

CERTAIN FUNCTIONAL AND ANATOMICAL
RELATIONS OF THE CORNU AMMONIS OF THE
MACAQUE MONKEY^{1, 2}

I. FUNCTIONAL RELATIONS

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TWO FIGURES

INTRODUCTION

Many neuroanatomists have studied the histologic structure of the hippocampal formation. Golgi ('03) and Ramón y Cajal ('01, '11) have contributed particularly to the knowledge of the finer structure and connections of the region. Further observations were made by M. Rose ('27) and by Lorente de Nó ('33, '34). The last author confirmed much of the earlier work and extended previous studies by subdividing the hippocampal area into various parts according to its fiber connections.

Recently, physiologists (to be quoted in more detail in the discussion) have reported conflicting findings on the function of the hippocampal area. The general opinion is that this region is involved, in some way, in somato-visceral associations and is concerned with emotion itself or in emotional expression. The available anatomical information does not seem to explain adequately the anatomical relations underlying such functions.

¹Monkeys used were generously provided by Parke, Davis and Company, Detroit.

²Part 1 and Part 2 of this study represent, in part, a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at The University of Michigan, 1958.

If the hippocampal formation does have some relation to emotion, or to the expression of emotion, and if, as many authors have concluded on histologic grounds (summarized by Brodal, '47), the hippocampal area is an effectory structure, it would seem possible that this structure could be considered as a supplementary or additional motor area. Such a supplementary motor region is a cortical area, other than area 4, which on stimulation produces body or head movements. Ferrier (1886) reported that stimulation of the hippocampal area in experimental animals gave movements of the mouth, similar to licking or smacking responses, and interpreted these movements as feeding responses, showing that this region took part in such reactions. More recently Penfield ('55) and Penfield and Erickson ('41) have denied that stimulation of the hippocampus in man gives any sort of movement.

In the present project, Ammon's horn has been investigated to determine whether it may act as a supplementary motor area, and, if so, over what anatomical paths the impulses mediating the motor functions passed. Furthermore, animals have been studied, after lesions of the hippocampus or of its discharge paths had been made, to determine whether there was any effect on their behavior.

The term hippocampal formation (or hippocampal complex) as it is used in the literature today includes the dentate gyrus, cornu Ammonis, and subiculum. At times the term has been extended to include the presubiculum and even the entorhinal area. The term hippocampus usually has indicated the cornu Ammonis alone although some earlier authors have used it as synonymous with hippocampal formation. In this study, the term hippocampal formation (or hippocampal complex or hippocampal area) will be used to indicate the complex of dentate gyrus, Ammon's horn and subiculum. The presubiculum and entorhinal area will be treated as separate entities. The terms hippocampus and cornu Ammonis (Ammon's horn) will be used interchangeably.

MATERIAL AND METHODS

There have been two main approaches to the problem. The first consists of electrical stimulation of the cornu Ammonis and its fiber paths with direct observation of any possible movements resulting from such stimulation. The second phase has been concerned with the study of the experimental animals after removal of parts, or all, of this region.

For stimulation of the hippocampus and fornix, 9 monkeys (*Macaca mulatta* and *Macacus cynomolgus*) of either sex were used. The weights of the animals varied from 2.4 to 16.3 kg. All animals employed in the experimentation were free of any observable disease and of neurologic symptoms. They underwent no training before the experiments were carried out. Light ether anesthesia was used in all the surgical procedures.

Stimulation was carried out either by exposing Ammon's horn and/or the fornix directly and applying the electrode to it, or by the use of the stereotaxic instrument. In acute experiments on three animals, a parieto-temporal craniectomy was carried out with the removal of the inferior half of the midportion of the superior temporal gyrus and the corresponding portion of the superior half of the middle temporal gyrus. In this manner the temporal horn of the lateral ventricle was opened and the hippocampus directly exposed. Then, by extending the lesion along the ventricle, the entire hippocampal-fornix system was revealed. Using a unipolar stimulating electrode applied to the cornu Ammonis or to the fornix and a rectal electrode, both connected to a Grass Co. 3C stimulator, the hippocampus was stimulated and the body movements noted. The stimulus strength varied from two to 12 volts. A stimulus duration of one millisecond and a stimulus frequency of 40 per second were constant throughout all the experiments. Motion pictures were taken of any movements resulting from such stimulation.

In 4 other animals the procedures were designed as survival experiments. The operation performed on these animals was limited to the exposure of the cornu Ammonis and the lesion in the lateral surface of the temporal lobe was kept as small as possible. In one animal a unilateral stimulation of the hippocampus was carried out; then, using a brain sucker, a small lesion was placed in the hippocampus at a site where ipsilateral face movements had been obtained. In another animal the same procedure was used except that the first experiment was followed by a similar one three weeks later. In this animal the lesion on each side was placed in an area where bilateral face movements had been obtained. In the remaining animals of this group the entire cornu Ammonis was exposed, stimulated, and then completely removed. This was carried out by several successive operations, one for each side of each animal. In one of these animals the second operation occurred one week after the first; in the other, the second procedure followed the first by 11 weeks. All animals of this group were observed daily up to the time of sacrifice.

