Chapter 6

Human Medial Temporal Activity Predicts Subsequent Memory: Dissociable Perirhinal, Hippocampal and Parahippocampal Roles in Verbal Encoding

6.1 Introduction

The previous chapters have addressed the role of anterior hippocampus in detecting mismatches between expectation and experience. In addition to reports of hippocampal novelty responses, there is considerable evidence from cellular recordings in non-human primates that neurones in perirhinal cortex are sensitive to relative stimulus familiarity (Brown and Aggleton, 2001; see chapter 1). The experiments so far described in this thesis, like all other functional imaging studies that manipulate relative familiarity, have failed to demonstrate an expected perirhinal response to novelty.

In this thesis, the lack of perirhinal activation may reflect differences between the human memory paradigms (as used in chapters 3, 4 and 5), and paradigms employed in measuring monkey perirhinal responses. The latter typically measure novelty-dependent responses in the context of delayed non-matching to sample recognition memory tasks (Brown and Xiang, 1998). By contrast, the novelty-dependent responses reported in this thesis were measured in the context of either episodic encoding (chapter 5), explicit rule learning (chapter 4), or item learning (chapter 3). It is, however, unlikely that task differences alone account for a lack of perirhinal novelty responses in the experiments described in chapters 3 to 5, as functional imaging studies of recognition memory also fail to find activation of perirhinal cortex for novel compared to familiar stimuli (Schacter and Wagner, 1999; Rugg and Henson, 2001).

An alternative explanation for the apparent lack of novelty-evoked perirhinal activation is that fMRI is relatively insensitive to perirhinal activity. The medial temporal lobe, particularly its anterior extent, is subject to fMRI susceptibility artifacts and signal drop-out (Ojemann *et al*., 1997), yielding smaller signal to noise in anterior medial temporal structures relative to other cortical regions. Thus fMRI may be relatively insensitive to activation in perirhinal cortex, which lies in anterior medial temporal lobe in the banks of the anterior extent of the collateral sulcus (Amaral, 1999). Although these sources of signal loss are not present in positron emission tomography (PET) images, the limited spatial resolution of PET may preclude dissociation of perirhinal activation from hippocampal or parahippocampal activation.

Although a human perirhinal role in novelty detection has yet to be demonstrated, recent electrophysiological data show that human perirhinal cortex participates in verbal encoding. Depth electrode recordings in human unilateral temporal lobe epileptic patients demonstrate that during verbal encoding, greater responses in perirhinal cortex, and hippocampus, are evoked by words subsequently recalled compared to words that are subsequently forgotten (Fernandez *et al*., 1999). This finding differs from previous event-related fMRI studies of the 'subsequent memory effect', which demonstrate that responses in parahippocampal cortex (posterior to perirhinal cortex) to words (Wagner *et al*., 1998; Kirchoff *et al*., 2000) and pictures (Brewer *et al*., 1998; Kirchoff *et al*., 2000) predict whether items are subsequently recognised. A further fMRI study demonstrated that verbal encoding-related activation in left anterior hippocampus predicts subsequent recognition (Otten *et al*., 2001). Hence, fMRI studies, in contradistinction to the human intracranial

recording data (Fernandez *et al*., 1999), have not demonstrated differential encoding-related perirhinal responses to subsequently remembered versus forgotten words.

The current experiment addressed whether the absence of perirhinal activation in subsequent memory fMRI experiments reflects a true lack of differential haemodynamic responses to subsequently remembered vs forgotten items, or decreased sensitivity of fMRI in these anterior perirhinal regions. To address this issue, the paradigm employed by Fernandez *et al*., (1999) was replicated exactly in the context of an event-related fMRI experiment. Critically, scanning data acquisition parameters were manipulated so as to increase sensitivity to anterior medial temporal responses (see Materials and Methods).

Fourteen normal subjects were instructed to rote encode 12 words presented during scanning. Following a distractor task, subjects freely recalled from the 12 words (figure 6.1a). This procedure was repeated 30 times for each subject. To test for encoding-related perirhinal responses, predictive of subsequent memory, encoding-related responses evoked by subsequently recalled words were compared with encoding responses to forgotten words. The provisional aim of the experiment was to determine imaging parameters sensitive to perirhinal activation to enable future investigation into the human perirhinal role in novelty detection.

The current paradigm also enabled a test of a previous fMRI result (Fernandez *et al*., 1998), which demonstrated posterior hippocampal activation during successful verbal encoding. In this forerunner to the event-related analyses of successful vs non-successful encoding activation (Brewer *et al*., 1998; Wagner *et al*.,

1998; Kirchoff *et al*., 2000; Otten *et al*., 2001), mean encoding-related activation was averaged over successive word presentations and correlated with total recall of these words. Given that encoding-related posterior hippocampal activation contradicts the position developed in this thesis that posterior hippocampus is engaged by familiar stimuli, perhaps reflecting episodic retrieval (Lepage *et al*., 1998), it was important to verify this result in the current experiment.

6.2 Materials and Methods

6.21 Subjects

Informed consent was obtained from 14 right-handed, native English speaking subjects (4 male, 10 female; age range 19 - 32 yrs; mean age 24.2; recruited by advertisement).

