THE HIPPOCAMPUS AND ITS ELECTROGRAPHIC ACTIVITY

Thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy in Psychology.

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ABSTRACT

The thesis is divided into two parts. The first part presents a theoretical investigation of the functions of the hippocampus. Three theories are critically examined : (i) the Douglas (1967, 1972) and Kimble (1968) proposal that the hippocampus forms the neural substrate of Pavlovian internal inhibition (hereafter referred to as the inhibitory theory); (ii) the Olton, Becker & Handelmann (1979) suggestion that the hippocampus serves as a "working memory" register; and (iii) the O'Keefe & Nadel (1978) hypothesis that the hippocampus functions as a cognitive map.

The adequacy of the three theories is tested against anatomical, physiological and behavioural evidence, and it is concluded that only the inhibitory theory is both internally consistent and able to accomodate the data. Furthermore, a detailed evaluation of criticisms of the theory (as presented primarily by Nadel, O'Keefe and Black 1975) reveals that many of the apparent anomalies in the literature are, in fact, consistent with the theory, while others are based on unsound data.

Further consideration of the anatomical and behavioural evidence suggests that the hippocampus gives rise to two seperate circuits: a dorsal circuit, subserving the functions of internal inhibition, and a ventral circuit, mediating external inhibition. It is posited that the latter circuit produces its disinhibitory effect via the mammillothalamic tract.

An additional consequence of the hippocampus being concerned with

internal inhibition is that it should, according to Pavlov (1927), also be involved with sleep. With a view to reconciling Pavlov's observations with those of more recent researchers, the sleep literature is briefly reviewed, and the common-sense notion that sleep is a time of rest for the brain is mooted. However, it is proposed that different neural circuits recuperate during different stages of sleep; specifically, it is suggested that the excitatory systems are inhibited (i.e. rest) during slow wave sleep, and that the inhibitory systems rest during paradoxical sleep. Physiological and behavioural evidence (with particular emphasis on the role of the hippocampus) consistent with this formulation is presented.

Part two of the thesis is an empirical study concerned with the electroencephalographic (EEG) activity of the hippocampus. It is argued, on the basis of hippocampal unit activity and its relationship to the hippocampal EEG and behaviour, that a desynchronised hippocampal EEG indicates an active hippocampus and is associated with behavioural suppression, and that hippocampal theta reflects a relatively inactive hippocampus and is associated with behaviours during which the hippocampus would be expected to be disengaged.

It follows directly from the above that theta, since it is present when the hippocampal pyramidal cells are quiescent, is unlikely to be a product of neural activity. The possibility that theta may be an artifact is therefore explored. It is proposed that brain movement is the artifact-generator, and evidence, drawn primarily from a qualitative comparison of the directly measured brain movement and concomitant EEG of rats, is presented to support this

contention. The hypothesis is further supported by a reinterpretation of several "paradoxical" findings in the EEG literature.

PART ONE :

THE HIPPOCAMPUS

1 ANATOMY OF THE HIPPOCAMPAL REGION

1.1. NOMENCLATURE

As defined in this review the hippocampal region consists of the allocortical hippocampal formation and the periallocortical retrohippocampal (parahippocampal) area. The hippocampal formation consists of the dentate gyrus and Ammon's horn (which together form the hippocampus) and the subiculum. The retrohippocampal area includes the presubiculum, postsubiculum, parasubiculum and entorhinal cortex.

In horizontal section the hippocampal region forms an S-shaped structure with the trailing end of the "S" capped by the dentate gyrus. The top of the S forms the entorhinal cortex, which leads into the subicular cortex. The reverse "C" formed by the base of the S represents Ammon's horn (see Fig. 1). Starting from the hippocampus proper, each of these areas will be considered in turn, with a final section on the septum.

1.1.1. The Hippocampus

1.1.1.1. Gross structure

Since the hippocampus is gradually displaced caudad as one ascends the phylogenetic scale, the following description refers mainly to the rodent hippocampus.

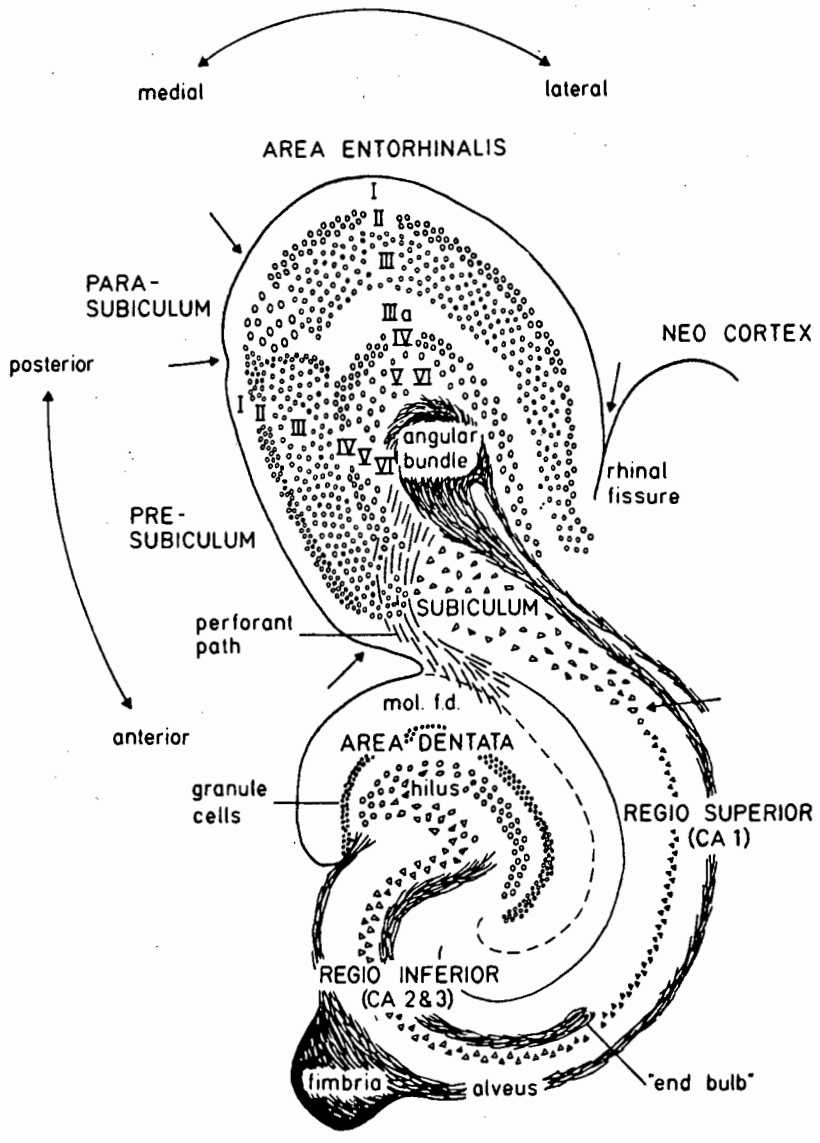

FIG.1. Horizontal section through the hippocampal region. (From Shipley 1975, Plate 1.)

The hippocampus is roughly in the shape of a ram's horn, which curls around the thalamus at an oblique angle such that its ventral pole lies in the temporal lobe, and its dorsal extension, a large fibre tract known as the fornix, meets the septum close to the midline. On its leading edge lies another fibre tract, the fimbria, which is continuous with the fornix rostrally, and also with a layer of fibres over the hippocampus known as the alveus. Medially the alveus crosses over to opposite hippocampus as the dorsal hippocampal commissure (psalterium). Another commissure,

the ventral hippocampal commissure, is found rostrally amongst the fibres of the fornix.

Since the hippocampus is a curved structure, its longitudinal axis is often referred relative to its septal and temporal poles : thus the anterior dorsal part is the septal pole, while the anterior ventral part is the temporal pole. The subiculo-dentate dimension refers to the transverse axis (Swanson and Cowan 1977). Proximal and distal are with reference to the dentate gyrus.

1.1.1.2. The dentate gyrus

The dentate gyrus forms a sheet of cells surrounding the free edge of Ammon's horn. In cross-section it therefore has two blades seperated by a crest. The blade lying alongside the hippocampal fissure is called the inner blade, while that next to the thalamus is referred to as the outer blade. The central area enclosed by the blades is known as the hilus of the dentate gyrus, or the fascia dentata.

The principle cell type found in the dentate gyrus is the dentate granule cell. These cells form a single layer and thus divide the dentate gyrus into three layers:

(i) Stratum moleculare formed by the dendrites of the granule cells and afferent fibres.

(ii) Stratum granulosum consists mainly of the soma of the granule cells and some basket cells (less than 1% - Seress 1978). The basket cell axons ramify within the granule cell layer and contact

many granule cells. There are few glial cells.

(iii) Stratum polymorphe, contained within the hilus. This is an exceedingly complex area. Besides the proximal parts of the axons of the granule cells (known as the mossy fibres) many other cell types are found here (see Amaral 1978).

1.1.1.3. Ammon's horn

The principal cell type of Ammon's horn are the pyramidal cells which, like the dentate granules, are packed together in a dense layer. On the basis of differences in pyramidal cells and their connections, Ammon's horn has been divided into a regio superior and regio inferior (see Blackstad 1956). For most purposes this is sufficient, but Lorente de No (1934) has distinguished no less than eight subfields with Ammon's horn. He described four major fields - CA1 (adjacent to the subiculum) to CA4 (within the hilus of the dentate gyrus) - with each of CA1 and CA3 further subdivided into three parts (CA1 a, b and c and CA3 a, b and c). Field CA1 is roughly equivalent to regio superior, while CA2, 3 and 4 approximately equal regio inferior. Since the CA2 and CA4 fields are small (in the rat at least - see Swanson and Cowan 1977), CA3 is often used synonymously with regio inferior.

In addition to divisions along the subiculo-dentate axis, there are clear indications that Ammon's horn can be divided, on connectional grounds, along the septo-temporal axis into at least two distinct fields (Swanson and Cowan 1977; Meibach and Siegel 1977a). Wimer et al (1980) go even further. On genetic grounds

they suggest that CA1 can be divided into a minimum of four fields.

Like the dentate gyrus and subiculum, Ammon's horn in cross-section appears as basically a simple three-layered cortex (allocortex) in contrast to the six-layered (periallocortical) regions of the presubiculum, parasubiculum and entorhinal cortex. Chronister and White (1975) make the rather interesting observation that it appears as though this simplicity is produced by the seperation of the primary cortical granule cells (in the form of the dentate granule cells) from the primary cortical pyramidal cells (in the form of the hippocampal pyramidal cells). In any event, on the basis of the type of pyramidal cells present, and the stratification of afferent and efferent fibres, the basic three layers of Ammon's horn can be further subdivided so that at least five strata can be recognised. Starting from the inner layer (i.e. from the ventricular surface) these are:

(i) Alveus - a fibre tract covering the surface of Ammon's horn carrying both efferent (mainly pyramidal cell axons) and afferent fibres and continuous with the fimbria laterally and fornix rostrally.

(ii) Stratum oriens - containing the basal dendrites of the pyramidal cells and the proximal parts of their axons. On the basis of various cell types found here, this stratum can be further subdivided into an alvear and superficial portion (Chronister and De France 1979). The alvear portion contains fusiform-spindle type neurons oriented parallel to the fibres in the alveus. The superficial portion contains displaced pyramidal

cells and polymorphic neurons oriented mainly parallel to the pyramidal cells.

(iii) Stratum pyramidale. This consists mainly of the pyramidal cell somas, with basket cells scattered amongst them. Two layers of this stratum can be differentiated - pars superficiale and pars profundum. Pars profundum is more loosely organised than pars superficiale, and becomes more pronounced towards the subiculum. This organisation appears to be reflected in differential connectional arrangements (Chronister and De France 1979). The CA4 pyramidal layer lacks the organisation apparent in the other fields. They lie scattered in the hilus of the dentate gyrus, intermingled with the mossy fibres.

As indicated above, pyramidal cell morphology varies from field to field within Ammon's horn. CA1 has the smallest pyramidal cells, and these become larger and larger as one approaches CA4. The apical dendrites of the pyramidal cells of CA1 are not as branched as those of the other fields and, in addition, they lack the large thorny processes found on the proximal parts of the dendrites of the cells of CA3 and CA4.

(iv) Stratum radiatum - contains the apical dendrites of the pyramidal cells and a large number of axons. Scattered amongst these are found several cell types. Some of the axons are Schaffer collaterals which arise from the pyramidal axons in stratum oriens of CA3 and CA4 and course up through stratum pyramidale. Also found in stratum radiatum of CA3 is an additional layer known as stratum lucidum, made up of mossy fibres from the dentate granule cells.

(v) Stratum lacunosum-moleculare - made up of the distal segments of the apical dendrites of the pyramidal cells, where numerous afferent axons terminate.

1.1.2. The Subiculum

The broadening of the CA1 stratum pyramidale seen near the subiculum becomes accelerated after the subicular border (this transition area has been named the prosubiculum by Lorente de No (1934)), so that the principal cell zone comes to occupy a large portion of the area between the alveus and the hippocampal fissure. Although the cellular area appears fairly homogeneous, it can be roughly divided into four zones (Lorente de No 1934; Sikes et al 1977). Except for that septal part of the hippocampus overlain by the corpus callosum, the subiculum runs the entire septo-temporal extent of Ammon's horn. At its most septal pole the subiculum abuts upon the retrosplenial cortex, and at its most temporal pole upon the entorhinal cortex.

1.1.3. The Pre- and Parasubiculum

The presubiculum forms the caudal border for most of the subiculum. Dorsally it is continuous with the postsubiculum, which is itself a ventral extension of the retrosplenial cortex. Like all periallocortex, it is a six-layered structure, the principal organisational feature being two cell layers, the laminae principalis externa and interna, seperated by a cell-poor layer, the lamina dissecans. From Golgi preparations (see Sikes et al 1977) it appears that communication between these laminae is primarily from lamina principalis externa to lamina principalis

interna.

The lamina principalis interna is continuous with the cellular area of the subiculum rostrally and with the same layer of the entorhinal cortex caudally, so that it appears almost as though an uninterrupted sheet of cells extends from the entorhinal cortex, round the angular bundle and along the alveus, to eventually narrow to form Ammon's horn (Edinger et al 1979; Sorensen & Shipley 1979). This organisation is particularly evident in the monkey. Here, the stratum pyramidale of CA1 is much wider (at the expense of stratum oriens) than that of the rat, and consequently the transition from subicular cortex less pronounced. It is only at the regio inferior border (where the CA3 stratum pyramidale becomes more dense) that a marked narrowing is apparent (see e.g. Van Hoesen & Pandya 1975b).

The lamina principalis externa of the presubiculum is not continuous with that of the entorhinal cortex, but is interrupted by the wedge-shaped parasubiculum, whose cells form a looser network than those seen in lamina principalis on either side of it.

1.1.4. The Entorhinal Cortex

The entorhinal cortex is usually divided into a pars medialis, a pars intermedialis and a pars lateralis. It is bounded laterally by the rhinal fissure, within which is found the prorhinal cortex (Steward 1976;Van Hoesen and Pandya 1975a), and beyond which lies the perirhinal cortex. Rostrally it is continuous with the periamygdaloid and prepiriform cortices and caudomedially with the

parasubiculum. Only pars medialis and pars intermedialis are found in the most dorsal extension of the entorhinal cortex and thus, at this level, the lateral part of the entorhinal area is actually pars intermedialis (Steward 1976).

The various areas of the entorhinal cortex, while having architectonic differences, share the same basic six-layered structure. According to Van Hoesen & Pandya (1975a) these are as follows:

Layer 1 - the molecular layer (outer plexiform zone) containing apical dendrites of cells in layers 2 and 3.

Layer 2 - primarily large stellate cells.

Layer 3 - medium-sized pyramidal cells.

Layer 4 - the cell-sparse lamina dissecans.

Layer 5 - smaller pyramidal and horizontal cells.

Layer 6 - a multilaminated layer composed of polymorph and spindle shaped cells.

1.1.5. The Septum

The septum is situated rostral to the hippocampus, and connected to it by the massive fibre bundle of the fornix. By virtue of these strong links alone, the septum deserves to be included in a discription of the hippocampal formation. However, even more compelling is the fact that in accallosal mammals (like the opossum) the septum and hippocampus are contiguous (Swanson 1978).

Swanson and Cowan (1979) distinguish four main areas in the rat septum - the lateral, medial, posterior and ventral divisions.

1.1.5.1. The Lateral Division

This is composed of the dorsal, intermediate and ventral parts of the lateral septal nucleus. It is the largest component of the septal region and is bounded dorsally by the corpus callosum and laterally by the lateral ventricle. Caudally it is continuous with the posterior nuclei of the septum, and rostrally reaches as far as the anterior hippocampal rudiment (taenia tecta) and the medial part of the prefrontal cortex. Some confusion has arisen in the literature because previous investigators (e.g. Andy and Stephan 1964) have called the intermediate part of the lateral septal nucleus the medial septal nucleus, and the ventral part, alone, the lateral septal nucleus.

1.1.5.2. The Medial Division

This consists of the medial septal nucleus and the nucleus of the diagonal band and contains the largest neurons of the septal region. The medial septal nucleus lies in the midline and is seperated from the lateral septal nucleus by the fibrès of Zukerkandl's bundle. At the level of the Island of Calleja, it expands ventrolaterally to continue as the nucleus of the diagonal band, which then runs caudally along the basal surface of the diencephalon to the hypothalamus.

1.1.5.3. The Posterior Division

The caudal extension of the lateral septal nucleus forms two cell groups - the septofimbrial and the triangular septal nuclei. The triangular septal nucleus lies medial to the septofimbrial nucleus, amongst the fibres of the ventral hippocampal commissure.

1.1.5.4. The Ventral Division

This is an heterogeneous structure with fibres of several major tracts - the fornix, the anterior commissure, the stria terminalis, the stria medullaris and the medial forebrain bundle - converging upon it. Swanson and Cowan (1979) suggest that the entire area (at least in the rat) be called the bed nucleus of the stria terminalis, with subdivisions of medial, lateral, posterior, sub-commissural and preoptic components. Rostrally this area is bounded by the nucleus accumbens, and caudally it lies dorsal to the lateral hypothalamic area.

1.2. CONNECTIONS OF THE HIPPOCAMPAL REGION

The connections of the hippocampal region will be considered in three parts : 1. intrinsic connections, 2. efferents, 3. afferents.

It should be borne in mind that the following account relies heavily on results obtained with the recently developed tracing techniques utilising retrograde and anterograde axonal transport of various markers. While there is no doubt that these techniques have revolutionised our understanding of neural connectivity, they

are by no means perfect. Besides the obvious problem of defining the effective limits of the injection site, there is still the "fibre-of-passage" problem. Although the autoradiographic method appears to be relatively immune from this (Swanson 1978), it is clear that horseradish peroxidase (HRP) can be taken up (at least) by fibres that are damaged along the injection track, or by use of too high a current during iontophoretic application. Although solutions have been proposed (e.g. Wakefield and Shonnard 1979), they carry restrictions that perhaps are unacceptable.

Furthermore, results obtained with the Graham and Karnovsky (1966) method for the visualisation of HRP reaction product (as opposed to more recent versions e.g. Mesulam 1976) should be treated with caution. Firstly, the reaction product is brown, and consequently easily confused with endogenous pigment (see De Vito 1980). Secondly, the method is relatively insensitive, which may be responsible for the fact that not all efferent neurons are necessarily labelled (see Nauta et al 1974). One possible reason for this could be that neurons with highly branched axons do not concentrate the enzyme to the same extent, and thus go undetected. For example, Siegel and colleagues (Edinger et al 1979; Meibach and Siegel 1977a,b), using the older HRP method, have consistently failed to demonstrate afferents to the septum from field CA3 - a region whose axons are known to branch repeatedly (Swanson et al 1980).

While the autoradiographic method offers a relatively "clean" analysis, it does suffer from the inability to unambiguously differentiate between labelled fibres and terminals. Thus label associated with fibres merely passing through an area may be

erroneously interpreted as indicating a synaptic connection with that area.

1.2.1. INTRINSIC CONNECTIONS

This section will deal with the commissural and longer associational efferents within the hippocampal region. This is due not to the unimportance of the short interneuronal connections, but simply because the available experimental anatomical methods are not adequate to the task. What is clear from an examination of Golgi material, however, is that these short interconnections are immensely complicated (e.g. see Amaral and Woodward 1977; Amaral 1978), and obviously play a crucial role in hippocampal functioning. Furthermore, it can no longer be assumed, merely because a cell is non-pyramidal in type and lies in stratum oriens or radiatum, that it is therefore necessarily an interneuron, since Chronister and De France (1979) have presented convincing evidence that some such cells are projection neurons. Similarly, Swanson et al (1978), using HRP injections into the contralateral hippocampus, have shown that non-pyramidal cells in the hilar region contribute to the commissural projections of that region.

Another complicating factor to be considered is that communication between hippocampal neurons may not take place exclusively via synapses. MacVicar and Dudek (1980), using intracellularly injected Lucifer yellow, have recently observed what appear to be soma-somatic and dendro-somatic gap junctions between pyramidal cells.

Finally, the problem of species differences must be taken into

account. Although it has been known for some time that projections vary across species (Valenstein & Nauta 1959), recent evidence (to be discussed below) makes it clear that these differences are more marked than was previously suspected.

1.2.1.1. Dentate Gyrus

The dentate granule cells give rise to the so-called mossy fibres which stream out along the transverse axis of the hippocampus to form en passant giant synapses with the thorny spines on the CA3 and CA4 pyramidal cells. Their ordered projection and peculiar terminations (which have one of the highest concentrations of zinc in the body - see Dencker and Tjalve 1979, and which appear to be associated with opiate receptors - Stengaard-Pedersen, Fredens & Larsson 1981) have provoked a great deal of interest and have been studied with a variety of techniques (Blackstad et al 1970; Haug 1973; Laurberg and Zimmer 1980; Lynch et al 1973; Swanson et al 1978).

The mossy fibres take two routes - the suprapyramidal bundle, above the stratum pyramidale in the stratum lucidum, and the infrapyramidal bundle in the stratum oriens. The infrapyramidal bundle does not extend beyond the hilar region (except for an extrahilar patch caused by fibres crossing the stratum pyramidale in the septal part of CA3b (Swanson et al 1978)), and thus only the CA4 and CA3c (and some CA3b) pyramids are in receipt of mossy fibre input to both their apical and basal dendrites.

It was believed that the granule cells of the inner blade of the dentate gyrus gave rise to the suprapyramidal bundle, and those of

the outer blade to the infrapyramidal bundle (Blackstad et al 1970), but Swanson et al (1978) have been able to show that there is considerable overlap in the projection from the two blades, communication taking place via fibres that cross through the pyramidal layer.

Mossy fibre connections are not restricted to CA3 and CA4 pyramids, but make extensive synapses with other cells (at least) in the hilar region. Collaterals are given off just below the granule cell layer to produce a dense juxtagranular plexus. In addition, Amaral (1978) points out that contact is made with many cell types within the hilus (including basket cells) - not just those neurons with specialised spines.

The general pattern of mossy fibre projections along the septo-temporal extent of CA3, as revealed by the primarily autoradiographic study of Swanson et al (1978), is far more complex than was originally thought.

In the septal third of CA3 the mossy fibres travel more or less transversely across the proximal two thirds of CA3, and then turn sharply through 90 degrees in the CA3a region to travel in a temporal direction parallel to the CA3/CA1 border, and thus form a dense plexus in this area.

Towards the middle third of CA3 the fibres gradually lose their distal longitudinal inclination, and thus travel essentially transversely across the breadth of CA3.

In the temporal third of CA3 the mossy fibres once again take an

increasingly steep temporal direction and attain the temporal pole of CA3. The fibres arising in the extreme temporal tip of the dentate once again travel transverse to the CA3 longitudinal axis, but are very short (0.5mm in length) and do not cross the full length of CA3.

1.2.1.2. Field CA4 and The Hilar Region

There is still considerable disagreement as to the connections of this area, or even whether it forms a part of Ammon's horn or the dentate area (Amaral 1978). Hjorth-Simonsen and Laurberg (1977) and Laurberg (1979) are of the opinion that it only projects to the dentate area and not Ammon's horn. However, Swanson et al (1978), on the basis of a large amount of material and using both retrograde and anterograde methods, conclude that it in fact has widespread connections with the hippocampal formation. They are supported in this contention by an HRP study of Sikes et al (1977), and by the Golgi studies of Lorente de No (1934) and Amaral (1978), who describe axons from CA4 pyramids joining the Schaffer collateral system. Even Laurberg (1979) noticed a few labelled cells in the hilus after HRP injections into Ammon's horn.

The projections of this area can therefore be summarised as follows:

(i) Projection to the dentate gyrus.

The CA4 area gives rise to an extensive ipsilateral and contralateral pathway to the dentate gyrus which appears to arise

from cells in the polymorph layer (Berger, Semple-Rowland & Basset 1980). The fibres course around the distal tips of the dentate blades (and sometimes through the granule cell layer) to attain the associational/commissural zone of the molecular layer (the inner one third of the molecular layer), and then travel rostrally and caudally to cover most of its septo-temporal extent. At septal levels the entire inner one third of the molecular layer is filled but this area of termination thins out and moves slightly away from the granule cell layer towards the temporal pole.

(ii) Projections to the hippocampal formation.

Swanson et al's (1978) results show a surprisingly wide projection of the CA4 area, both in septo-temporal extent and in the number of fields involved. Label was found over both strata oriens and radiatum in CA3 and CA1, as well as the pyramidal layer of the subiculum and layers 1 and 3 of the presubiculum (although it must be noted that the projection only involved the most proximal part of the presubiculum). Furthermore, the projections from any one area involved large parts of the septo-temporal axis of most fields, thus indicating a large degree of overlap. Only in the temporal pole is anything like a lamellar arrangement seen.

Swanson et al (1978) argue that their results support the observations of Lorente de No (1934) in that the distribution of part of the projection of the CA4 area is similar to the Schaffer collateral system of CA3, and should be considered a subcomponent of that system.

1.2.1.3. Field CA3

From Golgi preparations it is known that the axons of CA3 pyramidal cells give off a number of collaterals. The best known of these are the large, myelinated Schaffer collaterals which project to CA1 and make en passage contact with many pyramidal cells. The Schaffer collateral system arises primarily from subfield CA3c and, to a lesser extent, CA3b. According to Lorente de No (1934) CA3a does not contribute to this projection, but instead forms his so-called longitudinal association pathway, which extends septally and temporally in CA3a as a thin band parallel to the CA3/CA1 border. Recalling the peculiar distribution of the infrapyramidal mossy fibre bundle, there seems to be some parallel between those areas that receive mossy fibre input to both their apical and basal dendrites, and those areas that give rise to the Schaffer collaterals. It is interesting to speculate that perhaps the Schaffer collaterals arise exclusively from this population of neurons.

In addition to the above projections, Swanson et al (1978) report that, like CA4, CA3 has projections to the subiculum (mainly the deep half of stratum moleculare) and presubiculum (layers I and II). Unlike CA4, however, CA3 does not project to the dentate gyrus, although it does project to the CA4 area. While there is a general septo-temporal organisation in the projections (in that the septal part of CA3 projects to the dorsal subiculum, presubiculum and postsubiculum, and the temporal part of CA3 projects to the ventral subiculum and presubiculum), once again there is a large spread (and overlap). In a similar manner to that noted for CA4 projections, injections placed in the temporal

pole of CA3 tend to label only a restricted portion of the temporal or ventral projection fields. One striking exception to this, as noted above, are injections located in the CA3a subfield. Here even a temporal injection will produce a long tongue of label extending septally up the CA3/CA1 border in both stratum oriens and stratum radiatum. CA3a differs from the rest of the CA3 field in another respect also: it behaves more like CA1 in that it projects further caudally: to layers I and II of the parasubiculum, and layer IV of the entorhinal cortex. It should be noted that Berger, Swanson, Milner, Lynch & Thompson (1980) point out that they did not find a parasubicular projection from Ammon's horn in the rabbit. This does not necessarily indicate a species difference, however, since their injections involved the dorsal hippocampus. Available evidence (Hjorth-Simonsen 1971; Swanson and Cowan 1977) suggests that it is only the more temporal aspects of CA3a that project to this area.

Since, in addition to the areas already mentioned, CA3 projects to the contralateral hippocampal formation and (as will be seen later) bilaterally upon the septum, it is clear that if this area consists of a relatively homogeneous neural population, then each neuron must give rise to an extraordinary number of collaterals. That this may indeed be the case is suggested by the work of Swanson et al (1980). By the use of retrogradely transported markers of various colours, they were able to show that the commissural, ipsilateral associational, and septal projections, at least, all arise from the same neurons.

1.2.1.4. Field CA2

Lorente de No (1934) defined CA2 as an area containing large pyramidal cells similar to those found in CA3, but not in receipt of the mossy fibres. Although the existence of such an area has been challenged (see e.g. Blackstad 1963), Swanson and Cowan (1977) and Swanson et al (1978) do report a region on the distal edge of CA3a which does not have a mossy fibre input. That CA2 is likely to be functionally distinct is shown by the fact that certain types of opiate receptors are specific to this area (Duka et al 1981). Furthermore, Segal (1979) has found that CA2 is the only region in Ammon's horn in receipt of supramammillary fibres. Unfortunately, the area is so narrow that it is difficult to experimentally determine its projections. From the available material it appears as though its efferents are similar to those of CA3a.

1.2.1.5. Field CA1

CA1 does not appear to project to any part of the hippocampus : according to Swanson and Cowan (1977) and Swanson et al (1978) its projections within the hippocampal region are limited to the subiculum and entorhinal and perirhinal cortices.

The projection to the subiculum presents a curious echo of the mossy fibre projection to CA3. A similar lamellar type organisation is present, with septal parts of CA1 projecting in a narrow beam to the subiculum, and then turning sharply in a temporal direction, to travel a considerable distance. More temporal projections, on the other hand, adopt a straighter course

across the subiculum. Labelling is seen over most of the subiculum except the superficial part of the molecular layer.

A broader topographic organisation is evident in the projection to the entorhinal cortex. Injections in the septal pole label the perirhinal cortex (layer I and the deeper layers), while more temporal projections of CA1 reach progressively more ventral areas of both lateral and medial entorhinal cortices (principally to layer IV). However, these projection areas are large and there is a great deal of overlap in the distribution of fibres from various levels.

A possible species difference in these projections in rabbits is reported by Berger, Swanson, Milner, Lynch & Thompson (1980), based on anterograde transport of HRP. They saw no labelling in the perirhinal area, but did see label in the pre- and post-subiculum (layers III - IV), although they, too, found that CA3 projected further in the posterior and temporal directions than CA1.

1.2.1.6. Commissural connections of the hippocampus

Most of the projections discussed above are bilateral. In fact, the distribution of commissural terminals is very similar to the ipsilateral pattern. Not only is the regional distribution similar, but so is their laminar termination and the course which the fibres follow. Gottlieb and Cowan (1973) have therefore proposed the general principle that all commissural projections are mirrorred by an associational projection. The converse does not always hold, however. There are a few ipsilateral projections

which do not have an associated contralateral projection (e.g. from CA3 to the hilus). The commissural projections are homotopic, in that the densest termination is found in the area opposite that which has been injected, but the ipsilateral projections are usually stronger and more widespread.

1.2.1.7. The subiculum

The subiculum has been shown to project ipsilaterally to the presubiculum and entorhinal and perirhinal cortices in the rat (Kohler, Shipley, Srebro & Harkmark 1978; Swanson & Cowan 1977) and monkey (Rosene & Van Hoesen 1977). A combined autoradiographic and degeneration study in the guinea pig by Sorensen & Shipley (1979) revealed that the projections are to the deep layers of these structures (layers V and VI), and are topographically ordered along the dorso-ventral axis. Since the subiculum reaches further dorsally than the presubiculum, which in turn extends more dorsally than the entorhinal cortex, injections in the subiculum produce diagonal bands of label across these areas.

In addition to this caudal projection, Berger et al. (1980) have demonstrated a small rostral projection to CA1 in the rabbit. Arising from neurons located in a crescent-shaped area in the deeper layers of the prosubiculum and subiculum, the projection courses rostrally to attain the stratum lacunosum, and the deep portion of stratum oriens via the alveus. The cells of origin appear to be from a different population to those that receive CA1 afferents.

1.2.1.8. The presubiculum

A strong bilateral projection mainly to layers I and III of the medial entorhinal cortex only, has been described (Rosene & Van Hoesen 1977; Shipley 1975; Sorensen & Shipley 1979; Swanson & Cowan 1977). The organisation of the projection is unusual in that it forms a mirror-image of the presubiculum, that is, the proximal and distal parts of the presubiculum project to the distal and proximal parts of the entorhinal cortex respectively.

1.2.1.9. The postsubiculum

Swanson & Cowan (1977) report a bilateral projection to layer I of the parasubiculum and the entorhinal cortex.

1.2.1.10. The parasubiculum

There has been no systematic examination of this area but it appears that it projects to the contralateral parasubiculum (Swanson et al. 1978), and bilaterally to layer II of the medial entorhinal cortex (Blackstad 1956). The cells of origin of this latter projection appear to be mainly those in layer II (see Steward & Scoville 1976, Fig. 12).

1.2.1.11. The entorhinal cortex

A massive projection to the hippocampal formation arises from the

entorhinal cortex, and, indeed, this area is considered to be the major source of hippocampal afferents. The projection is bilateral - via the perforant and alvear paths ipsilaterally, and the crossed tempero-ammonic path contralaterally (Steward 1976; Swanson & Cowan 1977).

Fibres of the ipsilateral path travel first in the angular bundle (and alveus) and then ascend through the subicular cortex (where some probably terminate) towards the hippocampus. At the hippocampal fissure some fibres turn and run parallel to the fissure to attain the stratum lacunosum-moleculare of CA1, while others perforate it to fill the outer two-thirds of the stratum moleculare of the dentate gyrus, and the stratum lacunosum-moleculare of CA3.

The topographic organisation of the entorhinal projection to these two areas (i.e. CA1 on the one hand, and CA3 and the dentate gyrus on the other) is quite different, as shown by Van Hoesen & Pandya (1975b) in the monkey, and Hjorth-Simonsen & Jeune (1972) and especially Steward (1976) in the rat. In the dentate gyrus, the medio-lateral axis of the entorhinal cortex is reflected in a laminated pattern of termination along the dendrites of the granule cells. The pars medialis projects to the middle third of the granule cell dendrites, while the pars lateralis projects to the outer third. A similar organisation is present along the distal parts of the dendrites of the CA3 region.

In field CA1, however, the projections of the entorhinal cortex are distributed along the subiculo-dentate axis, such that pars medialis projects to the proximal parts of CA1, at the CA1/CA3

border, while the pars lateralis projection terminates in the distal end of CA1 and in the subiculum.

These different patterns of projection arise from separate groups of cells (Steward & Scoville 1976). The projection to the dentate gyrus (and probably CA3) arises from the stellate cells of layer II of the entorhinal cortex, and that to CA1 arises from the pyramidal cells of layer III. These same cell groupings appear to be responsible for the crossed tempero-ammonic pathway, but the layer II projection (to the contralateral dentate gyrus and CA3) is considerably weaker than the layer III projection to the contralateral CA1. The above findings have been confirmed in the mouse (Stanfield et al. 1979), but not the cat (Habets et al. 1980).

Finally, the entorhinal cortex also has a commissural projection to layer I of the contralateral entorhinal cortex (Blackstad 1956).

1.2.2. EFFERENTS OF THE HIPPOCAMPAL REGION

Until very recently it was thought that many of the efferents to be described below originated from Ammon's horn. It has become clear in the last few year, however, that the hippocampus gives rise mainly to short-axoned commissural and associational connections within the hippocampal region, and that it is the subicular complex, particularly the subiculum, which it the major source of both cortical and subcortical efferents (Swanson & Cowan 1975; Rosene & Van Hoesen 1977). These projecions will be

discussed in relation to each area within the hippocampal region.

1.2.2.1. Dentate gyrus and CA4 area

The projections of this area appear to be confined entirely to the hippocampal region (Swanson & Cowan 1977, 1979; Swanson et al. 1978).

1.2.2.2. Field CA3

(a) Rostral projections

Although there is some disagreement as to the organisation of these projections, there is nevertheless good general agreement as to the target structures (see Edinger et al. 1979; Meibach & Siegel 1977a, b; Swanson & Cowan 1977, 1979).

CA3 projects bilaterally upon the lateral septal complex, with the ipsilateral input being more marked. The input is organised such that the medio-lateral and septo-temporal axes of CA3 are reflected by a medio-lateral, dorso-ventral termination in the lateral septal nucleus, with a significant degree of overlap between adjacent areas of CA3. CA3 projections travel only in the fimbria, where they maintain their relative topographic relationship.

The projection is restricted to the more posterior parts of the

lateral septal complex, and there is evidence from degeneration studies (Raisman 1966) that it includes the posterior division of the septal area (i.e. the septofimbrial and triangular septal nuclei).

Although the medial division of the septum does not appear to receive a projection from the hippocampal formation, Swanson & Cowan (1977) point out that this does not preclude a direct hippocampal influence on the cells of this area, since these neurons possess long dendritic processes which protrude into the lateral septal nucleus. Furthermore, the lateral septal nucleus projects massively to the medial division, thus allowing for indirect control over this area.

(b) Caudal projections

The only area beyond the hippocampal region to which CA3 may project is the superficial layers of the cingulate cortex, and this only from its septal pole (Swanson & Cowan 1977). Rosene & Van Hoesen (1977), on the other hand, deny any such projection in the monkey.

1.2.2.3. Field CA1

(a) Rostral projections

In a manner similar to CA3, CA1 projects in a topographic fashion to the lateral septal nucleus, with the exception that it is

strictly ipsilateral and extends further rostrally. The projection is by way of the dorsal fornix as well as the fimbria, and probably includes the posterior division of the septal nucleus.

The projection to the more rostral part of the septal nucleus is of interest, since this appears to reflect a general trend in that CA1 has been shown to project even further rostrally, to the nucleus accumbens (Chronister & De France 1979; Newman & Winans 1980a) and perhaps other areas (Swanson & Cowan 1977). However, it seems that it is only the juxtasubicular component of CA1 which participates in these projections, and they will therefore be considered together with the projections of the subiculum.

(b) Caudal projections

CA1 projections are limited to the hippocampal region in the rat. In the marmoset monkey Schwerdtfecer (1979) has reported a few scattered cells projecting as far as the frontal and temporal neocortex, although, again, Rosene & Van Hoesen (1977) deny any projections beyond the subiculum in the rhesus monkey.

1.2.2.4. The subiculum

The efferents from the subiculum, perhaps even more than those of the hippocampus, are differentially organised along the dorso-ventral axis (Meibach & Siegel 1977a; Swanson & Cowan 1977; Swanson 1978), and will accordingly be considered separately.

1.2.2.4.1. Dorsal subiculum

(a) Rostral projections

The dorsal subiculum projects to the septum, thalamus and hypothalamus.

(i) The septum. All parts of the subiculum project ipsilaterally via the precommissural fornix in an ordered manner upon the lateral septal nucleus, overlapping the projection from Ammon's horn to a considerable degree. Meibach & Siegel (1977a) are of the opinion that the subiculum contributes the majority of fibres to this area, since the projection fills its entire rostro-caudal extent, and also probably includes the posterior division of the septum.

(ii) The thalamus. A projection to the anterior thalamus has been demonstrated in the rat (Meibach & Siegel 1977d; Sikes et al. 1977), cat (Edinger et al. 1979) and monkey (Rosene & Van Hoesen 1977). The cells of origin lie in a narrow band adjacent to the alveus and project via both the postcommissural fornix and the internal capsule to the anteroventral and anteromedial thalamic nuclei. On the basis of an HRP study it appears that the nucleus reuniens also receives afferents from the subiculum but, in contrast to the above projections, these arise from both the dorsal and ventral subiculum (Herkenham 1978).

(iii) The hypothalamus. A topographically organised projection via the postcommissural fornix to the medial mammillary nucleus

has been demonstrated (Meibach & Siegel 1977a; Swanson & Cowan 1977).

(b) Caudal Projections

The dorsal subiculum projects ipsilaterally to the superficial layers of the retrosplenial cortex in rat (Meibach & Siegel 1977c), monkey (Rosene & Van Hoesen 1977) and guinea pig (Sorensen 1980). In the latter study the efferents were found to be organised such that the septo-temporal and proximo-distal (with reference to the dentate gyrus) axes of the dorsal subiculum map onto the rostro-caudal and dorso-ventral axes of the retrosplenial cortex respectively.

1.2.2.4.2. Ventral subiculum

(a) Rostral projections

These are to the septum, nucleus accumbens, rostral forebrain, thalamus and hypothalamus.

(i) The septum. The ventral subiculum has precommissural efferents to the lateral septal and posterior septal divisions in a similar manner to the dorsal subiculum, but, in addition, projects to the bed nucleus of the stria terminalis (Swanson & Cowan 1977).

(ii) The nucleus accumbens. As indicated previously, CA1 participates in this projection. Although in the rat only the ventral hippocampal formation is involved (Chronister & De France 1979; Swanson & Cowan 1977), in the hamster the entire septo-temporal extent of the subiculum and the posterior part of CA1 project to this nucleus (Newman & Winans 1980a). However, CA1 does not appear to be involved in this projection in the monkey (Rosene & Van Hoesen 1977).

(iii) The rosral forebrain. The deeper layers of the infralimbic cortex (area 25), the posterior and medial parts of the anterior olfactory nucleus, and the molecular layer of the taenia tecta all receive afferents from the ventral subiculum, and possibly CA1 (Swanson & Cowan 1977). In the monkey the projections to the frontal cortex are more extensive and include the medial cortex ventral to the corpus callosum, and around along the orbital surface as far laterally as the medial orbital sulcus (Rosene & Van Hoesen 1977).

(iv) The thalamus. The only thalamic projection from the ventral subiculum appears to be to the nucleus reuniens (Herkenham 1978).

(v) The hypothalamus. The ventral subiculum is the source of the medial cortico-hypothalamic tract, which runs through the anterior hypothalamus to the capsular zone surrounding the ventromedial and arcuate nuclei, and ends in the medial mammillary nuclei (Meibach & Siegel 1977a; Swanson & Cowan 1977). This projection is not found in the cat (Edinger et al. 1979).

(b) Caudal projections

In the rat, the ventral subicular projections are limited to the hippocampal region, but in the monkey, efferents travel further along the inferotemporal cortex to reach the mediobasal nucleus of the amygdala (Rosene & Van Hoesen 1977).

1.2.2.5. The presubiculum (and postsubiculum)

(a) Rostral projections

The presubiculum appears to be the major source of thalamic efferents. In the rat it projects to the anteroventral and anteromedial nuclei (Meibach & Siegel 1977d; Swanson & Cowan 1977), as well as to the anterodorsal, lateral dorsal and lateral posterior nuclei (Swanson & Cowan 1977). In the cat the pattern is somewhat different. Kaitz & Robertson (1981) report a projection to the anteroventral, anteromedial and lateral dorsal nuclei, but not the anterodorsal or lateral posterior nuclei. In addition, they found labelling of the central dorsal, interanteromedial, central medial, reuniens and rhomboid nuclei. The projection is via both the fornix and the internal capsule, and arises from cells in the lamina principalis interna in both the rat (Sikes et al. 1977) and cat (Edinger et al. 1979), and is restricted to the more dorsal part of the presubiculum.

The presubiculum also projects bilaterally to the medial and lateral mammillary nuclei (Edinger et al. 1979; Meibach & Siegel

1977a; Swanson & Cowan 1977).

(b) Caudal Projections

The dorsal presubiculum (postsubiculum) is the main source of efferents to the retrosplenial cortex in the rat (Meibach & Siegel 1977c; Swanson & Cowan 1977), although in the guinea pig (Sorensen 1980) and monkey (Rosene & Van Hoesen 1977) this projection is exclusively from the dorsal subiculum.

In the monkey, the presubiculum participates in the projections of the subiculum to the temporal neocortex and amygdala (Rosene & Van Hoesen 1977). Unfortunately, however, the relative contribution of the different areas is not clear.

1.2.2.6. The parasubiculum

There is, unfortunately, litle information on the projections of this area.

1.2.2.7. The entorhinal cortex

Besides the massive projection to the hippocampal formation, the entorhinal (and perirhinal) cortex projects to the nucleus accumbens and the olfactory tubercle (Krayniak et al. 1981; Newman & Winans 1980a, b). Krayniak et al. (1981) indicate that the projection arises primarily from layers II and III of the anterior two-thirds of the entorhinal cortex.

Other than these rostrally directed projections, Van Hoesen & Pandya (1975a) have demonstrated reciprocal connections between the entorhinal and perirhinal cortices.

