List of appendices

Appendix 4

Anatomy of the septo-hippocampal system

A4.1 Introduction

Over 50 years ago Papez (1937) used mainly anatomical data as a basis for a theory that the limbic system is a crucial substrate of emotion. The key point of his theory was that limbic structures are intermediate between, and reciprocally connected to, the hypothalamus and the neocortex. 'This circuit would explain how emotion may arise in two ways: as a result of psychic activity and as a consequence of hypothalamic activity' (Papez 1937, reprinted in Arnold 1968, p. 306). The theory presented in this book (and particularly Chapter 10) emphasizes these same general anatomical relations—but provides a slightly different functional interpretation to that of Papez, and a considerably different detailed wiring diagram.

In particular, Papez proposed a specific role for the hippocampus based on the idea that 'the central emotive process of cortical origin may then be conceived as being built up in the hippocampal formation and as being transferred to . . . the cortex of the cingular gyrus [which] may be looked on as the receptive region for the experiencing of emotion as the result of impulses coming from the hypothalamic region, in the same way as the area striata is considered the receptive cortex for photic excitations coming from the retina' (Papez 1937, reprinted in Arnold 1968, pp. 305–6). We also view the hippocampus as a key structure in the control of emotion. But we will take a much wider view of its target output structures and propose a quite different function for the hippocampus and its relation with the cingulate cortex, as well as drawing a sharp distinction (Appendix 3) between the anterior and posterior cingulate cortex.

In this appendix we will provide considerable detail on the anatomy of the septo-hippocampal system. However, it should always be borne in mind that the septo-hippocampal system is itself embedded in a maze of cortical and subcortical systems and cannot be treated entirely in isolation. This is particularly important since the basis for Papez theory was the unusually rich interconnections between the different 'limbic' structures and the resultant multitude of recurrent loops in which the hippocampus was only one node (see also Miller 1991). We have given partial views of the anatomy of some of these structures in Appendices 2 and 3, but a complete theory would need them to be reviewed in much greater detail.

In addition to simplifying the anatomy with which we must deal by focusing on the septo-hippocampal system, we have simplified by concentrating on those features of septo-hippocampal anatomy which will be important for the analysis and theory which follows. For those wanting a fuller picture, O'Keefe and Nadel (1978) provide a thorough overall review of septo-hippocampal anatomy (see also De France 1976; Swanson 1978) and more recent developments are reviewed by Amaral and co-workers (Amaral 1987; Insausti *et al*. 1987*a*,*b*; Suzuki and Amaral 1994*a*,*b*), by Miller (1991, Chapter 3), and by Jakab and Leranth (1995), among others. Some topographic details of particular importance for our theory have only

recently appeared (Namura *et al*. 1994; Barbas and Blatt 1995; Risold and Swanson 1996). It should also be noted that, as in a number of other places in this book, we have assumed that connections are largely similar across species since many apparent discrepancies are tending to be resolved with more recent data (e.g. Insausti *et al.* 1997).

A4.2 Components of the hippocampal formation

Blunt dissection of the septum and the hippocampal formation in the rat (the species which provide the bulk of the pharmacological and lesion data in this book) gives us immediate reason to talk of a 'septo-hippocampal system'. As can be seen in Fig. 1.3A the hippocampal formation and septum can be removed from the brain as a single piece, requiring tissue to be torn only where the hippocampus is connected to the cortex and where the septum is connected to the diencephalon.

This region seems to call forth culinary similes. O'Keefe and Nadel (1978) liken its shape to a sausage. We prefer to think of it as a pair of bananas joined at the front. The almond-shaped area where the bananas join at their most rostral extent is the septal area. The fibres which connect the septal area and the hippocampal formation travel in two bundles: the fimbria which sweeps along the outside edges of the two bananas; and the dorsal fornix (*fornix superior*), which keeps to the midline and courses in the hollow between the bananas. These two bundles do not appear to differ functionally, and come together between the septum and hippocampus as a single bundle which is probably best termed the 'fimbria–fornix'. Interhemispheric connections between the two hippocampi are carried by fibres referred to as the ventral and dorsal hippocampal commissures or *psalteria*. The fibres of the ventral psalterium course in the fimbria of one side, cross the midline at the bottom of the fimbria–fornix and then descend in the fimbria of the other side. The smaller dorsal psalterium runs above the top of the hippocampal flexure, at the point where the hippocampus begins to turn down.

The same general topography and connections are maintained in the human case (Fig. 1.3B). But here, the hippocampus has been forced downwards and backwards by the expansion of the cortex and the fibres of the fornix–fimbria now form a long arching tract between the septum and hippocampus. The name hippocampus derives from its similarity, in the human case, to a head-down sea horse, where the fornix–fimbria represents the tail.

Because of the complex curvature of the hippocampi, and the variations in this curvature and the position of the hippocampus with species, the usual anatomical distinctions of anterior/posterior, dorsal/ventral have to be used with caution. Blackstad (1956) suggested that, instead, in describing locations along the body of the banana, one should use a septo-temporal axis: points on the banana close to the septal area lie at the septal pole; points close to the other end of the banana lie at the temporal pole, and *in vivo* are deep inside the temporal lobe. Despite his advice, those working with rats frequently refer to the septal end of the banana (which in this species is both dorsal and *anterior*) as 'dorsal' hippocampus and to the temporal end as 'ventral' hippocampus; while those working with monkeys refer to the septal end (which in this species is both dorsal and *posterior*) as 'posterior' hippocampus. We will keep to Blackstad's terminology throughout. 'Flexure' is used to refer to the portion in between the two poles and is unambiguous.

We may push the banana analogy further. A slice cut transverse to the septo-temporal axis (i.e. adjusting for the curvature of the banana so as to cut squarely across it; Fig. 1.3C) reveals two major interlocking U-shaped rows of large cells which can be thought of as the seeds of the banana or (to mix culinary metaphors) as the cream in a Swiss roll (Fig 1.3D). Most recent anatomical results are presented in terms of the flat sheets which would result if one were to unbend and unfold the Swiss roll and so retrieve the original single layer of sponge and cream from which it is constituted. A remarkable fact is that the banana (Swiss roll or sausage as you will) can be cut into transverse slices and much the same electrophysiological responses obtained from the slices as from the whole animal. We will consider the reasons for this shortly. Perhaps still more remarkably, given the superficial differences between Fig. 1.3A and Fig. 1.3B, slices from human hippocampus look and behave *in vitro* much like slices from, say, mouse hippocampus.

This similarity across species extends to the detailed circuitry of the septo-hippocampal system. The relative invariance of this circuitry is an important reason for believing that the basic operations performed by this system are similar across species. That they are not absolutely identical, and that the hippocampus plays a particularly important role in humans, is indicated by the fact that the human hippocampus is four times larger than would be expected in a basal insectivore of the same weight (Stephan 1983, cited by Amaral 1987).

The circuitry and general organization of the septo-hippocampal system is beautifully ordered and has made the hippocampus a favourite target for anatomists and physiologists. The two U-shaped rows of cells which provide the cream for our Swiss roll (which is here a better analogy than the banana) are the result of the folding and interlocking of two separate cortical sheets. The larger and more superficial of these two includes the hippocampus proper (‘Ammon’s Horn’ or *cornu Ammonis*), the smaller and more embedded is the dentate gyrus or *fascia dentata*. However, as we will see, we can view the smaller ‘dentate’ sheet as being the first subfield of the larger sheet since the latter is divided into a number of functionally discrete zones. Since the principal cell layer of this larger sheet can be followed, essentially unbroken, into the neocortex, the question arises as to where, in principle, this part of the ‘septo-hippocampal system’ should be seen as terminating; we must also decide where, in principle, the cortical components of the septo-hippocampal system start.