In an additional two animals, stimulation was carried out by the use of a No. 4 Lab-Tronics stereotaxic apparatus. The coordinates of the electrode placement were obtained by direct measurement. To do this the head of an autopsied monkey of approximately the same size as that of the monkey to be studied, and with the hippocampus exposed, was fixed in the stereotaxic apparatus. The tip of the electrode, fastened in the electrode carrier, was then placed in the hippocampus or fornix and the readings taken directly. Then during the procedure on the experimental animal, the electrode carrier was placed at the same coordinates. Since the electrode was not shifted after it was fastened into the carrier, the position of the tip of the electrode approximated the desired position in the hippocampus or fornix.

In one additional animal the lateral parts of the temporal lobe of each side were ablated as in the animals which had the bilateral removal of cornu Ammonis. Two craniectomies,

one on each side, were performed, the second following the first by 11 weeks. Thus the hippocampus was exposed but was not stimulated or injured in any way. By this procedure the animal could be used as a control for the two animals which underwent bilateral removal of Ammon's horn.

The survival times after the final operation on each animal varied from two to 7 weeks. Postoperative observations were made daily on these animals. The amount of activity, any possible paralysis or paresis, any signs of spasticity, any possible changes of mood, and the general behavior of the animal were noted.

The animals were sacrificed with an overdose of an anesthetic (evipal or ether) and each monkey perfused with 10% formalin. The brain was then removed from the skull, examined grossly, and photographed. Following this, the specimen was prepared according to the Marchi technique as modified by Swank and Davenport ('35). Using these procedures, a check was made on the electrode placement, the size of the lesion, and the completeness of the various sections made. The slides were also examined for the degenerated paths leading from the lesions. The results of the microscopic study will constitute part II of this investigation.

RESULTS

Adequate stimulation of the cornu Ammonis and the fornix produced definite somatic motor responses. These movements occurred according to a definite pattern which is illustrated in figure 1. The movements consisted of partial narrowing of the interpalpebral fissure (closing of the eye), flaring of the external nares, retraction of the corner of the mouth, turning of the neck to the side opposite stimulation (ipsilateral neck movement) or extending the neck (bilateral neck movement), elevation and flexion of the shoulder, flexion of the elbow, flexion of the wrist, and closing of the fist. Examples of these movements are shown in figure 2. These photographs are from frames of the motion picture records taken during the stimulation procedures.

Ipsilateral movement was almost always present, and the contralateral movement added to this to make a bilateral movement. Rarely, and only insignificantly, did an isolated contralateral movement take place. When contralateral movement occurred, it was a part of a bilateral movement. Turn-

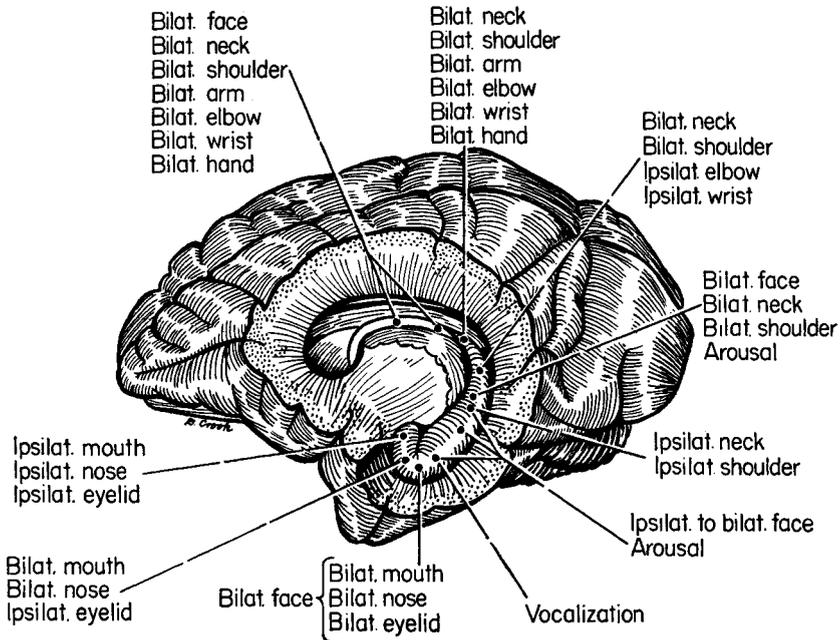


Fig. 1 Cutaway view of the hippocampus and fornix of a monkey brain, showing the type of movements obtained and the areas from which stimulation gave such movements. Abbreviations used: Ipsilat., movement of the area occurs on the same side as the side stimulated; Bilat., movement occurs on both sides to stimulation of either side.

ing of the neck is a complicated motion with respect to the contraction of muscles. To rotate the neck in one direction, muscles of both sides are in contraction, whereas to extend the neck some of these muscles on each side contract, and some relax. Thus, in a movement such as a turning of the neck away from the side of stimulation, the animal appears to move away from the side of the brain activated. This movement

involves a rather complicated muscular response. Since most of the muscles contracting in this action are on the side of stimulation, this movement has been called an ipsilateral response here and in figure 1.

