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Item, context and relational episodic encoding in humans

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Recent functional imaging work supports the view that item and relational memory depend upon distinct encoding operations within the medial temporal lobe. Specifically, emerging findings demonstrate that the level of engagement of perirhinal cortex predicts later memory for individual items, whereas the level of hippocampal processing correlates with later relational memory, or recovery of additional episodic details. Furthermore, recent functional magnetic resonance imaging evidence in humans suggests that medial temporal lobe cortical input structures, the perirhinal and posterior parahippocampal cortices, differentially participate in the encoding of objects and their context, providing domain-specific input to the hippocampus. Taken together, these data help to construct a working model of how distinct medial temporal lobe structures participate in episodic memory formation with domain-general relational binding mechanisms supported by the hippocampus and provide emerging evidence for domain-specificity within the perirhinal and parahippocampal cortices.

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Introduction

One of the most impressive characteristics of the human mind is the ability to use information gained from previous experiences to guide decision-making and behavior in novel contexts. For example, imagine you are at a dinner party and offer red wine to someone you have just met. She accepts, citing that she prefers red wine with steak, but white wine in most other circumstances. Months later, you meet her again at another dinner party at which pasta is being served. You offer her white wine, and she smiles in acknowledgement of your fine memory. This simple kindness would be impossible without the ability to form and retrieve memories that contain relationships between the elements or items present during a

previous experience (e.g. the guest and red wine) and the context in which those elements occurred (e.g. during a steak dinner).

A fundamental question in the science of memory is whether these different forms of memory — for the individual items in an episode versus for the relationship among those items — are expressions of distinct underlying mnemonic mechanisms [1–6] or, rather, reflect differing levels or strengths of a single encoding mechanism. Recent work has begun to illuminate how the different elements of an experience — the objects and the context — are encoded within the medial temporal lobe (MTL).

The following review focuses on recent functional magnetic resonance imaging (fMRI) data relevant to understanding the functional organization of the human MTL system by addressing first, whether distinct neuroanatomical regions within the MTL support item and relational memory formation, second, whether evidence supports a domain-specific role for human MTL cortical regions (perirhinal [PrC] and posterior parahippocampal [PhC] cortices) and third, the implications of these findings for psychological theories of memory formation. Because of the difficulty of obtaining good signal-to-noise in the human entorhinal cortex using functional imaging, a crucial gateway between PrC, PhC and the hippocampus, discussion herein focuses on the role of the hippocampus, PrC and PhC only.

Neuroimaging evidence for separable medial temporal lobe encoding mechanisms

Neuroimaging studies during the past three years have provided support for the broad notion that distinct MTL regions contribute differentially to episodic memory formation [7,8,9^{*},10^{*},11–15]. Specifically, subsequent memory (SM; [Box 1](#)) studies have demonstrated that the magnitude of activation in the human hippocampus during encoding correlates with later objective and subjective indices of relational memory. These indices have included remembering that two items were previously presented as a pair [10^{*},11,16], remembering the context in which an item was initially encountered [7,9^{*},12], remembering the color or spatial location of a previously presented item [14,17^{**}] (Dougal *et al.*, unpublished) and having a subjective sense of ‘remembering’ compared with that of ‘knowing’ [13].

