CHAPTER 3

Physiology of the Limbic System

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I. INTRODUCTION

The purpose of this chapter is to outline some aspects of the functions of the limbic system which may be helpful in understanding some of the clinical and EEG features of complex partial seizures. This review of the subject will be selective by its emphasis on the physiology of the amygdala, primarily because many aspects of the pathophysiology of complex partial seizures of temporal lobe origin are best understood in the light of current knowledge of amygdaloid function and of its relationship with temporal neocortical mechanisms (Gloor, 1972). Furthermore, information on amygdaloid physiology is more extensive and more firmly established than that on any other part of the limbic system. The hippocampus still remains, from the physiological standpoint, a somewhat enigmatic structure. Little is known of the physiological role of the piriform cortex with its main subdivisions, the prepiriform periamygdaloid, and the entorhinal area, except that the first two of these contain the cortical representation of the sense of smell (Fox, McKinley, and Magoun, 1944; Meyer and Allison, 1949). The physiology of the cingulate cortex and septal nuclei will not be considered in this chapter.

II. ELECTROPHYSIOLOGICAL STUDIES

A. Amygdala

1. Spontaneous Activity

The spontaneous activity of the amygdala is different from that of the cerebral neocortex and hippocampus. Rapid, spindle-like activity in the beta frequency band is often seen (MacLean and Delgado, 1953), which seems to be partially related to olfactory inputs (Feindel and Gloor, 1954) and is often synchronous with respiration. It also appears to be increased
with stimulation of the reticular formation (Feindel and Gloor, 1954) and with emotional stimuli (Lesse, Heath, Mickle, Monroe, and Miller, 1955; Lesse 1960); this may represent the amygdaloid arousal response.

2. Electrophysiological Studies on Afferent Connections to the Amygdala

There are few electrophysiological studies on the afferent connections to the amygdala. Olfactory and other sensory evoked potentials have been recorded (Berry, Hagamen, and Hinsey, 1952; Hugelin, Bonvallet, David and Dell, 1952; Dell, 1952; Wendt and Albe-Fessard, 1962). Unit discharges in response to olfactory and other sensory stimuli have also been recorded (Machne and Segundo, 1956; Creutzfeldt, Bell, and Adey, 1963). Recent work by Fuster and Uyeda (1971) to be described later in this chapter has defined some of the conditions under which sensory evoked unit discharges are most likely to occur in limbic structures.

Evoked potentials recorded with macroelectrodes can be elicited in the amygdala by stimulation of widespread areas of the cerebral neocortex, but the most prominent responses are evoked from areas of the cat cortex which are the homologues of insulo-temporo-occipital cortex in man (Niemer and Goodfellow, 1966). This has been confirmed in a recent study by Prelevic (personal communication) using single-unit recording techniques. The response of amygdaloid cells to cortical volley is usually that of excitation followed by inhibition.

Little is known about the electrophysiology of ascending pathways to the amygdala, which presumably originate in the hypothalamus and preoptic area and which travel through the stria terminalis and the ventral amygdalo-fugal pathway (Caruthers, Müller, Müller, and Gloor, 1964).

3. Electrophysiological Studies on Efferent Connections from the Amygdala

Single-shock and repetitive stimulation of the amygdala evokes responses in widespread areas of the brain. In the cat, the cortical projection field is confined to areas homologous with anterior temporal and insular cortex (Gloor, 1955a). Responses are also recorded from the piriform cortex and the hippocampus, the latter being particularly prominent with repetitive stimulation, which induces a recruiting type of response followed by considerable post-tetanic potentiation upon resumption of single-shock stimulation (Gloor, 1955a,b).

In subcortical structures, evoked potentials to amygdaloid stimulation are recorded from the septum, the basal midline telencephalic area below the septum, including the preoptic area, the anterior and posterior hypo-
thalamus, and the upper midbrain reticular formation (Gloor, 1955a). The shortest latency responses are obtained in the preoptic region and the anterior hypothalamus, including the area of the ventromedial nucleus of the hypothalamus. Responses in other areas show latencies which are considerably longer, suggesting that the responses are relayed to these regions through multisynaptic relays. In most of these regions the responses augment with repetitive stimulation, and in some areas can be elicited only with repetitive stimulation (Gloor, 1955b).

The ventromedial nucleus of the hypothalamus occupies a central position in this subcortical amygdaloïd projection field (Gloor 1955a,b; Dreifuss, Murphy, and Gloor, 1968; Murphy, Dreifuss, and Gloor, 1968b). Evoked potentials in this nucleus are of higher amplitude and exhibit a more complex form than elsewhere. In the cat, at least, they also show a distinct difference in morphology depending upon whether the neurons of this nucleus are activated through the dorsal projection pathway of the stria terminalis or through the ventral amygdalofugal pathway (Dreifuss et al., 1968). Stimulation studies have shown that the stria terminalis serves as the main efferent fiber bundle of the corticomedial nucleus of the amygdala, whereas the ventral amygdalofugal system mainly carries impulses originating from the basolateral amygdala (Gloor, 1955a; Dreifuss et al., 1968). The evoked potential in the ventromedial nucleus of the hypothalamus elicited by an afferent volley mediated through the stria terminalis consists of a large positive wave which is confined to the area of the nucleus, whereas a volley traveling through the ventral amygdalofugal system elicits a negative-positive field potential which again is confined to the area of this nucleus. Microphysiological studies have shown that the positive wave evoked by stria terminalis afferents corresponds to an inhibitory input and thus probably represents summed IPSPs. In contrast, the negative-positive field potential mediated by the ventral amygdalofugal system corresponds to an excitatory-inhibitory sequence, neurons of the ventromedial hypothalamic nucleus being excited concurrently with the negative deflection of the potential and inhibited with the positive deflection. Thus the negative component of the response probably represents summed EPSPs, while the positive component seems to represent summed IPSPs (Dreifuss et al., 1968). In the cat, the IPSPs in the ventromedial nucleus of the hypothalamus seem to be mediated by short interneurons occupying mostly the lateral part of the nucleus receiving inputs from both descending pathways (Murphy and Renaud, 1969). Volleys mediated by the stria terminalis and the ventral amygdalofugal pathway converge on the same ventromedial hypothalamic neurons (Dreifuss et al., 1968).

