

Dissociating intentional learning from relative novelty responses in the medial temporal lobe

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The establishment of a role for medial temporal lobe (MTL) structures in episodic memory has led to an investigative focus on the specific contributions and interactions between constituent MTL regions, including the hippocampus and surrounding medial temporal cortices. By dissociating an intentional stimulus-category learning condition from a passive viewing condition, we demonstrate, using fMRI, that novelty- and familiarity-driven responses in human anterior and posterior hippocampus, respectively, only occur during intentional learning. With increasing familiarity of stimulus-category associations, there is a shift in neuronal responses from anterior to posterior hippocampal regions. This anterior/posterior response gradient may reflect a weighting of functional hippocampal architecture related to encoding of novel and retrieval of familiar information. By contrast, perirhinal cortex is engaged by novel stimuli irrespective of task, highlighting this region as a component of a generic familiarity discrimination system. By introducing distinct stimulus types, we further demonstrate that these MTL responses are independent of stimulus complexity. Different patterns of activity for intentional learning vs. passive viewing indicate that intentional encoding/retrieval of stimulus-category associations and automatic novelty/familiarity assessment of stimuli are processed in anatomically dissociable neuronal ensembles within the MTL memory system.

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Substantial evidence indicates that medial temporal lobe (MTL) structures are involved in episodic memory (Squire, 1992). However, a consensus about the precise role of, and interplay between, hippocampus and adjacent medial temporal

cortices, namely perirhinal, entorhinal, and parahippocampal cortices, has not been established. Furthermore, recent animal (Moser and Moser, 1998) and functional neuroimaging data (Lepage et al., 1998; Saykin et al., 1999; Strange et al., 1999; Zeineh et al., 2003) suggest that different components of the hippocampus may possess distinct functional properties. An anterior human hippocampal response to novel stimuli is a consistent observation (e.g., Constable et al., 2000; Dolan and Fletcher, 1997; Fischer et al., 2000; Haxby et al., 1996; Martin et al., 1997; Saykin et al., 1999; Sperling et al., 2001; Tulving et al., 1996), which contrasts with electrophysiological recordings in animals where novelty responses are observed in the perirhinal cortex (Brown and Aggleton, 2001). Although some neuroimaging studies report posterior hippocampal responses to novelty (Rombouts et al., 1997; Stern et al., 1996), the majority of novelty-evoked activations in the posterior MTL occur in the parahippocampal gyrus (see Schacter and Wagner, 1999 for review).

Using functional magnetic resonance imaging (fMRI), we previously demonstrated a functional dissociation along the longitudinal axis of the human hippocampus (Strange et al., 1999). Anterior hippocampal responses were greatest for novel stimuli, adapting with repeated stimulus presentation, whereas posterior hippocampal responses increased as stimuli became more familiar (Strange et al., 1999). In this item-learning paradigm, subjects were required to encode novel items, with increasing item familiarity requiring increasing demands on episodic retrieval (Strange et al., 1999). Hence, in this paradigm and a recent replication of this anterior–posterior dissociation (Zeineh et al., 2003), it was not possible to dissociate effects of relative familiarity (novelty/familiarity) from intentional episodic memory (encoding/retrieval).

The present fMRI experiment was designed to investigate the topographical segregation of hippocampal responses to novelty and familiarity. Our primary aim was to dissociate the contribution of automatic registration of novelty/familiarity from intentional episodic encoding/retrieval on functional segregation along

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the longitudinal axis of human hippocampus. We previously postulated that the anterior hippocampal response to relative novelty is automatic in the sense that it is independent of both the nature of the novel stimulus and depth of processing (Strange and Dolan, 2001; Strange et al., 1999). In the current experiment, we dissociated novelty/familiarity from encoding/retrieval effects by introducing novelty under two task conditions: (1) intentional encoding/retrieval of stimulus-category associations and (2) a passive viewing condition in which subjects were pre-informed of category membership.

In addition to this task manipulation, the current paradigm differed from our previous approach (Strange et al., 1999) in three critical aspects. First, we used an event-related rather than a blocked fMRI design to examine activity evoked by correct categorization trials alone. Stimuli were segregated according to right/wrong such that feedback would not confound novelty or familiarity responses (i.e., more wrong responses during initial stimulus-category learning confound the novelty response, a criticism of our previous experimental design). Secondly, our previous study (Strange et al., 1999) involved presentation of complex stimuli, with subjects being presented with letter strings and having to process the position of letters relative to one another. Hence, in the current experiment, repetitive presentation of five classes of stimuli of varying complexity (Fig. 1A) allowed us to determine whether hippocampal novelty and familiarity responses are independent of the degree of stimulus complexity. Finally, stimulus category membership was arbitrary. Our previous paradigm was rule-based, leaving open the possibility that rule-learning could have contributed to our previous results (Strange et al., 1999).

Materials and methods

Subjects

Informed consent was obtained from 12 right-handed volunteers (8 male, 4 female; age range 22–38 years; mean 27.3 years normal or corrected-to-normal vision, recruited by advertisement). All subjects were free from neurological or psychiatric history. Ethical approval was obtained from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Ethics Committee.

Stimuli

60 different stimuli of 5 classes were used in this fMRI study: (1) colored rectangles, (2) drawings of animals, (3) photographs of faces, (4) photographs of natural scenes, and (5) spatial arrays of drawings of animals. Examples are given in Fig. 1A. Stimuli were presented in color (rectangles), white line drawings (drawings and arrays), and as greyscale images (faces and landscapes) on a homogeneous black background. Photographs of natural scenes and emotionally neutral male faces in frontal view were selected from the “Psychological Image Collection at Stirling (PICS)” (<http://www.pics.psych.stir.ac.uk>). Line drawings of animals were similar to a set of objects published by Snodgrass and Vanderwart (1980) and reworked in Photoshop 5.0 for Apple Macintosh (Apple Computer Inc, Cupertino CA). Spatial arrays comprised 4 sets of 4 individual line drawings of animals in 2D configurations. Each of the arrays used the same spatial locations on the screen, but with different members of a set in the particular positions. Stimuli were adjusted to be of approximately equal size

and manipulated such that each stimulus was centered in a 340 × 430 pixel image.

During fMRI scanning, stimuli were presented in central vision (horizontal visual angle 6.0°) for 1500 ms, with an onset asynchrony of 4.71 s. Each stimulus was followed sequentially by the cue ‘A B’ or ‘B A’, presented for 1500 ms, indicating the allocation of the response buttons, and then by visual feedback ‘right’ or ‘wrong’ (500 ms), written in white letters against a black background. A white fixation cross was present for 250 ms between each of the three presentation frames and during the interstimulus interval, as illustrated in Fig. 1A.

Behavioral task

The paradigm was composed of 6 experimental blocks, with 2 stimuli of the 5 types presented during each block. Each stimulus was displayed 6 times in random order; hence, the number of stimulus presentations per block was 60 leading to 360 stimulus presentations over the course of the entire experiment. Familiarity to stimuli occurred over the 6 repetitions, with a novel set of stimuli presented at the start of each block. In the case of spatial arrays, the 4 constituents of the array remained the same, only their relative positions were changed between blocks.

Subjects engaged in one of 2 tasks that alternated across the 6 blocks, with the starting task randomized across subjects. During the learning blocks, subjects were required to make push-button responses to judge category membership ‘A’ or ‘B’ for each stimulus. Visual feedback ‘right’ or ‘wrong’ was provided immediately. Category membership was arbitrary. For the 2 stimuli presented in a block that were of the same type, if one stimulus was randomized as being ‘A’, the other one of the same type was consequently defined as ‘B’. The start of each learning block was cued by the instruction ‘Learn’ displayed on-screen. Viewing blocks started with either the instruction ‘Press A’ or ‘Press B’, and during these blocks subjects pressed the appropriate button to all stimuli, with visual feedback provided immediately.

