Chapter 3

Functional Segregation within Human Hippocampus for Relative Familiarity

3.1 Introduction:

This chapter describes a study of novelty-related responses in the hippocampus. As discussed in chapter 1, the precise functional role of the hippocampus in episodic memory is unclear. Previous functional neuroimaging studies have demonstrated hippocampal sensitivity to recency of prior occurrence (e.g. Stern *et al*., 1996; Tulving *et al*., 1996; Dolan and Fletcher, 1997). Thus, one suggested role is that the human hippocampus indexes novelty. In these studies, subjects were familiarised with verbal (Dolan and Fletcher, 1997) or non-verbal (Stern *et al*., 1996; Tulving *et al*., 1996) stimuli and then, during scanning, responses to these familiar stimuli were compared with responses evoked by novel stimuli. Responses to familiar stimuli were shown to be lesser in magnitude than those to novel stimuli. A criticism of this experimental approach is that it does not address the dynamic aspect of novelty responses. Comparing responses to novel stimuli with responses to stimuli familiarised before scanning does not enable characterisation of the temporal evolution of hippocampal novelty responses. The experiment described in this chapter addressed this limitation by measuring haemodynamic responses to repeated presentations of novel stimuli and specifically testing for adaptation on subsequent presentations.

Novelty responses to verbal stimuli may be influenced by the fact that words have been previously encountered by subjects outside of the experimental setting, with recency and salience of that encounter varying across subjects. The responses evoked by ‘novel’ words, compared to ‘familiar’ words that subjects have previously been exposed to in the experimental context, are described as contextual (Dolan and

Fletcher, 1997; Kirchoff *et al*., 2000) or situational (Grunwald *et al*., 1997) novelty responses. In the current study, to minimise influences of previous encounters with stimuli outside of the experimental context, a finite state artificial grammar system (Reber, 1967) was used to generate novel letter strings. This approach speaks to the notion, described in chapter 1, that few items or places are completely novel, but novelty typically arises from new configurations of familiar elements (i.e. letters).

Critically, by introducing novelty in the context of an item-learning paradigm derived from an artificial grammar system, it was possible to disambiguate novelty responses that did and did not have behavioural relevance. In studies that have addressed the effect of novel stimuli on encoding-related activations (e.g. Haxby *et al*., 1996; Stern *et al*., 1996; Dolan and Fletcher, 1997), subjects were simply instructed to attend to and memorise presented stimuli. These studies cannot dissociate automatic novelty-evoked haemodynamic responses incidental to task demands from activations reflecting an interaction between novelty and the intentional encoding of individual items. In contrast, neuronal responses to relative familiarity during a recognition memory task (i.e. when subjects must make an old/new comparison; Tulving *et al*., 1996) are confounded by possible interactions between familiarity and differential response requirements. The processes engaged in making old/new judgements, particularly during retrieval from episodic memory, may confound an automatic novelty or familiarity response. In the current experiment, the nature of hippocampal novelty responses was explored by examining responses to two types of novelty: perceptual (non-behaviourally relevant) and exemplar (behaviourally relevant). Specifically, perceptual novelty pertains to the physical characteristics of stimuli (in this case visual characteristics), and exemplar

novelty reflects the semantic characteristics of stimuli (in this case grammatical status within a rule system). The task requirements were such that performance would improve if novel exemplars were encoded into episodic memory whereas perceptual novelty did not influence task demands.

Within the context of an fMRI experiment, exemplar and perceptual novelty were periodically introduced while subjects performed an item learning paradigm derived from an artificial grammar system. An artificial grammar system embodies a set of arbitrary rules governing the concatenation of symbols. In standard applications, subjects exposed to exemplars of such a grammar system learn to categorise, as "grammatical" (that is, conforming to the hidden rules) or "ungrammatical", subsequently presented symbol strings with an accuracy greater than chance (Reber, 1967; Shanks, 1995). It is widely assumed that this type of learning reflects the application of an implicit learning system, although this is itself controversial (Shanks and St John, 1994). For a review of the distinction between explicit and implicit learning and their relative contribution to artificial grammar learning, see Shanks and St John (1994). In this experiment the emphasis was on explicit learning, and consequently, a modified approach was implemented in which subjects were required to learn the grammatical status of consonant strings (the exemplars of the grammar system) that were presented repeatedly, with trial-by-trial feedback. Note that in standard applications, no feedback is provided. In brief, each consonant string was presented eight times, with each presentation requiring a grammaticality judgement for which explicit feedback was provided immediately. Thus, knowledge of the result of previous grammaticality judgements for a particular consonant string was used to enhance performance over subsequent presentations.

Exemplar novelty was introduced by periodically presenting novel consonant strings. Perceptual novelty was introduced by periodically changing the font in which exemplars were presented (see figure 3.1). Thus a given set of exemplars was presented eight times and the font changed after every three presentations of an exemplar set. Critically, the manipulations of exemplar and perceptual novelty were orthogonal (i.e. uncorrelated) thus enabling separable characterisation of hippocampal responses associated with each type of novelty. Note that the term hippocampus is used here, and all other experiments, to refer to the dentate gyrus, CA subfields and subiculum.

