Chapter 7

Anatomical and Neuromodulatory Bases for Functional Segregation within the Hippocampus

The functional MRI evidence presented in the previous chapters suggests that anterior and posterior hippocampal regions possess different functional properties. This chapter reviews evidence relating to the possible origins of this functional segregation. Given that the intrinsic circuitry of the hippocampus does not vary along its longitudinal axis, the two candidate mechanisms that could give rise to different functions of discrete hippocampal regions along the longitudinal axis are 1. distinct connectivity profiles and 2. segregated projections from neuromodulatory systems.

7.1 Anatomical basis: Connectivity

Much of the characterisation of hippocampal connectivity has been done in the rat. Rat hippocampal connectivity is largely homologous to that observed in the monkey and, by extension, to that in humans. The orientation of the rat hippocampus is, however, different to that in primates, with primate posterior hippocampus corresponding to rat dorsal hippocampus and anterior hippocampus corresponding to rat ventral hippocampus (Rosene and Van Hoesen, 1987). The rat equivalent of monkey parahippocampal cortex is named postrhinal cortex (Burwell *et al*., 1995) but, for clarity, is referred to here as parahippocampal cortex.

The hippocampus consists of a largely unidirectional transverse loop of excitatory pathways through dentate gyrus (DG), CA1, CA3 and subiculum, referred to as the ‘trisynaptic circuit’. Although this intrinsic pattern of connectivity seems to repeat itself along the longitudinal axis of the hippocampus (Andersen *et al*., 1971), afferent and efferent connectivity changes from the anterior to posterior poles. As

mentioned in chapter 1, the hippocampus connects to both subcortical and cortical structures (Van Hoesen and Pandya, 1975).

7.11 Cortical connections

7.11a Entorhinal cortex input to hippocampus

The major hippocampal cortical connections are channeled through the entorhinal cortex (EC), which projects to DG, CA subfields and subiculum (Hjörth-Simonsen and Jeune, 1972). Hjörth-Simonsen (1972) concluded that projections originating laterally in rat EC terminated in dorsal levels of DG, whereas projections arising from medial EC terminated in ventral DG. This lateral-to-medial topography of EC-DG projections has also been observed in the cat (Witter and Groenwegen, 1984) and monkey (Witter *et al*., 1989a). In the rat, further investigation found that the topographical organisation of EC-DG connectivity could be divided into three parallel zones (Ruth *et al*., 1982, 1988; Dolorfo and Amaral, 1998a). The three zones project in a topographical manner to distinct and partly non-overlapping regions along the longitudinal axis of the DG. The lateral EC connects to the dorsal (posterior) half of DG, the intermediate EC zone innervates the adjacent quarter and medial EC sends efferents to the ventral (anterior) quarter (Dolorfo and Amaral, 1998a). The novelty-dependent activations reported in chapters 3, 4 and 5 were observed in the anterior segment of human hippocampus. The encoding-related activation in hippocampal body reported in chapter 6 lies in the middle band of EC-DG projections. Hippocampal activations at the posterior extreme were observed for familiarity/retrieval.

