism. Such θ-related changes are likely to take the form of an alteration in the power spectra derived from these regions. The coherence of the two EEGs reflects an additional measure quantifying shared (correlated) activity that is separable from the individual power spectra. A detailed study of the changes in these measures is of importance in delimiting the dynamic structure and anatomical generality of the physiological state associated with hippocampal θ.

There are a number of ways in which a signal of marked rhythmicity may be created from a nonrhythmic form. Either enhancement or suppression may occur in the spectrum characterizing the signal at any stage in the development of θ, or both may occur simultaneously. The findings of Paiva et al. (1976) indicate that such bidirectional effects are possible at the level of the hippocampus, if not likely. Comparable effects at the level of the LH are also possible. Such effects are not self-evident, due to the dissimilarity of the ambient EEGs of these regions. In the present study, the stimulation-induced change in θ activity at the frequency of the peak and across the remainder of the θ range were summarized separately. In this way, the individual and joint properties characterizing the growth of θ-rhythmicity could be readily summarized with a reduced number of simplified, informative statistics.

The problem of ergodicity is not generally addressed in the literature. To directly assess this form of variability, it is necessary to evaluate the homogeneity of the data set for each animal under each conditon. Since power spectrum estimates are squared quantities, it is of critical importance to assure that the summary statistics are protected from the effect of outriders. A spectral screening procedure was developed for this purpose. Even with the combined data stabilizing precautions, distribution-free statistics were chosen to add further insulation from irregularities in the data structure.

While the purpose of this study was primarily descriptive, the technique was innovative. The paradigm itself was specifically designed to produce a test preparation for the examination of persistent rhythmic states in undrugged animals. The restriction of behavior, the experimental control of θ and the nature of the statistical procedures applied all contribute to the stabilization of the data required for this purpose.

CHAPTER II

METHOD

Subjects

Seventeen male Long Evans hooded rats were used as Ss. They were housed individually and maintained on an ad lib food and water schedule. All Ss were in excess of 350 g at the time of surgery (495 g median).

Surgery

Triple electrode arrays were constructed of individual .01 in diameter stainless steel twisted electrode pairs (Plastic Products Company). They were bent, cut, aligned and secured with dental cement prior to a final calibration. The intended simultaneous targets were the LH (A 5.8, L 2.0, H -2.5) the CA3 field of the dorsal hippocampus (A 3.2, L 3.5, H 1.66) and the dorsal pontine tegmentum subjacent to the locus coeruleus (A -2.0, L 1.25, H -3.6). DeGroot coordinates were used in conjunction with the Pellegrino, Pellegrino and Cushman (1979) stereotaxic atlas. Placements in pilot subjects had suggested that intersubject variation would allow enough scatter in the pontine target to permit a comparison with the studies of Vertes (1980) and Macadar et al. (1974).

During surgery, animals were anesthetized with 50 mg/kg IP Nembutal and supplemented with ether. Since the LH target was at the coronal plane of bregma, this landmark served as a cross validation of the rostral coordinates. The pontine electrode entered the skull immediately rostral to the lambdoid suture. When the coordinates for the LH electrode varied from those predicted from a bregmoid-dural reference, a correction was applied that biased the final target 1/3 of the total difference toward the skull landmark system. The final anticipated targets were always assessed for a best possible three-site hit by both systems and with prior verified placements before the array was implanted. After insertion, the array was secured to the skull with dental cement and stainless steel screws.

Histology

When all data were obtained from a S, it was sacrificed under Nembutal anesthesia by intracardial perfusion of a 10% Formalin solution. Frozen sections (35 μ) were cut from the fixed tissue and stained with the Kluver-Barrera technique by M. Tucker. Midpoints of the electrode tips were then determined.

Apparatus

Although Vertes(1980) used constant current pulse trains as stimuli, Paiva et al. (1974) and Lindley's group (e.g., Macadar et al., 1974) controlled the voltage of the stimulus applied. In the present study, the latter, constant voltage procedure was used. To preserve the related current and power information, the applied current was monitored during stimulation.

Constant voltage sinusoidal stimuli at 60 Hz were produced and timed by hardware designed and built by the investigator for the current purpose. A stimulus of this form was selected to allow the removal of stimulus artifacts by standard line frequency notch filters. The amplitudes of the stimuli were selected by piloting, setting the anticipated maximum current at 70 µA RMS. Intensities of .0, .7, 1.1, 1.4 and 1.7 V RMS were thereby chosen and identified as stimuli 0-4. In the earliest S̲ of the series, a .35 V condition was included in place of stimulus 3.

Data were obtained via source followers embedded in dental cement in the recording electrode plugs (Rosetto & Vandercar, 1972). Signals were amplified by means of Tektronix 2A61 differential amplifiers (.6-60 Hz with 60 Hz notch) and recorded on a seven channel FM tape via Mnemetron model LC converters. After low-pass filtering at 28 Hz through a Krohn-Hite model 3550 filter, off-line digitization of the data was performed on a Xerox Sigma Seven system (Queens College Computer Center) at an effective rate of 400 samples/sec for a total of 4096 data points per record.

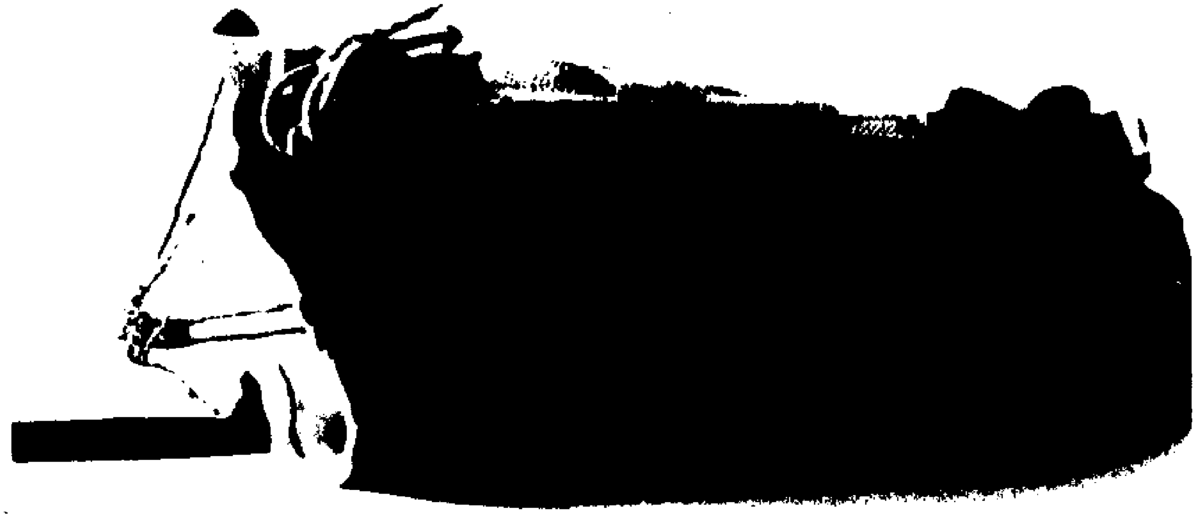
On the day of each experimental run, the amplifiers were calibrated with a .68 mV (ptp), 15 /sec square wave signal. On one such occaision, this signal was recorded onto the FM tape as well in order to attain a reliable calibration of the digitized data as well. Spectral properties of the test signal were also verified by this procedure.

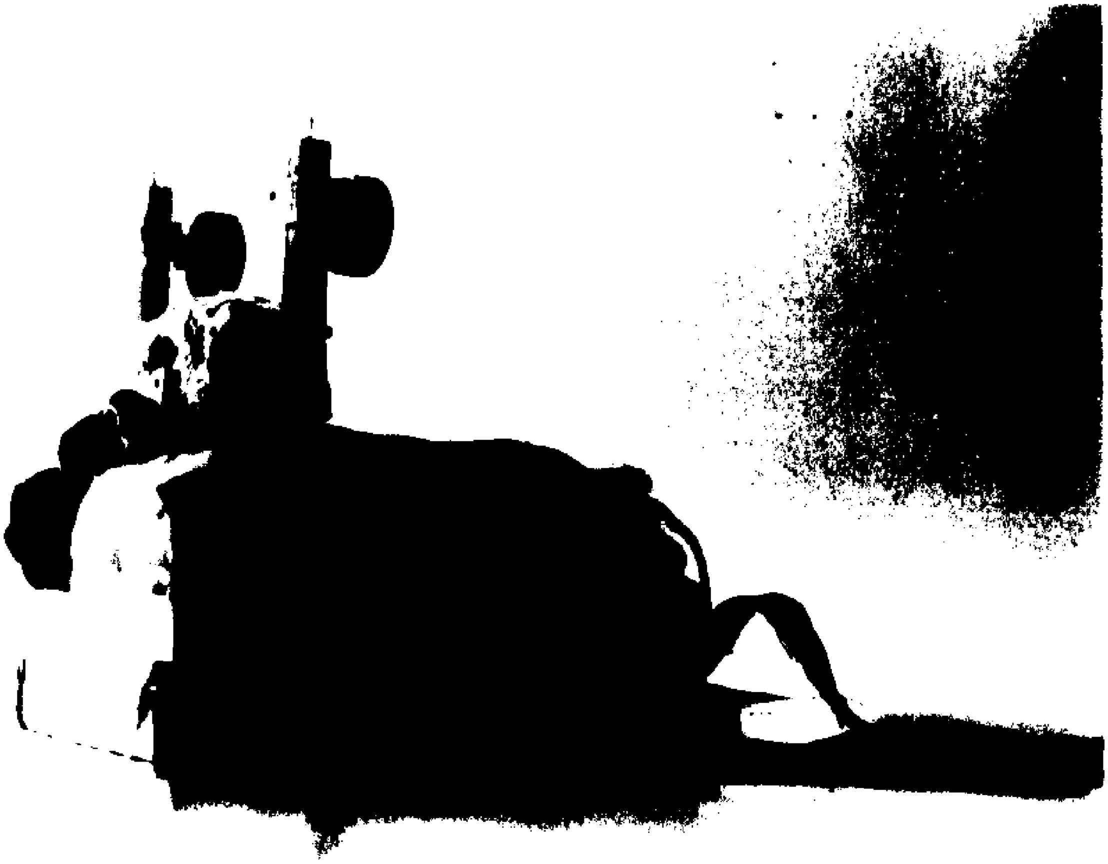
All within-S data processing was performed on a Sigma Seven system at the Queens College Computer Center. With the exception of the Fast Fourier Transform (FFT) subroutine, all programs related to the analysis and pretreatment of the data were written in FORTRAN by the investigator. They are therefore special purpose routines developed for the current use.

The initial Ss were restrained during the experimental session in a device previously used in this lab (Gilden & Kozakiewicz, 1976; Gilden, 1978). In this device, leather straps and a rigid neck brace enforced immobility. Except for these Ss, all animals were partially restrained by means of a funnel-shaped cloth restraint bag with a velcro seam adapted from Bellingham (1980). Modifications of the bag were developed in collaboration with Michael Budek and included a pair of snaps and a two-pass drawstring at the front of the bag (Figure 7a).

Complete restraint was assured by the use of a device adapted from the one previously used. The flat base was padded with foam rubber and cloth straps were used. A padded, guillotine-like neck brace was also developed to accept the bag enclosing the partially immobilized rat. Associated with this brace was a small

Fig. 7. Rat restraining device. A. Restraint bag with velcro seam partially separated to show open snap in front of it (right). At the front end of the bag, the drawstring may be seen emerging from a sleeve sewn into the fabric. From here, the second pass on the outside of the bag courses through a series of stabilizing loops, such as the one appearing at the top of the bag. A slip knot joins the ends in front of the metal stop. The rear drawstrings and the scoop-like shape of the back of the bag are also apparent. B. The restraint bag in situ in the restraining device with straps untied. The padded plexiglass neck brace and the stabilizing cloth strap (black) of the apparatus are seen in conjunction with the associated metal stop on the bag.





metal stop sewn into the top of the bag near the front drawstring. With the added assistance of a small cloth strap, the head of the restrained S was thereby stabilized. These relationships are shown in Figure 7b. Padding beneath and lateral to the head further restricted movement near the recording leads.

Restraint habituation and experimental runs were conducted in an electrically grounded, soundproof room. Auditory contact was maintained through an intercom system. Global postural changes, struggling and, most often, breathing patterns could thereby be evaluated as indices of the condition of the organism.

Procedure

Restraint habituation. After recovery from surgery, stress responses to restraint were systematically reduced. The original device required a habituation series in which valium injections (IP) were used to decrease the initial stress effects of restraint. While the first data-bearing animal adapted well to this device, later subjects required a less stressful restraint procedure. The restraint bag served this function quite well.

The restraint bag proved to be simple to implement. A rat would readily enter the funnel-shaped cloth bag of its own accord. Upon such entry, S was prevented from backing out by means of a rear drawstring. With the velcro-laden seam and the front snaps attached and Ss head protruding from the small opening, a first approximation of restraint could be enforced.

The addition of the front drawstring proved to be necessary to prevent energetic Ss from pulling their heads back into the bag. The influence of the front drawstring was distributed by means of a second pass around the outside of the bag through a few cloth stabilizing loops (see Figure 7b). The free ends were then tied by means of a slip knot configuration. The snaps helped to stabilize the velcro seam while allowing for a decisive release at the conclusion of a restraint period.

Once secured in the restraint bag, S was strapped into the restraining hardware. The neck brace was then lowered behind the metal stop on the front of the bag. An Ace bandage was then wrapped around the base to assure an evenly distributed restraint pressure. In general, experience with pilot animals has supported the view that struggling is inversely related to the spatial distribution and security of the restraining influences.

In view of the potential for inducing postural changes after stimulation of brain stem sites in a waking S (e.g., Sprague & Chambers, 1954), the safety of the animal and the stability of the acquired data required a means by which small head movements might be suppressed. This was achieved through the use of an additional padded block under the exposed head. Lateral pressure was likewise attained with padding. The restraint device was securely abutted against the wall of a small aluminum box, which provided the structure in which the final padding was secured.

While animals were briefly run through the restraint bag daily with little or no restraint (velcro not secured) during the habituation period, full restraint was enforced no more frequently than three times a week for a given subject. Restraint times were gradually elevated from a few minutes to 1-1.5 hr. This required approximately seven sessions of full restraint. Even during early sessions, when struggling was common, an animal would rarely balk at entering the bag. This was true immediately after release from restraint as well. To maintain this behavior, three runs through the bag without restraint were given immediately prior to and after each restraint run.

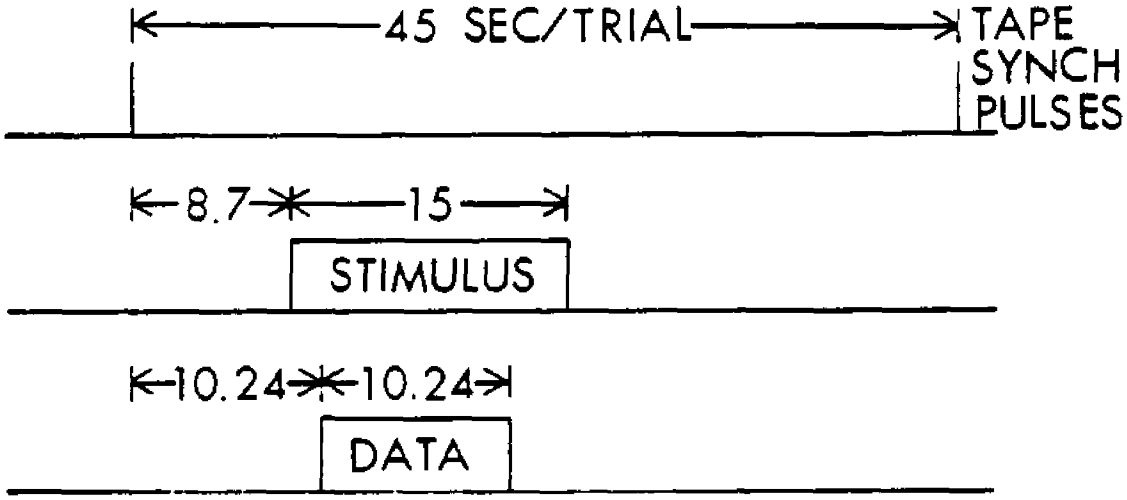
Behavioral response to stimulation. All _S_s were briefly tested for their responsivity to the pontine stimulus under direct visual observation on the last day of full restraint in the habituation series. Behavioral correlates of the different intensities of stimulation were noted when present. Those _S_s in which phasic movements occurred often enough to prevent the acquisition of valid data during the stimulation epoch were eliminated from further study. Among these were _S_s to which the stimulation appeared to be unduly traumatic. After this brief test period, _S_s were returned to the soundproof room to complete the habituation period with all electrical plugs connected to the implant.

On a day subsequent to the experiment, Ss were tested for self-stimulation at the pontile site whenever possible. Stimuli were the same as those delivered in the experiment, but were of short duration ($\leq$ .5 sec). Motor effects and avoidance tendencies were also noted. For the second half of all animals run in this study, the hypothalamic site was also tested.

Stimulation and data acquisition. Because of questions raised by pilot data regarding the possibility of a confound related to day to day variability, all data from all conditions were acquired in a single recording session. Each block of trials consisted of four presentations of each stimulus. The order of presentation of the trials within a block was a constrained random one in which the first and last five stimuli included all stimulation conditions. No two successive stimuli were from the identical condition. After each block, a break period of five or more timing pulses was allowed to elapse before beginning the next one. A minimum of four blocks were presented in forward and reverse order using an ABBA structure. Stimulus selection was manual, in accordance with this format. An additional block of trials was also presented if the state of the animal permitted it. When break periods and additional trials are accounted for, the length of an experimental session for a typical S was about 1.5 hr.

Stimulus timing was based on the presence of

Fig. 8. The relation of stimulation and data collection periods to the prerecorded timing pulse train.


45 SEC/TRIAL
TAPE SYNCH PULSES
8.7
15
STIMULUS
10.24
10.24
DATA

trigger pulses on a prerecorded tape channel. The interpulse interval was a constant 45 sec. After each pulse, 8.7 sec of recorded data were allowed to elapse before the stimulus was automatically delivered. As illustrated in Figure 8, off-line collection of the corresponding 10.24 sec data record was begun after a delay of 10.24 sec from the occurrence of the trigger pulse. The stimulus remained on for 15 sec. This arrangement served to protect the data record from contamination by onset and offset transients.

The initial operations of the primary analysis program included a final pretreatment of the data prior to Fourier transformation. First, any residual DC bias was removed from each data record. The resulting series was then cosine tapered over the first and last tenths of the data record to suppress the spectral side lobes of the effective data window (Bendat & Piersol, 1971). For each trial, power and cross spectrum, coherence, and phase angle summaries were obtained by taking means across 25 consecutive nonoverlapping 1 Hz bands (exactly 10 raw estimates per band). Since the filters were applied equally across all experimental conditions, no attempt was made to compensate for these influences.

The acceptance of data from any given trial into the final summary statistics for the associated condition required that it pass two overlapping artifacting procedures. The first and most direct procedure made use of written records taken during the experiment. All trials that were obviously contaminated by movement artifacts were immediately removed from further analysis. The implementation of this screening procedure is obvious. The second procedure, as described below, made use of the power spectrum estimates derived from the data records.

After restraint habituation, data were acquired from each S. During the course of the experiment, the restrained animal was placed in, but electrically isolated from, a grounded aluminum box. The EEG electrodes were therefore allowed to electrically float. During each stimulation epoch, as the data record was being recorded, the RMS amplitude of the applied current was monitored and recorded.

Data structure and the artifacting procedure. As described in Bendat & Piersol (1971), the power spectrum

$$\hat{G}_x (f) = \frac{2}{T} \left| X (f, T) \right|^2 \qquad \text{eq. 1}$$

where X is the Fourier transform of a temporal function x over time T. These functions occupy the frequency domain (f). The estimate $\hat{G}_x$ (f) is produced by the sum of the squared components of X. Since the Fourier transformation itself produces a complex value function of arbitrary phase, the theoretical error distribution therefore must follow

$$\frac{\hat{G}_x (f)}{G_x (f)} = \frac{\chi_2^2}{2} \qquad \text{eq. 2}$$

In a pilot study, the relationship of equation 2 was tested using as an estimate of G_x (f) the means obtained by averaging across 1 Hz bands and across 20 data records of 20.48 sec length (N=20 points x 20 records). A number of distinct frequencies were examined, including one corresponding to a peak in the spectrum. An extremely close fit was found to the theoretical distribution. Likewise, plots of log ($\hat{G}_x$) vs. cumulative probability formed a series of essentially identical curves that were shifted by a constant corresponding to the means of the individual spectra. Although these data were generated by a well habituated animal that was not subjected to stimulation, it is clear that under suitable conditions the hippocampal EEG is capable of exhibiting the properties required of a stable, stationary signal.