Amygdaloid stimulation also elicits single-cell discharges of hypothalamic neurons in areas outside the ventromedial nucleus (Egger, 1967; Murphy, Dreifuss, and Gloor, 1968b; Van Atta and Sutin, 1971, 1972). Often these exhibit excitation-inhibition sequences.
Repetitive amygdaloid stimulation greatly modifies the response patterns of hypothalamic neurons. With repetitive stimulation, an increase in excitability is observed in some areas or for some neurons, but the opposite, a decrease in the response, may also be seen, and some neurons cease to respond altogether under these conditions (Egger, 1967; Murphy et al., 1968a; Van Atta and Sutin, 1972).

The influence of the amygdala upon hypothalamic neurons is thus highly complex, excitatory and inhibitory influences being exerted upon a large population of hypothalamic neurons, the type of response being partially dependent upon the part of the amygdala stimulated and partially upon the rate of repetitive stimulation. To what extent these complexities reflect the normal conditions and those occurring during an epileptic discharge involving the amygdala remains unknown.

B. Hippocampus

1. Spontaneous Activity

A salient feature of the spontaneous activity of the hippocampus, at least in lower animal forms, is the so-called hippocampal theta rhythm, a rhythmic sequence of regular waves with a frequency ranging between 4 and 7 cycles/sec (Green and Arduini, 1954; Green, Maxwell, Schindler, and Stumpf, 1960). This activity is not continuously present, but originates in response to certain stimuli or behavioral situations. It is seen particularly in lower mammals and is hardly ever present in primates (Green, 1964). It has not been seen in man. It was originally postulated that in the awake animal, this rhythm represented the hippocampal arousal response, since it could be elicited by electrical stimulation of the brainstem reticular formation (Green and Arduini, 1954). Later studies, however, have shown that arousal per se may not be a sufficient prerequisite for the occurrence of this response and that it may be more closely related to some aspects of the Pavlovian orienting response (Grastyán, Lissak, Madaras, and Donhoffer, 1959). The occurrence of this rhythm or of shifts in its dominant frequency has also been observed in relation to certain aspects of the learning process or to changes in operant behavior (Adey, Walter, and Hendrix, 1961; Grastyán, Karmos, Verezckey, and Kellényi, 1966; Elazar and Adey, 1967; Lopes da Silva and Kamp, 1969; Kamp, Lopes da Silva, and Storm Van Leeuwen, 1971). However, it proved impossible to identify unequivocally the behavioral variable most closely related to these changes. Recent studies have suggested that the response may be related to “voluntary” movements (Vanderwolf, 1969). In the rat the theta rhythm is said to occur only under conditions in which the animal carries out movements which are not stereotyped and automatic and in which the motor sequence is not preprogrammed and fixed. Hippocampal theta activity is also present during REM sleep (Jouvet, 1962a,b; Passouant and Cadilhac, 1962).
The hippocampal theta rhythm is dependent upon a pacemaker in the medial septal nuclei giving rise to a cholinergic pathway ascending through the fornix to the hippocampus (Petsche and Stumpf, 1960; Petsche, Stumpf, and Gogolak, 1962; Stumpf, Petsche, and Gogolak, 1962; Gogolak, Stumpf, Petsche, and Sterc, 1968; Senba and Iwahara, 1974).

2. Electrophysiological Studies on Afferent Connections

Two main afferent connections to the hippocampus are known. The first is the perforant pathway, originating from the entorhinal cortex which makes contact with the apical dendrites of the hippocampal pyramidal cells and of the granule cells of the dentate gyrus (Lorente de Nó, 1934; Blackstad, 1958), the efferent axons of the latter, the mossy fiber system, again projecting upon apical dendrites of hippocampal neurons (Lorente de Nó, 1934; Blackstad, 1958; Blackstad, Brink, Hem, and Jeune, 1970). The second system consists of afferent fibers originating in the medial septal nuclei which ascend through the fornix and make contact with the basal dendritic region of the hippocampus (Powell, 1963; Petsche, Gogolak, and Stumpf, 1966). In addition, there are commissural connections which, through the hippocampal commissure, convey afferent impulses from the contralateral hippocampus (Blackstad, 1956).

These systems have been studied extensively by neurophysiologists, who have defined many of their electrophysiological characteristics. Perforant path volleys produce EPSPs in apical dendrites of pyramidal neurons of the hippocampus and of granule cells in the dentate gyrus (Gloor, Vera, and Sperti, 1963a,b; Andersen, Holmqvist, and Voorhoeve, 1966a,b; Andersen, Bliss, and Skrede, 1971; Lømo, 1971). When excitation in the apical dendrites reaches sufficient intensity, action potentials are generated by the pyramidal or dentate gyrus neurons. Similar response sequences occur when the commissural afferents arriving over the fimbria are stimulated, except that they synaptically engage the basal dendrites except in segment CA, where the apical dendrites are excited (Andersen, 1959, 1960a,b; Campbell and Sutin, 1959; Gloor et al., 1963b). Short axon recurrent pathways provided by the basket cells exert a recurrent inhibitory action on the pyramidal neurons (Andersen, Eccles, and Loyning, 1964a,b). Other inhibitory neurons are probably also present (Purpura, Prelević, and Santini, 1968).

One interesting aspect of perforant path volleys is that, during and after repetitive stimulation, the postsynaptic response is very greatly increased (Gloor, Vera, and Sperti, 1964b). After such a tetanic volley, a powerful post-tetanic potentiation is observed which may be permanent (Bliss and Gardner-Medwin, 1973; Bliss and Lømo, 1973). This represents one of the first demonstrated examples of a possibly permanent synaptic change in a neural system induced by repetitive stimulation. Such observations have great potential relevance for the physiological basis of memory and learning.
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3. Efferent Connections

Efferent connections from the hippocampus have been traced by evoked potential techniques into the septal area, the hypothalamus, the anterior and medial thalami, and the ventral midbrain tegmentum. Short-latency responses have also been recorded in the amygdala (Green and Adey, 1956). The subcortical projection field of the hippocampus has a similar distribution and extent to that of the amygdala. Single-cell discharges in preoptic and hypothalamic areas have been recorded, but details of the synaptic organization of hippocampal projections to the hypothalamus are much less well known than are those of the amygdaloid projection system (Dreifuss and Murphy, 1968; Van Atta and Sutin, 1971, 1972; Poletti, Kinnard, and MacLean, 1973). Frequently, inputs originating from the hippocampus, the amygdala, and the septum converge on the same hypothalamic neuron (Dreifuss and Murphy, 1968; Van Atta and Sutin, 1971, 1972).