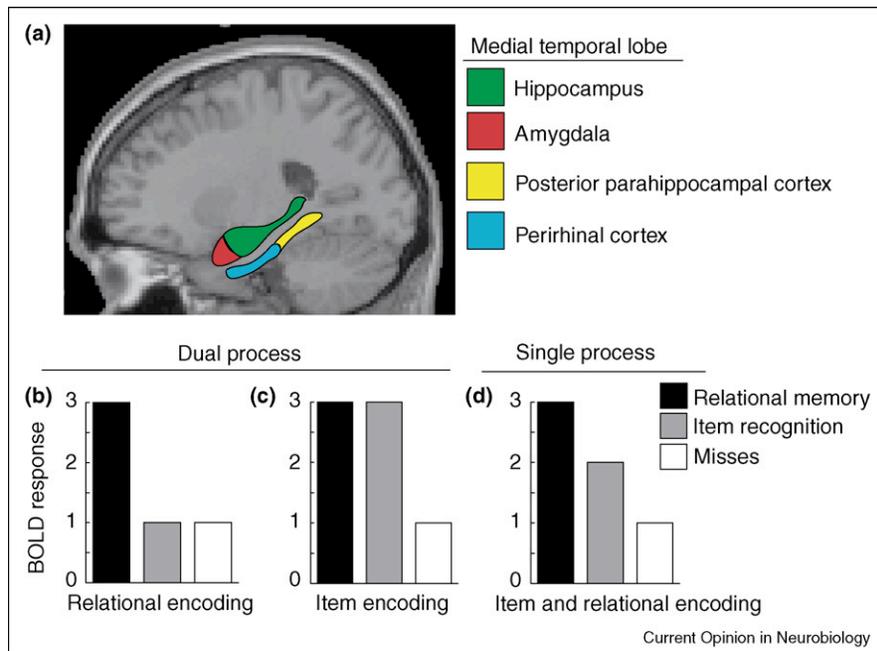
However, of utmost relevance to theories of memory is whether these effects are specific to relational memory or, instead, whether hippocampal processing additionally

Box 1 Measuring relational memory

The subsequent memory (SM) paradigm enables the analysis of brain activation patterns during the performance of an encoding task (e.g. making an abstract or concrete decision about each word) to be based on each individual subject's performance on a later memory test. One can, thus, compare brain activation during the encoding of words later remembered with that of those later forgotten [61]. This approach has been widely used to reveal the neural processes differentially supporting relational memory by contrasting the SM effects correlated with recognition of individual items from a previous study episode (i.e. item memory) with SM effects correlating with the recovery of additional episodic information (i.e. relational memory). Furthermore, the SM paradigm can be used to reveal patterns of brain activation correlated with both objective (e.g. source memory paradigms) and subjective (e.g. remember/know paradigm [62,63]) measures of relational memory. The advantage of objective tests is that mnemonic recovery can be verified. Their disadvantage, however, is that recollection is usually conditionalized on the recovery of only one bit of critical information, which raises the possibility that any given trial could be mislabeled as not involving memory of details when, in fact, many details – albeit not the specific kind of detail that the memory test is designed to assess – are available. By contrast, subjective memory tests enable an all-inclusive, albeit subjective, measure of relational memory because the subjects are asked to decide for any given trial whether they are able to recall any additional episodic details.

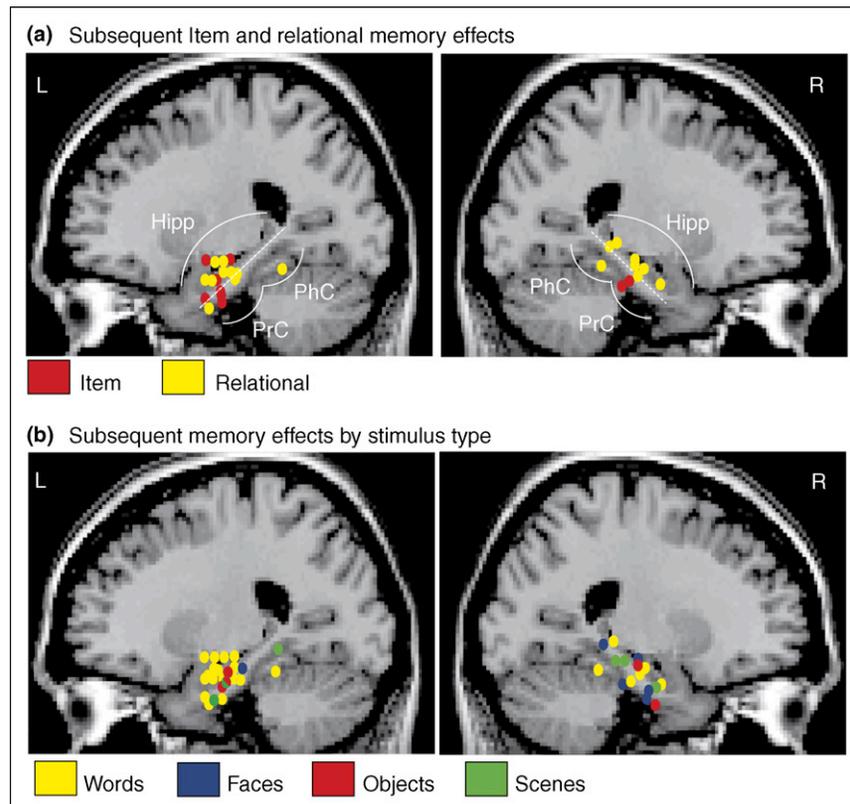
also supports item recognition. The finding that hippocampal processing supports item recognition would provide evidence for a single general encoding process. To test these predictions, it is necessary to assess both successful relational memory and successful item recognition. This would enable one to determine whether activation in a brain region is consistent with relational binding (Figure 1b), item encoding (Figure 1c) or, rather, shows a pattern consistent with a single encoding process supporting both item and relational encoding (Figure 1d).