3.2 Materials and methods:

3.21 Subjects

Informed consent was obtained from 14 right-handed, subjects (8 male, 6 female; age range 18 - 27 yrs; mean age 21.7). For this and all other experiments in this thesis, ethics approval was obtained from the National Hospital for Neurology and Neurosurgery Joints Ethics Committee.

3.22 Psychological task

The finite state grammar system in figure 3.1a was used to generate exemplar consonant strings under the constraint that all strings consisted of 4 letters. A total of 30 strings (e.g. JMQH), mixed with 30 arbitrarily chosen non-grammatical lures (e.g. JQMH), were presented, one every 3.2 s, over the course of the experiment. The

strings were presented serially to subjects in sets of 10 (5 grammatical; 5 ungrammatical) and presentation of this exemplar set constituted an activation epoch. Subjects were required to make an immediate judgement of each item's grammatical status by pressing the appropriate button. Visual feedback was given for each response. In the initial stages of the experiment subjects had no knowledge of the underlying rules of the grammar and responded by guessing. Each set of exemplar strings was presented eight times and was followed by a sensorimotor control epoch. The control epoch consisted of serial visual presentations of either PPPP or NNNN (5 of each), which also required one of two predetermined button presses. Across the eight presentations of an exemplar set subjects learned the status of individual items. After a particular set of exemplars was presented eight times, a novel set of 10 exemplar strings was presented, allowing the introduction of exemplar novelty (figure 3.1b). The eight presentations of an exemplar set constituted a block of the experiment hence the experiment consisted of 6 blocks defined by the onset of an exemplar change. The font in which exemplars were presented was changed every three exemplar set presentations (the fonts used were: arial narrow, bodoni MT, book antiqua, bookman oldstyle, century gothic, century schoolbook, chicago, courier, geneva, helvetica, monaco, monotype corsiva, new york, palatino, times, times italics).

3.23 Data acquisition

For each subject, data were acquired in two scanning sessions separated by a 5 min rest period. A total of 480 volumes were acquired per subject plus 6 ‘dummy’ volumes, subsequently discarded, to allow for T1 equilibration effects. Volumes were acquired continuously every 6400 ms. Each volume comprised sixty-four 3mm

axial slices, with an in-plane resolution of 3x3mm, positioned to cover the whole brain. The imaging time series was realigned to correct for interscan movements, co-registered with the subjects' structural T1 image (to enable overlay of functional data onto the subjects' structural data), and normalised into a space defined by the atlas of Talairach and Tournoux to allow group analysis. The data were then smoothed with a Gaussian kernel of 8 mm full width half maximum to account for residual intersubject differences (Friston *et al*., 1995a). For each subject, low frequency cosine functions were employed to model and remove low frequency drift in signal. The data were normalised for global effects by proportional scaling. It should be noted that for the analysis of hippocampal topography (figure 3.4) the data were smoothed with a Gaussian kernel of 6 mm full width half maximum to minimise correlations among selected regional responses that were nearby.

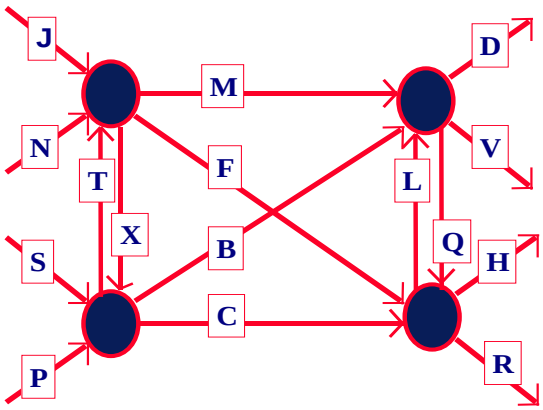
3.24 Data analysis

Data were analysed using Statistical Parametric Mapping (SPM97) employing a random effects analysis. Five scans were acquired during each activation and sensorimotor control epoch and entered into a general linear model to create one contrast image per epoch. For exemplar novelty, the six blocks of eight activation and control scans were collapsed further into one time series of the alternating 8 activation and 8 control conditions following exemplar change. The activations in these derived time series were modelled by using either a linear, or exponential, time by condition interaction (novelty-dependent activation). The ensuing contrasts for each subject were entered into a one-sample t-test across the 14 subjects. The analysis for effects of perceptual novelty was identical except that the final level contrasts consisted of the 3 activation and 3 control epochs following font

change. A small volume correction (S.V.C.; Worsley *et al*., 1996) was applied to the p values of the ensuing maxima on all reported hippocampal regions (see chapter 2, part II). Only those hippocampal regions that survive this S.V.C. at $p<0.05$ are reported, except for the left anterior hippocampal activation in response to exemplar novelty which was significant at trend, with S.V.C. yielding a p value of 0.067 ($p<0.005$ uncorrected).

