Review TRENDS in Cognitive Sciences Vol.11 No.3

Associative memory and the medial temporal lobes

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Associative recognition and recall depend on structures in the medial temporal lobes (MTLs). There is disagreement about whether associative memory is functionally heterogeneous, whether it is functionally distinct from intra-item associative memory and how the MTLs contribute to this kind of memory. Despite an increase in research on associative memory, work has lacked a theoretical framework to guide design and interpretation of studies. One view provides a useful framework by postulating that associative memories differ in the degree to which their informational components converge in MTL structures that create familiarity-supporting or recollection-supporting memory representations. Using this framework, we consider psychological, lesion and functional imaging evidence, highlighting how informational convergence in the brain underlies the associative nature of both memory and perception.

Introduction

Declarative memory comprises memory for personal experiences (episodic memory) and for facts and concepts (semantic memory). Declarative memory is essentially associative, linking together component parts (e.g. words and objects) either directly or via spatial, temporal or other kinds of relationships. These components are represented by neural activity in different parts of the neocortex that project to the medial temporal lobes (MTLs) where they are integrated to create associative memories. At retrieval, one component can cue recall of other components, which reactivates part or all of a 'memory'. Therefore, recall is inherently associative. Alternatively, previously encoded episodic or semantic information can be recognized. According to the dual-process model [1,2], recognition memory is mediated by recollection and familiarity. Recollection is cued recall of associated information within a recognition situation; familiarity involves no recall and occurs when exposure to information leads to a 'feeling' of memory.

Some researchers believe that familiarity occurs only for item memories and not for inter-item associations (e.g. Ref. [3]). However, others believe that familiarity also occurs for inter-item associations (e.g. Ref. [4]). Items (e.g. cars) comprise components (e.g. lights and windows) that are bound together in such a way that they are, typically, consciously perceived and remembered as single entities. Therefore, item memories are also associative. New items (e.g. unknown words or faces) can be created at encoding through a process of unitization or intra-item association, which binds components together, often using an established spatial framework (e.g. the layout of a face). This creates a representation that is usually perceived and remembered as one entity. However, there are no objective criteria for identifying whether unitization has occurred. The occurrence of unitization needs to be identified by markers other than the presence of familiarity. When two items are encoded together without an obvious 'object-creating' framework, it is difficult to prove that a new item has been created when the result does not 'feel' unequivocally like an entity. Intuitively, the speed with which new item memories are formed should depend on how easily components fit into a pre-existing template (e.g. a face framework). However, identification of such templates is subjective and, therefore, there might be disagreements. Progress is possible provided that associations that are agreed to be unitized carry measurable costs (e.g. greater difficulty in perceiving and recognizing components) that are not shared by equally well-learned associations that are agreed to be non-unitized.

Despite these difficulties, investigation is needed into whether the functional and neural bases of intra-item associative memory and non-unitized inter-item associative memory differ. Furthermore, inter-item associative memories have distinct characteristics that might have functionally and neurally different bases. Thus, within-domain associative memories are not perceived and remembered as one entity. They form between the same or very similar kinds of items (e.g. two faces; a door and a window) that are likely to be represented by activity in closely adjacent and interacting neocortical neurons. The items in these memories feel like they 'go together', but they do not form a single entity. Between-domain associative memories are also not perceived and remembered as one entity. They form between different kinds of items that might come from distinct sensory modalities (e.g. face–voice) or link items spatially, temporally or via another kind of relationship (e.g. A angered B). These items and relationships are likely to be represented by patterned activity in relatively distant and weakly connected neocortical neurons. This processed information feeds into the MTLs where it is integrated to create associative memories and possibly perceptual representations.

Declarative memory comprises intra-item, within-domain and between-domain associations that are bound into memory in the MTLs (Figure 1). How well each of these kinds of associative memories supports

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Available online 31 January 2007.