Only a subset of the studies examining episodic relational encoding contemporaneously enable the assessment of item encoding, which requires comparison of encoding activation during trials that lead to later successful item recognition with that during trials that lead to unsuccessful item recognition or missed items. However, of that subset, the overwhelming majority has provided evidence that hippocampal encoding activation is, indeed, specifically correlated with relational memory outcome, with hippocampal activation not distinguishing between items later recognized and those forgotten (Figure 1b). Conversely, in many of those same studies, activation in the PrC correlates with later item, but not relational, memory

Figure 1

The human medial temporal lobe and encoding activation predictions of single and dual process models. **(a)** Anatomical subregions of the medial temporal lobe displayed on a sagittal section taken from the Montreal Neurological Institute normalized template in SPM99 (Wellcome Department of Cognitive Neurology, London). **(b–d)** Hypothetical patterns of BOLD response in brain regions involved in item encoding, relational encoding or both as predicted by single and dual process accounts. A dual-process account predicts that a region important in relational encoding (b) will exhibit a pattern of activation distinct from one participating in item encoding (c). A single-process account would predict that brain regions important in memory formation show a pattern of brain activation consistent with both item encoding (i.e. item recognition > misses) and relational encoding (i.e. relational memory > item recognition). Data reviewed herein provide data consistent with dual encoding mechanisms, such as those schematized in (b) and (c).

Figure 2



Location of medial temporal lobe subsequent memory effects. **(a)** Peak subsequent memory effects taken from extant studies designed to directly contrast item and relational memory effects. Relational SM effects are predominantly seen in bilateral hippocampus and PhC while item SM effects are commonly seen in PrC. Data were plotted on left and right sagittal sections using MRIcro image viewer (<http://www.sph.sc.edu/comd/rorden/micro.html>). Peak coordinates from studies reporting Talairach coordinates were converted into approximate MNI coordinates (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>). **(b)** Peak subsequent memory effects plotted by stimulus type. Note the dominance of left lateralized SM effects in studies using verbal stimuli contrasted with bilateral effects for objects and scenes and primarily right lateralized effects for faces. Abbreviations: Hipp, hippocampus; L, left; PrC, perirhinal cortex; PhC, posterior parahippocampal cortex; R, right; SM, subsequent memory (data plotted are drawn from [7,9*,10*,11–16,17**,18,19*,37–39,40*] and Dougal *et al.*, unpublished).

[7,9*,10*,12] (Dougal *et al.*, unpublished, but see [18]; Figure 2a). Taken together, these data support the notion that episodic encoding is mediated by distinct encoding processes, and suggest that PrC mechanisms support the encoding of the individual elements of an episode, whereas hippocampal processing supports the relational binding of the individual elements together and/or the binding of these elements to the context of the episode. Unlike PrC and hippocampal SM effects, the data for the posterior parahippocampal cortex (PhC), are equivocal, with some studies reporting correlations with item memory [10*,18] and others with relational memory [7,9*,10*,12] (see below).