6.22 Psychological task

During fMRI scanning, words were presented in uppercase letters (white against black background), in central vision (horizontal visual angle 3 - 9°), and for a duration of 400 ms (randomised stimulus onset asynchrony; mean 2.5 s, range 2.3 to 2.7 s). All subject were presented with the same words (4-11 letters in length, 15-175 occurrences per million; Kucer and Francis, 1967) with presentation randomised across subjects. In each scanning session, subjects were presented with 12 words and instructed to use a rote strategy to memorise each word. That is, it was emphasised that they were not to use memory aids such as imagery or making sentences, stories or rows. The presentation of each list of 12 words was followed immediately by a 30 s distraction task (not scanned) during which subjects were instructed to count

backwards in threes (out loud), starting at a number between 81 and 99 displayed on the screen. The distractor task was followed immediately by the instructions, displayed on-screen, to free-recall the words presented in the preceding list, for which subjects were allowed 90 s (figure 6.1a). Immediately prior to scanning, the experimental procedure was explained to each subject and two training blocks were completed outside of the scanner. The psychological task was therefore identical to that used by Fernandez *et al*. (1999), except that here 30 lists of words were used as opposed to 20.

6.23 Data acquisition

For each subject, data were acquired in thirty scanning sessions. In each scanning session, 22 volumes were acquired plus 5 'dummy' volumes, acquired at the start of each session and subsequently discarded, to allow for T1 equilibration effects. Volumes were acquired continuously every 1750 ms. Each volume comprised twenty-four 2mm axial slices, with an in-plane resolution of 2.5x2.5mm and in-plane field of view of 160 mm, positioned to cover the perirhinal, entorhinal and parahippocampal cortices and the hippocampus. Prior to the acquisition of each slice, a slab-selective saturation pulse was applied to a coronal section positioned to cover the eyes and frontal pole (thickness 60 mm) to minimise frontal-occipital wrap-around and Niquist ghosting of the eyes. The scanned region and position of the saturation pulse are illustrated in figure 6.1b. An echo-time (TE; see chapter 2 part I) of 30 ms was used in order to minimise signal drop-out from the temporal lobes.

The imaging time series was first realigned to correct for interscan movement. Because of spatial distortion in the anterior extent of the frontal lobe (i.e. adjacent to the delineation imposed by the saturation pulse) this region was masked during realignment. The data were then normalised into a standard anatomical space (Talairach and Tournoux, 1988) to allow group analyses, and smoothed with a Gaussian kernel of 6 mm full width half maximum to account for residual intersubject differences (Friston *et al*., 1995a). Five sessions were discarded from one subject due to poor image quality.

6.24 Data analysis

Imaging data were analysed using Statistical Parametric Mapping (SPM99). Three types of analyses were performed. The first analysis employed an event-related model (Josephs *et al*., 1997) to compare encoding-related responses to individual words that were subsequently remembered vs words that were forgotten. The second was a covariate analysis, similar to that employed by Fernandez *et al*. (1998), which tested the voxel-wise correlation between mean activation within each list and the total number of words recalled from that list. Given that the first two words in each list were recalled better than later words (i.e. there was a significant primacy effect; see Results), in both analyses the first two words in each list were modelled separately from the remaining 10 words (the list body), so as to avoid confounding subsequent memory with the primacy effect. The third analysis specifically investigated the neuroanatomical correlates of the primacy effect and tested for an interaction between subsequently remembered vs forgotten items in the primacy positions vs the body of the list. All three analysis types were random effects analyses implemented using a two stage procedure (see chapter 2 part II).

6.24a Subsequent memory event-related analysis of the list body

The first analysis focused on the subsequent memory effect in the list body. Four effects of interest were therefore specified for each session: the events corresponding to subsequently remembered and forgotten words in the initial serial positions (1 and 2) and list body positions (positions 3-12). Trial-specific responses were modeled by convolving a delta function (or 'stick' function) that indicated each event onset with two basis functions to create regressors of interest. The basis functions used (see chapter 2 part II) were a synthetic, canonical haemodynamic response function (HRF) and a delayed HRF shifted to onset 3.5 s (i.e. two repetition times) later than the canonical HRF. The use of both an early and late response function followed suggestions that the time of maximal activation can be later for some brain regions (e.g. hippocampus) than the sensory regions on which the HRF is based (Otten *et al*., 2001). The covariates for the late HRF were orthogonalised with respect to those for the early HRF using a Gram-Schmidt procedure so as to give priority to the early covariate (Andrade *et al*., 1999), i.e. variance common to the early and late covariates is attributed to the early covariate.

Session-specific parameter estimates pertaining to the height of the HRF for each regressor of interest were calculated for each voxel (Friston *et al*., 1995b). A contrast of parameter estimates across sessions comparing subsequently remembered vs forgotten words in the list body was calculated in a voxel-wise manner to produce, for each subject, one contrast image for the subsequent memory effect in the list body. In the second stage of the random effects analysis, each subject's contrast image was entered into a one-sample t-test across the 14 subjects. An identical

procedure was employed to test parameter estimates for words in the initial positions, and for the delayed HRF modelling words in the list body. The analysis testing for subsequent memory effects using a delayed HRF did not yield any significant differential medial temporal activations.

6.24b Covariate analysis

The covariate analysis followed the same procedure except that for each session, the effect of interest was a continuous train of event-related responses modeling the entire word list body. The contrast weights applied to the session-specific parameter estimates were the total number of words recalled from the body of that session. Hence, one contrast image was calculated for each subject which embodied the correlation at each voxel between mean list body signal intensity and recall performance for that particular list body. Each subject's contrast image was then entered into a one-sample t-test across subjects.