Here, we will treat the entorhinal cortex as both the gateway for neocortical input to, and the first stage of, the ‘septo-hippocampal system’. We include the entorhinal cortex in the hippocampal formation because it receives input from the medial septum which causes it to produce theta activity (rhythmical slow activity; Appendix 5)—which is central to our theory of the neuropsychology of anxiety. In this, our ‘septo-hippocampal system’ is consistent with the expanded ‘hippocampal system’ favoured recently by Witter (1993) and by Eichenbaum *et al*. (1996). It should be noted that on this ‘theta’ criterion, the posterior cingulate cortex should also be included in the hippocampal formation (and is included in the behavioural inhibition system of this book). However, the posterior cingulate represents a reversal of the architectonic trend which progresses from the perirhinal and parahippocampal cortex, via entorhinal to subiculum; and we have covered the cingulate in some detail in Appendix 3. For the moment, therefore, we will treat the septo-hippocampal system as essentially separate from the cingulate.

A4.2.1 The sequential modules of the hippocampal formation . . .

An important characteristic of the hippocampal formation is the essentially unidirectional transmission of information between its parts. In much of the cortical mantle connections between areas are reciprocal. While there is minor reciprocity within the hippocampal system, and major polysynaptic feedback loops, a number of one-way connections within the hippocampal formation and between it and its immediate targets make the flow of information through the system much more one-way than for any other cortical system (although it is paralleled subcortically by the amygdala; see Appendix 2). We will consider its components in order, starting with the first which generates such a one-way flow (see Figs 1.3D and 9.4).

The entorhinal cortex has, like other neocortical areas, six layers of cells. At one edge, this six-layered sheet is contiguous with the rest of the neocortex; at the opposite edge, it is contiguous with the hippocampal formation. The sheet is itself divided into two. There is the lateral entorhinal cortex, which starts at the boundary of the entorhinal cortex with the neocortex; and there is the medial entorhinal cortex, which terminates at the boundary of the entorhinal cortex with the hippocampal formation.

The dentate gyrus is the next stage of hippocampal processing and is physically separate and quite distinct from the entorhinal cortex. The principal cells of the dentate gyrus are small and spherical and are therefore called granule cells (Fig. A4.1b). O'Keefe and Nadel (1978) suggested that the dentate should be divided into 'buried' and 'exposed' blades (Fig. 1.3D). However, unlike the entorhinal cortex, there appears to be no morphological or functional difference between groups of granule cells which would require further subdivision of the dentate gyrus.

Fig. A4.1 [plate for this figure to be recovered from Figure 3.4 of the first edition]

Fig. A.4.1 Examples of hippocampal cells. (a) CA1 and CA3 pyramids. (After Ramon y Cajal 1955, Fig. 475.) (b) Dentate granule cell and basket cell of Cajal. (After Lorente de No 1934, Fig. 10.) The regular packaging of these cells in the hippocampus gives rise to the distinctive layers whose names are shown to the left. (From O'Keefe and Nadel 1978.)

The hippocampus proper can be divided into four subfields on the basis of cytoarchitectonics. If you imagine the curved sheet of cells unrolled (so you now have a flat sponge cake rather than a Swiss roll), the medium-sized pyramidal cells farthest from the dentate gyrus constitute area CA1 (CA for *cornu Ammonis*), closer there is a transitional area, CA2, and then the giant pyramidal cells of area CA3 (see Fig. A4.1). Finally, closest to and enclosed by the dentate gyrus, there are scattered pyramidal cells designated area CA4.

Blackstad (1956) could find no difference between CA2 and CA3 and suggested that Ammon's Horn should be divided into two main parts: *refio superior* (CA1) and *regio inferior* (CA2, CA3). It should be noted that area CA1 is superior only in the septal/dorsal part of the hippocampus in rodents. In the extreme temporal/ventral part, because of the curvature of the banana, CA1 is effectively inferior. Possibly for this reason, the CA1–4 terminology is generally preferred to Blackstad's. Nonetheless, the paucity of references to area CA2 shows general agreement with Blackstad's view that CA2 is not a major distinct area. However, the increasing topographic differentiation being found in the hippocampus (see below) may in the end show this to be a real distinction. For the moment we have

ignored area CA2 as a distinct subfield in the same way as we have ignored the possibly distinct CA1/subiculum transitional zone which receives amygdala input (Appendix 3).

As shown in Fig. 1.3D, area CA1 appears continuous with an area where the cells are no longer neatly packed in rows. This is the subicular cortex, a transitional zone between the simple archicortex of the hippocampus and the six-layered neocortex of the entorhinal area. On the basis of cytoarchitectonics, Lorente de No (1934) divided this region into the prosubiculum (nearest CA1), the subiculum proper, and then (as one proceeds from *cornu Ammonis* towards and reaches the entorhinal cortex) the pre- and parasubiculum. The latter two areas, on connectional grounds, should probably be seen as input areas for the hippocampus (with their information relayed by entorhinal cortex), rather than being grouped with the prosubiculum and subiculum, which are output stages of the hippocampus.

A4.2.2 . . . and their connections

Both the medial and lateral entorhinal cortex relay information from other cortical areas to the dentate gyrus in the hippocampal formation. For our purposes, the main reason to distinguish the two areas is that they receive different, topographically organized, cortical inputs and project to different parts of the dendritic trees of dentate gyrus cells. However, they project to the same dentate cells. The fibres from the medial and lateral entorhinal cortex make up separate 'medial' and 'lateral' components of the 'perforant path'. The perforant path first courses in the angular bundle and in the upper layers of the subiculum (near the surface of the hippocampal banana) before perforating area CA1 to innervate the dentate gyrus (Fig. 1.3) and, to a lesser extent, other parts of the hippocampal formation. Most of the projection is ipsilateral, but there is also a small contralateral contribution. The lateral perforant path terminates on the distal third of the dendrites of the principal dentate cells, and the medial perforant path terminates on the middle third. Projections arising from the deep layers of the entorhinal cortex, however, can innervate not only proximal dendrites and somata of the granule cells but also interneurons (Deller *et al*. 1996). The co-termination of the medial and later perforant path on individual cells produces a major confluence of the different types of information originally received by the different components of the entorhinal cortex. The lateral perforant path also appears to contain fibres originating in the perirhinal cortex (Liu and Bilkey 1996, 1997; but see Canning and Leung 1997 for contrary data).

In both CA1 and the dentate the bulk of the entorhinal projections arrive on the spines rather than the dendritic shafts, appear to innervate principal cells and not interneurons, and appear to make excitatory rather than inhibitory connections (see Desmond *et al*. 1994). Dentate and CA1 appear to receive input from different entorhinal cells, located in layers II and III respectively (Steward and Scoville 1976).

Dentate granule cells project to the pyramidal cells of areas CA3 and CA4 via the 'mossy fibres'. Area CA4 of the hippocampus is the same area as that referred to as the hilus of the dentate gyrus and can be viewed as a second layer of cells within the dentate, as opposed to being a separate field in its own right. The scattered CA4 pyramidal cells will be among the 'hilar' neurons encountered in electrode penetrations of the dentate gyrus. CA4 receives a large part of its input from CA3 (see Scharfman 1994 for paired recording from CA3 and hilar cells) and appears to send its main output back to the dentate granule cells. Thus area CA3 appears to be the main throughway for information on from the dentate gyrus, while CA4 provides intrahippocampal loops: dentate–CA4–dentate; and dentate–CA3–CA4–

dentate (see also Frotscher *et al*. 1994). There are, however, inhibitory neurons in the dentate molecular layer which project directly to the subiculum (Ceranik *et al*. 1997).