Subjects were informed that category membership of a stimulus was arbitrary, and that they would have to guess the correct response for the first presentation of a stimulus within a block, with a 50% probability of making the correct choice. However, subjects were instructed that each stimulus was presented 6 times within a block and that they should endeavor to learn the correct association (‘A’ or ‘B’) of a specific stimulus within that particular block and achieve as many correct responses as possible. The response buttons for ‘A’ and ‘B’ changed depending on the random lateralization of ‘A’ and ‘B’ on the screen; i.e., if a correct choice for a particular stimulus was ‘A’, and the letter ‘A’ occurred on the right (‘B A’), a right-hand button would be correct. Thus, if the letter ‘A’ occurred on the left side (‘A B’), the left button would indicate the correct answer. This setup was chosen in order to avoid a simple arbitrary visuo-motor mapping (Wise and Murray, 1999), hence ensuring that subjects encoded the correct stimulus-category association into memory. Note that viewing blocks were identical to learning blocks in all aspects of experimental design and timing, except that subjects did not need to encode and retrieve stimulus-category associations, since the instruction at the onset of a viewing block already indicated the correct answer. Prior to scanning, subjects underwent a training session on a different set of stimuli to allow familiarization with the experimental task.

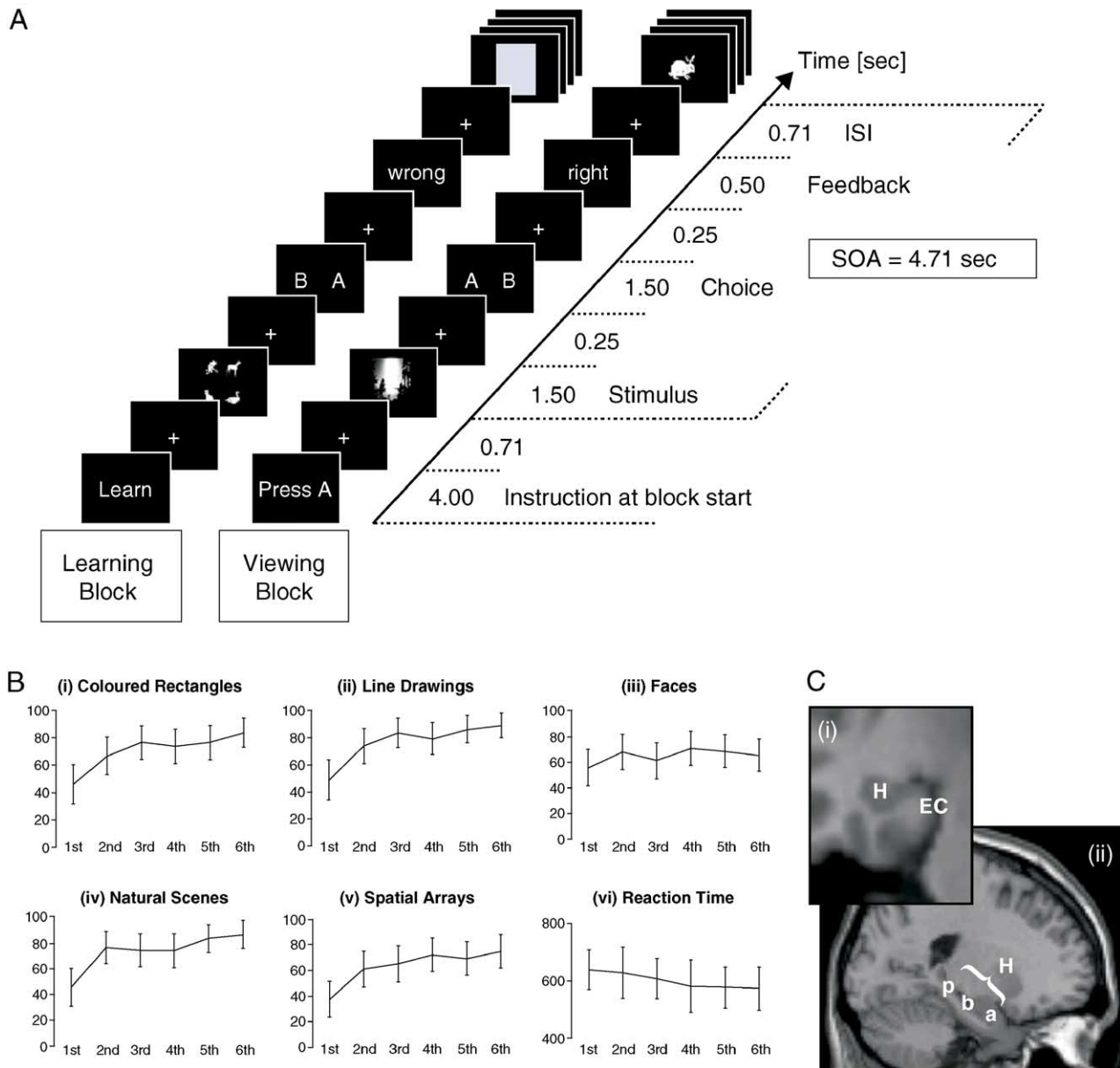


Fig. 1. Experimental set-up, behavioral results, and MTL anatomy. (A) Schematic of the fMRI design. The paradigm was composed of 6 experimental blocks with 2 stimuli of the 5 types presented during each block. Each stimulus was displayed 6 times in random order. Subjects engaged in 2 experimental tasks that alternated across the 6 blocks. During the learning blocks, subjects were required to make push-button responses to judge category membership 'A' or 'B' for each stimulus. Visual feedback 'right' or 'wrong' was provided immediately. The start of each learning block was cued by the instruction 'Learn' displayed on-screen. Viewing blocks started with either the instruction 'Press A' or 'Press B', and during these blocks subjects pressed the appropriate button to all stimuli. (B) Behavioral results. (i–v) Learning performances (% correct) differentiated by stimulus type. (vi) Reaction times (ms) collapsed across blocks and stimulus type within subjects and averaged across subjects (error bars here, and in subsequent plots, denote ± 1 SE). 1st to 6th refers to the number of stimulus presentation. Note that there was no significant repetition \times performance effect for face stimuli. (C) T1 MNI reference brain (Cocosco et al., 1997) in (i) coronal section demonstrating location of hippocampus (H; defined here as CA subfields, dentate gyrus and subiculum) and entorhinal cortex (EC) and (ii) sagittal section demonstrating location of subregions along the hippocampal longitudinal axis: (a) anterior hippocampus, (b) hippocampal body, and (p) posterior hippocampus.

Data acquisition

A Siemens Vision system (Siemens, Erlangen, Germany), operating at 2T, was used to acquire both T1-weighted anatomical images and gradient-echo echo-planar T2*-weighted MRI image volumes with blood oxygenation level-dependent (BOLD) contrast. For each subject, a total of 730 volumes were acquired plus 6 "dummy" volumes, subsequently discarded, to allow for T1

equilibration effects. Volumes were acquired continuously every 2500 ms. Each volume comprised 33, 3.3 mm axial slices, with an in-plane resolution of 3×3 mm, positioned to cover the cerebrum. The imaging time series was realigned to correct for interscan movement, slice-time corrected, normalized into a standard anatomical space (Talairach and Tournoux, 1988), and smoothed with a Gaussian kernel of 6 mm full width half-maximum as described previously (Friston et al., 1995a).

Data analysis

Imaging data were analyzed with SPM99 employing an event-related design (Josephs et al., 1997) within a random effects model. The experimental design allowed a parametric factorial analysis with repetition as the parametric regressor and task and stimulus type as discrete factors. The presentation of each stimulus was modeled by convolving a delta function (or ‘stick’ function) at each event onset with a canonical hemodynamic response function (HRF) to create regressors of interest. Correct and incorrect responses were modeled separately. The height of the modeled HRF was parametrically modulated to model repetition-dependent effects, i.e., the HRF for the 6 repetitions of each event type was multiplied by a linear decrease to model a repetition \times stimulus type interaction. Movement parameters, determined during realignment, as well as low frequency drifts in signal (cut-off 300 s) were modeled as nuisance variables.