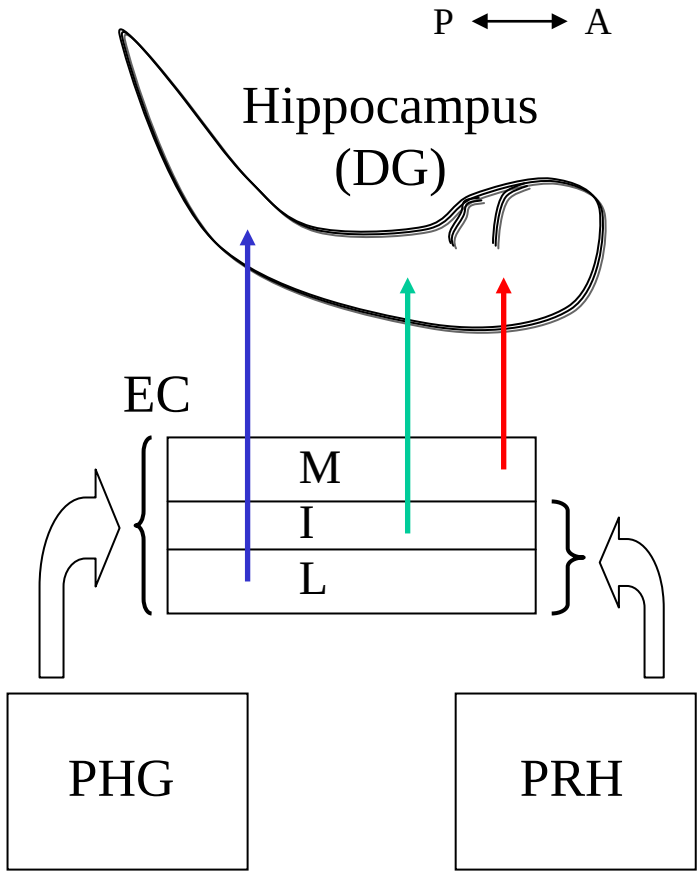
Although the three band-like zones are not entirely segregated, there is very little overlap between EC-DG projections (Dolorfo and Amaral, 1998a). Furthermore, the associational connections within EC respect this tripartite division, i.e. laterally situated entorhinal neurones that project to dorsal DG are not in direct communication with medial neurones projecting to ventral DG (Dolorfo and Amaral, 1998b). These findings raise the possibility that different levels of the entorhinal-hippocampal circuit along the longitudinal axis display a degree of autonomous information processing. The projection from EC to CA subfields also demonstrates dorsoventral topography corresponding to the lateral-to-medial origin of the EC fibres, but this is less pronounced than the EC-DG topography (Witter and Groenwegen, 1984).

7.11b Cortical inputs to entorhinal cortex

Each EC-DG band receives, partly via the perirhinal and parahippocampal cortices, its specific set of cortical and subcortical inputs (Deacon *et al*., 1983; Burwell and Amaral, 1998a, 1998b). Witter and colleagues (Witter *et al*., 1989b) suggested that in the rat, the projections to EC from sensory cortices are greatest to lateral and intermediate bands of EC, in turn implying that sensory cortices influence posterior (dorsal) hippocampus more than anterior (ventral) portions. This pattern of organisation poses a potential problem for the suggestion that anterior hippocampus mediates novelty detection. Detecting a change in the sensory environment requires that anterior hippocampus receive detailed sensory information. However, sensory information from all modalities does, in fact, reach all levels of the monkey medial-lateral entorhinal axis (hence all levels along the hippocampal longitudinal axis) via projections from perirhinal and parahippocampal cortices (Suzuki and Amaral,

1994). The parahippocampal cortex tends to project farther medially in the entorhinal cortex than the perirhinal cortex, suggesting that the parahippocampal region may have somewhat more influence on more anterior levels of DG (Suzuki and Amaral, 1994). The medial temporal cortical-EC connections and EC-DG connections in monkey are illustrated schematically in figure 7.1. A similar pattern of connectivity has recently been observed in the rat (Burwell and Amaral, 1998a), although the parahippocampal-medial EC connectivity was weak. In terms of novelty detection in humans, stronger connectivity between anterior hippocampus and parahippocampal cortex is particularly interesting because, in addition to anterior hippocampal responses, imaging studies demonstrate parahippocampal responses to novelty (e.g. Stern *et al*., 1996; Gabrieli *et al*., 1997; see Schacter and Wagner, 1999 and chapter 6). Low levels of connectivity between anterior hippocampus and perirhinal cortex supports the suggestion (Brown and Aggleton, 2001; see chapter 1) that 'novelty detection' in perirhinal cortex occurs independently of hippocampal mismatch detection.

Figure 7.1. Schematic diagram of monkey parahippocampal (PHG) and perirhinal (PRH) connections with entorhinal cortex (EC) and EC-dentate gyrus (DG) connections. Abbreviations: A: anterior; P: posterior; M: medial, I: intermediate and L: lateral divisions of EC.