With regard to hippocampal processing, a striking finding across these studies is that a very similar region of the hippocampus, namely the left anterior hippocampus, is often reported as the focus of relational SM effects (Figure 2a, left panel) [19*,20]. As most of these studies have used verbal stimuli as memoranda, it is possible that

the left lateralization of these effects is driven by the study materials. Indeed, examination of the location of SM effects across different categories of memoranda (e.g. faces, words, scenes and objects) reveals a striking left lateralization for verbal materials and right lateralized or bilateral effects for all other stimulus classes (Figure 2b). However, the anterior versus posterior focus of the hippocampal SM effect still remains a mystery, and raises the possibility that subregional functional architecture exists within the hippocampus [11,21,22].

Domain-specific episodic encoding along medial temporal lobe cortex

As briefly alluded to above, although PrC processes correlate with item memory in studies typically using words as memoranda, SM effects in regions further posteriorly along the parahippocampal gyrus (PhC) have been equivocal. Thus, the item versus relational dichotomy does not appear to have sufficient explanatory power to characterize the entire MTL system. However, much

evidence, primarily arising from animal work, has shown that PrC and PhC might be responsive to different aspects of an experience. These MTL cortical regions receive different complements of input from neocortical association cortex [23], and neurophysiological data support a distinction between the responses of neurons in PrC and those in the PhC during the processing of object and spatial/contextual information, respectively [24]. A simple extension of this notion to the human MTL cortex raises the possibility that the consistent finding of subsequent item memory effects in human PrC is driven by the fact that the precise bits of information, or 'items', that are presented to subjects represent a domain of information processing that is preferred by the PrC. Furthermore, this also begs the question of whether SM effects in PhC are domain-specific.

What exactly are the informational domains that human PrC and PhC represent? Evidence is mounting in humans to suggest that pictures of objects invoke robust activation of human PrC [25,26,27^{••},28]: similar to the animal work, an enhanced response has been observed here during novel object presentations, but not during presentation of a novel spatial arrangement of familiar objects [28]. However, the precise nature of the PrC representation remains unknown. It has been suggested that the PrC representation extends that supported by more posterior inferotemporal regions by incorporating multi-modal features [27^{••},29], abstract conceptual information [27^{••},30] and helps to disambiguate stimuli with highly overlapping features [31,32]. In other words, this recent body of work suggests that the PrC supports the representation of surface features or properties of objects (e.g. a banana is yellow and has a tough skin) in addition to, perhaps, non-surface features, such as semantic or conceptual properties (e.g. a banana is edible and tastes good; Figure 3). Indeed, supporting the notion that PrC mechanisms might bind together item-level features, a recent SM study reported PrC encoding activation correlating with later relational memory when the encoding task stressed item–feature integration (e.g. the color of the item) and the source test required recovery of that feature of the presented item [17^{••}]. Taken together with previous work, these findings suggest that the PrC is crucial for item encoding but might also support associative encoding between the multiple features of each item (this notion is crucially different from the notion that perirhinal processing is strictly related to the subjective sense of familiarity [9], because it additionally suggests that perirhinal computations contribute to the recollection of object and object features). A crucial question is how the neural mechanisms supporting the formation of within-item associations (e.g. yellow banana) differ from those supporting between-item (e.g. banana and peach), or relational, associations. One possibility, discussed by Cohen *et al* [2], is that the within-item associations are configural and less flexible than those between items.