6.24c Primacy analysis

This event-related analysis investigated the neuroanatomical correlates of the primacy effect and tested for an interaction between subsequently remembered vs forgotten items in the initial positions (positions 1 and 2) vs the body of the list. A single regressor was created to test this interaction and the only basis function used was the canonical HRF. To create the interaction regressor, for each list the two initial words were modelled as well as two body words chosen at random. These two body words were selected so as to match recall performance for initial words. If, in a given list, both initial words were remembered, the interaction regressor modelled

these two responses plus the event-related responses (multiplied by –1) for two recalled body words chosen at random. If both initial words were forgotten, their modelled responses were multiplied by –1 and the responses to two forgotten body words multiplied by +1. If one initial word was remembered, the interaction regressor consisted of the remembered and forgotten initial word and a randomly selected remembered and forgotten body word (modelled responses multiplied by +1, -1, -1, +1, respectively). The event-related responses to the remaining words in the body of each list were modelled as effects of no interest. The session-specific parameter estimates pertaining to the interaction were averaged across sessions, within subject, and the resulting contrast image entered into a one-sample t-test across the 14 subjects. To enable plotting of the fitted responses in figure 6.4, a separate analysis was conducted which modelled the four components of the interaction separately, i.e. remembered and forgotten words in the initial positions and two remembered or forgotten words in the list body randomly selected under the same constraints as for the original primacy analysis.

Sessions in which no words were recalled from the list body were not included in the three analyses, as these sessions may have reflected a failure at retrieval rather than at encoding. 10 sessions (out of a total of 420 sessions across subjects) were thus excluded, with no particular subject displaying more than 3 zero recall sessions. In all three analyses, movement parameters, determined during realignment, were entered as covariates of no interest to remove possible movement-related residual effects.

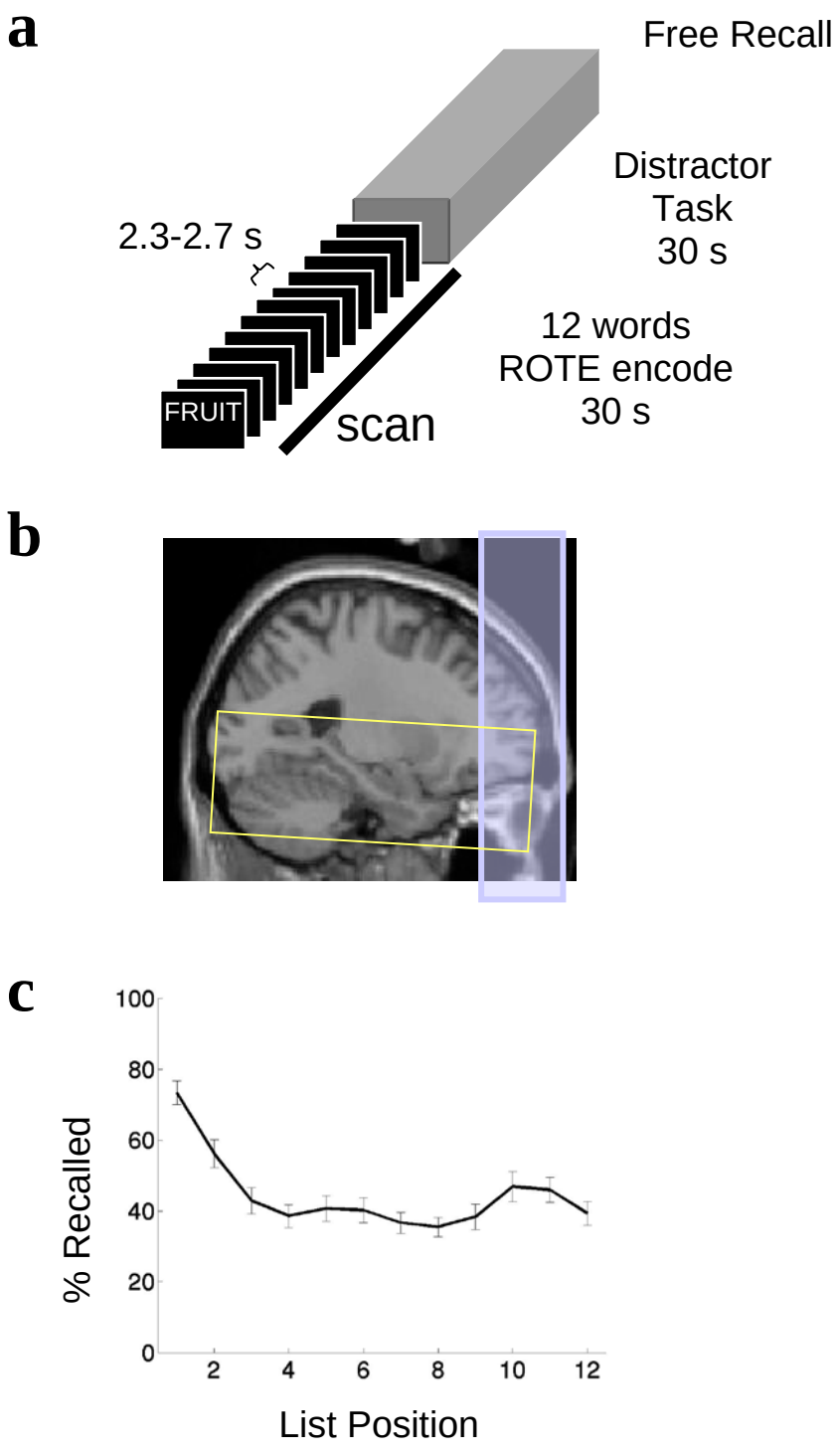
The default threshold for medial temporal activations in this thesis was $p<0.001$, uncorrected. In the current experiment, the threshold was set at $p<0.005$, uncorrected, because of the low signal to noise ratio in perirhinal cortex (Ojemann *et al*., 1997). Activation of posterior fusiform cortex in the primacy analysis survived this threshold and is also reported given that this region has previously been implicated in the subsequent memory effect (Brewer *et al*., 1998; Wagner *et al*., 1998; Kirchoff *et al*., 2000). All SPMs are superimposed on two T2* functional images. The first T2* image is the mean functional image (produced for each subject during realignment and then normalised) taken from one subject. The other T2* image is the normalised, mean functional image averaged across the 14 subjects. Voxel intensities in this image have been increased by a power of 5 to improve contrast and enable localisation of the collateral sulcus. Colour contrast of these T2* images has been inverted for illustration.