1.2.3. AFFERENTS OF THE HIPPOCAMPAL REGION

1.2.3.1. The Septum

It is now well established in the rat (Segal & Landis 1974; Swanson & Cowan 1979) and monkey (Amaral & Cowan 1980; De Vito 1980) that only the medial division of the septum projects to the hippocampal region. Essentially the entire hippocampal region is in receipt of fibres from both the medial septal nucleus and the nucleus of the diagonal band, although some areas appear to have a heavier input than others. The fibres travel via the fimbria, dorsal fornix and possibly the cingulum to preferentially innervate stratum oriens of CA3, the infragranular zone of the hilar region, the superficial layers of the parasubiculum, and the deeper part of the molecular layer of the subiculum, but the presubiculum and entorhinal cortex are also involved. CA1 has the least label of all, and it has been suggested that even this may be due to fibres of passage destined for the subiculum and beyond. Certainly other autoradiographic (Rose et al. 1976) and degeneration (Raisman 1966) studies indicate that CA1 does not receive a projection. It is important to note, however, that the septal projection is thought to be cholinergic (see e.g., Lynch et al. 1978; Mosko et al. 1973), and that acetylcholinesterase

histochemistry indicates that a sparse projection to CA1 may exist.

1.2.3.2. The amygdala

The amygdala has projections to the perirhinal and lateral entorhinal areas, the parasubiculum and the subiculum (Amaral & Cowan 1980; Kevetter & Winans 1981; Krettek & Price 1974, 1977). Krettek & Price (1977; see also Kevetter & Winans 1981) make the point that the various nuclei which constitute the amygdala have such different connections that it is misleading to consider them as a functional unit. Their analysis in the rat and cat indicates that three areas within the amygdaloid complex project to the hippocampal region:

(i) The lateral amygdaloid nucleus. Axons from here apparently travel in the external capsule to innervate layers III and IIIa of the ventral part of the lateral entorhinal area. A feature of the terminal distribution in the cat are the finger-like protrusions which occur between the cell islands of layer II.

This area also projects to the outer part of the subiculum.

(ii) The basolateral nucleus. Only the posterior division projects to the parasubiculum and the ventral part of the subiculum. Label is found in both the molecular and cellular zones in the subiculum, with a small overlap into CA1. In the parasubiculum label is confined to the junction of layers I and II of its posterodorsal part ("parasubiculum a" of Blackstad 1956).

This area also probably projects to the deep layers of the dorsal part of the lateral entorhinal cortex.

(iii) The periamygdaloid cortex (posterolateral cortical nucleus). Projects to the superficial layers (mainly I and II) of the ventral part of the lateral entorhinal area, and the molecular layer of the ventral subiculum.

In addition to these amygdaloid nuclei, Krettek & Price (1977) indicate that several areas associated with the amygdala also project to the hippocampal region.

The olfactory bulb and prepyriform cortex project to layer I of the entire lateral entorhinal cortex, and the endopiriform nucleus projects to layers I and II of the ventromedial part of the lateral entorhinal cortex, as well as to the superficial layers of the parasubiculum and ventral subiculum.

Kevetter & Winans (1981), supported by Beckstead (1978) in the rat, report that, in the hamster, the anterior cortical nucleus also projects to the hippocampal formation: to layer I of the ventral part of the lateral entorhinal area, and to the molecular layer of the ventral subiculum.

In an HRP study in the monkey Amaral & Cowan (1980) were able to confirm a projection from the ventromedial part of the basolateral nucleus, the periamygdaloid cortex and the endopiriform nucleus. The lateral nucleus and the anterior cortical nucleus were, however, free of label, although the closely associated areas of the claustrum, substantia innominata, anterior amygdaloid area and

the basal nucleus of Meynert were labelled.

1.2.3.3. The thalamus

The presubiculum seems to be the target for most thalamic efferents (Amaral & Cowan 1980). Indeed, Robertson & Kaitz (1981) found that injection of HRP into the rat presubiculum produced label in the laterodorsal, anteroventral, anterodorsal, anteromedial and reuniens nuclei.

Injections into larger areas of the hippocampal region in the monkey label, in addition, the parataenial, anterior paraventricular and central medial nuclei (Amaral & Cowan 1980; De Vito 1980).

Autoradiographic studies of the projections of some of these nuclei indicate the following pattern of termination (Robertson & Kaitz 1981):

(i) The laterodorsal nucleus projects heavily to the presubiculum and parasubiculum, and more sparsely to the medial entorhinal area. The label in the pre- and parasubiculum is peculiar in that it is not evenly distributed but forms columns from layer I to layer IV.

(ii) The anteroventral nucleus produces sparse labelling of layer I and the deep portion of the external granular layer of the presubiculum.

(iii) The anterodorsal nucleus projects sparsely to all layers of the presubiculum.

(iv) The anteromedial nucleus has a small projection to the medial entorhinal cortex, and to layers I and II of the presubiculum.

Fibres from the nucleus reuniens of the rat apparently do not innervate the presubiculum, but travel in the cingulum bundle to reach the entorhinal cortex, ventral subiculum and CA1 (Herkenham 1978). The projection to the entorhinal cortex is distributed to layers I and III, and in pars lateralis forms protrusions between the cell islands. The projection to the subiculum ends in the stratum moleculare, and that to CA1 in the stratum lacunosum-moleculare.

1.2.3.4. The hypothalamus

The main projection from the hypothalamus to the hippocampal region arises from the supramammillary area. This projection, first reported by Segal & Landis (1974), has been amply confirmed in the rat (Pasquier & Reinoso-Suarez 1976; Segal 1979) and monkey (Amaral & Cowan 1980; De Vito 1980).

Using the autoradiographic method, Segal (1979) traced the pathway through the medial forebrain bundle, the diagonal band (where a minor branch travels rostrally to innervate the taenia tecta) and the dorsal fornix to terminate in a dense band in the superficial half of the stratum granulosum and adjacent stratum moleculare of

the dentate gyrus. As mentioned previously, a restricted projection was also evident to the pyramidal layer of CA2. The projection was predominantly ipsilateral.

Besides the supramammillary projection, there appears to be a diffuse projection from scattered cells throughout the anterior-posterior extent of the hypothalamus (Amaral & Cowan 1980).

1.2.3.5. Brainstem afferents

Amaral & Cowan (1980) have identified several areas in the brainstem that apparently project to the hippocampal region. These include the ventral tegmental area, the raphe nuclei, the nucleus reticularis tegmenti pontis, the tegmental reticular fields, the central gray, the dorsal tegmental nucleus, and the locus coeruleus. Most of these areas contained only a few scattered cells and their functional significance is unclear. Here, only the raphe nuclei and the locus coeruleus will be considered, other than to say that the ventral tegmental area is probably the source of the dopaminergic input which is especially evident to the outer three layers of the entorhinal area (Lindvall et al. 1974), and that the reports of a projection from the interpeduncular nucleus (e.g. Baisden et al. 1979) should be regarded with caution (De Vito 1980).

1.2.3.5.1. The raphe nuclei

Both dorsal and median raphe nuclei contribute to the serotonergic afferents to the hippocampal region, although the median raphe accounts for the majority of the input (Azmitia & Segal 1978; Moore 1975).

The fibres from the dorsal raphe travel first in the medial forebrain bundle and then in the ansa lenticularis, passing through the amygdala to gain the entorhinal cortex and the temporal pole of the hippocampal formation.

The rest of the hippocampus is served by the median raphe, which projects via the cingulum bundle and both the fimbria and dorsal fornix. The fibres terminate most densely in the stratum lacunosum-moleculare of CA1, the stratum radiatum of CA3, and in the infragranular plexus of the hilus.

1.2.3.5.2. The locus coeruleus

The locus coeruleus' innervation of the hippocampal region is remarkably similar to that of the raphe nuclei (see Loy et al. 1980; Moore 1975). The axons course in the dorsal tegmental bundle to join the medial forebrain bundle, whence they split into three groups: one via the ventral amygdaloid bundle to the temporal hippocampal formation, another via the fornix to the septal pole of the hippocampus, and the third via the cingulum bundle to the posterior hippocampal formation. The pattern of termination within the hippocampus is also very similar to that of

the serotonergic projection in that the densest label is found in stratum lacunosum-moleculare of CA1, stratum lucidum of CA3 and (especially) the infragranular plexus of the hilus.

1.2.3.6. Cortical afferents

The degeneration experiments of Van Hoesen et al. (1972) suggest that the ventral and medial surfaces of the cerebral cortex are the main source of direct cortical projections. Since most of this work has used monkey material, these results will be reported separately.

(i) Monkey

Van Hoesen et al. (1975) report that the mediocaudal region of the orbitofrontal cortex, corresponding to Bonin & Bailey's area FF, projects to the perirhinal, and what they term the prorhinal, cortices, as well as to layer III of the lateral entorhinal area. The medial prefrontal cortex, on the other hand, projects not only to the entorhinal and presubicular cortices, but also via both the alvear and perforant paths to fields CA1-CA3 (Leichnitz & Astruc 1975). Interestingly, terminal degeneration was observed in stratum pyramidale as well as on the somata of basket cells in stratum oriens.

As far as the temporal lobe is concerned, virtually all areas comprising the inferotemporal cortex project to the hippocampal region. Van Hoesen & Pandya (1975a), using degeneration techniques, found that: area TF-TH projects to layers I and II of

the medial and intermediate entorhinal cortex; the perirhinal cortex projects to all layers and areas of the entorhinal cortex; and the general region incorporated in Brodmann's area 51 (periamygdaloid and prepiriform cortices) to layers I-III of the lateral and intermediate entorhinal areas. However, in a more recent study using the autoradiographic technique Van Hoesen et al. (1979) found that a wider area of temporal cortex projects further into the hippocampal region than had been suspected. Thus area TG projects to the parasubiculum; area TE and the perirhinal cortex project to the molecular layer of the subiculum; and areas TF and TH project both to the molecular layer of the subiculum and in a columnar fashion to the presubiculum. Furthermore, Schwerdtfecer (1979) reports the autoradiographically demonstrated projection from temporal cortex (Brodmann's areas 20 and 21) to the entorhinal cortex, the entire subicular complex, and, to a lesser extent, fields CA1-3.

Finally, the caudal cingulate gyrus has been found to project heavily to the presubiculum (Van Hoesen et al. 1972).

(ii) Rat

Cortical afferents in the rat have not been studied extensively, possibly because HRP studies have failed to demonstrate such projections (see Beckstead 1978; Swanson 1979). However, this appears to be due to a failure of the HRP technique, and autoradiographic studies have uncovered similar, if more circumscribed, projections to those seen in the monkey. Beckstead (1979), in a study of that part of the frontal cortex projected upon by the mediodorsal thalamic nucleus, describes efferents from

the prelimbic (area 32), anterior cingulate (area 24) and sulcal cortices to the hippocampal region. These areas innervate primarily the lateral entorhinal cortex and the dorsal presubiculum.

Afferents from the cortex on the ventral surface of the temporal lobe have already been described in the section on amygdaloid efferents. Briefly, the prepiriform and periamygdaloid cortices project to the lateral entorhinal area, and the periamygdaloid cortex projects to the ventral part of the subiculum as well (Krettek & Price 1977).

Lastly, preliminary results indicate that wide areas of the cingulate gyrus project to the dorsal part of the presubiculum and postsubiculum, and possibly to the subiculum and entorhinal cortex (Swanson 1978).

1.3. OVERVIEW

Although great strides have been made in detailing the major connections of the hippocampal region, there remain large gaps in our understanding. For example, the extrinsic projections of the parasubiculum have yet to be established. There remains, too, the pressing need to determine exactly which second order cells are contacted. A promising start in this direction has been made by utilising the axonal transport of tritiated adenosine, which is capable of transneural labelling (Schubert, Rose, Lee, Lynch & Kreutzberg 1977). Unfortunately, adenosine is transported both anterogradely and retrogradely, and thus can only be used in

systems without reciprocal connections - a situation too rare to make this technique of great value. It is clear, however, that until such time as a workable technique is perfected, the complete wiring circuit will remain speculative.

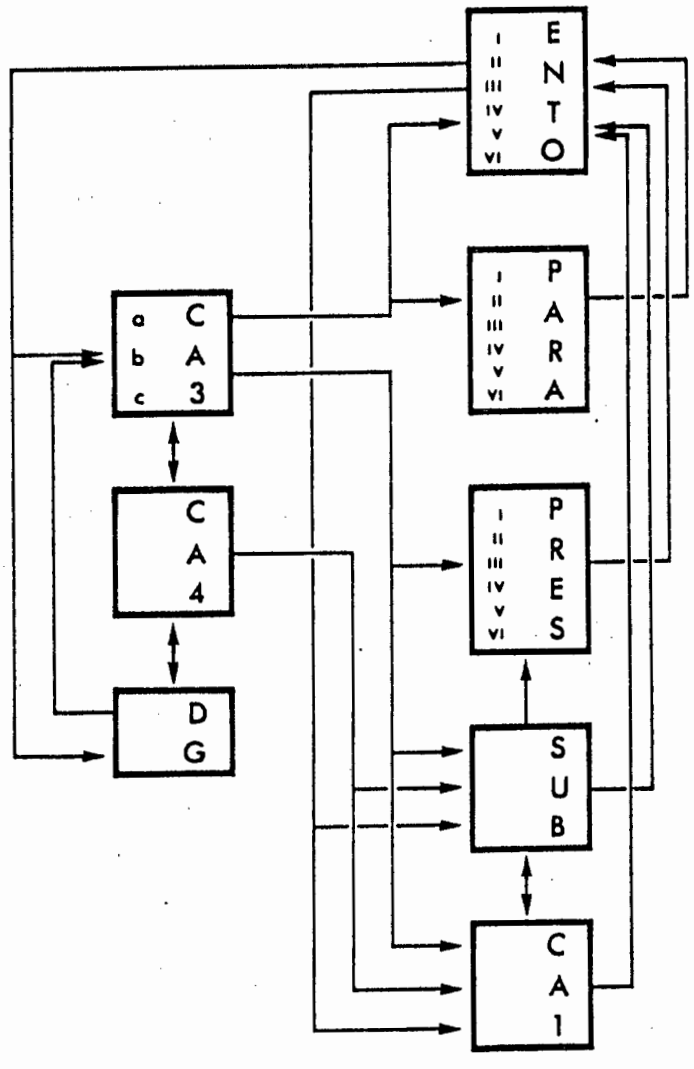

FIG. 2. The major intrinsic connections of the hippocampal region. Abreviations: DG - dentate gyrus; CA4-CA1 - Ammonic fields of the hippocampus; SUB - subiculum; PRES - presubiculum; PARA - parasubiculum; ENTO - the medial entorhinal cortex.

Fig. 2, compiled from evidence drawn from a variety of species, indicates the probable intrinsic connections of the hippocampal region. It should be noted that ENTO refers to the medial

entorhinal cortex only. While the lateral entorhinal cortex receives most of its input from structures lying outside the hippocampal region, the medial entorhinal cortex is a a major target for projections emanating from within the hippocampal region. The pre- and parasubiculum, for example, project almost exclusively to this part of the entorhinal cortex. It is thus apparent that the medial entorhinal cortex receives much of its input from areas that project via the superficial layers of these structures, and suggests that it may subserve a function quite different to that of the lateral entorhinal cortex.

There is, too, the question of the role of regio inferior. Several authors (Anderson 1975; Hjorst-Simonsen 1973; Rosene & Van Hoesen 1977) have emphasised the circular flow of information along the route: entorhinal cortex-DG-CA3-CA1-Subiculum. Reference to Fig. 2 makes it clear that this is an over-simplification. Firstly, there is the important observation of Steward & Scoville (1976) that regio superior and inferior receive a differential input from the entorhinal cortex, thus encouraging the view that these areas can operate independently. (In this regard it should be noted that even a massive input via the Schaffer collaterals will not produce excitation of the CA1 pyramids unless in the presence of some other permissive influence - Mesher & Schwartzkroin 1980). Secondly, CA3 projects to virtually the entire hippocampal region and is thus in a position to play a pivotal role in its functioning. Particularly interesting are the projections to layer II of the parasubiculum and layer III of the presubiculum. Since these layers project to layers II and III, respectively, of the entorhinal cortex, which in turn provide the differential input to regio inferior and

superior, it seems possible that CA3 may exercise control over some of the major inputs to the hippocampal region.

2 THEORIES OF HIPPOCAMPAL FUNTIONING

The large size and relatively simple anatomy of the hippocampus has attracted perhaps more attention than any other neural structure. The most influential theory to have emerged from the intensive investigations of the 60's and early 70's was that of Douglas (1967, 1972, 1975) and Kimble (1968) that the hippocampus was concerned with the inhibition or "braking" of behaviour. Evidence from the lesion literature supporting (and contradicting) this hypothesis (hereafter known as the "inhibitory" theory) will be briefly reviewed, and then the adequacy of two more recent formulations (the "working memory" theory of Olton, Becker & Handelmann 1979, and the "cognitive map" theory of O'Keefe & Nadel 1978) will be assessed.

It is perhaps as well at the outset to alert readers to a bias towards the inhibitory theory. While admitting this partiality, every effort has nevertheless been made to provide a fair and balanced view of the strengths and weaknesses of each theory.

2.1. THE HIPPOCAMPUS AND INHIBITION

2.1.1. Statement Of The Hypothesis

The idea that the hippocampus exerts some kind of inhibitory action on behaviour was stated most cogently by Douglas (1967), and has since been mooted, in one form or another, in a number of review articles (e.g. Altman, Bruner & Bayer 1973; Cormier 1981;

Gray, Feldon, Rawlins, Owen & McNaughton 1978; Kimble 1968; Numan 1978). Douglas (1972) has argued that the proposed inhibitory mechanism acts neither at the motor nor sensory level, but rather on the motivational forces underlying behaviour, and, together with Kimble (1968), has identified the hippocampus as the neural substrate of Pavlovian internal inhibition. Since a more detailed description of this concept is presented later (chapter 4), it will suffice here to note that the existence of internal inhibition was postulated by Pavlov (1927) to account for the decrements in responding seen under conditions of extinction and habituation.

2.1.2. Evidence In Support Of The Theory

Since the hippocampal literature has recently been extensively reviewed (O'Keefe & Nadel 1978), where possible reference will be made to this source. The evidence will be discussed under five main heads:

1. Simple non-reinforcement
2. Performance on DRL (differential-reinforcement-of-low-rates-of-response) schedules
3. Avoidance learning
4. External inhibition
5. The human amnesic syndrome

2.1.2.1. Simple non-reinforcement

Since non-reinforcement, by definition, induces internal

inhibition, it would be expected that hippocampectomised animals (also known hereafter as "hippocampals") would differ from normal on tasks where this is an important variable. Douglas (1972) lists the following behaviours as being based to a considerable extent on internal inhibition: habituation, extinction, reversal learning (first stage), latent inhibition, spontaneous alternation & complex maze learning. Each of these will be briefly discussed.

2.1.2.1.1. Habituation

A failure to show the usual decrement of activity with time on being placed in a novel environment or open field is a commonly reported effect of hippocampectomy (see O'Keefe & Nadel 1978, Table A14 p. 458). Douglas (1967) has argued that these results cannot be ascribed merely to a tendency to hyperactivity, since rats with large hippocampal lesions do not show increased running on an activity wheel. It seems, therefore, that the increased activity in the open field can be ascribed to a failure on the part of these animals to habituate to novel stimuli. In other words, they continue to explore the environment after control animals have stopped.

2.1.2.1.2. Extinction

The most direct consequence of hippocampectomy should, according to the inhibitory theory, be a loss of the ability to extinguish conditioned responses. Numerous studies, using a variety of species and tasks, have shown that hippocampal damage does cause

animals to persist longer than controls in emitting responses which are no longer reinforced (see O'Keefe & Nadel 1978, Table A26, p. 470).

2.1.2.1.3. Reversal learning

The great majority of experiments where reinforcement is switched from the previously reinforced choice to the non-reinforced choice show that hippocampals find this a particularly difficult task to master (see O'Keefe & Nadel 1978, Tables A18 & A19, pp. 463-464). They apparently cannot inhibit the urge to continue responding to the previously reinforced choice.

2.1.2.1.4. Latent inhibition

Latent inhibition (inhibitory preconditioning) involves the presentation of a stimulus for many trials without reinforcement, prior to being paired with an unconditioned stimulus (UCS). Since the initial presentations of the stimulus generate internal inhibition (the animal becomes habituated to the stimulus), the subsequent elaboration of a conditioned reflex is retarded relative to a conditioned stimulus (CS) that has not been pre-exposed. If the hippocampus is indeed the seat of internal inhibition, then hippocampals should not show the expected retardation. This is in fact found to be the case (Ackil, Mellgren, Halgren & Frommer 1969; Solomon & Moore 1975).

It is perhaps appropriate to mention at this point that, in

further support of the inhibitory theory, Kamin blocking (which is conceptually related to latent inhibition, and is discussed in more detail in Chapter 4) is also deficient in hippocampals (Rickert, Bennett, Lane & French 1978; Rickert, Lorden, Dawson & Smyly 1981; Solomon 1977).

2.1.2.1.5. Spontaneous alternation

In this procedure animals are typically allowed two unrewarded choices in a T-maze. Normal animals almost invariably alternate their choices, while hippocampals do not (see Douglas 1975). The inhibitory theory would predict this effect since spontaneous alternation can be seen as being dependent on internal inhibition. Thus, once an animal has made a choice, the stimuli which guided that choice (not having been associated with reward) will accrue internal inhibition. When next faced with the identical choice the animal will therefore tend to ignore that arm and choose the opposite one. For hippocampals, on the other hand (lacking internal inhibition), both arms remain equally attractive and they therefore choose randomly.

2.1.2.1.6. Complex maze learning

The inability of hippocampectomised animals to learn complex mazes (see O'Keefe & Nadel 1978, Table A20 p. 464) has been ascribed by Douglas (1972) to a loss of their ability to inhibit incorrect choices. Thus "lesioned subjects make repeated re-entries into blind alleys, as if not profiting by previous nonreinforced

instances. Many of the old-time maze learning analysts believed error avoidance (inhibition) to be extremely crucial in maze learning. Dennis & Sollenberger (1934) went so far as to claim that complex maze learning consisted almost entirely of the active elimination of erroneous pathways which, it should be noted, far outnumber the one single error-free path." (Douglas 1972, p. 533).

2.1.2.2. DRL performance

Practically all studies show that animals with hippocampal lesions fare badly on a DRL schedule if they are first shaped on a continuous reinforcement (CRF) schedule (see O'Keefe & Nadel 1978, Table A24 p. 468), but not if they have not received such prior training. In terms of the inhibitory theory, the DRL deficit is explained as being due to the intrusion of the behaviour learned when on the CRF schedule. When the animal is placed directly onto the DRL schedule, however, the delay between bar presses acts merely as part of a compound CS (Douglas 1972). Since there is no competing response which has to be inhibited, no deficit is seen.

2.1.2.3. Avoidance learning

Three types of task have been extensively used to assess the role of the hippocampus in aversive conditioning: Passive avoidance, two-way active avoidance and one-way active avoidance.

Passive avoidance tasks are those in which the valence of

reinforcement for a particular response is suddenly changed from positive to negative. Since the animal must withhold the previously rewarded behaviour in order to avoid punishment, hippocampals would be expected to show a deficit on this task. A large number of studies have in fact found this to be the case (see Altman et al 1973; Douglas 1967; Kimble 1968).

In contrast, hippocampectomised animals are superior to normal on two-way active avoidance (shuttle box) tasks (see O'Keefe & Nadel 1978, Table A22 p. 465). This appears to be the result of internal inhibition actually being prejudicial to rapid performance on this task. The animal is required to run from one box (A) to another (B) to avoid shock in A, and is then expected to return to A to avoid punishment in B. Normal animals perform poorly in this situation since they hesitate (i.e. inhibit the tendency) to enter a compartment in which they have previously received shock. Hippocampals, lacking internal inhibition, have no such problems and shuttle rapidly back and forth.

In one-way active avoidance tasks, on the other hand, where the animal is required to avoid punishment by running from the shock box to a safe compartment, hippocampectomy does not confer any advantage, and performance is usually found to be in the normal range (see O'Keefe & Nadel 1978, Table A21 p. 465).

2.1.2.4. External inhibition

The presentation of a novel stimulus produces an arrest of ongoing activity, together with an orienting response. Pavlov (1927)

postulated that this arrest reaction was due to what he termed external inhibition - a mechanism closely allied to internal inhibition. It would therefore be predicted that hippocampals, being unable to easily redirect (inhibit) their attention, would be less affected than normal by the presentation of a novel stimulus if they were engaged in motivated behaviour, but at least as, if not more, distractible if not so engaged. Reference to Table A13 of O'Keefe & Nadel (1978, p. 457) shows this prediction to be confirmed.

2.1.2.5. The human amnesic syndrome

Humans with suspected or actual hippocampal damage display a severe amnesia in that they cannot remember incidents in daily life after a gap of even a few minutes, and in formal tests seem incapable of paired-associate learning. This syndrome is clearly different from the behaviour of hippocampectomised animals, which show good retention over long periods. Various solutions have been proposed to account for the discrepency, including the possibility that the critical region for the memory dificit is not the hippocampus itself, but the white matter overlying it (Horel & Misantone 1974, 1976).

However, recent research has more clearly defined the nature of the deficit, and the general picture that has emerged fits rather well with the inhibitory theory. Weiskrantz and colleagues (see Weiskrantz 1978) have shown that amnesics <u>can</u> learn a list of paired associates as well as controls, provided that the number of alternative responses is severely limited by some rule governing

the relationship of the pairs of words (e.g. that they be semantically or phonetically related). However, what the amnesics cannot do is learn a second list having the same rule and same initial word as the first list. Under these conditions the amnesics have a high number of intrusion errors; that is, they persist in responding to the stimulus word with the paired associate from the original list. Furthermore, their deficit is not restricted to proactive interference: Even though they appear to have learnt little of the second list, if subsequently retested on the original list they now show retroactive interference, in that a high number of intrusion errors from the second list is seen (Winocur & Weiskrantz 1976). It thus appears that at least part of the memory impairment of the amnesics results from excessive interference: They cannot inhibit prior associations.

2.1.3. Criticisms Of The Theory

The inhibitory theory has been particularly strongly challenged by O'Keefe & Nadel (Black, Nadel & O'Keefe 1977; Nadel, O'Keefe & Black 1975; O'Keefe & Nadel 1978). The most cogent criticisms from Nadel et al. (1975) are presented below (see also pp. 81-84 for further discussion of some of these issues):

2.1.3.1. Habituation

Notwithstanding Douglas' (1967) arguments to the contrary, Nadel et al. maintain that the increased activity displayed by hippocampals in a novel environment is not hyperexploration, but

merely hyperactivity. They support this contention by citing the finding by Glickman, Higgins & Isaacson (1970) that hippocampals explore novel objects placed into the home cage significantly less than do normals.

2.1.3.2. Extinction

While admitting that hippocampals show extinction deficits in both lever-press and runway situations, Nadel et al argue that it is misleading to equate the two. The deficit found in the runway seems to be of a different type: It is very much larger than that seen in lever-press tasks, and is abnormally sensitive to the intertrial interval (in that short intertrial intervals reduce the deficit). Any theory of hippocampal functioning must be able to account for this difference. Furthermore, an extinction deficit is not an inevitable consequence of hippocampal damage. Extinction in many avoidance situations is either normal or superior to normal (Kaplan 1968; Nadel 1968; Niki 1962; Schmaltz & Giulian 1972).

2.1.3.3. Reversal learning

Nadel et al. draw attention to the fact that the deficit displayed by hippocampals in reversal learning of non-spatial two-choice discrimination tasks is not often the result of persistent responding to the previously rewarded stimulus. Rather, the animals switch to an inappropriate position habit and persist in that. Moreover, it is not the reversal per se that is difficult,

at least not for hippocampectomised primates, since several studies have shown that these animals are normal or superior to normal on object reversals: They only experience difficulty with spatial reversals (see O'Keefe & Nadel 1978, Tables A18 & A19 pp. 463-464).

2.1.3.4. Passive avoidance

Nadel et al. attack the general claim that hippocampals are deficient in passive avoidance. They point out that a more complete review of the literature shows that half of the studies fail to find a deficit, and that hippocampals are rarely deficient on tasks such as step-down or step-through passive avoidance, where a total cessation of responding is required (see O'Keefe & Nadel 1978, Table A23 p. 466). Furthermore, a feature of runway experiments, where a positively reinforced approach response is punished, is that hippocampals are not necessarily deficient on all measures of passive avoidance. For example, they may approach closer to the food dish, but often do not touch it sooner than normals.

2.1.3.5. Maze learning

Nadel et al. question the adequacy of the "inhibitory deficit" account of the failure of hippocampectomised animals to learn complex mazes. They point out that hippocampals show no impairment when cues are available at each choice point (Winocur & Breckenridge 1973). They also feel that the data obtained by

Leaton (1969) must be addressed. In this study animals were run in a maze with the blind alleys blocked off. When the blind alleys were opened, the hippocampals entered these alleys more frequently than did the controls.

A final piece of evidence against the inhibitory theory comes from the work of Solomon (1977) on the classical conditioning of the rabbit nictitating response (see Solomon 1979 for a review), who found that hippocampals did not display the expected deficit in Pavlovian conditioned inhibition. In this procedure a conditioned stimulus, CS1, is paired with a UCS, while a compound stimulus consisting of CS1 plus a second conditioned stimulus (CS2), is never so paired. According to Pavlov the discrimination between CS1 and the compound CS1 + CS2 is accomplished by CS2 acquiring powerful inhibitory properties. Thus, according to the inhibitory theory, hippocampectomised animals should not be capable of this discrimination. However, not only did Solomon find that hippocampals acquired the discrimination as well as normals, but he further showed that CS2 was a true conditioned inhibitor by a retardation-of-learning test (by pairing it alone with the UCS). Hippocampals and controls showed an equal retardation of the acquisition of the conditioned response.

2.2. THE HIPPOCAMPUS AND MEMORY

2.2.1. Statement Of The Hypothesis

The hypothesis that the hippocampus is involved in memory gained currency primarily as a result of data gathered from patients who underwent medial temporal lobe resections (with consequent hippocampal damage) in an attempt to alleviate, for example, uncontrollable epileptic fits. After the lesions these patients could recall events pre-surgery, but were amnesic for post-surgical events (Penfield & Milner 1958; Scoville & Milner 1957). Attempts to replicate this loss of recent memory by lesioning the hippocampus of animals were, however, generally unsuccessful (see Douglas 1967). Nevertheless, although these results rule out a general loss of memory, it can be argued that the tasks employed in the animal experiments are crude compared with those used in human work, and thus may be tapping a different type of memory. For example, lesioned humans, like their animal counterparts, have no difficulty in learning simple motor tasks (as measured by their performance). Their memory dificit appears on a verbal level when, in response to questioning, they deny all knowledge of the apparatus (see e.g. Weiskrantz 1978).

Reasoning such as this has led Olton and his colleagues (for a review see Olton et al. 1979) to develop a more sophisticated apparatus - the elevated radial-arm maze - for the testing of animals. From their results, they propose a distinction between working and reference memory. Reference memory procedures refer

to those aspects of the task that remain constant from trial to trial. In this sense reference memory resembles a more-or-less permanent memory store of general strategies or rules. Working memory procedures, on the other hand, refer to those aspects of the task which vary from trial to trial. In other words, working memory represents a temporary memory store for specific instances. For example, in a game of chess, the general rules and strategies (e.g. the way the knight moves) would be stored in reference memory, while the specific plan in a particular game (e.g. the square upon which one chooses to place the knight) would be stored in working memory.

Olton and co-workers suggest that the hippocampus subserves the function of working memory.

2.2.2. Evidence In Support Of The Theory

Using the radial-arm maze Olton et al. (1979) report that, when each arm of the maze is baited, normal rats quickly learn to avoid arms from which they have obtained food, and to enter only arms that they have not visited in that trial. Animals with lesions of the hippocampus or any of its major connections, on the other hand, show a deficit on this problem: They tend to re-enter arms that they have previously chosen. Olton et al. point out that the animals behave as though their reference memory is intact in that they appear to remember the maze, choose rapidly, and do not hesitate to eat the food when found. It is only their working memory which appears impaired since these animals seem unable to remember which arms they have already entered.

In a stronger test of the hypothesis, Olton & Papas (1979) used a 17-arm maze, of which eight arms were baited and nine never contained food. The task thus had clearly differentiable reference memory and working memory components. The reference memory procedure involved learning to avoid the nine unbaited arms (which were the same from trial to trial) and to only enter the eight baited arms. The working memory procedure involved remembering which of the eight baited arms had been entered on that trial. Animals were trained to criterion and then received lesions of the fimbria-fornix. Performance on both the reference and working memory components was initially impaired, but within about 30 trials (i.e. nearly the same as that required for initial acquisition), performance on the reference memory procedure returned to normal levels. Performance on the working memory procedure, on the other hand, remained at approximately chance levels. Olton et al. argue that because this dissociation between working and reference memory procedures is found using a within-subject, within-test design, explanations in terms of other variables are very unlikely.

Turning to the performance of hippocampectomised rats on alternation tasks, Olton et al. believe that their hypothesis can differentiate between studies which show a deficit and those which do not. Considering only studies with extensive damage to the hippocampus or its connections, Olton et al. categorize them according to whether they employ discrete test or sequential test situations. Discrete tests are defined as those having a long intervening period between each trial, and are invariably of the spontaneous alternation type. Since the first choice in this test varies from trial to trial, the animal can only alternate its

second choice by remembering its initial choice. Since this is a working memory procedure, the fact that hippocampals are almost always deficient on this task supports the hypothesis.

Sequential tests are defined as those having more than one test of alternation per trial, and, typically, each alternation is rewarded. Olton et al. believe that such tests have a major reference memory component since alternation can be achieved "by avoiding the choice made on any of the previous odd-numbered trials, repeating the choice made on any of the previous even-numbered trials, or learning a response pattern such as left-right-left-right-left." (Olton et al., p. 319). According to this view, then, it is not surprising that studies using such tasks (and others like it) often do not report deficits for their hippocampectomised animals (see Table 1 & p. 320 of Olton et al.).

Finally, Olton et al. submit that the data obtained from hippocampectomised rats trained either on CRF or DRL schedules provide support for their working-reference memory distinction. The severe impairment usually found on the DRL schedule, but not the CRF schedule, is in line with the hypothesis since the requirements of the CRF schedule are the same from session to session, and thus are mediated by reference memory. The DRL schedule, on the other hand, requires that the animal constantly shifts from making a response to withholding a response, and is therefore characterised by working memory procedures.

2.2.3. Criticisms Of The Theory

A major weakness of the hypothesis offered above is the lack of an adequate definition of the terms "reference memory" and "working memory". Olton et al. have opted for operational definitions, which do not easily lend themselves to descriptions or predictions beyond the task in question. As O'Keefe (1979) notes, some confusion is evident when Olton et al., in an attempt to more broadly characterise working memory procedures, say that the optimal strategy is to "forget the sample stimulus as soon as the trial is completed", and then immediately contradict themselves by pointing out that: "Working memory procedures have a major temporal component to them. The animal must remember not only which stimuli have been presented, but also when they were presented (on the present trial, or on some previous trial)."

Without a clearer conception of what working memory is, and how it operates, it is difficult to determine even whether the working - reference memory distinction is tenable. As Kimble (1979,p.335) points out "there is ambiguity for the subject as to which aspects of the environment are stable (and to be stored in a reference memory) and which are primarily of transitory value (and to be used in working memory)". Indeed, it seems doubtful whether working and reference memory are independent entities, since specific examples (from working memory) must be remembered in order to abstract the general rules for storage in reference memory. For example, in learning the radial-arm maze, reference memory must store the general strategy "remove food from one arm; do not re-enter that arm." It is difficult to imagine how such rules can be elaborated without ultimate reference to specific

instances, such as: "Entry to arm 3 produced reinforcement; re-entry to arm 3 did not." Since it is working memory which must register entry into specific arms of the maze, the conclusion seems inescapable that reference memory is dependent on working memory. If this analysis is generally true, then it follows that reference and working memory are not dissociable on the acquisition of a task, and renders many of Olton et al.'s arguments invalid.

These objections aside, the hypothesis does not fare well under direct test. For example, Douglas (1979) observes that rats with electrolytic lesions of, or chemical interference with, the hippocampal system perform very poorly (for both acquisition and retention) on linear mazes, even though these tasks are almost pure reference memory procedures. Furthermore, the explanations which Olton et al. advance to account for the difficulty which hippocampals have with DRL schedules, but not with sequential alternation tasks, are less than convincing. If animals can use reference memory to perform sequential alternation tasks, as Olton et al. claim, then they should be able to use a similar strategy with DRL schedules, since these are essentially sequential problems where the animal is required to alternate pressing a lever with a pause. Admittedly DRL schedules have a major temporal component to them, since the length of the pause is important. However, this is not the crucial variable either. Olton et al. miss the point that whether a lesioned animal can master the task or not, depends on its prior experience: An animal put straight onto a DRL schedule without previous CRF training does not show a deficit (Ellen & Aitken 1970; Ellen, Aitken & Walker 1973; Schmaltz & Isaacson 1966). The

hippocampectomised animal thus appears not to "suffer from a lack of working memory; rather, it would appear that a previously established reference memory keeps intruding ..." (Ellen 1979, p. 329).

Results from non-human primates are also at variance with the theory. As Olton et al. admit, delayed response and match-to-sample tasks are paradigmatic working memory procedures, and yet hippocampectomised monkeys perform well on these tasks (see Table 2 of Olton et al.).

Finally, data from human amnesics are difficult to interpret within the framework of the Olton et al. hypothesis. Such subjects have an intact immediate (short term) memory, in that they can, for example, repeat short strings of digits (see e.g. Squire & Cohen 1979; Weiskrantz 1978), and, although short term memory is not synonymous with working memory, it is clear that a short term memory capability would enable the subject to perform at least some working memory procedures.

2.3. THE HIPPOCAMPUS AS A COGNITIVE MAP

2.3.1. Statement Of The Hypothesis

Space can be represented in different ways. For example, there are the relative, egocentric spaces which use some part of the body as a reference point. Objects located relative to this

framework move as the organism moves through the environment. On the other hand, it is also possible to conceive of an absolute space, a map, which specifies the position of objects relative to an object external to the organism, and which are therefore independent of its movements. O'Keefe & Nadel (1978) believe that the brain represents space in both of these ways, and that they are stored in separate neural structures. The position of objects in relative space is represented by what they call the taxon system; the absolute, mapped space is represented by the locale system and is stored in the hippocampus. It follows directly, therefore, that damage to the hippocampus should result in a loss of place learning. It should also abolish exploration, since a function of the locale system is to initiate exploration to allow for the creation of maps. Other predictions from the theory derive from a comparison of the properties of the taxon and locale systems:

(i) Information storage in the taxon system is incremental, thus repeated exposure to a situation would lead to the formation of strong habits (i.e. the animal would display perseverative behaviour). This is in contrast to place learning which is all-or-none.

(ii) Information is stored in the taxon system on the basis of category inclusion; that is, two items with similar features would be stored in the same or neighbouring neural circuits. This means that considerable interference would result when the same cue is presented in different contexts. The locale system, on the other hand, stores items together with their spatial context, and thus avoids this type of confusion.

(iii) The effect of activation of taxon representations varies with the time after activation. This has the effect that behaviour based on the taxon system will be sensitive to the intertrial interval.

(iv) The locale system enables organisms to approach or avoid places that it cannot perceive, provided that they are both part of the same map. Bereft of this system, the animal is dependent on direct cues to guide approach/withdrawal responses.

2.3.2. Evidence In Support Of The Theory

The following resume relies to a large extent on O'Keefe & Nadel (1979). In keeping with the aims of this chapter, only evidence from hippocampal ablation studies is presented.

2.3.2.1. Exploration

As indicated previously, O'Keefe & Nadel deny that the excess activity shown by hippocampals in the open field is evidence of exploration. They see this merely as an example of hyperactivity, pointing out that hippocampectomised animals "do not systematically inspect the whole environment as does the normal rat. Instead, they adopt stereotyped behaviour patterns, typically running around the outside of the environment." (O'Keefe & Nadel 1979, p. 491). Furthermore, they do not show a decrease in this activity over time, as do normals, and so this cannot be exploration, since "given any meaningful definition of exploration

the notion of exploratory behaviour which does not decrement with repeated exposure to the explored situation is a logical contradiction" (O'Keefe & Nadel 1978, p. 256).

Finally, O'Keefe & Nadel submit that the evidence showing that hippocampals do not selectively investigate novel items in preference to familiar ones (Glickman et al. 1970) provides strong support for their position.

2.3.2.2. Extinction

The dramaticaly large extinction deficit seen in runway tasks is, according to O'Keefe & Nadel, due to the inability of hippocampals to act at a distance (see point (iv) above). Normals can associate a place, the goal box at the end of the runway, with non-reward and thus will not leave the start box. Hippocampals, on the other hand, can only appreciate this fact when they actually arrive at the goal box. Extinction for these animals will therefore be a slow decremental process, starting at the goal box and working backwards to cues at the start box.

2.3.2.3. Reversal learning

In line with the hypothesis, hippocampectomised animals perform very poorly on spatial reversal tasks. That this is not due to a general deficit in reversal per se is shown by the fact, alluded to earlier, that monkeys with damage to the hippocampus or fornix are as good, if not better, than normal at object reversals (Jones

& Mishkin 1972; Mahut 1971, 1972; Mahut & Zola 1973; Zola & Mahut 1973). The reason that lower animals with hippocampal damage are incapable of non-spatial reversals is because they switch to an inappropriate taxon hypothesis ("go to the left cue"). Monkeys, according to O'Keefe & Nadel, do not usually use such hypotheses.

2.3.2.4. Spontaneous alternation

The tendency to spontaneously alternate unrewarded trials in a T-maze illustrates an animal's drive to explore unfamiliar parts of the environment. The deficit which hippocampals display in this situation indicates an absence of this exploratory drive.

2.3.2.5. Maze learning

The possession of a spatial map would be of obvious benefit when learning mazes. The profound deficits displayed by hippocampals when faced with this task indicates a lack of such a map. Their much more limited taxon system does, however, allow them to solve maze problems when cues are placed at each choice point.

2.3.2.6. DRL performance

O'Keefe & Nadel (1979, p.492) explain the deficit that hippocampals have on this task as follows:

"Hippocampal rats have difficulty with DRL schedules when they are

pretrained on continuous reward, presumably since this strengthens the taxon-based lever press hypothesis and makes it more difficult to find an alternative taxon "collateral" behaviour. The provision of a cue signalling the end of the delay interval improves the lesioned rats' performance to the normal level."

2.3.2.7. Avoidance learning

(i) Passive avoidance. O'Keefe & Nadel draw a distinction between those passive avoidance tasks that involve avoidance of a place, and those that require avoidance of an object. They believe that hippocampals are only deficient on the former, and illustrate this with reference to a study by Nonneman & Isaacson (1973), where cats were shocked upon contact with a food dish. The hippocampectomised animals showed a deficit only in that they ran towards the place containing the food dish more quickly than normals. They did not touch the food more rapidly.

(ii) Two-way active avoidance. The superiority of hippocampals to normals on this task is easily explained by the cognitive map theory. Normal animals have difficulty with the shuttle-box problem since it requires them to return to a dangerous place. Hippocampals, on the other hand, lacking a concept of place, do not realise to where they are returning and thus do not experience any conflict.

2.3.2.8. Spatial delayed response and alternation

In the delayed response task one food well is baited in view of the animal, and then a delay is imposed before it is allowed to choose. Since this is a test of spatial memory, the fact that hippocampals are inadequate on this task (see O'Keefe & Nadel 1978, Table A25) provides support for the theory.

Spatial alternation, when tested in a T-maze, is a rewarded version of spontaneous alternation and, in line with the hypothesis, hippocampals also do poorly on this task (see O'Keefe & Nadel 1978, Table A25). When hippocampals are required to alternate lever-presses in an operant chamber, O'Keefe & Nadel suggest that the successful animals solve the task by adopting a strategy of positioning their body such that it reminds them to which manipulandum they must respond on the next trial.

2.3.2.9. Intertrial interval

O'Keefe & Nadel point out that some of the deficits that hippocampals display are peculiarly sensitive to the intertrial interval. Thus, the deficit found in extinction on a runway task, for example, is attenuated when massed trials are given (Jarrard & Isaacson 1965). They claim that this gives support to their contention that the taxon system is involved, since this system (by definition) is more dependent on the temporal aspects of its activation (see point (iii) p. 81).

2.3.2.10. The human amnesic syndrome

In order to account for the amnesia that humans display consequent to hippocampal damage, O'Keefe & Nadel have suggested that the human hippocampus, like the rest of the cerebrum, has undergone lateralisation. The right hippocampus still performs the same basic spatial mapping function found in lower animals, but the left hippocampus provides a semantic map for the organisation of the linguistic information that it receives from the left neocortex. Damage to the hippocampus would therefore remove both the semantic and spatial maps, but linguistic competence would not be totally lost since the corresponding taxon system would still be intact. However, since this system is inherently prone to interference (see point (ii) p. 80), retrieval under ambiguous conditions would be difficult and would result in an apparent amnesia.