C. Limbic Seizure Discharges

The limbic structures of the temporal lobe (amygdala, hippocampus, and surrounding piriform cortex) have a low seizure threshold when electrically stimulated (Gibbs and Gibbs, 1936; Jung, 1949; Kaada, 1951; Green and Shimamoto, 1953; Andy and Akert, 1955; Creutzfeldt, 1956; Passouant and Cadilhac, 1961). This corresponds to the clinical observation that these areas are often responsible for the origin or propagation of complex partial seizures. Seizure discharges elicited in these structures spread to the ipsilateral temporal cortex, deep midline structures (diencephalon and midbrain), and homologous areas of the contralateral hemisphere (Green and Shimamoto, 1953; Faeth, Walker, and Andy, 1954; Creutzfeldt, 1956; Gloor, 1957; Passouant and Cadilhac, 1961).

The neurophysiological mechanism of epileptic activity has been studied in particular detail in the hippocampus. Local application of penicillin to the hippocampus, as in the cerebral neocortex, readily produces interictal spike discharges in the hippocampal EEG which are associated with large paroxysmal depolarizing membrane potential shifts in pyramidal neurons. These in turn elicit a powerful inhibition in neighboring neurons through recurrent inhibitory pathways (presumably the basket cells). This recurrent inhibition presumably prevents the development of ictal discharge (Dichter and Spencer, 1969a). Indeed the latter is heralded by the gradually developing failure of these inhibitory mechanisms (Dichter and Spencer, 1969b).

The hippocampus is very prone to respond with sustained epileptic discharges to repetitive electrical stimulation of afferent pathways (Gloor et al., 1964b). Under these conditions recurrent intrahippocampal excitation, through short axon pathways in or near the pyramidal layer, seems to develop and is thought to be responsible for the buildup of seizure discharge.
This is often associated with a very large increase in the number and synchronization of single-unit discharges, which fuse into giant spikes. Coincident with this, a large standing DC potential dipole develops across the hippocampal pyramidal layer, the basal layers containing the cell bodies and basal dendrites becoming electronegative with reference to the apical dendrites. There is some evidence which suggests that this large transhippocampal DC gradient may contribute in an important way to the genesis and maintenance of hippocampal seizure discharge (Gloor et al., 1964b). The ease with which it develops in response to repetitive stimulation may be related to the exquisite seizure susceptibility of the hippocampus. Another contributing factor (possibly related to the development of DC shifts) may be that action potentials of hippocampal neurons, unlike those of most other neurons, are followed by depolarizing afterpotentials which may easily summate under conditions of repetitive firing (Kandel, Spencer, and Brinley, 1961).

III. FUNCTIONS INFLUENCED BY LIMBIC STRUCTURES OF THE TEMPORAL LOBE

Since anatomical and electrophysiological studies have shown that the projections of the limbic structures of the temporal lobe, particularly those of the amygdala and hippocampus, are predominantly directed toward septal, preoptic, and hypothalamic areas, one might expect these limbic structures to exert a considerable influence upon the functions regulated by those regions located at the base of the brain. Indeed, both stimulation and ablation experiments have shown that hardly any of the functions dependent upon septal, preoptic, and hypothalamic areas are exempt from some kind of influence exerted by the limbic components of the temporal lobe. These functions include autonomic activities, endocrine control, somatomotor functions, and complex behavioral mechanisms related to fundamental motivational states.

A. Autonomic Functions (Including Respiration)

Electrical stimulation of limbic structures of the temporal lobe elicits a wide range of autonomic changes, such as cardiovascular responses (increase or decrease of blood pressure, tachycardia and bradycardia, vasomotor changes), pupillary dilatation, salivation, increase or decrease in gastric motility and/or secretion, micturition, changes in uterine motility, piloerection, and lacrimation. Such stimulations also increase or decrease respiratory frequency and/or depth, and may produce temporary apnea (Kaada, 1951, 1960, 1972; Gastaut, 1952; Koikegami and Fuse, 1952a,b; Koikegami, Kushiro, and Kimoto, 1952; Koikegami, Kimoto, and Kido, 1953; Koikegami and Yoshida, 1953; MacLean and Delgado, 1953; Kaada,
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Andersen, and Jansen, 1954; Koikegami, Yamada, and Usui, 1954; Koikegami, Fusse, Yokoyama, Watanabe, and Watanabe, 1955; Anand and Dua, 1956; Koikegami, Dodo, Mochida, and Takahashi, 1957; Shealy and Peele, 1957; Wood, 1958; Wood, Schottelius, Frost, and Baldwin, 1958; Gloor, 1960; Magnus and Naquet, 1961; Zawiski, 1967; Lee, Thompson, and McNew, 1969; Bonvallet and Gary Bobo, 1970; Gary Bobo and Bonvallet, 1970; Smith and McHugh, 1970; Mogenson and Calaresu, 1973). These changes are particularly prominent upon stimulation of the amygdala and of the periamygdaloid piriform cortex. They are less often reported from hippocampal stimulation (Green, 1960, 1964). Evidently responses mediated by the sympathetic system, as well as others mediated by the parasympathetic autonomic system, can be elicited by such stimulations. No clear topographical pattern of representation of these various autonomic effects emerges from these studies (Gloor, 1960), even though a number of investigators have tried to establish such topographical schemes (Koikegami and Fusse, 1952a,b; Koikegami et al., 1952, 1953, 1954, 1955, 1957; Koikegami and Yoshida, 1953; Kaada et al., 1954; Bonvallet and Gary Bobo, 1972; Kaada, 1972). Only the representation of pupillary dilatation, cardiovascular and respiratory components of the defense reaction (see below) seem to be clearly localized in the basal nucleus of the amygdala, particularly its magnocellular part (Bonvallet and Gary Bobo, 1970, 1972; Gary Bobo and Bonvallet, 1970).

In contrast to the richness of autonomic effects induced by stimulation, there is a surprising paucity of autonomic changes following even bilateral and symmetrical lesions of the amygdala and adjacent limbic structures: no consistent autonomic deficits are found following such lesions. It seems, therefore, that limbic stimulations are quite capable of changing the excitatory state at lower levels of the central representation of the autonomic system, but that lack of input from limbic structures to these centers does not prevent them from discharging their basic homeostatic functions.