Subject-specific parameter estimates pertaining to each regressor were calculated for each voxel (Friston et al., 1995b). The parameter estimate images for 4 repetition \times stimulus type regressors for correct responses alone were entered into an ANOVA (sphericity corrected) to identify areas where activation varied as a function of stimulus type under each task. Note that repetition effects for face stimuli were not tested due to poor learning for this stimulus type (see Results). Employing a significance threshold of $P < 0.001$ (uncorrected) revealed no significant effect of stimulus type on medial temporal activation during the learning condition. During passive viewing, however, a small area of right hippocampal body (x, y, z coordinates 32, -20 , -16) showed a larger novelty response to colors than other stimuli. Critically, activation in this right hippocampal region was not present in any other analysis conducted, thus ensuring that all further activations were independent of stimulus type.

Parameter estimate images for each repetition \times stimulus type regressor for correct responses alone were then entered into separate one-sample t tests across the 12 subjects. We were interested in repetition-dependent medial temporal responses common to all stimulus types, i.e., responses that were independent of stimulus complexity. We performed a serial masking procedure such that novelty/familiarity activations obtained when testing repetition-dependent effects for one stimulus type were thresholded at $P < 0.1$ and used to mask activations measured in subsequent one-sample t tests. Given the relatively long stimulus onset asynchrony (4.71 s), we assumed that contrasts were minimally correlated and subsequently confirmed this empirically for MTL activations. The probability of an activation surviving this masking procedure for the 4 stimulus types, each thresholded at $P < 0.1$, corresponds to an effective threshold of $P < 0.0001$ (uncorrected). We report all medial temporal activations surviving this threshold. To test for a task \times repetition interaction for each stimulus type, contrast images were calculated by applying appropriate linear contrasts to the parameter estimates. The ensuing contrast images were entered into a one-sample t test and the serial masking procedure performed. Note that this serial masking procedure is mathematically identical to a conjunction analysis (Worsley and Friston, 2000) differing only in that a conjoint P value ensues from the latter.

With respect to the pattern of hippocampal activations reported previously (Strange et al., 1999), we had distinct a priori predictions allowing for uncorrected thresholding. Only effects

pertaining to correct responses were analyzed due to insufficient numbers of incorrect responses. To illustrate repetition-dependent effects, we constructed an additional model that was identical to that described above, except that each of the 6 repetitions of each stimulus type was modeled separately. The ensuing parameter estimates enabled us to plot a time series of repetition-dependent effects for the voxels that showed significant activation in our original analyses.

Results

Behavior

Subjects had to guess correct responses for the first stimulus-category associations within a learning block and performed at chance (50%). However, with increasing stimulus presentations, performance improved, as demonstrated by repeated measures ANOVAs testing for repetition \times performance effects collapsed across the four stimulus types ($F(3.2, 35.6) = 18.30$; $P < 0.001$) and for each stimulus type separately: colored rectangles ($F(3.3, 36.4) = 6.22$; $P < 0.005$), drawings of animals ($F(2.4, 26.6) = 7.00$; $P < 0.005$), landscapes ($F(3.3, 36.3) = 5.67$; $P < 0.005$), and spatial arrays ($F(3.6, 39.4) = 7.45$; $P < 0.001$). Reaction time decreased with stimulus repetition ($F(2.5, 27.9) = 3.62$; $P < 0.05$). These observations confirm progressive within-block learning, since in all cases the first of six stimulus presentations was entirely novel and could not be classified correctly on the basis of remembered stimulus-category associations. Significant performance effects were not found for face stimuli ($F(3.3, 35.9) = 1.76$; ns), probably due to difficulty in immediately discriminating faces from each other, nor for stimulus type \times repetition interactions ($F(5.7, 62.4) = 0.31$; ns), indicating that repetition effects count equally for the 4 stimulus types entering fMRI analysis. Learning performance and reaction time profiles are plotted in Fig. 1B, i–vi.

Functional imaging

The specific effect tested in our experiment was a repetition \times condition interaction common to the 4 stimulus types where learning was evident behaviorally. The data presented result from a serial masking procedure such that novelty/familiarity activations refer to repetition-dependent MTL responses found for all 4 stimulus types. Fig. 2 illustrates the hippocampal response to both novelty and familiarity during intentional encoding and retrieval of stimulus-category associations (learning condition). Modeling linear adaptation of neuronal responses as a repetition-dependent decline yielded significant effects in left anterior hippocampus, bordering with entorhinal cortex (Fig. 2A). The reverse comparison, testing for linear increases in activation to increasing stimulus familiarity, resulted in significant effects in left hippocampal body (Fig. 2B) and right posterior hippocampus.

Fig. 3 illustrates medial temporal responses to novelty and familiarity in the passive viewing condition, i.e., when no intentional learning was required. With stimulus repetitions, the right perirhinal cortex showed significant adaptation of novelty-related responses (Fig. 3A), whereas increasing stimulus familiarity was associated with significant effects in the left hippocampal body (Fig. 3B).

To assess modulation of MTL responses to relative familiarity by intentional learning vs. passive viewing (and vice versa), we tested for a task \times repetition interaction for each stimulus type