2.3.3. Criticisms Of The Theory

One of the most unsatisfactory aspects of the cognitive map hypothesis is that it has not been worked out in sufficient detail to allow for clear deductions from the model. A case in point is the "exploration" issue. O'Keefe & Nadel have argued strongly that there cannot be any exploration without a cognitive map, but it could equally well be argued that, lacking such a map, the animal would explore frantically in a futile attempt to construct one. Such an explanation would certainly provide a better fit of the data (viz. the bizzare behaviour and long lasting activation induced by novel environments), and would obviate the necessity

for facile arguments such as that of the concept of hyper-exploration being a logical contradiction (see p. 81-82). However, O'Keefe & Nadel have been forced to choose the former position for other reasons (e.g. it allows them to explain the deficit in spontaneous alternation as being due to a lack of exploration), and this is just the point: The reasons for choosing a particular argument are dictated by the data, they are not logical consequences of the model. As a result the whole treatment is disturbingly post hoc.

Gray (1979) has raised the same objection with regard to O'Keefe & Nadel's assignment of properties to the taxon system. He points out that they develop a theory of what the hippocampus does, but, "for the most part, it is not this theory that is used to explain the effects of hippocampal lesions. Instead, these effects are attributed to the properties of parts of the brain that remain intact after such lesions, that is, to the so-called taxon system. But the properties attributed to this system are not derived from general principles: they consist of just those properties that are able to account for the known consequences of hippocampal lesions ... This retrospective, rather than predictive, character of the discussion of the lesion data robs it of almost all conviction." (Gray 1979, p. 505).

Another unacceptable feature is the equivocation displayed by O'Keefe & Nadel in some of their arguments. A good example of this is seen in the defence offered by O'Keefe, Nadel & Willner (1979) to a challenge by Solomon (1979). In this article, Solomon argues that the results of classical conditioning experiments with the rabbit nictitating membrane response are incompatible with not

only the inhibitory theory, but also the cognitive map theory. Specifically, he points out that latent inhibition and Kamin blocking effects are not seen in hippocampectomised rabbits, while Pavlovian conditioned inhibition is still intact. Since the only thing that varies in these three paradigms is the relationship between the CS and the UCS, it seems reasonable to conclude that spatial factors play little part in determining the deficit found in the first two, but not the last task.

In their reply O'Keefe et al. agree that spatial factors play little role in the conditioned inhibition procedure employed by Solomon, and therefore that hippocampal lesions should have no effect. They are, however, unable to supply a satisfactory account of why a very similar procedure (that of Kamin blocking) does produce a deficit in hippocampals, and on these grounds alone it is possible to reject their contention that the cognitive map theory is not in need of revision. However, it is their explanation of the way in which hippocampal lesions affect latent inhibiton to which I would like to direct attention.

O'Keefe et al. point out that background cues (which they equate with the concept of "place") play an important role in classical conditioning. In particular, background cues, or environmental context, determine the novelty of a stimulus. For example, a stimulus that is no longer novel in one context, becomes novel when placed in a different context. This analysis has relevance for latent inhibition since novelty is a critical factor in its production. "In latent inhibition (LI) ... experience with a stimulus and hence a reduction in its novelty retards its subsequent associability with a US." (O'Keefe et al., p. 1283).

Thus, they argue, "These data suggest that the hippocampal mapping system is involved in LI: By defining the context of occurrence, the map makes novelty possible." (p 1283), and again "Our theory ... predicts an effect of hippocampal lesions on LI insofar as it is dependent on environmental context ..." (p. 1284).

While few would disagree with O'Keefe et al. that background cues are an important consideration in classical conditioning (Pavlov dealt with this point in some detail when discussing the concept of external inhibiton), there are some aspects of their explanation which deserve comment:

(i) O'Keefe et al. are uncharacteristically coy in their discussion. They are careful to say only that the hippocampus is "involved" in latent inhibition, and that hippocampal lesions will have an "effect" on latent inhibition: They do not specify the manner in which hippocampectomy might produce its effect, nor whether an increase or decrease is expected. Fortunately it is a simple matter to rectify this oversight. The logical extension of their argument is as follows: Since the hippocampus makes novelty possible, removal of the hippocampus would render all stimuli "non-novel". In other words, the hippocampectomised animal would experience novel stimuli as being no different from (as habituated as) pre-exposed stimuli of similar stimulus strength. [It is important to note here, that O'Keefe et al. are constrained from arguing the opposite, that is, that removal of the hippocampus would make all stimuli equally novel (which is the position maintained by the inhibitory theory), because this would entail abandoning their stand that hippocampals do not experience novelty and therefore do not explore.] From the above it can be deduced

that the cognitive map theory would predict that hippocampals would condition at the same rate to a stimulus regardless of whether it was novel or pre-exposed (which is true). However, it can be further deduced that this rate would be similar to that of intact animals when conditioned to a pre-exposed stimulus, and retarded relative to controls conditioned to a novel stimulus.

Since these predictions are the opposite to what is actually observed, it may provide an explanation for the reticence displayed by O'Keefe et al.

(ii) The concept of "place" can be understood in at least two ways: As a specific area uniquely defined by the stimuli contained within it, or as a specific area defined by its topographic relationships with other areas (as in a map). It is around this latter usage of the term that O'Keefe & Nadel (1978) developed their theory. However, in their attempt to deal with the uncomfortable facts derived from classical conditioning experiments, they invoke the former definition. This marks a radical departure from their original position, with quite different and much more profound consequences for behaviour. In the cognitive map theory as originally formulated, a hippocampectomised animal was quite capable of recognising a place from its distinctive grouping of stimuli, by means of the egocentric spatial functions of the taxon system. What it could not do was to relate that place to other places in a coherent spatial framework. The use of the new definition of place implies that the hippocampus is responsible for providing a spatial framework for stimuli within a place. In other words, the hippocampus is now being proposed as the substrate for spatial

perception. This is a far cry from mapping, and is quite untenable.

It is this type of glaring inconsistency that makes it seem almost trivial to point out the many other contradictions that keep cropping up, and invites reactions like that of the swingeing attack of Greene (1979). In that paper one of the aspects that is highlighted is the logical inconsistency of O'Keefe & Nadel's account of the deficits displayed by hippocampals in extinction and passive avoidance. It will be recalled that O'Keefe & Nadel claim that these deficits arise because of the inability of hippocampals to act at a distance. Thus, hippocampals continue to run down the alleyway because they cannot associate a distant place (the goal box) with aversive consequences. Yet these very same animals are able to associate this distant place with positive consequences, since they learn to approach the goal box at least as rapidly as controls.

Their discussion of the passive avoidance literature exposes yet another inconsistency. In their eagerness to discredit the inhibitory theory they are quick to point out that hippocampals are not usually deficient on step-down or step-through tasks. What O'Keefe & Nadel fail to do is acknowledge that this represents somewhat of a problem for their own theory as well. This is particularly so for the step-through paradigm. In this task the animal is typically placed in a large, open box with a door leading to a smaller compartment. When the animal enters this compartment, it is shocked, and the latency for the animal to re-enter is a measure of passive avoidance. The fact that hippocampals are normal on this task shows that they are capable

of place learning. Furthermore, it renders O'Keefe & Nadel's explanantion of the superior performance of hippocampals in the shuttle box (see p. 84) untenable, since the step-through task is formally equivalent to the shuttle box in that in both cases the animal is faced with a dangerous place.

Finally, one of the few experiments designed to rigorously test the propostion that the hippocampus has a purely spatial function has found the theory wanting. Olton et al. (1979) describe an experiment using a four-arm maze with interchangeable arms. Each arm had its own distinctive set of stimuli, and the problem could only be solved by the use of these intramaze cues (extramaze cues having been eliminated). At the beginning of each test a pellet of food was placed in each arm and in order to maximise reward, the rat was required never to re-enter arms from which it had already obtained food. To prevent the use of a spatial map the animal was confined to the centre after each choice, and the arms were interchanged. Since this represents a pure taxon-based problem, hippocampals should be unimpaired. In fact, animals which received fimbria-fornix lesions after being trained to criterion performed at chance levels throughout post-operative testing.

2.4. GENERAL COMMENT

Of the three theories it is clear that the working memory theory is the weakest, and will not be further discussed. The inhibitory theory, on the other hand, can accommodate a great deal of the

data and, unlike the cognitive map theory, is internally consistent. Nevertheless, serious criticisms have been made of the theory (for example, that it is only spatial reversal learning that is deficient in hippocampectomised primates) and it is the cognitive map theory, flawed as it is, which is best able to account for these results. In addition, the cognitive map theory can also claim important support from studies of hippocampal unit activity. This, and other evidence, will be critically examined in the following chapter in an attempt to more firmly establish which of these two theories warrants further consideration.

3 PHYSIOLOGY OF THE HIPPOCAMPUS AND RELATED STRUCTURES

It is not the intention of this chapter to provide a systematic account of the physiology of the hippocampus. Only aspects that are deemed particularly germane to the task of making a decision between the inhibitory and cognitive map theories will be considered. These are:

1. The role of the hippocampal projections to the nucleus accumbens. 2. The effect of endocrines on the hippocampus. 3. Hippocampal unit activity and behaviour.

3.1. THE HIPPOCAMPUS AND THE NUCLEUS ACCUMBENS

Predictions of the inhibitory theory as regards the physiological status of the projections of the hippocampal region are straightforward: The projections should exert an inhibitory effect on target structures, or, alternatively, if the projections are excitatory then the target structures themselves should exercise an inhibitory control over behaviour.

The predictions of the cognitive map theory are not so clearly specified, except in one regard: Part of the output from the hippocampal region should excite "motor circuits that programme exploratory motor patterns such as myostatial sniffing" (O'Keefe & Nadel 1979, p. 490). Since this is one of the few instances where the two theories generate clearly stated opposing predictions (i.e. inhibition as opposed to excitation of exploratory motor

circuits), considerable importance attaches to the outcome.

We can begin by noting that the hippocampus exerts a predominantly excitatory effect on all areas that have been tested so far. These include the anterior thalamus (Parmeggiani, Lenzi & Azzaroni 1974), the lateral septum (e.g. Chartock 1979), the ventromedial hypothalamus (MacLean 1975), the mammillary bodies (MacLean 1975; Kostopoulos & Phillis 1977) and the nucleus accumbens (DeFrance, Marchand, Sikes & Chronister 1980; Poletti & Sujatanond 1980). Many of these areas do, in fact, appear to have inhibitory effects on behaviour. For example, there is considerable evidence that the lateral septum is inhibitory. Stimulation of this area (but not the medial septum) inhibits aggressive behaviour (Brayley & Albert 1977; Siegal & Skog 1970), eliminates motor and vocal responses to painful stimuli (Abbott & Melzack 1978; Lico, Hoffmann & Covian 1974), inhibits the lordotic response (Moss, Paloutzian & Law 1974; Zasorin, Malsbury & Pfaff 1975), and suppresses drinking (Wishart & Mogenson 1970. For further evidence see reviews by Cormier 1981 and Numan 1978). Similarly, the ventromedial hypothalamus, which receives input from the ventral subiculum via the medial cortico-hypothalamic tract, appears to excercise inhibitory control over food ingestion, since lesions of this area produce the well-known hyperphagic syndrome (Hetherington & Ranson 1942). While the effect of the mammillary bodies on behaviour is not, as yet, firmly established, it is known that this area exerts an inhibitory effect on the anterior thalamus (Krieckhaus 1970, cited in Davis & Kent 1979). The function of the mammillary bodies, and the significance of the fact that this major hippocampal projection area inhibits another major projection area of the hippocampus (i.e. the anterior

thalamus) will be discussed in Chapter 5.

In view of the excitatory hippocampal connections with these inhibitory structures it is not surprising that stimulation of the hippocampus has been reported to result in gross inhibitory effects (Bland & Vanderwolf 1972; Vanegas & Flynn 1968; Votaw 1960). Indeed, it appears that the inhibitory effect of other structures may be mediated, at least in part, via the hippocampus. Jacobs, Trimbach, Eubanks & Trulson (1975) concluded that serotonin in general, and the median raphe nucleus in particular, exercise an inhibitory effect on behaviour via the hippocampus. This was inferred from the fact that administration of p-chlorophenylalanine (a serotonin depleting drug) or lesions of the median raphe nucleus (procedures which normally produce a marked hyperactivity in rats) do not produce an increase in the activity of hippocampectomised animals. As they further showed (via the administration of amphetamine) this could not be explained as being due to a "ceiling" effect.

Taken together, the above results tend to support the inhibitory theory, rather than the cognitive map theory. An even more decisive picture, however, emerges from an examination of recent evidence concerning the role of the nucleus accumbens in the control of behaviour.

3.1.1. The Nucleus Accumbens Septi (NAS)

Until very recently virtually nothing was known of the anatomy and physiology of this area. Uncertainty existed even as to whether

it should be classified as belonging to the septum or the striatum (Swanson & Cowan 1975). Over the last few years it has been firmly established that the NAS should be regarded as part of the striatal complex (the "ventral striatum" of Heimer & Wilson 1975) and that it exerts an inhibitory control over ambulation.

In the discussion that follows it should be understood that, although reference will be made almost exclusively to the NAS, manipulations to this area usually involve the rest of the ventral striatum and, as a result, imputations as to the role of the NAS in behaviour should properly refer to the whole of the ventral striatum. In this regard it is important to note that the other major component of the ventral striatum, the olfactory tubercle, shares important common connections with the NAS. In particular, the olfactory tubercle receives afferents from the hippocampal formation and is efferent to the ventral pallidum (Numan & Winans 1980b). Furthermore, it is clearly involved in a similar way to the NAS in the control of ambulation (e.g. see Pijnenburg, Honig, van der Heyden & van Rossum 1976).

3.1.1.1. Connections of the NAS

(i) Efferents. The projections of the NAS appear to be fairly restricted. There is general agreement that the substantia nigra and the area of the ventral globus pallidus (the "ventral pallidum" of Heimer & Wilson 1975) receive afferents (Conrad & Pfaff 1976; Newman & Winans 1980a; Swanson & Cowan 1975). It also seems likely that the NAS projects to the ventral tegmental area (Nauta, Smith, Faull & Domesick 1978; Phillipson 1979), and

perhaps the lateral hypothalamus (Swanson & Cowan 1975).

These projections are believed to be mainly GABAergic (Jones & Mogenson 1980a).

(ii) Afferents. Besides input from the hippocampal region, the NAS receives afferents from the following areas:

(a) Cortex. The posterior agranular insular, olfactory and perirhinal cortices (Newman & Winans 1980a) and the prelimbic, anterior cingulate and rostral sulcal cortices (Beckstead 1979).

(b) Amygdala. The basolateral and basomedial amygolaloid nuclei (Krettek & Price 1978).

(c) Thalamus. Parataenial, paraventricular and reuniens nuclei (Herkenham 1978; Numan & Winans 1980a; Swanson & Cowan 1975).

(d) Brainstem. The dorsal raphe (Numan & Winans 1980a) and the entire dopaminergic ventral midbrain, that is, cell groups A8, A9 (substantia nigra) and A10 (ventral tegmental area)(Fallon & Moore 1978). The dopaminergic input has an inhibitory effect on the NAS, while the serotonergic projection from the raphe is excitatory (e.g. see Redgrave 1978).

3.1.1.2. Ambulation and the NAS

As indicated above, the NAS has an inhibitory effect on ambulation. It is thought to exert this control by inhibiting a

"locomotor centre" situated in the ventral pallidum. Some of the reasons for this belief are given below:

(i) Electrolytic lesions of the NAS produce a dramatic increase in locomotor activity (Lorens, Sorenson & Harvey 1970; Pycock & Horton 1976; Teitelbaum, Giammatteo & Mickley 1979).

(ii) Removal of dopamine (DA) afferents by direct injection of 6-hydroxydopamine (6-OHDA) into the NAS produces a significant reduction in locomotion (Iversen & Koob 1977; Kelly, Seviour & Iversen 1975; Koob, Riley, Smith & Robbins 1978; Pycock & Horton 1976), presumably as a result of the disinhibition of the NAS leading to increased inhibition of the ventral pallidum.

(iii) Electrolytic (Teitelbaum et al. 1979) and 6-OHDA (Kelly et al. 1975; Koob et al. 1978) lesions of, and injection of haloperidol (Pijnenburg, Honig & van Rossum 1976; Teitelbaum et al. 1979) and spiroperidol (Teitelbaum et al. 1979) into the NAS, block amphetamine-induced hyperactivity. The critical area appears to be the posterior NAS, since electrolytic lesions here, but not of the anterior NAS, block the amphetamine response (Teitelbaum et al. 1979; Wirtshafter, Asin & Kent 1978).

(iv) Amphetamine (Pijnenburg et al. 1976) and DA (Anden & Jackson 1975; Jackson, Anden & Dahlstrom 1975; Jones & Mogenson 1980b) applied directly to the NAS inhibit it and produce an increase in ambulatory activity.

(v) While the above evidence arises from manipulations aimed directly at the NAS, interference at other points along the

ventral tegmental-accumbal-pallidal pathway provide additional support. Mogenson, Wu & Manchanda (1979) found that injection of picrotoxin into the ventral tegmental area (VTA) produced an increase in ambulation. This is presumed to result from the fact that picrotoxin, being a GABA antagonist, disinhibits the VTA. The consequent increase in the firing of the VTA DAergic neurons inhibits the NAS, thus releasing the ventral pallidum from inhibitory control and thereby producing an increase in locomotion. Some support for this interpretation is gained from the finding by Mogenson et al. that the increased ambulatory activity (resulting from the picrotoxin injected into the VTA) is attenuated by pretreating the NAS with spiroperidol (a DA antagonist).

(vi) Moving further along to the accumbal-pallidal projection, Jones & Mogenson (1980b) note that both electrolytic lesions, and manipulations which increase the GABA content of the ventral pallidum produce a decrease in locomotor activity. They then show that reducing the GABA content by injections of picrotoxin into the ventral pallidum produces an increase in ambulation. Furthermore, GABA injected into the ventral pallidum was found to attenuate the increase in ambulation produced by DA injected into the NAS.

3.1.1.3. Exploration and the NAS

The above account provides compelling evidence that the NAS is involved in the inhibition of ambulatory activity. Moreover, since ambulation is an essential component of exploration, several

investigators have suggested that the underlying function of the NAS may be to inhibit exploratory activity in general (e.g. Jones & Mogenson 1980b; Kelly et al. 1975; Koob et al. 1978). In support of this contention it may be mentioned that the hyperactivity seen after electrolytic lesions of the NAS appears to be novelty dependent, since ambulation levels return to normal after a period of habituation in the test chamber (Teitelbaum et al. 1979). Of even greater significance is the observation of Kelly et al. (1975) that 6-OHDA lesions of the NAS depress not only locomotor activity but also sniffing, a second major component of exploration. Conversely, they found that their 6-OHDA lesioned animals responded to the administration of apomorphine (which inhibits the NAS by stimulating the now supersensitve post-synaptic DA receptors) with a dramatic increase of ambulation associated with persistent sniffing. Finally, Fink & Smith (1979, 1980) have convincingly shown that rats with 6-OHDA injections into the anterolateral hypothalamus (which inter alia denude the ventral striatum of DA terminals) have a specific deficit in the exploration of novel spaces and objects. Although it appears from their material that the NAS is not solely responsible for these deficits, it is nevertheless clear that it plays an important role.

3.1.2. Comment

Given that the NAS is specifically concerned with the inhibition of locomotor activity and sniffing, and possibly with the inhibition of exploratory activity in general, it follows that the hippocampal region, by virtue of its excitatory projection to the

NAS, also plays a role in the inhibition of these activities. Since the cognitive map theory demands that the hippocampus should excite such activities, this represents a direct contradiction of that hypothesis, while at the same time lending powerful support to the inhibitory theory.

3.2. HORMONAL INFLUENCES ON THE HIPPOCAMPUS

Several hormones are known to interact with the hippocampus. These include thyrotropin releasing hormone (Ogawa, Yamawaki, Kuroda, Otuji, Itoga & Kito 1981), adrenocorticotrophic hormone (ACTH), the adrenal steroid corticosterone and the gonadal steroids estrogen and testosterone (see McEwen, Gerlach & Micco 1975). Since the purpose of this section is merely to illustrate how the effects of these hormones on the hippocampus can be used to decide the relative merits of the inhibitory and cognitive map theories, only a brief discussion of the effects of corticosterone and the gonadal steroids will be presented.

3.2.1. Corticosterone

Corticosterone is bound by cells of the hippocampus to a greater extent than cells in any other region of the brain (McEwen et al. 1975), and systemic administration has been shown to have a marked inhibitory effect on the neurons of the dorsal hippocampus (Pfaff, Silva & Weiss 1971), as does the direct application of dexamethasone (Michal 1974). This effect has led to speculation that high levels of circulating corticosterone might produce

behavioural effects similar to hippocampectomy and, conversely, that adrenalectomy, by lowering corticosterone levels, should result in the disinhibition of the hippocampus, thus allowing superior performance on tasks in which hippocampals normally show a deficit (see e.g. Devenport 1978). Recent research has partially supported this view. Micco, McEwen & Shein (1979) showed that adrenalectomised rats were superior to normal on extinction of a runway task, and that replacement of corticosterone abolished this effect. Adrenalectomy does not produce opposite effects to hippocampectomy on all tasks, however. Micco & McEwen (1980) were able to replicate the results of the Micco et al. (1979) study on the runway task, but found no effect of adrenalectomy on spontaneous alternation and exploration. As Micco & McEwen point out, however, this failure should not be too surprising in view of the complex interaction between corticosterone and ACTH levels (which have opposite effects on the hippocampus) on the one hand, and task type and behavioural arousal levels on the other. Another confounding factor could be that ACTH may have opposite effects on the hippocampus depending on whether it is in low or high concentration (see Sands & Wright 1979).

3.2.2. Gonadal Steroids

Although the hippocampus does not bind estrogen and testosterone to the same extent as corticosterone, it is nevertheless apparent that gonadal hormones do have an effect on cells in this area (McEwen & Pfaff 1970; McEwen, Pfaff & Zigmone 1970; Pfaff & Keiner 1973). One possible reason for the somewhat equivocal results of

these earlier studies is that recent work using more refined techniques has shown that uptake is mainly restricted to the ventral dentate granule cells (Morrell, Ballin & Pfaff 1977; Rees, Switz & Michael 1980).

One of the problems with trying to uncover direct effects of the gonadal steroids on the hippocampus is that these hormones are thought to act genomically, and thus would only manifest their effects after a delay of some hours (see McEwen et al. 1975). As a result, many of the standard investigative techniques are inappropriate. Thus, negative results from iontophoretic application of estrogen (Yamada & Nishida 1978) and testosterone (Yamada 1979) to hippocampal units, or to the incubation medium surrounding hippocampal slices (Teyler, Vardaris, Lewis & Rawitch 1980) are to be expected (although it must be admitted that the finding of this latter study that testosterone affects the activity of hippocampal slices from <u>female</u> rats, and that estrogen affects slices from <u>male</u> rats is difficult to explain).

More indirect measures, however, indicate that estrogen acts to inhibit the hippocampus. Terasawa & Timiras (1968, cited by McGowan-Sass & Timiras 1975) found that the threshold for electrically induced seizures of the dorsal hippocampus of rats was increased by some 250% during periods in the estrous cycle when estrogen and progesterone are at high levels. Ovariectomy abolished this effect, and injection of either estrogen or progesterone once again raised thresholds 7-12 hours after administration. This inhibitory action on the hippocampus dovetails well with the known locomotor-facilitatory effect of centrally (Stern & Jankowiak 1972; Wade & Zucker 1970) or

peripherally (Young & Fish 1945) applied estrogen.

The effects of testosterone on the hippocampus are less well established, but there are indications that it, too, may be inhibitory. For example, it has now been established that administration of testosterone to male animals produces "persistence" - a syndrome characterised by attentional rigidity and perseveration (see Thor 1980). The clear parallels with the effects produced by hippocampectomy are underlined by the finding by Thompson & Wright (1979) that testosterone given to male rats disrupts reversal learning, and that injection of cyproterone acetate (an androgen inhibitor) actually improves such learning relative to normal male controls. Again, the well known facilitation of locomotion produced by testosterone reinforces the impression that these effects may be mediated, at least partially by inhibition of the hippocampus.

3.2.3. Comment

It is clear that much work remains to be done before a comprehensive description of the effects of hormones on the hippocampus can be given. However, the point of interest here is not the adequacy of the above account, but the fact that there are hormonal effects on the hippocampus at all. Since hormones have a generalised effect on all cells that are sensitive to them, this presents particular problems for the cognitive map theory (which demands that specific neurons code for particular places). The non-specific, mass-action effect of hormones (be they excitatory or inhibitory) would obliterate the information content of any

such map, rendering the mapping system unacceptably dependent on the hormonal status of the animal.

The inhibitory theory, on the other hand, suffers no such problem. Since the hippocampal neurons are proposed to have a common function, mass-action effects are not only acceptable, but physiologically appropriate. Furthermore, the inhibitory effects of the hormones discussed above are exactly what would be expected from the inhibitory theory. For example, corticosterone is secreted under conditions of frustrative non-reward (Micco et al. 1979). The consequent inhibition of the hippocampus would result in an increase in exploration and the disinhibition of extinguished response tendencies, which is likely to lead to the discovery of other reward contingencies.

The effects of the gonadal steroids can be similarly explained. High levels of these hormones, by inhibiting the hippocampus, would promote ambulation (and exploration in general) with a resultant increase in the probability of finding a mate.

3.3. BEHAVIOURAL CORRELATES OF HIPPOCAMPAL UNIT ACTIVITY

Hippocampal unit activity has been examined under a variety of circumstances. These range from the highly unstructured, so-called neuroethological approach (O'Keefe & Nadel 1978), to the more restricted conditions pertaining in the operant and classical conditioning paradigms. These latter conditions are seen as belonging to the neuropsychological approach, and O'Keefe & Nadel (1978, pp. 190-194) have launched a strong attack on this

methodology. Their main objection appears to be that the neuropsychological approach takes too narrow a view of the environment and behaviour of the organism, which they feel is likely to either produce spurious correlations, or miss obvious ones altogether. The drawbacks of the neuropsychological approach "result from its premature application. When we first venture into the unknown, we need not the incisive beam of the proud penetrating laser, but the gentle diffuse illumination of the humble torch... The neuropsychological approach is too myopic..." (O'Keefe & Nadel 1978, p. 194).

The "gentle illumination" is, of course, provided by the neuroethological approach. This differs from the neuropsychological one in that "it seeks to study the activity of single units in as naturalistic a setting as possible..." and that "it seeks not to ask a preordained set of questions about a population of units, but instead treats each unit as an individual and attempts to describe the full range of its behaviour in as many different situations as possible.". The investigator "must temporarily purge his mind of as many preconceived notions about the function of that particular unit as possible." He must maintain a "Popperian scepticism". (O'Keefe & Nadel 1978, pp. 194-195).

O'Keefe & Nadel may be right in claiming that workers using the neuropsychological approach have tended to concentrate on certain issues at the expense of others, but to suggest that the alternative is to adopt the neuroethological strategy of "purging one's mind of preconceived notions" is, at best, naive. They are merely resurrecting the old Inductive-Deductive debate, a question

that has long since been firmly decided by metatheoreticians (especially Popper 1959,1963) in favour of the hypothetico-deductive model. Indeed, O'Keefe & Nadel are not shy about hypothesis testing : they clearly start out with the preconceived notion that hippocampal units are related to spatial variables. As Bures (1979) notes, it almost seems as though they are using the neuroethological approach as an excuse for less-than-rigorous methodology.

Nevertheless, this is the framework within which O'Keefe & Nadel have chosen to work, and the results of their investigations will be reported under that heading. Later sections will deal with unit recordings obtained during classical conditioning, and those obtained in operant situations.

3.3.1. "Neuroethological" Unit Studies

Besides O'Keefe & Nadel, the neuroethological strategy has been adopted by Ranck and co-workers (reviewed in Ranck 1975). The observations of this group will be considered first.

3.3.1.1. Ranck's results

Ranck distinguishes two general categories of neuron in the hippocampus: The complex spike cell and the theta cell. The main defining characteristics of the theta cells are:

(i) They increase their rate of firing if and only if the theta

rhythm is present in the hippocampal EEG.

(ii) They have a rapid rate of fire (almost invariably greater than 8 per second).

(iii) They have a short-duration extracellularly recorded spike (0.15-0.25 mSec.).

The theta cells constitute approximately 6% of the total number of cells in Ammon's horn and are almost certainly mainly interneurons, probably inhibitory basket cells (Fox & Ranck 1981, see note added in proof). Their most obvious relation to behaviour is that they increase their rate of firing during voluntary movement (ambulation, sniffing and general exploration). Conversely, they often slow down or stop firing when small amplitude irregular electrographic activity (SIA) is seen in the hippocampus, in conjunction with a cessation of motor activity (freezing).

The complex spike cells appear to be pyramidal cells. They have a long-duration spike (0.3-0.5 mSec.) and sometimes fire in brief, high-frequency bursts (the complex spike). If the complex spike is counted as one action potential then they usually fire very slowly (less than once per second) although they can go as high as 40 spikes per second for brief periods. The complex spike cells are very heterogeneous with regard to their relationship to behaviour. In contrast to the theta cells, each complex spike cell is correlated with a different type of behaviour. There is one generalisation that Ranck is able to make, however, and that is that complex spike cells tend to fire most rapidly during

behavioural inactivity and slow wave sleep, and slowest during quiet arousal and paradoxical sleep. Their activity therefore bears an inverse relationship to that of the theta cells, which fire slowly during slow wave sleep and behavioural inactivity, and rapidly during paradoxical sleep and behavioural arousal. This inverse relationship accords well with the suggestion that theta cells are inhibitory to the complex spike cells.

During the awake, active state three major categories of behaviour-related complex spike cells are seen:

(i) Approach-consummate cells. Cells in this group tend to fire when the rat is enaged in some type of consummatory activity, or in well-learned behaviour associated with consummation. Some cells fire only after consummation has been in progress for some time. Distraction during consummation often, but not always, causes the cell to stop firing. They could be related to motivation since several "drinking" and "eating" cells were found.

(ii) Approach-consummate-mismatch cells. These cells are correlated to behaviour in an identical way to approach-consummate cells, but in addition fire at their most rapid rate when an expectation as to the presence of reward is disconfirmed.

(iii) Appetitive cells. These are defined as cells which fire rapidly during some orienting or approach behaviours, but not during consummation.

These three cell types are unevenly distributed: Approach-consummate cells are found mainly in CA3, approach-

consummate-mismatch cells are found almost exclusively in CA1, and the majority of appetitive cells are seen in the dentate gyrus.

Ranck also recorded from cells in other parts of the hippocampal formation. An interesting observation was that most of the cells in the entorhinal cortex, parasubiculum and presubiculum have very specific behavioural correlates. He called these cells "specific orient cells" because they usually fire for 1-3 seconds when the animal orients to, or approaches a specific object.

3.3.1.2. O'Keefe and Nadel's results

On the basis of observations of unit activity in the freely-moving rat, O'Keefe & Nadel, like Ranck, divide hippocampal cells into two general classes: Place units and displace units. Displace units are related to the general behaviour of the animal, while place units depend on the location of the animal in the environment. However, location alone is not necessarily sufficient to activate place units: They are behaviour or stimulus dependent as well. Included in the category of place units is a sub-class of "misplace units" which fire maximally when expectations (e.g. of reward) are disconfirmed, or in the presence of novel objects. O'Keefe & Nadel point out that place units correspond with Ranck's complex spike cells, and that displace units are identical to Ranck's theta cells. Misplace units appear to be the same as approach-consummate-mismatch cells.

Although O'Keefe & Nadel claim to have identified place cells in the hippocampus from their neuroethological observations, they

admit that the evidence is not persuasive (O'Keefe & Nadel 1978, p. 205). In order to establish this identification more convincingly, O'Keefe & Conway (1978) have opted for a more neuropsychological strategy. This experiment will be reported in some detail since it is crucial to the cognitive map theory. It involved the rather ingenious arrangement of a light-emitting diode placed on the head of the animal, connected such that spikes from the cell under observation would produce brief flashes of light. A camera placed above the apparatus recorded the light-flashes relative to the animal's location.

The four rats used in the experiment were trained in a T-maze surrounded by curtains. The maze was rotated on different trials, but the position of the goal arm and non-goal arm were constant relative to four distinctive stimuli placed within the curtained environment. The animals were required to learn the position of the baited goal arm relative to the four cues, to a criterion of 9 out of 10 choices correct, and then were given additional training to visit the non-baited arm prior to returning to the start arm, where they were once again fed.

Recording, from the pyramidal cell layer in the CA1 region of the dorsal hippocampus, began once the animal had learned the task. Units were tested to see if they had a place field in an arm (defined as a greater number of spikes in that arm compared with the rest of the maze), as well as on the holding platform outside the curtained area (where the rats were kept between tests on the maze). About half the units were deemed to have place fields in both areas. Of the 25 cells that had place fields on the maze, 20 involved either the start or goal arm.

12 units were then selected for further study. This involved recording unit activity during four ground trials in which the maze stayed constant relative to the cues, followed by various test trials including: Rotating the start arm 180 degrees relative to the cross bar of the T and the spatial cues; removing all or some of the cues; removing the food. Following testing (which took place over a period of some hours) the microelectrode was withdrawn from the pyramidal cell layer. It was reinserted prior to the next recording session when a (presumably) new unit was tested.

Results inter alia showed that:

(1) Under constant environmental conditions the units showed preferential activity in certain parts of the maze. The preferred area differed from cell to cell, but there was a marked tendency for this area to include either the start or goal arms.

(ii) Rotation of the start arm prior to a test produced an almost total cessation of activity of units with place fields in that arm.

(iii) Removal of all the spatial cues resulted in most of the units (6 out of 8) losing their predeliction for firing in certain areas of the maze. This was reflected in an increase in firing in other areas of the maze, or a decrease in firing in the maze as a whole.

(iv) Removal of some of the spatial cues affected some units, but not others.

(v) Removal of the food in the goal arm affected all tested units which had a place field in this arm. One decreased firing, while three increased their activity. Another four units which did not preferentially fire in the goal arm were unaffected.

O'Keefe & Conway (p. 573) conclude from these results that there are units in the dorsal hippocampus that "signal the animal's position in an environment".

3.3.2. Unit Acitivity During Classical Conditioning

This section will consider only the work of the Thompson group (e.g. Berger, Laham & Thompson 1980; Berger & Thompson 1978a, b; Hoeler & Thompson 1980). Extensive work emanating from the laboratories of Olds (e.g. Hirano, Best & Olds 1970; Segal, Disterhoff & Olds 1972) and Vinogradova (reviewed in Vinogradova 1975) will not be reported since their results have been questioned on the grounds of not having controlled for the potentially confounding effects of the different states of arousal of their animals (Best & Best 1976; Mays & Best 1975). In any event, these earlier studies did not distinguish between pyramidal cell and interneuronal activity, which makes their results difficult to interpret.

Thompson and colleagues (see Berger et al. 1980 for references) have investigated the multiple unit activity of the dorsal hippocampus during the elaboration of a classically conditioned nictitating membrane response (NMR) in the rabbit (although Patterson, Berger & Thompson 1979 have extended their work to

include cats). Their experimental protocol usually involves the presentation of a tone (CS) for 350 mSec. Coincident with the last 100 mSec an airpuff (UCS) is directed at the cornea. Data are collected only for 750 mSec, starting 250 mSec before tone onset.

Their results show that hippocampal neural activity evidences a large increase during training; that this increase occurs prior to behavioural conditioning (in fact in the first few trials); that it occurs first in the UCS period and later, as behavioural conditioning occurs, spreads into the CS period; appears to model the amplitude-time course of the NMR, but nevertheless leads the NMR by 40-60mSec (in the 250 mSec CS-UCS condition); and, finally, that an increase in unit activity does not occur to CS or UCS if they have been consistently unpaired, or even to CS-UCS pairings where the CS-UCS interval is too short (50 mSec) for behavioural conditioning to occur. Most importantly, Berger & Thompson (1978b) have been able to identify pyramidal cells as being the neuronal substrate underlying these events: Most pyramidal cells showed positive correlation ratios with the NMR, whereas almost all putative interneurons were either unaffected or inhibited following tone onset. They point out that their results imply that at least 75% of pyramidal cells participate in the hippocampal response, and further speculate that the processes underlying the learning-dependent increase in unit activity may be similar to those underlying long-term synaptic potentiation seen in the hippocampus as a result of brief, high-frequency electrical stimulation (see Berger et al. 1980 for further discussion of this point, and see Baudry & Lynch 1980 for an hypothesis regarding the cellular mechanisms responsible for long-term

potentiation).

The Thompson group has also made an analysis of some of the inputs and outputs of the hippocampal formation during conditioning.

(i) Inputs. Berger & Thompson (1978a) found that medial septal units showed only a phasic excitation to tone and airpuff onset, which decremented with repeated stimulation. The response was quite unaffected by whether learning took place or not (i.e. whether the CS and UCS were paired or not). Clark, Berger & Thompson (1978, cited in Berger et al. 1980), on the other hand, found that unit activity in layers II and III of the entorhinal cortex showed a similar pattern to that seen in the hippocampus. However, unlike hippocampal activity, entorhinal activity remained constant or increased only slightly as training progressed.

(ii) Outputs. Berger & Thompson (1978b) also examined activity in two of the projection areas of the hippocampal formation - the lateral septal area and the mammillary bodies. As expected from an area that receives direct input from the hippocampus, lateral septal activity was found to be similar (though not identical) to hippocampal activity both within and across trials.

In contrast, neurons of the mammillary region, besides a slightly raised excitatory level, displayed no change with conditioning. Berger & Thompson point out that this is consistent with the fact that it is the subiculum which gives rise to the mammillary projection, and that this indicates that this subicular pathway, at least during NMR conditioning, is not being activated.

3.3.3. Unit Activity During Operant Conditioning

A series of studies by Deadwyler and colleagues (Deadwyler, West & Lynch 1979a, b; Deadwyler, West & Robinson 1981a, b) has examined the role of the dentate gyrus and its afferents in operant conditioning. The operant task required rats to learn to interrupt a beam of light by insertion of their snouts into a notch on one wall during the presentation of a tone. Water was then delivered from a spout on the opposite wall. Average evoked potentials (AEP's) to the tone were recorded from the molecular layer of the dentate gyrus, and unit activity from the dentate granule cell layer. In their later work Deadwyler et al. found that tone onset produced two distinct negative going peaks in the AEP, N1 and N2, and adduced evidence to the effect that N1 was the result of entorhinal activation (via the perforant path), and that N2 was due to the activity of the associational-commissural pathways (i.e. CA3/CA4 dentate projections). N1 and N2 were related in a reciprocal fashion such that N1 was largest (and N2 reduced or absent) when the tone was novel or when behavioural responding had been extinguished, and N2 was largest (and N1 reduced or absent) when discrimination performance had been well established. Deadwyler et al. interpret these findings as indicating that CA3/CA4 afferents to the dentate are activated only by biologically significant stimuli, and that entorhinal afferents are activated by unexpected or unpredictable events.

The role of the septum and entorhinal cortex was further investigated by lesioning these structures in different animals. As expected, the animals with entorhinal lesions did not show the N1 component of the AEP to tone onset under any conditions.

Medial septal lesions, on the other hand, had an effect such that N2 was present under all conditions (i.e. when the tone was novel and during extinction, as well as when it predicted reward). Deadwyler et al. point out that this effect of medial septal lesions is consistent with the report by Miller & Groves (1977) that such lesions increase the response of dentate granule cells to sensory stimulation, and indicates that the medial septum exerts a tonic inhibitory influence on CA3/CA4 neurons which is released on the appearance of biologically significant stimuli (see also Lynch, Rose & Gall 1978). This interpretation of the significance of septal and entorhinal projections to the dentate, as evidenced by the effect of lesions on N1 and N2, is supported by the parallel effects that such lesions have been found to have on behaviour. Deadwyler et al. (1981a) showed that septal lesions produced a broad generalisation gradient, while entorhinal lesions tended to produce a narrower response gradient than normal. However, these results were obtained from only one animal per response condition and obviously need to be replicted.

The earlier work of Deadwyler et al. (1979a,b) takes on particular significance when seen in the context of the above findings. They observed that the mere appearance of a tone-related evoked potential in the dentate gyrus was not sufficient to cause firing of the granule cells. It was only when the animal was required to discriminate between different tones that an effect was seen. Both the positive and negative (i.e. non-rewarded) tones produced evoked potentials, but only the positive tone produced a prolonged increase in neural firing, which returned to baseline upon emmission of the behavioural response. The negative tone produced a phasic increase in firing which rapidly returned to baseline

levels. When the tones were reversed in significance, granule cell activity reversed as well.

Adding these findings together, Deadwyler et al. (1981b) conclude that the nature of the septal and entorhinal inputs to the dentate gyrus allow the granule cells to respond differentially to the behavioural significance of stimuli. "The nature of this response depends on the position of the sensory stimulus along an abstract continuum anchored at one end by 'unexpectedness' or lack of behavioural significance and at the other by features that provoke maximum expectation of biologically significant events through associative learning." (Deadwyler et al. 1981b, p. 1183).

The generality of these conclusions for other cell types in the hippocampus is shown by a study by Sideroff & Bindra (1976), who recorded from the CA1 pyramidal cell layer. They, too, used an operant discriminative procedure whereby rats could obtain water in the presence of one tone but not another. Their procedure was unusual, however, in that the onset of both tones was preceded by an identical warning light. During initial pseudoconditioning there was a phasic increase in unit activity to the light, which habituated by the end of this period. When discrimination was well established the light produced a more sustained activation, which was further increased by the presentation of the positive tone. The negative tone, on the other hand, either had no effect or produced only a transient increase. Interestingly, when the animals were tested in a satiated condition, the response to the light was eliminated in 5 out of 9 animals, but the response to the positive or negative tones remained unaltered.

3.3.4. Comment

In view of the very different paradigms used and the variety of conditions under which these experiments were conducted, it is remarkable just how well most of the results complement each other. For example, there are obvious similarities between the observations of Ranck (1975) and those of Deadwyler et al. (1981a, b). The "specific orient cells" which Ranck noticed in the entorhinal cortex lend credence to Deadwyler et al.'s contention that the perforant path is activated by novelty, and his three major types of hippocampal cell (viz. approach-consumate-mismatch, approach-consummate and appetitive cells) clearly lie along the continuum that Deadwyler et al. outlined as important for dentate granule cell activation (viz. "unexpectedness" at one end, to "maximum expectation of biologically significant events" at the other). Similarly, the findings of the Thompson group are consistent with this view. Essentially, their results show that hippocampal neurons dramatically increase their activity upon onset of a stimulus which signals a biologically significant event (i.e. noxious stimulation of the cornea).

The only work which appears to be at variance with these observations is that of O'Keefe & Conway (1978), who believe that they have demonstrated "place" cells in the hippocampus. What their results actually show, however, is that under one set of environmental conditions some units preferentially fire in certain parts of that environment, and that this pattern is changed when the environment is changed. This may indicate that spatial cues affect the hippocampus (which would hardly be surprising since spatial factors play a role in virtually all interactions with the

environment), but to conclude from these results that such units "participate in the representation" of the environment is not only a vast logical leap, but is actually contraindicated by data from the experiment itself. For example:

(i) There is a clear dissociation of the spatial behaviour of the animal and the unit activity upon which it is meant to depend. O'Keefe & Conway (p. 578) acknowledge that "... although the place field of a place unit remained stable... under invarient conditions, changes such as rotating the maze relative to the environment or turning off the lights and changing the arms of the maze sometimes caused marked changes in the unit activity." This extreme lability of the place fields of these units required that elaborate precautions be taken to prevent any interpolated activity from disrupting them (see "Methods" section of O'Keefe & Conway). This stands in marked contrast to the robustness of the spatial behaviour of the animal itself.

(ii) The deliberate policy of not following the same cell for more than one session presumably arose because of the above mentioned lability of the place fields of these cells. Quite obviously, one of the primary requirements of a unit that is meant to code for spatial location is that it should reproduce that field exactly each time it is placed in the same environment.

(iii) The fact that the same units were activated in two very different environments (the maze and the holding platform) indicates that these units were not coding for a specific place. O'Keefe & Conway suggest that this could merely mean that each unit participates in the representation of several environments,

but the failure to find any common factor, in terms of topography or size, between these place fields argues against this. Furthermore, some of the units were extremely sensitive to even small changes in the curtained environment [e.g. unit 17 virtually ceased firing in the absence of the fan and with the addition of three lights (the so-called no light condition)], and yet fired robustly when placed in the radically different and well-lit environment of the outer laboratory. This lack of any consistency in the behaviour of the cell when viewed in terms of spatial outputs (field size or position) or spatial inputs (necessary and sufficient stimuli) implies the operation of factors other than spatial ones.

Another indication that O'Keefe & Conway's interpretation of the data is untenable is that both the Thompson and Deadwyler groups found that the large majority of pyramidal and granule cells participate in the hippocampal response. As pointed out previously, this kind of mass-action of the hippocampal neurons is incompatible with the fine-grained response required of them by the cognitive map theory.