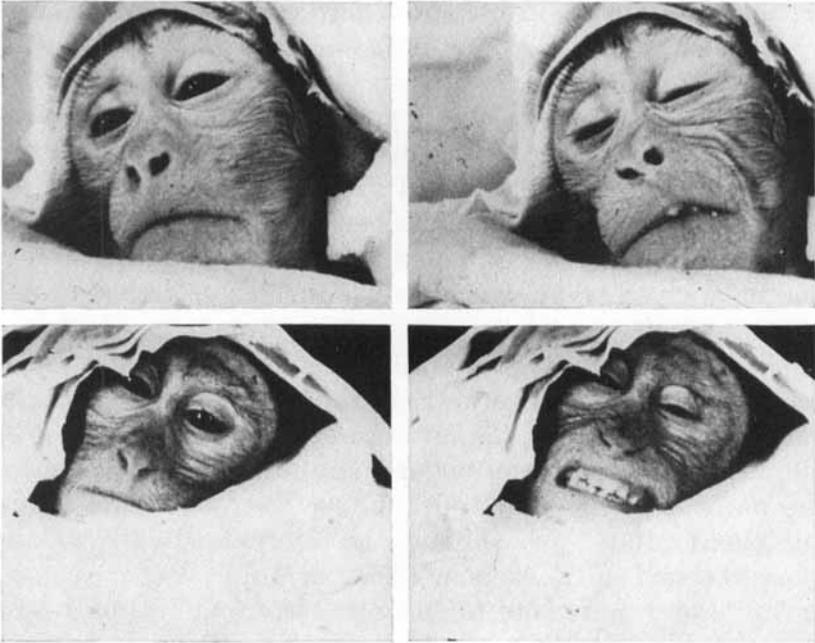


Fig. 2 Illustrations taken from a motion picture film demonstrating types of movement obtained. The left pictures illustrate the position of the animal just before stimulation was carried out; the right shows the response during stimulation.

As the illustration in figure 1 shows, the area for face movements, including ipsilateral and bilateral movements, occupies the entire anterior two thirds of the hippocampus. Movements of the neck and upper extremity are represented by the remaining third. In all the stimulations, lower extremity movement was never obtained as an isolated movement.

If the stimulus strength along the middle third of the cornu Ammonis was increased to a range of 6-12 volts, and allowed

to continue for approximately 15 seconds, the animal appeared to go into an "arousal" reaction. This was characterized by coordinated movements of all 4 extremities (as in running) and a rapid respiration. An extension of the neck occurred, the eyelids opened widely, the lower jaw moved in a chewing fashion, and a periodic to-and-fro movement of the head developed. The animal acted as if he were coming out of deep anesthesia. However, after cessation of stimulation, the animal gradually returned, over a period of 1.5 to three minutes, to the anesthetic level maintained before the stimulation began, even though no additional anesthetic was administered. Constant and repeated stimulations at this voltage, however, resulted in a lasting awakening response, so that more ether had to be given to the animal before further procedures could be carried out.

The areas marked ipsilateral in figure 1 gave only movements on that side. However, in the areas marked bilateral movements in figure 1, the results were actually ipsilateral or bilateral depending upon the strength of the stimulus and/or the position of the electrode. Using the same strength of stimulus (voltage) but shifting the electrode slightly (1 mm along the surface of Ammon's horn or 1 mm deeper) caused an ipsilateral movement to go over into a bilateral or a bilateral movement to change into an ipsilateral response. Similarly, if the electrode was not moved but the strength of the stimulus changed slightly ($\frac{1}{2}$ volt), the same result was obtained.

In two animals, the fimbria of the fornix was stimulated and a less well defined pattern was demonstrated across this structure. Stimulating medially on the fimbria gave bilateral face movements as before. Stimulation laterally gave weaker face movements, which were bilateral, and accompanied by bilateral neck, shoulder, and arm responses as described previously. The electrode diameter was 1.0 to 1.5 mm. The relatively small fimbria contains the accumulated fibers arising or terminating around the cells of a large area, the hippocampal complex. Considering this, it is reasonable that

a pattern of separate movements, such as were obtained when stimulating along the cornu Ammonis, was impossible.

The body of the fornix has an even more compact fiber arrangement than does the fimbria. Stimulation of it gave a generalized response with all the movements (bilateral face, neck, shoulder, arm, elbow, wrist, and hand) which had been obtained separately from the cornu Ammonis being present simultaneously.

In the series of acute experiments, selective sectioning was attempted in order to ascertain, if possible, at least a part of the pathway over which the impulses which mediated these movements traveled. Thus the body of the fornix was severed completely just posterior to the area where stimulation had produced movement. Ammon's horn was then restimulated along its entire length. Except for the "arousal" response, there was no change in the results described for the same stimulation before the section of the fornix. Only a very minimal "arousal" response of a very short duration could be elicited after the fornix section.

Stimulation of the body of the fornix anterior to the lesions, and at points within this fiber system where movements had been obtained before section of the fornix, gave no response. Stimulation of the fimbria posterior to the cut in the fornix gave the same results that had been obtained by similar stimulation of the fornix before its section.

In another animal, the hippocampus was carefully separated from the subiculum and lifted out of the surgical wound. Care was taken not to injure the fimbria or the fornix. Stimulation along the length of the hippocampus then failed to give any evidence of movement. There was no indication of "arousal." In this same animal, stimulation was then carried out along the subiculum from which the hippocampus had been removed. The same movements were obtained as had been elicited on stimulation of the cornu Ammonis before the separation from the subiculum. However, again, there was no indication of an "arousal" response.