 1364-6613/$ – see front matter doi:10.1016/j.tics.2006.12.003

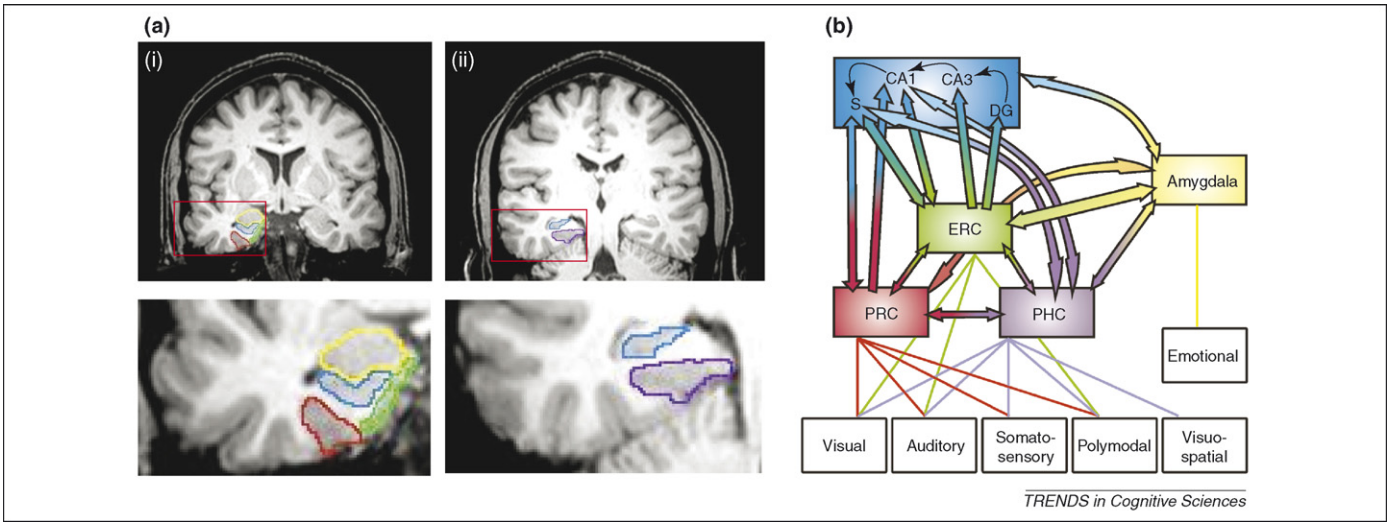

Figure 1. Medial temporal lobe components, connections and inputs. **(a)** An anterior (i) and a posterior (ii) coronal section of a normal brain. Beneath each section is an enlargement of the red boxed area, the left medial temporal lobe (MTL). The left perirhinal cortex (PRC) is shown in red, the entorhinal cortex (ERC) in green, the parahippocampal cortex (PHC) in purple, the hippocampus in blue and the amygdala in yellow. **(b)** The main interconnections of these regions. The kinds of processed sensory and emotional information that project to these areas from other neocortical regions are shown in white boxes at the bottom of the figure. Semantic inputs are not illustrated, but they perhaps reach the MTLs from temporal pole and frontal regions [79]. The inputs illustrated comprise information of which the low-level components have already been associated and which is projected into the MTLs where higher-level association occurs. The MTL is, therefore, a top-level association system, and the hippocampus is the highest-level associator within the MTL. It is disputed whether these top-level associations are of perceptions as well as memories [73,74]. Several subregions of the hippocampus are illustrated, including the subiculum (S), the dentate gyrus (DG), and the two largest fields of the hippocampus proper (cornu ammonis) that feature most often as related to memory processing (CA1 and CA3). Connections in (b) are specified in Ref. [80].

familiarity and recollection should be fully explored using appropriate memory-testing procedures (Boxes 1 and 2). Current views on how the MTLs support the processes that underlie these associations are discussed below, after which psychological, lesion and functional neuroimaging evidence that discriminates between these views are considered in turn.

The role of the MTLs in associative memory

One view that implies neurofunctional differences among intra-item, within-domain and between-domain memories states that different MTL structures mediate within-domain and between-domain memory in qualitatively distinct ways [4]. This domain dichotomy (DD) view proposes that the perirhinal cortex has a key role in mediating recognition memory for unitized associations and for non-unitized, within-domain associations (e.g. face–face associations) (Figure 2). The perirhinal cortex supports familiarity for these kinds of association. By contrast, within the MTLs, only the hippocampus helps mediate memory for between-domain associations (e.g. scene–sound). These associations include not only associations that involve space and time [5] but also non-spatiotemporal associations (e.g. face–voice). More generally, the hippocampus creates memory links between any associative memory or any individual component (e.g. eyebrows) and contextual or other information. These associative memories are highly interconnected, but flexible; therefore, recall of their individual or associated components can be triggered by many cues, including components, groups of associated components and study context information (Box 3).

The distinct functional roles of the perirhinal cortex and hippocampus are explained by a neural-network model [6]. In this model, it is proposed that the hippocampus binds its inputs into memories using a pattern-separation algorithm that makes distinct memory representations even of similar inputs [6]. Pattern separation is particularly suited to enabling pattern completion (i.e. cued recall). Therefore, the hippocampus supports associative recognition through recollection of encoding-context details that are linked to the studied association, which all acts as a cue in recognition tests (recall-to-accept). The hippocampus also supports recall using components as cues to retrieve other associated components (e.g. a face acting as a cue for a voice). By contrast, the perirhinal cortex, as a neocortical structure, binds its inputs into memory representations using a different, pattern-generalizing algorithm that identifies the common features, even in distinct inputs. When learning is rapid, this algorithm provides poor support for pattern completion but good support for familiarity.