The spectral artifacting procedure developed here is based on the expected χ^2/df distribution of power spectrum estimates. The distribution of the sum of χ^2 distributions is itself χ^2 with its degrees of freedom equal to the sum of its component distributions (Hays & Winkler, 1971). It is therefore clear that

$$\frac{\hat{G}_{x1} / G_x}{\hat{G}_{x2} / G_x} = \frac{\chi^2 / df_1}{\chi^2 / df_2} = F_{df_1,\, df_2} \qquad \text{eq. 3}$$

where $\hat{G}_{x1}$ and $\hat{G}_{x2}$ are means of $df_1/2$ and $df_2/2$ estimates of the true power spectrum value G_x. Equation 3 is formally the equivalent of a test of the significance of the difference between two variances. The two population means are assumed to be identical under the null hypothesis. The number of degrees of freedom for each χ^2 is twice the number of independent estimates summed to produce the associated mean estimate.

The use of equation 3 as an artifacting technique simply requires the separation of individual sequence means from the remaining data. For 10.24 sec data records, the estimates derived for 1 HZ averages have 20 degrees of freedom for each sequence. A test of one out of 16 trials would therefore be referred to F with 20 and 300 degrees of freedom. A significant ratio may be viewed as an indication that between-record stationarity has been violated. The use of such a procedure is analagous to setting amplitude limits for the automatic rejection of temporal data. A well defined spectral anamoly, rather than a temporal one, will thereby be rejected.

Pilot work has demonstrated that records blatantly contaminated by movement artifacts are characterized by plots of F ratio vs. frequency with a pattern of extremely large values (effectively impossible under the null hypothesis). The direct artifacting of data in the time domain has generally proven to be redundant. After these clearly artifactual sequences are eliminated, a few additional sequences are typically found to be in violation of an F ratio pattern consistent with a stable spectral structure.

In examining data derived from stimulated subjects, experience has shown that the stationarity requirement must often be relaxed. While a majority of the stimulated animals did generate data with the required stability, others produced data that diverged from stationarity to varying degrees. The rejection procedure, as pragmatically derived and applied to these data, required that none of the 25 1 Hz frequency bins averaged should have an F ratio more extreme than $9^{\pm 1}$ (component signal amplitude $3^{\pm 1}$ time remaining mean). No more than three estimates were allowed to be more extreme than $4^{\pm 1}$ ($2^{\pm 1}$ times mean). The final requirement was that no F more extreme than $6.25^{\pm 1}$ ($2.5^{\pm 1}$ times mean) should be accepted within the frequency range examined for θ.

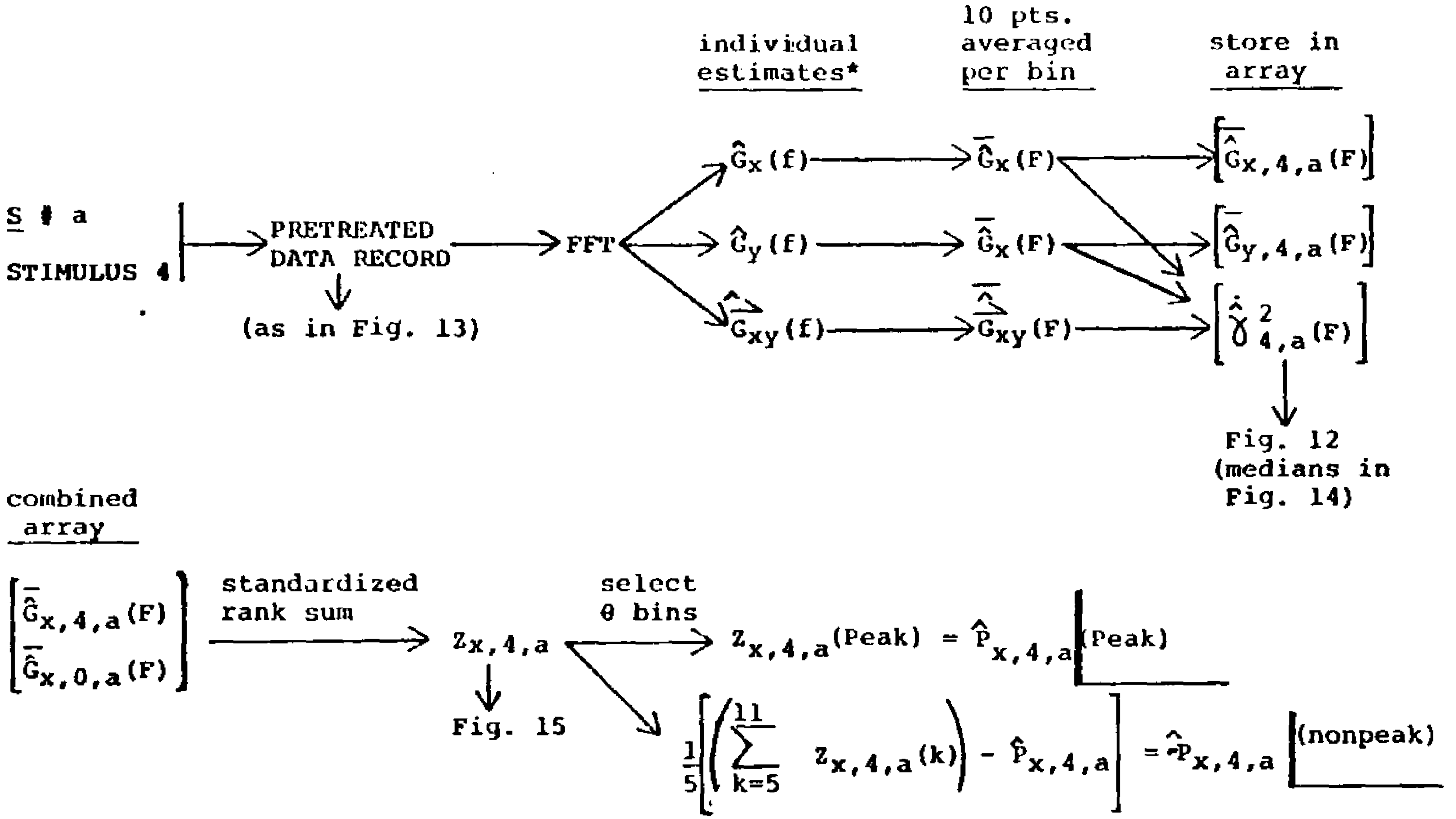
It must be emphasized that the application of these rejection criteria was essentially free of interpretation. Patterned F discrepencies were virtually always due to records with spectral compositions of abnormally high power. Because of this, and due to the skewing effect of sequences bearing large F ratios, cases in which more than one sequence erred were handled by eliminating the largest positive error first. When at times a sequence of lower power was necessarily rejected, the final level of stability was otherwise quite well established. Finally, qualitative differences were not found in statistics derived from partially (blatant artifacts eliminated) or completely (criteria attained) artifacted data.

Statistical methods. The variable nature of the underlying distribution of G_x estimates makes the usual statistical procedures quite suceptible to the distorting influences of outriders. One way of dealing with this problem is to transform the sequential averages obtained from each individual logarithmically. This procedure has been recommended for the analysis of stationary data (Bendat & Piersol, 1971). It has also been used in the comparison of physiological power spectra derived from the EEG of the hypothalamus and midbrain (Gilden & Kozakiewicz, 1976; Gilden, 1978). The resiliency and resolution of this technique varies with the magnitude and consistency of the departure from stationarity. As the logarithmic transformation of equation 2 suggests, this procedure is an excellent means of producing linearly related data for the purpose of pooling. When stationarity lapses, however, the χ^2 structure of equation 3 fails, leading to a failure of linearity.

In view of the lax criteria of stationarity required for this study, the use of standard parametric analysis procedures would introduce a bias of unpredictable magnitude into the statistical evaluation of the experimental influences. Nonparametric procedures, however, are not bound to a given data structure. The Wilcoxon rank sum test for independent samples was therefore applied to the trial-by-trial distribution of non-overlapping 1 Hz power spectrum means for the hippocampal and LH EEG of each animal. Each stimulus condition was in turn compared to the control data and expressed in final form as a standardized (z) score (Ferguson, 1976; Bradley, 1968). A comparison of critical z scores with the corresponding exact probability measure indicates that the occasional animal with data derived from relatively few sequences was subject to a slight, conservative error in the estimate of z. Exact probability procedures were therefore found to be unnecessary.

While a given S̲ would reliably produce θ at its own characteristic frequency during stimulation, this stability was not to be expected between S̲s. In pooling the data between animals, it was necessary to accomodate for the shifting frequency of the θ rhythm. It was therefore necessary to designate the frequency of the peak a posteriori from the obtained power spectrum. Because of the frequency range occupied by the spectral peaks of the different animals, "θ activity" was defined operationally to include the seven frequency bins scanning 3.9-10.7 Hz. Peak θ was defined as the maximum positive-going peak z score in this range. When the identified peak exceeded one bin in width, the means of the consecutive z estimates were taken for values in excess of z=1. This produces a conservative test for enhancement at the peak and is simultaneously a means of eliminating its influence from the mean of the remaining activity. The latter mean was used as an estimate of non-peak θ suppression effects. From an expected maximum of 16 data

Fig. 9. Flow diagram of mathematical and statistical operations. Figure numbers refer to illustrations of data from typical S as described in results. In the upper diagram, the generation of the median power spectra and coherence plots is shown for a hypothetical S # a for stimulus 4. In the lower diagram, the extraction of individual peak and nonpeak statistics is shown for channel x. These statistics were then tested, by the group statistics shown, to determine the discriminability of the directional displacements of the group mean. The presumed normal distribution of these scores across Ss was monitored separately (not shown).



GROUP STATISTIC:

$$t_{x,4,P} = \bar{\hat{P}}_{x,4,\cdot} / S_{\bar{P}}$$

$$t_{x,4,\tilde{P}} = \bar{\hat{\tilde{P}}}_{x,4,\cdot} / S_{\bar{\tilde{P}}}$$

*f = original 4096 consecutive frequency points while F = 25 average bins records for each experimental condition, the amplitudes of the EEG components in the 3.9-10.7 Hz range were summarized from 639-1753 cyclic periods of raw data. This maximum was subject to both reduction during artifacting and a further augmentation from additional blocks of trials.

As illustrated in Figure 9, the individual z estimates for peak and nonpeak categories were pooled across Ss for the purpose of group statistics. Since each z is, in effect, a standardized difference measure for a given S, a peak enhancement or nonpeak suppression effect may be tested simply by restandardizing the data and testing for the inclusion of zero in the appropriate tail. This is identical to a t-test for dependent samples in its origin and implementation. The Wilcoxon test thereby serves as both a within-S test and a between-S normalizing transformation.

If the underlying power spectrum distributions are identical, the Wilcoxon z scores are of necessity normally distributed with a mean of zero. The structure of the underlying distributions is of no importance. For small deviations in rank sum organization, a normal structure is also likely. With larger departures, the adherence to normalcy should be validated with the acquired data. The individual peak and nonpeak z estimates were therefore plotted in the form of a cumulative probability distribution. The degree of concordance with the normal was indicated by the product moment correlation of this curve with the theoretical normal z at the same probabilities. The variance, skewness and kurtosis of these data were also tested.

The pooling procedure used for the production of a single non-peak estimate is subject to contamination by the effects of a simple frequency shift in a spectral peak of constant amplitude. A control procedure was therefore implemented to test for the consistency of the non-peak region. Since nonrhythmic or slightly rhythmic EEG patterns may have a greater concentration of power in the lower frequencies, this procedure tests for a simple shift in frequency of an existing peak. Each suprapeak and subpeak bin was tallied according to the sign of its associated z score. Data were further pooled across subjects as well. A χ^2 test of independence was then applied.

To study the relationship between the frequency of the θ peak and the region stimulated, electrode placements were ranked according to the mean depth of each pair of tips (DeGroot system) ventral to the locus coeruleus. The frequency of the hippocampal peak was then determined for each S. A rank order correlation was applied as a test statistic.

As illustrated by Adey, Walter and Hendrix (1961), the coherence function is a measure of the stability of the phase relationship between two data records as a function of frequency. It is formally the standardized magnitude of the cross spectral density function (Bendat & Piersol, 1971), and is identical in form to a squared product-moment correlation coefficient. Thus, the coherence function (γ^2) between channel x and y may be expressed as

$$\gamma^2_{xy}(f) = \frac{\left| \vec{G}_{xy}(f) \right|^2}{G_x(f)\, G_y(f)} \qquad \text{eq. 4}$$

Since the cross spectrum $\vec{G}_{xy}(f)$ is a vector quantity, representing both amplitude and phase, the order of averaging used to estimate these quantities is not trivial. While standard useage dictates a vector mean, a magnitude mean may also be produced. In the case in which a maximal constant magnitude $\vec{G}_{xy}$ exists with random phase properties, these two means produce a γ^2_{xy} estimate of 0.0 and 1.0, respectively. Because of the difficulty inherent in the interpertation of a γ^2_{xy} magnitude estimate, the record-by-record estimates obtained in this study were based on a vector sum procedure. This method includes a tacit assumption of internal consistency within each data record. This is a restatement of the supposition that an identifiable spectral state may accompany a given stimulus condition.

Pilot data have at times revealed small but relatively consistent estimates of γ^2 across experimental trials of a given stimulus condition. After averaging over all trials for a condition in a S, the final γ^2 may degrade considerably, indicating that between-trial phase stability is poor. Even when this degradation is not extreme, the standard normalization procedures for γ^2 (comparable to Fisher's z_r) lose their precision for $\gamma^2 < .4$ (Enochson & Goodman, 1965). In view of these considerations, the same nonparametric procedures described for the examination of power spectra were applied.

The use of a nonparametric procedure to test the coherence function quite validly implies that the underlying γ^2 estimates may be inadequate as a measure of phase stability. It is reasonable, then, to inquire whether there is any stability at all in the trial-to-trial estimate of phase angle. An exact probability technique was therefore developed to this end.

To counter erroneous variability caused by data in the vicinity of the ±180° phase crossover, a S's sequential phase estimates were rotated successively about each individual estimate until an approximation of a least squares criterion was achieved. Phase deviations from this mean were thereafter treated as data for analysis. These values were then ranked and the upper and lower quartiles determined. Based on this interquartile range, an exact probability was calculated under a null hypothesis of a uniform distribution. Errors due to discontinuity were always in favor of the null hypothesis.

The independence of the phase distributions derived from two experimental conditions was also tested by reference to the interquartile range of the pooled deviation angles. A two tail exact probability (Fisher's exact test) was computed for the frequency of inclusion of values derived from both conditions within and without this range. These probabilities were calculated for data rotated under both separate (variability test) and combined (discriminability test) conditions. A rank sum test of the combined, rotated data was also performed as a test of central tendency.

The tests for phase properties were simple and made use of the interquartile range in a somewhat arbitrary fashion. In defense of this choice of limits, it should be noted that the interquartile evenly divides the probability structure of a distribution while offering a degree of resistence to distortion from the random occurrence of outriders.

CHAPTER III

RESULTS

Subjects

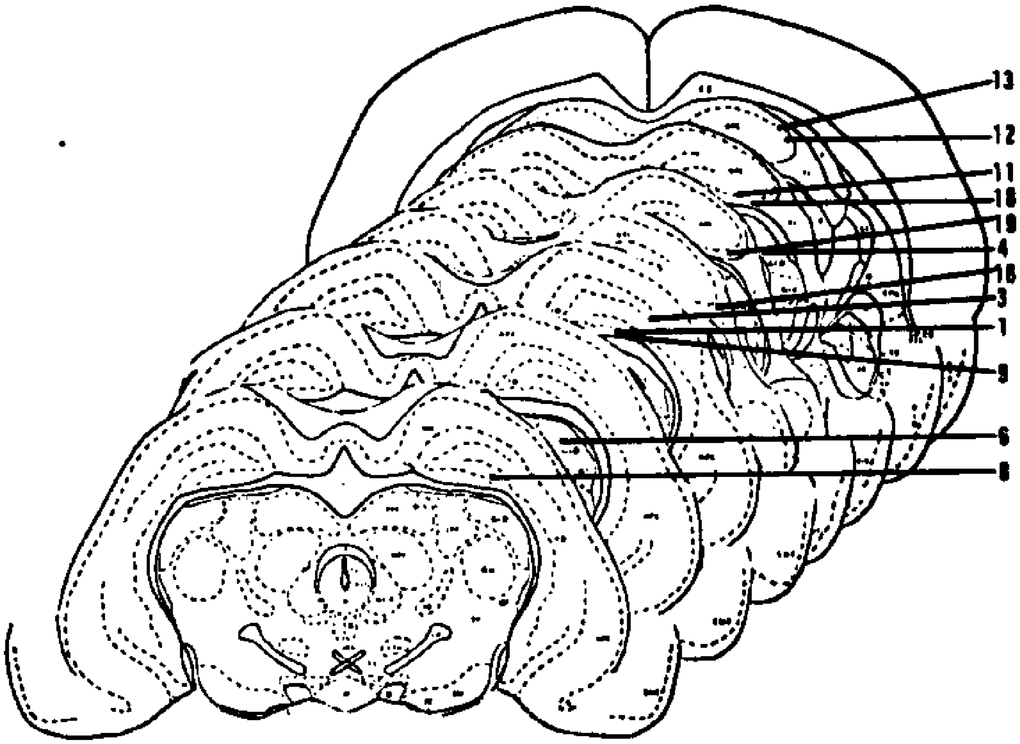
Of the 17 rats implanted, two died within three days of surgery. Two additional Ss were excluded from consideration due to inadequate habituation under initial restraint procedure. Of the latter pair, one also sustained a marked infection beneath the electrode cap. A final S was excluded due to intractability during stimulation. The results presented refer to the remaining 12 animals.

Histology

As indicated in Figure 10, hippocampal placements ranged from the lateral limits of the ventral granular-hilar zone into both subpyramidal and suprapyramidal layers of CA3. Hypothalamic electrodes were generally in ventral and lateral portions of the LH at the level adjoining the VMH. The postcommissural fornix bundle was not involved in any animal, although in one rat (S 9) the placement was perifornical. Stimulation sites in the eight data bearing subjects ranged from the locus coeruleus to tegmental sites as deep as the motor nucleus of the trigeminal nerve.