The importance of these autonomic responses with regard to seizures of temporal lobe onset is that many of the autonomic changes thus elicited are well-known clinical features of such attacks. Some are easily observable, such as vasomotor changes in the face, pupillary dilatation, salivation and respiratory changes; others require polygraphic recording techniques or must be inferred from subjective reports, such as sensations presumably related to changes in the activity of the heart or the gastrointestinal tract (e.g., epigastric sensation) (Penfield and Jasper, 1954).

B. Endocrine Functions

Limbic structures of the temporal lobe exert a definite influence upon the secretion of anterior and posterior pituitary hormones. Both stimulation and some lesion experiments have borne this out.
Amygdaloid stimulation activates and hippocampal stimulation inhibits ACTH secretion (Mason, 1958; Endröczi, Lissak, Bohus, and Kovacs, 1959; Mandell, Chapman, Rand, and Walter, 1963; Rubin, Mandell, and Crandall, 1966; McHugh and Smith 1967; Smith and McHugh, 1967; Salcman, Peck, and Egdahl, 1970; Matheson, Branch, and Taylor, 1971). Not all areas of the amygdala, however, seem to exert the same effect. There is evidence from both stimulation and lesion experiments that the facilitatory effect upon ACTH discharge is mediated by the basolateral amygdala; the corticomedial nuclei of the amygdala, on the contrary, seem to inhibit ACTH discharge (Bovard and Gloor, 1961; Eleftheriou, Zolovich, and Pearse, 1966; Matheson et al., 1971; Coover, Ursin, and Levine, 1973). In line with these observations is the fact that the amygdala (particularly the corticomedial portion), the hippocampus, and the piriform cortex preferentially take up radioactively labeled corticosterone (Stumpf, 1972).

A similar situation is found with regard to growth hormone secretion, which is activated in response to basolateral amygdaloid and hippocampal stimulation but inhibited when the corticomedial portion of the amygdala is stimulated (Ehle, Pennington, and Mason, 1970; Martin, 1972, 1973, 1974; Martin, Kontor, and Mead, 1973).

In view of the electrophysiologically demonstrated opposite synaptic effects exerted on the ventromedial nucleus of the hypothalamus by the two main amygdaloid subdivisions, the corticomedial portion discharging through the stria terminalis exerting a predominantly inhibitory action, the basolateral portion discharging through the ventral amygdalofugal pathway exerting a predominantly excitatory action upon the ventromedial hypothalamus (Dreifuss, Murphy, and Gloor, 1968), it is tempting to speculate that the contrasting effects on these endocrine responses obtained from basolateral and corticomedial amygdaloid stimulation or lesions may be explained in some way in terms of these opposite electrophysiological response patterns.

Gonadotrophic hormone secretion is probably mostly influenced by the corticomedial portion of the amygdala through its outflow via the stria terminalis. This part of the amygdala, the bed nucleus of the stria terminalis, as well as its projection area in the preoptic region, take up radioactively labeled estrogens more heavily than other brain regions (Stumpf and Sar, 1971; Pfaff and Keiner, 1972, 1973; Stumpf, 1972). Some uptake of estrogens is also found in the ventral hippocampus. The uptake pattern is similar but less clear for testosterone (Pfaff and Keiner, 1972; Stumpf, 1972). The exact role of these limbic structures in the regulation of gonadotrophic secretion is unclear. Some observations suggest that the corticomedial amygdala facilitates and the hippocampus inhibits gonadotrophic secretion (Velasco and Taleisnik, 1971). There is, however, also evidence that the corticomedial amygdala inhibits gonadotrophic hormone secretion: bilateral sectioning of the stria terminalis, for instance, in prepubertal rats accelerates
the onset of puberty, while chronic stimulation of the same pathways delays its onset (Elwers and Critchlow, 1960, 1961; Bar-Sela and Critchlow, 1966; Brown-Grant and Raisman, 1972). Sawyer (1972) suggests that the corticomedial amygdala contains two types of neurons: one type inhibiting gonadotrophic function in general, and another facilitating the ovulatory surge of pituitary LH release. An inhibitory role of the basolateral amygdala in gonadotrophin secretion is suggested by some studies (Eleftheriou and Zolovick, 1967; Zolovick, 1972). Amygdaloid stimulation is known to produce ovulation in several species (Koikegami et al., 1954; Shealy and Peele, 1957). Velasco and Taleisnik (1971) have shown that this response is mediated by the stria terminalis.

Amygda and hippocampus may have excitatory influences on thyrotropic hormone secretion (Zolovick, 1972). Some influence on prolactin secretion also appears probable (Tindal, Knaggs, and Torsey, 1967).

The neurohypophysis is also under the influence of the amygdala. Its stimulation produces an increase in the secretion of antidiuretic hormone. This effect seems to be mediated by the ventral amygdalofugal pathway (Hayward, 1972).

As is the case for the regulation of autonomic functions, bilateral lesions of limbic structures do not apparently interfere severely with the basic homeostatic and adaptive controls of pituitary hormone secretion, although they probably interfere with more subtle adaptive responses, most likely with those related to emotional responses mediated by environmental stimuli.

An interesting observation with regard to ACTH secretion was reported by McHugh and Smith (1967), who showed that amygdaloid stimulation given 15 min after intravenous injection of soluble hydrocortisone produced a total change in the plasma 17-hydroxycorticosteroid level which was no different from that produced by 1 hr of amygdaloid stimulation alone. If, however, the same injection preceded 1 hr of hypothalamic stimulation, the total increase in 17-hydroxycorticosteroids was significantly larger than with hypothalamic stimulation alone. These findings suggest that the amygdala is not a part of the basic homeostatic feedback circuit regulating ACTH secretion, but its role may be to alter the “set point” of this circuit. This would explain why amygdaloid stimulation produces the same elevation of 17-hydroxycorticosteroids regardless of whether the level had already been elevated artificially beforehand by intravenous injection of this hormone. A similar role of the amygdala for growth hormone secretion is suggested by the findings of Ehle et al. (1970). One may speculate, therefore, that the role of some limbic neuroendocrine control mechanisms may be to set the gain of the hypothalamic-pituitary feedback loop at a value that is appropriate in the light of some information received by limbic neurons. The importance of these endocrine mechanisms influenced by the limbic structures of the temporal lobe for the clinical symptomatology and natural history of complex partial is as yet unknown.
C. Somatomotor Mechanisms

Electrical stimulation of the amygdala and the surrounding piriform cortex may change the excitability in the motor system, either by increasing or decreasing the excitability of spinal reflex arcs. It may also alter cortically evoked motor responses, either by augmenting or diminishing them (Kaada, 1951). Spontaneous ongoing motor activity is usually arrested at the onset of amygdaloid stimulation (Kaada, 1951; Kaada et al., 1954).