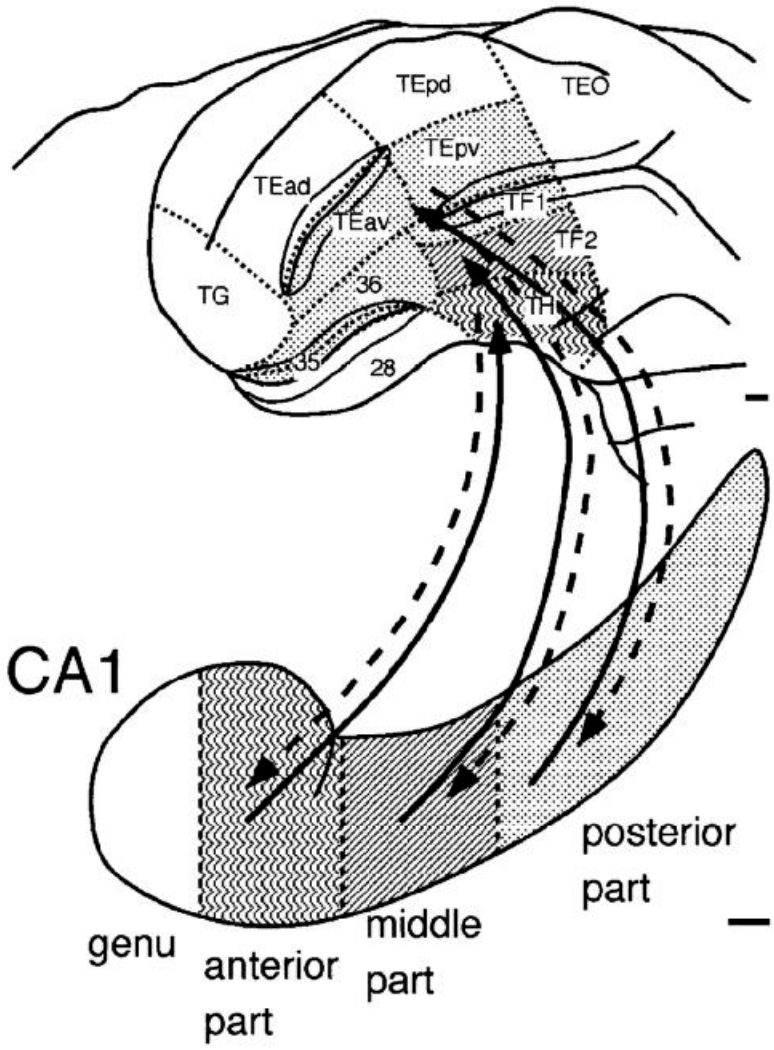


Figure 7.2 Topographical organisation of the connections between temporal cortex and CA1 of the macaque hippocampus (taken from Yukie, 2000). Abbrev: 35, 36: cortical areas 35 and 36 that make up perirhinal cortex. 28: cortical area 28, entorhinal cortex. TF and TH: cortical areas TF and TH of von Bonin and Bailey (1947) that make up monkey parahippocampal cortex. TE: inferior temporal visual areas. Scale bar = 1mm.

7.11c Medial temporal cortical inputs to hippocampus

A direct projection from perirhinal and parahippocampal cortices to monkey CA1 and subiculum has also been demonstrated (Suzuki and Amaral, 1990). In rats, the projection from perirhinal cortex to CA1 is limited to dorsal (posterior) hippocampus (Shi and Cassell, 1999), paralleling the indirect perirhinal-DG connection via the lateral EC. Perirhinal projections to monkey CA1 are also limited to posterior hippocampus (figure 7.2), whereas progressively more medial areas of parahippocampal cortex innervate more anterior levels of monkey CA1 (Yukie, 2000). Figure 7.2 suggests that perirhinal cortex does not directly project to the hippocampal body. This suggests that the encoding-related activations, predictive of subsequent memory, observed in these two regions in chapter 6 reflect parallel, independent encoding processes. However, figure 7.1 indicates that the perirhinal cortex and hippocampal body are anatomically connected at the level of entorhinal cortex, raising the possibility of co-operation between the two regions during successful encoding.