One animal with acceptable electrode locations was not included in the general summary statistics. This

Fig. 10. Histological verification of electrode placements in the 12 Ss described in the text. Adapted from Pellegrino et al. (1981).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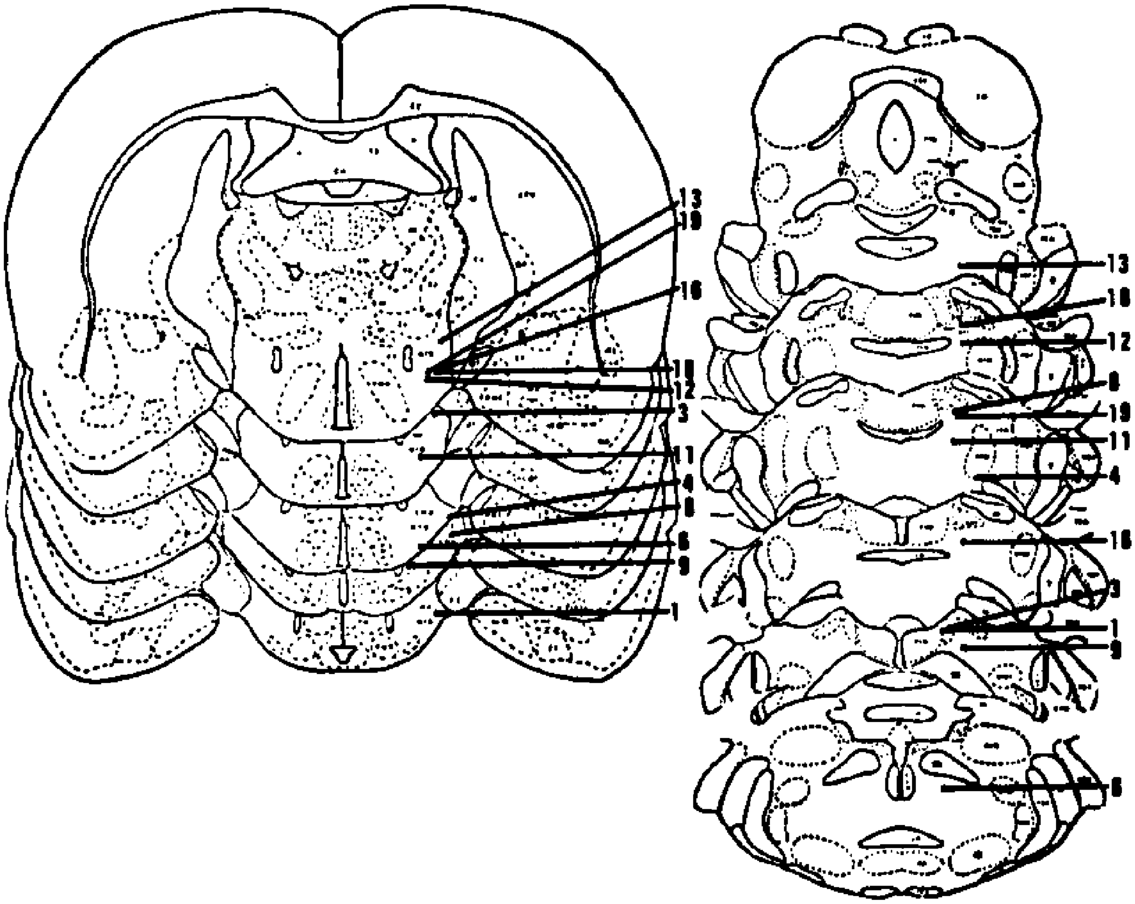
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animal (S 3) will be described separately. Animals 4 and 6 were also excluded from the summary statistics due to the inappropriate location of the hippocampal electrode. Subject 16 produced a highly regular θ rhythm, but quietly died in restraint before data could be acquired.

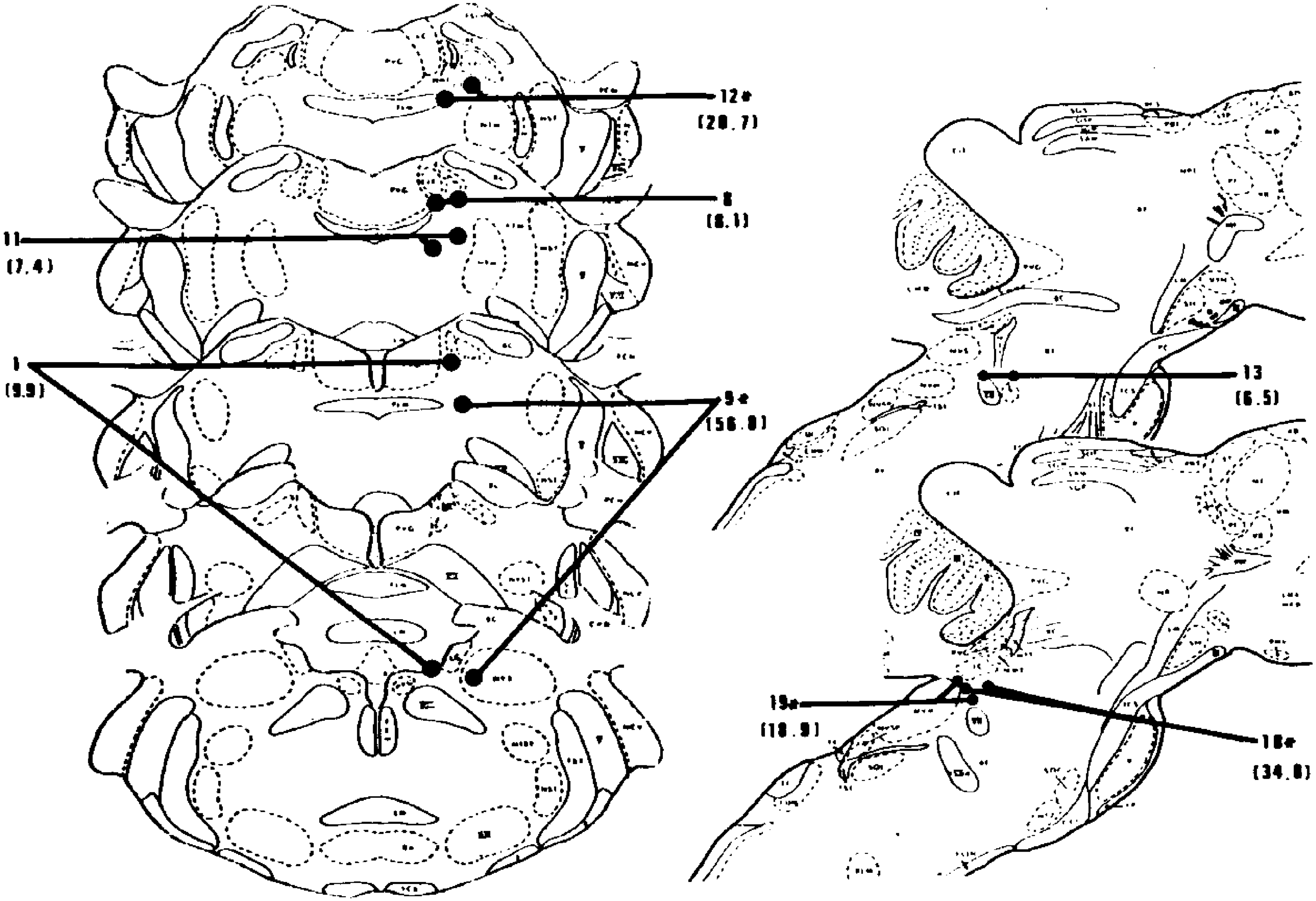
For all but the last few subjects, stomach tissue was viewed for evidence of ulceration. Despite the use of restraint in this paradigm, no pathology was ever seen.

General Characteristics of Summary Data

After artifacting, the median number of control trials accepted for analysis was 14.5 (mean of 14.6). For stimulus 4, a median of 11 trials (10.8 mean) were accepted. The difference reflects the increased movement tendency after stimulation at the higher intensities in some subjects. Since the median θ peak at stimulus 4 was at 7.8 Hz, the typical stimulation-induced peak was summarized from a total of 80 cyclic periods/trial. As a rule, parametric, median and rank sum measures exhibited changes in the same direction. The tenuous stationarity of the data and the statistical power observed in the latter tests substantiate their use.

In all Ss, the range scanned for θ attained an acceptable stationarity with the artifacting procedure used. Only three failed the general rejection criteria. Of these, two (one each for stimuli 3 and 4) differed only in scattered high frequency components about the θ

Fig. 11. Placements of the bipolar stimulating electrode tips for the eight data-bearing Ss. As an indication of the rhythmicity produced at each site, hippocampal power ratios are included from Table 2. Generators of strong rhythmicity (power ratios > 16) are indicated by asterisks. Adapted from Pellegrino et al. (1981).


12e
(20.7)
8
(6.1)
11
(7.4)
1
(9.9)
5e
(56.8)
13
(6.5)
19e
(18.9)
18e
(34.8)

range. Only one animal produced data that failed in the range below θ as well (stimulus 2). In view of the stability of the θ range in the former subjects, they were also included in the general analysis. An examination of the statistical data from these conditons reveal no obvious correlate of this discrepency.

At stimulus 4, the obtained cumulative probability distributions for peak and nonpeak z estimates approximated a normal distribution. When plotted on a normal probability scale, all peak plots and the LH nonpeak plot closely approximated the straight line defining the equivalent normal. Product-moment correlations between the z scores of these obtained distributions and the expected theoretical values varied between .98 and .99. for nonpeak δ^2, an r=.97 was obtained.

The nonpeak hippocampal data had a slight tendency to stray from normalcy. For these data, an r=.92 was obtained, indicating that 15% of the variance was not related to this linear source. A positive skew was also detected, both from direct observation of the plot and from an obtained $g_1=1.24$. The effect of this skew was to decrease the decisiveness of the suppression tested in the group statistics. All other data showed no evidence of skewing ($g_1 \leq .54$).

<u>Stimulus Current</u>

For each animal, a given stimulus produced a stable current reading. For any animal, the standard deviation

TABLE 2

Mean Stimulus Current Delivered (μA)

	Stimulus Condition			
S#	#1(.7 V)	#2(1.1 V)	#3(1.4 V)	#4(1.7 V)
18	8.2 ±. 6	13.2 ±. 7	18.9 ± .7	27.6 ±. 7
19	10.5 ±. 5	17.0 ±. 4	24.0 ±. 7	34.0 ±. 8
12	11.4 ±. 6	18.2 ±. 6	25.7 ±. 7	38.9 ± 1.0
11	13.3 ±. 7	21.6 ± 1.2	30.6 ± 1.7	45.7 ± 2.9
13	13.4 ±. 9	22.4 ± 1.6	32.9 ± 2.5	52.5 ± 1.3
8	15.5 ± 1.4	25.0 ± .9	34.7 ± 2.	52.3 ± 1.5
9	20.0 ± 9	30.9 ± 1.0	41.8 ± 1.0	60.0 ± 1.8
1	16.8 ± 1.0	31.8 ± 1.7	--	66.6 ± .9
Total	13.6 ± 3.8	22.5 ± 6.5	29.8 ± 7.6	47.2 ± 13.2
Power Range(μW)	5.7 - 14.0	14.5 - 35.0	26.5 - 58.5	46.9 - 113.2

TABLE 3

Individual Data

	Peak bin		Hippocampus		LH		γ^2		Phase at #4 peak	
S#	Stimulus #4 bin #	Total periods data #4/#0	Power ratio[a] at #4 peak	Trends[b]	Power ratio[a] at #4 peak	Trends[b]	Peaks #4/#0 (max #0 in θ)	Trends[b]	Stable θ in #0 or #4	Sig. for joint (j) indep (i) z (z)
8	6	763/817	8.1	P,S	1.2	p,S	.36/.28(.29)	P,s	0,4	-
1	7	968/452	9.9	P,s,-3(ns)	4.7	P,S	.76/.31(.31)	P,s	0,4	z
19	7	1097/968	18.9	P,S,2 ,-3	-	-,S	.22/.11(.23)	P,s	4	j
18	8	1266/968	34.8	P,S,2	-	p,S	.35/.11(.29)	P,s	4	j
9	9	1099/845	56.8	P,S,2	17.8	P,S	.96/.56(.79)	P,S	0,4	-
12	9	1183/1014	20.7	P,S,2R	2.3	p,S	.51/.13(.14)	P,-	4	j,i
13	9	676/338	6.5	P,S,2R	2.9	P,S	.60/.20(.57)	P,s	-	j and i at p=.06
11	10	1796/945	7.4	P,S,½,2R	1.2	P,s	.21/.06(.14)	P,-	4	j,i
3[c]	7	839/968	2.7	P,S	-	-,s	.11/.08(.16)	-,s	-	-
6[d]	7	645/645	14.2	P,S	1.1	-	.25/.25(.25)	-,s	0,4	z
4[d]	7	903/710	2.4	P,-	6.9	-	.15/.06(.19)	-	4	z

Note. - Based on stimulus 4 peak bin unless otherwise noted.

[a] Ratio of #4 median peak power (when present) to prior trough or level.

[b] P and S reflect peaking and suppression trends (lower case if > .05 1-tail). Numbers in hippocampal data indicate harmonics of θ peak ($p < .05$ 2-tail unless noted ns). Sign indicates direction of effect. R indicates a rebound from inhibition

[c] Locus coeruleus S.

[d] Thalamic S.

of the recorded current was typically less than 5% of the mean value and always less than 10%. Although stimuli of constant voltage were used, stimulation current varied considerably from animal to animal. As illustrated in Table 2, the intersubject variability increased with stimulus intensity. The applied current overlapped stimulus category ranges. It should be noted that the applied power was more separable. Only stimulus 3 delivered power with an intersubject range that overlapped its neighboring conditions.

The rank of the current recorded from a given subject was reasonably stable between conditons. Animal 18 consistently occupied the bottom of the range for all conditions. The power distributed to this animal during stimulus 4 was greater than that received by all but one animal tested with stimulus 3 (S 9). The stimulus 3 range, however, overlapped the stimulus 2 power received by three animals (Ss 1, 8 and 9).

Absolute current magnitude was not related to the frequency of the hippocampal peak. A rank order correlation computed for peak frequency vs. current at stimulus 4 was effectively nonexistent (ρ =.03).

Hippocampal θ

Ambient (control) levels of θ activity varied considerably from subject to subject. In median power spectrum plots, "peaks" in θ varied from a mere plateau to a factor of 2.5 times the power of the level at subjacent frequencies. All test statistics reflect changes from these nonrhythmic or slightly rhythmic modes of activity.

The spectral tuning of the hippocampal EEG at stimulus 4 is reflected by the relative height of its correlate in the median power spectrum (Table 3). Peaks in θ towered over troughs or plateaus at lower frequencies in the power spectrum by factors of 6.5-55. The most highly resolved peaks (> 10 times) scanned the 6.3-8.3 Hz bins. High resolution was not categorically linked to frequency, however, since θ peaks of relatively poor resolution (≤ 10 times) spanned the range from 5.3-9.2 Hz.

Electrode placements. The four Ss generating the purest θ (Ss 9, 12, 18 and 19; factors of 19, 20, 31 and 55) all had at least one electrode tip of the pair in the subpyramidal lamina of CA3 (compare with Figure 10). While two of these (Ss 12 and 19) had tips including or straddling the pyramidal cell layer, one (S 18) had both tips clearly below it. Placements for the four lowest θ generators included pyramidal cell and molecular layers (Ss 11 and 13) and the dentate-hilar zone (S 1). The remaining animal (S 8) had a placement straddling the oriens-alvear transition. It appears that it is possible for θ to characterize the local differential EEG of the regio inferior in general and subpyramidal loci in particular.

A rank order correlation between the distance of the mean of the stimulating electrode tips from the ventral limit of the locus coeruleus and the θ peak frequency of the median hippocampal power spectrum at stimulus 4 was computed. This measure indicated a significant correlation (ρ=.87; 2-tailed $p < .02$) of positive sign when computed from the eight data-bearing animals. The validity of the correlation is further supported by the data obtained from S 3, since this locus coeruleus placement was incapable of generating θ.

As indicated by the frequency-vs.-depth correlation, the frequency of the hippocampal θ peak appears to be related to the depth of the stimualtion site ventral to the locus coeruleus in a simple manner. The regularity of the rhythm, as indicated by the spectral power ratios, is a distinct property of the rhythm produced. If the power ratios of Table 3 are examined in concert with the locations of the stimulation sites shown in Figure 11, a pattern may be observed. All sites generating hippocampal θ with a power ratio > 16 (voltage ratio > 4) are contained within a zone at or dorsal to the dorsal limits of the medial longitudinal fasciculus (FLM in Figure 11) and ventral to the locus coeruleus (LC). For stimulation sites above or below this wedge of subcoeruleus tissue, the rhythmicity strays.

The data suggest a focus for the generation of highly rhythmic hippocampal θ in the diffuse subcoeruleus region.

It must be cautioned, however, that this maximum may be related to a proximity to the vestibular nuclei at caudal levels and/or the dorsal portions of the medial longitudinal fasciculus. This accords well with Vertes (1981) study in which placements within the fasciculus itself were noted to be effective in the generation of high frequency θ. A further elaboration on the nature of this zone must be resisted, due to the lack of appropriate statistical controls.

Nonpeak suppression. The average of the normalized rank sum (z) scores for θ frequency bins in which no peak appeared was found to decrease substantially with stimulation. For stimuli 1-4, the summarizing dependent t scores obtained were -2.42, -3.32, -5.56 and -7.35, resp. (df=7, 6, 6, 7; 1-tailed $p < .025$ to $p \ll .0005$). Suppression of some form or another was so general at stimulus 4 that even by globally pooling all individual nonpeak bins above or below the spectral peak, the total number of positive z scores was less than three for both LH and hippocampal data (N=44 and 46, resp.). The contingency table derived from such pooling of the hippocampal data obviously fails to support a difference between subpeak and suprapeak trends (continuity corrected $\chi^2=.51$; df=1; $p \approx .50$). It is therefore apparent that the stimulus led to a shift of power to lower values in the form of a continuum of suppression.

Peak enhancement. While the suppression of nonpeak θ with stimulation appears straightforward, it should be noted that the presence of a readily distinguishable θ peak was universal only at the two highest stimulus intensities. At stimuli 3 and 4, $t=4.78$ ($df=6$; $p < .005$) and 13.73 ($df=7$; $p << .0005$), resp. At stimulus 1, while one animal (S̲ 1) failed to show any peak, five (S̲s 8, 11, 12, 13 and 19) exhibited a dual z peak. Because of the criteria used to identify spectral peaks, lesser peaks were not discriminable from the background nonpeak activity. All but one (S̲ 11) of these five animals showed peaks that were not consistent with those detected in the median power spectra or in z score plots obtained from LH data. At stimulus 1, the test was applied only to cases in which a peak was evident. The inflated t score so obtained ($t=6.48$; $df=6$; $p= << .0005$) serves to indicate the potency of the effect when it is present, but obviously is lacking in generality. This criticism applies to condition 2 as well ($t=4.55$; $df=5$; $p < .005$).

Harmonics. Marked changes in hippocampal z scores often characterized harmonics of the θ peak frequency. While 6 out of 8 animals (S̲s 9, 11, 12, 13, 18 and 19) showed a substantial and significant increase in the region of the second harmonic for stimulus 4, the effect in three of these (S̲ 11, 12 and 13) was by means of a sustained rebound from a more generalized suppression. Two animals (S̲s 1 and 19) exhibited a relatively localized suppression in the vicinity of the third harmonic. Activity at half the frequency of the θ peak was present in both median and z plots of one animal as well (S 11). In the final animal (S 8), however, the nonpeak suppression effect was generalized across the computed spectrum.

While harmonic effects may be common and at times quite strong, the present evidence does not suggest that they are completely predictable or universal in their form. Despite these reservations, it should be noted that the only animals in which the median hippocampal spectrum was completely devoid of harmonic peaks were those characterized by low frequency θ peaks (Ss 8 and 12). Another low frequency θ generator in which the z plot failed to demonstrate an enhancement peak (S 1) did show a slight rise in its median plot (1.8 times trough amplitude) distributed across the range including the second harmonic. The median amplitude of harmonic peaks in other Ss ranged from 3.6-11. times prior trough levels.

Poorly resolved θ for stimulus 4 (< 10 times prior trough power) of high frequency was associated with subharmonics in both median power spectrum and z measures in S 11. In this animal the "subharmonic" was actually the dominant mode of activity. An intermediate position was occupied by S 13. This median power spectrum showed broad peaks centered at a frequency of $2^{\pm 1}$ times the narrowly delimited θ peak frequency. The high frequency component could be described as a true enhancement by rank sum criteria while the low frequency component took the form of a gap in the sub-θ suppression.

Lateral Hypothalamic θ

Ambient levels of power in the θ range were variable in the LH and failed to suggest a spectral peak. Four animals (Ss 8, 11, 18 and 19) showed no tendency to peak in θ. One animal (S 1) exhibited a plateau in the median power spectrum. The remaining three subjects exhibited small "peaks" of 1.2-1.5 times the power in the prior spectral bin.

Peaking and suppression during stimulus 4. Median LH power spectra exhibited θ peaks at stimulus 4 in four animals (Ss 1, 9, 12 and 13). While such peaks were generally small (2.2-4.7 times prior trough), S 9 produced a peak of 18 times the power of the nearby trough in the spectrum. This animal also exhibited a decisive LH second harmonic peak with a factor of 2.9 times trough power.

