Chapter 8

General Discussion

The experiments presented in this thesis used fMRI to test the hypothesis that human hippocampus is differentially engaged by novel versus familiar stimuli. Previous PET studies had implicated the hippocampus in processing recency of prior occurrence (Tulving *et al*., 1996), whereas novelty-related activations observed with fMRI were located primarily in parahippocampal gyrus (Stern *et al*., 1996; Gabrieli *et al*., 1997). This thesis presents four major findings. First is the demonstration that novelty-dependent responses in hippocampus are detectable using fMRI. Secondly, results from four experiments suggest a functional dissociation between anterior and posterior hippocampal regions with respect to the relative familiarity of study items. Responses in anterior hippocampus index stimulus novelty whereas responses in posterior hippocampus index familiarity. Thirdly, the anterior hippocampal response to novelty extends beyond processing recency of prior occurrence. It reflects mismatch between expectation and experience. This response may represent an important component of episodic memory encoding. Finally, the posterior hippocampal familiarity response may reflect retrieval of familiar stimuli.

8.1 Anterior hippocampus

8.11 Mismatch detection

The experiments in this thesis enable a precise characterisation of the anterior hippocampal response to novel stimuli. The introduction of exemplar novelty in chapter 3 demonstrated that left anterior hippocampal responses adapt with repeated presentations of the same stimulus. Chapters 3 and 4 showed that this region is also engaged when a particular attribute of the stimulus set is changed (i.e. the font or vocabulary of letter strings). The left anterior hippocampal response showed

adaptation after each perceptual change even though novel arrangements of letters were being presented on each trial (chapter 4). This led to the conclusion that anterior hippocampal sensitivity to recency of prior occurrence may reflect a more general role for this region in detecting mismatches between expectation and experience. The results of the oddball experiment presented in chapter 5 strengthened this claim by demonstrating that anterior hippocampus responds when the context, or predictive set, is violated. Critically, as oddballs became increasingly less unpredictable, and the degree of mismatch between expectation and experience decreased, the hippocampal response to oddballs showed adaptation.

Mismatch detection in anterior hippocampus occurred across a number of different experimental tasks: deep, shallow (chapter 5 part II) and rote (chapter 6) encoding, explicit rule induction (chapter 4), item learning (chapter 3) and relational processing (chapters 3 and 4). Furthermore, mismatch-evoked activation occurred in response to perceptual (chapters 3, 4, 5), exemplar (chapter 3), semantic (chapter 5), emotional (chapter 5) and situational (chapter 6) novelty. This task-independence and attribute-independence suggests a high degree of automaticity in the mismatch-detection operation mediated by anterior hippocampus. Although anterior hippocampal mismatch responses in this thesis were tested only in the visual modality, anterior hippocampal responses to auditory (Dolan and Fletcher, 1997) and tactile (Ploghaus *et al.*, 2000) mismatch have also been reported. Hence, the hippocampal role in mismatch detection is, like its more general role in episodic memory, multimodal (see chapter 1). The material-specific laterality of hippocampal function described in chapter 1 was also evident in hippocampal mismatch responses.

Verbal stimuli evoking mismatch between expectation and experience predominantly engaged left anterior hippocampus (chapters 3, 4 and 5 but see chapter 6).

8.12 The origin of hippocampal response adaptation

Animal cellular recordings (Miller *et al*., 1991; Brown and Xiang, 1998) and human functional imaging data (Schacter and Buckner, 1998) demonstrate that stimulus repetition causes response adaptation in inferior temporal regions. Adapting anterior hippocampal responses could, therefore, reflect reduced afferent input from these higher order visual areas. This explanation is nevertheless challenged by findings presented in chapter 3 and 5. There was no evidence of adapting activation to repeated presentation of novel letter strings (chapter 3) in visual areas, particularly inferior temporal cortex. It is possible, however, that inferior temporal activation did adapt with familiarity but that response profiles in these regions were not adequately modelled by the linear and exponential decay functions employed. In the case of neuronal responses to oddballs (chapter 5), all three classes of oddballs, and particularly perceptual oddballs, were shown to engage posterior fusiform cortex. Whereas the response in anterior hippocampus to all oddball types was shown to adapt across multiple oddball presentations, the response in posterior fusiform showed no evidence of adaptation.