One animal only, on stimulation of a point in the anterior part of the hippocampus (fig. 1), gave a loud, long continued cry of high pitch. With cessation of the stimulation this vocalization ceased at once but was repeated each time the stimulation was applied. This was not noted in any other experiments.

In 4 of the 9 animals stimulated, small lesions were made at points in the hippocampus where stimulation had produced various movements. The animals were then closely observed during the postoperative period for any changes of behavior that might occur. It was noted that small lesions of the cornu Ammonis, even if these were bilateral, had no effect on the behavior of the animal. After appropriate survival times, the brains of these animals were prepared for studies of the degenerated tracts.

In two of the 9 animals, an attempt was made to study the behavioral change in the animal after the cornu Ammonis was completely removed from both sides of the same monkey. In both animals, the hippocampus on the left was removed first. That on the right was removed one week later in one animal and 11 weeks later in the other animal. These animals were closely observed daily until the time of sacrifice, which was two and 7 weeks, respectively, after the second operation.

Sufficient time was allowed for recovery from the anesthetic before observations were made. Following the first procedure the animals were, on the whole, more docile than before, although in some respects they appeared more aggressive. When the keeper entered their cage, the animals would stand in a corner, bare their teeth, sometimes vocalize, and appear excited. They acted as does a normal monkey just before he attacks or runs from the keeper. These animals, however, did not run, and offered only slight resistance to being captured. However, upon being touched, they reacted violently, bit if possible, tried to escape, and, in general, reacted as does a normal monkey who has not undergone any surgery. No paralysis, no paresis, and no spasticity could be found in either animal. The animals moved about well, although they ap-

peared to have less inclination to do so than does an ordinary monkey. They both had normal feeding habits. A bilateral piloerection was noted over the cephalic half of the body in each case.

In the animal which underwent the second procedure one week following the first, the lesion was misplaced so that a considerable part of the thalamus was destroyed. After this second operation the animal never regained consciousness, although it lived for 10 days, allowing an attempt at degeneration studies. In the other animal, successful removal of the remaining hippocampus was accomplished. After the effects of the anesthetic had worn off, this monkey became very docile, with brief intermittent periods of violent activity. She exhibited very little spontaneous activity, though she did feed herself. There was no evidence of paralysis or spasticity. If the experimenter disturbed her, she took notice of his presence, but appeared to be unconcerned about it. Upon the application of a strong stimulus, such as a sharp needle or a severe pull on her neck chain, she would go into a brief period of violent activity, biting anything close at hand, and attempting to attack or escape. However, she quickly returned to a condition in which she exhibited no spontaneous activity. During the activity, the attack was often misdirected, consisting of what appeared to be purposeless but angry motions. During the survival period, up to the time of sacrifice (7 weeks), there was a gradual return of some spontaneous activity, but she remained definitely less excitable than a normal monkey.

In both of these experiments, in which the hippocampus was removed on each side, a portion of the temporal lobe was also ablated. For this reason, a control animal was subjected to two operations, separated from each other by 11 weeks. The hippocampus of each side was exposed in the same manner as before, a procedure which resulted in a lesion in each temporal lobe, but every precaution was taken not to disturb the cornu Ammonis in any way. Stimulation was not attempted on this animal. After the first operation the monkey behaved normally. There was no evident defect of any sort. She exhibited

the normal amount of activity, and a normal amount of hostility toward her keeper.

After the second operation, and up to the time of sacrifice (7 weeks), this control monkey showed an increased amount of spontaneous activity, a lack of fear, and a very high degree of curiosity. She placed anything she could pick up by hand in her mouth. However, after doing so, she rejected anything that was not the normal type of monkey food. She approached any person without fear. She placed the keeper's hand in her mouth, but never bit hard. It was discovered that one might safely handle her without gloves, something which is never permitted in The University of Michigan Anatomy laboratory in handling the normal monkey. She appeared less vocal than before operation. This behavior persisted until the time of sacrifice.

After all the procedures described, and after suitable survival times, the animals were sacrificed, and then the brains removed, photographed, and studied grossly. Slides were prepared for microscopic study. It was found that the operative procedures attempted had been successful.

DISCUSSION

Since the early studies of the hippocampus were primarily comparative, carried out on animals without the use of experimental lesions, Ammon's horn has become associated with the function of olfaction. Indeed, it is a part of the telencephalon which first develops, phylogenetically, in relation to the first or olfactory nerve. The degree of this association with olfactory functions has never been properly documented for primates. Even the earlier writers in the field suspected that the hippocampal complex did not serve solely for olfaction. Ferrier (1886), reporting results of stimulation of the hippocampus, localized in this structure "feeding reactions," basing his conclusions on the type of response that he obtained.

The function of Ammon's horn has been rather difficult to determine. In an attempt to analyze whether the hippocampus

had anything to do with olfaction, Swann ('34, '35) conditioned rats to an olfactory stimulus, and then removed large areas of the cerebrum. He found that removing the hippocampal complex and other rhinencephalic structures did not interfere with the conditioned response. Allen ('38, '39, '41) carried out a series of similar experiments on the dog using a much more complicated conditioned reflex. He found that complete removal of the hippocampal area, or section of the fornix, or removal of the entorhinal area did not change the conditioned reflexes. From these experiments it is easy to conclude that the hippocampus is not necessary, at least, for the primary olfactory reactions. This, however, does not eliminate the possibility that the hippocampus serves a different type of olfactory associative function.