All rats exhibited peak z increments during stimulus 4 at the same frequency as the peak observed in the hippocampal EEG. In one animal (S 9), the peak obtained from rank sum measures occupied the entire suprapeak band tested for θ as well. While all rank sum measures were synchronized between recording sites for this S, the frequency bin of the maximum was in the next higher frequency bin than the median peak. Both of these frequency bins, as well as the rest of the suprapeak range, exhibited a highly significant z.

Group statistics for stimulus 4 demonstrate both a significant peaking tendency ($t=4.61$; $df=7$; $p < .005$) and a significant suppression effect ($t=8.45$; $df=7$; $p \ll .0005$). There is again no evidence for a relationship between the sign of the individual z scores and a subpeak or suprapeak θ locus when pooled across subjects ($\chi^2=.79$; $df=1$ $p < .3$). The contrast between peaking and suppression effects could readily be identified in all *S*s.

It should be noted that while the group trend for the enhancement of LH power at the peak was significant at stimulus 4, it was not universal. In *S* 19, the stimulus 4 suppression effect was consistent and well-formed. The prominent peak arising from this level, however, only reached a level indistinguishable from the control distribution ($z= -.17$). This *S* clearly showed a sharpening of θ at the θ peak despite a noticeable lack of enhancement at that frequency.

Harmonics. Possible harmonic effects were less clear for the LH than for the hippocampus. At stimulus 4, four animals showed either peaks or rebounds from inhibition in the vicinity of the second harmonic (*S*s 8, 9, 13 and 18) although in one (*S* 8) this effect failed to attain significance. Two animals (*S*s 1 and 19) showed activity shifts localized at or near the third harmonic. One animal (*S* 18) exhibited a lesser peak immediately above the range scanned for θ that was not a simple harmonic of the θ peak. In another case (*S* 12) the suppression effect persisted throughout all nonpeak regions.

Low intensity stimulation. At stimulus intensities below that of stimulus 4, the measures obtained from the LH were quite erratic or idiosyncratic. For stimulus 1, there was a decided tendency for z scores to peak without obvious regard to the hippocampal peak. For the six cases in which a discriminable θ peak existed, a product-moment correlation of the (maximum) peak frequency bin number for hippocampal and LH z plots produced an $r = -.65$. While this is not a significant correlation with such a small N, it is clearly inconsistent with a synchronization of these shifts. The magnitude of the group statistic for the peak was $t=2.96$ ($df=5$; $p < .025$), indicating the decisiveness with which these influences were expressed in these six animals.

The θ peak data from LH derivations under stimuli 2 and 3 repeat the peculiarities evident in stimulus 1. For stimulus 2, one animal (*S* 13) produced data too contaminated by artifact to be included in the summary. Of the remaining seven animals, one showed no peak (*S* 18) and two (*S*s 1 and 8) peaked at a different frequency from that in the hippocampus. For stimulus 3, two (*S*s 18 and 19) of the seven animals tested showed no peak at all while a third (*S* 8) peaked below the range scanned for θ. For these two conditions, the group peak statistics obtained were $t=3.41$ ($df=5$; $p < .01$) and $t=2.75$ ($df=3$; $p < .05$), resp.

As a rule, while some subjects showed clear evidence of LH suppression in nonpeak regions (or all of θ in nonpeaking subjects), the effect approached statistical significance only when the peak was aligned with the hippocampal peak. For the entire group, the evidence for nonpeak suppression in the LH was significant for stimulus 1 ($t= -2.11$; $df=7$; $p < .05$), but not appreciable for stimulus 3 ($t= -1.84$; $df=6$; $p > .05$). For stimulus 2, the effect attained a higher level of significance ($t= -3.10$; $df=6$; $p < .025$). Group statistics derived from the mean of all individual nonpeak θ estimates for stimulus intensities below 4 also attained significance ($t= -1.96$; $df=7$; $p < .05$). The contamination caused by the presence of lesser peaks is certainly responsible for at least a part of the degradation of these statistics.

Correlation with hippocampal indices. Since hippocampal and LH power measures exhibit peaks in precisely the same frequency bins for stimulus 4, it might be supposed that their peak z scores also covary in a generally predictable manner. It may further be suspected that this correspondence is present in nonpeak portions of the spectrum as well. When rank order correlated, these two categories generated statistics of approximately the same magnitude and opposite sign. These correlations were not statistically significant ($\rho = -.36$ and $+.40$, resp.; $p > .05$). Considering the negative peak correlation so derived, it is safe to say that there is again no evidence that changes in the two recording sites positively covary at the dominant frequency. The maximal relative magnitude (stimulus 4 power ratio) of θ in the LH was likewise unrelated to the magnitude of hippocampal θ (ρ =.05; $p >> .05$). When viewed in concert with the frequency data presented for stimulus 1, it seems safe to suggest that the synchronization of maximal spectral peaks is not simply a manifestation of a single event marking both records simultaneously.

Coherence

Nonpeak suppression. Nonpeak measures for γ^2 showed what appeared to be a montonic increase in negativity with increases in stimulus intensity. No evidence for suppression was found for stimuli 1 and 2 ($t= +.33$ and $-.15$; df=7 and 6; $p > .05$). At stimulus 3, the effect attained significance ($t= -1.85$; df=6; $p < .05$), while stimulus 4, it became decisive ($t= -2.30$; df=7; $p < .05$). Pooled signs of subpeak and suprapeak θ estimates produced a continuity corrected χ^2=.075, clearly failing to suggest an interdependence. It should be noted that over one third of all individual z scores within the frequency range tested were above the mean. This is in sharp contrast to the corresponding measures for the power spectra, where positive deviations were rare (< 10%).

The monotonic increase in the magnitude of the suppression test statistic from stimulus conditions 1 through 4 is suggestive. The existence of lesser peaks necessarily degrades the estimate of this effect for stimuli below stimulus 4. Control coherence values were frequently below .1. In view of the roughly linear log plot typical of the LH power spectrum, the coherent activity so reflected is quite small. When digitization considerations are added to this, it becomes clear that this approach is biased against detecting a suppression effect for the nonpeak range. Despite the lower maximal significance level acquired, the suppression of coherence in nonpeak θ is similar to the effect on the individual power spectra.

Peak enhancement. The z plot of γ^2 showed a general tendency to peak in θ. This tendency was separable from the locus of the hippocampal or LH peaking tendency. For stimulus 1, only one animal (S 11) lacked a distinct peak in θ. Three animals (Ss 1, 18 and 19) showed a dual peak, while five (Ss 8, 9, 11, 13 and 18) had maximal peaks discrepent from that in the hippocampus. For the seven animals in which a peak occurred, the shift was even more decisive than that in the hippocampus ($t=11.85$; $p << .0005$). The product-moment correlations of the frequency bin number of the γ^2 peak vs. that in the hippocampus ($r=.29$; $N=6$) was small, while the LH correlation was infinitessimal ($r=.08$; $N=5$).

At stimulus 2, again only one animal (S 18) failed to exhibit a peak. At the same time, one additional animal (*S* 8) exhibited a significant peak discrepent from the frequency of that in the hippocampus. At condition 3, all animals showed θ peaks. Curisously, the three animals in which no LH peak appeared showed γ^2 peaks at difrent frequencies than the one in the hippocampus. This peak was significant in two of these (*S*s 8 and 19). Two subjects (*S*s 11 and 18) had multiple peaks in or below θ. Group statistics for the magnitude of the peaking tendency were pronounced. For stimulus 2, $t=6.20$ ($df=5$; $p < .005$), while for stimulus 3, $t=6.19$ ($df=6$; $p < .0005$). In stimulus condition 4, where the γ^2 peak was synchronous with the other measures and present in all subjects, the group measure was even larger ($t=12.32$; $df=7$; $p \ll .0005$).

Harmonics. At stimulus 4, five *S*s showed an enhancement of coherence at the second harmonic of the θ peak. This peak attained significance in four animals (*S*s 1, 9, 11 and 19). In *S* 1, this occurred despite a lack of a comparable effect in either power spectrum. In another animal (*S* 12), a nonsignificant biphasic effect was found. Two animals (*S*s 11 and 12) exhibited a significant coherence increase at half the frequency of the θ peak.

Correlation with other indices. Rank order correlations of the z scores derived from stimulus 4 within peak and nonpeak categories were performed between γ^2 and the power spectra. For hippocampal and hypothalamic peak values, $\rho = -.33$ and $+.43$, resp. Nonpeak values were much smaller and of opposite sign (+.14 and -.10, resp.). Correlations between the γ^2 measure and the product of the hippocampal X LH measures were also examined for evidence of a joint effect. These produced a $\rho = .0$ and $+.26$ for peak and nonpeak activity. None of these values attain significance at $\alpha = .05$.

The stimulus 4 power ratios of the LH and hippocampus were rank order correlated with the corresponding peak median γ^2 estimates. Hippocampal rhythmicity was not obviously related to signal coherence magnitude ($\rho = .27$; $p > .05$). The median signal coherence did appear to be related to the relative amplitude of the LH peak in reasonably linear fashion ($\rho = .89$; $p < .02$; $r = .84$; $p < .01$). The proportion of shared activity therefore appears to be related to the resolution of θ in the LH, but independent of hippocampal θ.

Phase Properties

Because of the variable magnitude of the signal coherence observed, only the phase properties of the two extreme stimulus conditions are of obvious relevance to the problem of shared activity. Of the data-bearing _S_s, only _S_s 11 and 13 failed to exhibit a phase distribution discriminable ($p < .05$) from a uniform distribution within the frequency range of the stimulus 4 power spectrum peak. For the former _S_, such stability did appear in an adjacent bin. The phase angles at the small control peaks were also stable for all cases but one (_S_ 13) in which the median hippocampal power spectrum peak exceeded its low frequency baseline by more than a factor of 1.1. The failure of this statistic for S 13 is not surprising since fewer clean data records were available than are required for its reliable use. The present evidence clearly suggests a degree of stability in the timing of the two signals despite the widely varying coherence values obtained.

Within the frequency range scanned by the narrowly delimited power spectrum peak of stimulus 4, phase angle distributions for the conditions were discriminable ($p < .05$) from each other by the exact test statistic in all Ss but 8 and 13 for independently or jointly rotated data. If the statistical requirements were relaxed to $p=.06$, S 13 would also produce discriminable data. Of those animals in which phase stability was found, both jointly and independently rotated statistics attained significance in all but two cases. A significant rank sum statistic supplemented this discriminability in only two cases. It is therefore likely that the obtained differences reflect changes in variability, rather than central tendency.

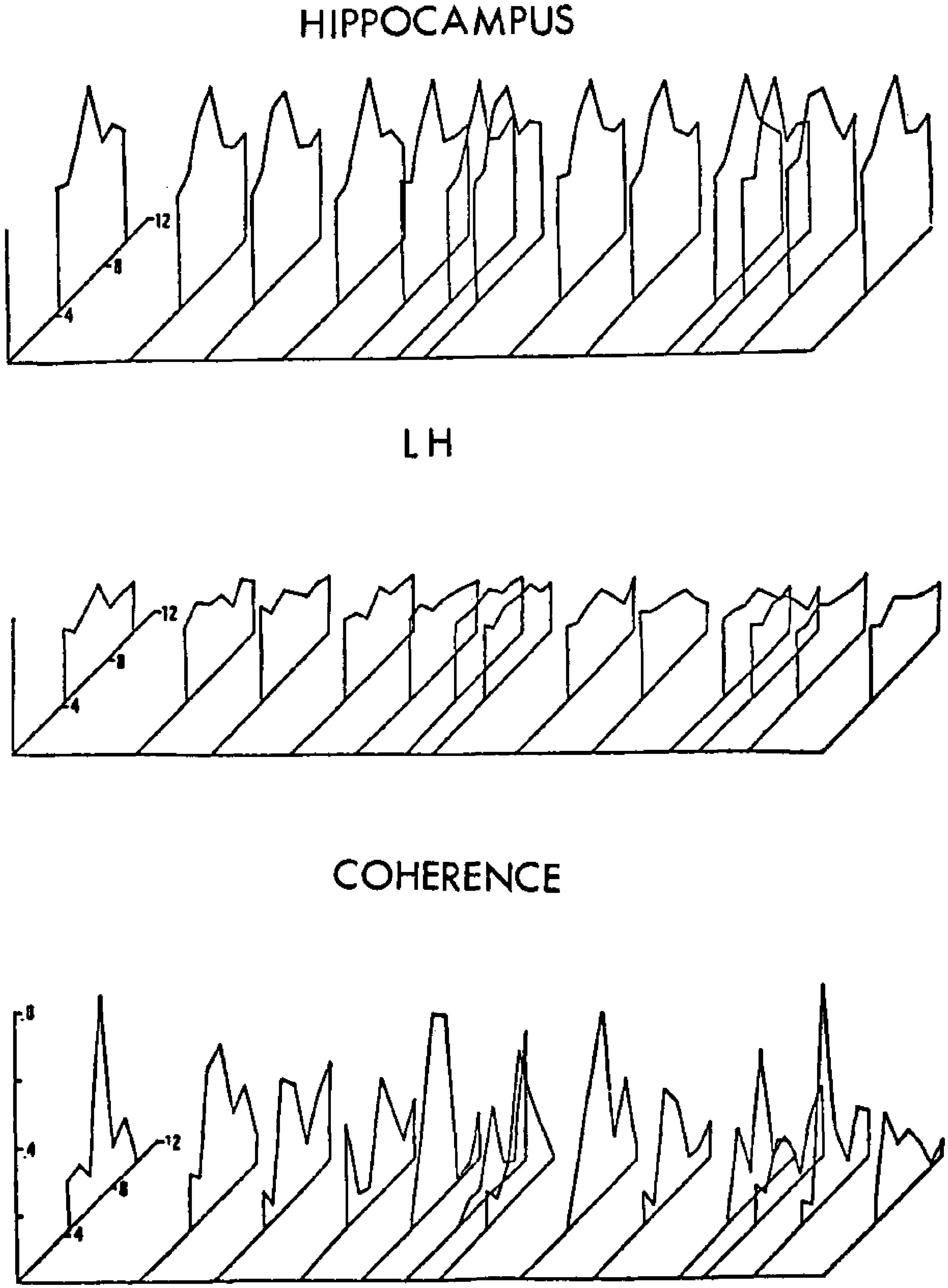
In summary, all Ss but the one characterized by the slowest θ during stimulus 4 showed evidence of change in their phase properties with stimulation. These measures serve primarily as an independent verification of the coherence increases at the θ peak. Since the coherence values obtained (Table 3) were often quite small and at times unstable, the results indicate a nontrivial, stimulation-induced phase stabilization of the paired EEGs.

Representative Data

As previously indicated, the significant group trends associated with the peaking and suppression effects were present in the individual S's data as well, particularly for stimulus 4. While some animals showed most or all of these changes in a robust fashion, others showed consistent but smaller trends that were individually nonsignificant, yet supportive of the group effect. The frequency at which peaking and harmonic effects occurred was quite variable as well. These properties speak against the validity of pooling the spectral data on a frequency-by-frequency basis. While it is possible to scale or synchronize the frequency dimension for the purposes of representing an intelligible summary plot (see Figure 16), the frequency specificity of the θ rhythm would be obscured by such procedures, particularly in regions of the suprapeak and subpeak effects. A more fruitful approach is to present the data from a typical subject in great detail, with reference made to both shared and idiosyncratic tendencies present in it.

General properties and stability of data. Animal 18 was selected as a representative S for the illustration of the present data. This S was at the approximate median with respect to the greatest number of relevant measures. These measures included the peaking tendency

Fig. 12. A variant of a compressed spectral array illustrating the characteristics of all acceptable data records for stimulus 4 in S 18. The duration of the experiment is represented in the horizontal axes. The variable interrecord interval reflects the stimulus randomization procedure. The log magnitudes of the hippocampal and LH power spectra (log $\mu V^2/Hz$) and the amplitudes of the signal coherence are plotted only for activity within the θ range. Vertical calibration = .8 for full scale on coherence axis; = log (10^3) for power spectra. An offset of log $(10^{1.5})$ has been applied to the power spectrum plots to aid in the interpretation of the LH data.

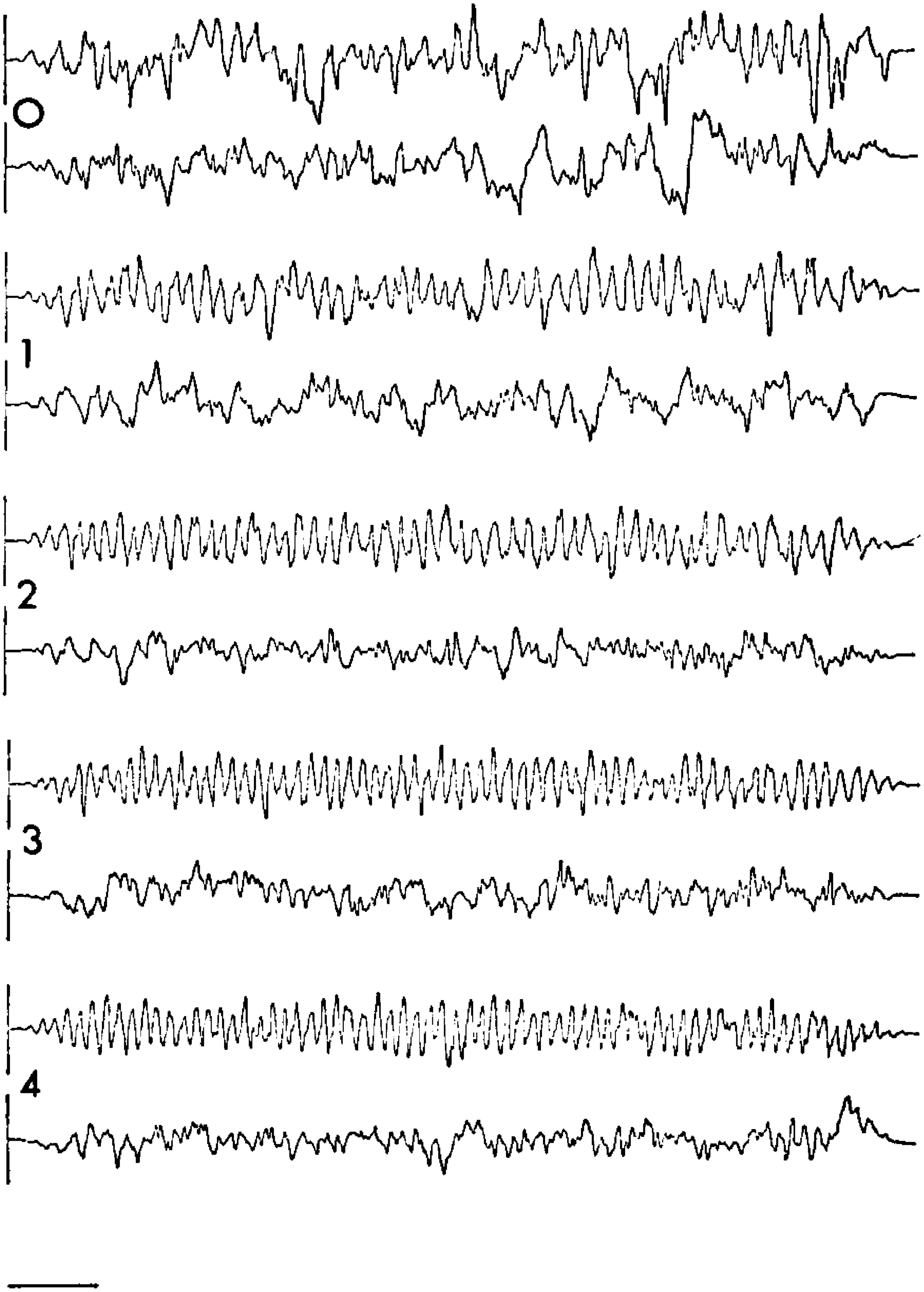

HIPPOCAMPUS
12
8
4
LH
12
8
4
COHERENCE
.8
.4
12
8
4

for the control data, stimulus 4 rank sum effects and peak frequency. Table 3 is of interest in comparing the stimulus 4 trends exhibited by *S* 18 with those of other animals. The θ range data for each individual data record acquired during stimulus 4 are presented in Figure 12. The relative stability of the hippocampal data and the volatility of the LH and γ^2 measures during the experimental session is apparent.