According to the DD view, the perirhinal cortex does not just bind intra-item components; within-domain components also converge and interact mainly within it, so it is easy for them to bind there. By contrast, between-domain components are likely to be represented in relatively distal, minimally interacting, cortical regions and will not converge adequately within the perirhinal cortex. Rather, they will converge mainly, if not solely, within the hippocampus, which is where between-domain associations will be bound, using the pattern-separating algorithm. These neuroanatomical ideas imply that convergence in the perirhinal (and perhaps parahippocampal) cortices is a matter of degree, so some between-domain associations might converge sufficiently within the perirhinal cortex to be bound there. How memory-binding convergence should be measured is unclear (Box 4), but these ideas suggest that dependence of associative recognition on recollection will increase as pre-hippocampal convergence reduces and familiarity-supporting memory representations weaken.

Box 1. How to measure associative memory

Memory for intra-item, between-domain or within-domain associations can be measured using recognition tests. To distinguish between different neural and functional accounts of associative memory, tests must reveal exactly what is being remembered and whether memory depends on familiarity or recollection. If recognition is to measure any kind of associative memory, it must tap the ability to discriminate between studied associations (targets) and unstudied associations (foils) that comprise recombinations of studied components. In recombination tests, studied intra-item and inter-item associations cannot be discriminated from their (unstudied) foils without memory for the associations between their components (Figure I in this box). This is because familiarity for components of studied and unstudied associations should be matched. Recognition tests that use foils that comprise associations between unstudied components should be avoided because such tests can be completed by identifying individual studied components so that memory for studied associations is not strictly necessary for success.

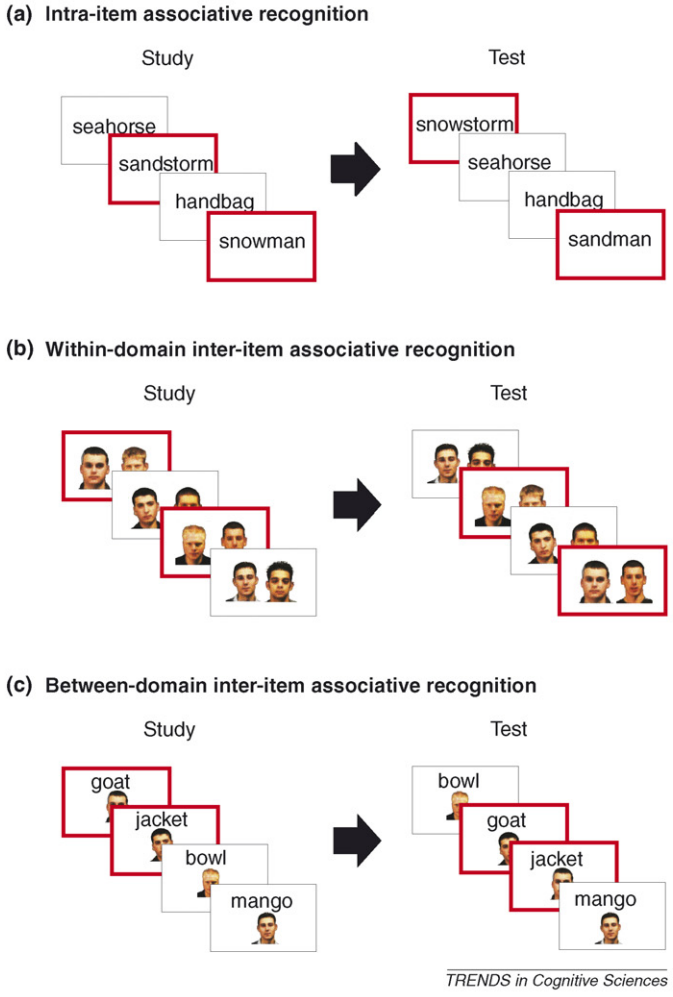

Figure I. Recombination associative recognition memory tests. The three sections illustrate recombination tests, which are the most appropriate means of examining what is remembered in intra-item **(a)**, within-domain **(b)** and between-domain **(c)** associative recognition tests. Associations, the components of which are recombined at the test (foils) stage, are shown with a red outline, compared with previously studied associations, which have no outline. These tests contrast with standard item-recognition tests, in which all components of the foils are completely unstudied. The main point to note about the recombination associative recognition tests is that the foils are constructed from studied components that did not appear together at the study stage. Therefore, they cannot be discriminated from the studied associations on the basis of the familiarity levels of their component parts. If familiarity underlies recognition discriminations between studied associations and recombination foils, then memory must be for the studied association. However, if recollection underlies recognition, then memory could be for more complex associative information. Thus, previously studied intra-item and within-domain associations can cue recollection of spatiotemporal contextual information that confirms recognition (recall-to-accept). Alternatively, recombined associations can be rejected when a component cues recollection of another component that occurred with it at the study stage (showing that the recombined component(s) could not have been associated at study), perhaps with linked source information (recall-to-reject). Therefore, with both kinds of recollection, recognition of studied intra-item and within-domain associations might depend on memory for between-domain associations. Measuring familiarity and what is being recollected is the best way to advance theory.