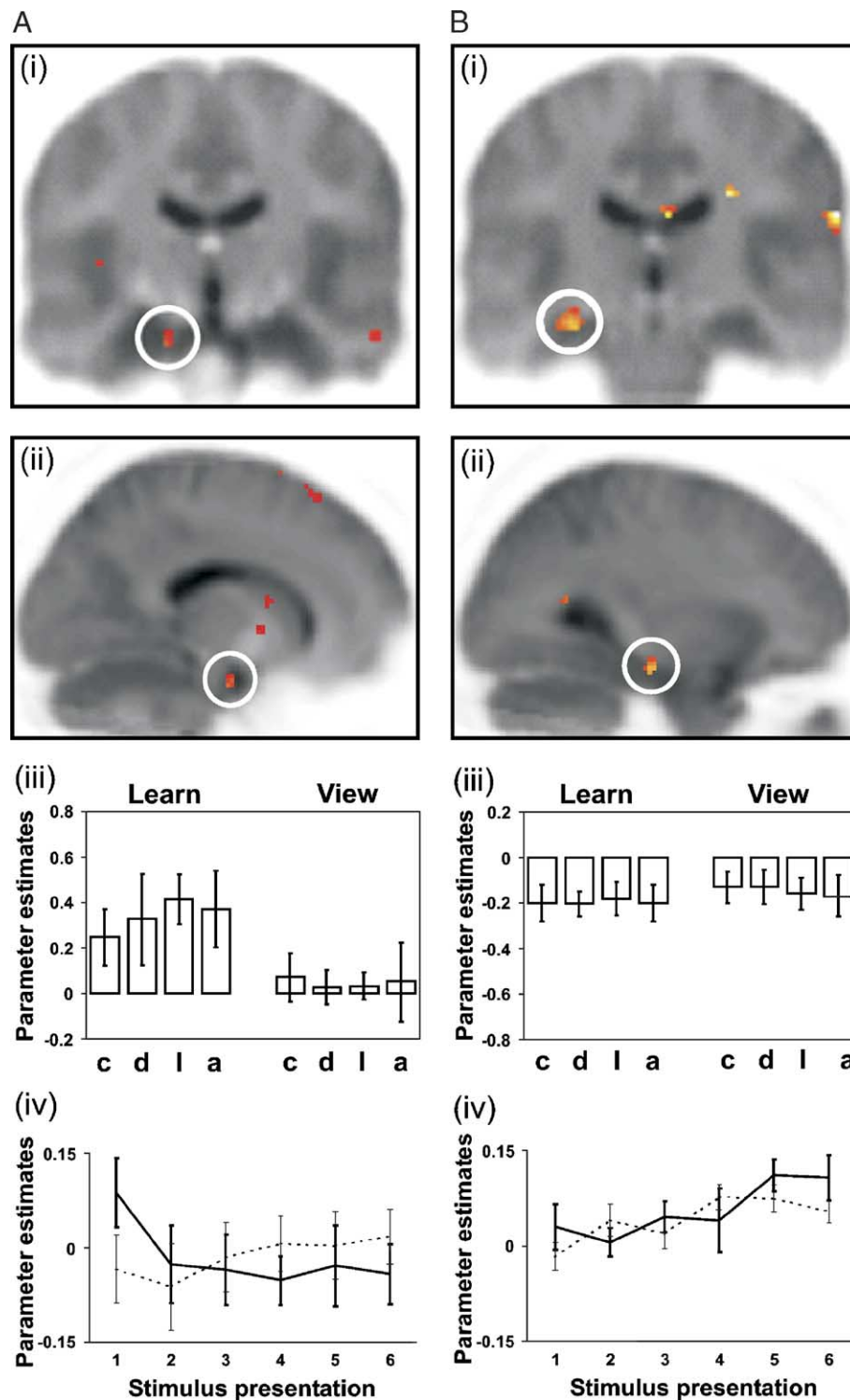


Fig. 2. Hippocampal responses to intentional encoding/retrieval of stimulus-category associations. (A) SPM superimposed on (i) coronal and (ii) sagittal sections of the average functional image from 12 subjects, showing linear adaptation of responses in the left anterior hippocampus (bordering with entorhinal cortex) with repeated presentations of novel stimulus-category associations (x, y, z coordinates $-16, -12, -26$, $P < 0.0001$). (B) SPM showing linear increase in activation in the left hippocampal body evoked by increasing familiarity with stimulus-category associations ($-30, -20, -18$, $P < 0.0001$). (A, iii–iv, and B, iii–iv) Graphic representation of activation at the given voxel as a function of repetition. (A, iii, and B, iii) Parameter estimate plots illustrating response changes to novelty (A) and familiarity (B), averaged across subjects, differentiated by stimulus type (c, colors; d, drawings; l, landscapes; a, arrays) and task condition (learn vs. view). (A, iv, and B, iv) Parameter estimates plotted for both novelty (A) and familiarity (B) during intentional learning, differentiated by stimulus repetition and task condition. Here and in subsequent plots, the dark line indicates responses during the learning condition and the dotted line responses during passive viewing.

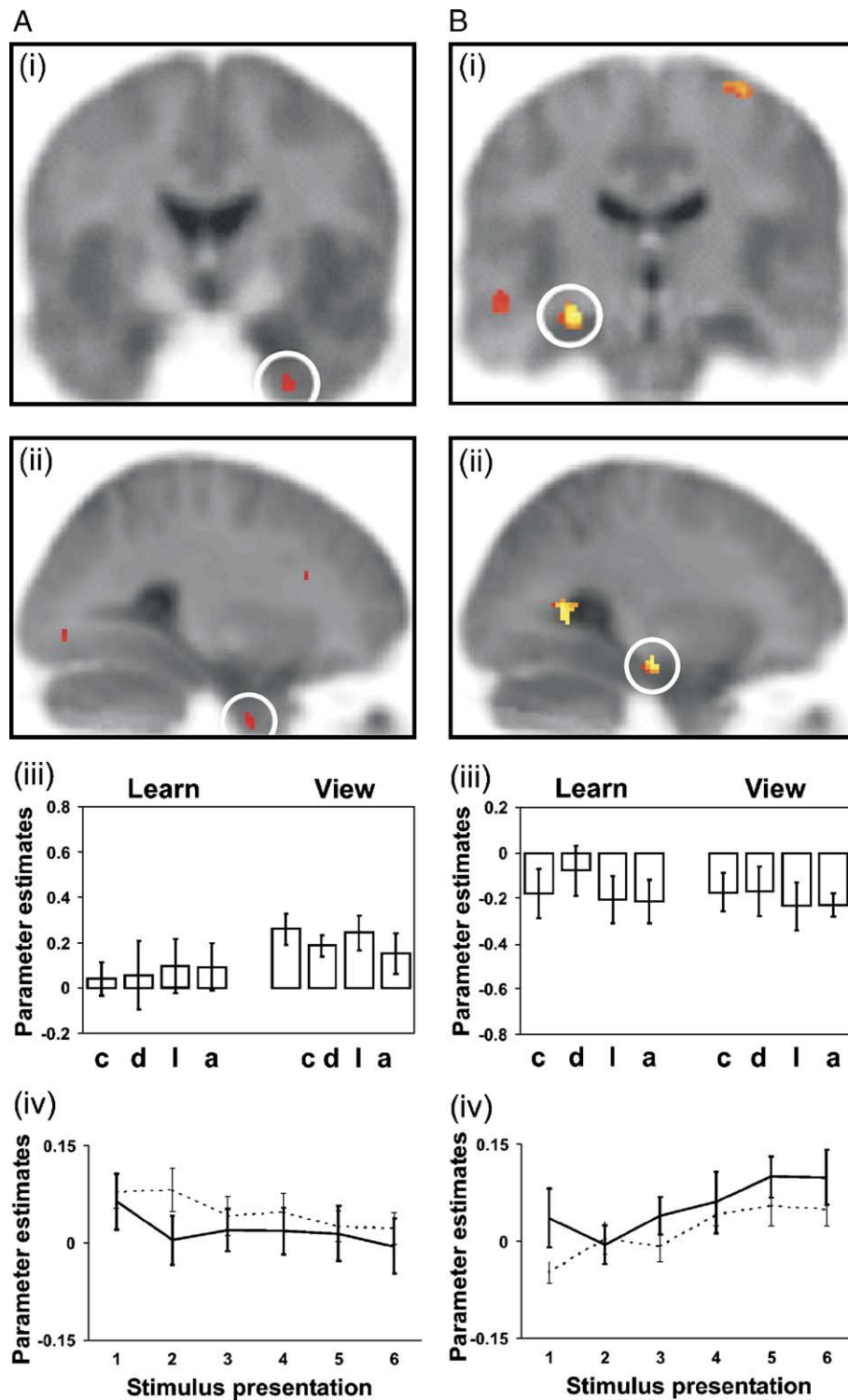


Fig. 3. Medial temporal responses to novelty/familiarity during passive viewing. (A) SPM superimposed on (i) coronal and (ii) sagittal sections, showing linear decline of right perirhinal activation, reflecting engagement by novel stimuli and adaptation with familiarity (30, -02, -44, $P < 0.0001$). (B) SPM showing linear increase in activation of the left hippocampal body to familiarity (-28, -18, -16, $P < 0.0001$). (A, iii-iv, and B, iii-iv) Graphic representation of activation at the given voxel as a function of repetition as for Fig. 2.

followed by serial masking. Testing for novelty effects for learning vs. viewing also tests for familiarity effects for viewing vs. learning and vice versa, i.e., a positive effect in the test of novelty responses for learning minus viewing could reflect a novelty response during

learning greater than during viewing or a familiarity response for viewing vs. learning. Thus, the nature of the interaction was determined by plotting response profiles for the ensuing activations. As illustrated in Fig. 4, novelty-dependent responses related