How do the observed anterior hippocampal novelty responses differ operationally from those seen in inferior temporal cortex following repetition? The decrease in neuronal responses following repeated presentations of a particular stimulus is referred to as 'repetition suppression', which is thought to reflect more effective stimulus processing of familiar stimuli (Desimone, 1996). Facilitated

processing of a repeated stimulus is one suggested explanation for adaptation of fusiform responses observed in functional imaging priming experiments (Schacter and Buckner, 1998). There is evidence, however, that the operation performed by hippocampus differs from repetition suppression. Cellular recordings demonstrate that inferior and medial temporal cortical responses, particularly perirhinal responses, are typically stimulus-specific, responding differentially to the relative familiarity of certain stimuli and not others (Young *et al*., 1997). Responses in hippocampus, however, do not show this stimulus-selectivity (Vinogradova, 1975; Rolls *et al*., 1993; Otto and Eichenbaum, 1992; Wiebe and Staubli, 1999). The quality of sensory information reaching novelty-sensitive cells in CA3/CA1 appears to be less specific than that arriving at earlier stages (Vinogradova, 1975).

Thus, whereas familiarity-dependent response suppression in inferior and medial temporal cortex is stimulus specific, hippocampal response adaptation appears to reflect abstracted, stimulus-general mismatch detection. In agreement with this proposal is the fact that hippocampal responses to oddballs showed adaptation expressed across successive presentations of *different* oddballs that deviated from the prevailing context along the same dimension. These observations suggest that hippocampal mismatch responses and subsequent adaptation do not reflect changes in afferent input from earlier cortical areas, but originate instead within the hippocampal circuitry.

8.13 Evidence against anterior hippocampal role in mismatch detection

There is evidence from both monkey cellular recordings and neuroimaging that argues against hippocampal sensitivity to novelty. Single unit recordings in

monkeys generally fail to detect hippocampal responses to novel versus previously presented objects (Brown and Xiang, 1998; see chapter 1). However, the proposed hippocampal role in detecting mismatch may explain this lack of hippocampal novelty responses. In these monkey experiments, contextually novel stimuli are continually presented, intermixed with familiar stimuli. With repeated exposure to different novel stimuli, these stimuli will rapidly become predictable, which could lead to a second-order adaptation of hippocampal mismatch responses. It would be interesting to test (in a manner analogous to that employed in chapter 5 part II) whether monkey hippocampal cells are more sensitive to novel stimuli presented at the beginning of these tasks, with this novelty response showing adaptation over the course of the experiment.

There are several classes of neuroimaging findings that do not support the proposed role of anterior hippocampus in novelty processing. Firstly, studies have reported greater anterior hippocampal activation for old vs new items, a pattern opposite to that being proposed. Schacter *et al*. (1997) demonstrated left anterior hippocampal activation during recognition of changed old items vs new items. Although a changed old item may evoke a similar mismatch response to a new item (see chapter 1), this finding is in direct contradiction to the observation by Dolan and Fletcher (1997) that novel category-exemplar word pairings evoke greater anterior hippocampal activation than re-pairings of familiar category and exemplars.

Gabrieli *et al*. (1997) demonstrated bilateral activation of anterior hippocampus during retrieval, where subjects were required to judge whether presented words corresponded to line drawings viewed in a previous encoding

session. Hence in this study, retrieval was potentially confounded by the formation of a novel association between words and line drawings. Eldridge *et al.* (2000) recently reported increased hippocampal BOLD responses during a recognition memory task to old words that subjects remembered having seen previously compared to both old words for which they only had a sense of familiarity and new words. The activation was, however, in the body of the hippocampus (y value of –23), and not in the anterior segment that I propose mediates mismatch detection. Activation in anterior hippocampus has, however, been demonstrated during retrieval of autobiographical memories (Maguire and Mummery, 1999).