An influential view that lies at the opposite extreme to the DD view is that intra-item and non-unitized kinds of associative memories, as well as recollection and familiarity, are processed in a qualitatively similar way by the main MTL structures (apart from the amygdala), although their contributions might differ in extent [7]. The view implies that input and regional cytoarchitectonic differences relate to forms of functional differentiation that have not, as yet, been described.

Other positions lie between these two views. One view holds that familiarity is found only for intra-item associations. Non-unitized associative memories, whether they are within- or between-domain, must rely primarily on hippocampally mediated recollection (e.g. Ref. [3]). This

view predicts that there should be minimal familiarity for face–face associations after one or two learning trials because there is subjective agreement that such associations are non-unitized. Another possible view is that hippocampally mediated, between-domain associative memories support familiarity as well as recollection. This view implies that familiarity for between-domain associations is neurofunctionally distinct from familiarity for perirhinal cortex-dependent unitized and within-domain associations. The predictions of these different views can be explored using psychological evidence.

Psychological evidence from normal subjects

The views described above make different predictions about how well recognition of within- and between-domain associations is supported by familiarity. There is evidence that recognition for rapidly acquired intra-item associations is well supported by familiarity (e.g. Ref. [3]). Most research on within-domain associations has focused on learning to associate unrelated pairs of words. Initially, this research suggested that there was little, if any, familiarity for rapidly learned associations, only recollection for them [8,9]. However, recent research has suggested that good levels of familiarity can be found for word–word associations [10,11].

Research also suggests that the level of familiarity that is found for rapidly learned word–word associations is a function of how pairs are encoded [11]. If unrelated word pairs (e.g. 'sea' and 'cube') are treated as compound words with specific meanings (e.g. a 'cube' to hold 'sea' water), then familiarity alone can discriminate at levels close to those that are achieved using recognition (where recollection can be used). However, when word pairs are encoded within a sentence that links them indirectly, then familiarity levels are poor [11]. This suggests that convergence within the perirhinal cortex is insufficient to create rapidly a within-domain association that supports familiarity. To achieve this, components need to be encoded directly together, without a mediator. When encoding links items using a mediator (e.g. a sentence), recollection becomes necessary for recognition at the test stage. No template exists for face–face pairs, another kind of within-domain association. However, using the familiarity-only procedure (Box 2), C. Bastin, M. Van der Linden, C. Schnakers, D. Montaldi and A.R. Mayes (unpublished) found that familiarity and recognition levels were close for rapidly learned face–face pairs. Subjects directly related paired faces by thinking about how well they went together.

There has been little research to examine familiarity for rapidly learned between-domain associations. Yonelinas [3] has shown that, whereas familiarity develops rapidly for studied faces versus recombination face foils (intra-item associative face memory), little familiarity is found under these conditions using inverted faces. No template links inverted face components, so non-unitized shape–position associations must be learned. This work suggests that familiarity levels are low for these rapidly learned between-domain associations. C. Bastin *et al.* (unpublished) also found that familiarity robustly supported rapidly learned face–face but not face–name associations, although the encoding method slightly influenced how strongly familiarity supported face–name associations. Although further work is needed, consistent with the DD view, it currently seems as though familiarity is more robust for intra-item and within-domain associations than for between-domain associations. However, lesion evidence is required to explore the role of the MTLs.

Human and animal lesion evidence

The DD view predicts that selective hippocampal lesions will disrupt recognition of between-domain associations but only mildly disrupt within-domain and intra-item associative recognition. The extent of the recognition deficit should be a function of how well familiarity memory can support recognition. The patient YR, who had relatively selective hippocampal lesions, showed the pattern of recognition that is predicted by this view. YR's item familiarity was normal [12] and her performance on item recognition tests, using recombination foils, was unimpaired, as was her discrimination on intra-item and within-domain associative tests [13]. By contrast, YR's recognition of between-domain associations fell significantly below that of controls (Figure 3). This is consistent with animal work that shows both fornix and hippocampal lesions disrupt rapid learning of non-spatial associations between visual stimuli and motor responses [14], as well as spatial associative recognition (e.g. Ref. [15]). Other animal work has used slow associative learning that would have relied on different neural mechanisms (e.g. Refs [16,17]).