6.3 Results:

6.31 Behaviour

The serial position recall curve averaged for all subjects is shown in figure 6.1c. A repeated measures ANOVA demonstrated a significant list position by performance interaction ($F_{4.4, 57.5} = 14.85$; $p<0.001$; Greenhouse-Geisser corrected for non-sphericity). A post-hoc Tukey test (degrees of freedom corrected for non-sphericity) demonstrated a significant primacy effect but no significant recency effect. The recency effect, enhanced memory for the last presented items, is thought to be medial temporal lobe-independent (Baddeley and Warrington, 1970), dependent instead on short-term memory systems and hence removed by the distractor task (Baddeley, 1990).

Figure 6.1 Experimental set-up and behavioural results. (a) Schematic of the experimental design. (b) Sagittal section of the T1 reference brain (Cocosco *et al.*, 1997) demonstrating location of transverse functional image acquisition (yellow) and the position of the slab-selective coronal saturation pulse (blue). (c) Behavioural results. Serial position curve for the 14 subjects. Recall performance was collapsed across sessions within subjects and averaged across subjects (error bars here, and in subsequent figures, denote ± 1 SE).

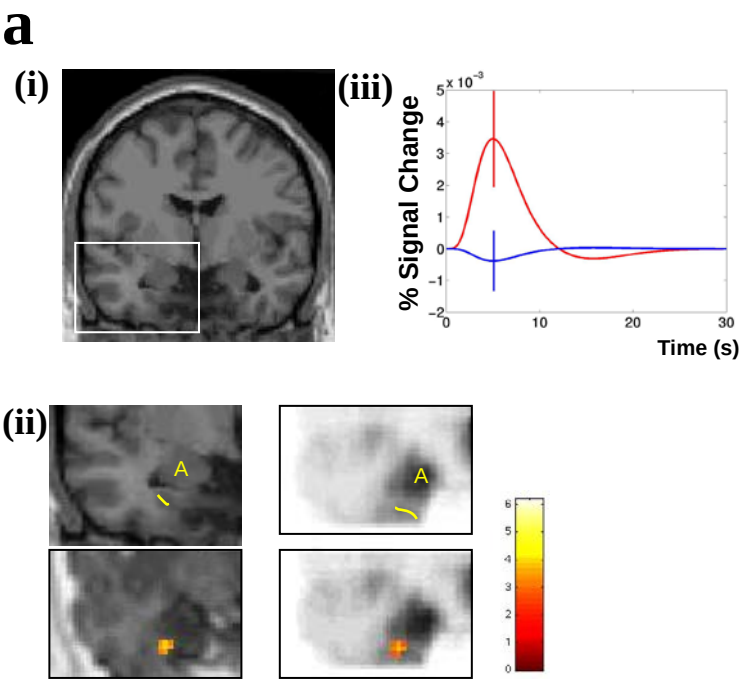


6.32 Functional imaging

The scanning parameters employed provided high spatial resolution T2* images of the medial temporal lobes, enabling different medial temporal structures to be discriminated. The first event-related analysis compared encoding-related activation evoked by subsequently remembered vs forgotten words. This comparison was restricted to the list body (serial positions 3-12) to preclude responses specific to the primacy effect observed in the behavioural data. This subsequent memory analysis demonstrated left anterior medial temporal activation, located in perirhinal cortex (figure 6.2a). Left hippocampal activation, located in the body of left hippocampus and bordering adjacent entorhinal cortex (Amaral, 1999), was also found to be predictive of subsequent memory (figure 6.2b). A weaker subsequent memory effect was also observed in right entorhinal cortex (figure 6.2b).

The covariate analysis demonstrated that mean activation in left perirhinal cortex during word list body encoding correlated with recall performance for that particular word list body (figure 6.3a). Word list body activation in left posterior hippocampus was also found to correlate with total performance. Intriguingly, posterior hippocampal activation was more significant when mean activation during the list body was compared to mean activation during presentation of the initial two words in each list. This comparison collapsed across all word lists and was therefore independent of memory performance (figure 6.3b).