Overt motor behavior induced by stimulation of this area may consist of masticatory movements, licking, and swallowing (Kaada, 1951, 1972; Gastaut, 1952; MacLean and Delgado, 1953; Baldwin, Frost, and Wood, 1954, 1956; Kaada et al., 1954; Jasper and Rasmussen, 1958; Magnus and Naquet, 1961). Sniffing (Kaada, 1951; Gastaut, 1952; MacLean and Delgado, 1953; Magnus and Naquet, 1961) and vocalization (Gastaut, 1952; MacLean and Delgado, 1953) are other motor responses elicited by stimulation of this region.

Contraversive conjugate deviation of head and eye may also result from amygdaloid stimulation (Kaada, 1951; Gastaut, 1952; Gastaut, Vigouroux, and Naquet, 1952; Kaada et al., 1954; Magnus and Naquet, 1961). This response has been likened to the Pavlovian orientation response (Gastaut et al., 1952) and may perhaps be part of a nonspecific arousal response produced by amygdaloid stimulation.

A peculiar motor effect which has been described as a response to amygdaloid stimulation is ipsilateral face twitching or contraction (Gastaut, 1952; MacLean and Delgado, 1953; Baldwin et al., 1954, 1956; Magnus and Naquet, 1961). This may occur concurrently with an afterdischarge and thus cannot be attributed to the spread of stimulating current to the 7th nerve (Frost, Baldwin, and Wood, 1958).

The relationship of hippocampal theta activity to some aspects of motor function as demonstrated by Vanderwolf (1969) has already been discussed above in the section on hippocampal electrophysiology.

Bilateral lesions in limbic structures of the temporal lobe do not produce any detectable motor deficit.

The somatomotor responses elicited by stimulation of the amygdala and neighboring limbic structures are well-known constituents of clinical seizures involving this area. This is particularly true for masticatory movements, swallowing, and licking (Penfield and Jasper, 1954).

D. Influence on Electrical Activity of Cerebral Cortex

Amygdaloid stimulation is capable of producing a desynchronization of the electrocorticogram which is very similar to that obtainable from stimulation of the reticular formation of the brainstem (Kaada, 1951; Feindel and Gloo, 1954). The response may perhaps reflect an indirect activation of the ascending brainstem reticular formation through the descending path-
ways originating from the amygdala and may be part of a general alerting response related to emotional changes produced by amygdaloid stimulation. The response bears some resemblance to the desynchronized pattern that is sometimes seen at the beginning of an epileptic attack in the electroencephalogram of patients with complex partial seizures. This desynchronized pattern is often associated with suppression of interictal spike activity. Both can be reproduced in man by electrical stimulation of the amygdala (Feindel and Penfield, 1954).

E. Behavioral Mechanisms

Electrical stimulation of the amygdala in freely moving animals with implanted electrodes may elicit behavioral changes which to some extent vary as a function of intensity of stimulation (Gastaut, 1952). Stimulations at or near threshold usually produce arrest of ongoing behavior as if the animal had been alerted by some stimulus (Kaada 1951, 1972; Gastaut, 1952; Gastaut et al., 1952; Kaada et al., 1954; Ursin and Kaada, 1960; Magnus and Naquet, 1961), and this may be associated with deviation of the head and eyes as seen during a Pavlovian orientation response (Gastaut et al., 1952). Gastaut (1952) reports that with higher intensities of stimulation the animal may look fearful and try to escape or hide, and with still higher intensities of stimulation may display a full-fledged defense reaction characterized by the species-specific display of angry behavior. Other investigators have also observed fear or defense reactions in animals in response to amygdaloid stimulation (MacLean and Delgado, 1953; Kaada et al., 1954; De Molina and Hunsperger, 1959; Ursin, 1960; Ursin and Kaada, 1960; Magnus and Naquet, 1961; Hilton and Zbrozyna, 1963; Kaada, 1972; Zbrozyna, 1972). The defense response is mediated through the ventral amygdalofugal system, but can also be initiated by stimulation of afferent pathways to the amygdala running through the stria terminalis (Hilton and Zbrozyna, 1963; Zbrozyna, 1972). Associated cardiovascular changes and pupillary dilatation appear to be mediated by the same system and are most strongly represented in the magnocellular part of the basal nucleus of the amygdala (Gary Bobo and Bonvallet, 1970; Bonvallet and Gary Bobo, 1972; Zbrozyna, 1972).

Rats will avoid self-stimulation through chronically implanted electrodes when these are located in the basolateral amygdala, but they avidly seek self-stimulation if the electrodes are placed in the corticomedial division of the amygdala (Wurtz and Olds, 1963). The above observations thus suggest that the basolateral amygdala, perhaps particularly the basal nucleus, and the ventral amygdalofugal system are particularly involved in the mediation and expression of avoidance behavior resulting in either flight or aggression; the corticomedial amygdaloid region, in contrast, seems to activate a reward system. Which particular forms of reward are involved is not entirely clear, but the lateral amygdala is believed to be involved. Eleftheriou and Benito recently demonstrated that the lateral amygdala has a more direct influence on the ventral tegmental area, indicating an important role in the expression of aggressive behavior.
but there is some evidence from lesion experiments that feeding behavior may be promoted by the corticomedial amygdala and inhibited by the basolateral amygdala (Lewinska, 1967; Fonberg and Sychowa, 1968; Fonberg, 1969a,b). The same may be true for sexual behavior (Wood, 1958; Eleftheriou and Zolovick, 1966). It is tempting to speculate that these positive and negative influences on avoidance behavior, feeding, and possibly sexual behavior may reflect the dual control mechanism exerted on the ventromedial hypothalamus by the amygdala, as demonstrated by electrophysiological studies which showed that ventromedial hypothalamic neurons are inhibited by stria terminalis volleys, but excited by those arriving over the ventral amygdalofugal pathway (Dreifuss et al., 1968). These behavioral observations also fit rather well with the results of neuroendocrine studies indicating that the basolateral amygdala activates, but the corticomedial amygdala inhibits ACTH secretion (Bovard and Gloor, 1961; Eleftheriou et al., 1966; Matheson et al., 1971; Coover et al., 1973).