One may, on a phylogenetic basis, compare certain anosmatic with certain macrosmatic animals. Many studies have been carried out on the cetaceans, especially by Ries and Langworthy ('37), Langworthy ('32), Breathnach ('53), Breathnach and Goldby ('54) and Addison ('15). These marine mammals have a very rudimentary development, or a complete absence, of the olfactory nerves. In spite of this, the above authors reported that the cornu Ammonis, although comparatively smaller than that in other mammals, is still present, and all component layers are recognizable. The dentate gyrus in these animals more closely reflects the absence of the olfactory nerve. Steward ('39) reported a case of human archiencephaly with an absence of the olfactory bulb and tract. The hippocampus was only slightly reduced, but the dentate gyrus was absent. In his review of similar human cases described in the literature, the author pointed out that the dentate gyrus was absent in all but one case of those reported. All patients had a fairly normal appearing cornu Ammonis. In contrast to these cases, Clark ('28) studied *Macroscelides* and *Elephantulus*, insectivores with very large olfactory nerves. The hippocampal formation of these animals is so large that it distorts the appearance of the rest of the brain.

M. Rose ('27) and S. Rose ('27) both studied the phylogenetic development of the hippocampal formation. They found that the layering in cornu Ammonis is more complex and more differentiated in primates and in man than in sub-primate forms and shows a greater density of cells and fibers, so that the hippocampus has a relatively greater thickness. These authors concluded, therefore, that the cornu Ammonis reaches its highest development in man.

On purely anatomical grounds, many of the earlier authors doubted that fibers arising in the olfactory bulb made direct connection with cornu Ammonis. Ramón y Cajal ('01, '11), Golgi ('03), and Lorente de Nó ('33, '34) reported that there were no direct connections from the olfactory bulb either to Ammon's horn or to the major portion of the entorhinal area. Most students of this area have considered that the entorhinal area is in intimate relation with the hippocampal formation including the cornu Ammonis. Studies of normal brains (rat, Gurdjian, '25; bat, Humphrey, '36; rabbit, Young, '36, and Clark and Meyer, '47; cat, Fox, '40; mink, Jeserich, '45) and of experimental material (monkey, Meyer and Allison, '49; marsupial, Adey, '53) have indicated that fibers from the olfactory bulb do not extend to the entorhinal area. Tertiary olfactory projections to the entorhinal area, cornu Ammonis, and dentate gyrus have been found in lower animals by some of these authors. If tertiary olfactory fibers reach the hippocampus, then the hippocampus is no less a projection area than the postcentral gyrus, which also receives tertiary fibers in its own projection system. Neither area serves a single function.

The above anatomical results have been verified physiologically, using the evoked potential technique, by Adrian ('42) in the hedgehog, Allen ('43) in the dog, and Fox, McKinley and Magoun ('44), and Berry, Hagamen, and Hinsey ('52) in the cat. By stimulating the olfactory bulb, and recording the resulting potentials, they found that the fibers arising from the area stimulated ended in the prepiriform cortex, anterior olfactory lobe, and olfactory tubercle. Only

after long latency periods did responses occur in the piriform lobe to such stimulation. There were no responses obtained in the septum, the diagonal band of Broca, or the hippocampus. MacLean, Horwitz, and Robinson ('52) obtained potentials in the piriform lobe after stimulating the olfactory bulb, but only after long latency periods. Berry et al. ('52) confirmed this and also obtained, after even longer latency times, potentials in the hippocampal formation. Thus the physiologic data support the anatomical data.

The studies of Ramón y Cajal ('01, '11), Lorente de Nó ('33, '34), M. Rose ('27), and S. Rose ('27) clearly demonstrated a prominent and relatively large fiber connection from the entorhinal area to the cornu Ammonis and dentate gyrus by way of the alveus and the perforating paths. These same authors also described afferent paths to the cornu Ammonis and the dentate gyrus from the presubiculum and the subiculum. Allen ('48) demonstrated perforating and alveus pathways by the Marchi technique in dogs. Pribram, Lennox, and Dunsmore ('50), using strychnine physiologic neuronography, stimulated the entorhinal area and obtained potentials in Ammon's horn. Since the cornu Ammonis receives a large number of afferents from the entorhinal area, subiculum, and presubiculum, it would be of interest to know the regions from which these latter three areas receive their afferent fibers. We have already noted that olfactory impulses play only a small part in the afferent supply of the entorhinal area.

Ramón y Cajal reported that fibers reach the entorhinal area from the cingulum, the adjoining temporal lobe area, and, in small number, from the prepiriform area. Additional anatomical studies of the afferent fibers to the entorhinal area are few. After experimental lesions had been placed in the monkey, Adey and Meyer ('52a), using Glees' silver technique, found degenerated fibers arising on the medial aspect of the frontal lobes and reaching the presubiculum by way of the cingulum. Adey ('51) placed lesions in the retrosplenial and posterior cingulate regions of the rabbit. He then used the

Glee's silver technique and found degenerated fibers arising in these areas, traversing the cingulum, and ending in the subiculum and presubiculum. Adey and Meyer ('52b), using the same technique, also found afferent fascicles entering the entorhinal area from the superior temporal gyrus. In a study of the commissural connections of the regions concerned, Cragg and Hamlyn ('57), in the rabbit, and Blackstad ('56), in the rat, reported that the entorhinal area is connected with the same area of the other side of the brain by the hippocampal and the anterior commissures, and that some fibers arising in the hippocampus of one side end in the entorhinal area of the other side.