Figure 3.1.The introduction of perceptual and exemplar novelty in the context of item learning. (a) The artificial grammar system. Grammatical four-consonant letter strings are formed by starting on the left and moving right in the direction of the arrows. (b) Experimental design. Every exemplar set presentation constitutes an activation epoch (red rectangle), each of which is followed by a control epoch (white rectangle). Every exemplar set is presented eight times after which a new set of exemplars is presented, allowing the introduction of exemplar novelty (upward arrows). Every three activation epochs the font in which exemplar strings were presented was changed, enabling the introduction of perceptual novelty (downward arrows). (c) Behavioural data averaged across all subjects expressed as a percentage of correct grammaticality judgements (error bars here, and in all subsequent plots, depict ± 1 SE). The data show improving grammaticality judgements as subjects become increasingly familiar with each set of exemplars. When a new exemplar set is presented performance falls, but across the entire experiment subjects gradually acquire more abstract knowledge about the grammar system and use this knowledge to maintain performance following change in exemplar set.

a



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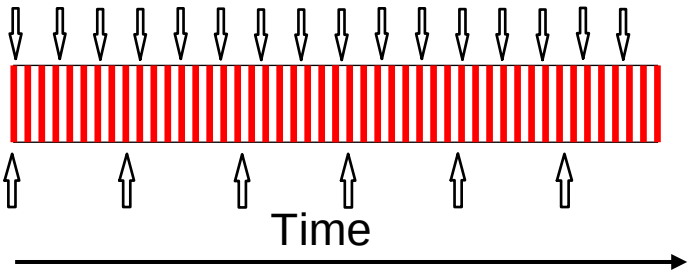

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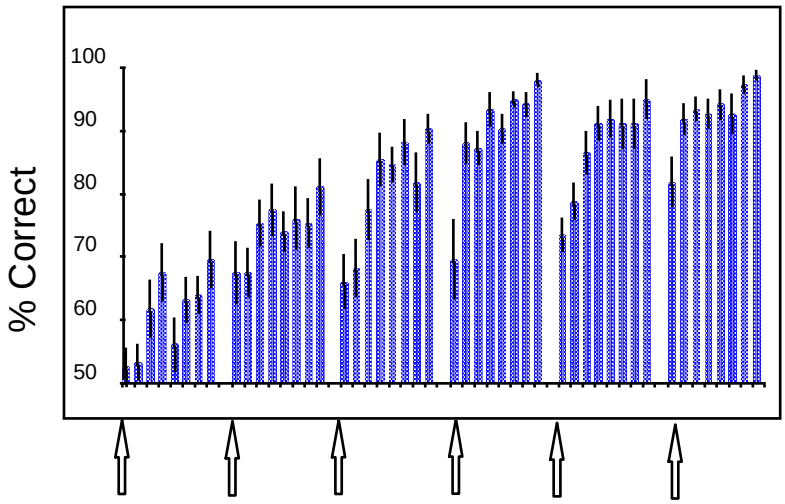


3.3 Results:

The specific effect tested was a condition (exemplar or perceptual change) x time interaction, where time refers to time elapsed following a change in either exemplar or font (i.e. the adaptation of haemodynamic responses following exemplar or perceptual changes). Figure 3.2 shows the hippocampal response to perceptual novelty and its modulation with time. A greater left anterior hippocampal response is seen for initial, relative to repeated, presentations of perceptually novel items, reflected in a significant linear time x condition interaction. This response shows adaptation with increasing font familiarity. Modelling exponential adaptation also yielded interactions, of lesser significance, in the same region.

The response of the hippocampus to exemplar novelty is shown in figure 3.3b, and was again assessed as a condition x time interaction. Initial presentation of novel exemplars was associated with activation in left anterior hippocampus, 10 mm superior to the region indexed by perceptual novelty. With repeated exemplar presentations, activation in this region again showed significant adaptation. This pattern of response in the hippocampus was best modelled as an exponential decline. Thus, a significant time x condition interaction was reflected in reducing activation, relative to the recurring baseline, in anterior hippocampus.

Strikingly, a reverse effect, reflecting increasing familiarity with exemplars, was seen in augmented bilateral posterior hippocampal activation (figure 3.3c). Hence, familiarity with the meaningful characteristics of stimuli (i.e. grammatical status within a rule system) augmented posterior hippocampal responses bilaterally.

Increasing font familiarity, which has no behavioural relevance, did not engage the posterior hippocampus. Thus, in bilateral posterior hippocampus a time x condition interaction was observed for, and only for, repeated exemplar presentations.

The plots presented in figures 3.3b and c show the BOLD response collapsed across the 6 exemplar changes and averaged across all subjects. Note that any variance due to abstraction of grammar system knowledge (perhaps reflecting implicit learning) will be expressed across the entire experiment. Any such effect in the present analysis can be discounted as the analysis involved collapsing data across the six blocks defined by the onset of exemplar change. Consequently, the emphasis is on explicit learning, driven by trial-by-trial feedback (subjects respond to repetition items on the basis of whether previous responses in the grammatical decision task were correct or incorrect). An interaction between hippocampal activation and abstraction of grammar system knowledge was, however, tested for. The effects of abstraction on the observed hippocampal activations would be expected to be stronger at the beginning of the experiment whereas effects of grammar knowledge application would be greater at the end of the experiment. Hence novelty- and familiarity-induced activations in the first half of the experiment were compared with the second half. No interaction was detected in the hippocampus in either the novelty or familiarity comparisons.