Two studies have observed right anterior hippocampal activation during spatial tasks requiring retrieval of routes (Maguire *et al.*, 1998a; Ghaem *et al.*, 1997) or landmarks (Ghaem *et al.*, 1997). As mentioned in chapter 7, there does not appear to be any dissociation in human hippocampal responses along the hippocampal longitudinal axis for spatial tasks. Furthermore, the anterior-posterior segregation for encoding and retrieval, respectively, does not appear to hold for spatial tasks. Hence, in addition to detecting novel visual stimuli (Tulving *et al.*, 1996; Martin *et al.*, 1997; Constable *et al.*, 2000; Fischer *et al.*, 2000), the right anterior hippocampus plays a role in spatial encoding and retrieval.

A second line of neuroimaging evidence demonstrating that anterior hippocampal function extends beyond mismatch detection comes from studies reporting anterior hippocampal activation between conditions where relative novelty is held constant. For example, Montaldi *et al.* (1998) presented old National Geographic photos during SPECT scanning while subjects engaged in either an

associative encoding task (in which they were to focus on what the picture was about, how the features related to each other within the picture, and the spatial locations of items) or a perceptual matching task (in which three photos were shown and subjects had to match the top photo with one of the other two). Greater left anterior hippocampal activation was observed for the associative encoding condition compared to the perceptual matching condition, despite relative novelty being equated across the two conditions.

Henke *et al*. (1997) presented subjects with pictures of a person and of a house simultaneously. Subjects were required either to decide if the person was an inhabitant or a visitor of the house, encouraging the formation of an association between the person and the house (associative encoding), or to make separate decisions about the person (male vs female) or house (exterior vs interior view). Stimulus novelty was equal across both conditions, only the task demands were varied, yet Henke *et al*. (1997) reported greater anterior hippocampal activation when stimuli were associatively encoded than when they were encoded separately. Another PET study (Vandeberghe *et al*., 1996) also reported anterior hippocampal activation between tasks which equated novelty. In this study, presentation of stimulus arrays evoked activation in left anterior hippocampus when subjects performed a semantic, associative task, but not when performing a perceptual, size judgement. Similar results were obtained by Mummery *et al*. (1998) when subjects were required to perform a semantic vs syllabic task on word triads. All three of these PET studies require an association to be made between multiple presented items according to their semantic attributes.

These findings highlight two important properties of anterior hippocampus. In addition to novelty-evoked activations, two other experimental manipulations have consistently engaged anterior hippocampus: stimulus complexity and a requirement for semantic processing. In the latter two studies (Vandeberghe *et al*., 1996; Mummery *et al*., 1998), anterior hippocampus was engaged during processing of stimulus arrays, which are complex stimuli evoking relational processing. This is relevant to the studies presented in chapters 3 and 4, which demonstrated anterior hippocampal activation in response to novel arrangements of letters. In this regard it is noteworthy that despite a lack of responses in monkey and rodent hippocampus to novel single objects, responses in rodent hippocampus have been observed to novel stimulus arrays (Wan *et al*., 1999).

Early neuroimaging studies that manipulated recency of prior occurrence and demonstrated hippocampal activation presented complex stimuli such as, for example, faces, scenes (Tulving *et al*., 1996), category-exemplar word pairs (Dolan and Fletcher 1997) or letter strings (chapters 3 and 4). However, more recent studies have shown that hippocampal activation in humans does not necessarily depend on stimulus complexity. For example, Kopelman *et al*. (1998) and Saykin *et al*. (1999) reported anterior hippocampal activation in response to contextually novel single words. The adaptive hippocampal responses to oddball words, demonstrated in chapter 5 part I, were, again, in response to single words. Furthermore, Menon *et al*. (2000) recently demonstrated that hippocampal activation to novel vs familiar pictures of landscapes was independent of their spatial complexity. This supports the argument that the critical variable for evoking anterior hippocampal responses is

mismatch between expectation and experience, and does not necessarily depend on stimulus complexity.