Figure 6.2 Medial temporal encoding-related activation predictive of subsequent memory. (a) Greater activation in left perirhinal cortex (x, y, z co-ordinates -30, -4, -36; Z=3.07; p<0.005) for subsequently remembered vs forgotten words. (i) Coronal section of the reference T1 image (y=-4) with the region displayed in (ii) indicated by the white rectangle. (ii) Top panel: Coronal sections of left temporal lobe of (from left to right) the T1 reference image and the average functional image from the 14 subjects. The yellow line indicates the collateral sulcus. A: amygdala. Bottom panel: The SPM (threshold p<0.01), demonstrating perirhinal activation in the depths of the collateral sulcus, is superimposed on the mean functional image from a single subject and the average functional image from the 14 subjects. The coloured bar indicates the T statistic of the activation. (iii) Fitted responses in left perirhinal cortex showing % signal change for remembered (red) and forgotten (blue) words (± 1 SE). The fitted response, here and in figure 6.4, is the HRF multiplied by its respective session-specific parameter estimate collapsed across sessions within subjects, and averaged across subjects. (b) Hippocampal/entorhinal responses predict subsequent memory. Activation in left hippocampus (-22, -26, -16; Z=3.74; p<0.001), bordering with left entorhinal cortex, was greater for remembered than forgotten words. (i) Coronal section of the reference T1 image (y=-26) with white rectangle depicting the region shown by the two coronal sections in (ii) below. (ii) Coronal sections of left temporal lobe of the T1 reference image (top panel) and the average functional image from the 14 subjects (bottom panel). The outline of the hippocampus (H) is traced in yellow. E: entorhinal cortex; PHG: parahippocampal gyrus. (iii) The SPM (threshold p<0.01) has been superimposed on a coronal section (y=-26) of the mean functional from a single subject (top panel) and the average functional image from the 14 subjects (bottom panel) to illustrate activation in left hippocampus. The coronal sections show that right entorhinal cortex (22, -26, -20; Z=2.78; p<0.005) was also predictive of subsequent memory. (iv) Fitted responses in left hippocampus as for (a).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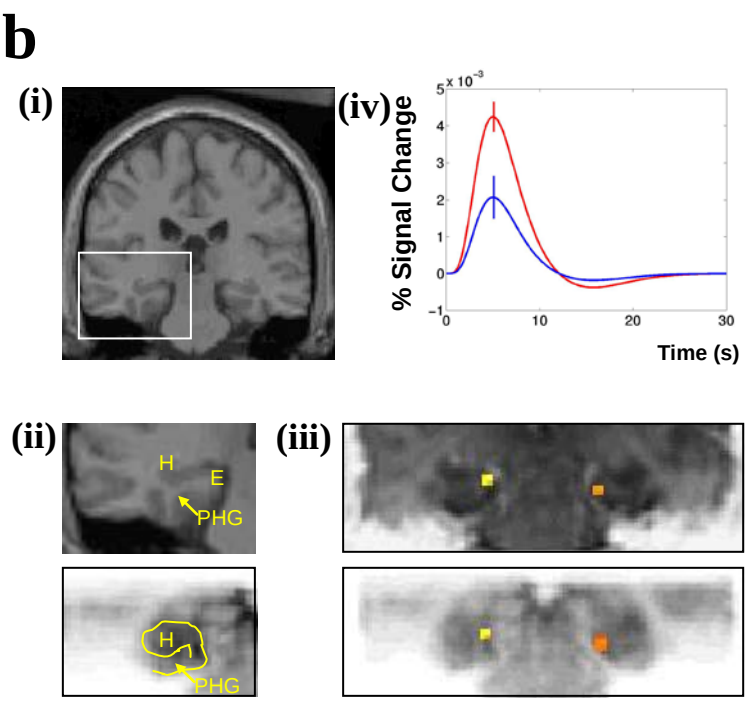
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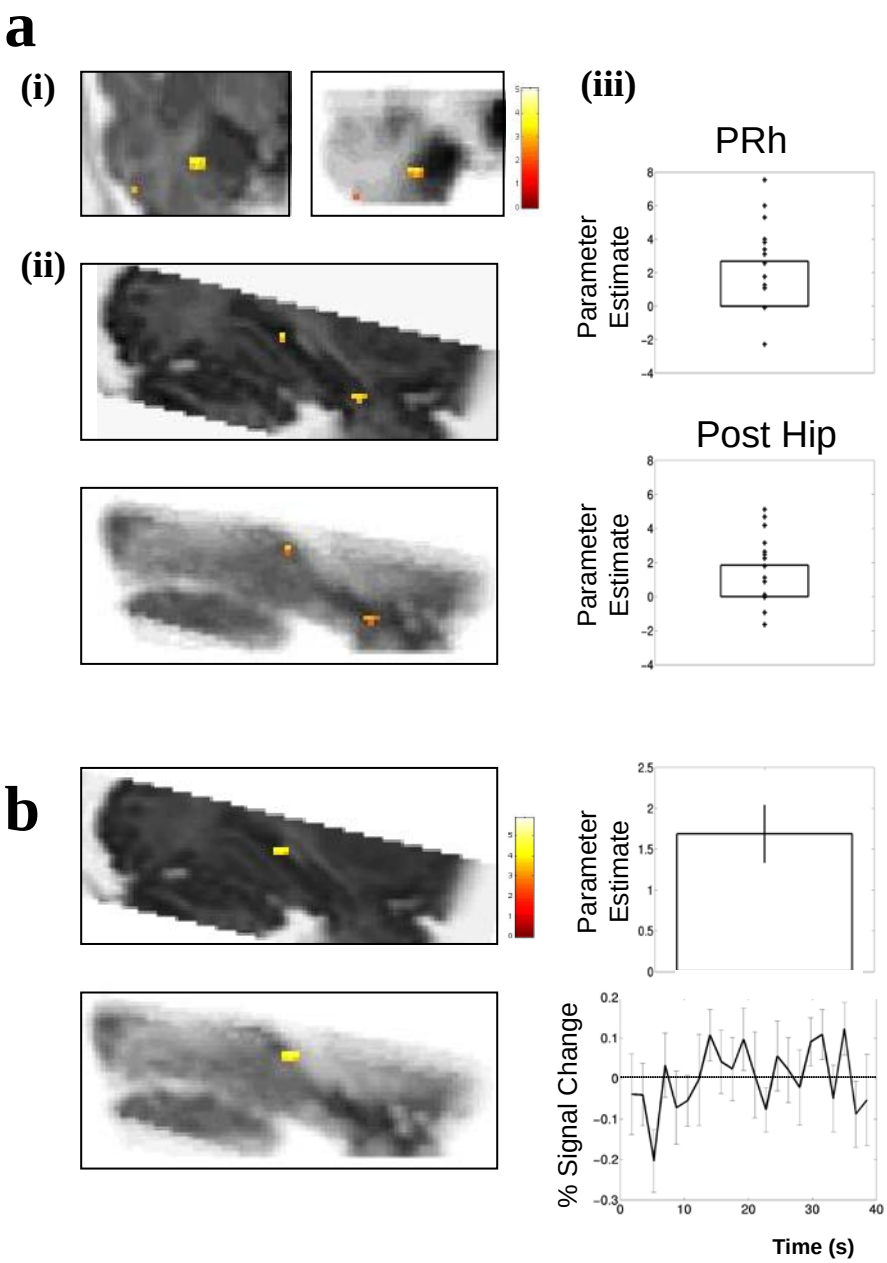