Hippocampal effects. Since the hippocampal electrodes were targeted at the CA3 field, the possible appearance of a relatively impure θ rhythm was anticipated. In some animals, however, a distinct θ pattern could be readily produced. The animal selected as typical on other grounds had a placement in which both tips were deep in the stratum oriens of CA3 (Figure 10). This subject produced a clearly rhythmic pattern at higher stimulus intensities. Figure 13 illustrates the induction of this rhythm with representative EEG records from each stimulus condition.

Another animal with a similar electrode palcement (*S* 16) also produced a stimulation-induced θ pattern of marked rhythmicity. While this animal did not survive to produce experimental data useable for statistical purposes, it did generate a hippocampal EEG during a stimulus 4 trial in which the appearance of induced activity at about 8 Hz was partially separable from its second harmonic. The resulting EEG visibly varied between a pure and mixed θ pattern, with θ suppression during the

Fig. 13. Representative raw data records for S 18 during stimuli 0 - 4. The top record of each pair is from the hippocampus, while the bottom one is from the LH. The cosine taper and DC balance procedures are evident. Calibrations are 200 μV and 40 μV, resp. Time calibration is 1 sec. For these data records, spectral peak-to-prior trough power ratios for the hippocampus are 2.3, 4.2, 5.0, 19.3 and 27.0, resp. Corresponding ratios for LH power are undefined, since no peak was evident in the power spectrum.


0
1
2
3
4

middle portions of the record.

When the representative hippocampal EEG records of Figure 12 are examined in concert with the median power spectra across all trials in the corresponding conditions (Figure 14a), a continuum is apparent in the development of θ rhythmicity. It should be emphasized that even when the raw data from a given animal failed to display any obvious rhythmicity during low intensity stimulation, the underlying changes tended to be continuous with those characterizing rhythmic θ at high intensities. As shown in Table 3, both peaking and suppression effects in the hippocampus progressed to clear and significant levels in all but one animal (S 1). In this subject, the suppression trend was quite general, but attained significance in only one bin. It was further contaminated by the presence of a positive anomaly in bin 11. In most animals (including S 1), the subpeak suppression persisted at significant levels into the frequency range below θ.

The median hippocampal power spectrum of S 18 shows a suppression of subpeak power at the lowest intensity stimulus (Figure 14a). This suppression is maintained in a somewhat less pronounced form in the suprapeak region. Upon comparison with the stimulus 1 plot of z vs. frequency (Figure 15a), the significance of these trends may be directly assessed. The resolving power of this statistic is apparent from the relatively

Fig. 14. Median plots of the spectral measures for stimuli 0 (filled circles), 1 (open circles) and 4 (filled squares) is S 18. Medians are based on 17, 16 and 13 data records, resp. A. Hippocampal log median power spectrum. B. LH log median power spectrum (note that at the highest frequencies stimulus 1 medians are indistinguishable from the control). C. Coherence. For this S, the growth and frequency shift of the hippocampal peak is evident in the median power spectrum plot. The growth of both hippocampal and LH suppression is also clear (compare with raw data in Figure 13).

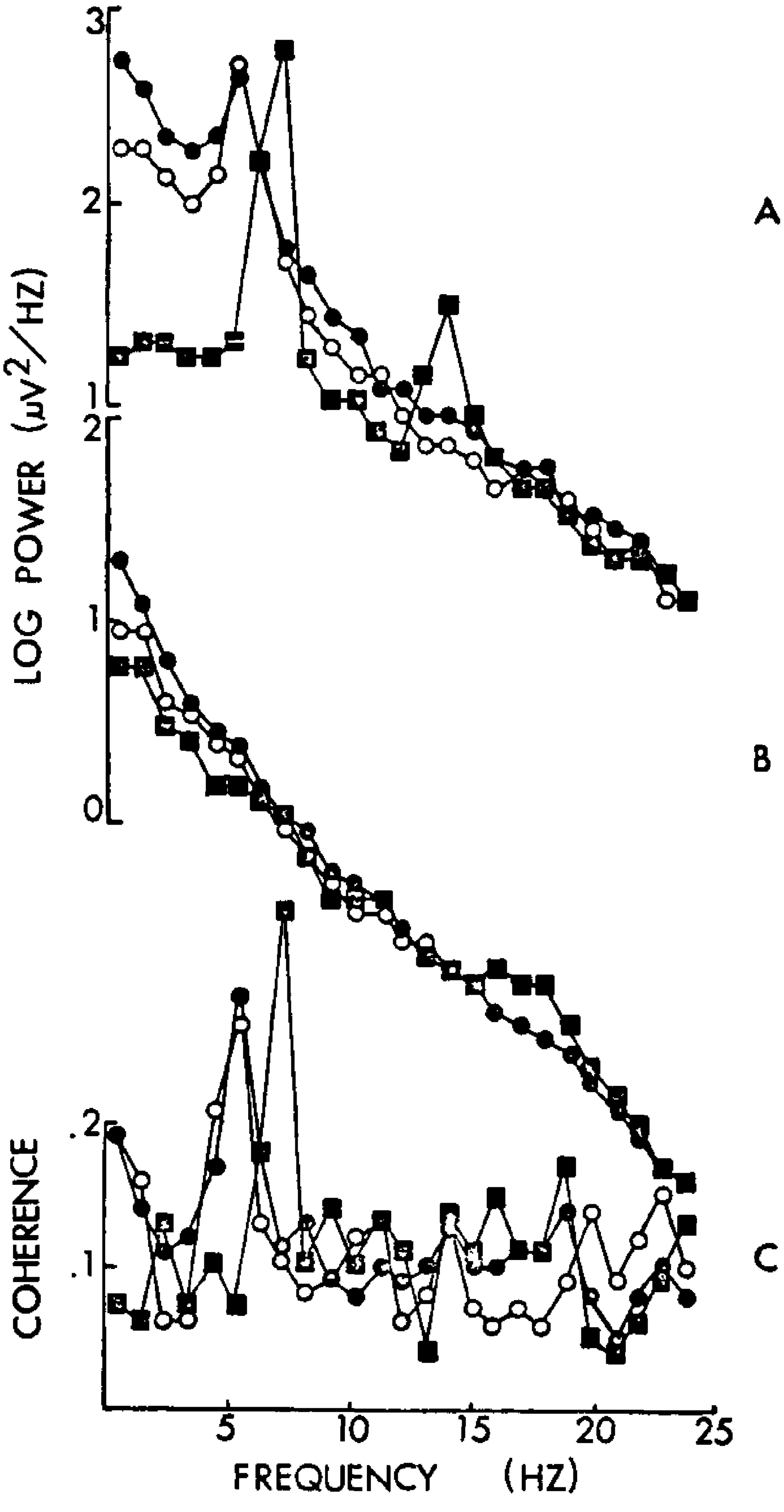
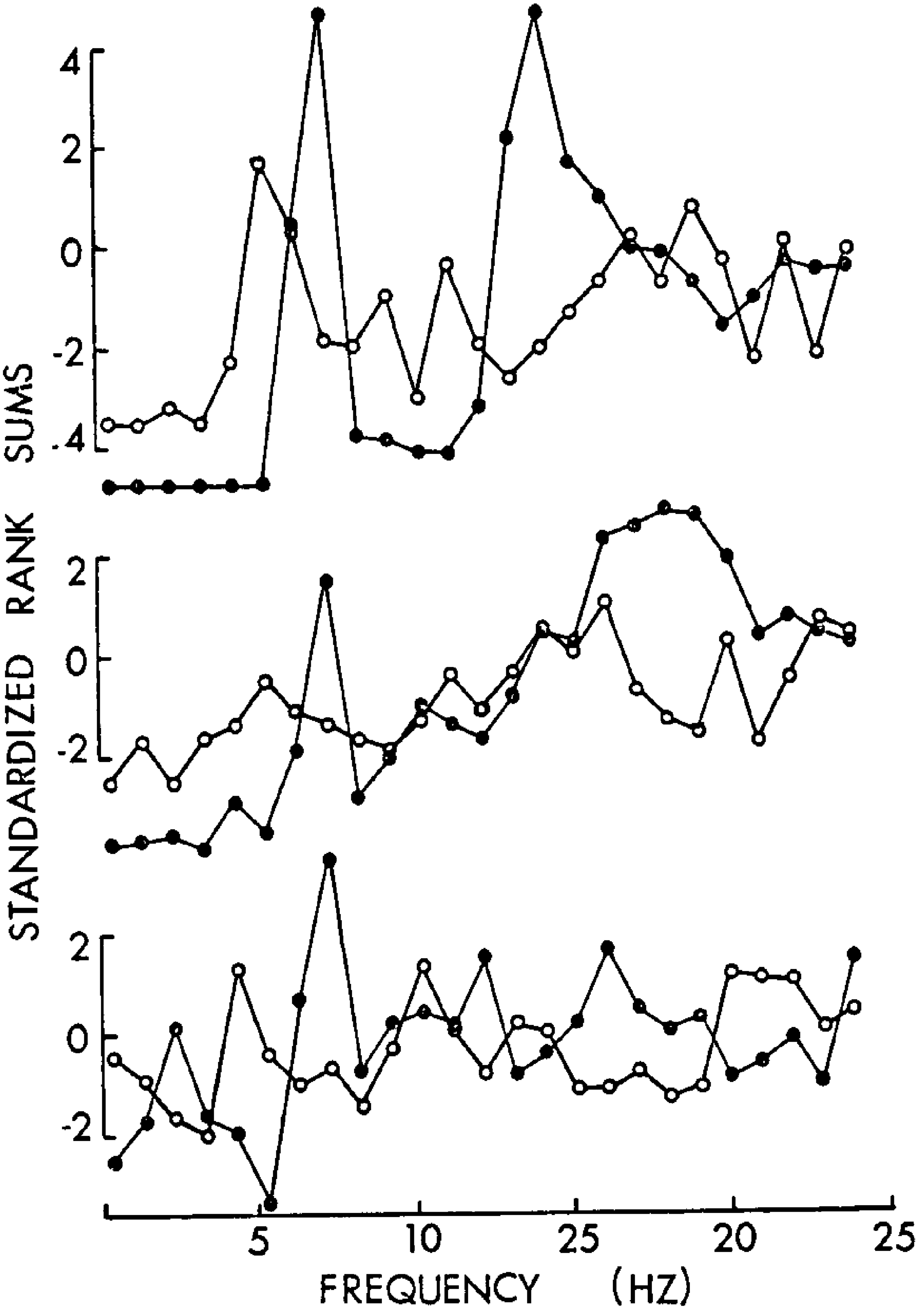

3
2
1
A
2
1
0
B
LOG POWER (µV²/HZ)
.2
.1
C
COHERENCE
5
10
15
20
25
FREQUENCY (HZ)

Fig. 15. Standardized rank sum plots for stimulus 1 (open circles) and stimulus 4 (filled circles) when compared with control data in S 18. A. Hippocampal power. B. LH power. C. Coherence.

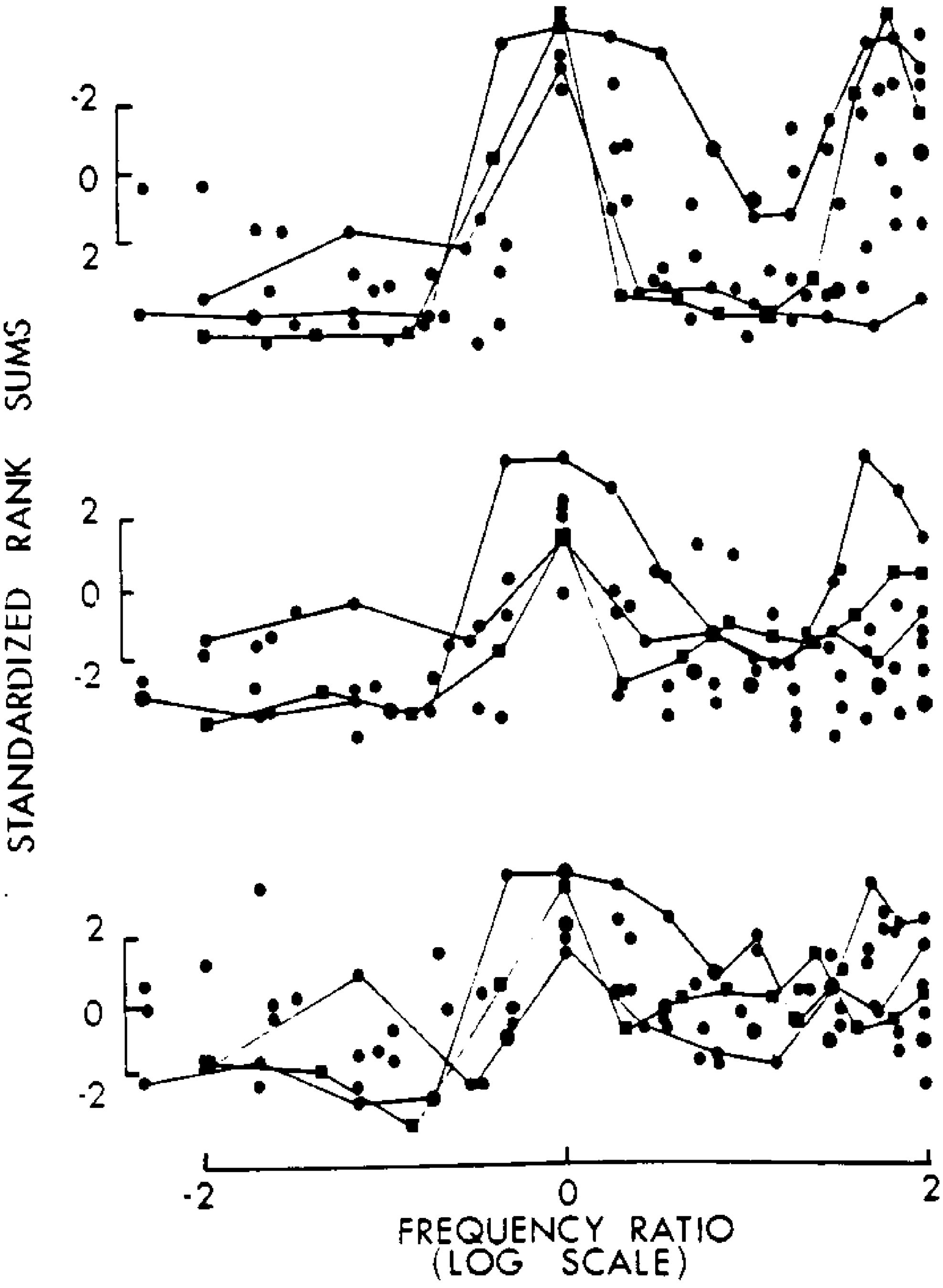

STANDARDIZED RANK SUMS
4
2
0
-2
-4
2
0
-2
2
0
-2
5
10
25
20
25
FREQUENCY (HZ)

large value attained at the peak. For stimulus 4, these trends are further exaggerated. Concurrently, the peak is shifted to a higher frequency. The suppression effect includes frequencies below θ as well as an extension above the range sampled in the group statistics. The saturation level of the statistic is also apparent. These data are presented again in Figure 16a in frequency-adjusted form to enable a comparison with data acquired from the rest of Ss.

A decisive second harmonic was present in the hippocampal record at stimulus 4. Such harmonic trends were not uncommon. In all but three (Ss 1, 8 and 13) of the eight data bearing animals, a significant peak or suprasuppression enhancement occurred in the vicinity of the second harmonic. A comparison of the distribution of hippocampal harmonic tendencies with the associated peak frequencies of the individual subjects (Table 3) shows that clear second harmonic peaks were found when θ peaks were in bins 7-9. In view of the visibility of the second harmonic previously described for S 16 during stimulus 4, as well as its separability from the θ waveform, a dual peaking tendency is likely at such frequencies. Suppression release enhancements without distinct peaks occurred only when the θ peak was in bins 9-10, while third harmonic suppression occurred only for bin 7 peaks.

Lateral hypothalamic effects. As may be readily discerned from Table 3, the influence of stimulus 4 on

Fig. 16. Standardized rank sums for stimulus 4 plotted as a function of scaled frequency for all data-bearing Ss. Frequency expressed in ratio to peak frequency and scaled logarithmically. Solid lines indicate the representative S (filled squares) and two extreme Ss. Data from one extreme S are characterized by particularly wide peaks (S 9), while in the other (S 8), the peaks are most poorly defined. The data from the remaining Ss are illustrated in the scatter of points around these cases. The exact frequency of the harmonics at ±2 are subject to an estimation error due to the use of the midpoint of the peak frequency bin as a reference. A. Hippocampal power. B. LH power. C. Coherence.


-2
0
2
2
0
-2
2
0
-2
STANDARDIZED RANK SUMS
-2
0
2
FREQUENCY RATIO
(LOG SCALE)

the EEG of the LH is less marked than in the hippocampus. All animals did show a readily discriminable peak-suppression structure in the band tested. A significant positive value was not, however, always attained at these peaks. The EEG of the LH in S 18 clearly is not characterized by a large enhancement of its median at peak frequency (Figure 14b). In keeping with its raw data (Figure 13), no discriminable LH peak corresponds to the hippocampal peak. The negligible difference in the median is not, however, reflected by the lack of an LH z peak. The peak exhibited in Figure 15B may fail to attain individual significance, but it is both consistent with and supportive of a group effect. It also stands in marked contrast to the surrounding zone of suppression. The wide peak that does attain significance is an idiosyncratic peak above the frequency of the second harmonic. A comparison of the LH data with the hippocampal trends displayed in Figures 14a and 15a emphasizes the independence of the power spectrum trends at the second harmonic.

The EEG of the LH of S 18 showed no persistent peaking tendency below stimulus 4. In this animal nonpeak suppression was persistant, however, attaining significance by stimulus 2. The small median decrease effect visible for stimulus 1 in Figure 14b is directly paralleled by the nearly significant rank sum suppression of Figure 15b. The small, fledgeling "peak" at this intensity exists only in its relation to the basal suppression level and the hippocampal peak. Figure 16b illustrates the generality of these trends across Ss.

Coherence effects. The strong peaking tendency of the z vs. frequency plot derived from the coherence function is manifested in S 18 by the appearance of a pair of nonsignificant positive peaks in the stimulus 1 plot (Figure 15c). The first of these peaks corresponds to a slight flattening of the control peak in the median plot. The general nature of the suppression at lower frequencies is suggested by the median data, as well as the depressed baseline from which the z peak emerges. Figure 16c also illustrates this trend.

The abruptly biphasic form taken by the z plot at stimulus 4 is idiosyncratic and partially reflects the shift in the frequency of the peak. The lack of segregation of the signed deviations according to their suprapeak or subpeak θ locus over the entire group of animals speaks against the generality of this influence in the production of the coherence peak. Three animals (Ss 1, 12 and 19) actually showed an equal or greater suppression in suprapeak regions. This S also failed to produce an enhanced coherence at the second harmonic. Enhancement peaks in the vicinity of the second harmonic were significant and readily identifiable in half of the data-bearing S.

Phase properties. In keeping with its status as a representative S, the phase specificity for S 18 at the frequency of the stimulus 4 spectral peak was discriminable from a uniform distribution in stimulus 4 data, but not control data. Likewise, the phase distribution at the frequency of the small control peak was stable in the control data, but not at stimulus 4. While both independent and joint rotation statistics supported the separability of the two phase distributions based on exact dispersion statistics, the rank sum statistic did not. This suggests a stabilization of phase properties, without a concomittent phase shift, as a result of a shift in peak frequency.

Behavioral Correlates of Stimulation

Restrained. During stimulus 4 trials, all but one animal (S 1) showed respiratory effects. These effects included a marked slowing or cessation of breathing. The expiratory phase tended to be exaggerated. At times, gasping occurred, this response being most typical at the offset of the stimulus.

The three animals (Ss 1, 9 and 13) in which peak median coherence values were maximum at stimulus 4 showed no noticeable tendency to move or movement suppression during stimulus presentation. These Ss exhibited peak maxima ranging from .6-.96. Peak enhancement in LH also tended to be more consistent and of greater amplitude in these subjects. A substantial median γ^2 peak appeared in a low frequency bin under control conditions in two of these (Ss 9 and 13). Both of them exhibited a strong ipsilateral rotation of the head into the padding at stimulus onset.