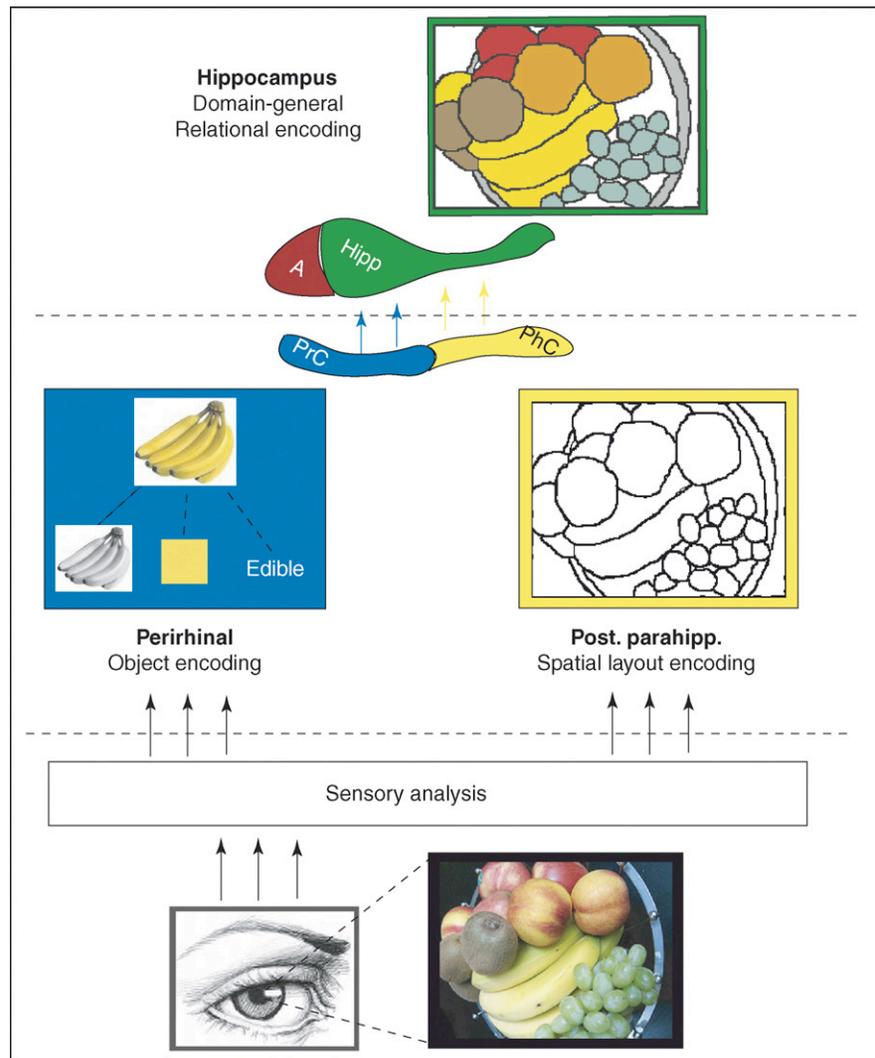
Future work should help to discriminate between the different forms of associative learning supported by MTL cortical regions and the hippocampus.

The human PhC contains a region at its most posterior extent that differentially responds during the viewing of scenes compared with during the viewing of objects and faces [33], suggesting that it is involved in the processing of spatial relationships. These findings fit nicely with recent rat work showing that lesions to postrhinal cortex (approximately equivalent to monkey PhC) lead to selective deficits in binding objects to a particular environmental context, but not in memory for the objects themselves [34]. Consistent with a purported role for PhC in encoding of spatial context, fMRI studies using pictures of landscapes as memoranda [35–39] or those asking subjects to imagine a spatial layout corresponding with a word [7,18], have reported SM effects in the PhC. In contrast, although relatively few studies have used objects as memoranda, those that have, or that have had subjects imagine a concrete referent of a word, report SM effects in PrC, but not PhC [17^{••},40[•]] (Figure 2b). Furthermore, preliminary, recent data have suggested that not only spatial context but perhaps also non-spatial context is represented in PhC [41], albeit in a more anterior region. Future work should help to reveal more about what contextual aspects of an episode are represented by the PhC, whether spatial and non-spatial context are represented in spatially distinct regions and, importantly, how PhC representations of context differ from the relational representations supported by the hippocampus.