Several investigators, using the evoked potential technique, have followed afferent impulses into the entorhinal area. Thus Patton ('50) and Patton and Amassian ('52) on stimulating fibers (presumably gustatory) of the chorda tympani nerve, and Dell and Olson ('51) on stimulating the visceral afferent fibers of the vagus nerve, recorded impulses in the entorhinal area of the cat. MacLean, Horwitz, and Robinson ('52) and Clark ('52) reported such potentials to auditory, visual, and somesthetic stimulation in rabbits, cats, and monkeys. Other investigators, using the same technique, have followed afferent impulses into the hippocampus itself. Robinson and Lennox ('51) obtained responses in the hippocampal formation to optic, auditory, and somesthetic stimuli in the cat, as did Green and Arduini ('53) in the rat, the cat, and the monkey. These last authors ('54) believed that stimulation of certain areas of the brain stem gives an arousal response in the hippocampus. On somesthetic stimulation Green and Machne ('55) found diffuse, but well defined, electrical activity of pyramidal cells in an area of the hippocampus.

Though the cornu Ammonis does not receive olfactory impulses directly from the olfactory bulb, it does receive such impulses by indirect pathways involving several synapses. Since this olfactory connection is far less prominent in man than in the lower mammals, probably reflecting the decrease

in olfactory function in primates, the hippocampus evidently takes on new functions. This does not remove the possibility that olfactory impulses still play a part in the working of the normal hippocampus. In addition to olfactory impulses, Ammon's horn, at least in the higher mammals, receives afferent impulses arising from a considerable variety of stimuli. It may then be concluded that the hippocampal formation, particularly cornu Ammonis, receives fibers mediating impulses from association centers in which various types of impulses are interrelated and that, in man, with the reduction in the olfactory system, olfactory connections play a much less important part — but still a part — in the functioning of this part of the hippocampal formation. The hippocampal formation then represents a somato-visceral association or correlation area. Such an area might well be related to the building up of emotion or at least of emotional expression.

Some neuroanatomists have emphasized the efferent functions of the hippocampus (Brodal, '47) and the fornix is often assumed to be its major efferent path. It would, then, not be surprising if stimulation of this area resulted in muscular movements which could be associated with emotional expression.

Since Papez ('37) developed his theory of emotion, which had its basis in reverberating and balanced circuits involving the hippocampal formation, the septal area, the mammillary body, and the cingulate gyrus, attention has been centered on the rhinencephalon as a whole and the hippocampal formation as a part of this system. Many of the reports concerning the hippocampus are portions of much wider studies of the limbic lobe in general. Reference will be made only to data of direct concern for an understanding of hippocampal function.

In our material, partial removal of the hippocampus on either or both sides appears to have had no effect on the behavior of the animals. Their behavior in the monkey colony appears to have been normal. Complete bilateral removal of

the hippocampus did not result in a sleepy animal but did produce a lethargic or apathetic monkey. Except for the lethargy, the animals appeared normal and fed themselves. They carried out basic functional needs. These animals were slow to anger and had only periodic episodes of increased activity.

After his ablations of portions of the hippocampus in the monkey, Simpson ('52) noted no effects in the postoperative period up to the time of sacrifice of the animals. His lesions were small, as were those in some of the monkeys used for our experiments. Evidently, lesions of the hippocampus must be large and bilateral before definite symptoms appear.

In a series of reports, Klüver and Bucy (Klüver, '52; Klüver and Bucy, '38, '39; Bucy and Klüver, '40, '55) described the results, in the monkey, of bilateral temporal lobectomy, including removal of the greater part of the hippocampal formation. These animals demonstrated "psychic blindness," "oral tendencies," hypermetamorphosis (reacting to every visual stimulus), absence of emotional reactions and increased sexual activity. Our monkey that had a portion of the temporal lobe removed on each side for the purpose of providing a control animal for the bilateral hippocampal section, showed the same symptoms except for the absence of emotional reactions, even though the hippocampal formation was still intact. This control animal was not observed for increased sexual activity. However, when bilateral hippocampal ablations were added to the lesion, the absence of spontaneous activity was evident, although there was never a complete loss of emotional reactions. Following the hippocampal lesions the animal had periods of great excitability and made angry-appearing motions although the direction of the attack was not well oriented. Our results suggest that the symptomatology seen in the Klüver and Bucy animals was largely due to the loss of areas in the temporal region other than the hippocampal formation.