Ablation studies have given additional and in many ways more revealing insight into the importance of the amygdala for behavior, especially with regard to its influence on basic motivational mechanisms. It is well known that bilateral removal of the temporal lobe, including the amygdala and part of the hippocampus, leads to the so-called Klüver-Bucy syndrome, which is characterized by emotional blunting, often appearing as a taming effect, changes in dietary habits and sexual behavior (particularly a form of uninhibited and inappropriate hypersexuality), "oral compulsive behavior," increased distractibility of the animal ("hypermetamorphosis"), and visual agnosia (Klüver and Bucy, 1937, 1938, 1939). From studies on more restricted lesions, it seems apparent that visual agnosia is largely the effect of removal of temporal neocortex, particularly inferior temporal neocortex (Milner, 1958; Kimura, 1963; Mishkin, 1966; Cowey and Gross, 1970; Iversen, 1973), whereas the changes in the animal's affective state, in its feeding, and its sexual behavior are primarily attributable to the bilateral loss of amygdaloid tissue (Gastaut, 1952; Schreiner and Kling, 1953; Rosvold, Mirsky, and Pribram, 1954; Weiskrantz, 1956; Wood, 1958).

More recent studies in feral free-ranging monkeys from which the amygdala was bilaterally removed have shown that the behavioral effects in wild animals released back into their natural habitat appear to be somewhat different from those observed in a caged laboratory animal. These animals do not appear to be particularly tame, nor has there been any evidence that they are hypersexual. What they seem to have irretrievably lost is their ability to make meaningful social contact with their peers and to reintegrate into the social hierarchy of their own group (Dicks, Myers, and Kling, 1969; Kling, Dicks, and Gurowitz, 1969; Kling, Lancaster, and Benitone, 1970; Kling, 1972). The animals seem to have lost the ability to interpret exteroceptive stimuli in terms of their motivational significance, especially in relation to their particular meaning in a social context, a func-
tation which presumably requires a fine and appropriate tuning of approach and avoidance reactions in response to appropriate stimuli emanating from conspecifics whose individual position in the social hierarchy must be correctly recognized. Evidently such stimuli are mediated through exteroceptive senses (in primates, particularly vision) and must lead to appropriate affective responses. It is equally evident that the significance of such stimuli is learned by the animal in the course of its individual life history.

This inability of amygdalectomized animals to relate exteroceptive stimuli to past experience in terms of their motivational significance does not seem to be confined to stimuli related to social behavior, but probably also pertains to other, more basic motivational drives such as feeding (Rolls and Rolls, 1973b), drinking (Rolls and Rolls, 1973a), sexual behavior, aggression, and defense (Weiskrantz, 1956). The disruption of behavior by such bilateral amygdaloid lesions is so severe that bilaterally amygdalectomized monkeys fail to survive in their natural habitat (Dicks et al., 1969). Some studies have indicated that the anterior temporal neocortex may subserve behavioral functions similar to those of the amygdala, especially with regard to social behavior (Akert, Gruesen, Woolsey, and Meyer, 1961; Myers and Swett, 1970; Myers, 1972).

The role of the hippocampus in behavioral mechanisms is much less clear (Green, 1960, 1964). Stimulation of the hippocampus, when care is taken to avoid the induction of a seizure discharge, results in no clear overt behavioral change (MacLean, 1957a,b; Passouant and Cadilhac, 1961). Increased grooming and pleasure reactions, including penile erection, is often seen following these hippocampal seizures (MacLean 1957b; Passouant and Cadilhac, 1961).

A striking behavioral deficit following bilateral hippocampal lesions is loss of recent memory, which has been particularly well documented in man (Scoville and Milner, 1957; Penfield and Milner, 1958; Delong, Habashi, and Olson, 1969; Milner, 1970; Penfield and Mathieson, 1974). A few studies in animals have suggested similar memory difficulties resulting from bilateral hippocampal lesions or inactivation (Kaada, Wulff Rasmussen, and Kveim, 1961; Avis and Carlton, 1968; Uretzky and McCleary, 1969; Kapp and Schneider, 1971; Sideroff, Bueno, Hirsch, Weyand, and McGaugh, 1974).

These observations on behavioral mechanisms influenced by limbic structures of the temporal lobe are pertinent to some of the clinical phenomena encountered in complex partial seizures. Thus a change in affect, especially the sudden and unmodulated feeling of fear, is a well-known experiential illusion in the course of such seizures (Jackson, 1879; Macrae, 1954; Penfield and Jasper, 1954; Williams, 1956; Bingley, 1958; Daly, 1958; Gibbs, 1958; Mullan and Penfield, 1959; Weil, 1959; Gloor and Feindel, 1963). Such feelings of fear are sometimes reproduced in epileptic patients with electrical stimulation in or near the amygdala (Penfield and Jasper, 1954; J.

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The tuning of approach stimuli emanating from an emotional hierarchy must be mediated through exteroceptive stimuli to lead to appropriate behavioral expression of such stimuli with a history.

Exteroceptive stimuli are not necessarily all present. It is equally probable that the feeding (Rolls and Gainville, 1956) and sexual behavior, aggressive, and defensive behavior by such animals as the rat or amygdalectomized monkey (Kleitman et al., 1969). Some of the emotional functions of the cortex may subserve in a similar manner in the survival of the species, with regard to filial care (H. J. Leiderer, 1961; Myers et al., 1967).

The function of the amygdala is not well known. When care is taken to remove damage to the amygdala (M. Cadilhac, 1961). It is presumed that while erection, is often apparent in amygdalectomized animals (Gastaut, 1957b; Passouant and W. D. D. Johnston, 1957). It is apparent from the data of Passouant and W. D. D. Johnston that the hippocampal lesions are loss of the ability to respond to olfactory stimuli (Kleitman et al., 1969; Wulff and Rasmussen, 1959; McMillan and McCleary, 1969; Frank, Weyand, and McCleary, 1969).