Similar results have been found in three hypoxic patients who have early and selective hippocampal damage [18]. These patients were unimpaired at recognizing pairs of words, non-words, unknown faces and famous faces after one or several study trials. By contrast, their recognition of object–location and face–voice associations was impaired, as was their recall. Furthermore, one of these patients showed normal ERP correlates of familiarity but not recollection [19]. Barbeau *et al.* [20] found that a post-encephalitic patient who had bilateral hippocampal damage showed impaired recall but relatively normal visual item recognition. Consistent with this, the patient's picture familiarity, but not recollection, was spared. Interestingly, the patient acquired recognition of abstract picture pairs at a normal rate, which was expected given her preserved visual familiarity and relatively focal right-sided MTL damage. Her extensive left parahippocampal gyrus damage explained her impaired recognition of single words and, therefore, also her impaired recognition of verbal–verbal and verbal–visual associations. Although other hippocampal patients have not been systematically tested, several have shown impairments on between-domain recognition [21–23].

The DD view predicts that within-domain recognition will fall within normal limits only when (i) associative components are directly linked at encoding so as to enable associative familiarity to form, and (ii) associative familiarity reliably indicates memory at test. Illustrating the encoding effect, three hypoxic amnesics who had putative hippocampal damage were found to be impaired at word–word recognition following an indirect sentence-encoding procedure, but they performed within normal limits following the word-definition direct-encoding procedure [11]. Following sentence encoding, Giovanello *et al.* [10,24] twice

found a similar deficit in word–word recognition in MTL-lesioned patients, some of whom had scans that suggested relatively selective hippocampal damage. Using the remember/know procedure (Box 2), they also found that this kind of encoding led to good recollection but poor familiarity in normal subjects [10]. Illustrating test effects, repetition made familiarity unreliable in YR [4] and in patients who had fornix damage [25]. Patients' old–new face recognition was relatively normal, but their recognition became impaired with test repetition. Face–face recognition deficits were probably found in other patients who had putative hippocampal lesions [23] because the testing procedure used foils repeatedly, which made familiarity unreliable. Associative familiarity should have developed for foil associations and made recollection necessary for identifying studied associations. The sensitivity of face–object associative recognition to different kinds of MTL damage in temporal lobectomy patients could also have been influenced by a similar testing procedure [26].

Some lesion data seem to conflict with the DD view. Thus, Stark *et al.* [27,28] used different pairings of face and house pictures and matched patient and control item recognition by providing easier conditions for patients. Use of this procedure indicated that hippocampally damaged patients were equally impaired at old–new item recognition, intra-item associations and within-domain associations. However, these findings probably arose because these patients had severe familiarity as well as recollection deficits (e.g. Ref. [29]). Although it remains unresolved why some patients who have apparently selective hippocampal lesions show familiarity deficits (e.g. Refs [29,30]) and others do not (e.g. Refs [12,19,20,22,31,32]), the DD view predicts that when familiarity, as well as recollection, is impaired, then intra-item and within-domain recognition will also be impaired. In general, lesion data favour the DD view, but it is important to find convergence within the neuroimaging literature.

Box 2. The modified remember/know procedure

Remember/know procedure [67,68]

Using the remember/know procedure, subjects are asked whether stimuli are recognized because they are remembered (recollected) or because they are known (familiar without recollection). Subjects sometimes say 'remember' not because they have recalled but because the stimulus felt familiar. Adequacy of instructions and training is variable and, therefore, reliability of familiarity and recollection reports is suspect. Even accurate reports lead to familiarity estimates that can vary greatly, depending on the assumed statistical relationship with recollection (Figure I in this box). This relationship is unknown and could vary.

Modified remember/know procedure [39]

In the modified remember/know procedure, subjects are trained how to identify when a stimulus has been recollected or when it has been found to be familiar without recall. Preferably, direct evidence of what has been recalled is required. Recognition, familiarity and recollection conditions are run separately. In the familiarity-only procedure, subjects focus on familiarity feeling judgements; they do not actively try to recollect but they report recollection if it occurs involuntarily. Because recollection levels are low, accurate estimates of familiarity are possible that are little changed by the familiarity–recollection statistical assumption (Figure II in this box, next page). In the recollection-only procedure, subjects actively try to recollect and report recalls-to-reject as well as recalls-to-accept (see Figure I in Box 1). Extensive work in our laboratory has shown that participants perform reliably on these tests [39].