Figure 6.3 Mean encoding-related activation. (a) Mean activation in response to the 3rd to 12th words in each list correlated with mean recall performance in perirhinal cortex (-32, -2, -30; Z=3.07) and posterior hippocampus (-30, -32, -4; Z=2.79). (i) The SPM (threshold p<0.01) demonstrating perirhinal activation in the depths of the collateral sulcus, is superimposed on coronal sections (y=-2) of left temporal lobe of the mean functional image from a single subject and the average functional image from the 14 subjects. (ii) The same SPM, demonstrating perirhinal and posterior hippocampal activation, is superimposed on sagittal sections (x=-30) of the mean functional image from a single subject and the average functional image from the 14 subjects. (iii) Parameter estimates for the correlation in perirhinal cortex (PRh; top) and posterior hippocampus (Post Hip). Each individual subject's correlation is shown. (b) Activation in left posterior hippocampus (-30, -28, -6; Z=3.58) is significantly greater during presentation of the 3rd to 12th words in each list than in response to the first 2 words, irrespective of recall performance. The SPM (p<0.01) is superimposed on a sagittal section (x=-30) to demonstrate posterior hippocampal activation. (iii) Parameter estimate for the mean posterior hippocampal haemodynamic response to body minus primacy words. (iv) The BOLD response in posterior hippocampus collapsed across sessions within subjects, and averaged across subjects (± 1 SE). The primacy words were presented within the first 5-6 seconds.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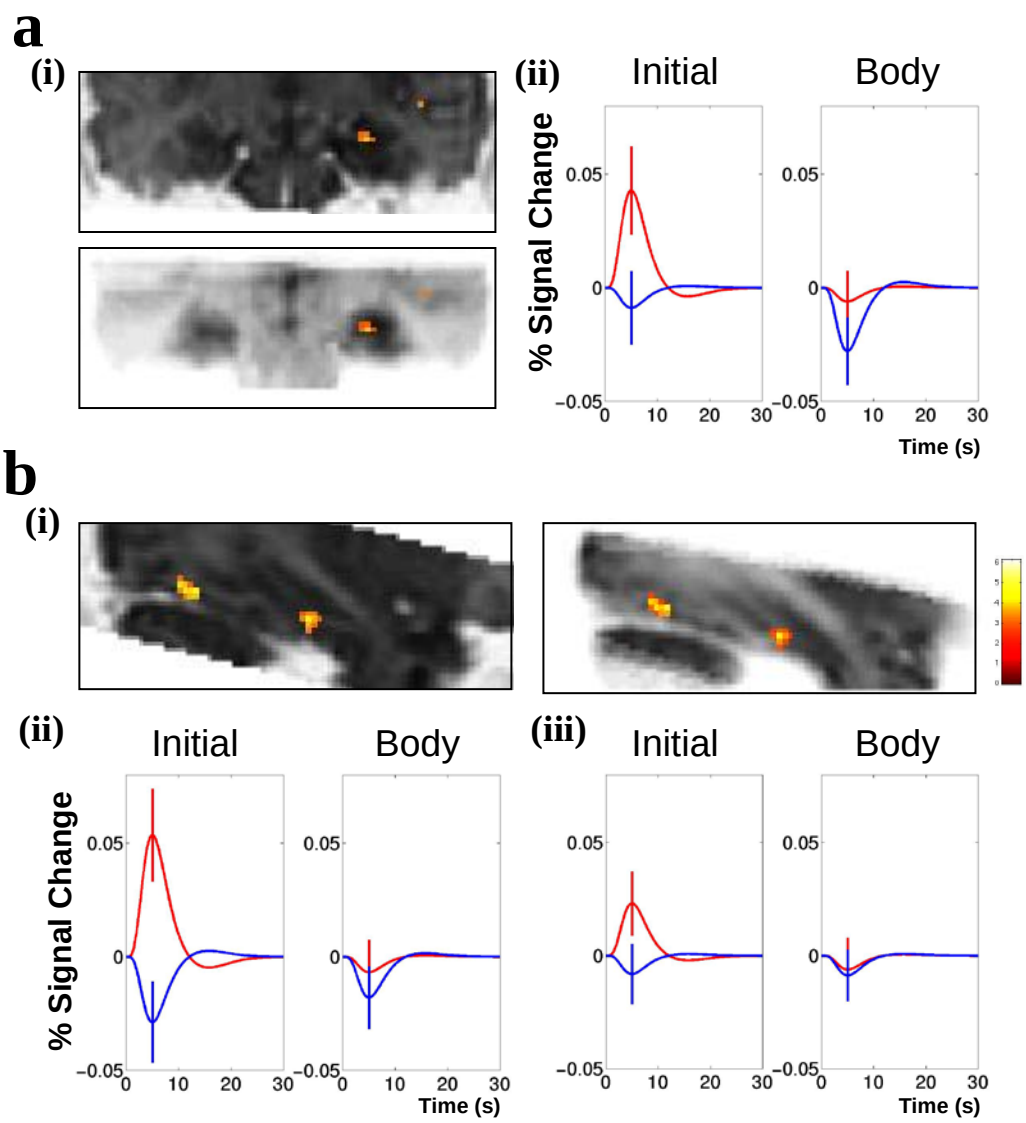
By contrast to the current behavioural data, medial temporal lobe epilepsy patients performing the same task do not demonstrate enhanced memory for initial list items (Fernandez *et al*., 1999). Given that these patients have medial temporal damage, it was hypothesised that the primacy effect may have a discrete neuronal substrate in the medial temporal lobe. Thus, the third analysis tested for an interaction between responses predictive of subsequent memory for the first two presented words in each list vs words presented later in the list body. In this analysis, significant effects were observed in right anterior hippocampus (figure 6.4a) and bilateral parahippocampal gyrus (figure 6.4b) in the medial temporal lobe, as well as in bilateral posterior fusiform cortex (figure 6.4b). The plots in figure 6.4 show that these regions predict subsequent memory only for initial words. Greater responses were observed for remembered vs forgotten initial words, but not for words presented later in each list. No significant activation was observed for the reverse comparison testing for subsequent memory effects greater for the list body than for initial words.