The CA3 pyramids have bifurcating axons, with one main branch exiting from the hippocampus in the fimbria, while the other main branch, the 'Schaffer collaterals', synapses with the dendrites of the CA1 pyramidal cells. A single CA3 cell can arborize over as much as two-thirds of the hippocampus, making contacts with between 30#000 and 60#000 cells (Li *et al*. 1994). The morphology of the CA3 pyramids is quite variable and shows some relation to distance from the hilus of the dentate so that 'both dendritic and electrical properties should be specifically calculated for each cell rather than assuming a 'typical' morphology' (Turner *et al*. 1995). The CA1 pyramids, in turn, send their axons in the alveus (a sheet of fibres which provides the distinctive gleaming white skin of the hippocampus) to the subiculum (as well as to both subcortical and prefrontal targets, see below).

It used to be thought that CA1 was the source of the massive efferent pathway which travels in the fornix and this is how the projection is shown in a figure by Andersen *et al*. (1971; reproduced in, for example, Miller 1991, Fig. 17). However, later electrophysiological (Andersen *et al.* 1973) and anatomical (Hjorth-Simonsen 1971; Swanson and Cowan 1975) experiments have shown that CA1 axons are largely destined, instead, for the subiculum—and Fig. 1.3D follows Andersen *et al*. (1971) but is modified to account for this. There is a projection from CA1 to the medial septum, which closes a number of loops (e.g. medial septum–dentate gyrus–CA3–CA1–medial septum; see Jakab and Leranth 1995).

The afferent and efferent connections of the subiculum are complex and will be considered in more detail below. However, for the purposes of the present section it need only be noted that the subiculum projects unidirectionally to the posterior cingulate cortex (area 29, see Appendix 3), to the entorhinal cortex (like area CA1), and to the lateral septum (like CA3).

The projection from the subiculum to the entorhinal cortex closes the major unidirectional loop: entorhinal cortex–dentate gyrus–CA3–CA1–subiculum–entorhinal cortex. Information both enters and leaves this loop at a number of points (e.g. the exit from area CA3 to the lateral septum, and the inputs to all levels from the medial septum). Also, there are projections which appear to short-circuit components of the loop, for example from the entorhinal cortex to areas CA3, CA1, and the subiculum in the forward direction (Steward 1976; Van Hoesen *et al*. 1979), and from the temporal one-third of CA3 and CA4 to the entorhinal cortex (Hjorth-Simonsen 1973), and from CA1 to the entorhinal cortex, in the backward direction. However, as we have noted already, the *generally* unidirectional flow of information in the hippocampal formation (and from the subiculum to the cingulate and prefrontal cortices) is distinctive in that usually 'cortico-cortical connections within the isocortex . . . are reciprocal: a region which is afferent to another region usually (but not always) receives efferents from that region as well' (Miller 1991, p. 58). As we shall see, this reciprocity tends to be true also of subcortical regions which connect with the hippocampal formation. The entorhinal–hippocampus proper–entorhinal loops are themselves enclosed in larger cortical and subcortical loops which return information to the entorhinal cortex, and all of which are rendered unidirectional by the entorhinal connection to the dentate gyrus and by the unidirectional subicular, CA1, or CA3 projections to the relevant areas (Fig. 9.4).

The main complicating factor in this picture of a set of simple, largely unidirectional loops is area CA3. As we have noted already, CA3 projects to area CA1 and the dentate ipsilaterally. It is also the source of the contralateral projections which interconnect the hippocampi of the

two hemispheres via the ventral and dorsal psalteria. Via these fibre systems, area CA3 is connected to all the major subfields (CA1, CA3, and the dentate gyrus) contralaterally. These extensive interconnections suggest that the CA3 pyramids are a nodal point for coordination of the whole hippocampal circuit.

A4.2.3 The organization of the hippocampal formation

So far we have presented the hippocampal formation as being a sheet of projection cells (pyramidal and granular) divided into zones which are connected in an essentially unipolar fashion. However, each of these zones contains a number of interneurons, of which the most important are the basket cells (Fig. A4.1; for a recent extensive review of hippocampal interneurons see Freund and Buzsáki 1996). Each basket cell is connected to a large number of adjacent projection cells. These can provide both recurrent inhibition (when they are activated by recurrent collaterals from the projection cells which they inhibit) and feedforward inhibition. As we will see, both of these processes are important for the production of rhythmical activity in the hippocampus and entorhinal cortex. The interneurons can have extensive dendritic arborizations both in the molecular layer of the dentate (see, for example, Soriano and Frotscher 1993) and in the CA3 region (Gulyás *et al*. 1993). There are thus numerous types of, presumed feedforward, inhibitory interneurons with dendritic arborizations in distinct layers, and hence receiving different afferent input. This suggests that they each have distinct functions (Gulyás *et al*. 1993).

The interconnections between the different subfields of the hippocampal formation are extremely regular both with respect to the topographical relationships between subfields and the termination of different afferent pathways within a subfield.

The topographical aspect is reflected in the fact that transverse slices from the hippocampal formation retain a significant part of the circuitry, and can include all of the ‘trisynaptic’ pathway between the dentate, CA3, and CA1. Thus, the interconnections of these areas appear organized in strips or ‘lamellae’ transverse to the septo-temporal axis of the hippocampus (Andersen *et al.* 1971; Rawlins and Green 1977; Fig. 1.3D). The lamellar organization at the anatomical level is much less discrete than was thought previously (Frotscher *et al.* 1994), and the apparent restriction of the passage of information to one lamella may be in part due to the inhibitory influence of one nominal lamella upon adjacent cells, perhaps mediated by the basket cells (Stuble *et al.* 1978). This circuitry is reminiscent of lateral inhibition in sensory systems, but the extent of inhibition may be modulated in a way that sensory systems are not (see also Bernard and Wheal 1994 for a detailed computer model of local connectivity). Thus, there may be as few as four ‘lamellae’ in terms of functional connectivity (Finnerty and Jeffreys 1993; see also Paré and Llinás 1994; Chrobak and Buzsáki 1996), but the actual activity may be much more restricted under certain conditions. For example, in an isolated whole brain preparation, perforant path-evoked responses ‘in the CA1 region spread in an all-or-none fashion through the entire transverse and septo-temporal extent of the hippocampal formation . . . [but] the longitudinal propagation . . . is abolished by low doses of anaesthetic’ (Paré and Llinás 1994, pp. 407–8); equally, the synchronous 200 Hz ripples associated with sharp waves in the hippocampus (Chrobak and Buzsáki 1996) may be the result of unusually low levels of inhibition.

However, in addition to the strong lamellar organization, there are excitatory connections between CA3 cells in different lamellae (Lebovitz *et al.* 1971; Hjorth-Simonsen 1973; Rawlins and Green 1977); these make up the rather poorly characterized longitudinal

association pathway described by Lorente de No (1934), which essentially runs at right angles to the lamellae. As we noted above, individual CA3 cells send collaterals through up to two-thirds of the septo-temporal extent of CA1 and also have quite extensive longitudinal ramifications in area CA3 itself (Li *et al*. 1994). At least under some conditions, therefore, the functional organization of the system is far from lamellar (Paré and Llinás 1994).

Nonetheless, septal-temporal stacking of lamellae is clear in the topography of inputs to the hippocampus from the septum and entorhinal cortex. In the latter case the topography appears to retain the 'dorsal trend'/'ventral trend' distinction which it inherits from the parahippocampal and perirhinal cortex, respectively—with the 'dorsal trend' being conveniently located in the dorsal (i.e. septal) hippocampus. The dorsal/ventral distinction also appears to involve a predominantly septal input to the dorsal (septal) portion of the hippocampus and a predominantly amygdaloid input to the ventral (temporal) portion.