There are also direct projections from rat perirhinal and parahippocampal cortices to the subiculum (Naber *et al*., 1999, 2000). The perirhinal- and parahippocampal-subicular connectivity is even more restricted along the longitudinal axis of the subiculum than EC-subicular connectivity. While a restricted part of EC gives rise to projections along approximately 25% of the subicular longitudinal axis, the perirhinal/parahippocampal projections reach less than 10% (Naber *et al*., 1999, 2000).

7.11d Hippocampal cortical efferents

The segregation of afferents along the longitudinal axis is also expressed in terms of efferents. Cells along the dorsal-to-ventral axis in CA1 and subiculum terminate along the lateral-to-medial axis of the EC (Köhler, 1985; van Groen *et al*., 1986; van Groen and Wyss, 1990). From the entorhinal cortex, information is relayed to perirhinal and parahippocampal cortices, which have extensive projections to the cortical regions from which the afferent information originated (Insausti *et al*., 1997).

7.11e Prefrontal cortical inputs to hippocampus

There are two major prefrontal-hippocampal pathways (Goldman-Rakic *et al*., 1984). One arises from dorsolateral prefrontal cortex (monkey areas 9, 9/46 and 46) and its medial extension (medial 9 and 9/32) and travels through the cingulum bundle to reach retrospenial cortex and posterior presubiculum (Morris *et al*., 1999). The other pathway originates in medial prefrontal areas and caudal orbitofrontal cortex and travels via the uncinate fasciculus to reach entorhinal cortex and amygdala (Van Hoesen *et al*., 1972; Morris *et al*., 1999). Although these two projections arrive in anterior and posterior medial temporal regions, it remains to be determined whether their inputs are segregated to anterior or posterior hippocampus.

Interestingly, hippocampal CA1 sends a strong projection to orbitofrontal cortex, a region also implicated in mismatch detection (Nobre *et al*., 1999). 70% of this projection arises from the anterior third of the hippocampus (Cavada *et al*., 2000). The return projection from obitofrontal cortex to CA1 is weak, if present at all (Cavada *et al*., 2000), which might suggest directionality in the processing of

unexpectedness; the anterior hippocampus detects a breach of expectation and engages the orbitofrontal cortex.

Recent neuropsychological data demonstrated that human orbitofrontal cortex is critical for suppressing currently irrelevant memory traces (Schnider and Ptak, 1999). Patients with orbitofrontal damage (accompanied by basal forebrain and medial hypothalamic damage) produced false positive, intrusive responses on repeated recognition tests. In this task, the target stimulus is changed from run to run and subjects must respond to the currently relevant target and suppress responses to stimuli that were targets in previous runs (Schnider and Ptak, 1999). Animals with orbitofrontal lesions fail to suppress previously established habits and continue to react to stimuli that are no longer rewarded (Jones and Mishkin, 1972; Meunier *et al*., 1997). In light of the strong connection between anterior hippocampus and orbitofrontal cortex, it is interesting that hippocampal lesions produce a similar pattern of impairment. As mentioned in chapter 1 (section 1.44), hippocampal lesions produce perseveration in the Morris water maze task in rats (Whishaw and Tomie, 1997). Crowne and Radcliffe (1975), on the basis of local EEG recordings in monkey hippocampus, suggested that the hippocampus is critical for switching responses to a new stimulus or extinguishing responses to a now punished or non-rewarded stimulus. The tendency for hippocampal animals to perseverate has been attributed to an inability to inhibit prepotent responses (Kimble, 1969). Hence, like patients with orbitofrontal damage, damage to hippocampus may impair suppression of currently irrelevant responses.

The similarity between hippocampal and orbitofrontal lesion-induced deficits in suppressing previously learned information, together with the fact that hippocampal-orbitofrontal connectivity arises primarily in anterior hippocampus, suggests that the hippocampal role in suppressing currently irrelevant responses (or memories) is a function of anterior hippocampus. In support of this suggestion, Schnider and Ptak (1999) demonstrated that amnesic patients with intact right anterior hippocampus did not make false positive responses in the repeated picture recognition task, despite extensive lesions to posterior medial temporal structures. The amnesic patient group that did make intrusive responses had, along with orbitofrontal, basal forebrain and medial hypothalamic damage, damage to bilateral anterior hippocampus (Schnider and Ptak, 1999).