Figure 3.2. Hippocampal region in which there is a significant time by condition interaction in response to perceptual novelty reflecting adaptation with familiarity. (i) Coronal section of a T1 weighted anatomical image (at y = -16) that conforms to the stereotaxic space. The image is taken from one of the 14 subjects. Superimposed on this section is a SPM (thresholded at p<0.01) indicating a left hippocampal decreasing linear time by condition interaction following introduction of a novel font. The section has been chosen to demonstrate left anterior hippocampal activation (x,y,z coordinates -22, -16, -24; Z = 3.25). (ii) Graphic representation of activation at this voxel relative to the baseline condition as a function of repeated presentation of fonts. The plotted time course shows the Blood-Oxygen Level Dependent (BOLD) response collapsed across the 16 font changes and averaged across all subjects. The downward arrow indicates the introduction of a novel font.

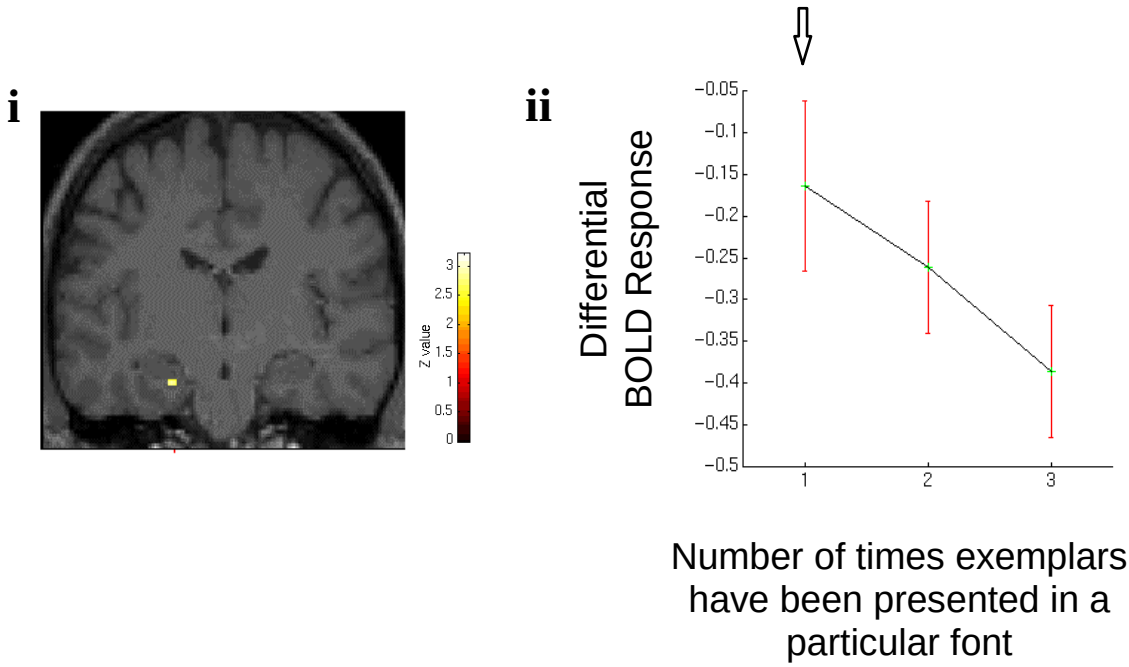
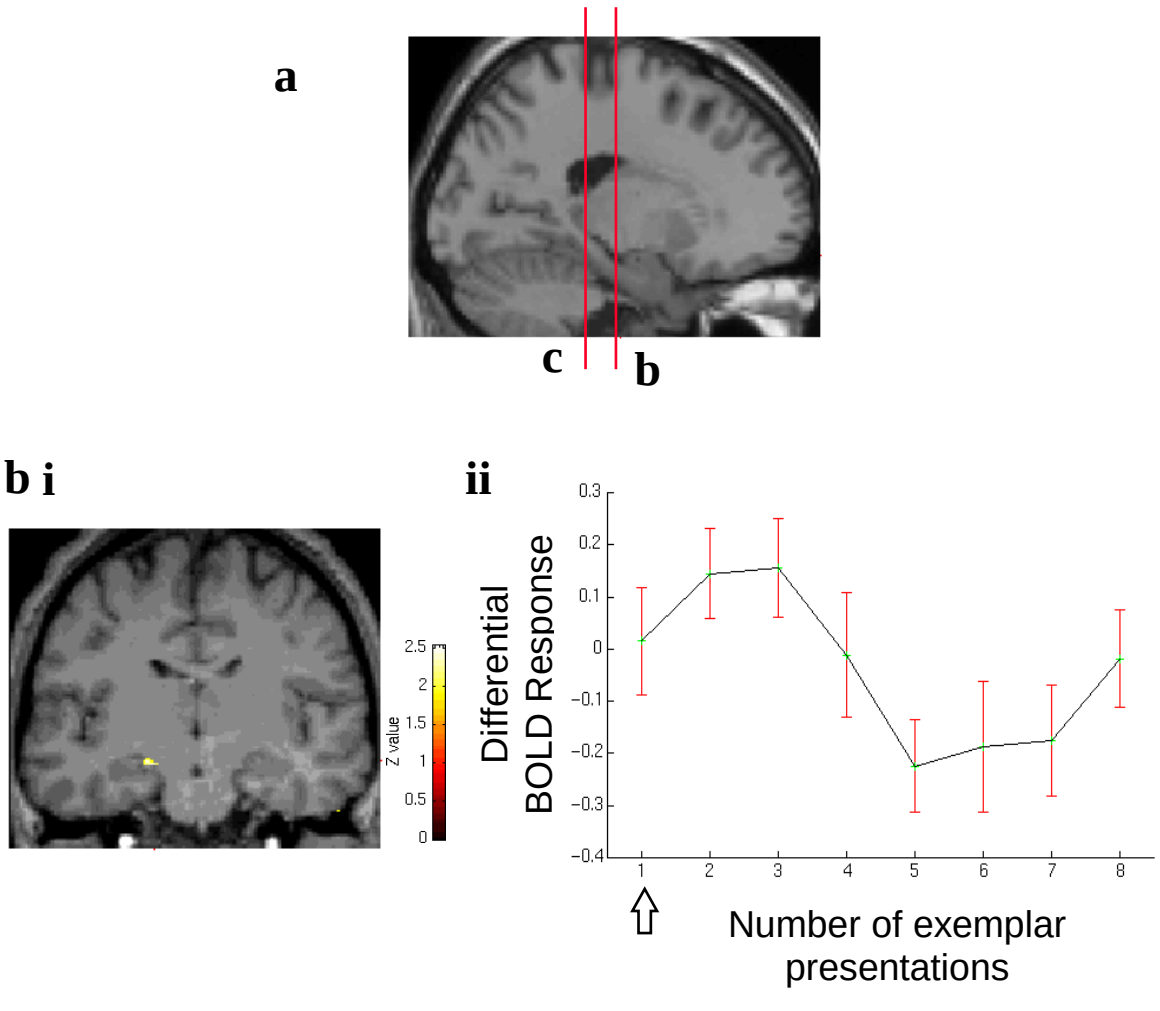