Anterior hippocampal activation observed by Vandeberghe *et al*. (1996) and Mummery *et al*. (1998) cannot be explained in terms of processing stimulus arrays, as arrays were presented in both activation and control conditions, with relative novelty equal between the two conditions. The activation condition differed from control in the requirement for semantic processing of these arrays. As discussed in chapter 5 part II, left anterior hippocampus plays a role in processing the semantic attributes of stimuli.

The anterior hippocampal sensitivity to meaning may explain why certain novelty comparisons have failed to engage this region. For example, nonsense (Martin *et al*., 1997) and impossible objects (Schacter *et al*., 1995), by definition novel as subjects will have never seen them before, do not preferentially engage anterior hippocampus relative to meaningful and possible objects respectively. It appears that superimposed on a sensitivity to mismatch, the anterior hippocampus plays a role in deriving meaning from, or associating, stimuli. A recent event-related fMRI study of face memory (Levroni *et al*., 2000) illustrates this point. At recognition, subjects were presented three types of faces: famous faces (FF), newly learned, non-famous faces (NL) that were presented during a previous encoding session, and novel, non-famous face foils (FO). Both the famous faces and non-famous face foils were contextually novel relative to the newly learned faces. Left anterior hippocampal activation was, however, only observed in the FF vs NL comparison and not in the FO vs NL comparison (Levroni *et al*., 2000). A possible

explanation for this observation is that in encountering a novel stimulus, a component of the anterior hippocampal mismatch response involves comparing and associating that stimulus with information stored in declarative memory.

In summary, the number of studies demonstrating anterior hippocampal activation to novel vs familiar stimuli outweighs those demonstrating the opposite response profile. However, additional cognitive processes, namely semantic, associative and spatial processing, also engage anterior hippocampus. With respect to the semantic and associative role of anterior hippocampus it was suggested in chapter 5 that mismatch detection and associative learning may represent a unitary function of the anterior hippocampus.

8.14 Anterior hippocampus and encoding

Lepage *et al*. (1998) suggested, on the basis of a meta-analysis of PET studies of episodic memory, that episodic encoding is a specific function of anterior hippocampus. It is argued here that this role for anterior hippocampus in episodic memory reflects functional specialisation for detecting mismatches between expectation and experience. Thus, these two views can be reconciled if the engagement of mismatch detection in response to an unpredictable stimulus is considered to be the physiological basis for awarding this stimulus preferential access to storage in long-term memory. A general role for the anterior hippocampus in enhancing episodic encoding is indicated by the same novelty-sensitive anterior hippocampal region being engaged by deep versus shallow processing (Henke *et al*., 1997, 1999; Otten *et al*., 2001), a manipulation, which like stimulus novelty, enhances episodic memory (Craik and Lockhart, 1972).

In direct contradiction to the suggestion that the response properties of anterior hippocampus are critical for efficient episodic memory encoding, damage limited to anterior hippocampus does not appear to cause severe episodic memory deficits. Anterior hippocampal volume reductions in chronic alcoholics do not correlate with episodic memory impairments (Sullivan *et al*., 1995). Furthermore, reports on semantic dementia patients (Chan *et al*., 2001) have described bilateral anterior hippocampal damage, with sparing of posterior hippocampus, in the absence of episodic memory impairments. It may be the case that anterior hippocampal involvement in episodic memory is limited to enhancing memory for novel stimuli. In support of this suggestion, anterior hippocampal responses were shown to only index successful encoding for initial, positionally distinctive words in a list and not later words (chapter 6). The hippocampal body, which was shown to mediate successful encoding for later list words (chapter 6), may play a more general role in episodic encoding.