Rotary responses to stimulation were common during the administration of the higher intensity stimuli. Often, a slight straying of the head toward the side stimulated accompanied low or mid-range stimulation, increasing in speed and decisiveness with increases of stimulus intensity. At times shrugging and changes in the facial musculative such as eye closure appeared. Vocalization and vigorous movement were rare, an observation guaranteed by the elimination of those rare animals that proved to be intractable. In this context, *S* 13 was the most extreme *S* to produce useable data.

In some cases, the rotary response approached a maximal level at intensities below conditon 4. Among these animals, two additional responses appeared as well. Muscular patterns in which tail movements occurred appeared in three animals (*S*s 12, 18 and 19). A conjunctive set of *S*s of equal number (*S*s 11, 12 and 18) developed irregular patterns of small movements of the head. A degree of head tremor variably occurred at these times. The appearance of these motor patterns was not linked with LH or γ^2 measures in any consistent or suggestive fashion. Two of the animals in which tail thrashing occurred (*S*s 18 and 19) exhibited LH peak enhancement in all-or-none, rather than continuous fashion. The electrographic effect occurred at a higher stimulus intensity than that required to produce the behavioral effect.

In view of the proximity of the pontine stimulation zone to trigeminal structures, the induction of jaw movement patterns by the presentation of the experimental stimuli might be expected. Chattering of the teeth was typical of stimulation sites nearest these loci, the effect usually occurring at stimulus offset. A number of bouts of chattering occurred during the experimental session in five Ss (Ss 4, 8, 13, 18 and 19). Only the S in which the vicinity of the motor nucleus was stimulated (S 4, a "thalamic" S) exhibited a noticeable tendency to chatter during data acquisition periods for control and low intensity stimulation epochs.

Unrestrained. In freely moving animals, the self-stimulation response to pontine stimulation was extremely rare. Only one animal (S 8) produced a clear self-stimulation response. The pontine site was found to be below the locus coeruleus and adjacent to the nucleus of the mesencephalic tract of the trigeminal nerve. One animal (S1) with a stimulation site at the medial border of the locus coeruleus showed sniffing and behavioral activation at times without self-stimulation. Even in animal 3, in which the locus coeruleus was directly stimulated, an ipsilateral rotation and a sporadic sniffing pattern were all that could be detected.

Stimulation of the pons in free-moving rats was generally neutral in its reinforcement properties. Despite the strength and generality of the rotary effects induced by these stimuli, escape responses were never encountered and marked signs of stress were seen in only one S (S 13). Maximal avoidance responses during attempted shaping trials always took the form of motionlessness. The only instances in which active behaviors were produced were those reflecting the motor substrate. These responses took on a forced quality.

The stimulus amplitudes used were of more than adequate range to support self-stimulation at other sites. Five animals were tested for LH self-stimulation as well. Of the four data-bearing animals tested (S 8, 9, 13 and 18), only S 8 failed to self-stimulate. Stimulation of the most ventral portion of the LH was mildly aversive in one "thalamic" animal (S 6).

Anomalous Electrode Placements

Locus coeruleus. While some animals failed to generate data due to poor health or a lack of adaptability to restraint under stimulation, three were excluded from the analysis for histological reasons. Of these Ss, the only animal with acceptable placements in the recording sites to be excluded was S 3. In this S, the stimulation electrode was located precisely within the locus coeruleus.

In general, as is evident from Table 3, S 3 was clearly anomalous. The form of this anomaly is continuous with the findings obtained from the other animals on both anatomical and physiological grounds. It is therefore of interest to separately examine the data produced by this animal.

Animal 3 failed to generate hippocampal θ in a form recognizable in time domain records. Under ambient (stimulus 0) conditons, a low level peak (1.9 times prior level) appeared in the median power spectrum at bin 6. This bin showed a slight, nonsignificant enhancement of the rank sum structure of hippocampal power in stimulus condition 4. Continuous with this was a significant bin 7 enhancement. Nonpeak suppression effects were consistently significant except for a single residual enhancement on the descending slope of the peak. The suppression was found to abruptly be released at bin 11. Sub-θ suppression in bins 1-2 continued after being broken by the appearance of a highly significant enhancement peak in bin 3. It is this lower peak at which the maximum of both rank sum and median plots occurred.

It should be noted that S 9 also showed a one bin discrepency between its median and rank sum peaks. In this case, a wide range of enhancement existed, however, and the median peak frequency was itself highly significant by rank sum criteria. In S 3, the effect is more appropriately described as a widening of the small ambient median peak toward higher frequencies. This influence is of interest in the description of the development of rhythmicity. The existence of a "subharmonic" of the θ peak is also not unique to this subject. Animal 11 also showed this pattern, although the θ peaks for these two *S*s were at opposite ends of the band. The difference may be quantitative, rather than qualitative.

Aside from the hippocampal trends, the changes induced by stimulation in *S* 3 were generally nonsignificant. Rank sum data for LH at stimulus 4 indicated a tendency toward suppression, but with a standardized (z) range of only -1.61 to +.48. Coherence medians for both control and stimulus 4 were of small magnitude (maximum of .16 in θ) and were irregular. Standardized rank sums for γ^2 ranged from -2.91 to +.16 with the two significant suppression values occurring in bins 5 and 10.

Despite the feeble coherence levels, phase estimates from the control and stimulus 4 were discriminable in bin 5 by the joint rotation Fischer exact test. Variability per se, as indicated by the independently rotated data, was not discriminable, nor was stimulus 4 discriminable from a uniform distribution anywhere but in bin 21. Control data, however, were stable in bins 5 and 10.

Thalamus. A second category of electrode placement anomaly that has instructive value is one in which the "hippocampal" electrode was actually located in the lateral geniculate nucleus of the underlying thalamus.

As can be seen in Figure 10, this occurred in two animals (Ss 4 and 6). The depth of these placements makes the comparability of the LH data with that obtained from other animals questionable. Upon gross dissection, S 6 was noted for the visibility of a discoloration near the ventral hypothalamic surface corresponding to the electrode track.

Both subjects with thalamic data exhibited significant standardized rank sums at stimulus 4 corresponding to median peaks in the θ range. For one animal (S 6), this effect closely resembled that seen in hippocampal sites. A small, ambient median peak in bin 7 became markedly pronounced. A significant rank sum suppression of nonpeak regions persisted both above and below the range sampled for θ, returning to near zero by bin 18.

The ambient median power spectrum for the thalamus of the second animal (S 4) did not resemble that of the hippocampus. The simple exponential decline typical of LH characterized the spectrum. In this animal, the application of stimulus 4 led to a meager peak in the median power spectrum occupying bins 6 and 7. This peak had a maximum of 2.4 times the magnitude of the prior level. Standardized rank sums were positive over the entire θ range, reaching its maximum possible value at the frequency corresponding to the median peak. The enhancement was significant in all frequency bins. The frequent occurrence of chattering during the experimental session may account for some of the peculiarities in these data.

The hypothalamic power recorded from both thalamic animals showed only nonsignificant changes. For S 4, sharp median peaks appeared in bins 9 and 18 in stimulus 4. The θ peak effect was therefore both nonsignificant and at a different frequency than that in the thalamus. The other subject showed a very small median peak corresponding to a meager standardized rank sum peak of $z=.83$. In general, nonpeak changes were also small and variable in sign.

Coherence changes were expectably uninteresting in the thalamic animals. For S 4, a maximum median γ^2 of .19 in the control condition was degraded by stimulation. In S 6, stimulus 4 failed to affect the .25 maximum. By comparison, only two of the data bearing animals (Ss 11 and 19) showed such low coherence values during stimulus 4 (see Table 3). Despite this, phase angle measures showed some indication of change. In S 6, all statistical measures for phase angle reached the .05 level of significance in bins 6 or 7. At stimulus 4, but not the control, S 4 had a phase angle distribution discriminable from a uniform distribution in bins 6-8. The joint rotation exact test attained significance in bin 6, while the rank sum test attained significance at the remaining two. In the latter test, the direction of change in these two adjacent bins was opposite.

CHAPTER IV

DISCUSSION

Hippocampal θ

The current findings verify the presence of identifiable θ rhythmicity in the local EEG of field CA3 of the dorsal hippocampus. While the generating sites cannot be identified with these techniques, the ability of differential subpyramidal records to produce regular θ activity suggests the involvement of the basal dendrites of the pyramids. The direct septal and recurrent basket cell influences might be expected to exert θ synchrony in a common-mode fashion. The slow rate of transmission in the region of the basilar processes (Andersen et al., 1966), however, would have the capacity to exaggerate local discrepencies by distributing them over time. Since hippocampal records from different laminae exhibited the same qualitative changes during stimulation, differences in the form of the raw EEG may be attributed to quantitative differences affecting the associated substrata.

The spectral structure of the hippocampal EEG in the awake, restrained rat is affected by stimulation of the dorsal pons in a number of ways. The most general of these is the initiation of influences capable of suppressing activity of inappropriate frequencies. This form of processing acts as though a narrow bandpass filter is applied to the ambient activity. This property is consistent with the resultant inhibitory influence universally attributed to the afferents of the hippocampal formation. Suppression of this form was reported after hypothalamic stimulation for some animals by Paiva et al. (1976).

The second category of change is directly related to the active oscillatory mode of the system. Influences in this category act to amplify activity corresponding to the spectral peak. Thus, the hypothetical bandpass filter is characterized by localized, frequency specific suppressive and enhancement properties within the range occupied by θ. Evidence exists for the intrahippocampal organization of inhibitory (Spencer & Kandel, 1969), frequency specific (Andersen & Lømo, 1970) and generative (Winson, 1975) capacities of hippocampal tissue, although the role of the septal projections must not be ignored.

The changes induced in the hippocampal EEG by low intensity stimulation tends to be variable and inconsistent. There is a tendency in some cases to increase activity at different frequencies rather than to simply enhance the existing maximum. Such ambiguities probably reflect the activity of the physiological substrate under ambient conditions, since genuinely stationary data are not to be presupposed.

The committment of the hippocampal EEG to a given frequency may take the form of a threshold function related to both enhancement and suppression mechanisms. When the threshold has not been attained, the activity of portions of the fledgeling peak will tend to compete for dominance. This would account for the scattered and multiple enhancement peaks noted for the rank sum measure in some animals. After the committment to a particular spectral mode has occurred, subsequent changes result in a bidirectional improvement of the signal-to-noise ratio of the rhythmic θ activity. The spectral locale thereby exhibits a center-surround antagonism that is comparable in form to the spatial properties of the sensory systems (e.g., Mountcastle, 1961; Kuffler, 1953). The transition from non-θ to θ-dominant EEG modes reflects this pattern in a continuous, rather than dichotomous fashion.

As the spectral peak sharpens, another property emerges as well. The frequency of the θ oscillator increases, resulting in a continuum of change in which both the power and frequency of the dominant activity of the EEG are affected. Stimulation of sites within the pontine tegmentum is therefore capable of producing θ of widely varying purity and frequency as a function of stimulus intensity in the unanesthetized, restrained rat. The maximal frequency of θ so induced is clearly dependent upon the locus of stimulation in a manner consistent with the findings reported by Vertes (1980) for the anesthetized rat. This contrasts sharply with the pattern obtained in the flaxedil immobilized cat (Macadar et al., 1974).

In the restrained rat, modes of EEG activity typified by θ at different frequencies have been found to share a common spectral structure. The only potential behavioral correlates of θ in the current study are those related to tonic rotational influences. It is apparent that the distinct subdivisions of θ differentiated from behavioral and pharmacological considerations (Vanderwolf, 1975) may actually lie along a spectral continuum when driven by stimulation of the dorsal pons. This is consistent with a single generating mechanism for θ peaks of all frequencies recorded here. The wide distribution of these peaks suggests that Vanderwolf's subdivisions may be related to the correlates of the general state characterized by θ in a quantitative form, rather than a shift in the generating substrate. An alternate possibility is that the generators of spontaneous and driven θ do not share the same characteristics. This possibility cannot be evaluated without further generalization of the current procedures to unstimulated, unrestrained Ss.

Stimulation-induced θ may be expected to reflect the mechanism of natural θ in a simplified form. It appears unlikely that stimulation epochs of such long duration would be capable of adding an additional rhythmic EEG component from sources normally incapable of rhythmicity. Pontile stimulation might, however, be expected to block brainstem rhythmicity. Such a disorganization may be of relevance to the respiratory changes (disorganization of rhythmicity) noted in the current study. The remaining nonrhythmic driving of septal pacemaker activity would therefore become dissociated from brainstem sources and come to dominate the rhythmicity of the hippocampal EEG. This diffuse pattern of activation may be related to natural tonic sensorimotor biases of behavioral relevance such as those of vestibular origin. To the degree to which slow brainstem potentials are linked to the generation of θ in the forebrain (Komisaruk, 1977), the properties of the θ-state produced here may be expected to stray from those of spontaneous θ. Under natural conditions, however, both forebrain and brainstem rhythms would come under each others mutual control to produce an integrated θ-state.

The bidirectional (enhancement/suppression) effects related to the incipient dominance of θ may appear in a readily discernable form even when a considerable proportion of the activity consists of slower activity, resulting in irregular patterns in the raw EEG (Figures 13-15). While CA3 activity may not characteristically exhibit the degree of tuning required for the predominance of θ rhythmicity to be obvious in raw EEG records, the same dynamic influences affect the spectral structure of both rhythmic and nonrhythmic data. This implies that the θ activity and large irregular activity described by others (e.g., Vanderwolf et al., 1975) may differ by degree and not quality.

Aside from the enhancement of the tuning or the frequency of the θ peak, the hippocampal EEG may exhibit further acceleration by means of its harmonic content. While activity at the second harmonic was not universally affected, rank sum peaks or rebounds from inhibition were quite common. This compares favorably with reports of the existence and stability of hippocampal activity localized in the vicinity of this harmonic (Boudreau, 1966; Holsheimer & Feenstra, 1977).

Second harmonics typified all but the slowest of θ patterns evoked at stimulus 4. The appearance of activity at half the frequency of the θ peak in cases of high frequency θ and the lack of a second harmonic with low frequency θ suggest that these two extremes may be protected from aliasing by these ancillary spectral properties. Since harmonic activity was partially separable from that at the associated θ frequency in one S, it appears to be a phenomenon in its own right and not merely a refection of the saturation properties of the θ wave.

Lateral Hypothalamic θ

The enhancement of θ activity at the highest stimulus intensity was not as potent in the LH as that in the hippocampus. While group statistics clearly substantiated the trend, individual significance was obtained in only half of Ss (see Table 3). In precisely these animals, median power spectral plots revealed peaks. In other animals, such as the representative S, the changes were much more subtle.

Suppression in nonpeak regions of the θ range was clearly present both in group and individual statistics during maximal stimulation. Since suppression and enhancement are independent methods of enhancing the discriminability of rhythmic activity, a bidirectional mechanism for the improvement of the signal-to-noise ratio of θ is again in evidence. A degree of spectral center-surround antagonism is therefore characteristic of θ mode activity in the LH as well as in the hippocampus.

The results obtained for stimulus intensities below the maximum indicate that θ in the LH is much more fragile than hippocampal θ. The most noteable exception to this rule is an animal with a perifornical LH electrode placement. The lack of a large positive correlation between hippocampal and LH rank sum peak frequencies at the lowest intensity stimulus is surely a reflection of the multiple peaking tendency and probably related to the mechanism by which the peak frequency is selected from a continuum of spectral candidates. The negative value obtained suggests that the resolution of this conflict is performed by at least partially separable processes in the hippocampus and in the LH. This interpretation is further supported by the negative correlations obtained for standardized rank sum measures under the most intense stimulus conditon.

Shared θ

In the description of the manner in which activity may be shared by two distinct brain regions, it is important to realize that such sharing may take two fundamentally different forms. In the simplest form, information is transmitted from site to site in a faithful, reproduceable form. While such systems need not be linear, the simplifying characteristics of a linear model make it of value as a first approximation.

The second way that activity may be shared is in a purely statistical form. Activity from a generating site may propagate by means of local oscillatory properties of the tissue, thereby requiring the active participation of a number of regions. Since this form of sharing may lead to an independence of the two generators, it may be better described as an assimilated wave form. Such activity is produced by independent oscillators tuned to the same frequency. In its most predictable form, this type of sharing may take a form characteristic of the transmission of activity through a system with variable phase or gain properties.

The appearance of θ rhythmicity in the LH, as reported by Komisaruk and Olds (1968), may be characterized by its close relationship to the hippocampal rhythm. The current findings support the existence of this relationship during hippocampal θ, even in cases where

LH rhythmicity is not obvious from the raw EEG. The magnitude of sharing was typically found to be small. High coherence values were only occasionally detected. The exact statistics applied to phase angle estimates do suggest that a discriminable stabilization of phase properties may typify a joint θ peak. This suggestion is reinforced by the marked enhancement of signal coherence exhibited by rank sum peak statistics.

In the current study, the most generalizeable property of activity in the θ band was found to be an inhibitory one. The result of this suppression is an increased signal-to-noise ratio at the predominant frequency characterizing θ. For the hippocampal EEG, this suppression is closely linked with a simultaneous consolidation and enhancement of activity into a narrowing band representing the rhythmicity of the raw EEG. It appears that activity in the LH is subjected to a comparable, but relatively independent, suppression. This inhibitory mechanism reflects a suppression of uncorrelated noise. It therefore is capable of accounting for the significant correlation between LH rhythmicity (LH power ratio) and the proportion of the activity shared with hippocampal θ (γ^2).

As coherent activity increases its dominance in the EEG of the LH, it generally becomes strengthened as well. This causes a shift in the distribution of power estimates to higher magnitudes at the common θ peak. With the aid of the previous reduction of background noise, signal coherence is further enhanced. The total effect appears to depend on the hippocampal EEG only as the source of a stable signal, rather than as a simple, direct driver of the EEG of the LH. It appears as though a gating function has been produced through the joint action of a general suppressive and a focal (peak) θ-enhancement mechanism.

While the actual proportion of coherent activity in the EEG of the LH and the dorsal hippocampus is quite variable between Ss and at times quite low, its tendency to increase during stimulation of the dorsal pons is statistically well-defined. The multiple peaks of the coherence rank sum measure illustrate both the dynamic nature of the sharing and its relative independence from the power spectra of the two underlying EEGs. In a well-developed θ pattern, enhanced signal coherence is confined to the frequency range of the shared peak.

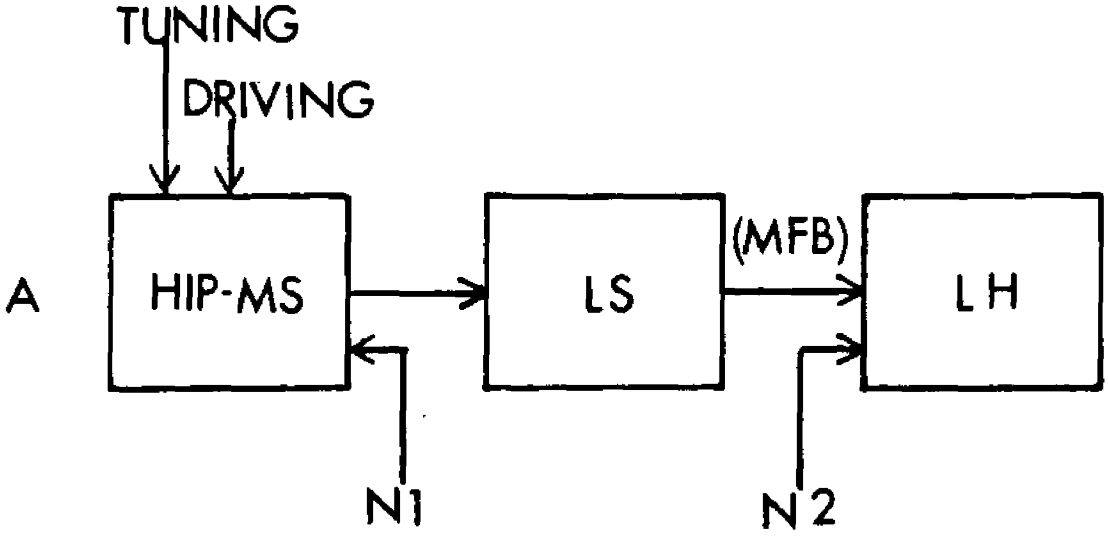
It should be emphasized that an increase in the spectral peaks for a pair of signals need not necessarily be associated with an increase in signal coherence. In fact, for an idealized linear system, an input-to-output coherence of unity will exist at any frequency for any arbitrary input signal. Since the coherence function is a spectral correlation function, its magnitude precisely reflects shared activity after normalization (Bendat & Piersol, 1971). It acts as an indication of the within frequency signal-to-noise ratio of one data record with a second record serving as a signal to be traced. If, for example, the vibration from a heavy motor is used as a signal, its contribution to be general din may be extracted directly from the coherence function in a frequency specific fashion. In the present study, the use of a well-defined physiological signal has allowed such signal extraction procedures to succeed, despite the presence of a considerable amount of noise from unrelated sources.