What is the relationship between response suppression and the proposed role of the anterior hippocampus in mismatch detection? With regards to a hippocampal role in extinguishing responses from episodic memory (recall that HM was not impaired in card sorting, suggesting that response suppression in the context of working memory is not hippocampus-dependent; see chapter 1), one hypothesis is that mismatch between response and expected outcome engages anterior hippocampus. Anterior hippocampus may then recruit orbitofrontal cortex to suppress current response contingencies. In other words, the hippocampal role in directing switches in behaviour suggested in chapter 1 may be mediated by anterior hippocampal-orbitofrontal interactions. During performance of a repeated recognition task, it may be that anterior hippocampus indexes change in the context in which stimuli are presented (i.e. which run or session) and engages orbitofrontal cortex to suppress memory traces from previous contexts that are now irrelevant.

However, intrusion errors committed by patients with hippocampal damage in repeated cued recall tasks (Warrington and Weiskrantz, 1974, 1978) are alleviated by dramatically changing experimental contexts between successive sessions (Winocur and Kinsbourne, 1978). The suggestion that anterior hippocampus indexes context changes assumes, therefore, that the context changes introduced by Winocur and Kinsbourne (1978) were so obvious that their acknowledgement was not hippocampus-dependent. It will be interesting to determine whether patients with damage limited to anterior hippocampus make false positive responses in repeated cued recall and recognition tasks.

7.11f Intrahippocampal longitudinal association connections

The evidence presented above demonstrates that segregation of hippocampal inputs originates in perirhinal and parahippocampal cortical areas and is preserved within EC and EC-DG connectivity. However, if the hippocampus operated as a unitary structure, it would be expected that, within the hippocampus, incoming information would be integrated across these functionally segregated domains along the longitudinal axis. There are two major longitudinal association fibre systems in the hippocampal formation; the longitudinal axon collaterals of CA3 pyramidal cells and the longitudinally-oriented axons of the mossy cells of the dentate hilus (Amaral and Witter, 1989). It is striking that even these fibres display segregated projections. Although their axons diverge extensively within the dorsal two-thirds and within the ventral third of rat hippocampus, few fibres cross between these subdivisions (Fricke and Cowan, 1978; Swanson *et al*., 1978; Ishizuka *et al*., 1990; Li *et al*., 1994). This suggests that cortical information entering either dorsal or ventral rat hippocampus may remain segregated.

7.12 Subcortical connections

Hippocampal subcortical connections, which exit the hippocampal circuit through the fimbria/fornix, are also topographically organised along the anterior-posterior axis. In the rat, dorsal, intermediate and ventral hippocampal regions project to cytoarchitectonically different sectors of the lateral septum. The dorsal half of hippocampus and subiculum give rise to only meagre projections to the most dorsomedial portion of the lateral septal nuclues. Progressively heavier, topographically organised projections to more ventral levels of lateral septal nucleus originate from more ventral levels of CA1 and subiculum (Swanson and Cowan, 1977; van Groen and Wyss, 1990; Risold and Swanson, 1996, 1997). Each of these sectors of lateral septal nucleus, in turn, innervates specific sets of nuclei in the hypothalamic region (Risold and Swanson, 1996, 1997). Ventral (anterior) subiculum also projects to hypothalamus and nucleus accumbens whereas dorsal subiculum projects to the mammilary bodies (Krettek and Price, 1977; Swanson and Cowan, 1977; Canteras and Swanson, 1992). Both ventral CA1 (van Groen and Wyss, 1990) and ventral subiculum (Canteras and Swanson, 1992) project to the amygdala. The strong efferent connections of the ventral hippocampus with hypothalamus and amygdala (Witter *et al*., 1989b; Canteras and Swanson, 1992; Risold and Swanson, 1996, 1997) suggests that anterior hippocampus may contribute to aspects of autonomic, endocrine, defensive or emotional control.