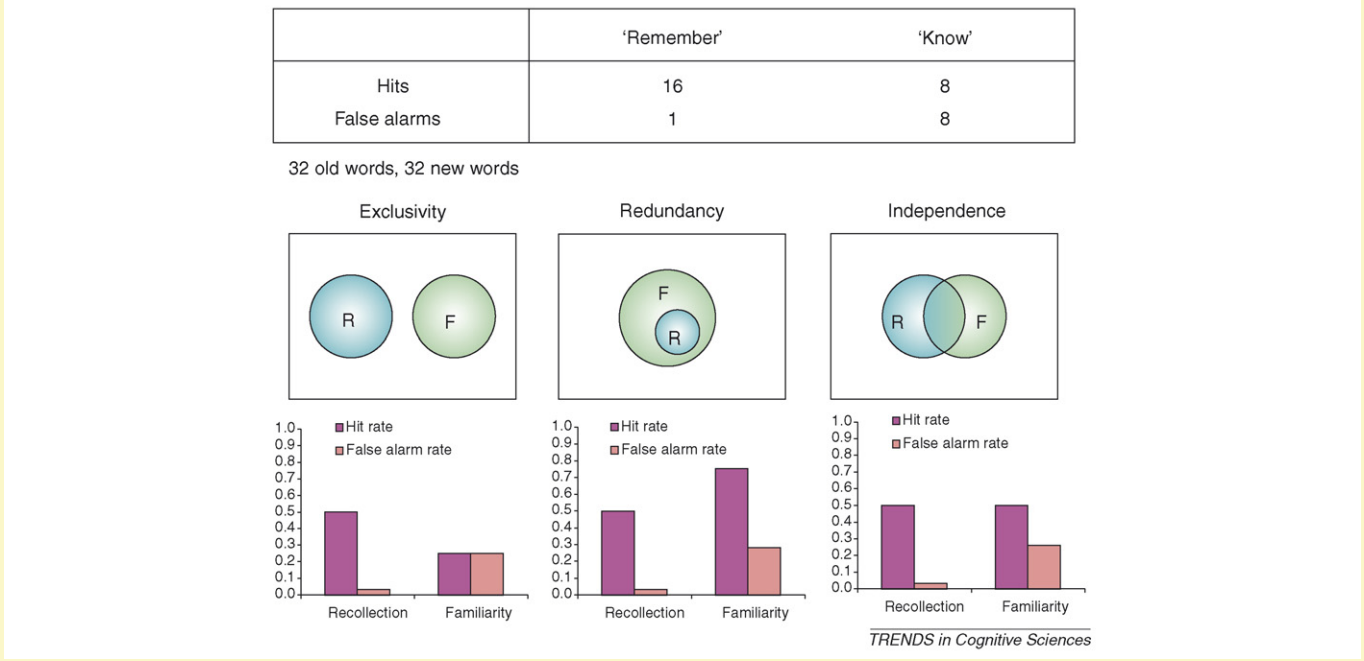

Figure I. Estimating familiarity with the standard remember/know procedure. These simulated data illustrate how much familiarity estimates can vary when levels of remember (recollection) responses are high, depending on whether one assumes that no recollected items are familiar (exclusivity), all are familiar (redundancy) or the same proportion of recollected as unrecollected items are familiar (independence). The issue is relevant because it is difficult to avoid circularity when searching for evidence to support one of these assumptions.

	'Remember'	'Know'
Hits	2	22
False alarms	1	8

32 old words, 32 new words

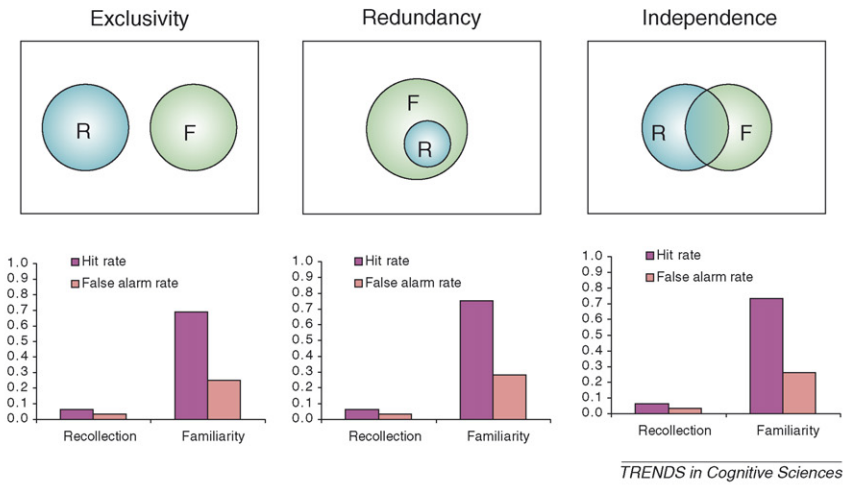

Figure II (Box 2). Estimating familiarity with the modified remember/know procedure. These simulated data illustrate that, when the familiarity-only procedure is used, remember responses (recollection) are rare. As a result, estimates of familiarity are very similar, regardless of whether one assumes that no recollected response is also familiar (exclusivity), all recollected responses are familiar (redundancy) or the same proportion of unrecollected as recollected responses are familiar (independence).