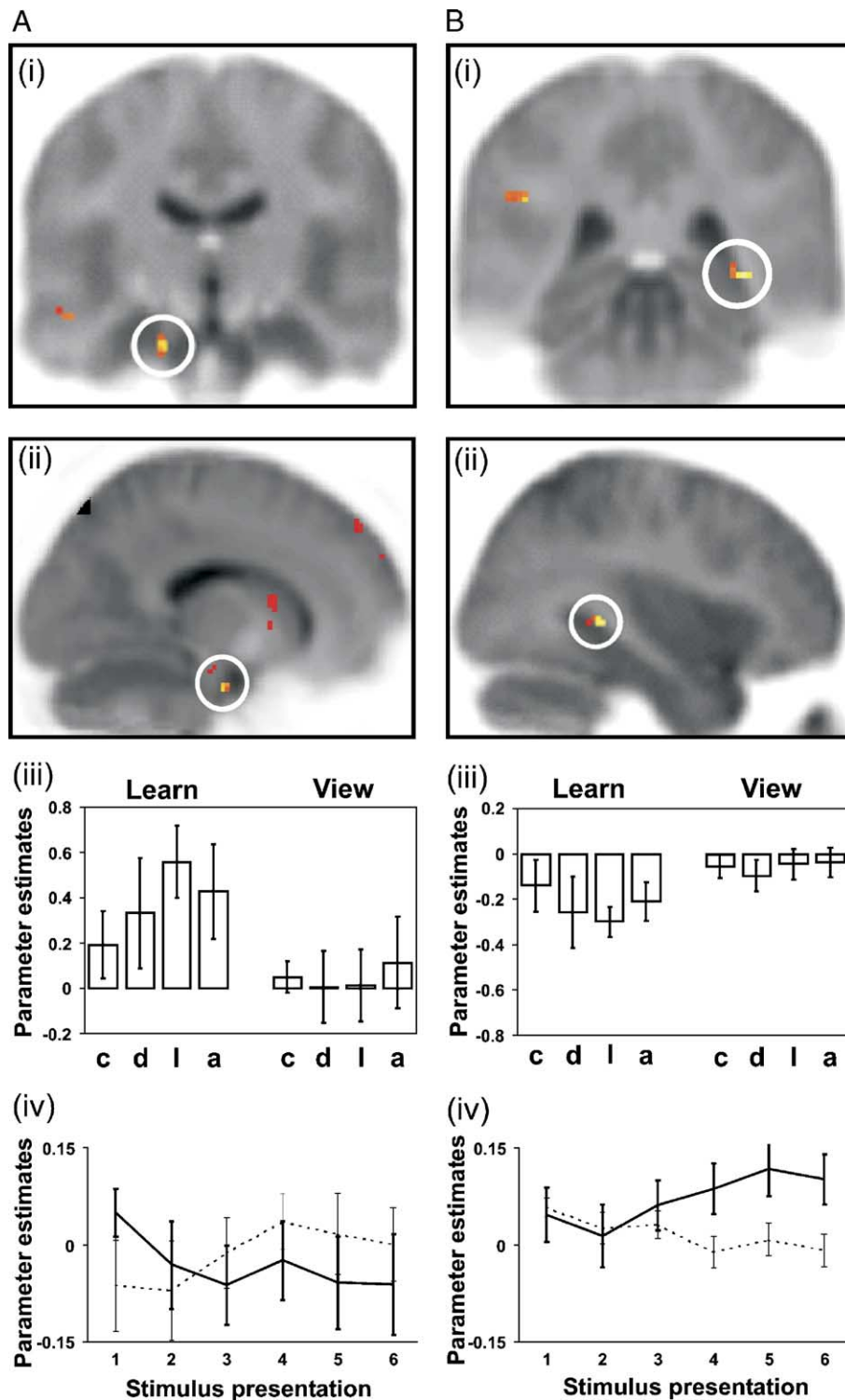


Fig. 4. Anterior and posterior hippocampal responses to novel and familiar stimuli, respectively, are evoked only during intentional learning and not passive viewing. (A) SPM showing adaptation of left anterior hippocampal/entorhinal response to novel stimuli only during intentional learning ($-16, -14, -28, P < 0.0001$). (B) SPM showing linear increase in activation of the right posterior hippocampus in response to increasing familiarity only during intentional learning ($36, -36, 00, P < 0.0001$). (A, iii–iv, and B, iii–iv) Graphic representation of activation at the given voxel as a function of repetition as for Fig. 2.

to intentional encoding were observed in the left anterior hippocampus alone (Fig. 4A), while the posterior hippocampus was engaged by increasing familiarity during intentional learning (Fig. 4B). The parameter estimates for hippocampal responses for each

stimulus type (Figs. 4A and B (iii)) and the repetition \times response profiles (Figs. 4A and B (iv)) demonstrate that during passive viewing there is no novelty response in the anterior hippocampus nor a familiarity response in the posterior hippocampus. Hence,

novelty only engaged anterior hippocampus during intentional learning. By contrast, enhanced right posterior hippocampal responses are evoked by familiarity processing only during intentional learning. No medial temporal region showed greater novelty or familiarity responses for passive viewing vs. intentional learning.

The parameter estimate plots presented in Figs. 2–4, A (iii) and B (iii), have been averaged across subjects, differentiated by stimulus type and task condition, and demonstrate the slope of repetition-dependent linear change in response (a positive parameter estimate indicates a within-block decline in response). There is no explicit baseline, thus responses are relative to the mean across the functional run. Note that there is no evidence for stimulus selectivity in hippocampal or perirhinal responses, suggesting that novelty detection is independent of stimulus type. The parameter estimates plotted for both novelty and familiarity in Figs. 2–4, A (iv) and B (iv), show repetition-dependent changes in activation collapsed across stimulus types and averaged across subjects differentiated by stimulus repetition and task condition. These data demonstrate a decline in novelty-related responses and an increase in familiarity-related responses, as a function of stimulus repetition, in anterior and more posterior MTL regions, respectively.

Discussion

Our results extend our previous finding of an anterior–posterior hippocampal segregation with respect to novelty and familiarity processing (Strange et al., 1999) and indicate that the sensitivity to novelty and familiarity are not explained by performance (as only correct responses were analyzed), acquisition of abstract knowledge from a rule system, or non-specific effects of a blocked fMRI design. There are a number of critical findings. Firstly, anterior and posterior hippocampal responses to novelty and familiarity, respectively, were only evident in the context of intentional learning of stimulus–category associations. By contrast, irrespective of encoding task, novel stimuli engaged right perirhinal cortex while increasing stimulus familiarity engendered activation in the left hippocampal body. Lastly, these differential medial temporal responses to relative familiarity were independent of stimulus complexity, i.e., medial temporal responses were observed for relatively simple stimuli (colored rectangles, simple line drawings) and complex stimuli (landscapes, arrays of 4 line drawings). This latter finding supports a view that hippocampal novelty detection operates independently of stimulus type (Menon et al., 2000).

At the onset of each intentional learning block, subjects had no knowledge of correct stimulus–category associations. Successful task performance on subsequent presentations required exclusive reliance on episodic memory processes. The left anterior hippocampus was engaged by novel stimuli during intentional learning, with responses attenuating within-block as stimuli were repeatedly presented and subjects' performance improved. Previous reports of novelty-dependent anterior hippocampal activation have not dissociated responses due to intentional encoding of novel stimuli from novelty detection per se (e.g., Constable et al., 2000; Dolan and Fletcher, 1997; Fischer et al., 2000; Haxby et al., 1996; Martin et al., 1997; Saykin et al., 1999; Sperling et al., 2001; Strange et al., 1999; Tulving et al., 1996; Zeineh et al., 2003). The fact that the anterior hippocampus was engaged by novel stimuli during intentional learning, but not during passive viewing, suggests that anterior hippocampal responses elicited during

intentional learning reflect active encoding of novel stimulus–category associations.

The sensitivity of the anterior hippocampus to relative novelty during learning is supported by observations that single human hippocampal neurons fire differentially to novel vs. familiar items (Fried et al., 1997). Furthermore, hippocampal sclerosis in epilepsy patients results in amplitude loss and peak delay of intracranial ERPs (AMTL-N400) to novel but not familiar stimuli (Grunwald et al., 1998). Our previous observation of anterior hippocampal responses to both behaviorally relevant and irrelevant novelty suggested that anterior hippocampal novelty responses are automatic and task-independent (Strange and Dolan, 2001; Strange et al., 1999). It is therefore surprising that we now find that the anterior hippocampus is only engaged by relative novelty during active encoding of stimulus–category associations. The effects observed here are, however, consistent with previous reports that the anterior hippocampus is driven by associative encoding (Henke et al., 1997, 1999). In addition to novelty-evoked activations previously reported, several studies have observed anterior hippocampal activations during associative or semantic tasks (Henke et al., 1997, 1999; Martin et al., 1997; Vandenberghe et al., 1996). Novelty responses may be intimately linked with an associative hippocampal function (Eichenbaum, 1997). When a novel stimulus is encountered, a component of mismatch detection and subsequent orienting may involve trying to compare and associate that stimulus with information stored in declarative memory. This leads us to suggest that novelty detection and subsequent associative learning may be common functions of the anterior hippocampus.