An alternative interpretation, which brings O'Keefe & Conway's results into line with other studies of hippocampal unit activity, is that the "place fields" of the cells are actually determined by the presence, or the absence of the expected presence, of biologically meaningful stimuli. According to this view, the fact that changing the spatial configuration affects the place fields of the units is not surprising, since changing the spatial cues is equivalent to a translocation of the reward area. In this regard it is pertinent to note that 80% of the units had place fields

associated with either the start arm or goal arm - both places where the rats obtained food. The other 20% of units that fired only in the non-goal arm could merely be instances where the animals mistook that arm for one of the reward arms (this is feasible since the animals were not highly trained in the task). Furthermore, the finding that 2 out of 8 units retained their place field in the absence of spatial cues, but in the presence of the food, suggests that it is the reward that is of primary importance. As suggested above, the other 6 units may well have fired when the rats, in the absence of guiding cues, went to the wrong arm expecting to find reward there. O'Keefe & Conway (p. 577), in arguing against the possibility that the place fields could be related to biologically significant events, point out that the units had place fields on the holding platform, and yet "the rat had not received any training on this platform nor had it ever been rewarded there". However, this hardly constitutes a convincing rebuttal in view of the fact that other rats had had plenty of opportunity to deposit "biologically meaningful stimuli" on the platform.

If this explanation of O'Keefe & Conway's results is correct, then it means that there is general agreement about the type of events that produce hippocampal activation. There is less certainty, however, about the functional significance of such activation. It is difficult to imagine, for example, the role that hippocampal activation may play in the nictitating membrane conditioned response, since hippocampectomy does not deleteriously affect its acquisition. In this regard Hoehler & Thompson (1980) have made an intriguing suggestion. They point out that the CS-UCS interval exerts a powerful effect on the temporal location of the CR (in

other words, that the CR must anticipate the time of UCS administration to be effective), and propose that the output of the hippocampus acts as a temporal marker to aid in the timing of this response. Berger et al. (1980) have further elaborated on this idea by noting that the response topographies of the averaged NMR and the hippocampal unit activity are similar, and suggest that the hippocampus may store the motor programme of the response to be produced, which is then released at the appropriate time.

While the proposal that the hippocampus is involved in the timing of the CR has much to commend it (see discussion by Hoehler & Thompson 1980), there are difficulties with the hypothesis as presented. Specifically, Thompson and associates see the hippocampus as exciting a response at the appropriate time, while the lesion literature indicates, rather, a loss of the ability to inhibit a response till it is appropriate. Pavlov's work, too, on the inhibition of delay (discussed more fully on pp. 128-130), indicates that the temporal positioning of the CR is accomplished by internal inhibiton acting to suppress the response until the appropriate time. In addition, the finding that hippocampectomy can actually improve the acquisition of a classically conditioned NMR (Schmaltz & Theios 1972), implies that the hippocampus normally acts to retard or inhibit the CR.

It follows from this formulation that hippocampal unit activity should increase with CS onset, and decrease just prior to CR production, which is what Deadwyler et al. (1979b) found to occur. The data of the Thompson group, however, appear to provide only partial support for this deduction in that their records show that the peak of hippocampal activity leads the CR peak, but that unit

activity extends well into the CR period. However, it should be noted that these are averaged responses with respect to CS onset. This is important because the CR and associated unit activity do not occur with a fixed latency after CS onset, and the temporal relationship that exists between these two factors (i.e. the CR and unit activity) will therefore be obscured. In particular, this means that the averaged unit activity may appear in the averaged CR period even if this never occurs on any individual trial. Certainly, inspection of individual trial examples (Berger et al. 1980, Fig. 7) reveals that there is very little spill-over of unit activity into the CR period (and what there is could be due to a contribution from interneurons which might increase their firing at this point in order to inhibit the pyramidal cells). Their Fig. 7 also reveals another source of distortion in the averaged results: Biphasic NMR's have a second peak of unit activity occurring long after NMR onset. Clearly, these instances should be excluded from the averaging process. A true reflection of the NMR/unit activity relationship could then be obtained by averaging unit activity with respect to the onset of the NMR, rather than to CS onset.

A further test of the above hypothesis, other than the re-analysis of the data already suggested, would be to establish a delayed reflex by gradually increasing the CS-UCS interval. Hippocampal activity should then show a sustained increase throughout the CS-CR period, in a manner similar to that seen in the Deadwyler et al. (1979b) study. Hoehler & Thompson have done this to a limited extent by shifting the UCS from 250 to 500 mSec. post-CS. Although reading of their data is difficult because of the averaging problem, it does appear as though unit activity,

starting after the usual 100-150 mSec latency, is increased throughout the CS-UCS interval.

A final issue that remains to be resolved is Berger et al.'s (1980) claim that the hippocampal unit activity represents a neuronal model of the NMR. While Berger et al. are the first to admit that the correlations between the shapes of these two events are based on averaged responses, and could be an artifact of the averaging method, they nevertheless feel that this represents a real underlying relationship. As evidence, they point to the fact that on 72% of individual trials when animals produced biphasic NMR's, the unit activity also showed a bimodal distribution. This correspondence between the topographies of the two responses suggests, they believe, that the motor response is an actual copy of the unit response. However, consideration of the circumstances under which biphasic NMR's are produced indicates otherwise. From an examination of their Fig. 7 it can be seen that such responses often occur as a result of mistiming: The NMR is released too soon, with the consequence that it is almost completed by the time the UCS is delivered. A second NMR is then initiated as an unconditioned response (UCR) to the UCS. Thus Berger et al. have erred in assuming that the biphasic NMR is merely a CR with an unusual shape. In fact, the two peaks are reflections of different events: Only the first peak in the unit activity is associated with a CR; the second peak occurs in conjunction with an unexpected UCS and the resultant UCR, and appears to be similar to the hippocampal response to the UCS seen early in training. Thus the mere fact that two peaks in the NMR are associated with two peaks in the unit activity is not a sufficient reason for believing that the motor response is a copy of, or even dependent

on, the neural activity. It seems more probable that the second peak represents activity involved in the resetting of the timing mechanism.

3.4. GENERAL COMMENT

Knowledge of the physiology of the hippocampus and its projections is still fragmentary and, as a result, much of the discussion in this chapter is speculative. Nevertheless, consideration of the evidence that does exist shows it to be compatible with the inhibitory theory, and to specifically contradict any explanations in terms of cognitive maps. Consequently, the cognitive map theory will be abandoned, and the next chapter will concentrate on evaluating the evidence against the inhibitory theory in an effort to establish whether modifications are necessary or possible.

4 THE INHIBITORY THEORY REVISITED

Although the inhibitory theory has emerged as the most powerful of those examined, it nevertheless appears to be vulnerable on a number of issues. In reassessing these criticisms it will be convenient to first present a more detailed account of the concept of internal inhibition, and the general behavioural profile that would be expected in its absence.

4.1. INTERNAL INHIBITION & HIPPOCAMPECTOMY

The existence of internal inhibition was proposed by Pavlov (1927) to account for phenomena he observed during his investigations into classical conditioning. Specifically, he found that repeating the CS while withholding the UCS (reinforcement) resulted in extinction of the CR. This was not the result of exhaustion, since a single application of the reinforcer could re-establish the CR, and nor was it the result of atrophy of the stimulus-response connection, since the mere passage of time restored the full amplitude of the reflex. Furthermore, the simultaneous presentation of an "extinguished" CS diminished or even abolished a CR to a second CS. Pavlov therefore concluded that the extinction of the reflex was due to an active central inhibitory process which he termed internal inhibition (see Fig. 3A). This was distinguished from external inhibition which was produced by the application of a novel stimulus. External inhibition had the property of inhibiting concurrent excitatory or inhibitory activities of the CNS. Thus a novel stimulus presented

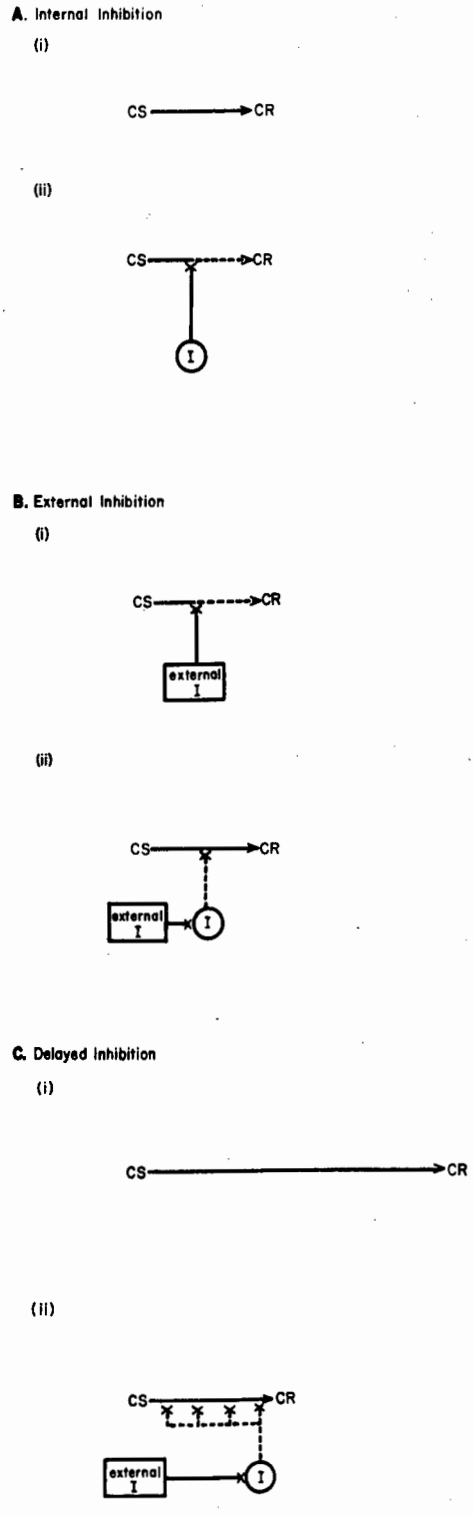

FIG. 3. A.(i) CS elicits CR in the presence of reinforcement. (ii) Withdrawal of reinforcement induces internal inhibition (I) which blocks the production of the CR. B. The presentation of a novel stimulus induces external inhibition (external I) which has the property of (i) blocking the production of any simultaneously active CR, and (ii) inhibiting any simultaneously active internal inhibition, thus releasing an extinguished CR. C. (i) Development of a delayed reflex. CS is presented for a prolonged period before reinforcement is applied. CR follows suit and only develops after a delayed interval. (ii) Disinhibition of delayed reflex. The presentation of a novel stimulus during the action of a delayed reflex results in its premature release. Crosses indicate inhibition, arrows excitation. A broken line indicates an inhibited connection.

concomitantly with a CS would inhibit the production of the CR, or, conversely, release (disinhibit) the CR if it had previously been extinguished (Fig. 3B). Pavlov categorised four types of internal inhibition depending on the manner in which the inhibition was produced. For example, inhibition of delay was established by only introducing the reinforcement after a fairly long period of action of the CS. Under these circumstances the CR did not appear at the start of the CS but also only after a delay. That the CR was being actively inhibited during this "time-out" period was shown by presenting a novel stimulus shortly after the onset of the CS. This resulted in the immediate release (disinhibition) of the prepotent response (Fig. 3C).

However, Pavlov's interpretation of these events has not gone unchallenged. Konorski (1948), in particular, has denied that the concept of inhibition is necessary in order to understand the above results, claiming that some, at least, could be explained simply in terms of competition amongst reflexes. For example, there is no need to invoke inhibition as an explanatory construct to account for the arrest of ongoing behaviour during the orienting response, since the orienting reflex would seem to be powerful enough merely to displace other behaviour. While there is merit to this point of view, it is clearly unable to explain effects like the disinhibition of extinguished responses which accompanies the orienting response. Furthermore, in the case where a novel stimulus is presented in competition with a strongly motivated behaviour, it is evident that some type of "brake" would be needed before behaviour could be redirected.

Although Konorski's arguments can be discounted for the most part,

they do serve as a useful pointer to the extent to which behaviour, which would normally be thought to be dependent on internal inhibition, would be unaffected by its loss. Perhaps the most common misconception in this regard is the belief that animals without internal inhibition would be unable to alter their behaviour and would be destined to perseverate previously reinforced responses under all circumstances. That this is not the case is illustrated by the observations of Huston & Borbely (1974) on the behaviour of thalamic rats (in which all neural tissue rostral to the thalamus has been removed). These animals appear completely devoid of internal inhibition: Once a behaviour, say rearing, has been established they will continue to rear even if the reinforcer (brain stimulation in this instance) is never again applied. However, this does not mean that they cannot stop this behaviour: if they are rewarded for crouching they will readily give up the incompatible behaviour of rearing. Thus, once again, we see an example of a change in behaviour being brought about by the displacement of one response by another. In this case, a newly rewarded response is shown to be capable of displacing a previously rewarded one. The difference between these animals and those with intact internal inhibition is that the displaced (and now unrewarded) behaviour never undergoes extinction. Thus, in any given situation, the animal sans internal inhibition will maintain, in a fully viable state, all behaviours for which it has been reinforced. Any chance reinforcement of one of these hypotheses (see Isaacson & Kimble 1972 for a discussion of the use of this term in this context) will therefore reinstate it immediately. As will be shown below, this point is crucial to an understanding of the behaviour of hippocampectomised animals in reversal learning.

Stated in general terms, the consequence of a loss of internal inhibition will be that the animal will come to be more directly under the control of external stimuli. In other words, it will lose the ability to direct its attention "at will": Factors such as stimulus intensity and stimulus strength (see Douglas 1975) will be decisive. In addition, since Pavlov maintained that the impact of every stimulus produces internal inhibition (reinforcement merely serving to keep it at bay), the loss of this braking effect will result in the animal being abnormally quick to associate stimuli with reinforcement (a characteristic of hippocampectomised animals, e.g. see Douglas 1967; Schmaltz & Giulian 1972; Schmaltz & Theios 1972), but the price paid for this rapidity of association is that the animal runs the risk of allowing stimuli that have only been fortuitously reinforced to gain control over its behaviour (i.e. it will be prone to superstitious behaviour) - again, a trait notably present in hippocampals (Devenport 1980; Devenport & Holloway 1980).

Finally, it is important to emphasise that animals without internal inhibition are normal in other respects: In particular, they will feel frustration at not obtaining an expected reward, and will try to avoid unpleasant places.

4.2. A RE-ANALYSIS OF CRITICISMS OF THE THEORY

The criticisms of the theory presented in section 2.1.3 will be dealt with below.

4.2.1. Habituation, Exploration & Novelty

Intact animals placed into a novel environment engage in systematic exploration in order to establish the biological significance of the stimuli impinging on them. Non-significant stimuli are rapidly habituated and little further attention is paid to them. Any change in a familiar environment (if it is not too intense) elicits exploration directed specifically at that aspect.

The behaviour of hippocampectomised animals, on the other hand, lacking internal inhibition, would be expected to be quite different. A novel environment would also elicit exploration, but of a less systematic character than that displayed by normals. Without the ability to concentrate attention on one stimulus at a time (by inhibiting the distracting effects of other stimuli), these animals would display erratic behaviour, darting from one stimulus to another and back again. Animals with large hippocampal lesions would not show habituation in the sense of a decrement of activity across trials, but might show some reduction of activity within trials due to the action of factors such as fatigue. This analysis suggests that an environment would never become familiar in the sense that non-novel stimuli would no longer attract attention. It follows from this that the introduction of a novel stimulus into a familiar environment would produce a response dependent only on its "noticeability" (i.e. extent to which it excites the nervous system - O'Keefe & Nadel 1978 p. 242) relative to other stimuli (regardless of their degree of familiarity). A highly noticeable stimulus would produce an exaggerated response which would not habituate with repeated

presentations (provided that the interpresentation interval was sufficiently large - see p. 136). However, novelty per se would not guarantee greater attention since the other stimuli in the environment are also "novel" (in that they have not been habituated). Therefore, if the other stimuli are of equal noticeability to the novel stimulus, the attention of the animal would be distributed equally among them, which would mean that, relative to controls, the hippocampectomised animal would pay less attention to the novel stimulus.

Thus the results of the Glickman et al. (1970) study, cited by O'Keefe & Nadel as evidence against the inhibitory theory, are in fact entirely consistent with the theory. Their hippocampectomised gerbils investigated novel objects placed into the home cage less than normals because the lesioned animals had to apportion their attention amongst other non-habituated stimuli in their environment. Some support for this interpretation is gained from the additional finding by Glickman et al. that the lesioned gerbils also spent less time at the apparently attractive activity of shredding nest material. Since hippocampal animals (including gerbils) are more active than normal in the home cage (Glickman et al. 1970; Jarrard 1968), this implies that the excess activity is being directed at other, familiar stimuli.

Seen from this perspective, the question of whether the elevated activity displayed by hippocampals can properly be considered to be exploratory is irrelevant, although O'Keefe & Nadel's contention that it merely reflects hyperactivity is difficult to sustain in the face of Kaplan's (1968) observation that increased activity is specifically produced by "interesting" stimuli, and by

the fact that activity in running wheels (see Douglas 1967) or small, stimulus-poor cages (Kaplan 1968) is normal. Furthermore, it is noteworthy that hippocampals do not necessarily display an excess of activity relative to controls upon initial exposure to novel environments (e.g. Kaplan 1968; Glickman et al. 1970): the excess arises because normals rapidly habituate to the situation while hippocampals do not.

Finally, studies showing that hippocampals react to a stimulus that has been pre-exposed hundreds of times in the same way as normals react to a novel stimulus (Ackill, Mellgren, Halgren & Frommer 1969; Solomon & Moore 1975), or that they do not prefer a novel stimulus to a negative (i.e. non-rewarded) one (Douglas & Pribram 1966), provide powerful support for the thesis that this syndrome is produced by a lack of habituation.

4.2.2. Extinction

O'Keefe & Nadel have made three points concerning the extinction deficits shown by hippocampals: (i) short intertrial intervals reduce the deficit, (ii) lever-press tasks show a smaller extinction deficit than runway tasks, and (iii) extinction in avoidance tasks is either normal or superior to normal. Each of these points will be discussed in turn.

4.2.2.1. Intertrial interval & extinction

Extinction is a complex phenomenon: non-delivery of an expected

reward, besides producing internal inhibition, also arouses negative emotional states like frustration and anger (Amsel 1958). If non-reinforcement is repeated with short intervals (i.e. under massed practice conditions) then each succeeding "dose" of frustration will build on the last until, eventually, the negative emotions aroused by the conditoned stimulus will become strong enough to allow withdrawal reflexes to dominate and displace the approach tendencies of the animal. Under these conditions, even without the benefit of internal inhibition, the animal will cease to respond. On the other hand, under conditions of distributed practice, the frustration aroused by each instance of non-reward is allowed time to dissipate. Thus any decrement in responding will be a function of pure internal inhibition. The finding that hippocampectomised animals appear to display extinction with massed practice, but not distributed practice, is therefore understandable. The "extinction" seen with massed practice is, however, not a true extinction: it is the result of a temporary reduction in approach strength produced by negative emotions, and can easily be distinguished from extinction proper. As is well known, extinguished responses spontaneously reappear with the passage of time, but each subsequent set of extinctions proceeds more rapidly. If the extinction shown by hippocampals with massed practice is the result of the build-up of frustration, then this should dissipate with time and subsequent extinctions should not show this progressive decremental character. This is, in fact, found to be the case (Jarrard & Isaacson 1965; Schmaltz & Theios 1972).

4.2.2.2. Lever-press vs. runway tasks

It should now be clear from the above why extinction deficits are not as marked in lever-press situations compared to runway tasks. Lever pressing occurs very rapidly and thus is particularly likely to produce high levels of frustration during extinction. Runway tasks, on the other hand, usually employ long intertrial intervals and are therefore a purer test of the presence of internal inhibition.

It follows from the above that a more marked extinction deficit would be obtained in Skinner boxes if a retractible-type lever were to be used, and presented only briefly with long intertrial intervals.

4.2.2.3. Avoidance learning and extinction

The extinction of conditioned avoidance responses has not been extensively examined in hippocampectomised animals, and the few examples cited by Nadel et al. (1975) that are available to me (Kaplan 1968; Nadel 1968; Schmaltz & Giulian 1972) offer little to support their contention. Two of the studies (Kaplan 1968; Nadel 1968) actually investigated the "extinction" of a conditioned emotional response (i.e. the freezing behaviour produced by a frightening stimulus). This is somewhat different to the extinction of an avoidance response (where the animal must do something to avoid punishment), and it is debatable whether extinction is involved here at all. Instead, it would seem that less freezing on the part of hippocampals (as shown by Kaplan and

many others) demonstrates a weakened ability to maintain freezing (i.e. less inhibition) rather than a greater ability to inhibit freezing behaviour. The study by Schmaltz & Giulian (1972) appears to be more appropriate since they used a lever-press avoidance task. However, their conclusion that there is no difference between hippocampals and controls in the extinction of this response is, perhaps, not altogether warranted. One of the main problems with this study is that the mean intertrial interval was only 18 sec. (counting from the end of one trial to the beginning of the next). Such short intertrial intervals are unsatisfactory, particularly when working with shock. As a result, one is uncertain of what the animals actually learned, much less what was being extinguished. It certainly does not appear to be a lever-press in response to the CS, since the animals pressed the lever more often during the intertrial intervals than during the CS presentations.

4.2.3. Reversal Learning

Spatial and non-spatial reversal learning will be discussed separately.

4.2.3.1. Non-spatial reversal learning

Reversal and extinction situations have a common element in that in both cases reinforcement is no longer associated with the old cue. It might be expected, therefore, that hippocampals would behave similarly in the two conditions and perseverate their old

response in the reversal task as well. However, as O'Keefe & Nadel point out, the deficit displayed by hippocampals on reversal tasks is only rarely due to perseveration. Although hippocampals often do perseverate their old choice longer than controls, the major reason for their poor performance is the adoption of an inappropriate position habit.

This type of objection is based on a superficial analysis, however: important differences between the two tasks have been overlooked. For example: (i) the pretraining given in the two situations is usually quite different, and (ii) reward is still present in the reversal situation (albeit associated with a new cue). The interaction of these factors, when considered within the framework of the inhibitory theory, can be shown to account for the behavioural results. An analysis of a "typical" study will make this clear.

Nonneman & Isaacson (1973) trained hippocampectomised and control cats on a brightness discrimination problem in which the animals had to choose a dark (non-illuminated) door rather than an illuminated one in order to gain access to food. No difference between hippocampals and controls was seen on acquisition. Reversal, however, produced a marked deficit on the part of the hippocampals, in that they showed a persistent position preference. Examanation of their experimental protocol reveals that, during pretraining, position habits were "eliminated" by forcing the animals to use the non-preferred door (neither of which were illuminated at that stage), and pretraining was terminated only once the animals displayed an equivalently strong approach response to both doors. The pretraining had thus

established three hypotheses which had yielded reinforcement: a) approach dark doors (since neither of the doors were illuminated); b) some form of alternation between the left and right doors; c) the position habit with which the animals started. The hippocampals would therefore begin acquisition training with all of these hypotheses in a fully active state since, as discussed previously, they are incapable of extinction. If, by chance, the correct strategy (i.e. (a)) was adopted from the start, then these animals would be expected to reach criterion more quickly than normal. On the other hand, if the wrong strategy was adopted, then long strings of perseverative responding would be expected, since reinforcement would still be obtained on approximately 50% of the trials, and frustration (even with short intertrial intervals) would, for the most part, be avoided. However, this does not mean that hippocampals would never solve the problem or change their strategy. Fortuitous reinforcement of an occasional deviation from their chosen hypothesis (for whatever reason - "error", mild frustration, etc.) would result in the instant conversion to the newly reinforced strategy, since all three are equally attractive. This process would continue until the correct strategy was reactivated, whereupon criterion would be reached. Depending on the sequence in which the three strategies were activated, some hippocampals would reach criterion more quickly than others, but, as a group, they would not be expected to differ much from the control group (although it should be mentioned that Nonneman & Isaacson did find it necessary to break position habits during the course of acquisition). The main difference between the two groups would be in their pattern of responding (see Isaacson & Kimble 1972 for a thorough analysis in this regard).

In contrast, reversal training would present particular problems for the hippocampal group since the task to be learned does not conform to any of their pre-established hypotheses. They would probably start by emitting the most recently reinforced response (i.e. approach the dark door), which, of course, now would never be reinforced. Depending on the intertrial interval this phase would vary in length: a short intertrial interval would ensure frustration build-up and a relatively rapid move away from this response. Unfortunately, Nonneman & Isaacson do not report the intertrial interval they used, but judging from the intertrial intervals used in the other experiments described in this paper, and the fairly quick relinquishment of this response, I would guess it to have been short. In any event, once an alternative response has been emitted which intersects with reinforcement, that particular hypothesis (i.e. either the positional or alternational strategy) will be re-instated for a while. The "approach the dark door" strategy, once having been discarded, will never again be rewarded, and thus will never be reactivated within a session. The only time it is likely to reappear is at the beginning of a session. Since, of the two remaining hypotheses, the positional hypothesis is the one most likely to intersect with reinforcement (and is guaranteed to be reinforced 50% of the time), it will be the dominant one. It would take a great many instances of reinforcement before an "approach the illuminated door" response would be strong enough to displace one of the other strategies.

Thus, it can be seen that the oft noted appearance of a position habit in reversal tasks is not only not in contradiction to the inhibitory hypothesis, but is actually predicted by it.

4.2.3.2. Spatial reversal learning

Mahut, in a series of studies (Mahut 1971; 1972; Mahut & Zola 1973; Zola & Mahut 1973), concluded that monkeys with hippocampal lesions were deficient on spatial reversals, while being normal or even superior to normal on object reversals. This set of experiments, besides providing considerable impetus to the cognitive map theory at the expense of the inhibitory theory, also implies that the primate hippocampus has a function different to that of rats and cats, since these latter species do show deficits in object reversals after hippocampal lesions (Becker & Olton 1980; O'Keefe & Nadel 1978, Table A19). In view of the unusual nature of these results, it is important that the experiments upon which they are based should be adequately controlled. However, even a casual inspection reveals that this is not the case. In fact, so badly have basic rules of experimental design been transgressed that no valid conclusions can be drawn with respect to the difficulty or otherwise of spatial versus object reversals.

In her first paper Mahut (1971) used a repeated measures design. Animals were first assessed on their ability to learn a large series of spatial reversals and then, after they had mastered the task, were tested on several object reversals. Compared to normals, hippocampectomised monkeys were significantly impaired on the spatial, but not the object reversal task. Mahut concludes from these results that hippocampals have a peculiar difficulty with spatial reversals. However, this conclusion is unjustified in that she failed to control for any order effect in the presentation of the tasks. Thus it is possible that the extensive training that the hippocampals received on the spatial reversals

(they had an average of 1467.5 trials compared to the normals' mean of 547.5 trials) may have helped them to perform well on the object reversal task. Indeed, Mahut mentions that the initial dismal performance of the hippocampals on the spatial reversals "improved dramatically" towards the end, an observation that indicates that these animals had finally gained "insight" into, or found a way of solving this problem that could have been of benefit in solving similar subsequent problems (see e.g. Harlow & Harlow 1949 for a discussion of "learning to learn").

The second paper in the series (Mahut 1972) is essentially a replication of the first, but monkeys with lesions of the fornix were used. The same methodological error is repeated (i.e. spatial reversal learning is tested before object reversal learning), despite the fact that there are clear indications that performance on reversal tasks is sensitive to prior training on other problems. For example, normal animals in this second study learnt the spatial reversal problem more than four times faster than normals in the first study, even though the protocols for the two experiments were virtually identical. The reason for this difference appears to be the inclusion of a spatial delayed alternation test prior to the spatial reversal task in the earlier paper.

In the third paper (Mahut & Zola 1973) fornicotomised and normal monkeys were compared in their ability to learn spatial and object reversals in both the tactile and visual modalities. Once again spatial reversals were administered before object reversals, but this time a more sophisticated experimental design was employed. In order to control for practice effects, a spatial reversal

re-test was given after the object reversal task. Thus the design was:

5 spatial reversals, followed by 5 object reversals, followed by a re-test on 2 spatial reversals.

This was done for first the tactile and then the visual modes.

The results for the tactile modality were that the fornicotomised animals showed the expected deficit on the spatial reversal task, were normal on the object reversal test, and were once again deficient on the re-test of spatial reversals.

The results for the visual modality were however, a revelation. After their experience with reversal tasks in the tactile mode, the lesioned group now no longer displayed a deficit on the same spatial reversal task which had produced such profound deficits in the first two papers. Although Mahut & Zola offer no explanation for this result, they do argue that it could not be due to a practice effect, since, in the tactile mode, the fornicotomised animals had been normal on the object reversals, and yet were deficient on the re-test of spatial reversals (i.e. after practice with object reversals). Ordinarily such an argument would be valid, provided that the re-test was identical to the initial spatial reversal task. Unfortunately, Mahut & Zola err again. The re-test was an abbreviated version of the original task: instead of administering the usual five reversals, they report the results of only two. Since there is ample evidence that the lesioned group do badly in the first part of the test and improve greatly in the latter half, this truncated re-test would have the

effect of obscuring any improvement that had actually taken place between the test and re-test. In fact, evidence of this biasing effect is clearly shown in the test and re-test of the visual spatial reversal task. Although the fornix group was not significantly different from the normal group on the initial test of five spatial reversals, Mahut & Zola report that they were inferior on the later re-test of two spatial reversals (albeit at the 5.3% confidence level!). When these monkeys were subsequently re-retested some months later on the full five spatial reversal test, they were once again found not to differ from controls.

The fourth and last paper in the series (Zola & Mahut 1973) is not actually a separate study. It is an examination of the results obtained on the visual object reversal test given in the third paper (Mahut & Zola 1973), and in which a "paradoxical" facilitation of the performance of the fornix group is reported. All the methodological objections raised with regard to the previous studies therefore apply here. Suffice to note that practice makes perfect. In the 1971 and 1972 studies the experience gained on spatial reversals allowed the experimental group to equal the performance of normals on the object reversal task. In the 1973 study practice with reversals in the tactile mode helped the lesioned group to achieve near-normal scores on spatial reversals in the visual mode. This further practice then allowed the experimental group to better the performance of normals on the object reversal task.

Finally, a discussion of the Mahut papers would be incomplete without consideration of a study by Jones & Mishkin (1972), since, in a sense, this experiment could be construed to be a control for

the procedures adopted by Mahut. Jones & Mishkin used the same repeated measures design as Mahut, but tested object reversals before spatial reversals. Contrary to expectations engendered by the arguments given above, their hippocampectomised monkeys were not significantly different to normals on the object reversal task, but showed a massive deficit in learning the spatial reversals. However, these results are not in conflict with the previous arguments for the following reasons:

(i) The Jones & Mishkin experiment is <u>not</u> comparable with the Mahut studies. Jones & Mishkin used a forced correction for errors procedure, while Mahut used a non-correction procedure. Since the forced correction method is known to ameliorate the deficit found with reversals in other hippocampectomised species (since it establishes an approach tendency to both stimuli), the results that Jones & Mishkin obtained on object reversals are what would be expected. (Even so, it is to be noted that the hippocampectomised monkeys still made more than twice as many errors as the controls on the first two reversals).

(ii) The results obtained on the spatial reversal task should be regarded with caution. This is indicated by the fact that on the initial spatial discrimination task (i.e. that part of the experiment where the animals had to learn a simple position habit, prior to it being reversed) the hippocampals were significantly worse than the controls (they made three times as many errors). Since hippocampectomised animals (including monkeys e.g. see Mahut 1971, 1972) are usually normal on this task, this could mean that one or more of the experimental group had become recalcitrant for some reason. This is a fairly common experience with both intact

and lesioned monkeys (e.g. see Jones & Mishkin 1972 p. 366; Mahut 1971 Table 5), and is of particular concern in the Jones & Mishkin study since the hippocampal group consisted of only three animals. In this regard it should be mentioned that the control group was artificially expanded from 3 to 9 animals (by the inclusion of data from another experiment) presumably to "iron out" just such idiosyncratic behaviour. In any event, whatever the reason for the results reported by Jones & Mishkin, it is clear that they cannot be accepted at face value.

In conclusion, owing to multiple methodological errors it cannot be inferred from the above studies that hippocampectomised monkeys are normal on object reversal tasks. While it is possible, or even likely, that hippocampals find it particularly difficult to alter position habits (see Samuels 1972), the weight of evidence nevertheless indicates that they experience difficulty with all types of reversals.

4.2.4. Passive Avoidance

In general terms passive avoidance can be defined as the ability of an animal to suppress an approach response for which it has been punished. Several factors determine the extent of this suppression:

(i) the strength of the approach response

(ii) the availability of internal inhibition to inhibit the response

(iii) the strength of the avoidance response (as a result of the punishment).

It is worth reiterating in this latter regard that hippocampals are normal or superior to normal in avoiding objects associated with punishment (e.g. Blanchard, Blanchard & Fial 1970). Nor do they suffer from a prepotent tendency to release approach reflexes under all circumstances (as displayed by animals with lesions elsewhere in the CNS which, upon receiving shock at the feeding dish, were observed by Kaada, Rasmussen & Kveim (1962) to actually jump forward into the dish, instead of backwards). It follows, therefore, that, lacking internal inhibition, the behaviour of hippocampectomised animals in a passive avoidance situation will be determined by the relative strengths of the approach and avoidance responses inherent in that particular task. If a weak approach tendency is punished, then the consequent withdrawal reflex will easily displace it and no passive avoidance deficit would be expected. If the approach response is well-established, and the punishing shock is weak to moderate, then hippocampals should accept far more shocks than controls. Should both the approach response and the shock be strong, then hippocampals would display a classic approach-avoidance conflict and gravitate towards the source, but not necessarily touch it (since the avoidance response would dominate at close range).

A final factor to be considered when assessing the performance of hippocampals on avoidance tasks is, again, the intertrial interval. A short intertrial interval means that subjects will be exposed to a number of shocks in quick succession. This will have the effect of making them very fearful, thus producing

sensitisation and rendering the shocks far more aversive. This point was made by Liss (1968) who showed that even small lesions of the hippocampus produced a deficit in passive avoidance, but only if the intertrial interval was long.

Bearing these points in mind, it is now possible to turn to an analysis of the actual results that have been obtained. O'Keefe & Nadel (1978) provide a list of more than 60 experiments which bear on this issue (their Table A23). At first sight, the results appear to support their claim that there is no general deficit in passive avoidance following hippocampectomy. A massive block of 30 experiments report no effect. [It is to be noted that the category referred to by O'Keefe & Nadel as "mixed" (deficit with one measure, typically latency; no deficit with another, typically shocks taken) is here considered (according to the analysis presented at the beginning of this section) as deficient.] However, closer scrutiny reveals that O'Keefe & Nadel have swollen the ranks of these experiments by including studies with lesions so small as to be insignificant, or, conversely, lesions so large that the hippocampal damage was incidental. In addition, they have included a category of studies (those on taste aversion) which clearly involve mechanisms very different to those involved in passive avoidance. Punishing a thirsty animal for drinking water from a particular dish does not make water less attractive to that animal: it must merely inhibit its approach to that particular dish. Making an animal sick after ingestion of a substance, on the other hand, renders all occurrences of that substance repugnant. Since the substance no longer elicits approach, there can be no approach-avoidance conflict, and there is no reason to suspect, therefore, that internal inhibition would

be involved.

Other studies which should be excluded are:

(i) Kaada et al. (1962) who used large lesions involving many extrahippocampal structures.

(ii) Myhrer (1975a, b) and Myhrer & Kaada (1975) who used very small lesions in an effort to isolate specific hippocampal outputs. This is not to say that such studies are unimportant, but it is unreasonable to include them in an assessment of hippocampal functioning as a whole. It is noteworthy that Myhrer (1975a) states that if the lesions were larger than intended (i.e. involved more of the hippocampus), then passive avoidance deficits were found.

(iii) De Castro & Hall (1975), Ross, Grossman & Grossman (1975), Thomas & McCleary (1974), and Van Hoesen, Wilson, MacDougall & Mitchell (1972) who used fornix lesions. There are good reasons for believing that damage to the fornix does not produce the same (or as great) an effect as damage to the hippocampus (besides the fact that fornicotomy generally does not produce deficits in passive avoidance!). For example, hippocampectomy reliably produces a defict in freezing (e.g. Blanchard et al. 1970), while fornicotomy either has no effect or actually increases freezing (De Castro & Hall 1975). In fact, Moore & McCleary (1976) came to the conclusion that lesions of the fornix actually enhance response inhibition. It is thus evident that output via non-fornical routes plays a significant role in hippocampal functioning. Indeed, it is only recently that it has been

appreciated just how great is the contribution of the projection via retro-hippocampal structures. Poletti & Sujatanond (1980) recorded unit activity in various forebrain structures following stimulation of the hippocampus in awake fornicotomised monkeys. Compared to intact subjects stimulation produced longer-latency unit activity (consistent with di- or multi-synaptic pathways), but the percentage of responsive units (on average) was reduced by less than half. In other words, the non-fornix projection was found to be at least as powerful as the fornix pathway.

Furthermore (and of particular significance in the context of passive avoidance), activation of the nucleus accumbens was well preserved (thus ensuring adequate inhibition of approach/ exploration activity), and the excitation of the ventromedial nucleus of the hypothalamus (VMH) was actually increased (thus allowing for inhibition of approach/consummation activity). This latter finding suggested to Poletti & Sujatanond that the hippocampus might have a dual effect on the VMH: excitation via the retro-hippocampal pathway and inhibition via the fornix. However, this seems unlikely in view of the fact that the fornix has a strong projection to the VMH and would therefore be expected to produce a much more powerful inhibitory effect than was actually observed. An alternative possibility is that, since fornix destruction removes several afferent pathways which have an inhibitory effect on the hippocampus [e.g. from the medial septum (Lynch et al. 1978), the supramammillary region (Segal 1979), the raphe nuclei (Segal 1975) and the locus coeruleus (Segal & Bloom 1976)], fornicotomy might result in a more easily activated hippocampus, stimulation of which could result in a greater than normal output via certain of the retrohippocampal pathways. If

these pathways (e.g. via the amygdala) were to be preferentially activated under aversively motivated conditions, then it could explain the lack of a deficit in passive avoidance after fornicotomy, and also the occasional report that small dorsal hippocampal lesions produce a better than normal ability to inhibit responses (Brunner, Rossi, Stutz & Roth 1970; Boitano & Isaacson 1967).

In addition to these exclusions, we can also reclassify those studies which have found deficits with one type of manipulation but not another. Thus Coscina & Lash (1969) and Dawson, Conrad & Lynch (1973) found deficits with large dorsal lesions, but not small ventral ones, and Liss (1968), as mentioned previously, demonstrated the importance of long intertrial intervals. Finally, the Brunner & Rossi (1969) study has been misclassified by O'Keefe & Nadel (i.e. they did find a deficit).

Thus the final number of separate studies which report that hippocampectomy does not produce a deficit on passive avoidance is 11. Table I presents these studies categorised according to the type of task. It can be seen that more than half are concerned with the step-down or step-through type task. Since similar arguments apply to both tasks, and because most of the studies cited used the step-down paradigm, only this task will be discussed. The typical procedure used here is to place an animal on a platform above an electrified grid. Any move to step down will therefore be punished, and the number of shocks accepted relative to controls is a measure of the passive avoidance deficit. Since the tendency to step down is not a strongly motivated response, this represents a situation where a weak

approach tendency is pitted against punishment. Since, as discussed previously, the withdrawal response would dominate under these conditions, internal inhibition is not necessary, and no deficit would generally be expected. To uncover a deficit, either

TABLE I

EXPERIMENTS REPORTING NO EFFECT OF HIPPOCAMPAL LESIONS ON PASSIVE AVOIDANCE

Step-down or Step-through	Kimble, Kirkby & Stein (1966) Nadel (1968) Ridell (1968) Winocur & Mills (1969) Blanchard et al. (1970) Brunner et al. (1970) Riddell (1972)
Consummation in an experimental chamber	Kveim, Setekleiv & Kaada (1964) Boitano & Isaacson (1967) Boitano, Lubar, Auer & Furnald (1968)
Consummation following locomotion	Boitano & Isaacson (1967) Hostetter (1968)
Punished 1-way active avoidance	Nadel (1968)

a very weak aversive stimulus would have to be used, or the strength of the step-down tendency would have to be increased. This latter procedure was adopted by Isaacson, Olton, Bauer & Swart (1966). They used a shaking platform, thus providing a more powerful motivation for the animal to alight. Under these conditions a passive avoidance deficit was found.

While the negative findings of studies using step-down tasks can be explained in terms of a lack of adequate motivation, the same cannot be said of the three studies which reported normal passive avoidance of an electrified water dish (Kveim et al. 1964; Boitano & Isaacson 1967; Boitano et al. 1968). These studies used thirsty rats, and the inhibitory theory would predict a deficit, provided that an approach response was first established to the dish. In fact, this was not done. In all three studies the water dish was electrified before the animals had ever drunk from it. Thus they were shocked on their first contact with the water without really having tasted it. The dish therefore represented a predominantly aversive stimulus and no passive avoidance deficit would be expected. The one study using this paradigm which did show a deficit (Brunner & Rossi 1969) differed in that their animals were allowed to drink from the dish before the shock was applied, thus establishing the requisite approach response.

There remain three experiments where a strong approach response was established and yet which found no passive avoidance deficit (Boitano & Isaacson 1967; Hostetter 1968; Nadel 1968). Of these the results of Boitano & Isaacson (1967) and Nadel (1968) can possibly be explained by the fact that they used fairly small lesions and short intertrial intervals. However, the results of

Hostetter (1968) cannot be so easily dismissed. She developed a strong approach response in her animals, and used fairly large lesions (34-58.5% of the hippocampus destroyed). The one procedural point that sets her study apart from others is that her animals were removed from the apparatus immediately after shock, and passive avoidance testing was only instituted 24 hours later. It seems just feasible that this procedure allowed for an "incubation of fear" effect (e.g. see Bindra & Cameron 1953; Kamin 1957) which could have increased the aversive nature of the situation to such an extent that it could override the approach tendency.

In conclusion, it can be stated that, with the possible exception of one study (Hostetter 1968), a passive avoidance deficit is a robust finding following hippocampal destruction, provided that:

(i) a strong approach response is established

(ii) a long intertrial interval is used, particularly with small lesions.

4.2.5. Maze Learning

Virtually all studies show that hippocampectomy disrupts complex maze learning (see O'Keefe & Nadel 1978 Table A20). However, as Leaton (1969) and Winocur & Breckenridge (1973) have demonstrated, hippocampals can solve complex mazes if cues are available at each choice point. The question that Nadel et al. (1975, p. 156) pose is: "Why are the animals with lesions, but not those without, so

dependent upon these intramaze cues?"

Fortunately, linear-type mazes were used in both the above studies, so a detailed analysis of the type of mistakes made by the animals is possible. Winocur & Breckenridge used a maze with the sequence LRLRRL, and found that the hippocampal group made an inordinate number of errors at choice points 3 and 5. Individual analysis revealed that the hippocampals, like the controls, quickly learned that the solution to the first 4 choices was an alternation between left and right, and adopted this as a general strategy. At choice point 5, therefore, all the animals went left instead of right. Controls, however, soon learned to inhibit this maladaptive strategy, while hippocampals persisted with it for a much longer period. When, eventually, the hippocampals did learn to make a second right response at choice point 4, they appeared to adopt the hypothesis that all right turns were followed by a second right turn, and promptly began to make a right turn after choice point 2, thus producing a second peak of errors at choice point 3. As Douglas (1979) point out, these proactive (choice point 5) and retroactive (choice point 3) interference errors are typical of an animal which lacks internal inhibition (see also the work of Weiskrantz on human amnesics - p. 69).

Thus, to answer Nadel et al., hippocampectomised animals experience no difficulty with mazes when cues are provided, because then they only have to learn one strategy (e.g. approach the white doors). Similarly, they have no difficulty with a maze without cues, provided that a constant strategy is required to solve it (e.g. go through all the left doors, or alternate left and right responses). The problem arises when mixed strategies

are required (e.g. alternate the first 4 responses, and then repeat the last choice). This is akin to a reversal task and requires the presence of internal inhibition.

4.2.6. Classical Conditioning & The Hippocampus

The last remaining criticism stems from the work of Solomon (1977; Solomon & Moore 1975) who showed that hippocampectomised rabbits had deficits in Kamin blocking and latent inhibition, but could acquire a Pavlovian conditioned inhibitor as well as controls. Briefly, the steps in the conditioning procedure for these three paradigms are as follows:

(i) Latent inhibition

Step 1: The CS is presented alone for many trials. Initially, presentation of the CS elicits orientation, but this habituates with repeated presentations since the CS is not associated with any biologically significant event. Since habituation is caused by internal inhibition, the CS comes to produce internal inhibition.

Step 2: The CS is paired with the UCS. Since the CS is an inhibitory stimulus, the conditioning process is retarded.