Perirhinal responses, predictive of subsequent memory for words in the list body, did not, therefore, show further enhancement for initial remembered words. A remaining issue was whether perirhinal responses demonstrated any differential response to subsequently remembered vs forgotten words when examining the first two serial position words alone. Recall that in the first analysis, words in these primacy positions were modelled separately (see Materials and Methods). Critically, a test of encoding responses to subsequently remembered vs forgotten initial items alone revealed greater activation in left perirhinal cortex for remembered items (x, y, z coords –24, -6, -34; $Z=2.72$; $p<0.005$). This activation was in the same perirhinal

region (within the spatial resolution of the analysis) as that demonstrating a subsequent memory effect for the list body (-30, -4, -36; Z=3.07; p<0.005; see figure 6.2a). There was, however, no evidence of a subsequent memory effect for these initial words in left hippocampal body, which may reflect less power in this analysis due to fewer events. Thus, perirhinal responses predicted subsequent memory for words in all list positions, whereas right anterior hippocampal, bilateral parahippocampal and fusiform responses predicted subsequent memory for initial words alone.

Figure 6.4 Neuronal correlates of the primacy effect. (a) A significant interaction between subsequent memory and list position (initial vs body) was observed in right anterior hippocampus (28, -16, -22; Z=3.09). (i) The SPM (threshold p<0.01) is superimposed on a coronal section (y=-16) of the mean functional from a single subject (top panel) and the average functional image from the 14 subjects (bottom panel). (ii) Fitted responses in right anterior hippocampus showing % signal change for remembered (red) and forgotten (blue) words in the initial and body positions (± 1 SE). (b) Posterior fusiform and parahippocampal activation predict subsequent memory for initial words only. (i) The SPM (p<0.01) is superimposed on a sagittal section (x=36) of the mean functional from a single subject (left) and the average functional image from the 14 subjects (right) to demonstrate right posterior fusiform (38, -68, -14; Z=3.91) and right parahippocampal (36, -24, -24; Z=3.25) activation. A significant interaction was also observed in left posterior fusiform (-42, -58, -12; Z=3.79) and left parahippocampal gyrus (-32, -26, -22; Z=3.04). Fitted responses in right posterior fusiform (ii) and right parahippocampal gyrus (iii) are plotted below.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6.4 Discussion:

Human *in vivo* electrophysiological recordings (Fernandez *et al*., 1999) in epilepsy patients provide a clear prediction that encoding-related responses in perirhinal cortex should be greater for subsequently remembered vs forgotten words. The imaging data reported here confirm this prediction. For verbal stimuli, encoding-related haemodynamic responses in left perirhinal cortex, measured with fMRI parameters that maximised sensitivity to anterior medial temporal activation, were significantly greater for remembered vs forgotten words.

The precise functional role of human perirhinal cortex in memory is not fully understood. Lesion studies and single-unit recordings in monkey demonstrate a perirhinal role in processing contextual novelty (Brown and Aggleton, 2001) and in associative learning (Sakai and Miyashita, 1991; Erikson and Desimone, 1999). In the current experiment, although all words in each list body were equally contextually novel, particular words may have been subjectively perceived as novel and account for encoding-related perirhinal activation. Alternatively, enhanced perirhinal activation could reflect associative encoding of successive words during rote encoding. A currently controversial issue is the role of perirhinal cortex in recognition memory (Aggleton and Shaw, 1996; Reed and Squire, 1997; Aggleton and Brown, 1999; see chapter 1). These findings, along with those of Fernandez and colleagues, imply that regardless of its role in recognition, perirhinal cortex supports an encoding process contributing to subsequent free recall.

In further agreement with electrophysiological (Fernandez *et al*., 1999) and fMRI (Otten *et al*., 2001) data, hippocampal activation was also found to predict subsequent memory. On the basis of a previous fMRI study of successful memory encoding (Otten *et al*., 2001), it was predicted that encoding would engage left anterior hippocampus. Hippocampal activation was, however, located in left hippocampal body, a region previously implicated in verbal encoding (Kopelman *et al*., 1998) and retrieval (Lepage *et al*., 1998; Schacter and Wagner, 1999). The predominantly left-sided perirhinal and hippocampal activation in this analysis might be expected, given the dominant role of the left medial temporal lobe in verbal memory (Milner, 1972). Fernandez *et al*. (1999) did not, however, find evidence of laterality of perirhinal or hippocampal electrophysiological responses predictive of subsequent memory, which may have resulted from reorganisation of function to contralateral medial temporal lobe structures secondary to unilateral sclerosis.