Figure 3.3. Dissociation in the anterior-posterior hippocampal axis for exemplar novelty.

(a) T1-weighted anatomical sagittal image with red lines indicating the anterior-posterior positions of the coronal sections demonstrated in (b) and (c). (b) (i) SPM showing enhanced left anterior hippocampal activation after the introduction of exemplar novelty followed by adaptation (threshold $p<0.05$). The coronal section has been chosen to demonstrate left anterior hippocampal activation (coordinates -18, -16, -14; Z =2.60). (ii) Graphic representation of activation at this voxel, relative to the baseline condition, against number of presentations of an exemplar set. The plot shows the BOLD response collapsed across the 6 exemplar changes and averaged across all subjects. The upward arrow indicates the introduction of a novel exemplar set. (c) (i) SPM (threshold $p<0.01$) showing that increasing familiarity with exemplars activates the posterior hippocampus bilaterally. The coronal section has been chosen to demonstrate right posterior hippocampal activation (coordinates 24, -34, -2; Z =3.63) and also shows left posterior hippocampal activation (coordinates -22, -38, -6; Z =3.67). (ii) Graphic representation of activation of the right posterior hippocampal voxel relative to the baseline condition as for (b ii).


a
c
b
b i
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Z value
Differential BOLD Response
Number of exemplar presentations
c i
ii
Z value
Differential BOLD Response
Number of exemplar presentations

3.4 Discussion:

3.41 Functional segregation

These data indicate a functional dissociation between anterior and posterior regions of the human hippocampus within the same experiment. The fact that both exemplar and perceptual novelty activated left anterior hippocampus suggests that this region processes novelty that is both behaviourally relevant (exemplar novelty) and irrelevant (perceptual novelty). Conversely, posterior hippocampal regions showed a familiarity effect that was expressed only for aspects of stimuli relevant to learning (i.e. grammatical status). These data therefore suggest that a function of the anterior hippocampus is to register mismatches between expectation and experience. Furthermore, if this novelty has behavioural significance (here a requirement to learn exemplar status) familiarity with these novel items engages posterior hippocampal regions.

At the time of conducting this experiment, PET studies had demonstrated anterior hippocampal responses to novelty (Tulving *et al*., 1996; Haxby *et al*., 1996; Dolan and Fletcher, 1997; Martin *et al*., 1997). However, fMRI studies of novelty had reported primarily parahippocampal responses (Stern *et al*., 1996; Gabrieli *et al*., 1997), an observation which may have reflected the fact that fMRI signal-to-noise is higher in posterior than anterior medial temporal lobe (Schacter and Wagner, 1999). The current experiment (reported in Strange *et al*., 1999) was, therefore, the first to demonstrate novelty-dependent anterior hippocampal activation. Subsequent fMRI studies have also reported anterior hippocampal responses to novel vs familiar stimuli (Saykin *et al*., 1999; Constable *et al*., 2000). To date, the majority of

functional imaging studies of medial temporal responses to novelty demonstrate activation of anterior hippocampus (Tulving *et al*., 1996; Haxby *et al*., 1996; Dolan and Fletcher, 1997; Martin *et al*., 1997; Saykin *et al*., 1999; Constable *et al*., 2000; Fischer *et al*., 2000). Although some studies report posterior hippocampal responses to novelty (Stern *et al*., 1996; Rombouts *et al*., 1997), the majority of novelty-evoked activations in posterior medial temporal lobe are located in parahippocampal gyrus (see Schacter and Wagner, 1999 for review).