The functional significance of the limbic structures of the temporal lobe...
lower animal forms, especially in submammalian forms, the main input to the amygdala is olfactory (Kappers, Huber, and Crosby, 1936). Even in lower mammals, the olfactory input to the amygdala is still a powerful and predominant one; it is only in primates that visual inputs to the amygdala become predominant. Comparative ethological studies of the role of olfaction in animal behavior have shown that the sense of smell in lower forms does not merely subserve the search for food or for a sexual mate. Much more subtle and more complex behavioral mechanisms are dependent upon it, such as affective bonding within a social group, dominance in the social group, signaling of aggressive intent, recognition of a conspecific as being a member of one's own group or as being a stranger, territoriality, and so on. (Atema, Todd, and Bardach, 1969; Schultze-Westrum, 1969; Pfaffman 1972; Rails, 1971). Olfactory cues involved in the regulation of these complex behavioral mechanisms are learned, not inborn, since they must be capable of relaying information of the type which could be paraphrased by such antropomorphic statements as "This is my mother" or "He belongs to our group," and so on. Such olfactory cues allow the animal to behave in a way that is appropriate to what it has learned in the course of its own individual life history. In primates the role of the sense of smell in shaping such complex behaviors has been superseded by vision. In monkeys in particular, visual percepts serve as the signals which provide the kind of information which in lower mammals are dependent to a large extent upon olfactory cues. Thus individual recognition, social bonding, dominance, signaling of aggressive intent, and so on, are, to a large degree, dependent upon the visual signals provided by facial expressions or bodily postures (Altman, 1962; Hinde and Rowell, 1962; Van Hooff, 1962; Marler, 1965; Ploog, 1970).

A beautiful illustration of the importance of vision to appropriately motivated behavior in the monkey is provided by the observation reported by Downer (1961, 1962). He split the corpus callosum, the anterior commissure, and the optic chiasm in a monkey in which one amygdala had been removed. This animal's responses to the environment were normal when the eye on the side of the amygdalec-tomy was occluded; it exhibited the aggressive-defensive attitude to a human being appropriate for a feral monkey. The animal's behavior, however, was radically altered when the eye opposite to the amygdalec-tomy was occluded. The previously fearful and aggressive monkey immediately became tame and approachable. The monkey had totally lost its previously overpowering fear and aggressive tendency toward human beings, but only as long as he was not touched. Obviously when this animal looked at the world through the hemisphere which lacked an amygdala, it was no longer capable of attaching motivational significance to the visual stimuli it received from its environment. A similar hypomotionality and "visual agnosia" was also produced in monkeys which received a unilateral temporal lobectomy, contralateral occipital lobectomy (1972).

The ability to function in a normal visual environment is not only dependent upon the ability to see, but also upon the ability to perceive a visual image. This ability was studied by Aschoff (1910), Aschoff and Dell (1910), and others who showed that damage of the temporal lobe will produce a visual agnosia. The ability to recognize objects, figures, and even to see color is lost. This is a devastatingly striking demonstration of the importance of the temporal lobe to visual function, and the close linkage of the visual system with the auditory system is well known.

It is true that sensory substitution can take place in conditions of partial sensory loss, but it is presumably less effective than in intact individuals. It is also true that the visual system can function quite efficiently when the other sensory systems are at a relative disadvantage, but it is also true that the visual system itself provides the sensory modality least subject to sensory substitution. This is true because the visual system is the most highly developed of all the sensory systems, and it is therefore less likely to be able to provide the same kind of information by another modality.

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forms, the main input to which is still a powerful and dominant smell cue. Such inputs to the amygdala have various implications of the role of olfactoriness in the behavior of smell in lower forms is present in the human for a sexual mate. Much of the behavior described is dependent upon the ability to recognize dominance in the social structure of the group, a conspecific as being male, female, in estrus, territoriality, and so on. (DeVries, 1969; Pfaffman 1969). The regulation of these complex behaviors probably begins in early life, as they are a fundamental component of the animal's ability to survive and reproduce. In monkeys in particular, the sense of smell is of great importance, both for social bonding, dominance, and for the recognition of familiar individuals or bodily postures and gestures (Pfaffman, 1962; Marler, 1965).

The ability of the olfactory system to appropriately motivate behavior has been observed in many species. For example, the anterior commissure of the cat, which connects one amygdala to the other, is highly developed in mammals and is thought to be involved in the processing of olfactory information. It has been suggested that the anterior commissure is involved in the integration of olfactory and visual information, allowing the animal to respond appropriately to complex stimuli in its environment. The anterior commissure is also thought to play a role in social bonding, as animals with lesions in this area show deficits in social behavior.

When tested in a novel environment, the anterior commissure of the cat was normal when intact, but was impaired when it was lesioned; it exhibited the same deficit when tested in a novel environment when intact, but was impaired when it was lesioned. The previously fearful and aggressive cat became less fearful and approachable. The cat, when presented with a new fear and aggressive stimulus, responded as if he was not touched. The anterior commissure was thought to be involved in the role of attaching motivational significance to stimuli from its environment. A similar effect was also produced in the rat after left temporal lobectomy, contralateral occipital lobectomy, and section of the corpus callosum (Horel and Keating, 1972).

These experiments therefore suggest that the temporal neocortex and the amygdala act in concert and constitute the functional substrate which enables the animal to relate environmental cues, in primates especially visual cues, to past experience and to internalized states of drive and motivation. The basic mechanisms of the latter are integrated in subcortical structures at the hypothalamic and upper brainstem level; the road of access to these structures from the cortical areas involved in higher perceptual mechanisms runs through the amygdala and its downstream projections. It is tempting to speculate that in man, speech cortex in the dominant temporal lobe may also have ready access to these amygdaloid mechanisms.

Recent behavioral and microphysiological studies by Fuster and Uyeda (1971) have given neurophysiological support to the hypothesis that limbic structures of the temporal lobe, particularly the amygdala, are involved in processing motivationally meaningful extreroceptive information. These investigators have trained monkeys to respond differentially to two complex visual patterns, one signaling a food reward and the other signaling a foot shock. Extracellular microelectrode recordings of single cells in the amygdala, the piriform cortex, and the hippocampus have shown that many neurons in these structures, especially in the amygdala, respond only to visual stimuli that have acquired a motivational significance, but do not respond to neutral stimuli. Furthermore, some cells respond specifically to one motivational situation, for instance stimuli signaling food reward, but fail to respond to those signaling foot shock, or vice versa. The number of cells exhibiting such differential responses is particularly high in the amygdala, which suggests that this structure is involved in the discrimination of motivational significance of extreroceptive stimuli. O'Keefe and Bouma (1969) have shown that in the cat, some amygdaloid neurons respond selectively to complex stimuli which may have acquired a special significance for the animal, such as the sight of a black mouse (or of a picture reproducing it), a low-pitched human voice, a simulated bird call, and so on.