To validate the proposed role for anterior hippocampus in encoding, the von Restorff effect (see chapter 5) should be tested in patients with circumscribed damage to this region. The prediction generated from the current argument is that these patients demonstrate normal memory for control words, but do not show enhanced memory for oddball words. It may be the case, however, that following damage to the anterior hippocampus, reorganisation occurs such that the functions normally mediated by anterior hippocampus are executed by other components of the medial temporal memory system. If patients with restricted anterior hippocampal

damage display a normal von Restorff effect, it would be important to compare the substrate of this effect relative to control subjects using functional imaging.

8.15 Implications for a mismatch detection role

The proposal that anterior hippocampus is sensitive to mismatch between expectation and experience suggests that this region is engaged by a much wider range of tasks than those deliberately manipulating relative familiarity or context violations. It follows that activation in anterior hippocampus would be enhanced by any task wherein subjects are unaware of what is coming next, relative to a task with a predictable sequence of events. This speculation is supported by results from simple motor sequence learning tasks in which subjects must make a button press with one of four fingers in response to one of four stimuli. Greater (right) anterior hippocampal activation is evoked by random (i.e. unpredictable) sequences than by ordered sequences (see figure 2 in Rauch *et al*., 1998; Katz Sakai, unpublished observations). Anterior hippocampus is activated by unpredictability in these tasks, despite the fact that motor learning is not medial temporal lobe-dependent (see chapter 1). Similar observations have been reported during single unit recordings in human hippocampus which demonstrate responses to task interruptions and transitions between tasks (Halgren, 1991). One critical implication of these results is that in designing future functional imaging studies of hippocampal function, it may be advisable to minimise any unpredictability in control conditions with which task-dependent hippocampal activation is compared.

A hypothesis that can be generated, in light of anterior hippocampal sensitivity to mismatch between expectation and experience, is that the hippocampus

is constantly engaged in extracting the regularities of the environment, thereby setting up an expectation. Anterior hippocampus is more strongly engaged when the regularities, or predictive set, must be updated i.e. following an event that violates expectation. This interpretation is in accord with the spatial theory of hippocampal function, as it could be suggested that place cells function to extract the spatial regularities of an environment (O'Keefe and Burgess, 1996). With regard to a possible semantic function of anterior hippocampus, it is interesting that semantic memories are, in fact, the regularities that arise from episodic memories.

8.2 Posterior hippocampus

The experiments described in this thesis provide less evidence pertaining to the functional properties of posterior hippocampus. In chapter 3 it was reported that behaviourally relevant familiar stimuli engaged posterior hippocampus. The fact that the task demands were such that retrieving the category membership of these familiar stimuli would improve performance led to the suggestion that posterior hippocampus is preferentially engaged by episodic retrieval. Chapter 6 demonstrated that words presented later in a list engaged posterior hippocampus to a greater extent than the initial words in the list. The rote nature of the encoding task, which can lead to a tendency to rehearse previously presented words, led to the conclusion that posterior hippocampal activation reflects stimulus rehearsal. Rehearsal of lists where word numbers exceed the capacity of short-term working memory systems requires that previously presented words are retrieved from episodic memory. It is difficult to explain the posterior hippocampal responses observed in chapter 3 in terms of rehearsal, as there was no reason for subjects to rehearse the grammaticality status of

familiar exemplars any more than novel exemplars. Hence, a posterior hippocampal role in retrieval is supported by both studies.