The sensitivity of the anterior hippocampus to novelty is further supported by event-related potentials recorded within the medial temporal lobes in epileptic patients (Grunwald *et al*., 1998). Damage to the hippocampus proper (patients with sclerosis) is associated with attenuated anterior medial temporal lobe event-related potentials for novel visually presented words with responses to repetitive presentations unaffected. Interestingly, in addition to the anterior medial temporal response to new words, word repetitions have been found to evoke a different potential (Smith *et al*., 1986), which may have a more posterior distribution along the longitudinal hippocampal axis than the anterior potential evoked by new words (Grunwald *et al*., 1998). Evidence from animal studies also supports functional segregation within the hippocampus for novel and familiar arrangements of letter strings. Wan *et al*. (1999) demonstrated that neurones in area CA1 of the rat hippocampus are sensitive to novel arrangements of stimuli, whereas neurones in the dentate gyrus and subiculum are sensitive to familiar arrangements. Functional imaging is not yet capable of reliably discriminating hippocampal subfields, but an interesting question is whether cellular recordings in rodents and primates will reveal similar dissociations along the hippocampal anterior-posterior axis.

The fact that hippocampal activation was left-sided can be expected given the putative role of the left hippocampus in verbal memory (Milner, 1972). The presentation of novel versus repeated words has been shown to activate the left hippocampus (Kopelman *et al*., 1998) whereas viewing novel versus familiar pictures of people, scenes and landscapes has been reported to activate right anterior hippocampus (Tulving *et al*., 1996). The lack of a right anterior hippocampal response to either exemplar or perceptual novelty may therefore reflect stimulus form, as suggested by a recent functional neuroimaging study (Martin *et al*., 1996) where the right hippocampus was more responsive to objects than words during encoding. The latter study (Martin *et al*., 1997) also observed left hippocampal activation during encoding of meaningful (as opposed to nonsense) stimuli. The current findings suggest that left anterior hippocampus is engaged by both behaviourally relevant, meaningful and non-meaningful novelty, whereas more posterior hippocampal regions are selectively engaged by highly familiar, meaningful stimuli. The proposed left hippocampal role in processing unexpectedness of stimuli (Schacter *et al*., 1995) would appear to be a function of the anterior portion of hippocampus.

A novelty / encoding hypothesis developed by Tulving states that novelty assessment plays a crucial role in determining whether information is encoded into long-term memory (Tulving and Kroll, 1995; see chapter 1). Interestingly, the regions of left anterior hippocampus activated in the present experiment lie in close proximity to an area previously shown, using positron emission tomography (PET), to be engaged during encoding of novel category-exemplar word pairings (Dolan and

Fletcher, 1997). Furthermore, intracranial potential studies have demonstrated that the left anterior medial temporal lobe response to the first presentation of words correlates with subsequent recognition (Grunwald *et al*., 1998) and delayed verbal recall (Elger *et al*., 1997) of these words. Although the present paradigm does not explicitly dissociate novelty assessment from episodic memory encoding, deliberately encoding novel exemplars into episodic memory would enhance performance whereas encoding font changes would not affect performance. Hence, the data are compatible with a view that the hippocampal response to novel exemplars is an important component in efficient episodic memory formation. The fact that anterior hippocampus is activated by perceptual novelty, which does not require deliberate engagement of episodic encoding, suggests that the anterior hippocampal response to novelty is automatic and independent of task demands.

By contrast, activation in bilateral posterior hippocampal regions, as exemplars become more familiar, may reflect more active processes involved in memory retrieval. Note that increasing familiarity with exemplars allows subjects to make grammaticality judgements on the basis of previous experience, suggesting that subjects engage episodic retrieval mechanisms as exemplars become more familiar [as indicated by exemplar theories of categorisation (Shanks, 1995)]. This suggestion is also in agreement with previous studies (Schacter *et al*., 1996; Heckers *et al*., 1998) where cued recall of words, previously repeatedly presented, activated posterior hippocampus.