By contrast, the posterior hippocampus is increasingly engaged by familiar stimuli only during the intentional learning condition. This observation supports our previous finding that this region is primarily engaged by familiarity with the behaviorally relevant aspects of those stimuli for which retrieval was demanded (Strange et al., 1999). Our results therefore demonstrate that anterior hippocampal responses are greatest during encoding of novel stimuli while activation of posterior hippocampus is evoked by increasing within-block retrieval. In other words, decreasing encoding demands, as a consequence of stimulus repetition, are paralleled by increasing retrieval effects, suggesting that episodic encoding and retrieval constitute topographically dissociable processes that are reciprocally modulated as a function of stimulus familiarity. This topographical parcellation is congruent with the Hippocampal Encoding/Retrieval (HIPER) model of memory formation, which suggests an anterior–posterior hippocampal gradient of encoding- and retrieval-related activity (Lepage et al., 1998). Schacter and Wagner (1999), however, argued the opposite dissociation, i.e., encoding and retrieval are mediated by posterior and anterior MTL, respectively, which does not accord with our findings. It should be noted, however, that the majority of posterior encoding-related MTL activations in the Schacter and Wagner review are in parahippocampal gyrus and not hippocampus as we demonstrate here.

In the current paradigm, retrieval-related posterior hippocampal activity was right lateralized as opposed to the bilateral activation previously observed (Strange et al., 1999). This could reflect the visual, as opposed to verbal (Strange et al., 1999), properties of the current stimuli (Kelley et al., 1998). Left anterior hippocampal engagement by novelty during intentional learning could, therefore, reflect a verbal encoding strategy adopted by subjects during initial presentation of stimuli. As stimuli become increasingly

familiar, retrieval of category membership may become increasingly reliant on visual properties resulting in a right posterior hippocampal retrieval response.

Activation of hippocampal body is observed with increasing stimulus familiarity following both intentional learning and passive viewing. This absence of an exclusive relationship with encoding conditions, including an intentional encoding condition that is likely to support subsequent episodic retrieval, would suggest that this region might code some low level memory functions such as stimulus-evoked familiarity. The anatomical location of this familiarity-related activation is crucial for the controversial debate on the topographical functional organization of the human hippocampus. The fact that in the present study novelty encoding- and familiarity-related hippocampal BOLD responses are in close anatomical proximity (y coordinates -12 vs. -20 , respectively) suggests that the low spatial resolution of PET or excess spatial smoothing with fMRI might preclude accurate topographical dissociation of the two response types (e.g., Schacter et al., 1999).

Given that the intrinsic circuitry of the hippocampus does not vary along its longitudinal axis, two candidate mechanisms that could give rise to different functions of discrete hippocampal regions along the longitudinal axis are distinct connectivity profiles and segregated projections from neuromodulatory systems. There is evidence for segregation of both connectivity profiles and neuromodulatory inputs along the longitudinal axis of the hippocampus. The connectivity of anterior hippocampus is well suited to encoding novel stimuli in so far as it receives rich polymodal sensory information via a parahippocampal projection to medial entorhinal cortex and anterior CA1 (Dolorfo and Amaral, 1998; Suzuki and Amaral, 1994). The anterior hippocampus also receives affective and interoceptive inputs from the amygdala and brainstem (Canteras and Swanson, 1992; Risold and Swanson, 1996, 1997; Witter et al., 1989). The anterior hippocampus is therefore capable of integrating physiological states of arousal with cortical sensory inputs during novelty detection. These properties are ideal for influencing the extent to which incoming sensory information is encoded into episodic

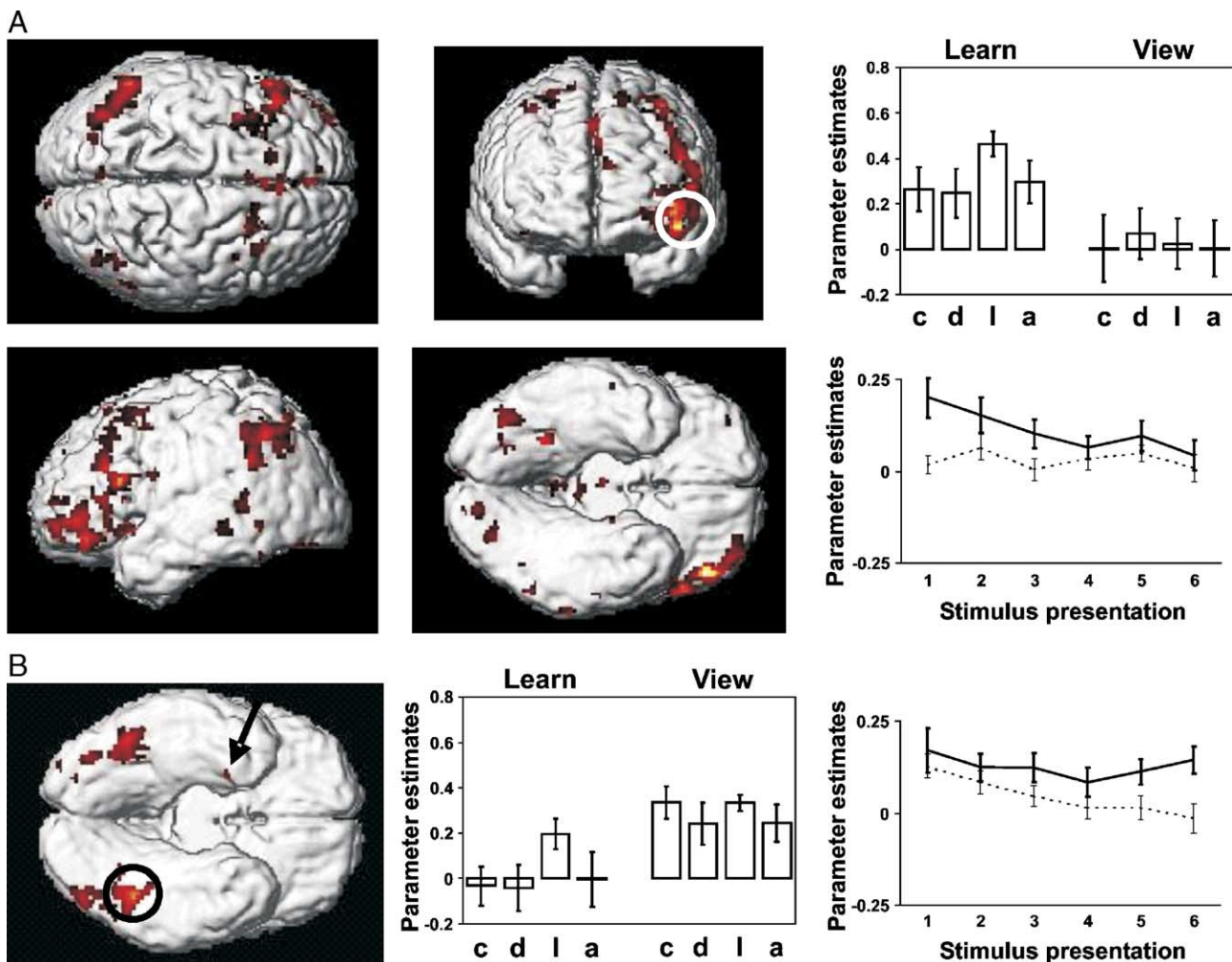


Fig. 5. Neocortical responses to novelty. (A) Activation in a bilateral frontal-parietal-fusiform network is observed during intentional encoding of novel stimulus-category associations in addition to the anterior hippocampal response shown in Fig. 2A. Responses in the left inferior prefrontal gyrus (-44 , 40 , -10) are plotted as for Fig. 2 and show a selective novelty response for the learning and not viewing condition. (B) Novelty responses during passive viewing are observed in the bilateral fusiform gyrus. Activation in left fusiform (-38 , -52 , -18) is plotted as above. \uparrow indicates the perirhinal activation shown in Fig. 3A.

memory. Conversely, the posterior hippocampus is extensively and reciprocally connected with polymodal sensory areas (Shi and Cassell, 1999; Witter et al., 1989), making this region equally suitable for encoding, retention, and retrieval of information. Also relevant to the current results is the observation that projections to the hippocampal body are segregated from those to anterior and posterior levels (Dolorfo and Amaral, 1998; Yukie, 2000). Processing within the anterior hippocampus is under a greater degree of neuromodulatory influence from cholinergic and monoaminergic systems than posterior hippocampus (Amaral and Kurtz, 1985; Gage and Thompson, 1980; Haring and Davis, 1985; Hoover et al., 1978; Verney et al., 1985; Wainer et al., 1985). Although the roles of neuromodulators in encoding vs. retrieval have yet to be established, the fact that profiles differ between anterior and posterior hippocampus implies a functional segregation.