Alternatively, both posterior hippocampal activations could equally be interpreted in terms of stimulus familiarity, as, in chapter 6, rehearsing stimuli leads to increased stimulus familiarity. However, in light of the frequent observation of posterior hippocampal activation during PET studies of retrieval (Lepage *et al*., 1998), an episodic retrieval function for posterior hippocampus is favoured. A further study is currently underway aimed at dissociating familiarity from episodic retrieval. This experiment is analogous to that presented in chapter 3 but category membership is arbitrary and task is blocked. The tasks are to either gradually learn category membership (A or B) to repeated presentations of stimuli, with trial-by-trial feedback, or respond always 'A' (or always 'B') to repeated presentations of stimuli, again with feedback. The former task requires intentional retrieval of category membership, as well as processing of familiarity whereas the latter task engages only familiarity processing. In addition, several stimulus types are presented, such as simple line drawings and arrays of line drawings, to test whether the novelty- and familiarity-dependent hippocampal activations observed in chapter 3 were due to spatial or relational processing engaged by letter strings.

8.3 Control considerations

8.31 Eye movements

The visual world that impinges upon the retina is constantly changing because our eyes do not stay still. Novelty in the visual domain, at the simplest level,

could be considered as a change in the retinal image. Ringo and colleagues have demonstrated, using single unit recordings, that a large number of cells in macaque inferotemporal cortex, parahippocampal gyrus and hippocampus are sensitive to saccadic eye movements (Ringo *et al*., 1994; Sobotka *et al*., 1997). In normal human subjects, novel stimuli evoke more exploratory eye movements than repeated, familiar stimuli (Daffner *et al*., 1992). Taken together, these observations could suggest that the hippocampal mismatch responses observed in this thesis reflect increased eye movements, with adaptation of hippocampal responses reflecting a decrease to the extent that subjects moved their eyes as stimuli became more familiar. A possible limitation in interpreting the experiments presented in this thesis is, therefore, that eye movements were not controlled for.

One possible solution to the eye movement confound would be to conduct an fMRI experiment where novel and familiar stimuli are presented under the conditions of fixation and free viewing. However, the view held by O'Keefe and Nadel (1978) is that the hippocampal role in the orienting response is to drive exploration of novel stimuli or environments (see chapter 1). In the case of an fMRI experiment presenting novel visual stimuli, 'exploration' would be mediated by increased eye movements. It could therefore, be the case that the responses observed in anterior hippocampus to novel stimuli reflect a signal to drive exploration (i.e. not the perceptual result of increased exploratory activity). Even if subjects fixated during presentation of novel stimuli, this signal to drive exploration would, most likely, remain. Hence, the proposed fixation experiment would remove the effects of increased sensory input caused by increased eye movements but would still not be able to distinguish between a mismatch response and an exploration-driving signal.

A counter-argument to eye-movements accounting for medial temporal responses is that cellular recordings in monkey anterior medial temporal cortex demonstrate familiarity-dependent neuronal response changes to visual stimuli during fixation (Miller *et al*., 1993). Furthermore, when visual fixation is not required, changes in neuronal responses occur well before the onset of eye movements (Fahy *et al*., 1993). In defense of an anterior hippocampal role in mismatch detection that does not merely reflect increased eye movements nor an exploration-driving signal, anterior hippocampal responses are evoked by novel, or unexpected, stimuli presented in the auditory (Dolan and Fletcher, 1997; Saykin *et al*., 1999) and tactile domains (Ploghaus *et al*., 2000). It is difficult to conceive of any 'exploratory' activity that could be evoked in the context of fMRI scanning by mismatch in these domains. Interestingly, parahippocampal gyrus has not been shown to be sensitive to auditory and tactile novelty. The fact that novelty responses in parahippocampal gyrus are limited to the visual domain suggests that the potential eye movement confound is more applicable to claims of novelty-sensitivity in this region (Stern *et al*., 1996; Gabrieli *et al*., 1997).