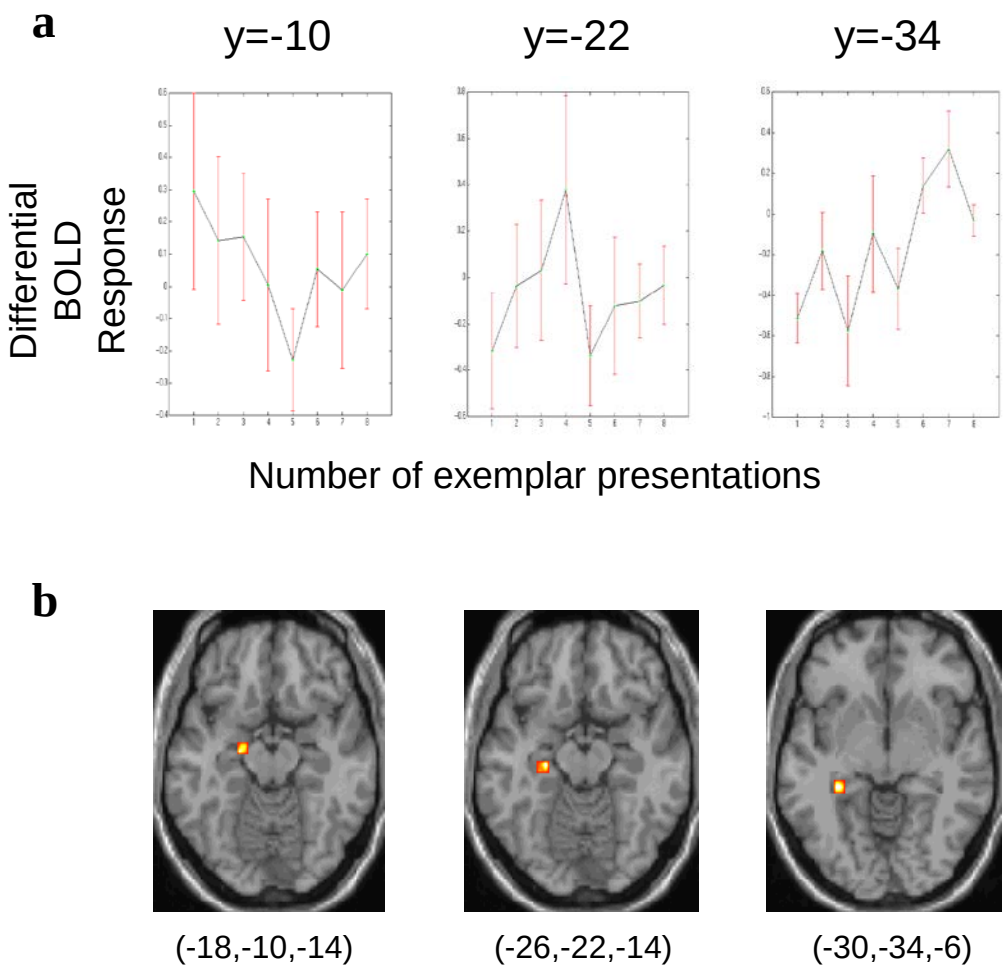
A recent meta-analysis of PET studies of episodic memory (Lepage *et al*., 1998) indicated that hippocampal activations associated with encoding are located

primarily in rostral (anterior) hippocampus whereas activations associated with retrieval were located in caudal (posterior) hippocampus. Although the current study design addresses novelty, its findings are relevant: if exemplar novelty and familiarity in the present paradigm are considered to involve an emphasis on encoding and retrieval respectively, then the data provide support for this functional divide within the hippocampus. However, it should be noted that a recent review of fMRI data (Schacter and Wagner, 1999) concluded that the posterior medial temporal lobe is associated with episodic encoding and suggested that PET studies demonstrate both anterior and posterior medial temporal activations during encoding. However, the majority of encoding-related fMRI posterior medial temporal lobe (MTL) activations were located in parahippocampal gyrus (Stern *et al*., 1996; Gabrieli *et al*., 1997; Aguirre *et al*., 1996; Schacter *et al*., 1997; Rombouts *et al*., 1997; Fernandez *et al*., 1998; Brewer *et al*., 1998; Wagner *et al*., 1998) whereas fewer encoding-related fMRI activations were found in the posterior hippocampus (Stern *et al*., 1996; Rombouts *et al*., 1997 - but only in 7 of 12 subject; Fernandez *et al*., 1998; Kelley *et al*., 1998). In contrast, the majority of anterior MTL encoding-related activations included in the Lepage *et al*. (1998) PET meta-analysis are focused within the hippocampus. It may, therefore, be the case that encoding engages both the anterior hippocampus and the parahippocampal cortex.

The observed anterior-posterior hippocampal functional divide suggests a functional topography related to familiarity. A post-hoc analysis of these data demonstrated that, with increasing familiarity for meaningful stimuli, there was a topographical spread of hippocampal activity in an anterior-posterior axis (figure 3.4). Although descriptive, this observation suggests that well-rehearsed memory

representations are associated with activity in more posterior hippocampal regions. This observation provides system level support for a theory of hippocampal function, the 'multiple-trace theory' (Nadel and Moscovitch, 1997) which states that re-activation and rehearsal of memories causes the formation of multiple memory traces within the hippocampus. A 'trace' could be described as a hippocampal neuronal assembly that binds together information processed in dispersed neocortical areas. The results of this experiment suggest these memory traces may actually be organised in a topographical manner related to the degree of familiarity with the processed material.

Figure 3.4. Topography of hippocampal activation as a function of relative familiarity. Activation in the left hippocampus spreads posteriorly as meaningful items (exemplars) become increasingly familiar. Three voxels within the left hippocampus, each separated by 12 mm along the transverse plane, were identified by an SPM constructed to detect any change in activation relative to baseline across the 14 subjects. (a) The BOLD response of the principal component within a 4mm radius of each chosen voxel is plotted relative to baseline. (b) The co-ordinate of each chosen voxel is shown below each plot along with the region from which the principal component was selected (superimposed on a transverse section of the T1 weighted anatomical image). Note that the left anterior hippocampal activation displayed in figure 3.3b peaks at the second/third presentation of the exemplar set. This activation is situated at y=-16 which, in the anterior-posterior axis, is midway between the first and second chosen voxels displayed in the current figure.