Hippocampus and relational processing

In contrast to the domain-specificity observed for human MTL cortex, hippocampal relational binding mechanisms are proposed to be domain-general ([3] but see [42]), as they forge these distinct object and contextual representations into a coherent episodic trace. In support of domain-generality, hippocampal SM effects have emerged from studies employing variable types of encoding tasks and stimuli from different representational domains (faces [10[•],11,16], words [7,9[•],12–14,17^{••},40[•]] [Dougal *et al.*, unpublished], scenes [12,37,40[•]] and objects [43]). Furthermore, there is a wealth of findings, not reviewed here, demonstrating hippocampal activation during episodic retrieval that differentially correlates with relational memory [10[•],21,43,44,45[•],46–50] (interestingly, evidence for differential perirhinal and hippocampal retrieval mechanisms is not as consistent as that seen during encoding, during which perirhinal, in addition to hippocampal, recollection effects have been reported. During retrieval, it is possible that a fast item recognition process precedes relational recovery through hippocampal mechanisms, but that this relational recovery then leads to additional engagement of perirhinal representations reactivating object and semantic representations.

Figure 3



Graphical summary of extant findings on the role of distinct MTL subregions in memory formation. It is thought that stimulus identity is processed in parallel to contextual information such as the spatial layout of a perceived environment. Emerging evidence suggests that perirhinal cortex processes and encodes high-level featural and semantic information of the elements within an episode while posterior parahippocampal cortex appears to be sensitive to the spatial layout, or context of an experience. Both of these regions provide input, primarily via the entorhinal cortex, into the hippocampus that subserves the relational integration of these elements into a coherent representation. Abbreviations: A, amygdala; Hipp, hippocampus; PhC and Post; Parahipp, parahippocampal gyrus; PrC, perirhinal cortex.

Because fMRI does not have fine temporal resolution, other techniques, such as MEG [51], are necessary to address this possibility).

In fact, the ubiquity of the correlation between hippocampal engagement and relational encoding is so striking that recent work has focused on determining whether relational processing could be a core process subserved by hippocampal mechanisms, one that even transcends the long-held notion that hippocampal function is specialized to support long-term explicit memory. For example, recent work with amnesiacs suggests that MTL damage leads to deficits of implicit or unconscious memory

[52–55], working memory [56,57,58**] and even perception ([59] but see [60]), as long as the information to be retained is relational in nature.

Conclusions: implications of these data for single and dual process accounts of memory

The evidence presented herein, along with many findings not covered in this review (e.g. data from neuropsychological patients, memory studies using subjective measures of recollection and familiarity, and fMRI data collected during retrieval), provides evidence that the hippocampus supports domain-general relational processing [2,3]. At the same time, evidence is emerging that

perirhinal and posterior parahippocampal mechanisms contribute to domain-specific item and spatial contextual encoding. It is important to note, however, that these dissociations do not provide evidence for the independence of item and relational memory. Indeed, a double dissociation between item and relational learning has yet to be shown. Specifically, extant data do not demonstrate that relational learning can occur without item encoding also occurring at the same time.

Given the lack of a double-dissociation, a single-process theorist might argue that the MTL system can be viewed as a 'single system' supporting episodic memory formation, albeit with different brain regions contributing to different aspects of the mnemonic trace (e.g. object and context encoding). This is a view to be taken seriously and suggests that it might be fruitful to move beyond discussions about single versus dual processes into more detailed debate regarding the form of representation and contribution of individual MTL regions to memory formation. Future work should focus on revealing the nature of representational capacities of the MTL cortical input structures, the PrC, PhC and the entorhinal cortex, taking advantage of their domain-specificity by both using optimal stimuli and adopting high-resolution MR techniques that are necessary to decompose the contributions of these neighboring MTL regions.

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Striking demonstration that amnesiac patients are impaired in working with relational representations even at very short delays, calling into question the long-held notion that the medial temporal lobe is important only for long-term memory. This study also further bolsters the notion that relational processing could be the fundamental process supported by hippocampal mechanisms. Furthermore, the authors demonstrate that the short-term relational memory impairment is domain-general, applying to both spatial relationships and face–scene relationships.

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