7.13 Anterior hippocampus and the autonomic system

The ventral hippocampus projects, via the lateral septum, specifically to neuroendocrine and preautonomic cell groups of the periventricular zone of the hypothalamus (Risold and Swanson, 1997). This hypothalamic zone is important for

the control of neuroendocrine and autonomic responses (Loewy, 1991). The reciprocal projections back to hippocampus are also topographically oganised and arise from the medial septum (Witter *et al*., 1989b). These reciprocal connections between hippocampus and septum enable hippocampal sensitivity to interoceptive signals as well as to effect changes in autonomic state, such as increasing physiological arousal in response to a novel stimulus. An autonomic function for anterior hippocampus accords with the proposed role of this region in novelty detection. Novel stimuli that evoke the P3a ERP have also been shown to elicit autonomic responses, indexed by skin conductance, in normal human subjects (Knight, 1996). Like the adaptive anterior hippocampal responses described in chapter 5 part II, repeated presentations of P3a-evoking stimuli result in adaptation of skin conductance responses. Patients with hippocampal lesions do not produce these autonomic responses (Knight, 1996) and it has been suggested that hippocampal-hypothalamic pathways (Risold and Swanson, 1996) subserve this peripheral autonomic orienting response (Knight, 1996). As mentioned earlier, these patients had lesions of posterior hippocampus (Knight, 1996). However, the hippocampal-hypothalamic projection passes posteriorly through the fornix to the septum, hence a posterior hippocampal lesion could disrupt signals to hypothalamus generated in anterior hippocampus. It remains to be determined whether anterior hippocampal lesions produce an equivalent impairment in generating autonomic signals to novel stimuli.

There is evidence for hippocampal-brainstem interactions at the cellular level. Deadwyler *et al*. (1981) recorded sensory-evoked responses from the dentate gyrus in rats that were being conditioned to respond to an auditory stimulus. Two negative

peaks were identified, one being responsive to unexpectedness in stimuli and the other being responsive to stimuli with acquired behavioural significance. Selective lesions revealed that information about event unexpectedness was transmitted to the dentate from EC via the perforant path, whereas information about biologically significant events was transmitted to the dentate from the medial septum (which receives its inputs from the brainstem). It was therefore suggested that a role of dentate gyrus relates to assessing the significance of information and to modulate the strength of memory storage accordingly (Deadwyler *et al*., 1981). It should be noted, however, that these recordings were made in dorsal (posterior) hippocampus. This suggests that although the strongest projections to septum and brainstem arise in anterior hippocampus, the reciprocal inputs from these regions affect the entire hippocampal longitudinal axis.

7.14 Anterior hippocampus and amygdala

As mentioned in the introduction, mismatch detection can also evoke a fear response such as startle. The fact that anterior hippocampus is sensitive to mismatch is therefore of relevance given that the amygdala, a structure critical for fear responses (Aggleton, 1992), is reciprocally connected with anterior hippocampus. Both ventral CA1 (van Groen and Wyss, 1990) and ventral subiculum (Canteras and Swanson, 1992) project to the amygdala. The reciprocal projection from amygdala to CA1 terminates preferentially in the ventral third of this subfield and amygdala-EC projections terminate primarily in medial EC, which projects to ventral DG (Krettek and Price, 1977).

Anterior hippocampus therefore shows stronger connectivity with amygdala than posterior hippocampus. Do anterior hippocampus and amygdala interact during novelty detection? Differential amygdala responses to novelty have been demonstrated in monkey (Rolls and Wilson, 1993) and humans (Halgren *et al*., 1980). There was, however, no evidence of novelty-evoked amygdala activation in the experiments presented in this thesis except in response to emotionally aversive oddballs (chapter 5 part I). It may be the case that anterior hippocampal-amygdala interactions during novelty detection are only engaged by an aversive novel or an aversive unexpected stimulus.

7.2 Neuromodulatory projections

In rodents there is evidence that the principal neuromodulatory systems all project preferentially to anterior (ventral) hippocampus. The density of dopaminergic, noradrenergic and serotonergic terminals arising from the ventral tegmental area, locus coeruleus and raphe nuclei is higher in ventral than dorsal hippocampus (Gage and Thompson, 1980; Verney *et al*., 1985; Haring and Davis, 1985). Gray's comparator theory (Gray 1982; see chapter 1) postulated that ascending monoaminergic inputs to the hippocampus have a critical role in identifying certain stimuli as important. As mentioned previously, important stimuli are often novel or salient. Furthermore, cholinergic projections are much stronger to ventral portions of hippocampus than dorsal levels (Hoover *et al*., 1978; Amaral and Kurtz, 1985; Wainer *et al*., 1985). This latter observation is relevant to the mismatch detection role ascribed to anterior hippocampus as it has been shown that novelty raises hippocampal acetylcholine levels in rats (Aloisi *et al*., 1997).