The role of the hippocampus in these complex behavioral mechanisms is unclear. It is unlikely that its primary role is to participate in motivational discrimination of extreroceptive stimuli, as is the case for the amygdala. In view of the human evidence on hippocampal function cited above, it is much more likely that its role is to consolidate memory traces, especially in situations where the information is received over the visual and auditory systems (Milner, 1970). In man there is evidence that the left and right hippocampi fulfill relatively specialized roles in memory function. Recent studies by Corsi (1972), for instance, have shown that the deficit in verbal memory after left temporal lobectomy is performed is proportional to the amount of left hippocampal removal; conversely the degree of nonverbal (visual) memory deficit is proportional to the amount of hippocampal re-
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mova in right temporal lobectomies (Milner, 1973). It is thus likely that the hippocampus, like the amygdala, receives fairly direct inputs from the ipsilateral temporal neocortex involved in perceptual mechanisms.

These functional considerations are of some significance with regard to the symptomatology of complex partial seizures. Thus experiential illus-
visions and hallucinations which often occur at the beginning of a seizure usually involve either the visual or auditory modes, or both. Their reproduction by cortical stimulation in patients who underwent surgery for epileptic seizures has shown that these responses can sometimes be elicited by electrical stimulation of the temporal neocortex (Penfield and Jasper, 1954; Penfield and Perot, 1963). These findings support the view that the temporal neocortex is involved in recording complex conceptual constellations in the visual and auditory modes and that it may be involved in the mechanism of their recall. The illusions of familiarity (déjà vu) or unfamiliarity which in some patients accompany temporal lobe seizure discharge can also sometimes be reproduced by stimulation of the temporal neocortex of the minor hemisphere (Penfield and Jasper, 1954; Mullan and Penfield, 1959). This may be taken as evidence that there are mechanisms in the temporal neocortex which are involved in the matching of present to past experience, a function which is of fundamental importance for assessing the significance of a perceptual constellation in the light of past experience. In many situations, this process of matching present to past experience undoubtedly must lead not only to a “decision” that a particular constellation of stimuli is familiar or, on the contrary, novel or strange, but also to emotional response which under normal conditions is appropriate to an earlier experience of a punishing or of a rewarding nature. We may conclude that when this happens, the stream of neural impulses related to this experience has reached the amygdala.

This integrated concept of temporal lobe function makes it possible to account for many of the well-known but complex clinical features of temporal lobe seizures. Often the clinical ictal event, by revealing a combination of visual and auditory perceptual phenomena, emotional responses (most often fear), autonomic changes, and disturbances of the recording of current memory, sketches in dim outlines how, in this part of the brain, information which we receive from the external world through our senses impinges upon and interacts with our personal memories and internalized states of motivation and affect.

References


COMPLEX PARTIAL SEIZURES


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DISCUSSION

Klass: Dr. Gloor, I would like to ask you about the responses from stimulation of the amygdala that you termed arousal or desynchronization—responses resembling the attenuation that occurs in a widespread fashion at the onset of quite a number of complex partial seizures. How frequently is the induced response asymmetrical between the two hemispheres? In the human, at the onset of the seizure, it frequently is.

Gloor: The low-voltage desynchronized EEG pattern at the start of a seizure is quite often asymmetrical. It may even be localized to the temporal lobe. This is why I am a little hesitant to equate the generalized desynchronized EEG pattern sometimes seen in response to amygdaloid stimulation with more restricted, similar responses and say the two are the same thing. It has been a long time since we did these experiments with Dr. Feindel—in 1954 to be exact. We stimulated the amygdala in the cat and looked at changes in the EEG.

As far as I recall, the low-voltage desynchronized pattern induced by amygdaloid stimulation was almost always generalized. Maybe there were a few instances when this change predominated on one side, but I don’t remember the details.

There are two possible explanations for this desynchronization response. Sometimes one may hold true, and sometimes the other. I don’t think with scalp EEGs you can clearly distinguish between the two possibilities. The first is a feature of the electrographic changes in any focal seizure, not just temporal lobe seizures. If you really get right at the focus, you see at the seizure onset a marked diminution of amplitude and there is very fast frequency low-voltage activity, which gradually builds up in amplitude. If this involves a relatively large area, it will appear as a localized flattening in the EEG at the onset of the seizure. The second is a generalized desynchronization analogous to an arousal response. When you see voltage depression and flattening all over the brain, it is this mechanism which is probably involved. I think maybe this is the kind of desynchronization we have seen in the cat with amygdaloid stimulation, which indeed resembles the desynchronization induced by the reticular stimulation. If you have desynchronization that is generalized, but predominating on one side, it is hard to know which of the two types you are really dealing with.

White: Dr. Gloor’s comment about the post-tetanic potentiation of the hippocampus from the perforant bundle was extremely exciting in the light of some of the morphology we are working on right now. I wanted to call it to the group’s attention. The perforant bundle projects onto dentate fascia at the tips and middle of the apical dendrites. Immediately beneath that area is a clear area at the base of the dendrite where you begin to find zinc. Zinc ion is located in the perikaryon of the granular cells and in those mossy fibers ending in a very strange kind of synapse on the base of the CA-3 dendrites.

The interesting thing about zinc which Dr. Longenecker and some others in our laboratory have been doing is that it tends to markedly potentiate the miniature end-plate potential of the neuromuscular preparation. The other thing about the zinc in the mossy fiber layer is that it is strictly related to the presynaptic membrane. The fact that it is a very prolonged behavioral effect is rather interesting in terms of that finding.

Further, CA-3, where this phenomenon is occurring, tends to project in columns
into the lateral septal area bilaterally in a cephalo-caudal relationship. How this relates to the geography of the dendrite arborization of Dentata Fascia is at the present time under study in our laboratory.

The effects of zinc on the presynaptic membrane are amazing in the neuromuscular preparation. I thought this was worthy of comment because I believe the reference to perforant pathway post-synaptic potentiation was particularly exciting in relation to the presynaptic effects of the zinc ion.