The covariate analysis provides further support for a human perirhinal role in successful verbal encoding. The locus of perirhinal activation in this analysis lies in close proximity (within the spatial resolution of the analyses) to the activation observed in the event-related analysis testing for subsequent memory effects in the word list body. In addition, the covariate analysis provides support for the role of posterior hippocampus in successful rote encoding proposed by Fernandez *et al*. (1998). In this early study, subjects were presented with 15 words, during which 3 fMRI scans were acquired, and subsequent recall tested after distraction. The average response in posterior hippocampus to every 5 presented words showed significant correlation with recall performance for these 5 words (Fernandez *et al*., 1998). However, the current data demonstrate that a more basic response property of

posterior hippocampus is that responses are greater for the body of the list than for the first two words. Fernandez *et al*. (1998) did not report a test for serial position effects at the behavioural level nor a test for a list position x successful encoding interaction in posterior hippocampus. The results presented here suggest that the posterior hippocampal activation observed by Fernandez *et al*. (1998) would be greater during encoding of the 6^{th} to 15^{th} words than the 1^{st} 5 words.

If posterior hippocampal activation reflects encoding of single-item information, activation would be expected to be at a constant level throughout each encoding list. Because activation was shown to increase during each word list, this implies that posterior hippocampus is mediating a supra-item encoding-related process. In the current paradigm, this supra-item process is likely to be a product of rote encoding strategy. Two potential candidate supra-item processes are the formation of associations between presented words or the rehearsal of previously presented words. If subjects had employed (against instruction) an associative strategy, it is likely that this process would be implemented from the start of each list. Furthermore, associative encoding typically engages anterior, not posterior, hippocampus (see chapter 8). It could also be argued that across the course of a list, the number of items to be associated would increase, reflecting increased demands on associative encoding. However, associating multiple items together requires these items to be held in mind, requiring considerable rehearsal of items. Thus increasing posterior hippocampal activation across each list may reflect increasing rehearsal of presented stimuli. Rehearsal of presented items benefits later recall, which would account for the observation that encoding-related activation in the same left posterior hippocampal region correlates with subsequent recall performance.

The observation of a primacy effect in the behavioural data, in the face of absent primacy in patients with medial temporal damage performing the same task (Fernandez et al., 1999), motivated an analysis of neuronal responses predictive of subsequent memory for initial words in each list. The analysis demonstrated right anterior hippocampal, bilateral parahippocampal and posterior fusiform activation that predicted subsequent memory for the initial two words of each list but not for later presented words. The fact that anterior hippocampal primacy activation was right lateralised may reflect sensitivity to the visual characteristics of situationally novel items. Critically, left perirhinal and hippocampal body activation, predictive of subsequent memory for words in the list body, did not show further enhancement for remembered initial words. Hence, successful encoding of initial words engaged regions additional to those demonstrated for the list body.

The primacy effect has been attributed to greater rehearsal of initial items (Rundus, 1971) or, alternatively, to enhanced encoding of initial items because of their relative distinctiveness (Murdoch, 1960). Neuroimaging studies have demonstrated responses in anterior hippocampus (Tulving et al., 1996; chapters 3, 4 and 5), parahippocampal gyrus (Stern *et al*., 1996; Gabrieli *et al*., 1997) and posterior fusiform cortex (Schacter and Buckner, 1998; chapter 5) to contextually novel or distinctive stimuli. In addition, intracranial recordings demonstrate that focusing attention on words evokes focal field potentials in posterior fusiform cortex (Nobre *et al*., 1998), and that rare target and distractor stimuli evoke parahippocampal and fusiform responses thought to reflect orienting (Halgren *et al*., 1995). The finding that regions where activity predicted subsequent memory for initial words are the

same as those implicated in the processing of novelty/distinctiveness suggests that primacy effects reflect distinctiveness in addition to any benefit from greater rehearsal.

Previous fMRI studies have demonstrated fusiform and parahippocampal encoding responses predictive of subsequent memory (Brewer *et al*., 1998; Wagner *et al*., 1998; Kirchoff *et al*., 2000). These responses were recorded, however, in the context of long stimulus lists, precluding the possibility that these activations were specifically due to primacy. Interestingly, the previous studies of subsequent memory that demonstrate parahippocampal and fusiform activation have included either a long (13 sec) inter-stimulus interval (Brewer *et al*., 1998) or null events, during which a fixation cross is presented instead of a stimulus (Wagner *et al*., 1998; Kirchoff *et al*., 2000). The stimulus following a null event (or long period of rest) could be defined, in principle, as situationally novel, capable of evoking an orienting response. Fusiform and parahippocampal responses mediating successful encoding may consequently reflect attentional orienting, either to situationally distinctive stimuli, as suggested by the current data, or to an item within a long list rendered distinctive by virtue of its low temporal probability. An interesting issue is whether fusiform and parahippocampal responses are maximal, and recognition memory enhanced, for stimuli following null events.

6.41 Summary

The current data support human electrophysiological evidence for perirhinal and hippocampal roles in successful verbal encoding. The previously reported posterior hippocampal role in successful encoding may reflect rehearsal of presented

items, supporting the position developed in this thesis that posterior hippocampus is engaged by familiarity/retrieval. Thirdly, novelty-sensitive neuroanatomical regions predict subsequent memory for the initial items in a list, suggesting that the primacy effect reflects enhanced encoding of positionally distinctive items. Finally, employing the current scanning parameters during studies that manipulate relative familiarity will enable human perirhinal novelty responses to be investigated without the limitation of decreased sensitivity to haemodynamic responses in anterior medial temporal lobe.