The degree of organization of terminals within a subfield is spectacular. The dendritic field above each cell layer is divided into distinct bands which have different amounts of heavy metals, reflecting biochemical differences in the different pathways each of which terminates in one of these layers (as with the termination of the medial and lateral perforant path in the dentate gyrus mentioned above). This layering can also be seen with the extensive cholinergic innervation of the hippocampus, which shows distinct but somewhat different bands. An interesting feature of these cholinergic bands, pointed out to us by Olga Vinogradova, is that they appear to mark the divisions between terminal fields. We consider the significance of this further in Appendix 5.

A final aspect of hippocampal organization is more contentious. As we briefly noted above, many studies have indicated apparently different connections for the dorsal (septal) and ventral (temporal) hippocampus. However, in a number of cases, particularly the cholinergic innervation, the difference between the septal and temporal hippocampus is most extreme at the two ends and shows a steady change from one end to the other with no clear dividing line between the two potential halves. Such organization is easy to understand as the result of some chemical gradient operating during development or as a simple consequence of a septal or temporal entrance to the hippocampus by the fibres concerned. If confirmed for the majority of the anatomical features which show septal–temporal differences, this would suggest a nominally linear coding of some dimension or dimensions along the axis of the hippocampus.

However, a smooth gradation from one pole to the other of the hippocampus does not match the fairly discrete division of 'dorsal' and 'ventral' trends observed in the posterior, frontal, and mesial (cingulate) cortex (Appendix 3). This gradation probably arises from the tendency for input to the entorhinal cortex to mix the two streams (Fig. 10.4), and we will also see later that the implied dorsal/'where', ventral/'what' distinction is matched by the distribution of number and nature of spatial receptive fields in the hippocampus—and that these also appear to show a smooth gradation. This apparent mixing of dorsal and ventral trend information (and the capacity for occasional spread of information beyond 'lamellar' boundaries) will be important for our theory—and is linked with the outputs of the hippocampus which we will consider shortly. In this context, it should be noted that the subicular output is to the posterior but not the anterior cingulate, and to the dorsal but not the ventral trends in the frontal cortex. Thus, one possible reason for such a unidirectional flow of information in the hippocampal system is that the dorsal and ventral trend information is brought together and amalgamated in a way which would cause major problems if there were direct feedback to the sources of

that information. Once processed, the output is returned to the dorsal (inhibitory) components of the frontal and mesial cortex, but not necessarily to the areas from which the original information was sent.

A4.2.4 The septal area

The septal area is much smaller than the hippocampal formation and much less regular in its anatomy. It contains a number of different nuclei and is traversed *en passage* by a variety of different fibre pathways. Although it is closely connected to the hippocampal formation (Fig. 1.3A,B) only some of its nuclei are involved in those connections and the diverse connections of the others suggest that the septal area is not a functional unit at all.

Despite this diversity, 'the septal area' has been a major target of research in physiological psychology. The main reason for this has never been stated, but is likely to be less than respectable: it is very easy to make discrete lesions of the septal area by passing current through an electrode placed there. This is because (Fig. A4.2) the septal area is bounded on either side by the lateral ventricles and, above and below, by two bundles of commissural fibres: the corpus callosum, and the anterior commissure (although the septal area extends both anterior and posterior to the latter). The electrical properties of these structures limit the spread of current, so that the area bounded by them can be reproducibly destroyed with minimal damage to other structures. If electrical homogeneity were a guarantee of functional unity, this would be a splendid technique; unfortunately, it is not.

Fig. A4.2 [plate for this figure to be recovered from Figure 3.6 of the first edition]

Fig. A4.2 A frontal section through the anterior commissure of the rat to show the major divisions of the septal region, except for the posterior group, which lies more caudally in the vicinity of the ventral hippocampal commissure. Klüver–Barrera stain; scale, 0.5 mm. BST, bed nucleus of stria terminalis; C, caudate nucleus; LS_d, LS_i, LS_v, dorsal, intermediate, and ventral parts of lateral septal nucleus; MePO, median preoptic nucleus; MPO, medial preoptic area; MS, medial septal nucleus; SI, substantia innominata; VL, lateral ventricle; ac, anterior commissure; cc, corpus callosum. (From Swanson 1978.)

The septal area may be regarded as having four major divisions (Swanson and Cowan 1976; Swanson 1978): medial, lateral (or dorsolateral), ventral, and posterior. The medial and dorsolateral divisions are most closely related to the hippocampus, but are physically separated from it by the posterior division.

The medial septal division has, by some, been further subdivided into the medial septal nucleus (dorsally) and the vertical and then horizontal limbs of the diagonal band of Broca as one proceeds more ventrally; however, this subdivision is arbitrary. Such distinction as needs to be made is topographic. The medial septum–diagonal band complex (MS/DBB) can be viewed as an essentially linear set of subnuclei starting with the most caudal and lateral parts of the horizontal limb, moving to the vertical limb and thence to the medial and finally the lateral aspects of the medial septal nucleus. The pathways taken by the fibres and the targets of those fibres move from most rostral and ventral portions of the cortex with the horizontal limb to progressively dorsal and then caudal and ventral sites. Fibres projecting to the hippocampus move from a supracallosal route to the dorsal fornix and then to the fimbria as the source moves from the vertical limb to the medial portion of the medial septum and then to the lateral portion (Meibach and Siegel 1977*a*; Rawlins *et al.* 1979; Gaykema *et al*. 1990).

In concert with this the terminal fields in the hippocampus move from the septal to the temporal end of the hippocampus. The medial septal projection to the hippocampal formation is largely ipsilateral, but a small contralateral projection also exists (Mellgren and Srebro 1973; Lynch *et al.* 1978). As we shall see in the next appendix, this septo-hippocampal projection is the main controller of the frequency of theta (rhythmical slow electrical activity) in the hippocampus. The same is true of the medial septal projection to the entorhinal cortex. However, the input to the cingulate cortex (because it travels supracallosally) originates in the vertical limb rather than the medial septum and can remain intact with medial septal lesions, a fact which will later be of significance.

The lateral septal area can be further subdivided, on the basis of neuronal size and packing density, into dorsal, intermediate, and ventral parts. However, as with the medial septal area, these divisions are not of great functional significance except with respect to topographic mapping of the projections from the hippocampal formation: cells in the septal (dorsal) part of the hippocampal formation project to the dorsal part of the lateral septum; cells in the temporal part project to the ventral part of the lateral septum; cells in the flexure project to the intermediate part of the lateral septum (Fig. 9.5; Meibach and Siegel 1977*b*; Swanson and Cowan 1975; see also Risold and Swanson 1996, discussed below). The projection from the subiculum to the lateral septum is similarly organized but is unilateral, in contrast to the CA3 projection which terminates in the lateral septal area both ipsilaterally and contralaterally. Thus, the CA3 projection to the septum shows the same tendency to contralaterality as the CA3 projections to subfields of the hippocampal formation. It now appears that there are only very sparse connections from the lateral to the medial septal area (Leranth *et al.* 1992; Witter *et al*. 1992).[1]

The posterior division of the septal area is less central to the septo-hippocampal system than the medial and lateral divisions, but it also has a close relationship with the hippocampus. It consists of two cell groups, the septo-fimbrial nucleus and the triangular nucleus. Both receive similar projections from CA3 and the subiculum to that received by the lateral septal area.

The ventral division of the septal area contains the bed nucleus of the stria terminalis, to which can be added the nucleus accumbens. The former has its strongest relations with the amygdala (although it receives some afferents from the subiculum about which we will have more to say). The latter has now been reclassified as the ventral striatum (Heimer and Wilson 1975). The bed nucleus of the stria terminalis is dealt with in Appendix 2, and will not be considered further. However, we will return to consideration of the role of the ventral striatum when we consider the details of the interaction of the septo-hippocampal system with motor control systems.