In terms of receptor distributions, it has been demonstrated that dopamine D2 receptors are expressed as a double gradient in the human hippocampus. DG and CA3/4 express a greater number of D2 receptors in anterior hippocampus relative to posterior, but the subiculum shows the reverse gradient (Ryoo and Joyce, 1994). The functional role of this double gradient is, as yet, unknown. However, it is interesting that in anterior hippocampus, which it is argued mediates novelty detection and encoding, D2 receptors are found at the inputs to the trisynaptic circuit. In posterior hippocampus, which I suggest mediates retrieval or processing of familiar stimuli, receptors are at the output of this circuit. Pharmacological manipulations during functional imaging studies of the hippocampus may provide valuable insight into the mechanisms that underlie how functional segregation within the human hippocampus is realised.

7.3 Functional segregation for spatial learning

Moser *et al*. (1993) found that the impairments in spatial learning tasks in rats with total hippocampal lesions could be produced if only the dorsal hippocampus was lesioned. By contrast, rats with lesions restricted to ventral hippocampus showed no impairment in the Morris water maze task relative to sham-operated control rats (Moser *et al*., 1993). Although place cells (see chapter 1) have been demonstrated in both dorsal and ventral rat hippocampus (Poucet *et al*., 1994), the proportion of cells with spatial correlates is lower in ventral hippocampus with generally wider and less selective place fields there than in dorsal hippocampus (Jung *et al*., 1994).

There is a suggestion that the posterior hippocampus in the macaque monkey is also specialised for spatial processing. Monkeys trained in a spatial delayed matching-to-sample task have a higher proportion of neurones active in the delay period in posterior than anterior hippocampus (Colombo *et al*., 1998). There were no topographical differences in hippocampal neuronal firing during a non-spatial version of the same task. In humans, however, functional imaging data have provided no obvious distinction between anterior and posterior hippocampal roles in spatial memory. Table 7.1 lists the loci of spatial encoding and retrieval activations from the PET and fMRI studies reviewed by Schacter and Wagner (1999) and Lepage *et al*. (1998).

Table 7.1: Spatial encoding and retrieval activations from PET and fMRI studies. *y* co-ord: *y* stereotaxic coordinates from the brain atlas of Talairach and Tournoux (1988). np: *y* co-ord not provided by authors. A: anterior; P: posterior; PHG: parahippocampal gyrus; L: left; R: right; B: bilateral; Enc: encoding task; Ret: retrieval task. The *y* co-ord dividing anterior and posterior hippocampus (-26) is the same as that used by Lepage *et al*. (1998) and Schacter and Wagner (1999).

PET

A/P	L/R	*y* co-ord	Retrieval/ Encoding	Task	Reference
A	R	-16	Ret	Recall routes. Successful – Navigational control	Maguire *et al*., 1998a
A	R	-18	Ret	Recall route – rest	Ghaem *et al*., 1997
A	R	-20	Ret	Recall routes. Successful – Unsuccessful	Maguire *et al*., 1998a
A/P	L	-26	Ret	Recall routes. Successful – Unsuccessful	Maguire *et al*., 1998a
P	L	-28	Enc	Encode route – view film	Maguire *et al*., 1996
P	R	-32	Ret	Recall route – rest	Ghaem *et al*., 1997
P	L	-32	Enc	Encode route – view film	Maguire *et al*., 1996
PHG	R	-40	Enc	Encode environment – motion decision	Maguire *et al*., 1998b
PHG	L	-44	Ret	Recall routes – rest	Ghaem *et al*., 1997