3.42 Temporal dynamics of hippocampal responses

The profile of anterior hippocampal adaptation conforms to a pattern observed using direct recordings from novelty-sensitive single hippocampal neurones (Rolls *et al*., 1993; Fried *et al*., 1997), although the time scale in our study is greater. In left anterior hippocampus, clear response adaptation relative to first presentation does not occur until the third (perceptual novelty; figure 3.2) or fifth (exemplar novelty; figure 3.3b) presentations. In single unit recordings, adaptation is evident in the response to the second presentation of a given stimulus (Rolls *et al*., 1993; Fried

et al., 1997). Slower adaptation of cellular responses has, however, been observed in rabbit hippocampus by Vinogradova (1975; see chapter 1). The slow modulation of the hippocampal haemodynamic response is important for interpreting other functional imaging studies that manipulate relative familiarity. For example, encoding-related hippocampal activation to novel word pairs has been observed relative to word pairs that had been presented twice previously (Dolan and Fletcher, 1997). Hippocampal novelty responses to single presentations of different scenes were observed relative to responses to one repeatedly presented scene (Stern *et al*., 1996). Furthermore, functional imaging studies of recognition memory typically only expose subjects to study items once during study. During subsequent recognition, these studies have largely failed to show hippocampal activation for the new minus old (novelty) comparison (see Rugg and Henson, 2001 for review). However, if study items are presented twice, the anterior hippocampal response to new stimuli presented at recognition is greater than that to previously presented, old items (Tulving *et al*., 1996). It appears, therefore, that the temporal profile of hippocampal response adaptation is such that subjects must be exposed to stimuli more than once in order to observe a significant difference in hippocampal responses to new versus old items.

Conversely, clear differences in exemplar familiarity-evoked enhanced responses in posterior hippocampus are apparent if first and sixth presentations are compared (figure 3.3c). Functional imaging studies of recognition have reported posterior hippocampal responses to old versus new items following two presentations of stimuli at study (e.g. Schacter *et al*., 1995) but also following single presentations of stimuli (e.g. Schacter *et al*., 1997). Haemodynamic response enhancement for

familiar stimuli can therefore occur with the second presentation of a stimulus. It is unclear, however, from these studies whether the enhanced posterior hippocampal response to familiar stimuli reflects familiarity or a deliberate engagement of episodic retrieval. Interestingly, retrieval-related posterior hippocampal activation is observed following repeated stimulus presentation at study. Schacter *et al*. (1996) and Heckers *et al*. (1998) demonstrated posterior hippocampal activation during retrieval of words that had been presented four times previously versus retrieval of words that had been presented once. It should be noted, however, that difference in posterior hippocampal activation at retrieval in these studies might not only have been due to differences in the relative familiarity of retrieved items. Subjects engaged in a deep encoding task (semantic judgements) during presentation of repeated words whereas the words that were presented once were studied using a shallow task (perceptual judgements). This manipulation of depth of processing (Craik and Lockhart, 1972) confounds the interpretation that retrieval-related posterior hippocampal responses were a function of the familiarity of the stimuli being retrieved.

Single cell recordings in the monkey demonstrate firing patterns specific to familiar stimuli (Brown and Xiang, 1998). These neurones, located primarily in perirhinal cortex, show significant changes in response 4-8 mins after stimulus presentation (Xiang and Brown, 1998), hence exhibit similar temporal dynamics to the increasing haemodynamic responses observed in posterior hippocampus with exemplar familiarity (each activation epoch lasted approximately 8 min). However, perirhinal familiarity neurones index familiarity by decreasing their response rate (Xiang and Brown, 1998) whereas the posterior hippocampal haemodynamic

response increases with familiarity. These opposing cellular response profiles do not however, rule out the possibility of an interaction between the two regions in signalling familiarity.

3.43 Summary

The results of the present study demonstrated a left anterior hippocampal response to both types of novelty and adaptation of these responses with stimulus familiarity. By contrast to these novelty effects, bilateral posterior hippocampal responses increased with increasing exemplar familiarity. These observations suggest a functional dissociation within the hippocampus with respect to the relative familiarity of study items. Neuronal responses in anterior hippocampus index mismatch between expectation and experience while posterior hippocampal responses index familiarity to stimuli that have behavioural relevance. These findings add to recent evidence for functional segregation within the human hippocampus during learning.

A key observation in patients with hippocampal lesions is that the severity of anterograde and retrograde amnesia correlates with the extent of hippocampal damage (Zola-Morgan *et al*., 1986; Rempel-Clower *et al*., 1996; Nadel and Moscovitch, 1997). The observed left anterior hippocampal role in generic novelty detection might suggest that anterior hippocampal lesions will impair new learning and hence account for the anterograde component of the amnesic syndrome. The extent of retrieval impairment may, because of the observed anterior-posterior familiarity gradient, reflect both the extent of posterior hippocampal damage and the degree of familiarity for the event being retrieved. This suggestion is supported by

the famous patient HM (Scoville and Milner, 1957), who had bilateral resection of the anterior hippocampus but sparing of posterior hippocampus (Corkin *et al*., 1997), and exhibits dense anterograde amnesia but can recall memories acquired before surgery. Patient NT (Warrington and Duchen, 1992) and the patient described by Kartsounis *et al*. (1995), who both had bilateral lesions along the entire anterior-posterior axis of the hippocampus, do not exhibit characteristic sparing of remote memories and show retrograde amnesia for all time periods tested. Intriguingly, 25 years ago Penfield speculated that the temporal extent of retrograde amnesia is dependent upon the posterior extent of hippocampal resection (Penfield and Mathieson, 1974). The findings of a functional segregation within the human hippocampus provide a basis for understanding the diversity of memory deficits consequent upon damage to distinct regions of the hippocampus.