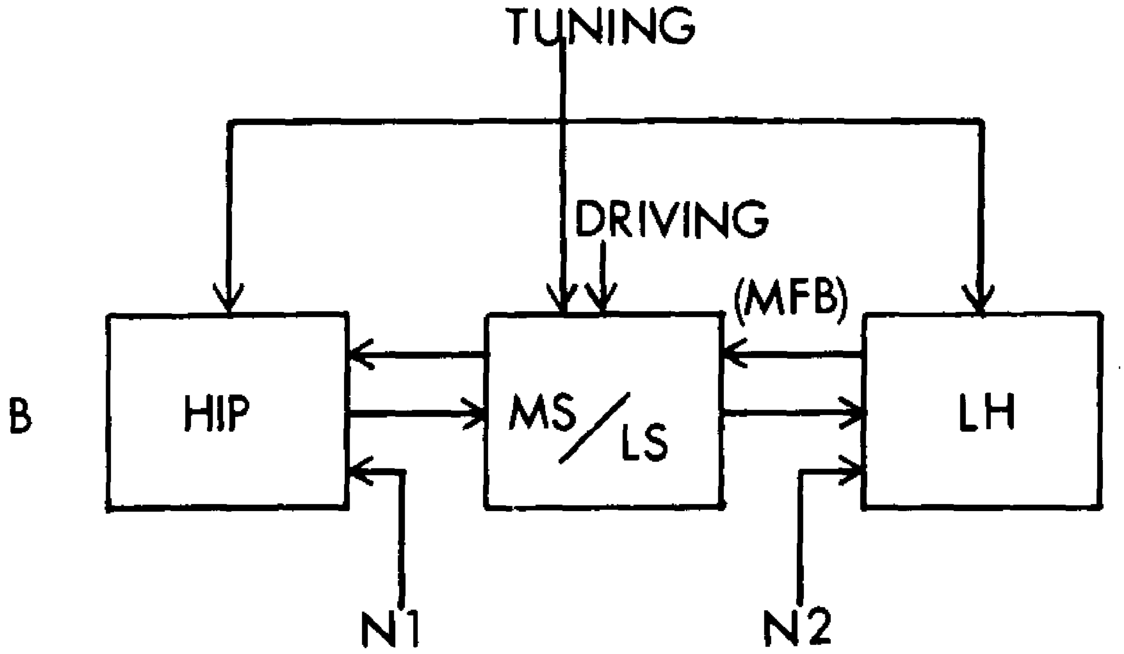
Although the characteristics of θ-rhythmicity in the hippocampus and the LH are similar in form, the relationship of the activity at these two sites to the signal coherence may differ. Rhythmicity at the LH is predictive of coherence magnitude, but a similar relationship was not found for hippocampal rhythmicity. The other correlations computed for the frequency and rank sum measures obtained from the power spectrum and coherence estimates are collectively suggestive, despite their individual lack of statistical significance. At the highest stimulus intensity, where all peaks were synchronized, the correlations derived from the standarized rank sum measures suggest that the decisiveness of the peaking tendency in γ^2 and the LH power may be positively related to each other but inversely related to hippocampal power. An antagonism is also suggested by peak frequency correlations for these measures with low intensity stimulation. Maximal peaking trends exhibited by the three measures were often out of synchrony. A negative correlation characterized the relationship between hippocampal and LH power as well.

As illustrated in Figure 17, the known anatomical and physiological relationships between the LH and the hippocampus may be simplified in two distinct fashions. The two models so produced reflect a transmission route (A) and a more statistical (B) approach to the sharing of θ. In both models, the bidirectional septohippocampal projections are presumed to represent the substrate of hippocampal θ. The driving influence is the generally nonrhythmic reticuloseptal input. As suggested by Komisaruk (1977), this input may also contain a rhythmic component as well. This component would tend to synchronize the septohippocampal projections to attain a correspondence between forebrain and brainstem rhythms. Ascending modulatory influences, such as the aminergic projections, affect the excitability of the tissue, thereby biasing or tuning its spectral characteristics. Finally, a representable noise contribution, unrelated to the shared rhythmicity, is present in each of the individual EEGs.

The flow of information from the septohippocampal θ generator is unidirectional in model A. The MFB acts as a conduit by which the descending influences affect the LH. As long as the noise levels retain a degree of constancy, LH θ will vary in a manner that closely follows hippocampal θ. If model A were correct, it should be

Fig. 17. Reduced models for the characteristics of θ sharing between the dorsal hippocampus (HIP) and the LH. In both models, θ activity is generated by means of bidirectional septohippocampal projections and driven from medial septum (MS). Further amplitude and spectral biases are introduced by other tuning influences. The descending precommissural fornix projection progresses to the LH by means of lateral septal (LS) intercession. Uncorrelated noise (N1 and N2) is depicted as being directly applied to the two regions for the purpose of simplification. Model A reflects a simple transfer of activity from the hippocampus to the LH. The interaction between the medial and lateral septum is ignored. In Model B, the activity of the LH is granted a more influential status. The septal interface is viewed here as being only partially separable. All pathways shown have been documented by anatomical techniques.


TUNING
DRIVING
A
HIP-MS
LS
(MFB)
LH
N1
N2


TUNING
DRIVING
(MFB)
B
HIP
MS/LS
LH
N1
N2

possible to trace and identify any arbitrary signal at LH levels.

Model B illustrates the more complex relationships that derive from a more generalized view of the same anatomical and physiological substrate. The flow of information is not as well delimited as in model A. The LH-MFB projection from the basal telencephalon is viewed as a reflection of an active substrate with spectral properties that are neither passive nor devoid of consequences for the septal interface. The differences between the ascending and descending projection systems are therefore quantitative, rather than qualitative. Both generative and filtering properties may be important characteristics of both paths. The suggested generators need not produce waveforms described by simple spectra.

In model B, the septum has the capacity to drive and synchronize activity within the θ range from the otherwise independent EEG sources. It is for this reason that the relationship between the two signals may be most aptly described as statistical. It is theoretically possible for the power spectrum of a signal to remain unchanged, despite an increase in its coherence with a rhythmic tracer signal. The data from <u>S</u> 19 most typify this phenomenon. Under conditions in which the two components are highly synchronized with each other, the two models share similar properties.

With the relationship illustrated in model B, it is possible for local or extended EEG generators and filters to produce a gating effect on the transmission of hippocampal θ. In certain states, the tuning mechanisms may effectively block the progress of θ by suppression influences alone. It should be noted that the feedback projection from the LH itself is not required for gating to occur.

While simple deterministic models, such as the one depicted in model A, are quite appropriate for signals which are themselves completely predictable, the EEG may be better described by a random noise model (Isaksson & Wennberg, 1975). As the spectral tuning of a signal increases, it may begin to approximate a deterministic waveform, while retaining its probabilistic structure. In view of the relative volatility typical of the spectral structure of the EEG of the LH in the presence of a well-defined hippocampal signal (see Figure 12), it appears that lapses in ergodicity (or stationarity) lead to an even poorer fit by a deterministic model. For these reasons, a statistical description of the data is optimal for the assessment of the EEGs and their relationship to each other.

E. Roy John (1967) viewed the assimilation of exogenous rhythms into the EEG as a reflection of the coupling of local modes of activity into a compatible common mode. Such shared characteristics were seen as properties of widespread representational systems of behavioral relevance. Since these assimilated rhythms may appear in the absence of the original source under appropriate (behavioral) conditions, they are clearly produced by intrinsic oscillatory mechanisms tuned to mimic the sensory pattern.

The assimilation of rhythms in regions not generally characterized by strongly rhythmic activity may take a simplified form. It may occur as an increase in the stability of the apparent transfer properties relating the regions. This stabilization is closely related to changes in the signal-to-noise ratio of the presumed output. The degree of separability of the EEGs of the hippocampus and the LH, as illustrated by the apparent gating properties observed here, suggests that participation of the LH in a more widespread common mode of activity may be limited by variables related to the property of sharing itself. The amplitude of the rhythmic pattern within the hippocampal EEG is not related to the participation of the LH in this pattern in a simple, linear fashion. The rhythmic state characterized by an enhanced cooperation of the LH EEG in the ongoing θ rhythm may therefore be considered to reflect a common mode of endogenous origin with characteristics indistinguishable from John's proposed representational system.

The usual usage of the term assimilation implies a mutual separability of the two signals. There is no evidence suggesting that rhythmic LH θ may have a local origin in the intact, waking rat. It is not difficult, however, to envision a degree of competition between activity in the hippocampus and that in other sites (e.g., other limbic structures) for control of the LH-MFB continuum. While evidence for this more dynamic form of sharing is weaker than for the existence of gating, the obtained correlations between standardized rank sum and peak frequency collectively speak against any simple, direct control of LH θ by the dominant component of the hippocampal EEG. Further investigations are required to substantiate these trends.

In view of the close anatomical relationship between the hippocampus and the LH by way of the precommissural fornix, it is surprising that so little of the local EEGs may typically be regarded as shared. The apparent rhythmicity of the unit response of the VMH to LH volleys (transformed data from Oomura et al., 1967) and the reports of clearly rhythmic θ in the LH (Komisaruk, 1971) both suggest that a clearly delimited θ pattern in the hippocampus should be reflected in the hypothalamic EEG in an obvious fashion. Despite the occasional appearance of highly coherent θ, typical coherence levels are definitely low and volatile enough to confound any attempt to categorize changes in terms of a strictly linear model. The finding of relatively infrequent unit responses in the LH after hippocampal volleys (Polletti et al., 1973) may thus have a correlate in the gross EEG.

The quantitative contribution of shared θ to the EEG of the LH is typically small. Despite these small magnitudes, the relative shifts in the underlying distributions of the spectral measures during pontile stimulation are robust for group data as well as clearly discernable in the individual data. The current findings suggest that hippocampal θ may be used as a tracer signal for the extraction of shared activity from nonrhythmic or slightly rhythmic EEGs derived from related structures in an unanesthetized animal. They do not suggest that a sufficiently stable linkage exists between the hippocampus and the LH to allow arbitrary hippocampal EEG patterns to serve this function. The techniques developed here may be applied to successively generalized recording conditions. With this inherently holistic approach, the structure and organization of the physiological states correlated with spontaneous θ may be studied.

Behavioral Implications

Although pontile stimulation could hardly be described as inducing voluntary behavior in awake, restrained animals, the motor substrate was clearly activated in most cases. In view of the tonic ipsilateral rotational effects noted in this study, it may be relevant to recall that Vertes (1980) reported a focus for the generation of high frequency θ in the medial longitudinal fasciculus in anesthetized Ss. In the current study, high frequency θ could be elicited from sites ventrolateral to this bundle, but not from the most dorsal loci.

Rats with unilateral lesions in the region of the locus coeruleus have been reported to rotate contralaterally when given apomorphine or amphetamine (Pycock, Donaldson & Marsden, 1975). Despite this consistent finding related to motor control, it must be emphasized that effective unilateral stimuli invariably affect the hippocampal EEG bilaterally (Vertes, 1980). Aside from the apparent bilateral innervation of the hippocampus from aminergic sources (Moore, 1975), secondary commissural and reticular pathways are available to assure the unity of the two hemispheres in the generation of θ in the forebrain.

The general lack of reward properties for stimulation in the vicinity of the locus coeruleus and the subjacent noradrenergic bundle is not readily explained. Segel and Bloom (1976a) reported self-stimulation behavior at rates above 500 presses/hr (40-100 μA at 40 /sec in $\geq$ .25 sec trains) at locus coeruleus sites along the ventricular surface. In the present study, the only S̲ in which self-stimulation occurred at the pontine site had a placement adjacent to the ventral limits of both the locus coeruleus and the mesencephalic nucleus of the trigeminal nerve. While it is possible that conditioning established during restraint acted to antagonize the acquisition of the self-stimulation response, there is no evidence to suggest that θ as examined here is related to the activation of the reward substrate itself.

In a study reported by Van Der Kooy and Phillips (1977), self-stimulation in the rat was reported for placements in the motor nucleus of the trigeminal nerve. Placements dorsal to this nucleus also supported self-stimulation, while medial placements did not. These findings led them to argue for a response-oriented theory of reward.

In the present study, chattering movements of the teeth appeared at times during the course of the experiment, most notably at the offset of a stimulus of relatively high intensity. The only animals in which more than one bout of chattering occurred during the experimental session were those in which the region stimulated was in or immediately adjacent to the trigeminal structures. While the motor effects are consistent with those reported by Van Der Kooy and Phillips after motor nucleus stimulation, the reinforcement properties are not. These sites were quite capable of generating hippocampal θ.

While many stimulation sites may be presumed to have activated the ascending noradrenergic bundle (Ungerstedt, 1971), the evidence is inconsistent with a locus coeruleus origin for the θ generating effects observed in this paradigm. It may be noted that in the free-moving animal such properties may arise indirectly as a correlate of movement. The vestibular projections onto the occulomotor nuclei by means of a medial longitudiral fasciculus trajectory (McMasters, Weiss & Carpenter, 1966) suggest that an alternative machanism may be of relevance to θ as studied here.

In the curarized rat (Winson, 1975b), rotational stimuli are capable of inducing θ. In the cat, eye movements elicited by caloric irrigation are also accompanied by θ (Sakai, Sano & Iwahara, 1973). It is not unreasonable to assume that a similar imbalance in the balance-seeking sensorimotor substrate related to Ss physical orientation in space is induced by the electrical stimulation of the dorsal pons.

Theoretical Significance

The activation of a balance-seeking mechanism need not have as its sole consequences a purely reflexive sensorimotor displacement of the organism. Such a mechanism may operate at a level that overlaps voluntary and appetitive movement categories as well. These high order properties generally involve the induction of sensorimotor biases that also lead to displacement in space. The attentional and orienting correlates originally proposed for hippocampal θ are likewise subsumed by this broadened conceptualization. An active correction mechanism energized by such an imbalance may also share some of the "error-evaluate" properties posited for hippocampal function by Douglas and Pribram (1969). It is defensible to treat these diverse functions as facets of a single integrated system precisely because in the past the alternative classifications have led to conflicting views of processes that may, in fact, be identical. There is no a priori reason why ancient anatomical regions specialized for integration should maintain functional properties that are simply and meaningfully described by high order psychological terms.

The behavioral significance of the state characterized by regular θ activity may at times be best described at a level far removed from the sensorimotor substrate. From the spatial properties attributed to hippocampal function, θ may be viewed as a correlate of the displacement of the state of the organism from an optimal locus. In this conceptualization, θ is again an index of the efficient operation of an unbalanced neurobehavioral feedback loop. Aside from tonic influences on widespsread areas of the sensorimotor substrate, access to more specialized mechanisms by the θ system must also be presumed. In view of the behaviorally significant sensorimotor predispositions that have been induced in the cat by the stimulation of the hypothalamus, the ventral tegmentum and central gray of the midbrain and the midline thalamus (Bandler & Flynn, 1974; Bandler, Chi & Flynn, 1972; Flynn, Vanegas, Foote & Edwards, 1970), hippocampal access to such nonspatial mechanisms is probable by virtue of the well established projection routes. The psychological domain implicated at this point is motivational, in keeping with the view of hippocampal function taken by Jarrard (1973).

The information processing characteristics of the hippocampus are related to its two sources of input. The cortical contingent delivers information in a highly processed form. The septal projections are capable of inducing a generalized rhythmic activity, while direct brainstem projections affect the excitability of the tissue. The degree to which these projections share separable functional correlates is as yet largely unknown. Their cooperation in the maintenance of functional states is even less clearly understood. Analytical and integrative considerations are both of obvious importance to a comprehensive overview of such a wide-ranging system.

The topographic cascading of information from the association fields onto the entorhinal cortex and thence through the hippocampus is reminiscent of the topography noted in the sensory systems. In the visual system, the visual field itself is mapped directly onto the neurological substrate in both mammals (Thompson, Woolsey & Talbot, 1950) and insects (Braitenberg, 1967; Larsen, 1966). Topography of projection and function are far from synonomous, however. Units in both mammals (Hubel & Wiesel, 1962) and flys (Biship, Keehn & McCann, 1968) show contextual responses as well. There is evidence that the optimal stimulus in the mammalian units may actually be a grating of the appropriate orientation (Albrecht, DeValois & Thorrell, 1980) indicating an important role for spatial frequency in the processing of visual information (Campbell, 1974). It appears then, that both local and contextual considerations are of importance even within the sensory projection systems.

A distinction between specific and general or contextual processes at the level of the hippocampus is evident in the electrophysiological literature. One mode of activity may be characterized by its rhythmic properties at unit and gross levels. This form of activity is statistically stable and similar under widely divergent behavioral conditons. Such activity may be ascribed the status of a continuum of state.

As demonstrated by the current findings, the organization of the state typified by θ activity is stabilized spectrally by both enhancement and suppression mechanisms. Highly rhythmic activity in the hippocampus is further accompanied by a decisive enhancement in the degree to which lower sites share in it. It is unlikely that such sharing is without functional consequence.

The second type of electrographic activity is situation specific or transient in nature. This type of activity is typified at a unit level by the activity of complex spike cells. O'Keefe and Nadel (1978) have suggested an interaction between these specific informational features and the general timing influences of θ mode activity in their model of hippocampal function. An alternate view of the proposed interaction is that a specific case of state dependent learning is in evidence. This interpretation insists on no particular behavioral correlate of spontaneous hippocampal θ. Likewise, neither learning nor behavior must of necessity be linked with regular θ activity. Instead, it serves as a unifying ground upon which situational influence may be expressed. The ability of exogenous rhythms to become assimilated by the brain in a behaviorally significant form (John & Killam, 1960) may also be viewed as a manifestation of this process.

The analogy between representational systems, the physiological states in state dependent learning paradigms and the reference beams of holograms should not be ignored. When the memory-related models of hippocampal function are recalled, the significance of θ is not blatantly apparent. It is not difficult, however, to envision an economical system wherein tonic sensorimotor, motivational and mnemonic contexts are organized by the same modes of physiological activity. In this hypothetical system, the traditionally delimited domains of motivation and memory are separable only by virtue of the particular cluster of correlates within the related state. In effect, this is a restatement of Lashley's equipotentiality (Lashley, 1950) in which its relevance is purposely extended into the domain of motivation.

The view of the nervous system proposed here is one in which identical mechanisms are implemented for the production of diverse psychological epifunctions. While their articulation may shift the predominant effect into various domains, the active participation of widespread regions in common modes of activity represents an elementary functional core. Although designed to address specific considerations related to the spectral structure of hippocampal and LH θ, the current techniques may be generalized to study the accessibility of any persistent, modestly stable mode of activity to different anatomical loci. The importance of these properties of shared activity has the potential scanning the domains of motivation, learning and sensorimotor function in an integrated, logically continuous fashion.

In the current study, the relatively low or volatile magnitudes typical of θ in the LH and its coherence with hippocampal θ may reflect a partial disengagement of the LH-MFB from limbic control. A comparable disengagement of forebrain θ from brainstem generators has been suggested in the disorganization of hippocampal rhythmicity during such automatic behaviors as licking and chewing (Komisaruk, 1977). The rhythmicity of the brainstem itself may have been disorganized by the pontile stimulus used in the current study.

The degree of forebrain disengagement may have been exaggerated by the behavioral paradigm used. While the use of restraint produces a data set which is relatively homogeneous, it also severely reduces the range of behaviors possible for a S. Under free-moving conditions, the shared influences described here would be expected to increase in both magnitude and variability.

The current findings are suggestive of a mechanism by which the activity of the LH is incorporated into the rhythmic state exemplified by hippocampal θ. This mechanism is based on the probabilistic nature of the spectral structure of the EEG. It is likely that the passage of such organized rhythmicity to the LH-MFB reflects the inclusion of the sensorimotor, motivational and emotional correlates of this anatomical substrate into a widespread forebrain control system.