Perirhinal cortex, located in the banks of the anterior extent of the collateral sulcus (Amaral, 1999) and corresponding to Brodmann's area 35 and 36 (Amaral et al., 1987), was engaged by novel stimuli during passive viewing. This activation did not show an interaction with task, suggesting task-independent sensitivity to novelty. Of particular relevance to the interpretation of this result is monkey electrophysiological data demonstrating greater responses in perirhinal neurons to novel objects than repeated presentations (Brown and Xiang, 1998). This has led to a proposal that the perirhinal cortex assesses prior occurrence based on stimulus familiarity (Brown and Aggleton, 2001; Brown and Xiang, 1998) which may function relatively independently of the hippocampus (Wan et al., 1999). Our results therefore support the possibility of a discriminatory mechanism in the perirhinal cortex that may be central for allowing sensory input access to long-term memory stores. It should be noted, however, that recent human electrophysiological (Fernandez et al., 1999) and fMRI (Strange et al., 2002) data demonstrate perirhinal responses during successful rote encoding of verbal stimuli. In these previous paradigms, there was no novelty manipulation suggesting that the perirhinal role in episodic memory extends beyond discrimination of relative familiarity.

Our results also support recent data suggesting that single-item vs. associative or relational encoding is mediated by separable subregions within the medial temporal lobe, with the former engaging perirhinal cortex and the latter mediated by hippocampus (Davachi et al., 2003; but see Stark and Squire, 2003). We demonstrate that encoding novel stimulus-category associations engages the anterior hippocampus whereas registration of novel stimuli in the passive viewing condition (not requiring associative processing) evokes perirhinal activation. The recent findings (Davachi et al., 2003) compliment the animal literature, which demonstrates greater hippocampal responses in response to novel spatial arrays of stimuli, whereas perirhinal responses index novel single stimuli (Jenkins et al., 2004; Wan et al., 1999). Hippocampal and perirhinal novelty responses in the current study were, however, equivalent across all stimulus types, which included novel single stimuli and novel spatial arrays. We specifically compared responses evoked by novel spatial arrays vs. novel line drawings (and vice versa) as arrays were composed of 4 line drawings. Significant effects within MTL were not observed in either comparison, neither during learning nor passive viewing. Thus, we are unable to extend this finding in animals to human MTL.

To illustrate that medial temporal responses occur as part of a novelty/familiarity discrimination network of brain regions (Tulving et al., 1996), we briefly report activations outside of MTL (Fig.

5). Novelty responses during learning were observed in the left inferior prefrontal cortex (Fig. 5A), frontal operculum, premotor cortex, anterior cingulate and parietal cortex, and bilateral fusiform gyrus. Familiarity responses during learning (i.e., retrieval-related responses) were observed in the right superior temporal gyrus. During passive viewing, novelty engaged the bilateral fusiform gyrus (Fig. 5B) whereas familiarity engaged the bilateral inferior temporal gyrus, temporal pole, and medial prefrontal cortex. Fig. 5 therefore demonstrates neuroanatomical regions for which there is prior evidence for their role in memory and novelty detection. Familiarity/retrieval cortical responses are reported descriptively. Left inferior frontal responses have been observed to novelty (McCarthy et al., 1997) and during episodic encoding (e.g., Wagner et al., 1998), with a recent suggestion that this region is engaged by the intention to encode whereas MTL mediates successful encoding (Reber et al., 2002). Fusiform responses that decline with repetition (i.e., are novelty sensitive) are well described (see Henson, 2003 for review).

The anterior-posterior dissociation of hippocampal responses to relative novelty and familiarity became apparent when active encoding/retrieval of stimulus-category associations was required. Left anterior hippocampus, bordering with entorhinal cortex, was more sensitive to novel stimulus-category associations than to novel stimuli per se, with posterior hippocampus selectively engaged by retrieval of these associations. These findings are compatible with accumulating evidence that hippocampal regions are critically involved in the formation and retrieval of associations between separate components of presented material (Brown and Aggleton, 2001; Henke et al., 1999; Suzuki and Eichenbaum, 2000; Vargha-Khadem et al., 1997; Yonelinas, 2002). In contrast, the capacity for episodic memory tasks that are not associative in nature, including relative familiarity discrimination, is supported by the perirhinal cortex.

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References

- Amaral, D.G., 1999. Introduction: what is where in the medial temporal lobe? *Hippocampus* 9, 1–6.
- Amaral, D.G., Kurtz, J., 1985. An analysis of the origins of the cholinergic and non-cholinergic septal projections to the hippocampal formation of the rat. *J. Comp. Neurol.* 240, 37–59.
- Amaral, D.G., Insausti, R., Cowan, W.M., 1987. The entorhinal cortex of the monkey: I. Cytoarchitectonic organization. *J. Comp. Neurol.* 264, 326–355.
- Brown, M.W., Aggleton, J.P., 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev., Neurosci.* 2, 51–61.
- Brown, M.W., Xiang, J.-Z., 1998. Recognition memory: neuronal substrates of the judgement of prior occurrence. *Prog. Neurobiol.* 55, 149–189.
- Canteras, N., Swanson, L.W., 1992. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHA-L anterograde tracing study in the rat. *J. Comp. Neurol.* 324, 180–194.
- Coccosco, C.A., Kollokian, V., Kwan, R.K.S., Evans, A.C., 1997. BrainWeb: online interface to a 3D MRI simulated brain database. *NeuroImage* 5, S425.
- Constable, R.T., Carpentier, A., Pugh, K., Westerveld, M., Oszunar, Y., Spencer, D.D., 2000. Investigation of the human hippocampal