(ii) Kamin blocking

Step 1: CS1 is paired with the UCS.

Step 2: a new CS (CS2) is presented together with CS1, and

both are paired with the UCS. The introduction of CS2 initially causes an orienting response and dishabituation of the experimental situation. However, because it is not associated with any significant change, CS2 plus the experimental situation is rehabituated. The association of internal inhibition with CS2 therefore antagonises conditioning of CS2 to the CS.

Step 3: CS2 is presented alone. Because CS2 has not become conditioned to the UCS, no CR is produced.

(iii)Conditioned inhibiton

Step 1: CS1 is paired with the UCS.

Step 2: a new CS (CS2) is presented together with CS1, but they are never paired with the UCS. As before, CS2 initially causes dishabituation, but, because it is associated with a significant change (CS1 no longer predicts the UCS), it is not habituated. However, because CS1, in the presence of CS2, is never associated with the UCS, the compound CS1+CS2 undergoes extinction. CS2 therefore becomes an inhibitory stimulus on account of extinction, not habituation.

The fact that hippocampals are normal in the conditioned inhibition paradigm indicates that they do have internal inhibition, and seriously challenges the generality of the inhibitory theory.

Solomon (1979) and Moore (1979) believe that these data indicate

that the hippocampus is concerned with the "tuning out" of irrelevant stimuli. In other words they are suggesting that the hippocampus plays a part only in habituation, and not other forms of internal inhibiton (e.g. extinction). While this certainly accounts for their results (in that both the latent inhibition and Kamin blocking effects depend upon habituation, while conditioned inhibition depends upon extinction), it does not explain why hippocampals should have a deficit, say, in passive avoidance. Besides, as we have seen, hippocampals do have a marked deficit in extinction. Particularly important are Schmaltz & Theios' (1972) results in this regard, since they used a preparation very similar to that of Solomon (i.e. shock motivated conditioning of the NMR). They found that large hippocampal lesions did produce an extinction deficit, although, since they used a short intertrial interval (60 sec.), a deficit was not seen in the first extinction session, but became more and more evident with subsequent sessions as internal inhibition became more firmly established in the controls. Furthermore, the results of Rickert, Lorden, Dawson, Smyly & Callahan (1979), although not presented as such, could be interpretted as indicating that hippocampal damage does impair conditioned inhibition. Their study was actually designed to investigate "overshadowing" (a paradigm which has features common to both Kamin blocking and conditioned inhibition) in hippocampectomised rats. In their experiment a compound stimulus consisting of a light and a tone (LA) was paired with footshock, while another compound stimulus consisting of the same light and a different tone (LB), was never so paired. They then used the suppression of a previously established lever-press response to assess the degree to which the rats discriminated between the two compound stimuli and their elements. The suppression ratio was

calculated from the formula X/(X+Y), where X equals the number of responses made during the presentation of the CS (for 60 sec.), and Y is the number of responses recorded for a similar period immediately prior to CS onset. A suppression ratio of less than .5 therefore indicates that the stimulus has caused suppression of lever pressing. Their results (as measured from their Fig. 2) are presented in Table II. As can be seen, the

TABLE II

MEAN SUPPRESSION RATIOS TO THE COMPOUND STIMULI AND THEIR ELEMENTS

GROUP	LA	A	L	LB	B
Controls	.18	.32	.52	.47	.65
Hippocampals	.09	.30	.21	.34	.63

controls suppressed only to the presentation of the element A and its compound LA which were consistently associated with footshock. Their lever pressing was unaffected or increased during the presentation of the elements L and B, and the compound LB. In contrast, the hippocampals suppressed (i.e. reduced their lever-pressing by about half or more) during the presentation of all elements or their compounds which had been even partially associated with footshock (L was associated with shock 50% of the time by virtue of its inclusion in the compound LA), thus evidencing a deficit in overshadowing. The only stimulus to which they did not suppress was the element B which had never been

associated with shock. It will be noticed that the hippocampals suppressed far more to LA than to LB, and on this basis Rickert et al. conclude that the hippocampals discriminated between these two stimuli (which, in effect, means that they showed conditioned inhibition since the stimuli have a common element). However, the fact that suppression was seen to both stimuli renders this conclusion suspect. It is possible that the difference was produced by some passive perceptual transform, rather than an active discrimination process. Indeed, there is a strong suggestion that this may be the case, since the hippocampal group's suppression ratios for the compound stimuli LA and LB can be derived in a straight-forward manner from the suppression ratios of the constituent elements. Thus, L has a suppression ratio (SR) of .21, which is the equivalent of -.29 below zero suppression (i.e. .5). B has an SR of .63 which equals +.13 above zero. Adding L and B together we get -.29 +.13= -.16 below zero. Thus the predicted SR for LB = .5 -.16 = .34. Similarly, for LA, the SR of A = .30, which equals -.20 below zero. Adding L and A we get -.20 -.29 = -.49 below zero; that is, an SR of .01. Since these predicted values are very close to the observed values for LA and LB, it seems reasonable to conclude that their suppression ratios are derived passively from factors such as the associational strength and intensity of their respective elements: they are not discriminated between in the real sense of the term. The control group's suppression ratios to LA and LB, on the other hand, do not bear this simple relationship to their elements (predicted values: .34 and .67 respectively). There is therefore an active discriminative process at work here (presumably internal inhibition) which the lesioned group lacks.

Taken together, the above data suggest that perhaps Solomon (1979) and Moore (1979) have placed too much reliance on the one experiment of Solomon (1977), especially in view of the fact that only the dorsal hippocampus was destroyed in that study. Both the Rickert et al. (1979) and the Schmaltz & Theios (1972) studies employed lesions involving both the dorsal and ventral hippocampus. Furthermore, it is of some interest that Rickert, Lorden, Dawson & Smyly (1981) found that it is the ventral hippocampus that is important for Kamin blocking. Large dorsal lesions were only effective in preventing blocking if they included the fimbria (as Solomon's lesions did). What is being suggested, then, is that Solomon's experiment should be repeated using larger lesions. It seems that lesions of the dorsal hippocampus plus the fimbria (thus destroying the rostral projection of the ventral hippocampus) may be sufficient to prevent habituation, but that to prevent extinction (and therefore conditioned inhibition), especially using an aversive UCS, may require the destruction of the caudal output of the hippocampus as well.

4.3. COMMENT

With the possible exception of Solomon's (1977) results, all of the criticisms levelled at the inhibitory theory have proved, upon closer examination, to be unfounded. It is therefore concluded that the theory as originally formulated by Douglas (1967, 1972) and Kimble (1968) be retained unmodified.

5 FRACTIONATION OF THE HIPPOCAMPAL SYNDROME

Several studies utilising discrete lesions have attempted to establish whether a differentiation of function exists within the hippocampus (e.g. Jarrard 1976, 1978; Myhrer 1975a). Unfortunately, the interpretation of these results is problematic since destruction of any one area invariably interrupts fibres to and from others. Unequivocal results are unlikely to be obtained until such time as a "transparent" lesioning technique is developed (i.e. one which destroys cell bodies, but leaves fibres of passage intact), and although some progress has been made in this direction with the introduction of the cytotoxic drug kainic acid, it has not proved to be ideal (see e.g. Mason & Fibiger 1979). Thus, by default, it would appear to be more profitable to examine the projections of the hippocampal region for evidence of a differentiation of function, rather than to seek it within the hippocampus itself.

As indicated in Chapter 1, the projections of the hippocampal region can be classified according to rostral-caudal and dorsal-ventral axes. That is, the dorso-rostral and dorso-caudal projections reach the cingulate cortex via the anterior thalamic nuclei and the retrosplenial cortex respectively, while the ventro-rostral output innervates the basal forebrain and hypothalamus, and the ventro-caudal projection attains the same structures, probably via the amygdala (Poletti & Sujatanond 1980). Since the work of Poletti & Sujatanond indicates that the rostral and caudal outputs from the ventral hippocampal region appear to affect the same structures in the same way (see p. 151), it will

be assumed that the rostral and caudal outputs from the dorsal hippocampal region have a similar complementary relationship. However, the possibility that the dorsal and ventral projections may subserve different functions is suggested by the fact that the dorsal output (which exits via the anterior thalamus), is inhibited by the ventral output (via its projection to the mammillary body see p. 95). Thus it appears as though there are two separate circuits emanating from the hippocampal region; one ascending to the cingulate gyrus, and the other descending to the basal forebrain and diencephalon. The two circuits are connected by the massive inhibitory pathway that constitutes the mammillo-thalamic tract (see Fig. 4).

5.1. FUNCTION OF THE DORSAL CIRCUIT

Davis (1981; Davis & Kent 1979) performed tractotomies on the dorsal rostral hippocampal projection, just beyond the point where it exits from the fornix. This procedure produces very small lesions which interrupt most of the direct hippocampo- and septo-thalamic fibres without injuring either the fornix or the thalamus. He found that the tractotomies produced effects remarkably similar to total hippocampectomy in that lesioned animals displayed increased locomotor activity, superior shuttle box performance, lack of behavioural contrast, impaired passive avoidance, and deficits in extinction. This is an unexpected result since it suggests that internal inhibition is dependent on the integrity of the dorsal circuit alone. It is also surprising since it implies that the cingulate cortex is intimately involved with internal inhibition and yet, as Douglas (1967) has pointed

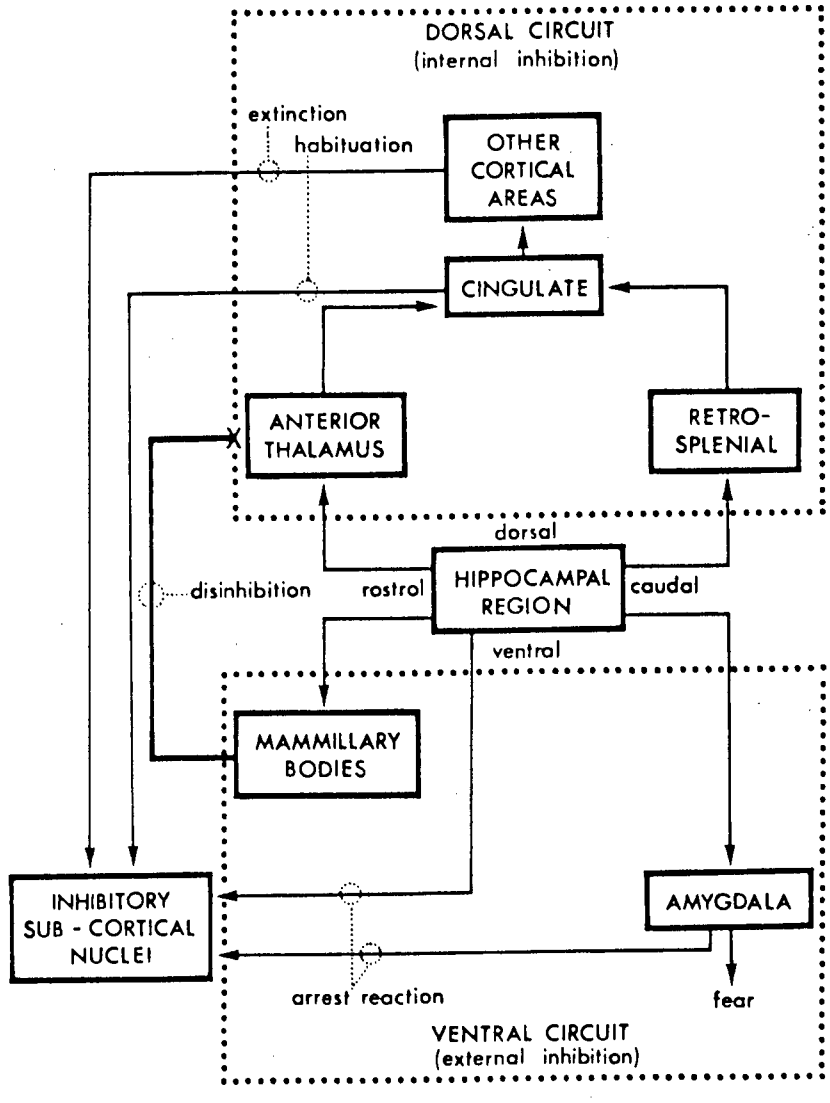

FIG. 4. Schematic diagram of the connections of the hippocampal region. The dorsal projections are suggested to be responsible for internal inhibition, while the ventral ones are posited to underlie external inhibition. For further discussion see text.

out, cingulectomy appears to produce opposite effects to hippocampectomy on some tasks. However, a likely resolution of this apparent paradox is supplied by the recent work of Vogt, Rosene & Pandya (1979). They have shown that the anterior (and lateral dorsal) thalamic nuclei project almost exclusively to the caudal-most part of the cingulate cortex, an area that is usually (at least partially) spared in studies employing cingulate

lesions. The dual nature of the cingulate gyrus has been confirmed by Baleydier & Mauguiere (1980), and both groups have stressed that the posterior cingulate is differentiable from the anterior cingulate cortex on physiological as well as anatomical grounds.

Given that it is the posterior cingulate cortex which is involved with internal inhibition, it is of interest to follow these projections further. Baleydier & Mauguiere (1980) report that, in the monkey, this area projects, inter alia, to the following structures:

(i) Cortex: the anterior cingulate cortex; the medial aspect of the parietal cortex and the ventral bank of the intraparietal sulcus; the arcuate and principal sulci of the frontal lobe; the superior temporal sulcus of the temporal lobe; the perirhinal cortex and the hippocampal region.

(ii) Thalamus: the medial pulvinar and the laterodorsal, anteroventral and anteromedial nuclei.

(iii) The caudate nucleus

(iv) The lateral pontine nuclei.

It is unfortunately beyond the scope of this chapter to present a detailed account of the functions of each of these projection areas. However, the possible roles of the cortical areas and the caudate nucleus will be very briefly considered.

5.1.1. The Cortical Projection Areas

a) The dorsolateral prefrontal cortex (i.e. the area including the arcuate and principal sulci).

There is considerable evidence that this area has important inhibitory functions. Low frequency stimulation of the prefrontal cortex in rats inhibits lever pressing and running in an activity wheel (Wilcott 1979), and damage to this area results in increased motor activity in a variety of species (Brutowski 1965). Numan (1978) reviews evidence showing that animals with prefrontal lesions have deficits on DRL and reversal tasks, and Warren, Coutant & Cornwell (1969) found that cats with lesions of the gyrus proreus had a profound deficit in the extinction of appetitively reinforced responses. Particularly interesting is the finding by Van Hoesen, Vogt, Pandya & McKenna (1980) that monkeys with periarcuate ablations have great difficulty in discriminating between a compound stimulus and one of its elements - in other words, they show a deficit in Pavlovian conditioned inhibition. The similarity between these effects and some of those seen after hippocampectomy is clear, and encourages the belief that the hippocampus might exert part of its inhibitory effect via the prefrontal cortex. In fact, this is the conclusion reached by Teitelbaum (1964). He found that hippocampal and proreal ablations produced similar impairments on the reversal of a tactile discrimination problem, and that lesions of both structures together did not lead to any additional effect.

Further insight into the essential deficit seen after dorsolateral prefrontal lesions is provided by the results obtained by Moll &

Kuypers (1977). They report that monkeys with unilateral lesions could not learn to use the contralateral limb to reach around a transparent barrier to obtain a reward: all reaching responses were directed straight at the target. Similarly, Deuel & Dunlop (1979) found that monkeys trained pre-operatively to respond to the presentation of a stimulus by touching their ears (reinforcement being delivered at the base of the stimulus), after prefrontal lesions responded by reaching directly towards the stimulus. The work of Denny-Brown, too (for a review see Langworthy 1970; see also Teitelbaum 1967 pp. 109-114), shows that damage to the dorsolateral prefrontal cortex in man and other animals results in the release of approach reflexes. For example, a stimulus applied to the palmar or plantar surfaces elicits strong grasp reflexes, and stimulation of the face produces rooting and sucking reflexes. Patients with such lesions appear to lose control over their approach reflexes: once an object has been grasped, it cannot be voluntarily relinquished.

(b) Other cortical projection areas.

Denny-Brown's observations were not limited to the prefrontal cortex. Like Schnierla (1965), he has emphasised the organisation of behaviour in terms of approach and withdrawal reflexes, and has further proposed that these reflexes have separate neuroanatomical representation. He found that destruction of the anterior cingulate area produced effects similar to those seen after dorsolateral prefrontal lesions, while extirpation of the inferotemporal cortex appeared to produce a release of specifically visual approach reflexes, in that the animal compulsively retrieved and mouthed small objects (see also e.g.

Horel, Keating & Misantone 1975).

Damage to the parietal cortex produced results opposite to those reported above. Lesions of the anterior parietal cortex resulted in the release of tactile withdrawal reflexes (e.g. a stimulus applied to the foot elicited the Babinski sign, and stimulation of the palmar surface produced an extension of the fingers), while lesions of the posterior parietal cortex resulted in a release of visual withdrawal reflexes (avoidance of brightly lit areas and moving objects).

While Denny-Brown's observations may need to be refined in terms of the specific control exercised by different regions, what is truly remarkable is the extent of the overlap between those areas that he has designated as important for the inhibiton of approach and withdrawal reflexes (see Langworthy 1970, Fig. 1, p. 7), and the neocortical projection areas of the posterior cingulate gyrus (cf. Baleydier & Maugiere 1980, Fig. 4.). This certainly supports the contention that the posterior cingulate area is involved with internal inhibition, and raises the possibility that at the cortical level this control is differentially organised with respect to the appetitive or aversive properties of stimuli.

While the foregoing analysis has concentrated on the projections of the hippocampal region to the neocortical convexity (via the posterior cingulate), it should be noted that almost the identical cortical areas that receive projections, project back upon the posterior cingulate (Baleydier & Maugiere 1980; Vogt et al. 1979) which, in turn, projects to the hippocampal region. It is thus difficult to determine the direction of control (i.e. hippocampus

to neocortex, or vice versa). However, in view of the fact that the inhibitiory deficit is produced by disruption of the hippocampothalamic projection alone (thus leaving most of the other hippocampal projections, and the neocortical-hippocampal connections intact), it seems likely that it is the hippocampus which has the executive function. This being the case, the question arises concerning the route by which the neocortex might exercise its inhibitory effect on behaviour at the behest of the hippocampus. With reference to the prefrontal cortex, it is interesting to find that this area addresses many of the same inhibitory subcortical loci to which the hippocampal region projects either directly, or via the cingulate cortex. For example, Beckstead (1979) has demonstrated that the rat homologue of the prefrontal cortex projects to the striatum (see below for evidence of the inhibitory nature of this structure), the nucleus accumbens, the olfactory tubercle, the lateral septum, and parts of the hypothalamus.

5.1.2. The Caudate Nucleus

Since rodents do not have a separate caudate and putamen, the term "striatum" will be used interchangeably with caudate in what follows.

There seems little doubt that the caudate is an inhibitory organ. Unilateral (Kitsikis & Rougeul 1968) or bilateral (Buchwald, Wyers, Lauprecht & Heuser 1961; Plumer & Siegel 1973; Plumer, Siegel & Cicala 1973) low-frequency stimulation has been shown to inhibit a variety of behaviours, while high-frequency (i.e.

blocking) stimulation produces behavioural activation (Buchwald et al. 1961; Forman & Ward 1957).

The results of lesion studies, too, have supported this contention, with reports of increased activity in the open field (Kirkby 1973; Schmaltz & Isaacson 1972), loss of response suppression in an operant task (Hansing, Schwartzbaum & Thompson 1968), deficits in extinction (Schmaltz & Isaacson 1972), and a general heightened level of reactivity to environmental and physiological stimuli (see Polgar, Sandberg & Kirkby 1981). Bilateral caudate destruction also produces obstinate progression (Mettler & Mettler 1942) - a condition marked by the inability to inhibit forward motion in the face of an obstacle, and unilateral caudate lesions produce ipsiversive circling behaviour (e.g. Hansing et al. 1968; Glick, Meibach, Cox & Maayani 1980).

Further evidence for the inhibitory role of the caudate comes from the effects of psychopharmacological agents on the nigro-striatal system. The caudate and the substantia nigra are linked by reciprocal inhibitory pathways (the dopaminergic nigrostriatal tract, and the GABAergic strionigral pathway) and any manipulation which results in the elevation of DA produces behavioural activation, and vice versa. For example, an activating drug like amphetamine increases the effect of DA by preventing its reabsorption by the pre-synaptic membrane (Williams & Karacan 1976). This causes a profound inhibition of the caudate neurons (Groves, Rebec & Segal 1974) and consequent behavioural excitation. Conversely, major tranquilisers such as haloperidol and chlorpromazine block the post-synaptic DA receptors, thus releasing the caudate neurons from DA-mediated inhibition, and

allowing them to exert an inhibitory effect on behaviour.

While this converging evidence from stimulation, lesion and drug studies firmly establishes the caudate as an inhibitory structure, it is less helpful in determining the specific role that the caudate plays. In this regard the aforementioned fact that unilateral striatal lesions produce circling is of some interest. Compulsive circling is in fact produced by any procedure which results in an imbalance in the DA content of the caudate nuclei, turning occurring away from the side which has the highest DA concentration (James & Starr 1978; Martin & Haubrich 1978). Since DA is inhibitory to the caudate, this contraversive turning can be seen as a release phenomenon, and it would therefore be expected that caudate lesions should produce a similar effect. In fact, as previously mentioned, caudate lesions have been reported to cause ipsiversive circling. However, this appears to be due to the fact that relatively small lesions were used in these studies. Small lesions, while destroying some caudate neurons, actually produce a greater disruption of DA terminals (see Marshall, Berrios & Sawyer 1980, Fig. 3), and therefore cause ipsilateral turning.

This DA-controlled postural asymmetry is made even more intriguing by the demonstration that the nigrostriatal pathways on either side of the brain are reciprocally related such that an increase in activity on one side produces a decrease on the other (Nieoullon, Cheramy & Glowinsky 1977a), and that unilateral visual or somatic stimulation causes a similar imbalance in DA release in the caudate nuclei on either side (Nieoullon et al. 1977b). This type of "push-pull" mechanism suggests that the striatum could be involved in the orienting response, and, indeed, there is much

evidence to support this contention. High frequency stimulation of one caudate almost invariably produces an orienting response to the contralateral side (Forman & Ward 1957), which habituates upon repeated application and can be dishabituated by the presentation of a novel stimulus (Ursin, Sundberg & Menaker 1969). Moreover, Marshall et al. (1980) have shown that unilateral destruction of the DAergic input to the striatum blocks orientation to the contralateral side, and that injection of apomorphine (a DA agonist) into the affected striatum restores orientation. These results indicate that activation of the nigrostriatal tract, by inhibiting the caudate, releases the orienting response to the contralateral side, and that the caudate acts to inhibit orienting. In other words, it appears as though habituation may be one of the functions of the caudate. If this were the case, then the hippocampus could be seen as an inhibitory memory store, which would register repititious stimuli and activate the caudate to inhibit the orienting response. Although there is little direct evidence to support this suggestion, there is evidence to show that the hippocampus does act via the striatum. For example, unilateral high-frequency stimulation of the hippocampus produces an orienting response to the contralateral side (Kaada, Jansen & Anderson 1953; Votaw 1959) in a manner similar to that seen after such stimulation of the caudate, and unilateral lesions of the hippocampus have been shown to modulate nigrostriatal asymmetry (Glick et al. 1980).

5.1.3. Conclusion

The dorsal circuit of the hippocampus accesses structures with

diverse and complex functions, yet common to all of these areas is a basic involvement with some aspect of inhibition. Evidence already cited indicates that the striatum is one of the main inhibitory centres and is responsible (at least) for habituation, while the neocortical projection areas appear to be involved in the inhibition of approach and withdrawal responses. Particularly interesting from the perspective of hippocampal functioning is that, once released by damage to the respective cortical areas, these maladaptive approach and withdrawal responses never extinguish. It seems possible, therefore, that the cortical areas may be responsible for the extinction of appetitively and aversively motivated behaviour. If this is so, then it indicates that the dorsal circuit alone forms the neural substrate of internal inhibition.

5.2. FUNCTION OF THE VENTRAL CIRCUIT

As pointed out previously, transection of the dorsally directed hippocampothalamic fibres produces a syndrome similar to that seen after hippocampectomy. However, Davis (1981) notes one important exception to this general similarity: tractotomised animals engaged in goal-directed behaviour were as sensitive as controls to the distracting effects of a novel stimulus. Specifically, he found that the running speeds of the experimental and control groups in an alley were disrupted to an equal extent by the introduction of sandpaper floors - a result different to that obtained with hippocampectomised animals (Riddell, Rothblat & Wilson 1969; Wickelgren & Isaacson 1963). Thus it appears that one of the primary characteristics of external inhibition (the

inhibition of ongoing behaviour by a novel stimulus) is present in animals which have intact ventral projections of the hippocampal formation. It therefore seems worthwhile considering the possibility that while the dorsal circuit mediates internal inhibition, the ventral circuit might be responsible for external inhibition (see Fig. 4).

If this were the case, then it would be expected from the characteristics of external inhibition that the ventral circuit should have the following properties:

(i) Direct access to a number of inhibitory loci through which it could bring about a rapid arrest of ongoing behaviour.

(ii) Access to an area through which it could produce an arousal of fear (caution) in the face of a stimulus of unknown significance.

(iii) It would probably have connections which promote an orienting response

(iv) It must be able to bring about disinhibition by inhibiting internal inhibition.

Some evidence to indicate that the ventral circuit does, in fact, have these characteristics is presented below.

5.2.1. The "Arrest" Capability Of The Ventral Circuit

This point has been dealt with previously. The ventral circuit has a direct excitatory influence on a number of inhibitory areas (the nucleus accumbens; the olfactory tubercle; the lateral septum; the ventromedial hypothalamus), stimulation of which could cause an abrupt arrest reaction. While the dorsal circuit also reaches these loci, it does so only after several synapses - suggesting that its inhibitory effect on behaviour is conditional, perhaps upon factors such as lack of reinforcement.

5.2.2. The Arousal Capability Of The Ventral Circuit

The fact that the ventral caudal projections of the hippocampal region reach the amygdala is of interest here, since the amygdala has been implicated in the control of fear (e.g. Werka, Skar & Ursin 1978). The amygdala is commonly considered to consist of two groups of nuclei, the corticomedial and the baso-lateral groups, which have antagonistic functions. This is indicated, for example, by the fact that although lesions of the amygdala usually block the autonomic aspects of the orienting response, some subjects actually show an elevation (see Pribram & McGuinness 1975). Similarly, Henke (1980) has shown that destruction of the ventral amygdalofugal pathway reduces stomach pathology induced by immobilisation stress, while lesions of the stria terminalis aggravate such pathology. From his work it appears that it is the medial amygdala that facilitates the stress reaction, and it is significant that it is to this part of the amygdala that the

hippocampus projects (see p. 46). It is possibly the disruption of this pathway which produces the "boldness" which is so commonly commented upon following hippocampal lesions.

5.2.3. The Orienting Response & The Ventral Circuit

The ventral circuit, by virtue of a synapse in the bed nucleus of the stria terminalis (see p. 44), has connections with a number of brainstem nuclei, including the ventral tegmental area, the raphe nuclei and the locus coeruleus (Swanson & Cowan 1979). There is evidence that each of these areas has an inhibitory effect on the caudate.

(i) The raphe nuclei provide a serotonergic input to the caudate (Pasquier, Kemper, Forbes & Morgane 1977), stimulation of which inhibits the caudate neurons (Davies & Tongroach 1978).

(ii) The ventral tegmental area has a DAergic projection to the caudate (see Deniau, Thierry & Feger 1980; Koob, Balcon & Meyerhoff 1975; Pasquier et al. 1977), and DA is known to be inhibitory to caudate neurons (Davies & Tongroach 1978).

(iii) Although the locus coeruleus does not appear to have a direct caudate projection, O'Donohue, Crowley & Jacobowitz (1979) have shown that transection of the noradrenergic ventral tegmental bundle decreases DA concentration in the caudate. This implies that the locus coeruleus normally acts to promote the release of DA, thereby inhibiting the caudate.

Since the caudate inhibits the orienting response, the above evidence implies that the ventral circuit, by suppressing the caudate, should have a facilitatory effect on orienting. One way to demonstrate this would be to test the orienting response in animals with unilateral hippocampal damage. Such damage would remove an inhibitory influence from the ipsilateral caudate, and, since the caudate inhibits orienting to the contralateral side, therefore should have the effect of producing an ipsilateral orienting bias to symmetrically presented novel stimuli. Such an effect has in fact been found by Saporta & Greene (1974).

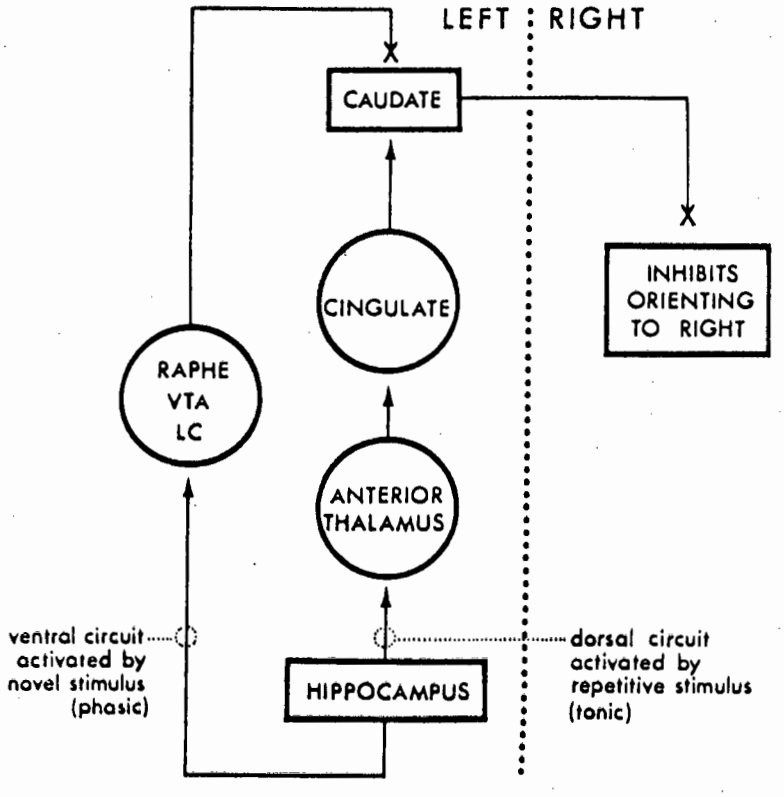

FIG. 5. Showing the dual connections of the hippocampal region with the striatum. The hippocampus is suggested to initiate habituation via the dorsal circuit, but to promote an orienting response via the ventral circuit.

It will be recalled that the dorsal circuit is suggested to have an inhibitory effect on the orienting response, which may appear

to contradict the above. However, these opposite effects of the hippocampus are not really antagonistic as they occur under different conditions. It is only novel stimuli which activate the ventral circuit: The dorsal circuit is activated in order to habituate repetitive signals. Fig. 5 shows the suggested connections.

5.2.4. Disinhibition & The Ventral Circuit

One of the more intriguing aspects of external inhibition is that it has the ability to inhibit internal inhibition. Since a major target of the ventral circuit is the mammillary bodies (MB), and since this structure inhibits the dorsal circuit at the point of the anterior thalamus, it seems possible that the MB might be the route through which the disinhibitory influences are funnelled. The major effects to be expected after destruction of this area would therefore be that animals would not show dishabituation or disinhibiton. It follows directly from this that the general behaviour of these animals, like that of hippocampals, would be marked by rigidity and inflexibility (i.e. they would be unable to easily switch hypotheses). However, the reason for this inflexibility would be the opposite to that of hippocampals: it would result from an excess of internal inhibition, since strategies that had been extinguished would not be disinhibited by changes in the environment, and thus the demands of new circumstances could not be met.

These and other predictions of this hypothesis are considered below in relation to the available literature.

His main reason for rejecting better-than-normal extinction as an explanation is that in his Expt. 2, MTT lesioned cats exhibited normal extinction of a one-way active avoidance task. As previously pointed out, however, the two tasks are very different. Shuttle box avoidance places the animal in a conflict situation and therefore generates a great deal of internal inhibition. This effect would be potentiated in the MTT animals, and they would be even more reluctant than normal to shuttle. They would thus be likely to fail to avoid sooner than controls, which would allow them to experience the change in reinforcement contingencies, and therefore extinguish the response, more quickly. In the one-way avoidance task, on the other hand, there is no particular reason for the experimental animals to fail to make an avoidance response, and thus experience the changed conditions, sooner than the controls. They would therefore not be expected to show superior extinction in this task.

With regard to the difficulty that MTT-lesioned animals experience in the shuttle box, it is of interest to note that amphetamine repairs the deficit (Krieckhaus 1965). This is understandable since amphetamine inhibits not only the caudate, but also the nucleus accumbens (Rebec & Zimmerman 1980), thereby removing, at least partially, the source of excess inhibition.

5.2.4.3. Reversal learning

A deficit would be expected here, since adequate performance on this task requires the disinhibition of an extinguished response. Two studies (Krieckhaus & Randall 1968; Thompson, Langer & Rich

1964) have examined the role of the MB in reversal learning. In the first study Krieckhaus & Randall trained rats in an appetitively-motivated position habit in a T-maze. The MTT lesioned group readily acquired the position habit, but showed a surprising refractoriness during reversals: they displayed excessively long latencies, or even refused to run the maze at all. While Krieckhaus & Randall found this result difficult to explain, it is exactly what would be predicted from the present hypothesis. Consider a T-maze with arms A and B. In the acquisition of a preference for arm A, the response to B undergoes simultaneous extinction. Now, under reversal conditions, when the reward is removed from A, this change in the situation produces disinhibition of the response to B in the normal animal. In the MTT lesioned animal, however, no disinhibition occurs. The response to B remains extinguished, while the response to A also undergoes extinction. Since the response to both arms comes to be inhibited, the nett result is the observed reluctance of the animals to run the maze. It is worth emphasising, once again, that these long latencies cannot be ascribed to hypoactivity: the MTT lesioned animals acquired the initial position habit easily, and in tasks not involving internal inhibition such animals are not different from normal (Kimm et al. 1967, Expts. 1 & 2; Ploog & MacLean 1963; Thomas et al. 1963, Expt. 2).

In the second study (Thompson et al. 1964) a similar, but shock-motivated task was used. They found their MB and MTT lesioned group to be deficient in reversals, and that the deficiency was exacerbated by increasing the intertrial interval from 30 sec. to 30 min. The same arguments as above would apply here, but in this case the animals have no option but to run the

maze. Since the response to both arms is extinguished, the likelihood of choosing either arm should be at chance levels. This is what is observed with long intertrial intervals (see their Fig. 2. Note also that this pattern is different from the perseveration displayed by their hippocampectomised group). Short intertrial intervals bring about an improvement in performance because, as discussed previously in relation to the behaviour of hippocampals, the effects of punishment received in the wrong arm have not been allowed time to dissipate. The short-term additional aversive properties of that arm will therefore tilt the balance in favour of the opposite arm.

5.2.4.4. Alternation

Although it has not yet been tested, the hypothesis predicts that MB lesioned animals should spontaneously alternate at least as well as normals. Performance on reinforced alternation, on the other hand, would depend on prior training conditions. A defict would be expected only if an approach response to one arm had already been extinguished. A study by Rosenstock, Field & Greene (1977) illustrates this rather well. MB lesioned rats which received pretraining on a position habit in a T-maze were found to be impaired relative to controls in learning to alternate in the same apparatus. However, if they had had experience with alternation prior to surgery (i.e. if the alternation hypothesis was established first) then no deficiency post-surgery was seen.

It should be mentioned that the imposition of a 5-sec. delay did produce an impairment under both conditions. This is surprising

since delay per se has not been found to affect the performance of MB lesioned animals on other tasks (Kim et al. 1967). However, in the Rosenstock et al. study the rats were tested in a fully automated apparatus (i.e. they were not handled between trials), and the delay was imposed by locking a gate in the starting stem. It is difficult to evaluate the effects of this manipulation. Lacking a clear distinction between trials, the locked door might merely be frustrating for normals, but MB lesioned animals might treat it as an extinction condition.

5.2.4.5. Maze learning

Maze learning has been found to be disrupted by MB lesions (Thompson 1974), which is to be expected given the inflexibility of behaviour which is proposed to follow from destruction of this area. (For a discussion of behavioural inflexibility and maze learning, see pp. 155-157).

5.2.4.6. Classical conditioning

Since MB lesions are postulated to produce an excess of internal inhibition under some circumstances, it follows that animals with this lesion will show a normal or supranormal latent inhibition effect. It might be expected that Kamin blocking and conditioned inhibition would be similarly affected, since they, too, rely on internal inhibition. However, a more detailed examination of the mechanisms involved suggests that dishabituation plays a crucial role in these latter discriminations (see pp. 157-158), and that

MB lesions will therefore prevent these effects. For example, the first stage of Kamin blocking involves the establishment of a conditioned response to CS1. In stage two, a novel stimulus (CS2) is introduced simultaneously with CS1, and the two together are paired with the UCS. In the normal animal the introduction of the novel stimulus produces dishabituation of the experimental situation, but, because it is not associated with a change in that situation, it, and the experimental situation, are rehabituated together. CS2 therefore is associated with internal inhibition, and conditioning to it is accordingly retarded. In the MB lesioned animal, however, dishabituation cannot take place. CS2 therefore never undergoes habituation and does not become an inhibitory stimulus. Conditioning to CS2 therefore takes place normally. The finding by Rickert et al. (1981) that both hippocampal and MB lesions prevent Kamin blocking is thus consistent with the hypothesis.

5.2.5. Conclusion

Lesions of the hippocampus and one of its major output stations, the MB, produce behavioural effects which are complexly interrelated. On some tasks they are similar, while on others opposite results are obtained. The hypothesis that the MB plays a role in inhibiting internal inhibition provides a framework for understanding this relationship.

6 THE HIPPOCAMPUS, INHIBITION AND SLEEP

6.1. INTRODUCTION

One of the most contentious of Pavlov's assertions was that sleep and internal inhibition were linked. The sixth and final chapter in this section has the dual aim of reconciling Pavlov's observations on sleep with those of more recent researchers, and exploring the role that the hippocampus might play in such a formulation.

6.1.1. Sleep as an active process

Early formulations, no doubt influenced by the radical behaviourism of the time, held that sleep was the natural state of the brain and that stimulation was required in order to produce arousal (see Bremer 1954; Kleitman 1963). Thus sleep was accomplished by a "deafferentation" of the brain by reducing visual, auditory and somasthetic input. This passive view of sleep directed attention not to the state of sleep, but to the mechanism of waking, and handsome dividends were collected when Moruzzi and Magoun (1949) established the presence of a "waking centre" in the mesencephalic reticular formation.

Ironically it was Moruzzi and his group who later paved the way for the overthrow of the old order. They showed that a pretrigeminal mid-pontine preparation displayed an excess of wakefulness, thereby indicating that an active process was necessary to induce sleep (Batini et al 1958). There is now

impressive evidence in favour of this view. It has been shown that chemical (Hernandez-Peon & Chavez Ibarra 1963) or high frequency electrical (Sterman and Clemente 1962) stimulation of the lateral preoptic area of the hypothalamus results in a rapid (+/- 30 seconds) onset of sleep, even in the face of a strong competing drive. Similarly, stimulation of the vago-aortic (Puizillout and Foutz 1977) and other (Kukorelli and Juhasz 1976) autonomic nerves induces a rapid sleep onset. In order to understand what this active process might be, it is necessary to turn to a behavioural analysis.

6.1.2. The inhibitory basis of sleep

One of the most thorough investigations into the phenomenon of sleep was conducted by the Pavlov school (Pavlov 1927). While engaged in studies on classical conditioning, Pavlov and his co-workers were troubled by the insistent intrusion of sleep in their animals. Initially this was regarded only as a technical problem, and various strategies were devised in order to keep the dogs awake. Later, however, Pavlov realised that it was only during the action of inhibitory stimuli that sleep was evident. For example, the repetition of a CS without reinforcement soon produced drowsiness in an animal. Similarly, during the elaboration of a delayed reflex (see p. 130), parallel with the development of internal inhibition, there was a progressive change from drowsiness to eventual sleep. This would appear soon after the onset of the CS, and the animal would only awaken at the moment of release of the CR.

Results such as these persuaded Pavlov that sleep and inhibition

were one and the same thing - that sleep was, in fact, "a widely irradiated inhibition".

This view has been challenged on the grounds that the experimental situation was such as to encourage sleep (Konorski 1948), which rather begs the question of what the relevant variables are. Pavlov is more explicit. He found that one of the most effective ways of combating sleep was simply the elaboration of a new reflex. In other words, sleep or arousal was dependent not on the experimental situation, but on whether the CS aroused excitation or produced inhibition.

Powerful evidence in favour of Pavlov's inhibitory theory of sleep was adduced by the extraordinary results of Oswald (1960), who found that bright flashing lights and strong electric shocks, synchronised to the beat of loud jazz music, soon induced sleep in his subjects (and this with their eyes taped open!). That this sleep was not due to some kind of sensory overload is evidenced by the fact that the subjects awoke if one of the stimuli was administered asynchronously.

Further evidence comes from physiological studies. It has been found that those areas of the CNS that are necessary for sleep are also associated with inhibition. For example, destruction of the raphe nuclei (Jouvet 1967) or of the lateral preoptic area (Nauta 1954) produce insomnia. Stimulation of these same areas produce behavioural inhibition (Siegel and Brownstein 1975; Clemente 1969), and the latter study alsdo showed mono- and polysynaptic reflex inhibition.

Nevertheless, despite the convincing evidence linking inhibition and sleep, there are certain data with which it is difficult to reconcile the theory. One of the most obvious is that sleep consists of two distinct phases.

6.1.3. The dual nature of sleep

The discovery that sleep is not a unitary phenomenon is usually credited to Aserinsky and Kleitman (1953), who found that infants displayed vigorous eye movements during sleep. This led to all-night recordings of adults, which established that they too showed periods of rapid eye movements (REMs), concomitant with a desynchronised EEG. This unusual state, appropriately termed paradoxical sleep (PS), was found to alternate with slow wave sleep (SWS) (as the deeper stages of orthodox sleep are called) approximately every 90 minutes. There were usually five cycles per night, with the PS phase lengthening as the night progressed. Overall, some 25% of sleep time was spent in this stage.

Research was further stimulated by the finding that vivid dreams were almost exclusively associated with PS (Dement and Kleitman 1957) and there was even evidence to the effect that the type of REMs reflected the content of the dream (see Koulack 1972). Several avenues of research have confirmed that PS represents a period of intense CNS activity, rivalled only by a state of convulsions. Cerebral blood flow (Kety 1967), neural firing (McGinty et al 1974), neural transmission (Jouvet 1967) and brain temperature (Kawamura and Sawyer 1965) are generally increased above waking levels. This CNS activation is prevented from expression by a profound atonia of the antigravity muscles as

evidenced both by EMG recordings and the inhibition of spinal reflexes (Pompeiano 1967). Not all of the CNS excitement is successfully contained, as shown by twitching of the extremities and fine muscles of the face, middle ear and eyes. Activation of the ANS is shown by fluctuations in heart and respiratory rate and penile erection. To this general picture of an aroused brain must be added the rider that PS represents a "deeper" stage of sleep in that it is more difficult to arouse a subject, whether by reticular formation (RF) stimulation or external stimuli (unless the stimuli are meaningful (Okuma et al 1966)).

Finally, an important and intriguing aspect is that both SWS and PS are "needed", in that if a subject is deprived of either, then a rebound excess of that type of sleep is seen when uninterrupted sleep is once more allowed (Dement 1960). This oft repeated demonstration of the inability of the one type of sleep to substitute for the other underscores the now widely accepted view that these two types of sleep are distinct and subserve different functions.

6.1.4. Theories of paradoxical sleep

What exact function a highly active CNS could serve in the middle of a state of insentience and bodily quiescence has stimulated a vast amount of research, but, as Dement (1973) has reiterated, "the biological riddle of the decade" is in no imminent danger of being solved.

Most theories have tended to concentrate on one of the more prominent features and to make that the raison d'etre of PS. A few

examples of the more widely known theories will serve as illustration.

(i) The ontogenetic hypothesis. Roffwarg et al (1966) have noted that a curious characteristic of PS is that it is more prevalent in the young of the species. Depending on the degree of prematurity, it occupies between 50% - 80% of sleep time in the neonate. They justifiably point out that any theory of PS must take account of this ontogenetic aspect. Their solution is that PS serves to provide endogenous stimulation for the structural differentiation of the developing brain. Unfortunately, the role of PS in adult sleep is left unclear.

(ii) Perhaps in order to account for the above objection Ephron and Carrington (1966) have proposed a homeostatic theory. This suggests that the prolonged neural inactivity during SWS leads to a loss of corticaL "tone". This must be counterbalanced by periodic excitation to maintain this tone within "adaptively appropriate limits".