This highly condensed survey of the connections within the septo-hippocampal system is partially summarized in Fig. 9.4. This figure emphasizes the fact that the septum, hippocampal formation, and entorhinal cortex are remarkably well equipped for talking to each other. Unfortunately, we have no clues, so far, as to what they talk about. The usual way to get an anatomical clue as to the kind of information with which a neural structure deals is to ask about its connections: where does its information come from, and where does it send its results to?

A4.3 Connections of the septo-hippocampal system

There are, then, three major points through which the septo-hippocampal system talks with the outside world: the entorhinal cortex, the septum, and the subiculum. The entorhinal cortex and MS/DBB provide input and the subiculum and lateral septal area provide output. Some of the subicular output relays in the lateral septum. The entorhinal area also provides output to the same areas as the subiculum, except that it does not project to the lateral septum. The input from the entorhinal cortex to every stage of the hippocampal formation, and the linear transfer of information within the hippocampal formation, might suggest a range of options between 'quick and dirty' and 'slow and sophisticated' transmission of the same information. However, we will argue later that it in fact reflects the capacity for specific logical operations (equivalent to *and* and *or* in computing; Fig. 10.3). A crucial fact for our theory is that 'the descending output is organized in such a way that different hippocampal regions map in an orderly way onto hypothalamic systems mediating the expression of different classes of goal-oriented behaviour' (Risold and Swanson 1996, p. 1484; Fig. 9.5); and there is an apparently similar topography for hippocampal projections to the frontal cortex (Barbas and Blatt 1995) which can, likewise, be viewed as being concerned with goal-oriented behaviour (Appendix 3).

The MS/DBB and the entorhinal cortex are the two main sources of input to the primary stage, the dentate gyrus, of the essentially unidirectional aspects of the hippocampal formation. The medial septal area and entorhinal cortex are also reciprocally connected (see Jakab and Leranth 1995). Both the medial septal area and entorhinal cortex also project to all other subfields of the hippocampal formation and to the posterior cingulate.

There is extensive aminergic input. In addition to the cholinergic input from the medial septal area, the entire septo-hippocampal system (i.e. septum, hippocampal formation, and cingulate and entorhinal cortex) also receives diffuse monoaminergic input (serotonergic, noradrenergic, dopaminergic; see Appendix 10). As we discussed in Chapter 6 (see also Appendix 10), it is likely that all the aminergic inputs are modulatory in nature.

There are also GABAergic inputs from the septum which can have a net excitatory effect by inhibiting inhibitory interneurons, as they appear to do in all hippocampal fields (Fig. 9.6; Freund and Antal 1988). These will prove important for our discussion of the control of theta activity. By contrast, the parvalbumin-positive, presumed GABAergic, cells in the entorhinal cortex do not appear to project to the hippocampus (Wouterlood *et al*. 1995).

The lateral septum and the subiculum are the two most obvious sources of output from the hippocampal formation. 'Until the mid-1970s, the prevailing view of the extrinsic connectivity of the hippocampal formation was that '[it] received sensory information from a variety of cortical regions [and] was thought to funnel this sensory information through the [fimbria/fornix] to the mammillary bodies. [This] was such an obvious efferent pathway [that] little thought was given to alternative hippocampal efferents' (Amaral 1987, p. 226). Since that time the fornix–fimbria has grown no smaller and yet recent 'memory'-oriented views of the hippocampus have essentially ignored the role of the subcortical outputs of the hippocampus, except to note in passing that cutting the fornix–fimbria (which disconnects both subcortical output and input) produces effects very similar to those of hippocampal lesions. If hippocampo-cortical relations were the main basis for hippocampal function, it is difficult to see why subcortical disconnection should have such major effects (or why the hippocampus should be so prominent in relatively unencephalized species). Indeed, it is worth noting that the septum as a whole 'undergoes a progressive increase . . . in size in primate development. Among primates it attains its greatest degree of development in the

human brain' (Andy and Stephan 1976, p. 3). So, while not showing the immense expansion of the neocortex, the septum cannot be considered vestigial or unrelated to the more human functions of the brain.

The medial septum also provides some descending (probably non-cholinergic) output to the diencephalon, in particular to the interpeduncular nucleus (from which it receives a return projection), and, in the brain stem, to the central grey, and, topographically, the raphe nuclei (see Jakab and Leranth 1995).

An important feature of most of the external connections (subcortical as well as cortical) of the septo-hippocampal system as a whole, which has become clearer since the first edition of this book, is that they are, in principle, reciprocal. However, they are not usually immediately reciprocal. We can trace fairly immediate extra-hippocampal recursive paths for the information via loops which, like the intra-hippocampal dentate–CA3–CA4–dentate loop already discussed, are essentially unidirectional. As we follow cortical *or* subcortical information on its way to the hippocampus, then, we are not dealing with simple linear relay systems, but often with immediate two-way traffic, or longer recursive, feedback loops.

As we noted, the links of the unidirectional hippocampal loop are occasionally bypassed by additional 'leap-frogging' connections from one subfield to a non-adjacent subfield. Similarly, CA1 has direct connections with prefrontal, parietal, temporal, and cingulate cortices (see Miller 1991, p. 52 and his Table 2) which, therefore, bypass the subiculum. At least in the rat, the projection from CA1 to the frontal cortex seems to be predominantly from the temporal/ventral part, with a somewhat different distribution for cells projecting to the medial and lateral prefrontal cortex respectively. Some cells show collateral projections to both the medial and lateral prefrontal cortex and their distribution is similar to that of cells with medial projections (Verwer *et al*. 1997).

A4.3.1 Inputs to the septo-hippocampal system

The afferents to the entorhinal cortex have been described in detail in the rhesus monkey by Van Hoesen *et al.* (1972, 1975; Van Hoesen and Pandya 1975) and more recently by Amaral and co-workers (Insausti *et al*. 1987*a*,*b*; Suzuki and Amaral 1994*a*,*b*). It is not clear to what extent the same afferents exist also in the rat (Beckstead 1978). A summary of the various results is presented in Fig. 10.4 in the printed text. As O'Keefe and Nadel (1978, p. 126) comment in relation to an earlier figure presented by Van Hoesen 'This figure makes it clear that there is a cascading of inputs from a number of cortical areas through all adjacent regions leading ultimately to the entorhinal cortex. This pattern of inputs to the entorhinal area strongly suggests that the hippocampus is concerned not with information about any particular modality, but rather with highly analysed, abstracted information from all modalities.'

The data summarized in Fig. 10.4 refer mainly to the visual inputs, which are particularly strong in the monkey. There are similarly organized inputs from the auditory and somaesthetic systems. A rather more direct olfactory input to the entorhinal cortex, originating in the olfactory bulb itself or relaying in the pre-pyriform cortex, has been described in rats and cats (Swanson 1978; Wilson and Steward 1978; Habets *et al*. 1980*a*,*b*). In macaques this direct olfactory input (and a number of other inputs) appears to terminate in a restricted part of the entorhinal cortex (Insausti *et al*. 1987*a*,*b*; see also Amaral *et al*. 1987). Thus, the cortical input to the entorhinal cortex is largely from the perirhinal,

parahippocampal, and cingulate cortices (with the posterior cingulate projections most likely constituting closure of the hippocampal–cingulate–hippocampal loop). The perirhinal and parahippocampal cortex, in turn, are the sites of convergence of inputs from the highest levels of the unimodal association cortices.

It should be noted here that (see Fig. 10.4) the parahippocampal and perirhinal cortices have quite different topographic organization of their reciprocal connections with entorhinal cortex. Their inputs thus coincide in complex ways—neither of them is segregated to a unique area of entorhinal cortex. This suggests integration rather than segregation of the information they carry, as does the septo-temporal gradient of connections of the entorhinal cortex with the hippocampus proper (Suzuki and Amaral 1994*a*,*b*).