FMRI

A/P	L/R	*y* co-ord	Retrieval/ Encoding	Task	Reference
PHG	R	-40	Enc	Encode environment – perceptual control	Aguirre *et al*., 1996
PHG	B	np	Ret	Recall environment – perceptual control	Aguirre *et al*., 1996
PHG	B	np	Ret	Recognise/Recall environment – visuomotor control	Aguirre and D'Esposito, 1997

These results do not provide convincing evidence for functional segregation along the human hippocampal longitudinal axis for spatial memory. Half of the PET studies show activation in anterior hippocampus and half posterior. The remaining studies show activation of parahippocampal gyrus, in accord with the fact that the majority of visuo-spatial information reaching the hippocampus arrives via the parahippocampal cortex (Suzuki and Amaral, 1994; Burwell and Amaral, 1998b). The lack of segregation within hippocampus for spatial memory may reflect the projection pattern of the parahippocampal region. As described above, parahippocampal cortex projects to all mediolateral levels of EC hence to all levels of the hippocampal longitudinal axis.

In their review of dorsal-ventral differences in rat hippocampal connectivity, Moser and Moser (1998) suggested that dorsal hippocampus is primarily involved in spatial memory. Although this may be the case in rats, the role of posterior hippocampus in humans extends well beyond spatial learning. Posterior hippocampal activation has been observed during encoding of words (chapter 6; Fernandez *et al*., 1998), visual associations (Rombouts *et al*., 1997), and novel pictures (Stern *et al*., 1996), as well as during retrieval of words, objects and faces (Lepage *et al*., 1998).

A recent study has provided evidence of functional differentiation along the longitudinal axis of the hippocampus for spatial processing on a lamellar scale (Hampson *et al*., 1999). Using an electrode array that allowed many cells to be monitored at known distances apart in the hippocampus, evidence was presented suggesting that different spatial and non-spatial aspects of a task are represented in alternating hippocampal lamellae (thin, functionally isolated slices of hippocampus

perpendicular to the long axis). The two topographies were found to be interleaved such that each cluster coding for one of two positions also contained clusters for both response types (Hampson *et al*., 1999). Although these data, because of their micro-spatial resolution, do not speak to the fMRI results presented in this thesis, the alternating lamellar pattern argues against an entire level of the hippocampal longitudinal axis (i.e. anterior, body or posterior hippocampus) being dedicated exclusively to spatial processing.

Theta oscillatory activity (chapter 1) has been shown to be relatively synchronous over large areas of hippocampus (Mitchell and Ranck, 1980; Fox *et al*., 1986; Bullock *et al*., 1990). Hence, it has been suggested (O'Keefe and Nadel, 1978) that one of the functions of theta is to lock together in simultaneous oscillation disparate areas of hippocampus. These observations imply that theta synchrony would be expressed along the hippocampal longitudinal axis. If hippocampal responses measured with functional imaging reflect theta oscillations, this would imply that hippocampal activations would cover large portions of the hippocampus. This was not the case in any experiments presented in this thesis. Even at low thresholds hippocampal activations were circumscribed. This observation suggests that even if oscillatory activity is synchronised across anterior and posterior hippocampus, the BOLD response remains segregated to anterior or posterior regions.

7.4 Conclusion

In summary, there is substantial evidence for segregation of connectivity and neuromodulatory inputs along the longitudinal axis of the hippocampus. These profiles provide anatomical and neuromodulatory bases for the hippocampal functional segregation argued in this thesis. The connectivity of anterior hippocampus is well suited to a mismatch detection role. Polymodal sensory information reaches the anterior hippocampus via a parahippocampal projection to medial EC and anterior CA1. The anterior hippocampus also receives affective and interoceptive inputs from the amygdala and brainstem. Processing within anterior hippocampus is under a greater degree of neuromodulation by cholinergic and monoaminergic systems than is the case for posterior hippocampus. The anterior hippocampus is therefore capable of integrating physiological states of arousal with cortical sensory inputs during novelty detection These properties are ideal for influencing the extent to which incoming sensory information is encoded into episodic memory.

Posterior hippocampus is extensively and reciprocally connected with polymodal sensory areas, making this region equally suitable for encoding, retention and retrieval of information. The observation that posterior hippocampus is under less influence from neuromodulatory systems may be more advantageous to a storage and retrieval function.