(iii) In a somewhat similar vein, Berger (1969) has postulated that the inactivity during SWS leads to a disruption of the sensitive mechanisms underlying stereoscopic vision. To maintain their viability, periodic conjugate eye movements are necessary.

(iv) Dement (1969) has proposed that some kind of "neural energy" or drive accrues during SWS and that PS subserves the function of some kind of safety valve which allows the CNS to "blow off steam".

(v) Snyder (1966) points to the vulnerability of animals during SWS. He observes that animals often wake briefly at the transition from PS to SWS and suggests that this allows the animal to ensure that no danger threatens.

It is clear that none of these theories is entirely satisfactory. They are either inconsistent with the data (see for example Berger's (1969) appraisal), or are inadequate to account for general characteristics of PS like, for example, the rebound phenomenon. The role of SWS is left uncertain and the mechanisms underlying SWS and PS and their alternation are unspecified. Furthermore, most of these theories are predicated on the assumption that PS is contingent on SWS. Yet Carskadon and Dement (1977) have been able to induce PS sleep independently of SWS by simply subjecting normal adults to a 30/60 minute sleep/wake cycle. Under these conditions SWS and PS tend to seperate out, with one sleep period devoted to SWS and the next to PS.

In order to understand such results, it is necessary to have a broader concept of the function of sleep. In this regard it would be useful to look at sleep deprivation studies.

6.1.5. The effects of sleep deprivation

It is a reasonable assumption that, whatever function sleep may subserve, it will become apparent as a deficit when sleep is denied. However, this expectation has not been fulfilled. Although the common-sense notion that sleep has recuperative properties has received indirect support (see Oswald 1976), the results of sleep deprivation studies <u>per se</u> have been

disappointing. There were intitial reports of gross psychopathology, but it soon became apparent that prolonged sleeplessness in normal, healthy individuals results in surprisingly little alteration in psychological functioning. Kleitman (1963), for example, has pointed out that, although the attention span is reduced, little intellectual deterioration is seen, provided the test is of short duration.

One consistent finding has been that the subject must be constantly active in order to stay awake. Rest for even a moment results in sleep. Movement thus appears to be a most potent anti-sleep agent. Dement (1972) has even gone so far as to express the opinion that provided the individual is fit enough, sleep could be staved off indefinitely.

Results such as these have given rise to a feeling of scepticism as to whether sleep has any function at all. According to this view (expressed most cogently by Webb 1974) sleep is an adaptive mechanism which serves an evolutionary function by keeping the organism out of harm's way during a period when it is ill-equipped to move around.

It is, of course, a moot point as to whether an animal is less vulnerable during a hyporesponsive state such as sleep (cf. Snyder 1966). Surely, as Berger (1969) has pointed out, it would be of far greater survival value to rather impose a rest state on the organism where movement, but not consciousness, is curtailed. In fact, when one considers the enormous evolutionary advantage to be gained from being able to operate 24 hours per day, one can only wonder at the fact that animals that do not sleep, with both

daylight and infrared vision (as in some snakes), have not evolved.

No, sleep is too ubiquitous to be brushed aside merely as an evolutionary ploy. Sleep is obviously necessary, and yet all that results from sleep deprivation, as Webb (1974) has wryly summed up, is sleepiness. But is this as facile an observation as it first appears? Are we not in danger of making one of Ryle's (1962) category mistakes? If we redefine sleepiness as an inability to stay awake, then we have indeed found a deficit - a deficit in those factors which cause wakefulness. Thus it seems reasonable to propose that one of the main functions of sleep is the restoration of such processes of the CNS as are necessary for the maintenance of prolonged periods of consciousness (in the absence of massive proprioceptive input).

6.1.6. Synthesis

To sum up : there are two distinct types of sleep which are somehow related to internal inhibition and which subserve the needs of consciousness. Now it is taken as axiomatic that both excitation and inhibition are necessary for the normal expression of consciousness. Further, both of these processes are tonic and fatigueable, and therefore require periodic rest in order to remain in optimal condition. It is proposed that this rest is taken seperately : that SWS represents the time of rest for the excitatory system (E-rest), and that PS represents the time of rest for the inhibitory system (I-rest).

6.2. A SIMPLE MODEL

In order to investigate the implications of the above hypothesis, it is necessary to develop a simple conceptual model of how excitation and internal inhibition are organised in the CNS. To this end it will be convenient to use the extinction of a response as a model, since it is one of the simplest phenomena utilising internal inhibition.

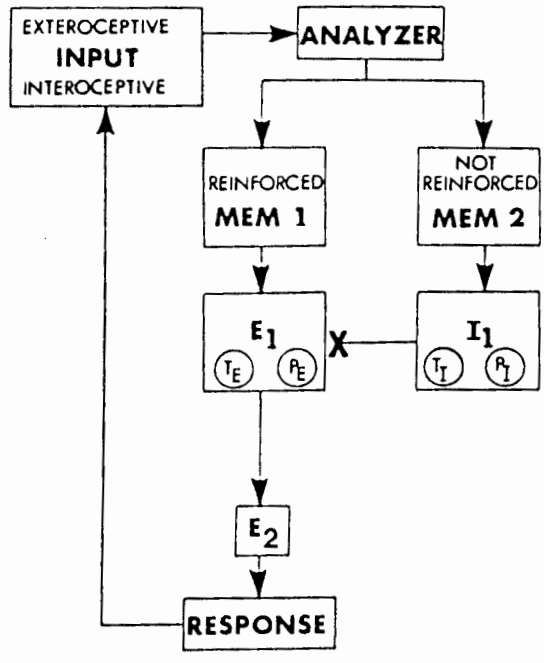

FIG. 6. A simple model to account for extinction. An input which has previously been associated with reinforcement will activate MEM1, which will in turn excite the appropriate response via E1 and E2. If reinforcement is withdrawn, MEM2 will be enabled thus causing I1 to inhibit the output. TE and TI represent tonic excitatory and inhibitory neurons which require periodic rest. Arrows and crosses indicate excitation and inhibition respectively.

Pavlov's work indicates quite clearly that the neural components of an extinguished response are still active, but that their expression is blocked by internal inhibition. Fig. 6 indicates how this could be achieved : a stimulus which has previously been

associated with reinforcement will excite the appropriate response via the excitatory memory store (MEM 1) and the excitatory motivational/motor integration units E1 and E2. Should reinforcement be withdrawn, the inhibitory memory store (MEM2) would be enabled, thus blocking E1 by activation of the inhibitory centre I1.

Central to the theory of sleep outlined above, the excitatory (E1) and inhibitory (I1 and MEM2) systems are suggested to contain two types of neurons, phasic and tonic, which subserve different functions. Since the phasic neurons (PE and PI) can regenerate during their interburst intervals, it is the tonic neurons (TE and TI) which, having no such respite, are postulated to require periodic rest in order to replenish their energy and neurotransmitter supplies (see Model et al 1975). Since it would be obviously maladaptive to allow them to run down to the extent that the organism would be incapable of reacting adequately in an emergency, it is hypothesised that the two systems are connected in such a manner that an imbalance will cause rest (inhibition) of the one which is most exhausted. While inactive, the system will be able to recuperate, and it is the purpose of sleep to restore the balance between the two systems. Since I1 already has an inhibitory connection with E1, in order to achieve reciprocity, it is only necessary to add another inhibitory centre (I2), connected such that stimulation by E1 would produce inhibition of I1 (Fig. 7).

It is clear that the connections I1 - E1 - I2 - I1 represent a positive feedback circuit such that an imbalance of either E1 or I1 will result in the total inhibition of the weaker component (in

the absence of any external competing influences). This carries the corollary that, while the one is resting, the other will be released and operate at maximal output. For example, should I1 become predominant (due to the action of an inhibitory stimulus, say) then E1 will become somewhat depressed, resulting in a lessening of action of I2 and thus further releasing I1. This positive feedback loop would continue until E1 was profoundly depressed. The organism would now obviously be hyporesponsive, since only strong or meaningful stimuli would be able to produce sufficient arousal to counteract the inhibition. In other words this would constitute a state of slow wave sleep, or E-rest.

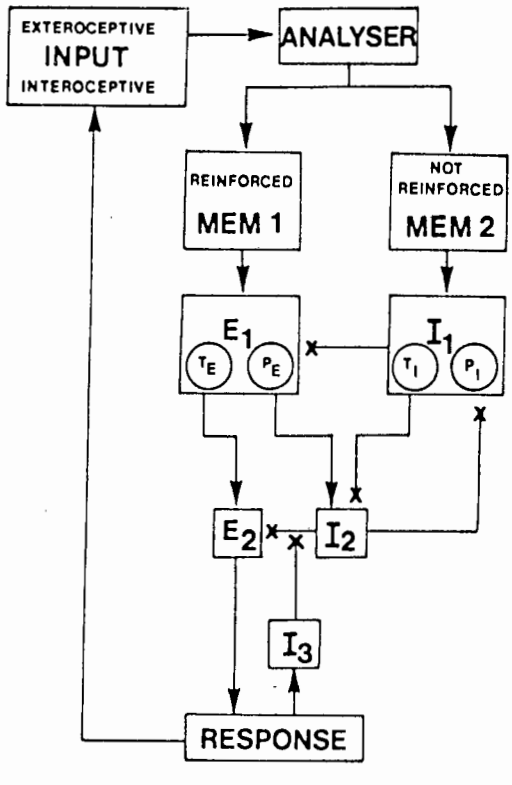

FIG. 7. An extension of Fig. 6 to show what connections are necessary to ensure that the tonic excitatory and inhibitory neurons are rested. For full explanation see text. Symbols as in Fig. 6.

On the other hand, if E1 were to become dominant, I2 would become increasingly stimulated by E1, eventuating in the inhibition of I1. This would constitute a state of I-rest, and the resulting explosive release of excitation would produce, of course, the phenomena seen during paradoxical sleep.

In order to prevent this neural activity from finding expression in muscular activity, a further inhibitory connection must be made from I2 to E2 (Fig. 7). Since E1 excites I2, spinal inhibition during PS will be proportional to CNS excitation - a fact supported by Pompeiano (1967).

During waking, the inhibition of E2 by I2 must obviously be prevented, so a final inhibitory connection is made from I1 to I2 (Fig. 7). Thus, since ordinarily an organism is subjected to an array of both excitatory and inhibitory stimuli, the excitatory effect of E1 on I2 will be balanced by the inhibitory effect of I1 on I2, and a state of dynamic equilibrium will result (i.e. alert wakefulness).

It would be easy to expand the model to include a "biological clock" to account for circadian rhythms, but in the interests of simplicity this will not be further explored.

6.2.1. The cyclical nature of sleep

During the period when I1 is inhibiting E1 (E-rest), E1 is being regenerated and, of course, some I1 is being used up. Thus, there will come a time when E1 will be of greater strength than I1, and this will start off a new positive feedback cycle in the opposite

direction. I2 will become increasingly stimulated by E1, eventuating in the inhibition of I1 and E2 (i.e. I-rest).

During this period I1 will be similarly recharged, which will eventually set off another cycle as soon as I1 is greater than E1. This process will continue (if the organism is left undisturbed) until both E1 and I1 are balanced, at which point the animal will wake. It is obvious that the longer the intervening wake period, the more E1 and I1 will be used, and the more cycles can be expected in the ensuing sleep period before parity is reached.

It is quite possible, of course, that a time will come during the sleep period when E1 and I1 will momentarily balance and waking will occur even though they are not fully charged. The likelihood of this happening will greatly increase at, or near, the switchover point from one type of sleep to another and, indeed, it is well documented that waking or gross body movements often mark the changeover from PS to SWS and vice versa (Kleitman 1961; Snyder 1966).

Most activities would normally use equal amounts of excitation and inhibition, and this is reflected in the fact that SWS and PS each command approximately 25% of sleep time (the rest of the sleep period presumably being spent on cycling between the two states). However, if a person was denied PS, then a large inhibitory deficit would accrue, and when undisturbed sleep was once more allowed a rebound increase in the percentage of PS would be seen, since more I-rest would be required.

6.2.2. The primacy of SWS

The fact that SWS almost invariably precedes PS requires some explanation. The model would seem to indicate that during wakefulness, if E1 became dominant, perhaps due to some arousing event, then I2 would be stimulated to inhibit I1 and E2, thus precipitating a PS-onset sleep. However, it should be noted that the inhibitory effect of I2 on E2 is prevented by proprioceptive feedback acting via I3. Should this system be deficient, a disorder associated with narcolepsy, known as cataplexy, results. It is distinguished by the fact that any strong emotion initiates a sudden paralytic attack. Significantly, if the cataplectic state continues for a prolonged period, it develops into a full-blown PS episode (Rechtschaffen and Dement 1969).

PS onset sleep is not restricted to narcoleptics. Young children, too, frequently display this phenomenon. In terms of the model, this can be understood as being due to the underdeveloped state of their inhibitory systems. Prolonged activity will therefore result in I1 being depleted before E1. The resultant excess of excitation will stimulate activity (the proprioceptive feedback of which will prevent PS) and play will become more and more frantic. The child is then said to be "overtired". If the child is now put to bed (thus limiting proprioceptive feedback) a dramatic, rapid sleep induction is observed.

The importance of proprioceptive feedback is further demonstrated by the fact that a state of paralysis somewhat similar to PS, so-called animal hypnosis, can be induced in animals by combining intense arousal (fear) with physical restraint.

Normal adults can also show PS-onset sleep if they are PS deprived, and mention has already been made of the work of Carskadon and Dement (1977) with 30/60 minute sleep/wake cycles.

6.3. SOME PHYSIOLOGICAL EVIDENCE

Although the model developed above is intended to be purely conceptual and is deliberately over-simplified, its value would obviously be enhanced if it could be shown to have some physiological relevance. Accordingly, an attempt has been made to place it in a neuroanatomical framework.

The main excitatory centre (E1) is suggested to be part of the descending reticular formation, while analysis of information is carried out by the sensory receptors and their terminations in the neocortex. MEM1 probably comprises parts of the thalamus and hypothalamus, since diencephalic animals are still capable of learning operant tasks (Huston and Borbely 1974). Clearly the hippocampus, which has already been suggested to act as an inhibitory memory register, would fill the role of MEM2, and the striatum and ventral striatum (i.e. nucleus accumbens and olfactory tubercle) would constitute the main inhibitory centre, I1. It is sufficient, for the present purposes, to note that the substantia nigra would seem to be ideally situated to play the part of I2. It is connected with the major brain stem nuclei (Pasquier et al 1977) and has the requisite reciprocal inhibitory connections with the components of I1.

Using the above as a tentative anatomical base, the model proves to explain physiological data tolerably well. For example, in line

with the hypothesis, McGinty et al (1974) have noted that, in contrast to the general pattern, neurons in areas involved with behavioural inhibition tend to increase firing during SWS and decrease firing during PS. As alluded to earlier (p. 109, and dealt with in detail in chapter 8), this is true for the hippocampus, and also the caudate (Rougeul et al 1966). Furthermore, we can predict that if the model is correct and the different sleep stages are determined by the relative strength of the excitatory or inhibitory systems, then while the animal is in one sleep state, it should be possible to induce the opposite state by artificially raising the strength of the inhibited system. Thus, if the animal is in a state of PS, stimulation of the hippocampus or other inhibitory structure should flip the system back into SWS, and, indeed, such is the case (Smythies 1970 p.108). The converse holds too. Jouvet (1967) states that high-frequency stimulation of the pontine or mesencephalic reticular formation during SWS will trigger the appearance of PS, provided a refractory period immediately after a preceding PS episode is allowed for. Similarly, intravenous infusion of the excitatory drug physostigmine during SWS, hastens the onset of PS in humans (Sitaram et al 1976).

The situation is more complicated in the awake animal. Prolonged stimulation of El might be expected to use up large amounts of excitation with the result that subsequent sleep should show an increase of E-rest. Although this is so, Frederickson and Hobson (1970) found that constant electrical stimulation of the RF for several hours (using several electrodes alternately to prevent neural damage) produced an excess of I-rest as well. This seemingly contradictory result is explicated by the experiments of

Dell et al (1961), who reported that in the anaesthetised or decorticate preparation, RF stimulation resulted in the expected increase of spinal reflexes. However, in the awake, intact animal, RF stimulation actually produced a decrease in spinal reflex amplitude, thus indicating that RF stimulation induces a cortically mediated excess of inhibition. Since this would be predicted to produce a subsequent PS rebound, the results of Frederickson and Hobson (1970) are consistent with the model.

The model also helps clarify the perplexing finding by Satinoff et al (1971), that while PS deprivation results in the expected increase in forebrain excitability, it produces strong inhibition of the hindbrain. This would be predicted in terms of the release of I2 with the weakening of I1.

A final point which requires clarification is the fact that PS is far more prevalent in the newborn than in the adult. This excess PS can hardly be ascribed to an increased need of I-rest due to large-scale inhibitory utilisation, since the neonate's forebrain inhibitory system is very poorly developed (see Chase 1974), and besides, the more premature the infant, the more abundant is PS. The solution lies in drawing a distinction between function and cause. While the function of PS may be I-rest, the cause of PS is I1 inactivity, with consequent release of E1 and I2. Since I1 is so poorly developed in the neonate it will be inactive most of the time, so one would expect PS to be the dominant sleep type. This explanation is strongly supported by the finding that ablation of the caudate nucleus in the adult rat increases the incidence of PS by some 250% (Corsi-Cabrera et al 1975).

6.4. PSYCHOLOGICAL IMPLICATIONS

If the relationship between excitation and inhibition and states of sleep outlined above is correct, then manipulation of PS should affect any psychological variables which are dependent on a substrate of internal inhibition, and vice versa. That these two physiological sleep states do have distinctive psychological concomitants is shown by the fact that several optical illusions have been found to be augmented after waking from PS. Of particular interest are the experiments of Lavie and Sutter (1975), working with the phi phenomenon. This is an illusion of apparent motion when two lights are flashed on and off at an optimal frequency. Concordant with the concept of PS being a period of I-rest, they found that the upper and lower limits of the frequencies at which the phi phenomenon was reported were wider than normal if tested immediately after waking from PS, and narrower than normal after waking from SWS.

6.4.1. PS deprivation and hyperactivity

One of the more straightforward predictions of the model is that PS deprivation (PSD), by preventing the recovery of internal inhibition, should result in an inhibitory deficit. Unfortunately, the interpretation of results from deprivation studies using animals is complicated by the difficulty of adequately controlling for the deprivation procedure. Nevertheless, it is the opinion of two recent reviewers (Fishbein and Gutwein 1977; Vogel 1975) that PSD does result in increased central and neural excitability and motivated behaviour. General activity, too, is increased (Albert et al 1970), and in this

regard it is interesting to note the similarity between PSD animals and children with minimal brain dysfunction. Especially intriguing is the fact that they both display a paradoxical response to activating drugs like amphetamine. Instead of performance being disrupted it is actually improved (Hartmann 1973).

This result can be understood if one accepts that both groups suffer from a lack of internal inhibition. In the case of the PSD animal, I1 and MEM2 are deficient, and in the case of the hyperkinetic child it seems possible that, since the hippocampus is the most sensitive part of the CNS to anoxic trauma (Green 1964), MEM2 is damaged. Now, as mentioned previously, it appears that amphetamine, a sympathomimetic drug, acts by way of potentiating the catecholamine systems of the brain. It is known that stimulation of the substantia nigra inhibits the caudate by releasing DA, and that amphetamine potentiates this effect (see Groves et al 1974). Thus amphetamine seems to produce part of its excitatory effect by disinhibition.

Furthermore, Groves et al (1974) have shown that amphetamine produces a biphasic effect on the caudate neurons - first a modest increase and then a profound decrease in the firing rate. This biphasic response suggests that amphetamine also potentiates a system which has an excitatory effect on the caudate (MEM2 ?) which is later overpowered by the inhibitory effects of dopamine. This interpretation is supported by the results of a related experiment where Groves et al found that blocking of the amphetamine-induced dopamine inhibitory effect, by the administration of haloperidol (which on its own caused little

change in unit activity), not only restored the caudate firing to normal, but actually resulted in a 300% increase in the firing rate.

If we accept the argument that amphetamine has a dual excitatory and inhibitory effect on I1, then we are in a position to explain why amphetamine has a differential effect on nervous systems with an inhibitory deficit. Normally, I1 is innervated by both I2 and MEM2, and as we have seen, amphetamine potentiates both systems, but the inhibitory effect of I2 overpowers the excitatory effect of MEM2. The nett effect is an increase in motor output. However, in the case of the PSD animal and the hyperkinetic child, both suffer from a weakened I1. Therefore I2 will already be released and will be inhibiting I1 near maximally. The excessive amount of dopamine thus released will cause a decrease in the number of post-synaptic receptor molecules (see Romero et al 1975) on the caudate neurons, thus making the caudate tolerant to dopamine. The administration of amphetamine to this system will now have a quite different effect. The increase of dopamine brought about by this drug will produce little further inhibition of the caudate (since it is hyporesponsive to dopamine), but the potentiation of the effect of MEM2 will produce a significant increase in the excitation of the caudate, and a relative decrease in motor output will be observed. Based on this analysis, the model would predict that the administration of smaller amounts of amphetamine, along with haloperidol, would be more effective in controlling hyperkinetic children, and that, contrary to normal, such children would show an increase in PS following stimulant administration.

6.4.2. Learning

Since the act of learning requires the extinction of incorrect responses, one would expect this use of internal inhibition to be reflected in an increased need of I-rest. Fishbein and Gutwein (1977) have recently reviewed evidence showing just such a relationship. PS was augmented during the training period, but fell back to control levels once the task was well learned.

Since learning produces a need for more PS, it would be expected that PSD would have a deleterious effect on learning. However, the situation is far from clear . In addition to the aforementioned confounding variables associated with the PSD technique, different tasks have produced conflicting results (see Vogel 1975), and herein lies the source of a tentative solution advanced by Holdstock and Verschoor (1973). Pointing to the fact that PSD disrupts the acquisition of passive avoidance but not active avoidance tasks, and complex maze but not simple maze retention, they suggest that the effects of PSD may be task-specific. Such a solution is completely consonant with the I-rest theory of PS, since, as we have seen, internal inhibition is essential for the performance of passive avoidance and complex maze tasks, is unnecessary for a simple T-maze task, and is actually prejudicial to the rapid performance of two-way active avoidance tasks. This explanation is clearly supported by a careful study by Plumer et al (1974) who showed that PSD facilitated the acquisition of a two-way active avoidance task. The idea that PSD produces a temporary inhibitory deficit is further enhanced by the finding that post-training PSD impairs passive avoidance performance, but if 24 hours' recovery is allowed, the impairment disappears

(Fishbein 1971). It is surely no coincidence that lesions of the hippocampus produce essentially the same results (i.e. impairment of passive avoidance, and facilitation of two-way active avoidance tasks).

6.4.3. Depression

One of the more obvious features of depression is psychomotor retardation. Without wishing to detract from the psychological causes of such a condition, it does not seem unreasonable to suggest that an underlying substrate of internal inhibition is involved. Once started, the excess inhibition sets up a vicious circle, with less contact with the environment leading to lack of reinforcement, resulting in increased withdrawal, etc. To the extent that this is so, the I-rest theory of PS would predict a consequent increase in the amount of PS. This is found to be true in a large number of cases (Hartman 1973). Furthermore, the theory indicates that one way of reversing the dynamics of depression would be to prevent PS, thus frustrating any attempt to restore internal inhibition. This would not alter the cause of the depression, but would deny the hardware necessary for its expression. In one of the more exciting developments in this area, Vogel (1975) has shown that PSD is indeed an effective anti-depressant. Deprivation of SWS, on the other hand, produces lethargy and depression (Agnew et al 1967).

It has been pointed out (Stern and Morgane 1974) that the traditional methods of treatment for depression [electroconvulsive therapy (ECT), amphetamine, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs)] all produce a marked suppression of

PS, and the suggestion has been made that these methods may in fact be efficacious because of this effect.

It is interesting to speculate on the manner in which these different treatments produce PS depression. Amphetamine, the tricyclics and MAOIs all increase the synaptic availability of the catechol- and indoleamines by decreasing their rate of degradation. One effect of this, as shown above, is to increase the inhibitory effects on the forebrain inhibitory system, thus producing behavioural activation. The resultant under-utilisation of internal inhibition decreases the need for I-rest, and thus less PS is seen.

The mechanism of action of ECT is more obscure since it is a non-specific agent. However, a clue is afforded by the fact that the inhibitory system of the forebrain is far more sensitive to insult than the excitatory system. A familiar example is that of alcohol. Moderate intake of this non-specific neural depressant disrupts first the inhibitory system (with consequent release of excitation), and only after heavy drinking is the whole CNS depressed. In fact, alcohol intake over a number of days results not in a depression of neural activity, but in a marked CNS arousal (Akiskal et al 1974) due, I submit, to the suppression of inhibition (which, incidentally, also results in a reduced need for I-rest, i.e. PS suppression).

This vulnerability of the inhibitory system is more pertinently illustrated by the case of the hippocampus. This organ is extraordinarily susceptible to seizures, whether induced by electrical, chemical or mechanical means (Green 1964) and, as

Cohen and Dement (1966) have so clearly demonstrated, it is the production of seizures, whether by drugs or ECT, which has PS reducing properties. Furthermore, Rondouin et al (1975) have recently shown that seizures of the hippocampus alone suppress PS, and like Cohen and Dement (1966), they found no compensatory PS rebound. Finally, it is known that ECT produces effects similar to those seen after hippocampectomy (see Douglas 1975). Thus it seems justified to suggest that ECT produces its effect by convulsing the hippocampus. Since the hippocampus forms part of MEM2, this will have the initial effect of discharging I1, thus producing SWS. It seems a reasonable supposition that the convulsions and their aftermath will leave the affected structures in a state of temporary functional ablation, thus removing an excitatory input to I1. During this time the patient will be in a state similar to the hyperkinetic child, with under-utilisation of inhibition, and consequent diminished PS. This suggestion is concordant with results showing that hippocampectomy reduces PS in cats (Kim et al 1975), and further elucidates the relationship (in man) between ECT, memory loss, mood elevation and hippocampal damage.

Although ECT-produced PS suppression does not result in PS rebound, drug mediated PS depression, if chronic, does. Again, as Stern and Morgane (1974) have pointed out, this can be explained in terms of drug tolerance. For example, in the case of chronic amphetamine administration, caudate neurons will become insensitive to dopamine, with the result that when amphetamine is withdrawn, normal levels of dopamine will be ineffective in switching them off. The caudate will therefore become excessively active, producing excess inhibition and concomitant mood

depression. An inhibitory debt will accrue due to this overuse of inhibition, and this will be repaid during sleep by increased I-rest.

6.4.4. Bipolar depression

The above account of how an activating drug can produce mood elevation by disinhibition, and then, upon withdrawal, release of internal inhibition with consequent mood depression, gives some indication of how bipolar depression may arise.

If we assume that the chronic overstimulation of the inhibitory system during depression will result, as above, in tolerance of I1 to that neurotransmitter then, when the neurotransmitter levels eventually return to baseline, they will be ineffective in stimulating I1. Thus E1 would be released and mania would result. When excitation fatigued, I1 would dominate and SWS would ensue. Little PS is seen (Hartmann 1973) since internal inhibition has been conserved during the day.

Fig. 8 illustrates in highly schematic form the periods during which inhibition is most active during depression (Fig. 8a) and mania (8b) as compared with normal (8c). It can be seen that inhibition and excitation have seperated out in the two conditions and that depression and mania are 180 degrees out of phase with each other as far as inhibiton with respect to sleep is concerned. It is clear that they can therefore be seen partially as disorders of sleep. (It must be emphasised that it is not just a matter of sleep. There is also a propensity for the inhibitory system to be under- or over-responsive.)

One of the methods, therefore, of restoring the balance between inhibition and excitation would be to break the sleep/wake pattern which maintains their seperation. Mention has been made of PSD for depression, and even total sleep deprivation has been found effective (Bhanji and Roy 1975), though less so, since both E-rest

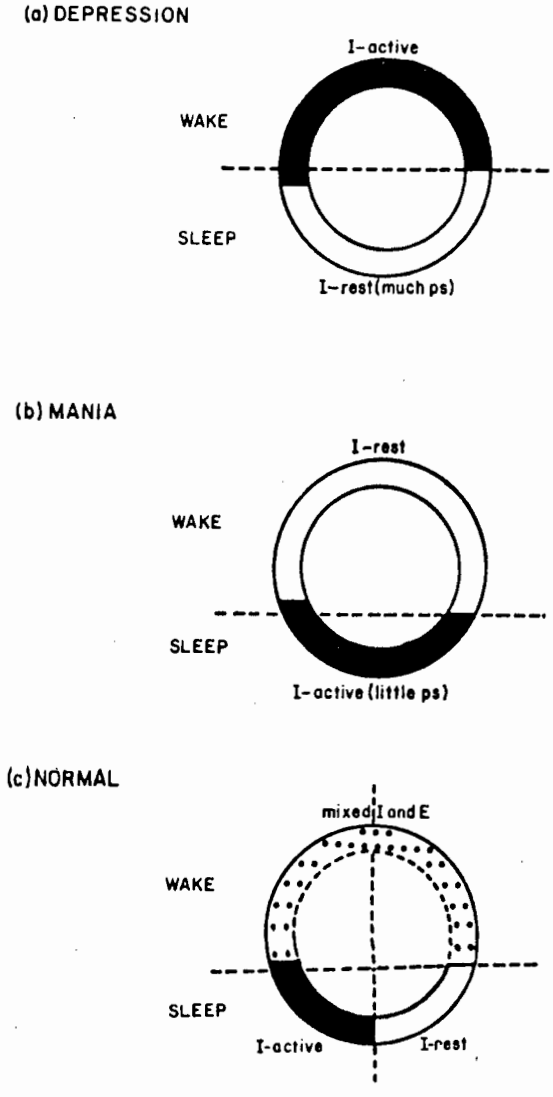

FIG. 8. A schematic representation of the relationship between inhibition and sleep in (a)depression, (b)mania, and (c)under normal conditions. The dark area indicates periods of inhibition, the white area excitation, and the dotted area indicates mixed excitation and inhibition. It can be seen that depression is the inverse of mania. In depression, inhibition is active during wakefulness, whereas in mania inhibition is active during sleep.

and I-rest are prevented. It is noteworthy that sleep deprivation can reset the cycle so effectively that mania results. If the present analysis is correct, then it seems probable that mania, too, could be managed by the same methods as for depression, i.e. prolonged total sleep deprivation. Although this normally has activating effects, in the case of mania it would result in almost exclusive E-rest deprivation with consequent stabilisation.

6.4.5. Personality

In a manner akin to the preceding section, one would expect personality variables which have a differential demand on inhibition to be distinguished by the amount of PS they require. A good example might be Eysenck's (1967) introversion-extraversion dimension, since introverts can be characterised as being "inhibited", and extraverts "uninhibited" personalities. Inasmuch as these psychological appelations reflect underlying internal inhibition, the aforementioned relationship should hold.

Hartmann (1973) provides evidence to support this contention. In a study of long (9 hours, plus) and short (6 hours or less) sleepers, he found that they had similar amounts of SWS, but that they differed in the amounts of PS they displayed. Short sleepers averaged about 60 minutes, and long sleepers approximately 120 minutes of PS (compared to the norm of 90 minutes). The results of personality inventories indicated that the group with less PS were extraverted, superficial and non-worriers, while the group with more PS were introverted, worriers and tended to depression.

Several investigators have also found the converse relationship.

PSD in humans alters personality in the direction of a loosening of inhibition. For example, Vogel (1975, p. 754), commenting on the results of PSD obtained by Dement (1964), describes one subject as a taciturn, inhibited, puritannical person who "became after 14 nights of REM sleep deprivation awakenings voluable and annoyed, and wanted to go to a burlesque show and to a tavern and cheat a waitress". Similarly, Greenberg and Pearlman (1974) report one of their experiments using the Rorschach, where they found that PSD produced changes "best characterised as ... emergence of conflictual content which had been more effectively suppressed in the baseline protocol".

6.4.6. Dreams

That the intense neural activation seen during PS is accompanied by equally intense mental activity, often of a bizarre nature, can hardly be denied. It has been pointed out, most notably by Foulkes (1962) that mental activity can occur during other stages of sleep, but, both qualitatively and quantitatively it is not of the same order. One exception to this rule would appear to be the work of Broughton (1968), who has been widely cited as showing that nightmares occur during SWS, not PS. However, it should be noted that he carefully differentiates nightmares from terrifying dreams (which do occur during PS). Nightmares, as he defines them, are periods of intense ANS activation produced/accompanied by respiratory depression and a feeling of being smothered. There is little mental content.

The fact of dreams, their association with PS, and the peculiar nature of the thought processes which constitute them, represent a

challenge which any theory of sleep must meet. Freud (1953) has contributed, more than any other man, to our understanding of dream-thought processes. He identified four types of mechanisms - condensation, displacement, symbolism and regression - which he felt described the distortions found in dream-thought. Of these, condensation, for our purposes, is the most important, since "it is the easiest to observe, and to it is mainly due the sense of foreignness that dreams give us, for it is a process with which our waking thought is not familiar" (Jones 1973,p. 42). It refers to the fact that elements of dreams are often over-determined they contain many diverse thoughts fused into one image. The result may be a composite figure constituted by the fusion of traits belonging to more than one actual person, or a neologism, produced, for example, by the fusion of two names, as in Norekdal (the classic example), from Nora and Ekdal. (It is interesting that Jones (1973) notes that these neologisms are similar to those met with in the psychoses.)

In order to account for these distortions, Freud felt compelled to evoke complex underlying psychical mechanisms like "censorship", the function of which was to "protect the sleep of the dreamer" -a disappointing circularity. A more parsimonious view can perhaps be gained by considering Freud's concept of free-association, together with the I-rest theory of PS.

Under normal waking conditions, free-association unfolds in an orderly, logical fashion, and yet each stimulus word or image must have many associations. It is, clear, therefore, that irrelevant and inappropriate associations must be inhibited by the "set" of the person. But, since internal inhibition is inactive during PS,

the normal logical flow of ideas would be upset during dreaming. One would expect tortuous, meandering thought to be prevalent, since there would be a great increase in the incidence of irrelevant, rhyming and clang associations. Instead of the serial connection of ideas, maintained by the inhibition of any other simultaneously arising associations, multiple, parallel chains of association could be set up, one result of which might be the illogical fusing together of many ideas into a compound image (see Fig. 9).

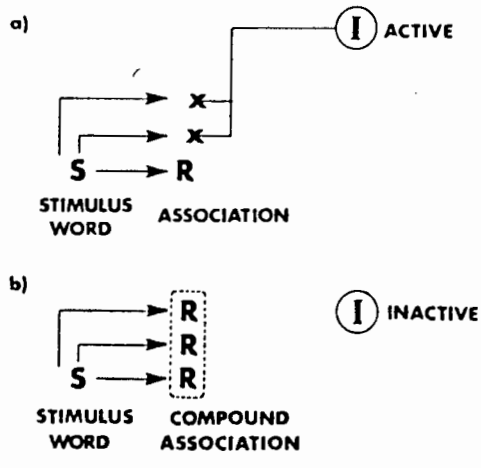

FIG. 9. a. Waking Thought: Inhibition is active and prevents spurious associations to the stimulus word. Only one idea is therefore present at any one time. b. Dream Thought: Inhibition is inactive during PS, therefore many associations can be made to the stimulus word. The result is that several ideas may be present simultaneously, producing condensation. A similar mechanism may be responsible for the "word salad" produced by some schizophrenic individuals.

Some support for the notion of the involvement of internal inhibition in the prevention of spurious associations, is derived from the studies of Van Buren et al (1966). They disrupted the normal functioning of the caudate nucleus by applying electrical stimulation, and presented test phrases during this period. When the patients were required to repeat them after the stimulation

PART TWO:

HIPPOCAMPAL THETA

7 A BRIEF HISTORY OF ANIMAL ELECTRICITY

7.1. OF LEYDEN JARS AND ELECTRIC FISH

1745 is probably an appropriate place to start a history of the electroencephalogram (EEG) since it marks the birth of the Leyden jar, fathered separately by von Kliest and van Musschenbroek. Although static electrical machines were available before this time, the strong shocks obtainable from this new instrument allowed for spectacular demonstrations which captured the public imagination. Hoff (1936, pp. 161-162) records, for example, that Abbe Nollet "discharged a Leyden flask through 180 of the King's guards at Versailles in the presence of the King, who was greatly amused. Being inflamed by the success of this experiment, he performed it on the entire membership of a Carthusian monastery, who, holding hands, formed a line just over a mile in length, and upon discharge of the phial all gave a sudden spring at the same instant, and felt the shock equally."

There followed a spate of reports on the ability of electricity to provoke contractions in normal and paralysed human muscles and, within a decade, Caldani (Professor of Anatomy at Bologna where Galvani was a student) was reporting on the effects of electrical stimulation of dog and frog nerve-muscle preparations. In the meantime the widespread use of electricity for medicinal purposes served to entrench it in the public mind as a physiological agent of extraordinary power. Thus the Zeitgeist was set for the maturation of ideas concerning "animal electricity". Up to this time the belief was that muscular contraction was brought about

through the action of "animal spirits", manufactured in the brain and conveyed to the muscles by the nerves - a view proposed by Galen some 1500 years previously. However, this "spirit" was difficult to demonstrate and, in view of the facility with which electrical stimuli acted on muscles, it occurred to several authors that electricity had all the characteristics of an ideal animal spirit.

At first the idea was treated with caution and even scepticism, but these doubts were quieted by the careful experimentation, first by Walsh and then by Cavandish in the 1770's, on the electrical nature of the electric ray and electric eel. The final barrier to the acceptance of animal electricity fell when Walsh finally demonstrated to fellow scientists that a spark was produced by the shock of the electric eel, around 1776-1777 (Walker, 1937).

7.2. THE GALVANI-VOLTA DEBATE

7.2.1. Luigi Galvani (1737-1798)

It is with this background of growing interest in animal electricity that one can understand why "few investigations have stirred the imagination, or have exerted as great an influence on the history of both physics and physiology" (Hoff 1936, p. 157), as the publication in 1791 of Galvani's "De viribus electricitatis in motu musculari commentarius".

His researches started with the chance observation of an assistant that muscular contractions were produced when the nerve of a frog

nerve-muscle preparation was touched with a scalpel. It was then noticed that the contractions only occurred in conjunction with the generation of sparks by a nearby electrostatic machine. It seemed obvious that the machine was affecting the nerve, but when Galvani insulated the preparation, the contractions upon sparking still continued. This puzzle drove Galvani to consider whether atmospheric electricity might not be the causative agent, since he had noticed contractions of frog preparations hung by copper hooks to the iron railings outside his house. Accordingly he spent several rather fruitless days observing preparations outdoors until he grew impatient, and began to press the hook fastened to the backbone against the iron railings. He was immediately rewarded with the sight of vigorous contractions. In great excitement he reports as follows:

"I next took the animal indoors and laid it on an iron plate, and having pressed the hook fastened to the backbone against the plate, behold, the same contractions , the same movements! I tried the same thing repeatedly, in other places, at different times and on various days, and using other metals, with the only difference that the contractions varied with the metals used, being stronger by some, and by others, weaker. Finally we observed that other bodies which conducted electricity poorly or not at all, such as glass, gum, resin, stone, or wood did not give similar results; no muscular contractions or movements could be seen. Naturally such a result gave rise to much reflection and the idea grew that in the animal itself there was an indwelling electricity." (Galvani in Hoff 1936,p. 158).

The idea was that the muscle acted as a Leyden jar, and

contraction resulted from the discharge of the electric fluid, from the inside of the muscle via the nerve to the outside, the applied metal merely serving to conduct the electricity. In his subsequent development of this theory Galvani offered nothing new. He "simply adopted the curent theory that animal spirits were distilled off from the blood in the brain, and substituted animal electricity for animal spirits" (Hoff 1936, p. 167).

It is interesting to note that the solution offered by Galvani did not accomodate the original puzzle which initiated the investigation, viz. that sparking of the electrostatic machine produced contractions in his preparation, provided that it was earthed. In fact the phenomenon had been explained in 1799 by Mahon in terms of the "returning stroke" even before Galvani made his initial observations.

7.2.2. Allesandro Volta (1745 - 1827)

Galvani's (1791) paper produced a flurry of activity as workers the world over attempted to replicate his results. Chief among these was Volta, who enthusiastically endsorsed Galvani's discovery. Volta had already established an enviable reputation in the field of electricity. He had explained the workings of the capacitor (condenser), and had developed the most accurate and sensitive electrometers of the time. Using these instruments, he now set to work to examine the implications of Galvani's findings. Assuming that the muscle was like the Leyden jar, he attempted to measure its charge, and found this to be almost vanishingly small. When he tried to do the converse, and estimate the magnitude of charge that was required to cause muscular convulsions, he found

that different types of preparations formed a series : a living frog required a fairly strong shock, a decapitated frog less, the nerve-muscle preparation used by Galvani responded to a barely measurable amount of electricity, and when this preparation was wrapped in metal leaf, the contractions resulted from a charge beyond the limits of measurement.

The suspicion thus grew in Volta that metals played at least a part in the production of the electricity which caused the contractions. Walker (1937) is of the opinion that Volta was either directed or encouraged in this view by the work of Bennet on the "adhesive electricity" of metals (Bennet, Cavallo and Volta were close friends and kept each other informed of their progress). Even before the publication of Galvani's "De veribus electricitatus", Bennet, using an ingenious device which multiplied any charge applied to it, was able to show that metals had small charges associated with them (adhesive electricity), which differed in sign and amount with the type of metal (Walker 1936).

This knowledge, together with a) Galvani's comments on the size of contraction being dependent on the metals used, and b) the puzzle of why two metals were required to produce contraction if their purpose was only to conduct the discharge of the muscle, caused Volta to discard the Leyden jar theory and by 1792 he was in a position to assert that the contractions were due to "the effects of a very weak artificial electricity which is excited in a way of which no-one had any suspicion, namely by the application of two coatings of different species of metals." (Volta in Walker 1936, p. 97).

The nerve-muscle preparation was just a very sensitive electrometer and he used it in this way to construct a scale of electronegativity for various substances, which he later verified using a Nicholson's doubler in a manner similar to Bennet. He used this scale to select the best combination of metals to build what later became known as the Voltaic pile.

Volta's repudiation of animal electricity did not go unchallenged. In 1794 a mysterious document appeared, describing the production of muscular contraction in the absence of metals or any other source of electricity. The tract carried a Bologna imprint but is unsigned, and, although Galvini and his nephew, Aldini, referred to it subsequently without acknowledging it as their own, there is evidence that they were both involved. One possible implication of this, as Fulton and Cushing (1936) point out, is that there may have been disagreement as to the propriety of publishing the article.

In any event, the treatise maintained that contraction of a preparation could be effected by merely touching the vertebral column to the leg muscle, and represented the strongest evidence yet for the existence of animal electricity as conceived by Galvani. Volta, however, remained unimpressed. He suggested that the contractions were due to a current produced by the contact of the heterogeneous tissues of nerve and muscle. Although this explanation is rather disparagingly dismissed by Brazier (1959), it seems to me that Volta was correct. This was no last desperate bid to maintain a thesis in the face of contrary evidence. Volta had no need of this : he was widely respected, had had his point about metallic electricity conceded, and was on the verge of

making one of the greatest discoveries of all time. No, Volta was in fact speaking with the backing of experimental evidence. According to Walker (1936), he already knew by 1796 that, besides different metals, different electrolytes in contact with each other also produce a current, which principle was later to be exploited in the Leclanche or concentration cell.

7.3. THE RISE OF GALVANISM

Volta's invention of his pile in 1800 provided the world with its first source of steady current. New phenomena were quickly reported, and by 1820 Oersted had discovered the magnetic field around an electrified wire. Within a year several investigators had produced galvanometers of the moving magnet type (Humphreys 1937), which were then rapidly refined and instruments of great sensitivity were soon available to physiologists.

The main thrust of their research was directed at an examination of Galvani's theory. It is ironic that the results of this research, using instruments made possible by Volta's discoveries, were interpreted as a vindication of Galvanism. For the most part, the movements of the galvanometer were treated as a measure of animal electricity flowing through the organism, rather than a sign of underlying chemical changes.

Although this was a very fertile period with many contributors, the most outstanding figure in electrophysiology was undoubtedly du Bois Reymond. Following Mattenecci's lead (who had in 1841 shown that a current flowed between the inside of a muscle and its surface - the "injury current"), he at first concentrated on

muscle physiology, demonstrating that the injury current was reduced during tetanus. He called this reduction the "negative variation". Switching from muscle to nerve, he made his most momentous discovery when he reported in 1848 that the injury current between the cut end of a nerve and its surface also showed a negative variation during activity. This, he felt, fulfilled the dream of physiologists to establish the identity of the "nervous principle" with electricity.

7.4. THE DISCOVERY OF THE EEG

7.4.1. Richard Caton (1842 - 1926)

Du Bois-Reymond's discovery established the credentials of electroencephalography, for, if peripheral nerve activity was accompanied by electrical changes, it seemed emminently reasonable that the workings of central groups of neurons should be similarly represented.