The direct input from the olfactory system to the entorhinal cortex might seem anomalous, given the fact that other inputs to the hippocampus reflect the highest levels of sensory processing and, furthermore, are polymodal. However, it is clear that considerable processing and storage of olfactory stimuli occurs in the olfactory bulb (Freeman 1991). Olfactory stimuli are also likely to require the least processing of major sensory stimuli for identification of an upcoming goal. The entorhinal cortex also receives input from certain thalamic nuclei (the nucleus reuniens, and the paratenial and periventricular nuclei), from the amygdala (Krettek and Price 1977; Segal 1977; Beckstead 1978), from the pre- and parasubiculum (whose connectivities appear to differ from each other; Caballero-Bleda and Witter 1994), and from the lower levels of a range of structures which control goal-oriented behaviour (Fig. 9.4).

As discussed in Chapter 6 (see also Appendix 2), the projection from the amygdala to the hippocampus is much stronger than that from the hippocampal formation to the amygdala, appearing to be a major feedforward input. However, the return projection from the hippocampal formation does not appear to constitute feedback from the hippocampus but, rather, a route whereby the hippocampus can control the amygdala.

The major output of the entorhinal cortex is to the dentate gyrus, with lesser outputs to the other levels of the hippocampal formation. The entorhinal cortex also has what can be presumed to be return projections to perirhinal and parahippocampal cortices, as well as a projection to the posterior cingulate, which (like its projections to the various levels of the hippocampal formation) can be presumed to be feedforward rather than feedback. In the context of the theory developed later, the output to the posterior cingulate can be viewed as an input to the final stage of the behavioural inhibition system. Other outputs of the entorhinal cortex are treated below as outputs from the septo-hippocampal system.

A similar funnelling and then spreading of information appears to occur with the subcortical input to the septo-hippocampal system which controls hippocampal rhythmical slow activity. For example, one key external relay for this information (see next appendix) is the medial supramammillary nucleus (SUMM). At SUMM, the intensity of the afferent drive is converted to the frequency of rhythmical slow activity, and the frequency information is then sent in the medial forebrain bundle to the medial septum (including, most probably, the diagonal band; Vertes 1988). Other frequency transducing nuclei appear to do the same. The MS/DBB then distributes the inputs from all these sources throughout the hippocampal formation. In keeping with the reciprocity we have seen with cortical inputs to the entorhinal area, and between the entorhinal area and hippocampal formation, MS/DBB receives feedback from the hippocampal formation, and SUMM receives return input from the septum

and/or the hippocampal formation (Kirk and McNaughton 1991; Appendix 5). (However, recent data suggest that theta-controlling cells of SUMM may send collaterals to the hippocampus and the septum and that, within the septum, this structure innervates cholinergic and GABAergic cells indiscriminately; Borhegyi *et al*. 1998.)

The medial septum–diagonal band complex is also 'densely innervated by different lateral hypothalamic regions. . . . The distribution pattern of hypothalamic inputs maintains an orderly mediolateral arrangement [for all the cholinergic basal forebrain]. . . . Axons originating in the medial portion of the lateral hypothalamus reach cholinergic cells primarily in more medial and ventral parts of the substantia innominata and in the magnocellular preoptic nucleus and the HDB. Axons from the medial hypothalamic cells contact cholinergic neurons primarily in the medial part of the HDB and in the MS/VDB complex' (Jakab and Leranth 1995, p. 418; HDB, horizontal limb of the diagonal band of Broca; MS, medial septum; VDB, vertical limb of the diagonal band of Broca).

The principal noradrenergic projection to the septo-hippocampal system originates in the locus coeruleus and is described in Appendix 10. It travels in the dorsal ascending noradrenergic bundle, entering the septum in the medial forebrain bundle and terminating in the medial and lateral septum. To reach the hippocampus, the dorsal bundle splits into three parts: a supracallosal route, a septal route, and a ventral route passing through the amygdala. It terminates diffusely throughout the septo-hippocampal system. The majority of noradrenergic synapses in the hippocampal formation (as elsewhere) are regularly spaced varicosities, suggesting a modulatory or neurohormonal role. However, synapses in the hilus of the dentate, where the projection is particularly heavy, are of the conventional type (see McNaughton and Mason 1980).

The locus coeruleus receives some feedback from the hippocampal formation. This appears to be largely from the temporal (ventral) portion of the subiculum (Swanson 1978). Swanson points out that the connections of this area (see below) suggest that it is more closely related to the amygdala than the rest of the septo-hippocampal system, and it may be significant that the projection from areas CA3 and CA4 to the entorhinal cortex is also predominantly from the temporal part of the hippocampus.

The serotonergic innervation of the septo-hippocampal system is also described in Appendix 10. It originates in the raphe nuclei of the brain stem (Fig. 6.6). Efferents from the raphe nuclei follow essentially the same three routes as the noradrenergic fibres from the locus coeruleus. Those that take the ventral route to innervate the temporal part of the hippocampus originate in the dorsal raphe. Fibres from the median raphe enter the septal area in the medial forebrain bundle and then pass infracallosally in the fornix–fimbria and supracallosally in the cingulum bundle to reach the septal parts of the hippocampus. The median raphe, in addition, innervates the medial septal area and the dorsal part of the lateral septal area. The dorsal raphe innervates the anteroventral part of the lateral septal area and the ventral striatum (nucleus accumbens). Since the dorsal and median raphe innervate the entorhinal cortex, there is serotonergic input (as there is noradrenergic input) of some type to all parts of the septo-hippocampal system and to the posterior cingulate.

The dopaminergic innervation of the septo-hippocampal system is less extensive than either of the other two monoamines, but tends to follow a similar pattern. The lateral septal area and horizontal limb of the diagonal band receive, via the medial forebrain bundle, a projection from cell group A10, in the ventral tegmental area. A10 also projects to the entorhinal area

and extensively to the nucleus accumbens (Segal 1977; Beckstead 1978; Lindvall and Björklund 1978; Eaton *et al*. 1994). There is also a small dopaminergic innervation of the hippocampus from the same source (Wyss 1977; Schwab *et al*. 1978; Simon *et al.* 1979), primarily to the subiculum and CA1 and generally matching 'the hippocampal areas projecting to the nucleus accumbens' (Gasbarri *et al*. 1993, p. 445). A13, in the medial zona incerta, projects to the horizontal limb of the diagonal band (see Eaton *et al*. 1994).

The areas we have considered so far, although reciprocally connected to the septo-hippocampal system, can be viewed as primarily afferent to it. It is interesting, in this context, that the entorhinal cortex, medial septal area, locus coeruleus, and raphe nuclei each provide parallel access to what appears to be the same information for *all* levels of the septo-hippocampal system. There is also extensive opioid input to all aspects of the hippocampal formation. This opioid input appears to be involved in quite distinct functions in the different subfields (Commons and Milner 1995).

A4.3.2 Outputs of the septo-hippocampal system

The lateral and posterior septal nuclei, by contrast to the medial septum, can be viewed as primarily targets of efferents from the septo-hippocampal system. They receive input from the subiculum (which can be viewed as the primary output station of the septo-hippocampal system, see below) and, in distinction to other targets of the subiculum, from area CA3. (The lateral septum also receives a projection from the dorsolateral prefrontal cortex; Tanaka and Goldman 1976). The lateral (and medial) septum projects to the mammillary bodies and lateral hypothalamus (of which more below), and also to the dorsomedial hypothalamus and preoptic area. The lateral but not medial septum projects to the supramammillary nucleus (Swanson and Cowan 1976), the periaqueductal grey, the dorsal raphe, and the dorsal tegmental nucleus (see Jakab and Leranth 1995). The septo-fimbrial and triangular nuclei (which like the lateral septum receive input from the subiculum and area CA3) project through the stria medullaris to the habenular nuclei; and the triangular nucleus also projects, via the fasciculus retroflexus, to the interpeduncular nucleus in the midbrain (Swanson 1978). These connections are illustrated in Figs A4.3 and A4.4.