- formation using a randomized event-related paradigm and Z-shimmed functional MRI. *NeuroImage* 12, 55–62.
- Davachi, L., Mitchell, J.P., Wagner, A.D., 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. U. S. A.* 100, 2157–2162.
- Dolan, R.J., Fletcher, P.C., 1997. Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388, 582–585.
- Dolorfo, C.L., Amaral, D.G., 1998. Entorhinal cortex of the rat: topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. *J. Comp. Neurol.* 398, 48–52.
- Eichenbaum, H., 1997. Declarative memory: insights from cognitive neurobiology. *Annu. Rev. Psychol.* 48, 547–572.
- Fernandez, G., Effern, A., Grunwald, T., Pezer, N., Lehnertz, K., Dümpelmann, M., Van Roost, D., Elger, C.E., 1999. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science* 285, 1582–1585.
- Fischer, H., Furmark, T., Wik, G., Fredrikson, M., 2000. Brain representation of habituation to repeated complex visual stimulation studied with PET. *NeuroReport* 11, 123–126.
- Fried, I., MacDonald, K.A., Wilson, C.L., 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18, 753–765.
- Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., Frackowiak, R.S.J., 1995a. Spatial registration and normalisation of images. *Hum. Brain Mapp.* 2, 165–189.
- Friston, K.J., Holmes, A.P., Worsely, K.J., Poline, J.-B., Frith, C.D., Frackowiak, R.S.J., 1995b. Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* 2, 189–210.
- Gage, F.H., Thompson, R.G., 1980. Differential distribution of norepinephrine and serotonin along the dorsal–ventral axis of the hippocampal formation. *Brain Res. Bull.* 5, 771–773.
- Grunwald, T., Lehnertz, K., Heinze, H.J., Helmstaedter, C., Elger, C.E., 1998. Verbal novelty detection within the human hippocampus proper. *Proc. Natl. Acad. Sci. U. S. A.* 95, 3193–3197.
- Haring, J.H., Davis, J.N., 1985. Differential distribution of locus coeruleus projections to the hippocampal formation: anatomical and biochemical basis. *Brain Res.* 325, 366–369.
- Haxby, J.V., Ungerleider, L., Horwitz, B., Maisog, J., Rappaport, S., Grady, C., 1996. Face encoding and recognition in the human brain. *Proc. Natl. Acad. Sci. U. S. A.* 93, 922–927.
- Henke, K., Buck, A., Weber, B., Wieser, H.G., 1997. Human hippocampus establishes associations in memory. *Hippocampus* 7, 249–256.
- Henke, K., Weber, B., Kneifel, S., Wieser, H.G., Buck, A., 1999. Human hippocampus associates information in memory. *Proc. Natl. Acad. Sci. U. S. A.* 96, 5884–5889.
- Henson, R.N., 2003. Neuroimaging studies of priming. *Prog. Neurobiol.* 70, 53–81.
- Hoover, D.B., Muth, E.A., Jacobowitz, D.B., 1978. A mapping of the distribution of acetylcholine, choline acetyltransferase, and acetylcholinesterase in discrete areas of rat brain. *Brain Res.* 153, 295–306.
- Jenkins, T.A., Amin, E., Pearce, J.M., Brown, M.W., Aggleton, J.P., 2004. Novel spatial arrangements of familiar visual stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a *c-fos* expression study. *Neuroscience* 124, 43–52.
- Josephs, O., Turner, R., Friston, K.J., 1997. Event-related fMRI. *Hum. Brain Mapp.* 5, 243–248.
- Kelley, W.M., Miezin, F., McDermott, K., Buckner, R.L., Raichle, M.E., Cohen, N.J., Ollinger, J.M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Petersen, S.E., 1998. Hemispheric specialisation in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 20, 927–936.
- Lepage, M., Habib, R., Tulving, E., 1998. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 8, 313–322.
- Martin, A., Wiggs, C.L., Weisberg, J., 1997. Modulation of human medial temporal lobe activity by form, meaning and experience. *Hippocampus* 7, 587–593.
- McCarthy, G., Luby, M., Gore, J., Goldman-Rakic, P., 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J. Neurophysiol.* 77, 1630–1634.
- Menon, V., White, C.D., Eliez, S., Glover, G.H., Reiss, A.L., 2000. Analysis of a distributed neural system involved in spatial information, novelty, and memory processing. *Hum. Brain Mapp.* 11, 117–129.
- Moser, M.-B., Moser, E.I., 1998. Functional differentiation in the hippocampus. *Hippocampus* 8, 608–619.
- Reber, P.J., Siwiec, R.M., Gitelman, D.R., Parrish, T.B., Mesulam, M.M., Paller, K.A., Gitelman, D.R., 2002. Neural correlates of successful encoding identified using functional magnetic resonance imaging. *J. Neurosci.* 22, 9541–9548.
- Risold, P.Y., Swanson, L.W., 1996. Structural evidence for functional domains in the rat hippocampus. *Science* 272, 1484–1486.
- Risold, P.Y., Swanson, L.W., 1997. Connections of the rat lateral septal complex. *Brain Res. Rev.* 24, 115–195.
- Rombouts, S., Machielsen, W., Witter, M., Barkhof, F., Lindeboom, J., Scheltens, P., 1997. Visual association encoding activates the medial temporal lobe: a functional magnetic resonance imaging study. *Hippocampus* 7, 594–601.
- Saykin, A.J., Johnson, S.C., Flashman, L.A., McAllister, T.W., Sparling, M., Darcey, T.M., Moritz, C.H., Guerin, S.J., Weaver, J., Mamourian, A., 1999. Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. *Brain* 122, 1963–1971.
- Schacter, D.L., Wagner, A.D., 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9, 7–24.
- Schacter, D.L., Curran, T., Reiman, E.M., Chen, K., Bandy, D.J., Frost, J.T., 1999. Medial temporal lobe activation during episodic encoding and retrieval: a PET study. *Hippocampus* 9, 575–581.
- Shi, C.-J., Cassell, M.D., 1999. Perirhinal cortex projections to the amygdaloid complex and hippocampal formation in the rat. *J. Comp. Neurol.* 406, 299–328.
- Snodgrass, J.G., Vanderwart, M., 1980. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J. Exp. Psychol. [Hum. Learn.]* 6, 174–215.
- Sperling, R.A., Bates, J.F., Cocchiarella, A.J., Schacter, D.L., Rosen, B.R., Albert, M.S., 2001. Encoding novel face-name associations: a functional MRI study. *Hum. Brain Mapp.* 14, 129–139.
- Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings in rats, monkeys and humans. *Psychol. Rev.* 99, 195–231.
- Stark, C.E., Squire, L.R., 2003. Hippocampal damage equally impairs memory for single items and memory for conjunctions. *Hippocampus* 13, 281–292.
- Stern, C.E., Corkin, S., Gonzalez, R.G., Guimaraes, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Suigura, R.M., Vedantham, V., Rosen, B.R., 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. U. S. A.* 93, 8660–8665.
- Strange, B.A., Dolan, R.J., 2001. Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus* 11, 690–698.
- Strange, B.A., Fletcher, P.C., Henson, R.N., Friston, K.J., Dolan, R.J., 1999. Segregating the functions of human hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 96, 4034–4039.
- Strange, B.A., Otten, L.J., Josephs, O., Rugg, M.D., Dolan, R.J., 2002. Dissociable human perirhinal, hippocampal and parahippocampal roles during verbal encoding. *J. Neurosci.* 22, 523–528.
- Suzuki, W.A., Amaral, D.G., 1994. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J. Neurosci.* 14, 1856–1877.
- Suzuki, W.A., Eichenbaum, H., 2000. The neurophysiology of memory. *Ann. N. Y. Acad. Sci.* 911, 175–191.
- Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.
- Tulving, E., Markowitsch, M.J., Craik, F.I.M., Habib, R., Houle, S., 1996.

- Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb. Cortex* 6, 71–79.
- Vandenberghe, R., Price, C., Wise, R., Josephs, O., Frackowiak, R.S.J., 1996. Functional anatomy of a common semantic system for words and pictures. *Nature* 383, 254–256.
- Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., Mishkin, M., 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277, 376–380.
- Verney, C., Baulac, M., Berger, B., Alvarez, C., Vigny, A., Helle, K.B., 1985. Morphological evidence for dopaminergic terminal field in the hippocampus of young and adult rat. *Neuroscience* 14, 1039–1052.
- Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., Buckner, R.L., 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 281, 1188–1191.
- Wainer, B.H., Levey, A.I., Rye, D.B., Mesulam, M.M., Mufson, E.J., 1985. Cholinergic and non-cholinergic septohippocampal pathways. *Neurosci. Lett.* 54, 45–52.
- Wan, H., Aggleton, J.P., Brown, M.W., 1999. Differential contributions of the hippocampus and perirhinal cortex to recognition memory. *J. Neurosci.* 19, 1142–1148.
- Wise, S.P., Murray, E.A., 1999. Role of the hippocampal system in conditional motor learning: mapping antecedents to action. *Hippocampus* 9, 101–117.
- Witter, M.P., Groenewegen, H.J., Lopes da Silva, F.H., Lohman, A.H.M., 1989. Functional organisation of the extrinsic and intrinsic circuitry of the parahippocampal region. *Prog. Neurobiol.* 33, 161–253.
- Worsley, K.J., Friston, K.J., 2000. A test for a conjunction. *Stat. Probab. Lett.* 47, 135–140.
- Yonelinas, A.P., 2002. The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517.
- Yukie, M., 2000. Connections between the medial temporal cortex and the CA1 subfield of the hippocampal formation in the Japanese monkey (*Macaca fuscata*). *J. Comp. Neurol.* 423, 282–298.
- Zeineh, M.M., Engel, S.A., Thompson, P.M., Bookheimer, S.Y., 2003. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science* 299, 577–580.