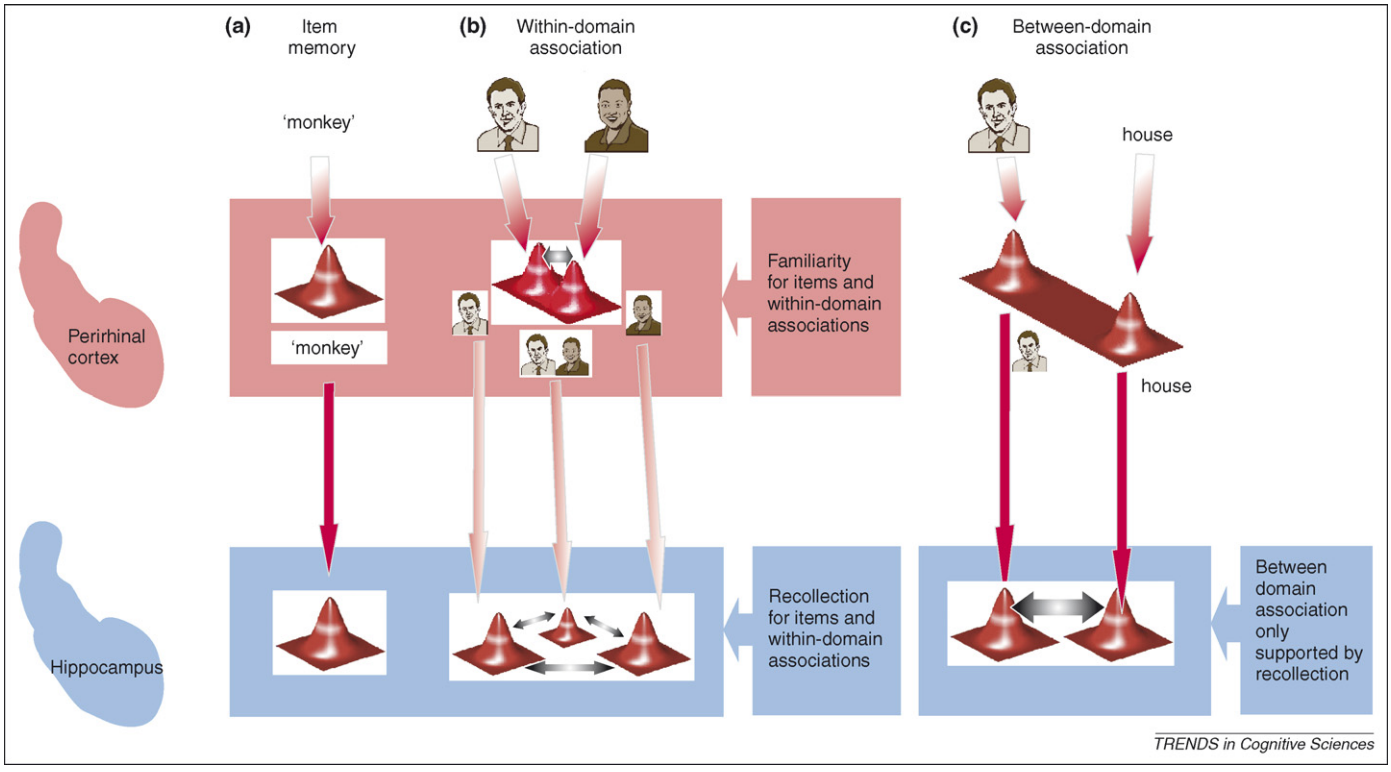

Figure 2. The domain dichotomy (DD) view. **(a)** The input of an already-unitized memory representation of an item (the spoken word 'monkey') is strengthened in the perirhinal cortex. The main input to the hippocampus is this unitized familiarity representation, not its components. This input is flexibly bound to contextual information in the hippocampus, supporting recollection. **(b)** A within-domain input of a directly encoded face pair is bound so as to create a non-unitized familiarity representation in the perirhinal cortex. The hippocampus probably receives an input that comprises this newly formed association and its components separately and creates flexible, recollection-supporting associations between all these inputs, and between them and contextual information. **(c)** Between-domain inputs (e.g. a face and the written word 'house') do not converge sufficiently in the perirhinal cortex to create a familiarity-supporting memory representation. However, these components are flexibly interconnected in the hippocampus and bound to contextual information, supporting recollection.

Box 3. The distinction between relational and conjunctive memory

The widely used relational and conjunctive memory distinction [69,70] resembles the distinction between recollection-supporting and familiarity-supporting memory representations, and both distinctions should be seen as sub-types of associative memory (Figure I in this box). It has proved difficult to discriminate between relational and conjunctive memory experimentally, to identify their neural bases and to confirm their properties [71]. Progress should be made in future work by taking familiarity and recollection measures of relational and conjunctive memory.