Fig. A4.3 [plate for this figure to be recovered from Figure 3.14 of the first edition]

Fig. A4.3 A parasagittal section through the forebrain of the rat to show the close relationship between the septum and hippocampus, which are reciprocally connected by fibres running in the fimbria. This section also shows the major sites in direct receipt of septo-hippocampal projections, including the habenula, anterior thalamic nuclei, mammillary body, and ventromedial nucleus of the hypothalamus. Klüver–Barrera stain; scale, 1.0 mm. AV, anteroventral nucleus of the thalamus; BST, bed nucleus of the stria terminalis; DBB, nucleus of the diagonal band of Broca; DG, dentate gyrus; H, habenula; LS, lateral septal nucleus; OT, olfactory tubercle; M, mammillary body; VL, lateral ventricle; VMH, ventromedial nucleus of the hypothalamus; ac, anterior commissure; cc, corpus callosum; dhc, dorsal hippocampal commissure; fi, fimbria; fr, fasciculus retroflexus; fx, fornix; mt, mammillo-thalamic tract; sm, stria medullaris. (From Swanson 1978.)

Fig. A4.4 [plate for this figure to be recovered from Figure 3.16 of the first edition]

Fig. A4.4 The major sites in receipt of direct septo-hippocampal projections. The efferent connections of the ventral part of the subiculum and the bed nucleus of the stria terminalis are shown in the next figure. ATN,

anterior thalamic nucleus; HAB, habenula; IPN, interpeduncular nucleus; LS, lateral septal nucleus; MAM, mammillary bodies; MPO–AHA, medial preoptic and anterior hypothalamic area; MS, medial septal nucleus; PS, posterior septal nuclei; SB, subicular complex. (From Swanson 1978.)

This apparent complexity has recently been shown to reflect a remarkable degree of order (Risold and Swanson 1996), the nature of which is particularly important for our theory. The output levels of the hippocampus (CA3–CA1–subiculum) can be thought of as strips, each of which sends glutamatergic projections into a topographically matching strip of the lateral septum, which in turn maps topographically into the hypothalamus. Orthogonal to this, the septal (dorsal) end of each hippocampal strip maps into one 'end' of its appropriate lateral septal strip and progressively more temporal (ventral) portions map topographically into the remainder of the same lateral septal strip and thence into the hypothalamus. Thus, to a first approximation, the two-dimensional sheet that is the unfolded CA3–CA1–subiculum maps into a vertically oriented sheet in the hypothalamus, with the CA3–subiculum dimension mapping to dorsal–ventral in the hypothalamus and the septal–temporal dimension mapping (very approximately) to the posterior–anterior hypothalamus (Fig. 9.5). Thus the hippocampus can be said to contain a map of 'hypothalamic space'. Furthermore, the predominant output from CA3 and CA1, as well as a significant output from the subiculum, is to 'hypothalamic systems mediating the expression of different classes of goal-oriented behaviour' (Risold and Swanson 1996, p. 1484).

The subiculum has the most complicated connections of the areas we have been considering. The subiculum proper has been, and probably should be, viewed primarily as a source of efferents from the septo-hippocampal system. It has distinctively unidirectional connections with the majority of its target areas. However, later stages of the subicular complex receive afferents from the cingulate cortex, temporal cortex, frontal cortex (in monkeys), and occipital cortex (in cats) (Miller 1991, his Table 2, p. 53; Van Hoesen *et al.* 1979), as well as from subcortical areas such as those mentioned above, and also the nucleus reuniens of the thalamus (which also projects to CA1 and the entorhinal area; Segal 1977; Beckstead 1978; Herkenham 1978).

The outputs of the subiculum can be divided into three classes. First are those it shares with the lateral septum (either directly, for example the ventromedial hypothalamus, or by virtue of the fact that it projects to lateral septum). These can be viewed as a confluence of CA3 and subicular information. They include the ventromedial hypothalamus, lateral hypothalamus, dorsomedial hypothalamus, and preoptic area. Second are those it shares with the entorhinal cortex (which we will discuss below). Third is the output to the mammillary bodies which it shares with both the entorhinal cortex and lateral septum. The septo-hippocampal projection provides the main source of afferents to the mammillary bodies.

Thus, directly or at one remove, the subiculum can influence all of the output targets of the septo-hippocampal system. These can then be divided into three groups: those receiving indirect input from area CA3, but not from the entorhinal cortex (the majority of the hypothalamic nuclei); those receiving direct input from the entorhinal cortex (the dorsal and ventral striatum, dorsomedial thalamus, and the anterior cingulate, see below); and those receiving direct input from the entorhinal cortex and indirect input from CA3 relayed by the mammillary bodies (amygdala, anterior thalamus, prefrontal cortex, posterior cingulate).

The principal *cortical* targets of subicular and entorhinal efferents appear to be the frontal and cingulate cortex (see Appendix 3), although there are some reported weak connections to other areas (Miller 1991, p. 54). Given the subcortical topography of hippocampal outputs, it

is interesting to note that there are signs of similar organization of prefrontal connections (Barbas and Blatt 1995). However, as we remarked above, by far the largest outflow from the subiculum is in the post-commissural fornix, a massive continuation of the fimbria–fornix that sweeps down in two columns, one in each hemisphere, through the septal area posterior to the anterior commissure (hence 'post-commissural'). The targets of this subicular/entorhinal efferent are the anterior thalamus and the mammillary bodies in the hypothalamus. In the anterior thalamus, the principal target is the anteroventral nucleus, but perhaps also the anterodorsal and anteromedial nuclei (Swanson and Cowan 1975). The mammillary bodies also project to the anterior thalamic nuclei (along the mammillothalamic tract). Further convergence is provided by the fact, noted above, that the medial and lateral septum also project to the mammillary bodies. All of these routes provide the means for the hippocampal formation to influence processing in various aspects of the prefrontal and cingulate cortices (see Chapter 9, Fig. 9.4). The amygdala also receives projections from each of the entorhinal cortex, subiculum, and mammillary bodies.

'The medial and lateral mammillary nuclei [also] receive projections from . . . the dorsal and ventral tegmental nuclei of the midbrain . . . there has been little evidence of other projections terminating in the mammillary complex' (Amaral 1987). The dorsal and ventral tegmental nuclei, in turn, receive inputs from a number of septo-hippocampal target areas: the prefrontal cortex, cingulate, medial and lateral septum, dorsomedial hypothalamus, and habenula (which receives input from the lateral septum). While the anatomy of the dorsal and ventral tegmental nuclei is very uncertain at present, it appears that they represent a number of short and long loops which can return information to the mammillary bodies.

The most ventral part of the subicular complex gives rise to a pattern of outputs that is very different from the projections of the remainder of the subiculum. However, lesions of the hippocampal formation usually spare the ventral subiculum. It is difficult to tell, therefore, how germane these outputs are to the theme of this book. However, given the high degree of topography which we have discerned in the hippocampus as a whole, it seems likely that the ventral subiculum is just the first of a number of differentiable subareas to have been noticed.

The ventral subicular output is summarized in Fig. A4.5. This travels in the medial corticohypothalamic tract, which winds round the medial side of the descending columns of the fornix, then descends vertically through the preoptic area towards the anterior and middle regions of the hypothalamus (Raisman *et al.* 1966). As noted above, Swanson (1978) views the ventral subiculum as closely related to the amygdala. Like the amygdala, it projects to the bed nucleus of the stria terminalis and to the ventromedial nucleus of the hypothalamus. In addition, it receives a projection from the amygdala itself.