CHAPTER V

SUMMARY

A number of anatomical pathways exist for the transmission of information between the hippocampus and the LH. Both ascending and descending pathways rely heavily upon septal intercession (Saper, Swanson & Cowan, 1979; Swanson & Cowan, 1975; 1976). The rhythmicity of the hippocampal EEG is clearly influenced by some of them as well (Anchel & Lindsley, 1972; Paiva et al., 1976). Within the hippocampus, the regio inferior is the field that most unambiguously maintains reciprocal relations with the septum (Andersen, 1975; Raisman, 1966).

The descending fornix pathways have been shown to by physiologically active in the rat by evoked potential procedures (Miller & Morgenson, 1972). They are capable of modifying drinking and self-stimulation behavior arising from LH stimulation as well (Miller & Morgenson, 1971). Miller (1972) has reported a close correspondence between the form of the evoked potential and the unit response of the LH after fornix stimulation. The ambient gross activity of the LH is nonrhythmic in motionless animals (Gilden & Kozakiewicz, 1976; Oomura et al., 1967). In free-moving rats, however, θ activity has been reported to episodically label the gross and unit activity of the LH-MFB system (Komisaruk, 1971; Komisaruk & Olds, 1968).

Investigations of brain rhythmicity have generally used two distinct approaches. The first approach, used extensively by Vanderwolf (Vanderwolf, 1969; Vanderwolf et al., 1975), makes use of free-moving animals. These techniques allow the discovery of the EEG correlates of behavior at the expense of an increased variability of the data base itself. To produce stabilized data, some investigators have resorted to the use of drugged animals (e.g., Apostal & Creutzfeldt, 1974; Macadar, Chalupa & Lindsley, 1974; Vertes, 1980). Because of the reduction in the variability of the EEG, this alternative allows a more conclusive assessment of the properties of the rhythmicity. The improvement is particularly important when higher order correlations, such as signal coherence or crosscorrelation functions, are required. The problem with such studies is that their applicability is certain only in the state in which they were conducted. Unfortunately, the properties of hippocampal θ have been shown to vary with the administration of various drugs (Vanderwolf, 1975; Winson, 1975; 1976).

The present study was conducted to describe the spectral changes underlying the induction of θ-rhythmicity in the hippocampus of undrugged rats and their relation to shared (correlated) EEG activity in the LH. In order to assure the validity of the changes observed, it was important to limit the study to the investigation of a simplified subset of those EEG patterns generally typified by the presence or absence of θ. In contrast to most studies of θ conducted with awake, undrugged animals, great care was therefore taken to assure that distinct, reproduceable EEG states could be evoked experimentally. For this reason, θ was produced by stimulation of the dorsal pons in restrained rats.

Method

Subjects and Surgery

Data were acquired from 8 male Long Evans rats with suitable electrode placements. All Ss were in excess of 350 g at the time of surgery (495 g median). Individual .01 in diameter stainless steel twisted electrode pairs (Plastic Products Company) were targeted at the LH (A5.8, L2.0, H-2.5), the CA3 field of the dorsal hippocampus (A 3.2, L 3.5, H 1.66) and the ipsilateral dorsal pontine tegmentum subjacent to the locus coeruleus (A -2.0, L 1.25, H -3.6). DeGroot coordinates were used in conjunction with the Pellegrino, Pellegrino and Cushman (1979) stereotaxic atlas. Animals were implanted under 50 mg/kg IP Nembutal and supplemented with ether. The electrode array was secured to the skull with dental cement and stainless steel screws. After the experiment, Ss were sacrificed under Nembutal by intracardial perfusion of a 10% Formalin solution. Frozen sections (35 μ) were cut from the fixed tissue and stained with the Kluver-Barrera technique.

Apparatus

Constant voltage sinusoidal stimuli at 60 Hz were produced and timed by hardware designed for the present purpose. A stimulus of this form was selected to allow the removal of stimulus artifacts by standard line frequency notch filters. The amplitudes of the stimuli were selected by piloting, setting the anticipated maximum current at 70 µA RMS. Intensities of .0, .7, 1.1, 1.4 and 1.7 V RMS were thereby chosen and identified as stimuli 0-4 (a .35 V condition was included in place of stimulus 3 in S 1). The RMS current was also monitored during stimulation.

Data were obtained via source followers embedded in dental cement in the recording electrode plugs (Rosetto & Vandercar, 1972). Signals were amplified by means of Tektronix 2A61 differential amplifiers (.6-60 Hz with 60 Hz notch) and recorded on a seven channel FM tape via Mnemetron model LC converters. After low-pass filtering at 28 Hz through a Krohn-Hite model 3550 filter, off-line digitization of the data was performed on a Xerox Sigma Seven computer system at an effective rate of 400 samples /sec for a total of 4096 data points per record. With the exception of the Fast Fourier Transform (FFT) subroutine, all programs related to the analysis and pretreatment of the data were specifically developed for the current use.

Animals were restrained by means of a modified version of the Bellingham (1980) restraint bag and an associated rigid restraining device. This device and its use are described elsewhere.

Procedure

Behavioral response to stimulation. All subjects were briefly tested for their responsivity to the pontine stimulus under direct visual observation on the last day of full restraint in the habituation series. Behavioral correlates of the different intensities of stimulation were noted when present. Those subjects in which phasic movements occurred often enough to prevent the acquisition of valid data during the stimulation epoch were eliminated from further study. Among these were subjects to which the stimulation appeared to be unduly traumatic.

On a day subsequent to the experiment, subjects were tested for self-stimulation at the pontile site whenever possible. Stimuli were the same as those delivered in the experiment, but were of short duration ($\leq$ .5 sec). Motor effects and avoidance tendencies were also noted.

Stimulation and data acquistition. All data from all conditions were acquired in a single recording session. Each block of trials consisted of four presentations of each stimulus in a constrained random order.

Stimulus timing was linked to the presence of trigger pulses on a prerecorded tape channel. The interpulse interval was a constant 45 sec. After each pulse, 8.7 sec of recorded data were allowed to elapse before the stimulus was automatically delivered. Off-line collection of the corresponding 10.24 sec data record was begun after an additional delay of 1.5 sec. The stimulus remained on for 15 sec. This arrangement served to protect the data record from contamination by onset and offset transients.

Prior to Fourier transformation, any residual DC bias was removed from each data record. The resulting series was then cosine tapered over the first and last tenths of the data record to suppress the spectral side lobes of the effective data window (Bendat & Piersol, 1971). For each trial, power and coherence summaries were obtained by taking means across 25 consecutive nonoverlapping 1 Hz bands (exactly 10 raw estimates per band). Since the filters were applied equally across all experimental conditions, no attempt was made to compensate for these influences.

The acceptance of data from any given trial into the final summary statistics for the associated condition required that it pass two overlapping artifacting procedures. All trials that were obviously contaminated by movement artifacts were first removed from further analysis. The second procedure made use of the power spectrum estimates derived from the data records. The latter procedure (described elsewhere) served to eliminate residual records containing artifactual transients while improving the ergodicity of the data set.

To further protect the data from the effect of possible outriders related to any residual inhomogeneity of the data, the Wilcoxon rank sum test for independent samples was applied to the trial-by-trial distribution of power spectrum means for the hippocampal and LH EEG of each animal. For every 1 Hz band, each stimulus condition was in turn compared to the control data and expressed in final form as a standardized (z) score (Ferguson, 1976; Bradley, 1968). In pooling the data between animals, the θ peak frequency was determined a posteriori from the obtained spectra.

Theta activity was defined operationally to include the seven frequency bins scanning 3.9-10.7 Hz. Peak θ was defined as the maximum positive-going peak z score in this range. When the identified peak z exceeded one for more than a single frequency bin, the means of the consecutive z estimates were taken. This produces a conservative test for enhancement at the peak while eliminating the influence of the peak from the mean of the remaining (nonpeak) activity. From an expected maximum of 16 data records for each experimental condition, the amplitudes of the EEG components in the 3.9-10.7 Hz range were therefore summarized from 639-1753 cyclic periods of raw data. This maximum was subject to both reduction during artifacting and a possible augmentation from an additional block of trials.

The individual z estimates for peak and nonpeak categories were pooled across Ss for the purpose of group statistics. Since each z is, in effect, a standardized difference measure, enhancement or suppression may be tested simply by restandardizing the data and testing for the inclusion of zero in the appropriate tail. This is identical to a t-test for dependent samples in its origin and implementation.

Results

General Characteristics of Summary Data

After artifacting, the median number of control trials accepted for analysis was 14.5 (mean of 14.6). For stimulus 4, a median of 11 trials (10.8 mean) were accepted. The difference reflects the increased movement tendency after stimulation at the higher entensities in some subjects. Since the median θ peak at stimulus 4 was at 7.8 Hz, the typical stimulation-induced peak was summarized from a total of 80 cyclic periods/trial. As a rule, parametric, median and rank sum measures exhibited changes in the same direction.

Stimulus Current

For each animal, a given stimulus produced a stable current reading. For any stimulus voltage the corresponding current varied considerably from animal to animal. The intersubject variability increased with stimulus intensity. While the applied current overlapped stimulus category ranges, only stimulus 3 delivered power with an intersubject range that overlapped its neighboring conditions.

Hippocampal θ

Ambient (control) levels of θ activity varied considerably between Ss. In median power spectrum plots, θ activity varied from a mere plateau to peaks of up to 2.5 times the power of the level at subjacent frequencies. All test statistics reflect changes from these nonrhythmic or slightly rhythmic modes of activity.

The spectral tuning of the hippocampal EEG at stimulus 4 is reflected by the relative height of the corresponding peak in the median power spectrum. Peaks in θ towered over troughs or plateaus at lower frequencies in the power spectrum by factors of 6.5-55. The most highly resolved peaks (> 10 times) spanned the 6.3-8.3 Hz bins. Peaks of relatively poor resolution ($\leq$ 10 times) spanned the range from 5.3-9.2 Hz.

Electrode placements. Stimulation and recording sites for each of Ss are displayed in Figure 10. The rank order correlation of the distance of the stimulating electrode tips from the ventral limits of the locus coeruleus and the θ peak frequency of the median hippocampal power spectrum at stimulus 4 was statistically discriminable from zero (ρ=.87; 2-tailed $p < .02$). The validity of the correlation is supported by the data obtained from an additional S with a placement within the locus coeruleus which did not produce θ. This is consistent with the findings of Vertes (1980), and contrasts sharply with those of Macadar et al. (1974).

The peak/baseline power ratios were examined in concert with the locations of the stimulation sites. All sites generating hippocampal θ with a power ratio

> 10 (4 Ss) were contained within a zone at or dorsal to the dorsal limits of the medial longitudinal fasciculus and ventral to the locus coeruleus (LC). For stimulation sites above or below this wedge of subcoeruleus tissue, the rhythmicity was less well-defined.

Nonpeak suppression. The average of the normalized rank sum (z) scores for nonpeak frequency bins decreased substantially with stimulation. For stimuli 1-4, the summarizing dependent t scores obtained were -2.42, -3.32, -5.56 and -7.35, resp. (df=7, 6, 6, 7; 1-tailed $p < .025$ to $p << .0005$). Suppression of some form or another was so general at stimulus 4 that positive z scores were exceptionally rare in nonpeak bins.

Peak enhancement. While the suppression of nonpeak θ with stimulation appears straightforward, it should be noted that the presence of a readily distinguishable θ peak was universal only at the two highest stimulus intensities. At stimuli 3 and 4, t=4.78 (df=6; $p < .005$) and 13.73 (df=7; $p << .0005$), resp. At stimulus 1, while one animal failed to show any peak, five exhibited a dual z peak. Because of the criteria used to identify spectral peaks, lesser peaks were not discriminable from the background nonpeak activity. All but one of these five animals showed primary peaks that were not consistent with those detected in the median power spectra or in z score plots obtained from LH data.

Harmonics. Marked changes in hippocampal z scores often occurred in the vicinity of harmonics of the θ peak frequency. While 6 out of 8 animals showed a substantial and significant increase in the region of the second harmonic for stimulus 4, the effect in three of these was by means of a sustained rebound from a more generalized suppression surrounding the spectral peak. Activity at half the frequency of the θ peak was present in both median and z plots of one animal while in another the suppression effect was generalized across the entire computed (nonpeak) spectrum. The only animals in which the median hippocampal spectrum was completely devoid of harmonic effects were two characterized by low frequency θ peaks.

Lateral Hypothalamic θ

Ambient levels of power in the θ range in the LH showed no general tendency to peak in θ without stimulation. One animal exhibited a θ plateau in the median power spectrum. The three most rhythmic cases exhibited small LH "peaks" of 1.2-1.5 times the power in the prior spectral bin.

Peaking and suppression during stimulus 4. Median LH power spectra exhibited θ peaks at stimulus 4 in three animals (2.2-4.7 times prior trough). The most rhythmic S (S 9) produced a peak of 18 times the power of the nearby trough in the spectrum. This animal also exhibited a decisive LH second harmonic peak with a factor of 2.9 times trough power.

All rats exhibited peak z increments during stimulus

4 at the same frequency as the peak observed in the hippocampal EEG. Group statistics support the significance of the peaking tendency (t=4.61; df=7; $p < .005$) and an even more pronounced significant suppression effect (t=8.45; df=7; $p \ll .0005$).

Harmonics. Possible harmonic effects were less clear for the LH than for the hippocampus. At stimulus 4, four animals showed either peaks or rebounds from inhibition in the vicinity of the second harmonic. Two animals showed activity shifts localized at or near the third harmonic. One animal exhibited a lesser peak immediately above the range scanned for θ that was not a simple harmonic of the θ peak. In another case the suppression effect persisted throughout all nonpeak regions.

Low intensity stimulation. At stimulus intensities below that of stimulus 4, the measures obtained from the LH were quite erratic or idiosyncratic. For these stimuli, there was a decided tendency for z scores to peak without obvious regard to the hippocampal peak.

As a rule, while some subjects showed clear evidence of LH suppression in nonpeak regions (or all of θ in nonpeaking subjects), the effect approached statistical significance only when the peak was aligned with the hippocampal peak. For the entire group, the evidence for general nonpeak suppression in the LH was significant for stimulus 1 (t= -2.11; df=7; $p < .05$) and stimulus 2 (t= -3.10; df=6; $p < .025$), but not for stimulus 3

($t= -1.84$; df=6; $p > .05$). The contamination caused by the presence of lesser peaks is certainly responsible for at least a part of the degradation of these statistics.

Correlation with hippocampal indices. Since hippocampal and LH power measures exhibit peaks in precisely the same frequency bins for stimulus 4, it might be supposed that their z scores also covary in a generally predictable manner. It may further be suspected that this correspondence is present in nonpeak portions of the spectrum as well. The data failed to support this supposition. When rank order correlated, these two categories actually generated statistics of approximately the same magnitude and opposite sign ($\rho = -.36$ and $+.40$, resp.; $p > .05$).

If a given S had a rhythmic hippocampal EEG, the degree of rhythmicity in the LH could not be predicted. At stimulus 4, peak/trough power ratios for θ in the LH were unrelated to those from the hippocampus ($\rho =.05$; $p >> .05$). In an analagous fashion, for the six cases in which discriminable θ peaks existed at stimulus 1, a product-moment correlation of the peak frequency bin number for hippocampal and LH z plots produced a negative correlation ($r= -.65$; $p > .05$).

Coherence

Nonpeak suppression. Nonpeak measures for γ^2 showed what appeared to be a montonic increase in suppression with increases in stimulus intensity. At stimuli 3 and 4, the effect attained significance (t= -1.85 and -2.30; df=6 and 7; $p < .05$). Over one third of all individual z scores within the frequency range tested were above the mean. This is in sharp contrast to the corresponding measures for the power spectra, where positive deviations were rare (< 10%). The suppression was therefore less continuous for signal coherence than for the individual power spectra.

Peak enhancement. The z plot of γ^2 showed a general tendency to peak in θ. For stimulus 1, only one animal lacked a distinct peak in θ. Three animals showed a dual peak, while five had maximal peaks discrepent from the frequency of the hippocampal peak. For stimulus 3, all animals showed θ peaks. The three animals in which no LH peak appeared showed γ^2 peaks at different frequencies than the one in the hippocampus. In stimulus condition 4, where the γ^2 peak was synchronous with the other measures and present in all subjects, the group measure was even larger (t=12.32; df=7; $p << .0005$).

Harmonics. At stimulus 4, five Ss showed an enhancement of coherence in the vicinity of the second harmonic of the θ peak. This peak attained significance in four animals. In one S, this occurred despite a lack of a comparable effect in either power spectrum. In another animal, a nonsignificant biphasic effect was found. Two animals exhibited a significant coherence increase at half the frequency of the θ peak.

Correlation with other indices. The proportion of activity shared by the LH and the hippocampus appears to be related to the prominence of θ in the LH, but independent of hippocampal θ. Correlations of the stimulus 4 peak/trough power ratios for the LH and hippocampus vs. the corresponding peak median γ^2 estimates were examined. Although hippocampal rhythmicity was not obviously related to signal coherence magnitude (ρ=.27; $p > .05$), the LH ratio was (ρ=.89; $p < .02$). Rank order correlations of γ^2 peak z scores vs. hippocampal and hypothalamic peak values for stimulus 4 were not inconsistent with this relationship (ρ = -.33 and +.43; $p > .05$). Similar results were not obtained for less rhythmic activity than that characterizing the peaks produced by stimulus 4. Nonpeak correlations were much smaller in magnitude (+.14 and -.10; $p > .05$). The product-moment correlations between the corresponding peak frequencies during stimulus 1 were also small (r=.29 and .08; N=6 and 5).

Individual Data

In order to present the stimulus 4 rank sum data from all *S*s in a compatible form, the frequency axis of Figure 16 has been transformed logarithmically. The generality of both peaking and suppression trends is evident from these data. Figures 14 and 15 illustrate these trends in a *S* at the approximate median with respect to control peaking tendency and stimulus 4 peak frequency

Stress-related responses, however, were rare. The intensity of the stimulus was sufficient to support self-stimulation at the LH site.

Discussion

The present data suggest that two distinct mechanisms are responsible for θ-rhythmicity produced by brainstem stimulation. The most general mechanism leads to a suppression of activity. Since this suppression tends to spare the spectral locale of the peak, the signal-to-noise ratio of θ activity is improved by the removal of irrelevant activity. The second means by which rhythmicity is enhanced is the increase of activity at the spectral peak itself. This process is more pronounced in the highly rhythmic EEG typical of hippocampal θ than in the θ activity of the LH.

The dual (enhancement/suppression) nature of the spectral changes underlying the induction of θ-rhythmicity in the hippocampus has previously been reported for the anesthetized cat (Paiva et al., 1976). Since it is also present in the EEG of the LH, it is not merely related to the elaboration of rhythmicity by virtue of local oscillatory properties peculiar to hippocampal tissue. It is likewise certain that a strong, persistent rhythmicity is not required for both enhancement and suppression to be statistically well defined.

Although the characteristics of θ-rhythmicity in the hippocampus and the LH are similar in form, the amount of activity at each of these sites may be differently related to the coherence of the two signals. Rhythmicity (peak power ratio) at the LH is predictive of the proportion of shared activity (γ^2 magnitude). One cannot, however, predict shared activity from a knowledge of hippocampal rhythmicity. Correlations computed between rank sum measures also suggest this relationship, despite their failure to attain statistical significance. In view of the variability of LH θ possible during periods of stable θ in the hippocampus (e.g., Figure 12), a parsimonious interpretation is that the conduction of a stable rhythm is variably impeded or "gated" through the MFB. The variability of LH θ may therefore be due largely to a changing accessibility of the MFB to this rhythm.

Important motivational (Anand & Brobeck, 1951), reward (Olds, 1962) and sensorimotor (Turner, 1973) properties have been attributed to the region of the LH-MFB. The ability to monitor changes in the accessibility of this region to θ activity therefore has potential importance to neurobehavioral models which address the widespread distribution of patterned activity throughout the brain (e.g., John, 1967; 1972; Pribram, 1971). The reliable assessment of θ activity will allow this rhythm to serve as an endogenous tracer for the study of motivational and mnemonic processes supported or accessed by its correlated physiological state.

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