It was this hypothesis which inspired Caton to pply himself to the localisation of function in the cortex. Fritsch and Hitzig in 1871 had already shown by means of electrical stimulation that motor control had localised representation in the cortex, and in 1875 Caton was able to show that areas thus demarcated showed a negative variation when the motor acts were voluntarily performed, thus strongly supporting the localisation theory. He reported as follows :

"In every brain hitherto examined, the galvanometer has indicated

the existence of electric currents. The external surface of the gray matter is usually positive in relation to the surface of a section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function. When any part of the grey matter is in state of functional activity its electric current usually exhibits negative variation." (Caton in Brazier 1961, p. 7).

This report is notable for the fact that, firstly, the neural mass appeared to behave just as did muscles and peripheral nerves - the inside was negative with respect to the outside, and activity produced a reduction in this potential difference, by apparently making the active area more electronegative, and, secondly, the recording of "feeble currents of varying direction" was, of course, the discovery of the EEG.

Caton's subsequent work was directed mainly at his goal of localisation of sensory function, which he pursued with a fair degree of success. In 1877 he described an experiment where a "search was made to discover an area related to impressions on the retina. A point was found on the posterior and lateral part of the hemisphere in which, in three rabbits out of seven experimented on, variation of the current was seen to occur whenever a bright light was thrown upon the retina." (Caton in Brazier 1961, p. 10).

A similar search for the area concerned with auditory perception

failed, however. He also mentioned that changes in mental state were often accompanied by fluctuations in current.

In parentheses it might be mentioned that in 1889 he described a rather interesting series of experiments where he used his electrophysiological expertise to show that noxious stimuli applied to the skin produce a reflex action on the viscera.

However, despite the possibilities inherent in these observations the lack of adequate communications denied him the wide readership he deserved and his work was neglected.

7.4.2. Adolf Beck (1863 - 1939)

Ignorant of Caton's pioneering work, several investigators rediscovered the EEG in the following decade, but it was not until Beck published his thesis in 1891 that knowledge in this area was materially advanced. He was a prolific worker and explored the phenomenon in much greater detail than had previous researchers. His first experimental subjects were frogs, and he found the rostral portions of the intact CNS to be negative with respect to the caudal parts. Mindful of the work of du Bois-Reymond, he believed this negativity to be indicative of neural activation. Later, using dogs, he proved this to his satisfaction by using direct electrical stimulation of the cortex. "If my assumption concerning the relationship of the change in functional current to the origin of the active state in certain centres is correct, namely that the development of electronegativity in an area of cortex really indicates the creation of an active state in centres located there, then on direct stimulation of that site an

electronegative swing should result... the experiments proved that it was right.... Since during stimulation of the eye by light there was a positive deviation of 21 mm, and on direct stimulation of the occipital cortex close to the negative electrode there was deviation of 80 mm in the same direction, does this not prove that this same cortical region went into an active state during stimulation by light?" (Beck in Brazier 1961, p. 35).

Like Caton, he found that the steady potential that exists between electrodes on the cortex had a superimposed oscillation which he called "active independent current". He believed these oscillations to indicate activity even though he found that they were blocked upon sensory stimulation. "In addition to the increase or decrease in the original deviation during stimulation of the eye with light, rhythmic oscillations that have been previously described disappeared. However, this phenomenon was not the consequence of light stimulation specifically, for it appeared with every kind of stimulation of other afferent nerves." (Beck in Brazier 1961, p. 33).

Another major inovation was made by Beck in 1911 when he simultaneously stimulated and recorded from different parts of the CNS, thus using evoked potentials to establish functional connections.

7.4.3. Hans Berger (1873 - 1941)

The turn of century brought an increasing sophistication, both in instrumentation and knowledge, to electrophysiology. The membrane theory of nerve conduction was proposed in 1902, and recordings of

artificially induced epileptic convulsions were made by Kaufman in 1912. In the same year the first photographic records of the electrical activity of the brain were published by Neminsky, who named them electrocerebrograms.

This activity was watched with intense interest by Berger. He had an abiding belief in the paranormal, and thought that the electrical waves might provide a means for studying such phenomena. He first attempted to replicate the work done on animals, without much success. When, however, he turned his attention to humans,he was richly rewarded. Using his young son as a subject, he obtained his first records in 1925. They showed a sinusoidal signal with a frequency of about 10 Hz - much simpler and more regular than any of the animal work. These alpha waves exhibited the same blocking upon sensory stimulation that had been obtained with animals, but Berger felt that this effect was a correlate of attention rather than a direct result of stimulation. He based this conclusion on the fact that mental effort alone, such as solving arithmetic problems, blocked the waves, and that alpha-blocking produced by sensory stimulation habituated on repetition. Berger accepted Neminsky's nomenclature of alpha and beta waves, but preferred the term electroencephalogram. He also initially accepted Beck's conclusion that alpha waves indicated activation and beta waves inactivity, but latterly he reversed this opinion.

In 1929 Berger presented his findings to a disbelieving world. His known interest in psychic phenomena, his lack of expertise in electrophysiology, and the very rhythmicity of his records, combined to make for a sceptical audience. Thus, although he

extended his observations to include a wide variety of clinical material, a large part of his later writings was devoted to fending off suggestions that his records were artifactual.

Scepticism vanished, however, when Adrian and Mathews (1934) replicated Berger's findings. Their authority was sufficient to convince many that the phenomenon was genuine, and research expanded rapidly. The foundations of clinical electro-encephalography were laid in 1935, when Gibbs et al. discovered the wave-and-spike pattern typical of petit mal epilepsy, and in 1936 when Grey Walter demonstrated that brain tumours could be located by the abnormal EEG which surrounded the area.

Workers were also quick to recognise the potential of the EEG as a research tool. Bremer (1935), for example, used it as an objective measure of the state of consciousness of his encephale and cerveau isole preparations in his investigations of the sleep/wake cycle.

The increasing acceptance of the EEG in clinics and laboratories was not, however, matched by a similar increase in an understanding of its electrogenesis. Early formulations proposing that the rhythmical alpha waves were produced by the synchronous firing of neurons (Adrian & Mathews 1934) had to be discarded when Li & Jasper (1953) reported that cortical spike potentials and synchronous EEG activity were uncorrelated. Indeed, they found it possible to stop neural firing altogether (by inducing anoxia) and still record large amplitude slow waves. Later theorists (Bishop 1956; Bremer 1953; Purpura 1959) thus concentrated on dendritic potentials as the possible EEG generators, but evidence was slow

in forthcoming due to the complexity of the cortical cytoarchitectonics. Cognisance was therefore taken of the advice of Renshaw, Forbes & Morison (1940), who directed attention to the simpler structure of the hippocampus.

7.5. HIPPOCAMPAL THETA

Although the hippocampal EEG had been recorded as early as 1938 by Jung & Kornmuller, it was not until 1954 that Green & Arduini systematically investigated the electrographic activity of this structure. Using an immobilised rabbit preparation, they observed a strikingly regular, large amplitude sinusoidal waveform in the theta frequency range (4 - 7Hz). This hippocampal theta rhythm could be elicited by a wide range of arousing stimuli, and exhibited an inverse relationship with the electrocorticogram, being present when neocortical activity was desynchronised, and vice versa. They therefore posited that theta represented the paleocortical analogue of arousal.

Subsequent work has forced substantial revision of these classical observations. For example, the inverse relationship of the hippocampal and neocortical EEGs is by no means invariant. Both synchronisation (see p. 273) and desynchronisation (see e.g. Bennett 1971) can be recorded simultaneously from these two areas. Green & Arduini's terminology, too, has proved inadequate. Several smaller mammals (e.g. rats and gerbils) can display a hippocampal "theta" rhythm in excess of 10Hz, which lies far beyond the limits of theta as classically defined. For this reason Vanderwolf (1969) has proposed the more general term RSA (rhythmical slow activity) to replace theta. In addition, he has

suggested that the term SIA (small amplitude irregular activity) be used to describe a fast-wave, desynchronised hippocampal EEG, in order to avoid confusion with a third type of hippocampal electrographic activity composed of large, but irregular, slow waves (for which he has suggested the term LIA - large amplitude irregular activity). While the terms SIA and LIA have found general acceptance, the term "theta", although technically inaccurate, has remained entrenched and will be used here.

Perhaps the most controversial aspect of the Green & Arduini paper, however, is their interpretation of the functional significance of theta, and it is to this issue that the following chapter is addressed.

8 THE FUNCTIONAL SIGNIFICANCE OF THETA

The controversy engendered by Green & Arduini's (1954) assertion that theta reflects an activated hippocampus has been fuelled by the lack of clarity concerning the machanism of EEG generation. Several authors (Bennett 1973,1975,1979; Black, Young & Batenchuk 1970; Douglas 1967; Grastyan, Lissak, Madarasz & Donhoffer 1959; Rhodes 1969) have argued on the basis of logical, theoretical and observational grounds that theta in fact indicates an inactive hippocampus, and that it is hippocampal EEG desynchronisation which represents hippocampal activation. Others have maintained that this is unlikely since theta varies in frequency and amplitude under specific conditions. "If the occurrence of a theta rhythm is a way of keeping the hippocampus inactive, it is hard to imagine why frequency shifts should be necessary and why they should depend on the animal's behaviour" (Gray 1970, p. 477).

As a first step towards resolving this issue it would be fruitful to examine the pattern of the hippocampal EEG that occurs under conditions when the inhibitory theory would predict that the hippocampus would be clearly either in a resting or active state.

8.1. EEG CORRELATES OF HIPPOCAMPAL INACTIVITY

Two conditions during which the hippocampus would be expected to be in a fairly prolonged resting state are paradoxical sleep (see Chapter 6) and exploratory activity (see pp. 101). It is remarkable that , virtually without exception, all workers are agreed that theta is the exclusive accompaniment of both of these activities (see O'Keefe & Nadel 1978, Table A11(b) for PS, and

Table A5 for exploration). Such unanimity is unusual, and strongly suggests that theta is a correlate of hippocampal inactivity. Even more convincing, however, is the evidence from studies of hippocampal unit activity during these behaviours. (Note: much of the evidence presented below has been discussed elsewhere (Hirschman 1981), but is repeated here for the sake of completeness.)

8.1.1. Unit Activity During Paradoxical Sleep

PS represents an ideal opportunity for assessing the activity of hippocampal neurons with regard to theta, since virtually uninterrupted theta is present throughout this state. Most studies have reported a decrease in the rate of firing during PS (Delacour 1980; Mink et al 1967; Ranck 1973), and discrepant findings (e.g. Noda et al 1969) have been clarified by Ranck's distinction between projection (output) cells and interneurons (Fox and Ranck 1975,1981; Ranck 1973). Using this classification it has been convincingly shown that hippocampal output cells are strongly inhibited during PS, while interneurons (which generally are thought to inhibit output cells) fire rapidly. Since it is only via its output neurons that the hippocampus can exert any influence, the conclusion seems inescapable that, in this case, theta indicates an inactive hippocampus.

8.1.2. Unit Activity & Theta During The Waking State

In general, findings have been equivocal: some units increase their rate of firing during theta, while others decrease it

(Lidsky et al 1974; Mays and Best 1975; O'Keefe and Dostrovsky 1971). Delacour (1980),however, was able to make a more definite statement. He found that during the elicitation of a classically conditioned neocortical desynchronisation (which is usually associated with hippocampal theta), hippocampal type I (output) units were clearly inhibited. Certainly it is the conclusion of Ranck (1975) that different output neurons are concerned with different types of behaviour, rather than the presence of theta. The only cells which show a consistent activation during theta are interneurons. While a recent study by Bland et al (1980) disagrees with this finding, it should be noted that they used urethanised animals - a fact which makes interpretation of their results difficult (Mercer et al 1978).

It is perhaps not surprising that sampling the activity of a minute percentage of neurons during the waking state (when many stimuli occur simultaneously) does not present a clear picture. To assess the general excitability level of large numbers of neurons at any particular point in time it is perhaps more appropriate to turn to evoked potentials. Segal (1978), using unrestrained rats, produced evoked potentials in the hippocampus by stimulating the hippocampal commissural fibres. He found that during theta the primary wave of the evoked potential was much reduced, while the late component was enhanced. This result is consistent with the interpretation that the output neurons (which are the first to receive the commissural activation) are in a more inhibited state during theta, while the interneurons (which fire secondary to the output neurons) are in a more excited state. This interpretation is supported by the recent work of Leung (1980) who, besides confirming Segal's results, also showed that the evoked population

spike (a synchronous postsynaptic firing of hippocampal neurons) was smaller during behaviours associated with theta than during those associated with LIA.

Additional evidence comes from the finding that amphetamine, which is routinely administered to induce theta, has been shown to inhibit hippocampal unit activity (Segal and Bloom 1976), and that theta can be recorded during locus coeruleus (LC) stimulation (Macader et al 1974; Robinson et al 1977), even though such stimulation specifically inhibits what appear from their firing characteristics to be hippocampal output neurons (see Segal & Bloom 1976). (Note: Robinson et al (1977) have argued that theta production during LC stimulation is due to current spread, but this presumably does not alter the fact that LC mediated inhibition is still operative).

8.2. EEG CORRELATES OF HIPPOCAMPAL ACTIVITY

There is considerable evidence that the absence of theta in the hippocampal EEG is an indication of hippocampal activation. For example, two conditions during which the hippocampus would be expected to be in a clearly activated state are slow wave sleep (SWS) and during the cessation of ongoing behaviour produced by the presentation of a novel or unexpected stimulus. The former involves the activation of internal inhibition (see Chapter 6) and the latter external inhibition (see pp. 67-68). Once again there is very good agreement that LIA is seen during SWS (see O'Keefe & Nadel 1978, Table A11(a)), and that SIA is the almost invariable consequence of the presentation of a novel stimulus which produces an arrest reaction (e.g. Brown 1968; Grastyan et al. 1959; Lucas,

Powell & Murphree 1974; Pickenhain & Klingberg 1967; Vanderwolf 1969; Whishaw 1972). It is interesting that these two activities are accompanied by different EEG patterns (i.e. LIA during SWS, and SIA during the arrest reaction), but it should be noted that LIA contains a considerable amount of fast activity. It seems reasonable to suggest, therefore, that LIA signifies a state intermediate between the extreme hippocampal activation shown by SIA, and the relative inactivity during theta. Certainly, the idea that SIA is an indication of intense hippocampal activation is supported by the finding that SIA is associated with strong behavioural and spinal reflex inhibition (Yokoto & Fujimora 1964).

Studies of hippocampal unit activity, too, support the above conclusions. As discussed previously (p. 109), Ranck (1975) has shown that hippocampal output cells fire rapidly during SWS, while interneurons are relatively quiescent. Unfortunately unit activity during SIA has not been as intensively investigated, since this EEG pattern, at least in the rat, occurs for only brief periods of time. However, Ranck (1975 p. 216) does have the following to say: "The other mode of firing was the slowest mode of firing, which frequently involved the theta cell going off. It was usually, but not always, associated with a small-amplitude irregular activity of the slow waves as described by Vanderwolf (1971). This occurred immediately after some external stimulus while the rat stood or lay motionless. This often appeared to be freezing. This mode was especially common when a rat was awakened by an external stimulus and did not occur if the rat awakened spontaneously. It is only in these special situations that a theta cell stopped or slowed, even for periods of less than about 1/2 s." Since the theta cells to which Ranck refers are, in all

probability, interneurons (see above), and since their activity level bears an inverse relationship with that of the output cells, the above observation implies that the output cells are highly active during SIA. A relationship between SIA (i.e. EEG fast activity) and pyramidal cell activation is also suggested by the work of Whishaw, Bland & Bayers 1978). From their records it can be seen that as an electrode traverses the hippocampus, fast activity (15 - 55Hz) is closely related to the pyramidal and granule cell layers. Furthermore, when they destroyed approximately 90% of the granule cells by X-irradiation, the amount of fast activity was reduced dramatically, while theta was left relatively unaffected.

Finally, it is worth noting that precisely the same relationship has been demonstrated with regard to the neocortex. Steriade (1978) has clearly shown that it is the activity of the large output cells of the neocortex that is closely related to neocortical EEG desynchronisation: The interneurons show the opposite behaviour, being active during synchronous EEG activity.

8.3. IMPLICATIONS FOR THE GENESIS OF THETA

Taken together, the above evidence implies that it is the activity of the large and numerous output cells which cause EEG desynchronisation, and that , in the hippocampus as elsewhere, it is EEG fast activity that indicates activation.

The fact that theta is present when the output neurons are inhibited represents somewhat of a puzzle - if theta is not produced by the output neurons, what then does cause theta? The

possibility that interneurons (which do fire in phase with theta) might be involved is mitigated by the fact that they are few in number (less than 7% according to Fox & Ranck 1975).

Thus, in the absence of a suitable neural substrate, I would like to submit the rather radical proposal that theta may be an artifact. Specifically, I would suggest brain movement as the artifact generator, since it has long been established as a source of EEG artifact (see e.g. Li & Jasper 1953; Walsh 1956), and can be produced by any agent which causes fluctuations in cerebrospinal fluid pressure (e.g. respiration - especially sniffing - heart beat, head movements, and vigorous body movements). Such an explanation would account for the objection raised by Gray (1970)(see above) as to the lability of theta: if theta was an artifact produced in the manner described, then it would be expected to show frequency shifts and be dependent on the animal's behaviour.

Experimental evidence in support of this contention is described in the following chapter.

9 EXPERIMENTAL EVIDENCE FOR THETA BEING AN ARTIFACT

Although artifacts due to movement are widely recognised, these are usually thought of as being confined to gross movements of the animals producing cable artifacts, etc. Less commonly considered is another source of artifact caused by the movement of the electrolyte relative to the electrode. One reason for this neglect probably arises from the belief that electrodes of identical material immersed in the same solution have zero potential difference between them, and thus would not generate voltages upon movement of the solution. However, as Geddes (1972, p. 8) notes, identical electrodes in physiological saline do in fact produce voltages which, depending on the material, can be in excess of 100 mV. Thus, movement of the electrode-electrolyte interface should, in theory, be capable of producing voltage fluctuations of the order of 200 μV.

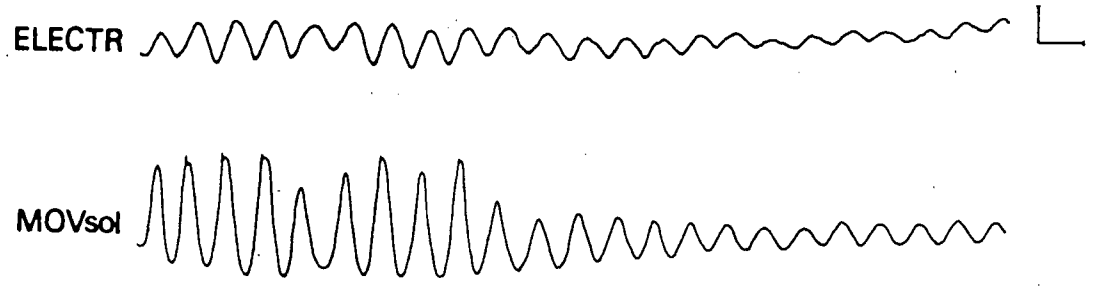

FIG. 10. Illustrating the fact that electrodes in Ringer's solution produce voltage fluctuations (ELECTR) when the solution is caused to move (MOVsol). Cal.: 20 μV, 1sec.

Fig. 10 provides evidence to support this contention. The upper channel shows the output from stainless steel electrodes (held in the electrode-carrier of a stereotoxic instrument) inserted into a beaker of Ringer's solution. The lower channel records displacement of the solution, as measured by the photoreflective

method of Teague et al (1969) (see General Method). Ripples were set up in the liquid by either tapping the bench upon which the beaker stood, or by dropping small objects into the solution. It can be seen that there is a one-to-one correspondence between the two measures. It should be noted that, although the electrode voltages are an order of magnitude less than that required by the theory, larger potentials could easily be achieved by more vigorous disturbance of the solution, but this tended to break up the surface and result in irregular activity. No such constraints would apply to a gel pulsed in the manner described. A more appropriate test of the model, then, would be to record the potentials produced by electrodes placed in the mechanically pulsed brain of a dead animal.

9.1. "THETA" IN DEAD ANIMALS

Brain movement can be produced by any agent which affects intracranial pressure. The most obvious candidate is the pressure pulse produced by the heartbeat, but this is weak in comparison to the effects produced, say, by movement of the head relative to the body. Another potent source of intracranial pressure fluctuation is respiration. This is due to the close links that exist between the thoracic and cerebral venous systems. As a consequence, any increase in thoracic pressure (as in expiration), by forcing blood out of the thorax and into the cranium, produces a concomitant increase in intracranial pressure, and vice versa. Accordingly it was decided to use thoracic manipulation as a method for inducing brain pulsation in dead animals.

9.1.1. General Method

9 1.1.1. Subjects

Approximately 200 rats of varying age, strain and sex were used in the series of experiments to be described.

9.1.1.2. Surgery

9 1.1.2.1. Acute preparations

(i) Subjects were placed in a stereotaxic frame and the bone removed from the right skull between bregma and lambda. In most cases the cortex was then aspirated to expose the hippocampus. (ii) Experiments using dead animals followed exactly the same procedure. Death was induced by an overdose of halothane anaesthetic or by a small injection of local anaesthetic into the medulla. Criteria of death were : respiration ceased for at least 5 minutes, flat EEG, loss of pupillary reflexes, and heart either stopped or beating less than once every 2 seconds. Brain movement was produced by pumping the thorax by hand, and a pneumograph around the chest recorded these manipulations.

9.1.1.2.2. Chronic preparations

Bipolar stainless steel electrodes (0,3 mm in diameter), insulated except for 0,5 mm at the tip and with a vertical tip seperation of 1,5 mm, were aimed at the dorsal hippocampus and implanted in the

usual way. Two additional leads were fixed into the acrylic cement to allow for the connection of a pneumograph. The animal was earthed via a screw over the occipital cortex. All electrodes were connected to a six-prong IC mounter which was cemented to screws in the skull and leads were taken from a complementary "component holder". The connection thus obtained proved to be extremely stable. A recovery time of at least 4 days was allowed before experimentation commenced.

9.1.1.3. Anaesthesia

Acute preparations were initially anaesthetised with halothane and pressure and incision points injected with a local anaesthetic (lignocaine). Once surgery was completed, halothane was withdrawn and replaced with ketamine hydrochloride (Ketalar, Parke Davis; 50 mg/Kg i.p. and half thereafter every 30 minutes). This compound is not a CNS depressant, and theta can be recorded during its administration.

9.1.1.4. Theta induction

When necessary, theta was induced by natural stimuli only, e.g., rubbing the animals' fur.

9.1.1.5. Recording

Recording was accomplished with a 6 channel Beckman type R Dynograph.

9.1.1.5.1. EEG

Both unipolar (stereotaxic frame as reference) and bipolar electrode configurations were employed. In most acute preparations the electrodes were placed directly onto the surface of the exposed hippocampus.

9 1.1.5.2. Respiration

This was measured by means of thermistor placed in front of the nares, or by means of a pneumograph tied around the thorax. The pneumograph consisted of a piece of rubber tubing (internal diameter 2 mm) filled with copper sulphate solution and plugged at both ends with copper electrodes. Changes in diameter of the tubing brought about by thoracic movement produce fluctuations in a current passed between the electrodes.

9.1.1.5.3. Brain movement

The photoreflective method of Teague et al (1969) was employed. It consisted of a battery-powered light source which illuminated an area approximately 1 mm in diameter. The resultant reflections from the surface under investigation were collected by a phototransistor (Mullard BPX25) powered by a 30 volt battery. Voltage fluctuations were measured across 10 k ohms. The phototransistor was housed at one end of a hollow wooden cylinder. The other end extended several mm beyond the phototransistor and was placed just over the illuminated area. This served to ensure that only reflections from the area of interest would be recorded. The light source and phototransistor were mounted on a single

support attached to the stereotaxic frame.

9.1.1.6. Presentation of results

In order to obtain high contrast photographs, most of the results were traced.

9.1.2. Results

It proved easy to produce brain movement and concomitant EEG waves by thoracic manipulation in dead animals. The electrographic activity was similar to theta both in form and amplitude (200 - 500 μV), as can be seen from Fig. 11. Large brain movements and

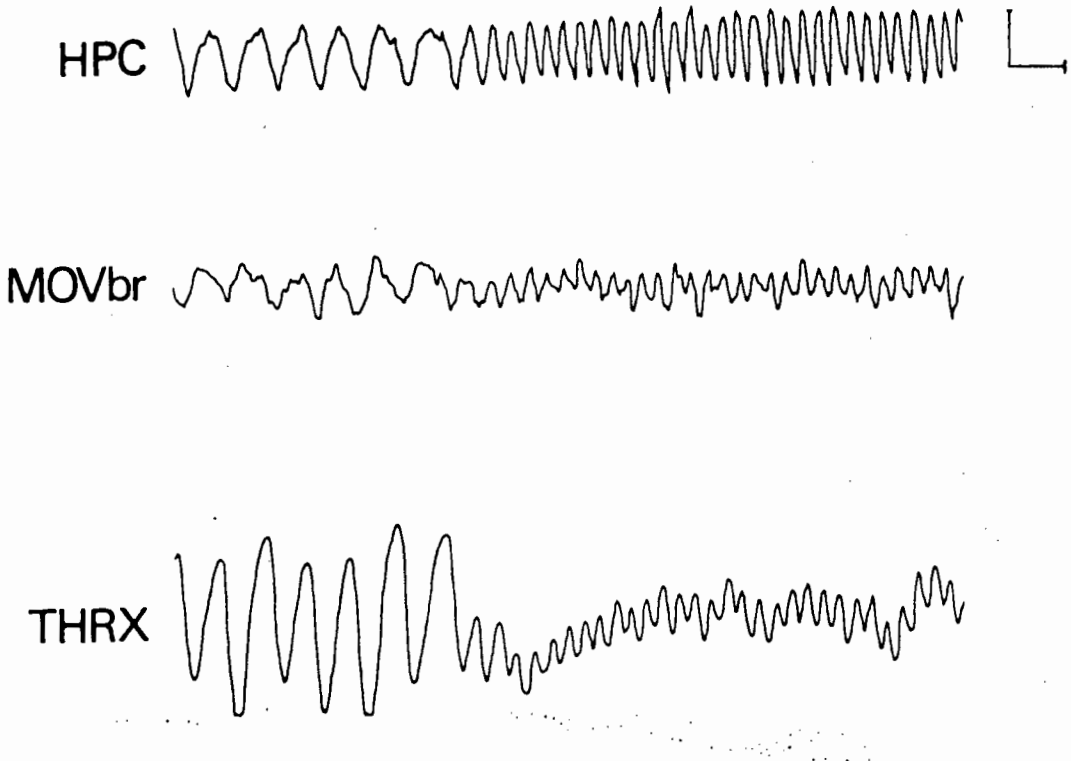

FIG. 11. Theta in a dead animal. Brain movement (MOVbr) was produced by thoracic manipulation (THRX), and the "theta" thus produced is similar in form and amplitude to normal theta. Cal.: 200μV, 1sec.

associated EEG excursions could also be produced by any activity which produced movement of the spine, such as moving the body relative to the head. Other manipulations which did not cause brain movement were ineffective in producing voltage fluctuations.

It should also be noted that it became more difficult to produce recordings as time from death increased, no doubt due to the increasing difficulty of producing pulsations in the vascular system.

9.1.3. Discussion

The results demonstrate clearly that (at the very least inactive) neural tissue pulsations must be reflected in the EEG, providing that they are of sufficient amplitude. In fact, as mentioned previously, it has long been established that brain pulsations do occur in the normally respired and vascularised animal, and that these do cause EEG fluctuations (see, for example, Li and Jasper 1953; Walsh 1956). However, no systematic observations of this phenomenon have been undertaken and the following experiment was designed to compare neural tissue movement and concomitant electrographic activity.

9.2. THETA AND BRAIN MOVEMENT

9.2.1. Method

The hippocampus was exposed by aspirating the overlying neocortex, and its movement monitored by means of the photoreflective

technique outlined in the General Method. The EEG was recorded from electrodes placed directly on the hippocampal surface.

9.2.2. Results

The recordings showed a striking similarity (Fig. 12 and also Figs. 13 and 15). A one-to-one correspondence between theta and neural tissue movement was seen. This relationship was present throughout the recording session, and has been observed in over 50 animals.

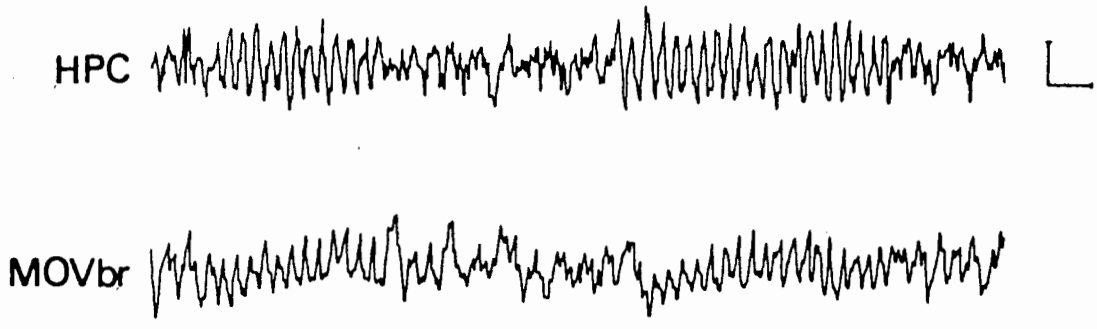

FIG. 12. Theta and brain movement. Hippocampal pulsations (MOVbr) show a striking similarity to the hippocampal EEG. Cal.: 500μV, 1sec.

9.2.3. Discussion

Objections could be made as to the validity of the method employed in this study to measure brain movement. It could be argued, for example, that minute variations in tissue colour might confound the results. In order to guard against this possibility some experiments employed a piece of gold leaf placed over the exposed area as a reflector. In addition, this measure of brain movement has been validated against a mechanical transducer (Teague et al

1969). Considering the limitations of the photoreflective method (it is only sensitive to movement of a smooth surface in a vertical plane, while electrodes are responsive to movement in all planes), the concordance between the observed brain movement and the EEG is remarkable.

It follows directly from the above that, since brain movement is caused by various physiological parameters such as heartbeat and respiration, it should be possible to demonstrate a correspondance between these factors and the EEG. This prediction is tested below.

9.3. THETA AND HEARTBEAT

Since the beat of the heart is a relatively weak cause of brain movement, it is not surprising that only occasionally are heartbeat and theta observed to be in synchrony (Komisaruk 1970; Whishaw et al 1972). Cardiac contraction would only be capable of producing theta-like artifacts under conditions when it was beating more strongly than normal, and, indeed, this can easily be demonstrated under curare. If a mildly noxious stimulus is applied to the animal (e.g., pinching its tail), there is a sudden increase in the strength of cardiac contraction and a resultant momentary phase-locking of heartbeat and theta. To establish more convincingly that it is heartbeat which is causing theta in these instances, it is necessary to create conditions under which the strength of cardiac contraction is increased for a prolonged period. One way in which this could be achieved is to overanaesthetise animals to the point of respiratory depression. The resultant anoxia would reflexly induce stronger cardiac

contractions which should, if the theory is correct, produce theta (even though theta is normally not seen during deep anaesthesia). Fig. 13 is an extract from one such experiment where a rat was overanaesthetised with halothane. A beautiful theta rhythm is evident which bears a one-to-one correspondence to brain movement and heartbeat. The depicted relationship lasted for several minutes.

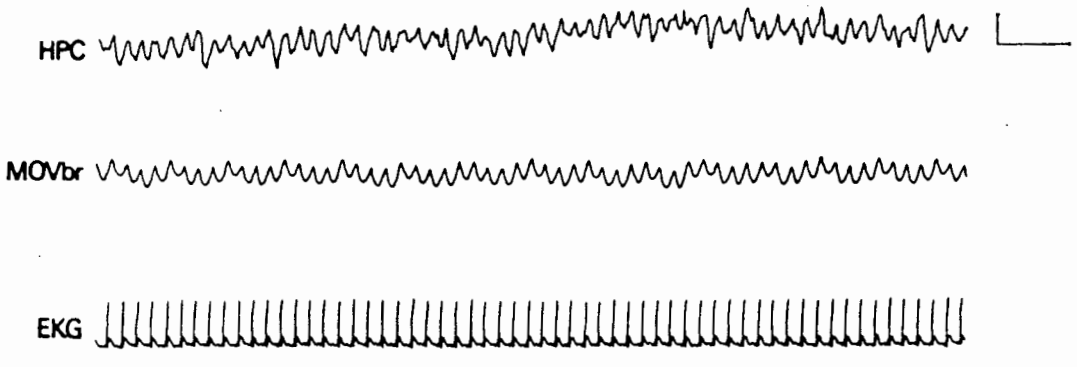

FIG. 13. Theta and heartbeat. Under conditions of respiratory depression, the consequent increase in strength of cardiac contraction causes brain movements sufficiently large to produce theta. Cal.: 200μV, 1sec.

Owing to the very deep anaesthetisation, it would be most unlikely that these results could be interpreted as theta modulating heart-rate.

9.4. THETA AND SNIFFING

9.4.1. Method

Animals were prepared as outlined under General Method. Respiration was monitored either by means of a pneumograph tied around the thorax or a thermistor placed in front of the nares.

9.4.2. Results

The results were surprisingly clear-cut. Respiration was found to bear a highly significant relationship to the hippocampal EEG. In particular a burst of sniffing was associated with a train of theta waves, and each sniff corresponded in a phase-locked manner with each theta wave. This relationship was invariable over long periods of recording (in excess of 30 minutes). Fig. 14 is an

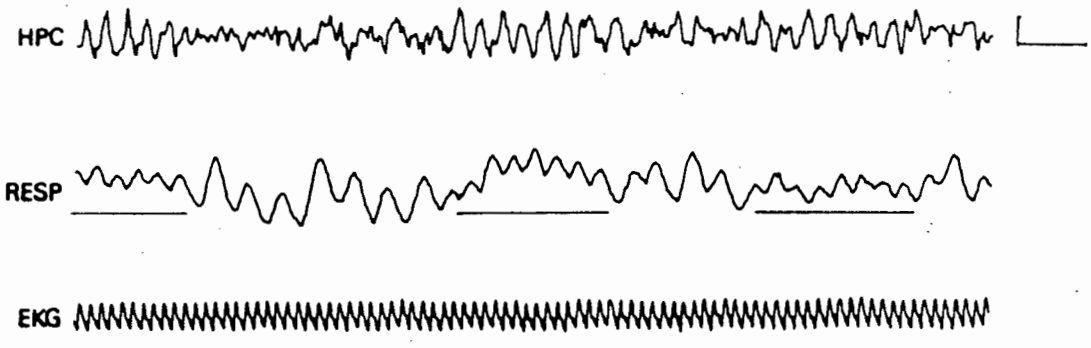

FIG. 14. Theta and respiration (RESP) in the lightly anaesthetised animal. Bouts of sniffing (underlined) are invariably associated with theta, and each sniff corresponds with each theta wave in a one-to-one manner. Cal.: 500μV, 1sec.

excerpt from a recording lasting 10 minutes, and is typical of the results obtained. Three trains of theta waves are shown, associated with three bursts of sniffing (underlined) and each sniff is related in a one-to-one manner with each theta wave. Fig. 15, from another animal, shows in more detail the correspondence between theta, neural tissue movement and respiration. The large amplitude deflection resulted from a sharp intake of breath as the animal changed from normal respiration to sniffing.

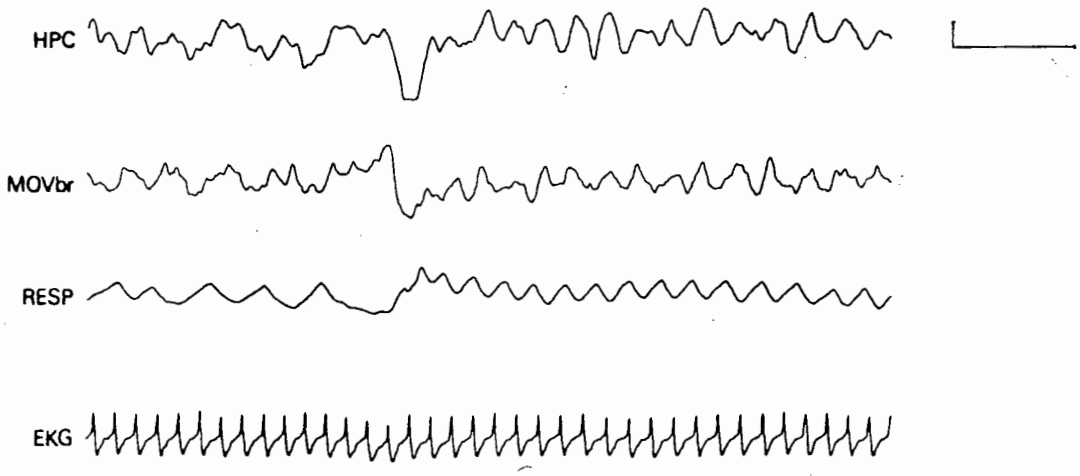

FIG. 15. A record showing in more detail the correspondence between theta, hippocampal movement and respiration. The large deflection marks the transition from normal respiration to sniffing. A one-to-one correspondence between the three measures is present. Cal.: 500μV, 1sec. (From Hirschman 1981.)

9.4.3. Discussion

Although, in terms of the model, it is understandable that sniffing is more effective than normal respiration in producing EEG excursions (since sniffing involves forced expiration and thus produces higher intrathoracic pressures), the fact that the relationship between sniffing and theta is so clear is, possibly, somewhat surprising. Recourse to the literature, however, reveals that similar observations have repeatedly been reported (e.g. Gault & Leaton 1963; Hurwitz & Bremner 1972; Ito 1966; Komisaruk 1970; Kurtz & Adler 1973; Li & Jasper 1953; Lippold 1973; Macrides 1975). In fact, so good was the correspondence in the Gault and Leaton (1963) study that they suggest that the slow wave activity recorded from the olfactory bulb could be used as an alternative measure of respiration. Similarly, Komisaruk (1970) found

vibrissae movement (which, as Welker (1963) has shown, is related in a one-to-one fashion with sniffing) to be so highly correlated with theta that he proposed that theta exerts a direct control over whisker movement.

Perhaps, in retrospect, it is not so surprising that theta and sniffing have been found to be so closely related, since there are striking parallels between the characteristics of theta and those of sniffing. For example, it is remarkable that both the frequency and total amount of theta vary inversely with an animal's position on the phylogenetic scale (Bennet et al 1978). Thus theta is very prevalent in rats, with a frequency that can go as high as 12 Hz, is less common in cats (frequency up to about 8 Hz), and is rarely seen in the higher primates. Sniffing displays a similar pattern. The lower animals are more reliant on olfactory cues and therefore spend a greater percentage of time sniffing, and, since they are smaller, sniff at higher frequencies. Rats, for example, have been observed to sniff at 11 Hz (Welker 1963). It is also significant that theta is in evidence in paradoxical sleep, which is the only stage of sleep where strength of cardiac contraction is increased and polypnea is present.

9.5. THETA & RESPIRATION IN CLOSED-SKULL PREPARATIONS

Since most of the experiments described above were conducted under the simplifying condition of anaesthetisation, and with an open skull, it might be assumed that these results pertain only to such preparations. That such is not the case is illustrated by Fig. 16, which is reproduced from Lipold (1973, p207). It can be seen that theta bears a one-to-one relationship to sniffing even

though the animal is unanaesthetised and the recording is made from scalp electrodes (i.e. the skull is intact).

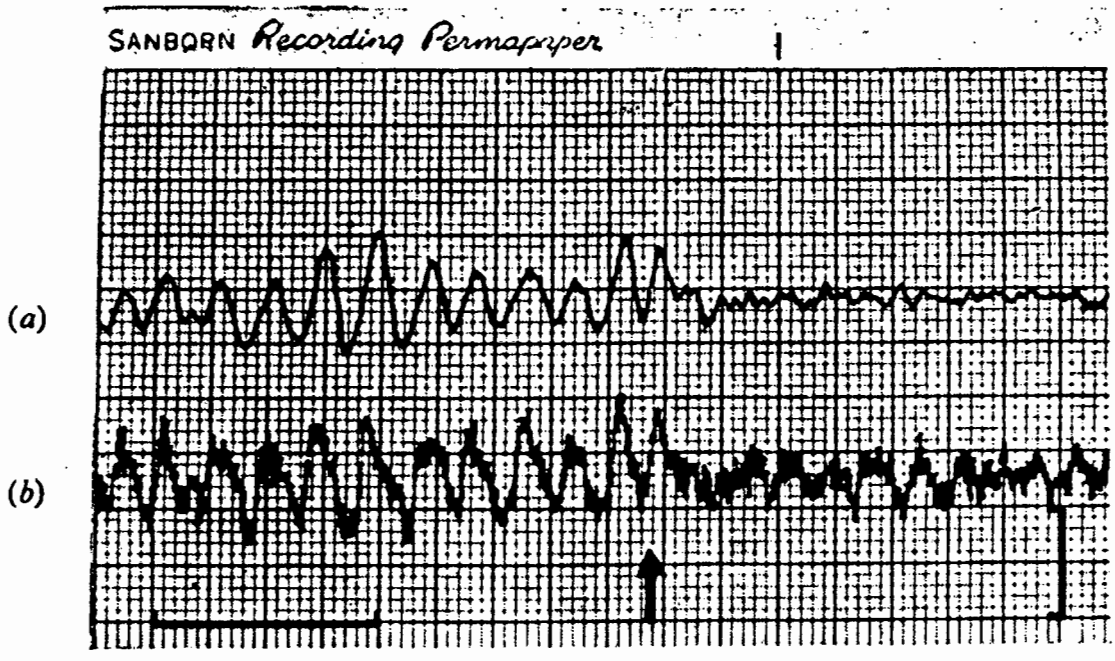

FIG. 16. Recording of theta from an anaesthetised rabbit. (a) is the EEG recorded from scalp electrodes, (b) is respiratory excursions recorded from an anemometer. At arrow, ether pad placed under nostrils. Respiratory excursions ceased (temporarily). Cal.: 50μV, 1sec. (From Lippold 1973, by permission of the author.)

Notwithstanding the results presented in previous sections it might stil be argued that theta modulates sniffing, or possibly, that a third factor underlies both sniffing and theta, and that their co-variance is purely fortuitous. To establish the causality of the above relationship more convincingly, there must be an unequivocal demonstration that respiration can produce theta in the unanaesthetised, closed-skull preparation. This would be accomplished if rate of respiration were to be manipulated and theta was found to follow suit.

9.5.1. Method

Two animals with chronic implants were curarised (tubocurarine: 2 mg/Kg i.p.) and artificially respired with a Bird respirator with a stroke-volume of approximately 8 cc. Prior to being fixed in a stereotaxic head holder, cotton wool was inserted into the external auditory meati to make the procedure as painless as possible.

9.5.2. Results

As Fig. 17 shows, theta was found to bear a one-to-one relationship to the respirator, and faithfully followed changes in the respirator setting. It should be noted that theta was not always present, but when it was, it bore the above relationship.

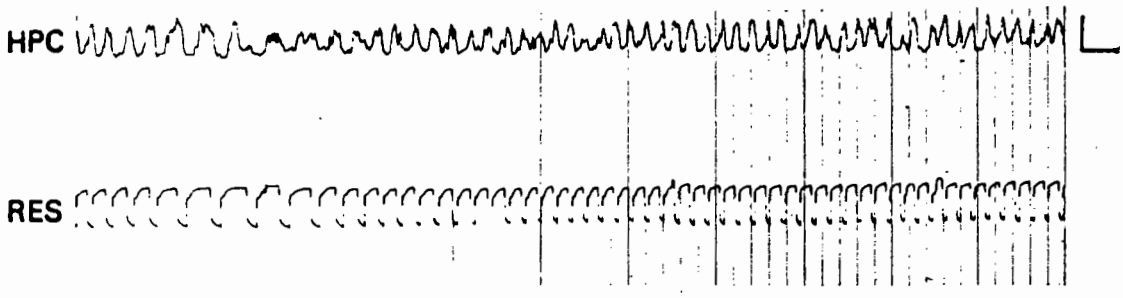

FIG. 17. Theta waves induced by the respirator (RES) in a curarised rat. Theta follows the respirator frequency, provided that the pressure is adequate. Cal.: 200μV, 1sec.