Bard and Mountcastle ('48) removed all of the neocortex in the cat so that only the rhinencephalon was left. The ani-

mals developed a very placid disposition. If, then, parts of the rhinencephalon, including cornu Ammonis, were added to the lesions, the animals began to show rage reactions. Earlier, Bard and Rioch ('37) had noted that lesions of the rhinencephalon (with part of the neocortex still present) produced rage reactions. Bard and Mountcastle postulated that the neocortex regulates a rage center, which is probably located in the hypothalamus, and that the rhinencephalon inhibits this center. With the neocortex removed, the inhibition is still present. If the rhinencephalon is destroyed, then the inhibition is released, and there is a lower threshold for stimuli setting up rage responses and a resulting lack of emotional control. Rothfield and Harman ('54) confirmed these findings and, in addition, noted that complete removal of the neocortex, together with bilateral section of the bodies of both fornices, resulted in a lowering of the rage threshold. Spiegel, Miller, and Oppenheimer ('40) found that bilateral lesions of the hippocampal formation and the fornix produced rage reactions in cats. It appears then that the hippocampus, as a part of this complex may regulate, to some extent, the emotional expression of the animal.

Cairns and Mosberg ('51) and Dott ('38) found no obvious defects in a man with bilateral fornicotomy (as is necessary in the removal of a colloid cyst of the third ventricle). Milner and Penfield ('55) and Scoville and Milner ('57) reported a series of patients who had a loss of memory after bilateral lesions of the hippocampal formation. The latter authors noted that, following such lesions, there is not only a loss of recent memory but also of retrograde and antegrade memory. The amount of memory loss is proportional to the amount of destruction of the hippocampal formation, but the lesion must be bilateral. In a brain from the autopsy of a man who had died of a chondrosarcoma, Nathan and Smith ('50) found a very degenerated hippocampus, although the case history revealed no loss of the sense of smell. The record showed that this patient was slow to anger, quiet, and had never, to the knowledge of the clinicians lost his temper.

That a lesion in the hippocampus may give an animal which, under certain conditions, shows rage reactions and, under other conditions, is unusually quiet is not so surprising as might appear at first. Our animal with bilateral hippocampal ablation was quiet, lethargic, and apathetic. However, on stimulation, she gave a rage reaction, often disoriented, but persisting for a short time. It is suggested that the hippocampus exerts a control over emotional expression, the discharge mediating the control at any one moment being the resultant of proper balance of various impulses reaching the hippocampus and the hypothalamus. In the lesions described, this balance is upset, and the behavior of the experimental animal reflects not only the effects of injury to the hippocampus but the results of imbalance of function in other regions of the brain as well. Hippocampal lesions alone do not eliminate all cortical influences on the hypothalamus. Animals may well be lethargic, but upon stimulation have an unusual emotional behavior due to lack of proper control over hypothalamic responses by the hippocampus. However, with the absence of both rhinencephalon and neocortex, there may be a complete release of the lower centers, the discharge of which results in the outward signs of emotion. Whether the hippocampus has any effect on intellectual functions can not be determined by these experiments.

Ferrier (1886) reported that stimulation of the hippocampus resulted in a lip-smacking response and certain other facial movements in the monkey. More recently MacLean ('55) has noted a turning of the head of a cat away from the stimulus and a sneering expression of the face when he stimulated the hippocampus. Penfield and Erickson ('41), Kaada ('51), and Penfield ('55) have denied any such movements. In numerous other studies on the effects of stimulation of the hippocampus no mention is made of actual somatic motor responses according to a pattern. It is possible that the parameters of stimulation were such that movements were not obtained in the experiments. Previous experiments

done by us (Votaw, '57) have shown that stimulation of the hippocampus will produce movements.

The present experiments have shown that stimulation of the hippocampus results in a definite pattern of somatic motor movements. Since these movements are eliminated when the hippocampus is separated from the subiculum, and since the pattern changes in accordance with a definite plan after only slight shifting of the electrode, the resulting movements are not due to current spread from the unipolar electrode, but the results of stimulation of the area directly below the electrode.

There is, then, a definite pattern of somatic motor movements found along Ammon's horn and this area appears to act as an independent supplementary motor area. In this pattern, the area for the face is very large, and for the upper extremity small; no area existing for the lower extremity. This is in accordance with the belief that this area is related to emotional expression, since the face and the upper extremity are the areas of the body most used in such expression. On increasing the strength of stimulus, a convulsive clonic type of movement is seen. This suggests a coordinated mechanism for the running of the animal as in fear or flight.

Electroencephalographic studies of the hippocampus by Akert and Andy ('53), Green and Shimamoto ('53), Passouant, Gross, Cadilhac, and Vlahovitch ('54), and Andy and Akert ('55) show that the hippocampus has a very low threshold for seizure activity and a characteristically long afterdischarge. They noted that these seizures spread readily to the rest of the limbic lobe and then, with a greater latency, to the cortex as a whole. Green and Arduini ('53) found evidence of an electrical "arousal" response in the hippocampus as a result of visual, auditory, olfactory, and somesthetic stimulation. This "arousal" response is reflected over the entire cerebral cortex. It can also be elicited by stimulation of the ascending reticular activating system.