8.32 Attention

It is unlikely that anterior hippocampal mismatch responses are secondary to increased attention to novel or unexpected stimuli. An attentive difference to a distinctive stimulus can only be generated once the stimulus is recognised as novel or unexpected. For hippocampal responses to be secondary to increased attention, the mismatch signal to engage attention must be generated elsewhere in the brain. As mentioned above, it is unlikely that this signal is generated at earlier stages in the visual system. Furthermore, it was suggested in chapter 5 part I that enhanced

responses in posterior fusiform to semantic and emotional oddballs were the result of increased attention, implying that responses in this regions were not the source of increased attention.

Prefrontal cortex may mediate the engagement of attention in response to a novel stimulus (Daffner *et al.*, 2000). In chapter 5 part I, right prefrontal cortex was shown to recruit inferior parietal lobule, a region widely considered important for attention, during presentation of oddball stimuli. Critically, there was no evidence that oddball-evoked activation in right prefrontal cortex covaried with oddball-specific activation in anterior hippocampus. Mismatch detection in anterior hippocampus is therefore unlikely to reflect increased attentional processes engaged by prefrontal cortex.

8.33 Task control

In the experiments presented in chapter 3, 4 and 5, there are certain aspects of experimental design that, in retrospect, could be improved. It would be worth repeating the experiment in chapter 3 without the artificial grammar learning component. Although there was no significant interaction between hippocampal responses and acquisition of abstract grammar knowledge, abstract knowledge acquired across the duration of the experiment gradually decreases subjects' reliance on episodic memory (and, by extension, reliance on hippocampus) in maintaining performance (Fletcher *et al.*, 1999). Presenting the same stimuli in the context of a purely episodic task (no abstract structure with strings arbitrarily assigned to 'left button press' category or 'right button press' category) may produce more robust hippocampal activations. Furthermore, in light of the 'second order novelty' effect

observed in chapter 5 (hippocampal responses to oddballs adapting with repeated occurrences of oddballs) it would have been interesting to test whether anterior hippocampal responses to exemplar and perceptual novelty decreased across the course of the experiment with repeated introductions of these two forms of novelty. This was not possible as any second order novelty effect in this experiment is confounded with acquisition of abstract knowledge.

In chapter 4, stronger evidence that subjects were performing on the basis of abstract rules would have been obtained had there not been a decrease in performance at the start of epochs in which the rule remained the same. This performance decrement at the start of exemplar change and no change epochs was interpreted as subjects anticipating rule change. In terms of the imaging data, this performance confound was removed by comparing only correct responses. Removing control epochs should eliminate the performance decrement at the start of no change epochs, because it was at the transitions between control and activation epochs that subjects anticipated a rule change. However, exemplar change introduced in the absence of intervening control epochs could still be initially interpreted by subjects as rule and exemplar change. A solution would be to remove the factorial nature of the design and introduce only rule or exemplar changes in the context of continuous category judgements without intervening controls. Importantly, this would enable a characterisation of relative decreases in anterior hippocampal activation following rule changes that are not influenced by any effects of rule change anticipation.

A further criticism in using the experimental design in chapter 4 to study novelty responses is that the occurrence of the no change condition was less probable than the others (out of the 4 epoch types, 2 have rule changes and 2 have exemplar changes whereas only one has no change). The reference no change epoch may, because it is salient in the sense of being infrequent, have engaged the anterior hippocampus to some degree. This could have decreased sensitivity in testing for exemplar and/or rule change-evoked hippocampal responses.

The oddball experiment presented in chapter 5 would have been more informative had memory been assessed in scanned subjects. This would have enabled an analysis of subsequent memory similar to that employed in chapter 6. Memory was not assessed with a recognition test because the von Restorff effect is more prominent in free recall than recognition (Fabiani and Donchin, 1995). Recall should have been tested at the end of each 19-word list, in a manner identical to that employed in chapter 6. Of great interest would have been the interaction between remembered vs non-remembered items and oddballs vs controls, as this would provide direct evidence for the neuroanatomical correlates of the von Restorff effect.