Fig. A4.5 [plate for this figure to be recovered from Figure 3.17 of the first edition]

Fig. A4.5 The efferent connections of the ventral part of the subiculum and the bed nucleus of the stria terminalis, two parts of the septo-hippocampal complex which are closely related to the amygdala. ACB, nucleus accumbens (ventral striatum); AON, anterior olfactory nucleus; BST, bed nucleus of the stria terminalis; CTF, central tegmental field; HAB, habenula; HYP, hypothalamus; LC, locus coeruleus; LS, lateral septal nucleus; MAM, mammillary body; POA, preoptic area; PT, parataenial nucleus; PVT, paraventricular nucleus of the thalamus; SUB_v, ventral subicular complex; TT, taenia tecta; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area; 25, infralimbic area. (From Swanson 1978.)

Finally, we must consider the output from the subiculum and entorhinal cortex to the dorsal and ventral striatum, and to the dorsomedial thalamus (which receives input from the dorsal and ventral striatum). The dorsal and ventral striata can be viewed as the input stages to two parallel, motor programming systems which also receive inputs from the prefrontal cortex (to the dorsal and ventral striatum) and from the primary motor (to the dorsal striatum) and the limbic (to the ventral striatum) cortex. Unlike the hypothalamic, cortical, and defence systems we have been considering so far, the subiculum/entorhinal input to these motor systems enters only at the highest subcortical levels. However, the feedback to the septo-hippocampal system (Fig. 9.4) can be from the lower levels of these systems (e.g. from the ventral tegmental area, A10).

A4.4 Conclusions

The specific outputs and inputs of the septo-hippocampal system are mostly deep within the brain and so do not offer us any specific clear insight into its function. However, we would argue that the subcortical outputs of the hippocampal formation are clearly at least as important as the cortical outputs and, furthermore, that (both subcortically and cortically) goal-oriented systems are not only heavily targeted but are topographically mapped into the hippocampal formation. This suggests that the hippocampus is involved in some aspect of the control of goal-oriented behaviour. How it is involved and what computations it carries out are not so obvious.

From both cortical and subcortical areas the septo-hippocampal system receives multimodal sensory information that appears to be very highly processed. Furthermore, it is the site of convergence of these sources of input, with both medial septal and entorhinal inputs to all levels of the system and to all septo-temporal extents of the hippocampus. Nonetheless, there is highly topographic organization of these inputs and of the outputs from the hippocampus (e.g. Namura *et al*. 1994; Barbas and Blatt 1995; Risold and Swanson 1996; McDonald and Mascagni 1997; Totterdell and Meredith 1997). This fact, coupled with the (approximately) lamellar and laminar organization of the hippocampus proper, makes the septo-hippocampal system look like a massively parallel device for carrying out a series of specific (and, given its inputs, high level) computations. Such circuitry can be made to do a wide variety of marvellous things, depending on the assumptions that one makes about the precise nature of its inputs and the settings of appropriate parameters. By itself, therefore, this perspective on the circuitry does not help us to understand its function.

Perhaps more informative is the general organization of the connections of the septo-hippocampal system viewed as a whole. This system has at its core a set of essentially unidirectional connections. This architecture is almost unique in the context of the tendency to immediate reciprocal connection which characterizes the neocortex and many of the subcortical structure to which the hippocampal formation is connected. This unidirectionality extends to the connections of the septo-hippocampal system with its principal cortical targets, the prefrontal and cingulate cortices, and its principal subcortical targets, the hypothalamus, dorsal and ventral striatum, and dorsomedial thalamus. The two main exceptions to unidirectionality are the amygdala and the anterior thalamus, which send feedback to the subiculum. In the case of the amygdala, we have argued that its input to the subiculum (like its input to the entorhinal cortex) is feedforward rather than feedback. Even in these two cases, potentially reciprocal connections are made only with the subiculum and not with other components of the system. The forward connections within the hippocampus include a number which leap-frog particular levels. The most extreme example of this is the entorhinal

cortex, which makes connections with every level of the hippocampal formation and also bypasses the hippocampus entirely to make connections with a large number of the targets of subicular output.

Coupled with this unidirectionality of the system as a whole there are a large number of connections from various points within and outside the system which terminate in the entorhinal cortex, thus closing loops of many different lengths. There is also one internal set of loops connecting the dentate, CA3, and CA4.

Thus, we can follow a series of structures, each connected to the previous one (CA3–CA1–subiculum–posterior/anterior cingulate–prefrontal cortex), where every one provides a return projection to the entorhinal cortex. This connectivity provides for a very great potential level of recursive processing. There is also a degree of nesting of loops. Thus, CA3 sends return connections to CA4, the dentate, and the entorhinal cortex. CA1, the subiculum, and the prefrontal cortex send return connections to the entorhinal cortex and perirhinal cortex (while the perirhinal cortex projects to the subiculum and posterior cingulate).

In the disposition of the external loops, a nodal point seems to be occupied by the subicular cortex (Fig. 9.4). A noteworthy point is that this region apparently starts out in receipt of the same information that is recirculated to it in several different ways, some longer, some shorter. Thus, Van Hoesen *et al*. (1979) report extensive inputs to the subicular cortex from the same areas in the temporal lobe that project also to the entorhinal area, and the subicular cortex also receives input from the entorhinal area itself.

Thus the subicular cortex receives information from the neocortex via the temporal lobe; information from the same source, but relayed directly by the entorhinal area; and information which passes through the entorhinal area and trisynaptic hippocampal circuit, to be finally relayed by CA1. It then sends this multiply digested information out, only to have it come back yet again after a trip through the anterior thalamus both directly and via the mammillary bodies. The information from the anterior thalamus can also be sent to the cingulate cortex, whence it returns via direct projections to the entorhinal cortex or relayed to the entorhinal cortex via the parasubiculum. Of course, it is not ‘the same’ information. If it were, we should need to suppose that a large part of the brain does nothing but echo back the news that it receives.

A similar redundancy appears to hold with respect to the cortical and subcortical inputs to the septo-hippocampal system. ‘The same’ sensory information is funnelled (a) as a multimodal stream from the cortex to the hippocampus by way of the entorhinal cortex, and b) again in a multimodal stream, from the midbrain reticular formation by way of the septum. In some cases the same information is received by the septum and the entorhinal cortex, as they are innervated by collaterals of the same cells (originating in the hippocampus, amygdala, midline thalamus, and hypothalamus, including the supramammillary area; Calderazzo *et al*. 1996). The septo-hippocampal system, and particularly the hippocampal formation, thus receives apparently sensory information from both cortical and subcortical structures and then relays ‘the same’ information back to the cortex and subcortex, presumably now modified by the information of the subcortical or cortical input, respectively.

As noted above, the existence of so many recurrent loops makes it impossible to deduce from anatomical considerations alone the nature of the information handled by the septo-hippocampal system. To do this will require the information of the following appendices.

However, it seems likely that the purpose of the loops themselves is to provide recursive processing of whatever information is input to the systems concerned. The implications of this recursion have been largely ignored by previous theories of the hippocampus (including that of the first edition of this book). We discuss this issue in detail in Chapter 1 and deal with it further in the theory presented in Chapter 10. For the moment, however, we note that none of the current theories of hippocampal function has any explanation as to why it should have such extensive long and short loop recursion.

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Notes

1. For a contrary view concerning the degree of sparseness and an in-depth review of the dorsolateral septal nucleus, see Gallagher *et al*. (1995). For a somewhat more complicated view of the medial and lateral septal area based on six medial–lateral laminated layers, see Jakab and Leranth (1995); but see also later section on septo-hippocampal connections).