9.5.3. Discussion

The finding here that theta can be produced by artificial respiration supports earlier reports to this effect (Li and Jasper 1953) and contrasts with Komisaruk's (1970) failure to find such a

relationship. It seems possible that this discrepancy can be ascribed to a difference in ventilation pressure. It will be recalled that sniffing is a more effective agent than normal respiration in producing theta-like artifacts, since it produces higher intrathoracic, and hence intracranial pressures. Similarly, if the respirator pressure is inadequate, it is unlikely to produce theta. That Komisaruk may indeed have been using too low a ventilation pressure is suggested by closer inspection of the data upon which he bases his claim. Fig. 18 is

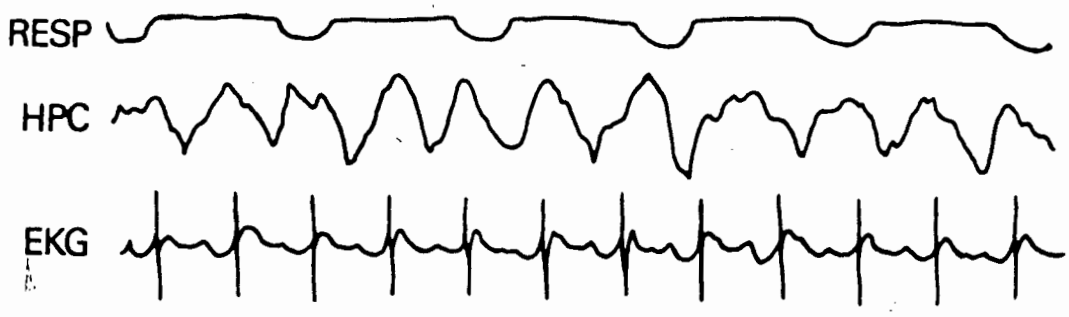

FIG. 18. The relationship between respirator setting (RESP), hippocampal EEG and heartbeat in the curarised rat (from Komisaruk 1970, Fig.3F). Komisaruk's figure was enlarged and the channels shifted slightly to allow for propogation delay. This reveals, except for one extended theta wave which accomodates two heartbeats, a one-to-one relationship between theta and heartbeat, which probably indicates that the animal is being underventilated.

an enlargement of Komisaruk's Fig. 3F with the channels shifted slightly to allow for propogation delay. It can be seen that, although there is clearly no one-to-one relationship between the respirator and theta, heartbeat (except for one extended theta wave which accomodates two heartbeats) does bear such a relationship . This close correspondence between heartbeat and theta (which is unusual under normal circumstances) probably indicates that the animal is being underventilated, since this would increase the strength of cardiac contraction and hence its

ability to pulse the brian.

9.6. THETA & SNIFFING IN THE UNRESTRAINED ANIMAL

9.6.1. Method

Five rats with chronic implants were prepared as outlined in the general method. Respiration was monitored via a pneumograph.

9.6.2. Results

Sniffing was invariably accompanied by an extremely regular, high amplitude theta rhythm, which usually bore a one-to-one relationship to the sniffing (Fig. 19). This was not always the case, however, the phases sometimes slipping in the middle of a record. In addition, a much more irregular theta could sometimes be observed without any concomitant sniffing.

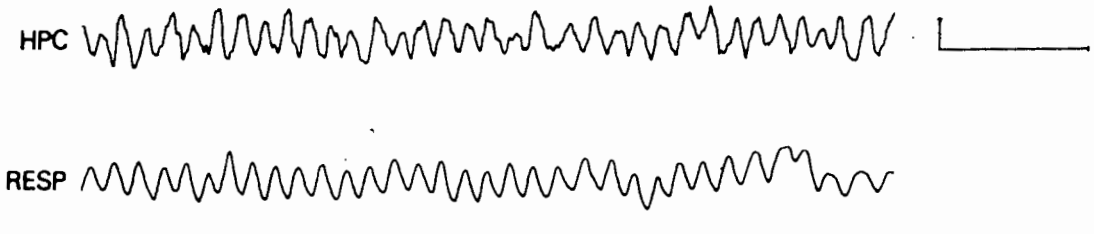

FIG. 19. Theta and respiration in the unrestrained rat. Sniffing bears an almost one-to-one relationship to theta. Cal.: 200μV, 1 sec.

9.6.3. Discussion

The concordance between theta and sniffing in this more complex situation provides additional evidence that the previous results were not peculiar to the experimental conditions. Furthermore, the findings of this experiment have been confirmed in a careful study by Macrides (1975) of the relationship between sniffing and theta in the freely-moving hamster. As in this study, Macrides shows that within a sniffing bout, theta sometimes drifts out of phase with sniffing, and that theta can occur independently of sniffing. He therefore concludes that the one-to-one relationship often observed between sniffing and theta is caused by theta in some way modulating sniffing. However, in the light of the evidence presented in this paper it seems more reasonable to conclude that sniffing-related theta is artifactual.

The fact that there is sometimes a phase-slip during a sniffing bout might seem to imply that only that theta which is in one-to-one correspondence with sniffing is artifactual. However, it should be pointed out that in the unrestrained animal other variables such as heartbeat or any rhythmical activity (e.g., running, and especially head movements) may produce intracranial pressure changes sufficiently large to override the effects of sniffing. In this regard the observations of Welker (1963) are pertinent. He has shown that "sniffing" is in fact a complex behaviour, consisting of four components: polypnea, vibrissae movement, snout movement, and a rapid series of discrete head movements and fixations. Some of these components can occur independently of the others, and Macrides (1975) supplies evidence to the effect that two of these at least (polypnea and vibrissae

movement), can drift out of phase with each other. It seems entirely feasible that head movements could similarly drift. At such times one would not expect sniffing to correspond with theta, since head movements are a very potent source of brain movement. Should the asynchrony between head movements and sniffing become too great, one might anticipate that the animal would pause briefly to resynchronise the various components, and, indeed, Macrides (1975) notes that often, when theta and sniffing are out of phase, "a small discontinuity" occurs which serves to reinstate exact correspondence .

The above argument suggests that, since many variables combine to produce brain movement, only by recording intracranial pressure changes and subtracting these from the theta record would we arrive at a "true" theta. However, even this procedure would not guarantee an artifact-free record owing to the distortion

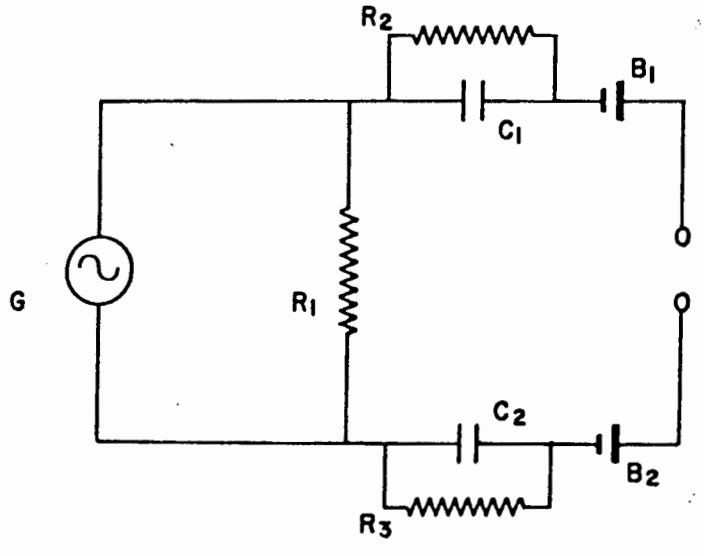

FIG. 20. A simplified equivalent circuit of electrodes in contact with a biological generator (G) (after Geddes 1972, p.40). The capacitors C1 and C2, along with the resistor R1, form a high-pass filter which distorts the waveform generated by G.

introduced by chemical events at the electrode-electrolyte interface.

9 7. ELECTRODE-PRODUCED DISTORTION

The nature of the electrode-electrolyte interface is such that the electrode is capacitatively coupled to the electrolyte (see Fig. 20) and thus acts as a high-pass filter. The consequent distortion will not materially affect recordings in the simple condition (as pertains in the anaesthetised preparation) when only one factor (say heartbeat) is powerful enough to produce significant neural tissue movement. Under these conditions heartbeat, neural tissue movement, and the EEG will be in a one-to-one correspondence. However, in the complex condition, when two or more variables contribute to brain movement, then the compound waveform applied to the electrodes is differentiated. Smaller peaks are accentuated at the expense of larger, slower waves, and the resultant EEG will not necessarily bear a simple relationship to the waveform from which it arose.

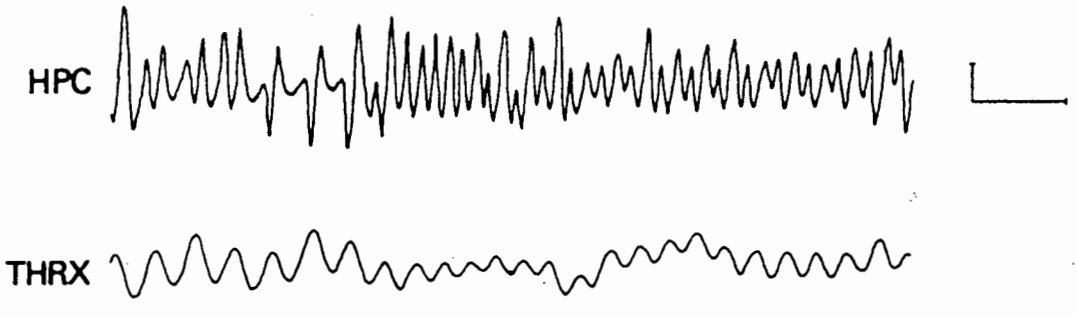

FIG. 21. Demonstrating the differentiating power of the electrode-electrolyte interface. A record from the hippocampus of a dead animal shows a two-to-one relationship to thoracic manipulation. For explanation see text. Cal.: 200μV, 1 sec.

Evidence of the differentiating power of the electrode-electrolyte interface is illustrated in Fig. 21. The top trace is a record from the electrodes in the brain of a dead animal, and the bottom channel shows thoracic manipulation. It can be seen that there is a two-to-one relationship between the EEG and thoracic pumping, even though brain movement (not shown in this particular record) follows thoracic excursion faithfully. This effect is produced by squeezing high up on the thorax, thus applying pressure to the heart as well. The result is that two pulses are set up, one in the arterial system (via the heart), and one in the venous system (via the thorax). Since the pulses follow different routes, they arrive at the electrode at slightly different times. Although their time of arrival is so close that brain movement only displays a single peak, the electrode-electrolyte filter system is sufficient to differentiate the signal and produce two distinct peaks in the EEG.

Fig. 22 demonstrates that differentiation may be able to acount for some theta records that show no obvious correspondence with heartbeat or respiration, for when the brain movement signal is passed through a high-pass filter, the resultant signal shows a similarity to the hippocampal EEG.

9.8. GENERAL DISCUSSION

The evidence presented above provides a strong indication that theta may be, at least in part, an artifact of brain movement. Certainly the relationships observed between theta and behaviour are compatible with such an interpretation. For example, voluntary movement or exploration (Vanderwolf 1969) is associated

(especially in lower animals) with sniffing, as is the orienting response (Grastyan 1959), and general arousal (Klemm 1970). However, the emphasis placed by this report on the role of sniffing in artifact generation should not be misinterpreted. This is merely due to the fact that sniffing is one of the more accessible variables which produce brain movement. It is certainly not the only factor and studies which dissociate theta from respiration (e.g. Whishaw and Schallert 1977) do not therefore prove that theta, either in these cases or in general, is not artifactual.

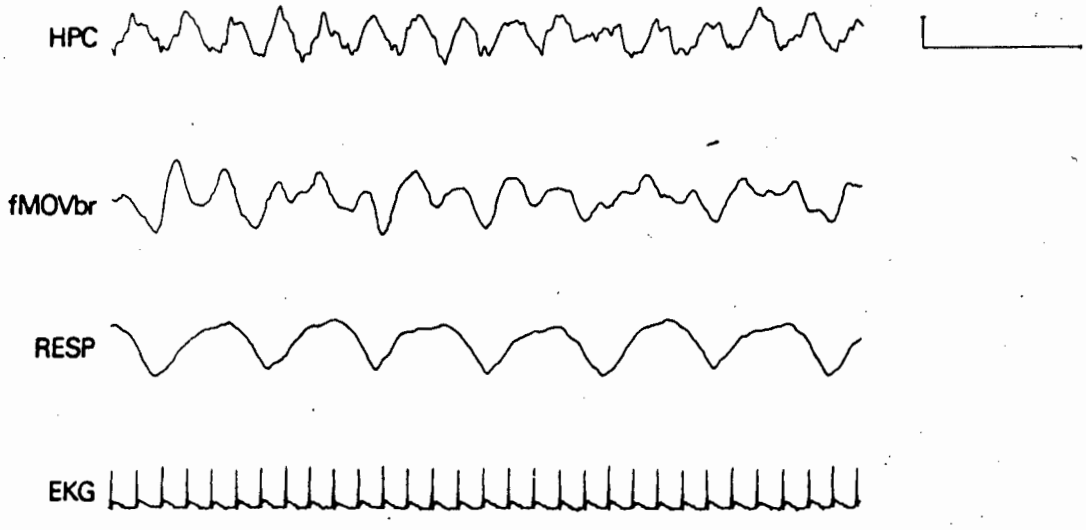

FIG. 22. Illustrating an occasion when theta bears no obvious relationship to either respiration or heartbeat. When, however, the brain movement signal is passed through a high-pass filter, the resulting signal (fMOVbr) shows a close resemblance to theta. Cal.: 200 μV, 1 sec.

There are certain data, however, which do, at first sight, appear to present difficulties for the hypothesis. For example, Whishaw (1972), while agreeing that sniffing during exploration is always accompanied by theta, has shown that sniffing during immobility is not. Since brain movement is presumably produced by sniffing under both conditions, the fact that theta is not seen during

immobility indicates that brain movement is not a sufficient condition for the generation of theta. A similar point has been made by Vanderwolf & Robinson (1981 p. 505) in a rebuttal of the present hypothesis. They note that theta "cannot be recorded from the rat hippocampus during the isoelectric period following a hippocampal seizure even though the rat walks about actively, and its brain, presumably, continues to move to the same extent as it does in the normal state."

However, this argument misses the point that the artifact voltage is a function not only of the amplitude of brain movement, but also the PD that exists between the electrodes. Thus, even large movements will produce no discernable voltage if the PD is small, and vice versa. Furthermore, given the nature of the tissue with which the electrodes are in contact, the PD would not be expected to remain constant. Recent work has made it clear "that the ionic microenvironment in cortex changes substantially with normal and pathological cellular activities" (Benninger, Kadis & Prince 1980 p. 165). For example, small increases "in extracellular potassium concentration, $[K^+]_o$, are detectable in the spinal cord in response to a noxious tail pinch, are present in the striate cortex after photic stimulation, and occur in the reticular formation after spontaneous bursts of action potentials. More significant changes in $[K^+]_o$ are recordable during repetitive discharges associated with epileptiform activity ..." (Hablitz & Lundervold 1981, pp. 410-411). Since the PD is dependent upon the ionic concentration, this means that it (and therefore the artifact voltage) will vary with the level of neural activity, even if brain movement is of a constant amplitude. Evidence which has a direct bearing on this issue derives from experiments where

manipulation of the thorax by hand was attempted in lightly anaesthetised animals. It was found that though the hippocampal EEG usually followed the induced brain movement, on occasion the entrained theta waves were blocked by a low amplitude, desynchronised waveform. Fig. 23 shows one such instance.

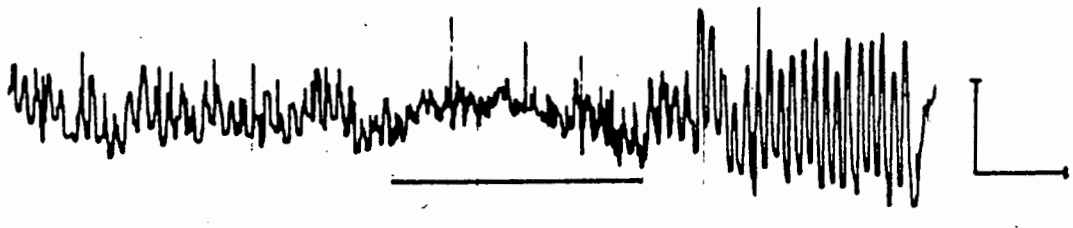

FIG. 23. Recruitment of theta waves produced by thoracic manipulation in a lightly anaesthetised animal is blocked by desynchronised activity (underlined). Cal.: 200μV, 1 sec.

Thoracic manipulation was maintained throughout this section of the recording, but the quality of the induced theta varies markedly. It is of low amplitude and somewhat irregular initially, then is blocked completely, only to return suddenly at a much larger amplitude. Since on other comparable occasions brain movement was found to follow thoracic excursions with complete fidelity, the conclusion is inescapable that some change has occurred during the underlined portion of the recording which prevents the normal transduction of brain movement into EEG voltage fluctuations. Given the argument above, a plausible explanation for this blocking phenomenon is that it is caused by neural activity which, by altering the chemical environment of the electrodes, reduces the PD and thus diminishes the amplitude of the artifact. Thus, to answer Vanderwolf & Robinson, even assuming that brain movement is similar pre- and post-seizure (and this is by no means certain since brain movement depends upon, among other things, blood pressure), these movements will not

produce EEG fluctuations if the massive neural firing during the seizure temporarily diminishes the PD.

In a second objection, Vanderwolf & Robinson make the claim that brain movement is not a necessary condition for the production of theta, since intracellular recordings of theta (Fujita and Sato 1964) show that theta can be recorded in the absence of significant brain movement. This is an important point since in microelectrode work the brain is commonly considered to be stabilised when no visible movements are detectable. It is of some interest, then, to look at the research of Teague, Elfert, Timm and Bradley (1969), who distinguished two types of brain movement: Brain displacements, which are slowly varying, relatively large amplitude movements (for example, approximately 50μ displacement for each 10mm Hg change in systolic blood pressure), and brain pulsations, which are rapidly fluctuating, small amplitude movements, falling in the range of 5 - 20μ. Since it is this latter type of movement that I have recorded and found to be so closely related to EEG excursions, it is evident that (i) very small movements are "significant" in that they can produce artifacts, and (ii) that the larger neurons of the CNS (such as the hippocampal pyramidal cells from which Fujita & Sato (1964) obtained their recordings) should easily be able to accommodate movements of this order (and might also explain why it is so difficult to obtain stable recordings from the smaller neurons).

10 A REINTERPRETATION OF SOME STUDIES

It is clear that the demonstration that artifacts indistinguishable from theta can be produced under certain conditions, carries the implication that some reports may be confounded by the inclusion of such material. Indeed, there are several instances where puzzling or frankly contradictory results have been reported which can be resolved if an artifactual genesis of theta is considered. The following examples will serve as illustration.

10.1. THE DIRECTION & SPEED OF PROPAGATION OF THETA

The origin and spread of theta in the rabbit was investigated by Petsche and Stumpf (1960), using a three-dimensional array of electrodes. Their results showed, inter alia, that:

(i) Lateral leads showed theta to spread caudally over the hippocampus, while, surprisingly, more medially placed electrodes recorded waves moving in a rostral direction as well.

(ii) Propogation was of a spherical nature, spreading from "a region in the frontal upper parts of the diencephalon".

(iii) Theta could be recorded from all parts of the brain caudal to the septum, with points of maximum amplitude being found in the hippocampus, particularly the CA3 region.

These results can easily be accounted for if theta is assumed in this case to be an artifact generated as described previously. First, however, it is necessary to consider in more detail the

manner in which thoracic pressure changes are transmitted to the brain. Bering (1955) has demonstrated that these pressure changes are only transmitted to the CSF when they enter the spongy tissue of the choroid plexuses, the most important of which lie along the medial wall of each lateral ventricle and the roof of the third ventricle. Figs 24A and B show in schematic form the relevant vascular anatomy. Venous drainage of the choroid plexus of the lateral ventricle takes place in a rostral direction, mainly by way of the choroidal vein. This exits at the foramen of Monro and then turns sharply back to join the internal cerebral vein, which also drains the choroid plexus of the third ventricle, but in a caudal direction.

It is thus apparent that a pressure wave (indicated by arrows in Fig. 24A) moving up the great cerebral vein will enter the choroid plexus of the third ventricle in a rostral direction, and the choroid plexus of the lateral ventricle in a caudal direction. Therefore:

(i) Lateral electrodes, being over the lateral ventricles, will record theta moving caudally, while more medially placed electrodes, being near the third ventricle, will record theta moving rostrally as well.

(ii) The foramen of Monro (a region in the frontal upper parts of the diencephalon) will appear to be the site or origin of the theta waves since it is the most rostral point from which waves moving caudad would be seen.

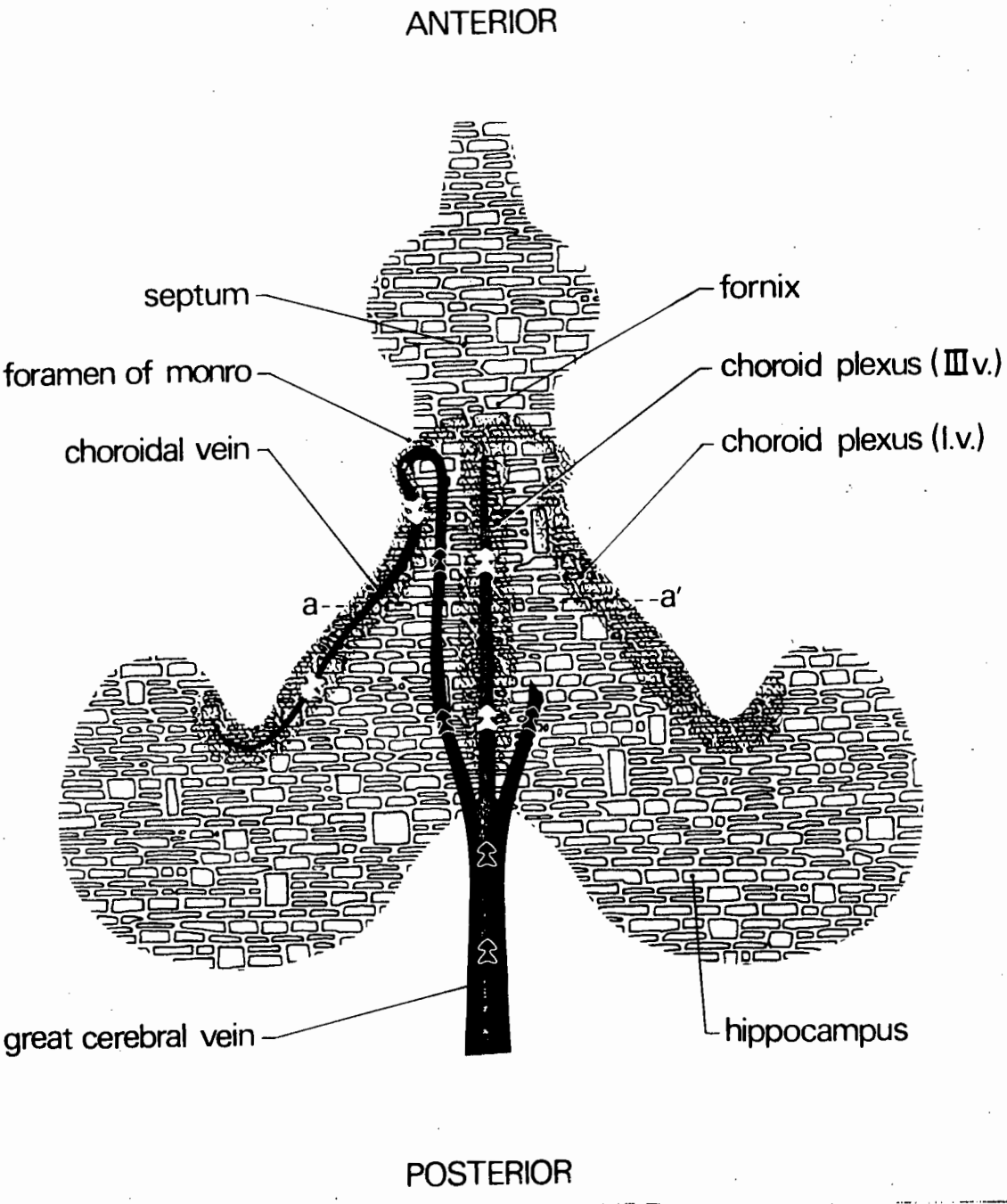

FIG. 24A. A schematic dorsal view of the hippocampus and its relationship to the choroid plexuses and their venous supply. Arrows indicate the direction of pulse propogation. Solid arrows indicate the areas where the pulse is transmitted to the surrounding neural tissue. It is thus apparent that tissue movement near the choroid plexus of the third ventricle (choroid plexus IIIv.) will occur as a wave moving in a rostral direction, while that surrounding the choroid plexus of the lateral ventricle (choroid plexus 1.v.) will appear as a wave moving caudad.

(iii) Since the hippocampus forms the roof of the third ventricle and the medial wall of the lateral ventricle, and is thus sandwiched between the two pulse generators (see Fig. 24B), tissue movement, and thus theta, will be particularly prominent in this region. Seeing that the dentate gyrus and CA1 are near to the choroid plexus of the third ventricle, and the choroid plexus of the lateral ventricle runs along the border of CA3 (see Fig. 24B) the highest amplitudes will be seen here.

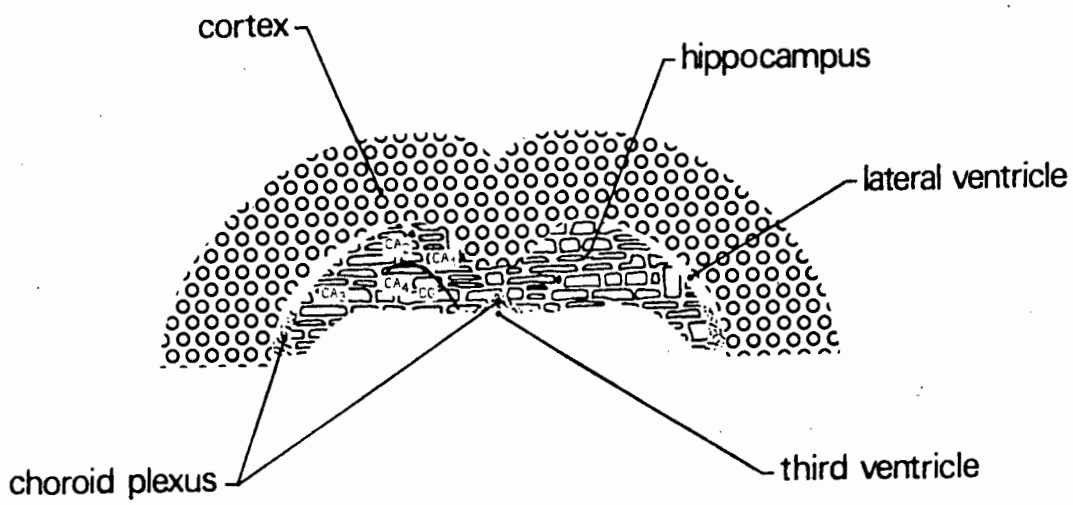

FIG. 24B. A schematic cross-section of the hippocampus showing its architechtonic fields, taken at approximately the level of a - a' in Fig. 24A. The choroid plexus of the third ventricle lies near CA1 and the dentate gyrus (DG), while the choroid plexus of the lateral ventricle lies near CA3.

It is interesting that Bland et al (1975) failed to replicate Petsche and Stumpf's findings in this regard. Although they found the greatest theta amplitude in the dentate gyrus, they were unable to record significant theta activity in the CA3 region. However, this disparity can be ascribed to differences in preparation. Petsche and Stumpf used an intact brain, while Bland et al's procedure involved the complete exposure of the lateral ventricle, and consequent destruction of its choroid plexus. Thus

the only remaining generator of artifactual theta would be the choroid plexus of the third ventricle, which lies near the dentate gyrus.

Petsche and Stumpf (1960) were also able to measure the speed of propagation of theta by measuring the lag at different recording sites. They found that it was almost linearly related to frequency, with a range between 20 - 80 cm/sec. This low figure poses serious problems for any neuronal theory of theta production. Green et al (1960, pp. 418-419) comment: "The mode of spread of the theta rhythm across the surface of the hippocampus is obscure. It is too slow to be considered a simple all-or-none propagation. An anterior-posterior rate of 20 - 80 cm/sec. could only be due to a path in which many successive cells, arranged anteroposteriorly, become excited successively. It is difficult to justify such an arrangement on anatomical grounds."

The model proposed here can account for this slow propagation speed if it can be shown that the speed of propagation of the vascular pressure wave is similar. This can be calculated by determining the delay between respiration and the resultant brain movement, and then dividing into the distance between the thorax and the foramen of Monro. In order to determine the phase lags between the wave forms, a section of the respiratory channel was traced and then matched to theta. The amount the tracing had to be shifted to obtain a best fit gave a measure of the lag. (Theta was used instead of brain movement because the EEG and pneumograph both depend upon electro-chemical processes, and therefore should have similar response times. The results would not have differed materially if brain movement had been used.) Using an average

value of 4,5 cm for the thoracic-foramen distance, the speed of the pressure wave, like theta, was also found to be frequency dependent, being approximately 30 cm/sec at 4 Hz and 40 cm/sec at 6 Hz. Considering the limitations of the measuring technique and the difference in preparations, this is in excellent agreement with the results of Petsche and Stumpf (1960), who obtained values of 20 cm/sec and 50 cm/sec at the respective frequencies.

Finally, Petsche and Stumpf (1960) made the intriguing discovery that, as a monopolar electrode traverses the cortex, crosses the lateral ventricle, and enters the hippocampus, a reversal of polarity occurs such that theta recorded from the hippocampus is 180 degrees out of phase with theta simulatneously recorded from the cortex.

This reversal of phase can be understood if one considers that a pulse arising in the ventricle will cause the neural tissue above and below it to move in opposite directions. This means that electrodes placed equidistant on either side of the ventricle are bound to produce voltages which are out of phase. In order to test this argument, monopolar electrodes (stereotaxic frame as reference) were inserted on either side of the lateral ventricle of a dead animal and its thorax pumped. The recordings were found to be phase-reversed (see Fig. 25). As a control, brain movement was produced by displacing the body relative to the head. This causes movement of the brain as a whole, i.e., there is no differential brain movement. Under these conditions the signals were in phase. Similarly, when the hippocampal electrode was raised to the cortex, the recordings were in phase regardless of how brain movement was produced. Once again, it should be noted

that it became more difficult to produce recordings which were out of phase as time from death increased.

The possibility that this explanation is correct is strengthened by the fact that Petsche and Stumpf (1960) did not only obtain a phase reversal when the electrode entered the hippocampus: Theta was found to be phase reversed when the electrode crossed any discontinuity in the brain (for example, from the occipital cortex to the underlying superior colliculus). In other words, a phase reversal occurs whenever the electrode crosses a space where the tissue above and below it is free to oscillate in opposite directions.

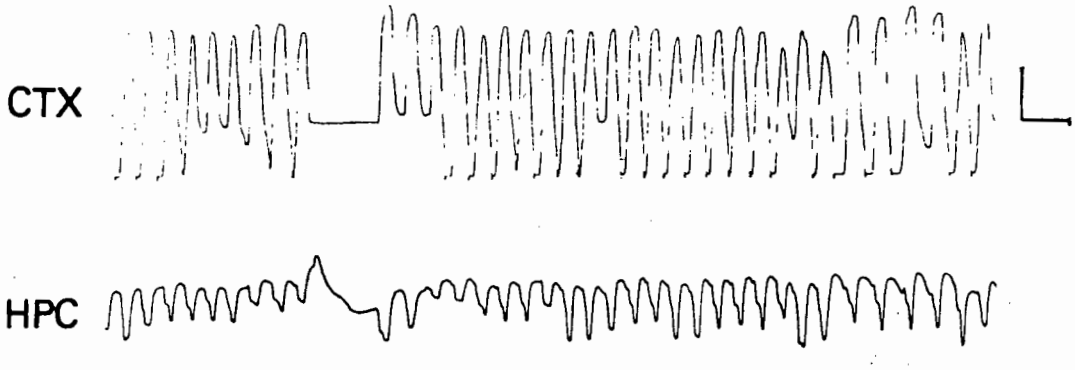

FIG. 25. A recording from two monopolar electrodes, one in the neocortex (CTX) and one in the hippocampus of a dead animal. When brain movement was produced by thoracic manipulation the signals from the two sites were 180 degrees out of phase with each other. Cal.: 200μV, 1sec.

However, differential brain movement is not the only way in which phase reversal can be brought about. Movement of any area which is chemically non-homogeneous with its surroundings will also produce phase-reversed voltage fluctuations in monopolar electrodes placed on either side of it. Such conditions do seem to apply in those parts of the CNS where well-defined cell layers exist. It seems

almost certain that these strata will be associated with ion concentrations different from the surrounding tissues. The finding that phase reversal occurs across the pyramidal and granular cell layers (Green et al 1960; Winson 1974) is therefore understandable.

10.2. NEOCORTICAL THETA

As has been mentioned previously, theta is not restricted to the hippocampus, but can be recorded from most parts of the brain, including the neocortex. The locus of generation of this neocortical theta has been the subject of some controversy. On the one hand, it has been shown that it cannot be generated within the neocortex. Gerbrandt et al (1978), using the technique of cortical spreading depression to suppress neocortical activity, found that, if anything, the amplitude of neocortical theta actually increased. They therefore concluded that it was passively spread by volume conduction from the hippocampus. On the other hand, there is good evidence to show that neocortical theta does not come from the hippocampus. For example, theta is not always seen in the neocortex when it is present in the hippocampus, thus ruling out simple volume conduction, and, conversely, theta can sometimes be recorded from the neocortex when it is not present in the hippocampus (McFarland et al 1975), thus indicating an independent neocortical site of generation. Although Gerbrandt et al (1978) attempt to account for this latter observation by recourse to multiple generators of theta within the hippocampus, it must be pointed out that McFarland et al (1975) were recording from the dorsal hippocampus. It would be surprising, to say the least, if theta could spread from the ventral hippocampus to the

neocortex without being seen in the dorsal hippocampus. In any event, the recent findings by Feenstra and Holsheimer (1979) that theta undergoes phase reversal and changes in amplitude in the cingulate cortex clearly indicates an independent site of neocortical theta generation.

This state of affairs is paradoxical only if theta is considered to be exclusively of neural origin. Taking an alternative view, it will be appreciated that the neocortex, overlying the lateral ventricle as it does, will be pulsed contemporaneously with the hippocampus. Therefore if both structures are relatively inactive, they will both display theta. However, if one is active, then only that tissue that is inactive will display theta.

10.3. INTRACELLULAR THETA

Fujita and Sato (1964) recorded intracellularly from hippocampal pyramidal cells during ongoing hippocampal theta activity. Their records showed rhythmical swings of the baseline, often on a massive scale (as much as 36mV), 180 degrees out of phase with extracellularly recorded theta. These baseline oscillations were interpreted as representing membrane depolarisations and hyperpolarisations and promised, at least partially, to explain the genesis of extracellular theta. However, a number of their observations are inconsistent with this interpretation, the most obvious being that neuronal firing seems independent of the supposed membrane potentials. Huge depolarisations do not produce firing, while, on the other hand, firing often occurs from a point of hyperpolarisation. In order to accomodate these results, the authors are obliged to offer such explanations as: depolarisation

produces "inactivation of the spike initiation mechanism", and "during the hyperpolarisation ... spike initiation is shifted to the hyperpolarising direction".

These explanations do some violence to classical theory, and the results can perhaps be more parsimoniously understood as movement artifacts masking the true underlying neuronal events. This is in line with the afore-mentioned observations of investigators such as Li and Jasper (1953) and Walsh (1956) who traced the cause of baseline fluctuations to brain movement. Indeed, Li and Jasper (1953) were able to eliminate baseline movements by immobilising the brain by draining the ventricles and applying pressure to the cortex. If Fujita & Sato had employed similar precautions they might well have obtained a straight baseline, deviations from which would have indicated true depolarisations and hyperpolarisations which would have born the classical relationship to neural firing.

The fact that intracellular and extracellular theta records differ in amplitude and phase can be seen as the result of the difference in composition of intracellular and extracellular fluid. Thus if the intracellular electrode has a large, negative potential difference relative to the indifferent electrode, while the extracellular electrode has a small, positive potential difference, then movement of the respective electrode-electrolyte interfaces will produce waves 180 degrees out of phase, with amplitudes proportional to their potential differences.

Some evidence to support the above argument is provided by an experiment where Fujita and Sato (1964) injected current into a

cell, either in a depolarising (positive) direction, or a hyperpolarising (negative) one. As expected, depolarisation increased neural firing (26A), while hyperpolarisation inhibited it (26B). What it surprising, however, is that the intracellular theta rhythm decreases in A, and is markedly increased in B. In other words, the behaviour of the cell (as evidenced by neural firing) and the supposed membrane potential (as evidenced by theta) are shown to be completely dissociated. These results can easily be explained if the intrracellular theta rhythm is actually a movement artifact. Passing a current into the cell in a depolarising direction makes the inside of the cell less negative with respect to the reference electrode, i.e., the potential difference between the two electrodes is reduced. Thus movement of

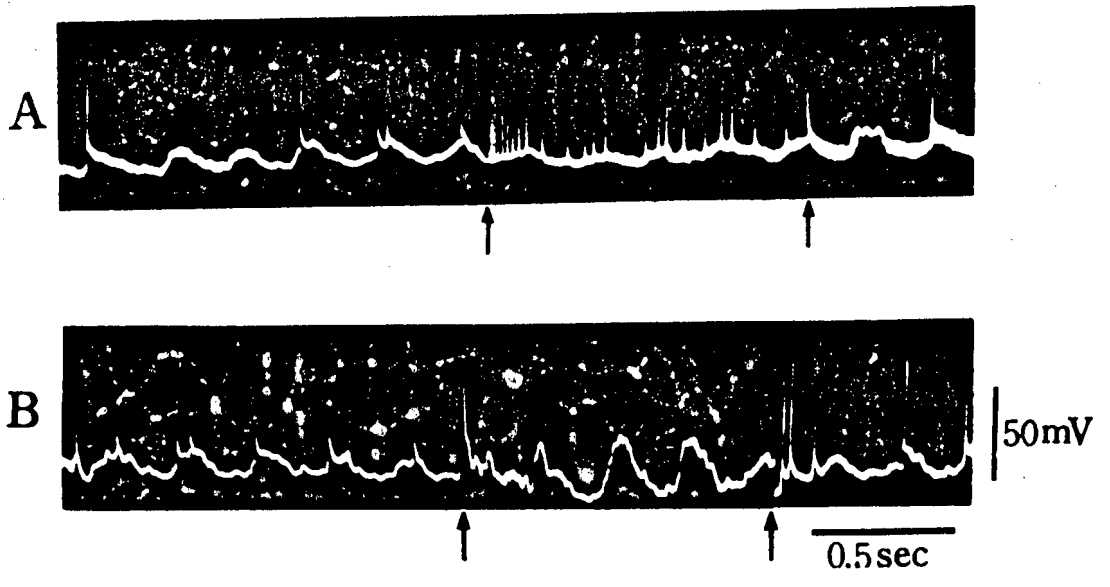

FIG. 26. Intracellular recording from CA2 pyramidal cell layer. In A, between two arrows a currrent of 8.3×10^{-10} was passed in a depolarising direction. In B, a current of same intensity was applied in hyperpolarising direction. K^+ -citrate electrode was used. (From Fujita and Sato 1964, by permission of the author and publisher.)

the electrode-electrolyte interface will produce smaller voltages and theta will therefore become smaller. Similarly, When a

hyperpolarising current is passed into the cell, the potential difference between the intracellular electrode and the indifferent electrode will be increased, and movement will therefore result in a larger theta amplitude.

10 4. TWO TYPES OF THETA?

Vanderwolf's (1969) hypothesis that theta is related to voluntary movement has come under strong pressure from reports that theta can be recorded during immobility (Harper 1971; Klemm 1976) and anaesthesia (Kramis 1975; Whishaw 1976; this report). Accordingly, he has suggested that there are two types of theta - one associated with movement and one with immobility. He bases this claim on drug studies which show that large doses of atropine (in excess of 25 mg/Kg i.p.) block the theta associated with immobility, but not that associated with movement (Vanderwolf and Robinson 1981). It would be tempting to conclude that Vanderwolf has succeeded in pharmacologically dissociating artifactual from "real" theta, especially in view of the fact that movement related theta has proved resistant to all other drugs that have been tried. However, as Vanderwolf and Robinson (1981) note, drug studies raise "many problems of interpretation". One cannot assume that the blocking of theta by atropine is due to the blockade of hippocampal cholinergic synapses, since the drug produces a variety of other effects. For example, one side effect is to produce peripheral vasodilation (Bowman and Rand 1980), thus lowering blood pressure (Allen et al 1972). This could mean that weaker sources of brain movement which are dependent on a reasonable level of blood pressure would be blocked, while leaving more potent, movement associated factors unaffected. This

possibility is supported by the fact that I have found that phentolamine (Regitine, Ciba-Geigy: 2 mg/Kg i.p.), which has a specific depressor effect, also tends to suppress all but the most intense, movement associated theta.

10.5. THE SEPTUM AND THETA

The fact that theta has been found to be dependent on the integrity of the septum and its connections (via the fornix) with the hippocampus (Green and Arduini 1954), may seem to provide evidence that theta has an exclusive neurobiological origin. However, there are other possible explanations. One is that since the septum and fornix straddle the foramina of Monro, lesions of these areas might well interfere with the blood supply of the choroid plexus, thus preventing vascular pulse transmission and consequent neural tissue movement.

A second possibility arises from the fact that the medial septal nucleus (ablation of which prevents theta) has been shown to exert an inhibitory effect on the hippocampus (Miller and Groves 1977). Thus its destruction will release the hippocampus, resulting in excess neural activity and therefore a predominantly desynchronised hippocampal EEG.

10.6. OTHER ELECTROENCEPHALOGRAPHIC ACTIVITY

The demonstration that theta can be produced by neural tissue movement raises the possibility that other synchronous electrographic activity could be similarly caused. Certainly the finding by Bradley and Elkes (1953) that the EEG could be

dissociated from its behavioural correlates by the administration of drugs, and the reports that a normal EEG could be recorded in humans after the underlying cerebral hemisphere had been totally removed (Obrador and Larramendi 1950; Marshall and Walker 1950) coupled with the previously mentioned work of Li and Jasper (1953), do suggest that this may be so.

The large, slow wave activity of the olfactory bulb (the Ottoson potential) is a case in point. As mentioned previously, this activity has been found to be closely related to respiration (Gault and Leaton 1963; Macrides 1975). This strongly indicates that the Ottoson potential, too, could be a result of respiratory induced neural tissue movement - a conclusion reinforced by the report by Walsh (1956) that "variation in spike height ... could be traced to small intracranial oscillations of the olfactory bulbs which arose from the animal's respiratory or cardiovascular movements". Furthermore, both slow and fast synchronous activity are present even in the completely isolated olfactory bulb (Von Baumgarten et al 1962), thus ruling out the possibility that the observed relationship could be due to olfactory input.

Perhaps the most convincing evidence implicating neural tissue movement in the genesis of synchronous EEG activity comes from the work of Kennedy (1959) regarding human cortical alpha.

Kenneddy (1959) has advanced the hypothesis that alpha is caused by heartbeat. Quite obviously this cannot be a one-to-one relationship as has been found above with animals, since the heartbeat in humans is far too slow. However, Kennedy suggests that, in humans, the increased force with which blood is pumped

into the brain is sufficient to set up vibrations within the neural mass - thus producing several oscillations for each beat. This contention is supported by Berger's own observations that, for any individual, there is a constant number of alpha waves for every heartbeat (see, for example, Gloor 1969, p.90) - a fact which no doubt greatly added to his uncertainty as to the nature of alpha.

More direct evidence is adduced from a simple model constructed by Kennedy (1959). This consisted of a ceramic pot containing a bimetallic strip and filled with gelatin. When the pot was pulsed at normal heart rate, electrodes on the outside of the pot recorded a waveform indistinguishable from alpha.

Extrapolating from his model, Kennedy reasoned that any discontinuity in the cranium would act as a shock-absorber, thus damping the oscillations of the neural tissue and preventing alpha. This would explain why a small percentage of the population do not display alpha. As a crucial test of his hypothesis he found a non-alpha subject with a rather obvious defect in the temporal bone of the skull. Restoring the integrity of the cranium with an appropriately shaped piece of plastic produced prominent alpha waves, which displayed all the usual characteristics of alpha, including alpha-blocking upon eye opening!

To account for alpha-blocking Kennedy appeals to the concept of local autoregulation of blood supply, claiming that the flow of blood to an active area would "detune" the lobe and thus produce desynchronisation. However, this explanation does not seem entirely satisfactory. As an alternative I would suggest that, in

view of the results reported above, desynchronisation is brought about by neural activity.

Kennedy's hypothesis also allows for a solution to a puzzle which has been the source of much speculation. It has been known for some time that alpha-like activity can be recorded from other parts of the body besides the head. This activity, known as physiological tremor, is indistinguishable from alpha. It waxes and wanes in a similar manner, and also disappears during sleep (Lippold 1973). This suggests the possibility of some common underlying factor, and, in the light of Kennedy's results with alpha, it should come as no great surprise to find that physiological tremor, too, is caused by body vibrations set up by the beat of the heart (Yap and Boshes 1967).

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