MacLean and associates have published a series of papers (MacLean, 49, '54, '55, '57a, '57b; MacLean, Flanigan,

Flynn, Chul, and Stevens, '55) in which they have stimulated the hippocampus in conscious animals (predominantly cats). They have confirmed the findings reported above. They noted that during stimulation, and during the rather long latent period of building up of the convulsive response which immediately follows stimulation, no movement occurs other than a limited contralateral turning away of the head. However, during the long afterdischarge of impulses, the animals ceased any spontaneous movement and appeared to fix their attention on some object in the environment. Testing showed that the animal was actually in a state of subconsciousness. On stimulation he appeared ready to fight, but the motions were purposeless and disoriented. Gastaut ('53) had also obtained similar findings and had correlated his results with very low seizure thresholds and with the possibility that the hippocampus is concerned with temporal lobe epilepsy. This seizure activity takes place in the limbic system without appreciable alteration of neocortical activity. Akert and Andy ('53) and Andy and Akert ('55) have obtained similar results. These investigators report that, during the hippocampal discharge, a cat is indifferent to a mouse, but will attack as soon as the seizure is completed. Liberson and Akert ('55) also confirmed these results and suggested that this area may be greatly concerned in epileptic disturbances of awareness and mental confusion.

There is an increasing number of reports on human autopsy material from patients with temporal lobe epilepsy. In a significant number of these cases, as reported by Sano and Malamud ('53), Meyer and Beck ('55), Falconer, Denis, Meyer, Mitchell and Pond ('55), and Corsellis ('57), there is a sclerotic condition of both hippocampi. When present, it is of a characteristic nature, and seems to be associated with the severity of the epilepsy. However, it is not present in all cases. Green, Clemente, and DeGroot ('57) have succeeded in producing an epilepsy in the cat by placing lesions in Ammon's horn.

The present study has indicated that surgical section of the fornix did not eliminate or even affect the motor pattern obtained from the hippocampus. However, separating the hippocampus from the subiculum eliminated the movements obtained from stimulation of Ammon's horn. It is evident that the discharge of the somatic motor responses is by way of the temporal lobe. There are several extrapyramidal motor pathways from the temporal lobe as reported by Youmans ('56), Schneider and Crosby ('54), Crosby ('55), Mettler ('35), Whitlock and Nauta ('56) and DeJonge ('58). The movements obtained from stimulation of the hippocampus are, perhaps, a part of the normal functioning of the hippocampus, mediated by way of the temporal lobe and not by way of the fornix. Thus the fornix is not the only efferent pathway of the hippocampus.

It will also be remembered that stimulation of the fornix in our monkeys gave responses of the face and upper extremity musculature. After cutting the fornix, stimulation on the hippocampal side of the cut gave the same results as did the stimulation in the same area before the section was made. However, stimulation of the fornix on the side toward the septal area from the cut no longer gave the movements that were obtained from the same area before the section. It seems probable that when movements occur secondary to stimulation of the fornix, the impulses pass to the hippocampus and thence through the temporal lobe. It is not possible to agree with Allen ('44) that all of the fibers of the fornix are hippocampal in origin or with Sprague and Meyer ('50) that, "the fornix represents the only known efferent pathway of the hippocampus."

Slight variation in stimulus causes a change in the response obtained with respect to laterality, but does not disturb the basic pattern. If the cellular units for bilateral and unilateral movements are diffusely arranged within the above pattern, then bringing in more cellular units by increasing the strength of the stimulus accounts for the differences. Therefore, the response to stimulation of the posterior two thirds

of the hippocampus depends on the number of units functioning at a given time.

The function of the fornix is made somewhat obscure, since cutting it has no effect on the movements obtained from stimulation of the hippocampus. From studies quoted above we see that there are probably fibers within the fornix which are afferent with respect to the hippocampus, carrying some of the sensory information to this area. However, no evidence has been presented as to the exact function of the fibers in the fornix which are efferent with respect to the hippocampus.

It appears that the cornu Ammonis receives fibers mediating impulses from association centers where both somatic and visceral functions are represented. This allows for the correlation of impulses arising from two types of stimuli; those that relate the individual to his external environment (somatic) and those that relate the individual to his internal environment (visceral). Ammon's horn itself may serve such a correlative function. This system may represent the mechanism used in orienting the individual to both his external and internal environment, thus regulating the individual's emotional orientation. The efferent discharge of the hippocampus results after such somatic and visceral factors have been properly balanced. The movements obtained from this discharge, then, may represent an emotional response. When this entire system functions properly, the animal will make the appropriate response to either external or internal stimuli. Thus the hippocampus becomes a part of one of the arcs necessary for the emotional orientation of the individual.

SUMMARY

1. An investigation of the function of cornu Ammonis in monkeys has been carried out by stimulation and ablation experiments.

2. The cornu Ammonis has been shown to represent a supplemental motor area.

3. The cornu Ammonis exhibits a pattern of somatic motor movement when stimulation is carried out. This pattern is not affected by fornix section but is completely eliminated by separating the hippocampus from the subiculum.

4. The pattern as reflected from anterior to posterior on cornu Ammonis relates to movements from face to neck to upper extremity.

5. Stimulation of the middle third of cornu Ammonis can cause a generalized "arousal" response.

6. Bilateral ablation of small parts of the cornu Ammonis in an animal has no visible behavioral effect on the animal.

7. Complete ablation of the cornu Ammonis of both sides in the same animal produces an apathetic, lethargic, and quiet monkey. There is a loss of spontaneous movement with intermittent short periods of increased activity, characterized by an attack reaction which is poorly oriented.

8. It is suggested that the cornu Ammonis is concerned in the overall balance of discharges associated with somato-visceral associations and in the emotional orientation of the animal.

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