Chapter 6 can be criticised for choice of encoding task. The inter-subject variability in encoding strategies employed during rote encoding is likely to be greater than that say during the deep or shallow tasks imposed in chapter 5. A rote encoding task was chosen, however, so as to replicate the electrophysiological experiment of Fernandez *et al*. (1999).

8.4 The hippocampus as part of a distributed limbic-neocortical novelty detection network

Responses to novel stimuli have been reported in a wide range of brain regions. Functional imaging studies demonstrate novelty-dependent activation in prefrontal, inferior temporal and limbic cortices (Tulving *et al*., 1996; Schacter and Buckner, 1998; Kirchhoff *et al*., 2000). Furthermore, specific forms of novelty, such as emotional and semantic unexpected stimuli, engage neuroanatomical regions sensitive to the attribute of this stimulus conferring context violation (chapter 5). In electrophysiological studies, novelty P3a potentials are reduced in amplitude after focal damage in either dorsolateral prefrontal or posterior association cortex (Knight, 1984; Knight *et al*., 1989; Yamaguchi and Knight, 1991) as well as hippocampus (Knight, 1996). Intracranial electrodes have recorded novelty-related field potentials in several brain regions, including prefrontal and posterior association cortex, in addition to cingulate and limbic areas (Baudena *et al*., 1995; Halgren *et al*., 1995). The results presented here suggest that the human hippocampus is a critical element of this novelty detection network. Anterior hippocampus is engaged by stimuli that produce a mismatch between expectation and experience.

In addition to frequent demonstrations of hippocampal mismatch responses, right prefrontal cortex, particularly right inferior frontal sulcus, has been consistently implicated in oddball detection (Opitz *et al*., 1999; Kirino *et al*., 2000; chapter 5 part I). Repetition-sensitive responses are common in the inferior convexity of the monkey prefrontal cortex (Miller *et al*., 1996). This region in monkeys corresponds to the human inferior frontal activation observed in response to oddballs (chapter 5,

part I). These prefrontal neurones, like medial temporal cortical neurones, signal both stimulus recency and familiarity (Brown and Xiang, 1998). Interestingly, prefrontal neurones, like hippocampal neurones, carry less detailed sensory information than medial temporal cortical neurones (Miller *et al*., 1996), suggesting that both prefrontal and hippocampal neurones index mismatch while medial temporal cortical responses reflect stimulus-specific novelty detection.

In chapter 5, oddball responses in right prefrontal cortex, at least for perceptual and emotional oddballs, did not show evidence of adaptation across multiple presentations of oddballs. Hippocampal and prefrontal roles in mismatch detection therefore dissociate. A plausible account of these differing roles is that mismatch detection in prefrontal cortex occurs within the time scale of working memory (Baddley, 1992). This time frame would explain why right prefrontal responses do not adapt across sessions, as working memory is limited to a few experimental trials and, thus, does not operate across sessions. In support of this suggestion, transitions in response requirements during a working memory task engage the same oddball-sensitive inferior frontal region (Konishi *et al*., 1998). By contrast, mismatch detection in anterior hippocampus occurs in the context of episodic memory. Adaptation to multiple presentations of oddball stimuli occurs because the hippocampus can 'remember' oddball presentations that occurred previously.

8.5 Conclusion

The conclusion from the experiments presented in this thesis is that anterior hippocampal responses reflect mismatch between expectation and experience. This

process may be critical for encoding information into episodic memory and may partly explain the impairments in acquiring new episodic memories subsequent to hippocampal damage. By contrast to the anterior hippocampal role in mismatch detection, posterior hippocampus appears to be functionally specialised for retrieval from episodic memory. Segregation of cortico-hippocamapal, subcortico-hippocampal and neuromodulatory projections along the longitudinal hippocampal axis provides an anatomical basis for the observed functional dissociation between anterior and posterior hippocampal regions. Functional segregation within human hippocampus may provide a basis for understanding the memory deficits arising from damage to distinct regions of the hippocampus.