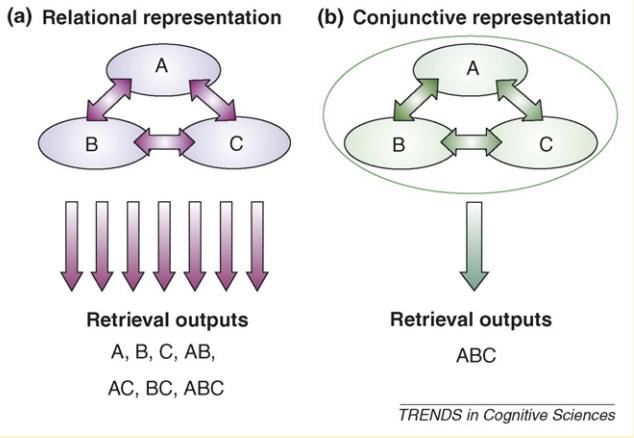

Figure I. Relational and conjunctive representations. **(a)** Relational associations are postulated to be hippocampally mediated and comprise components that are bound in a viewpoint-invariant and independent manner [69–71]. Relational associations are flexibly accessible: their components can cue recall of any combination of components. Therefore, relational associations resemble recollection-supporting associative memories. **(b)** Conjunctive associations are postulated to be neocortically dependent and comprise components that are, in some sense, merged in a viewpoint-invariant fashion so as not to be separately accessible (illustrated by 'boxing in' the conjunctive memories) [69]. Thus, conjunctive associations are similar to associative familiarity-supporting memories in which the components cannot be separately accessed.

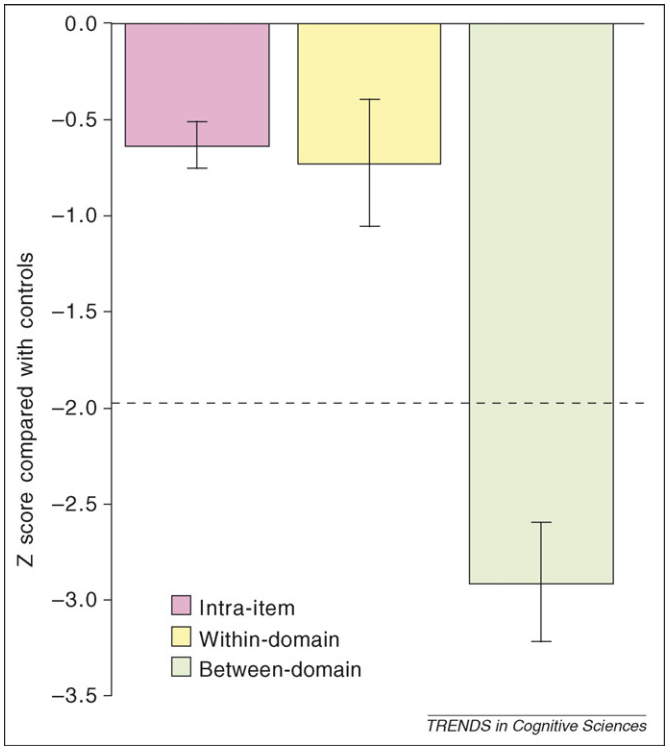

Figure 3. YR's average performance on tests of intra-item, within-domain associative and between-domain associative recognition tests. The intra-item recognition tests used face features and composite words with recombination foils at the test stage. The within-domain associative recognition tests used words and faces. The between-domain tests used many different stimuli and it was striking that, although YR's word-pair recognition was relatively normal, she was impaired when recall was required and when attempting to recognize the temporal order or spatial location of studied pairs. However, YR's recognition was not only impaired for associations that involved spatiotemporal components; she was also impaired at recognizing other between-domain associations (e.g. word definition; animal–occupation name; face–voice; face–spoken name). The dashed line indicates the cut-off for significant impairment ($z = -1.96$; $P < 0.05$). Error bars indicate the standard error of the mean. Data summarized from tables in Ref. [4].

Functional imaging studies in humans

If the MTLs create (encode) and reactivate (retrieve) associative memory representations, encoding leading to subsequent memory should involve the same MTL sites as retrieval, unless the MTL itself produces memory feelings [33] or the information that is encoded and remembered is not the same. Several studies have shown that encoding that leads to item familiarity activates the perirhinal cortex (e.g. Refs [34,35]) and that familiarity itself deactivates this region (e.g. Refs [36–38]), but hippocampal familiarity-encoding or familiarity-retrieval effects are not found (e.g. Refs [35,39]). However, the hippocampus is affected by encoding and retrieval that involves recall [35].

Functional imaging studies that discriminate between the DD view and its rivals must do three things. First, they must determine whether both encoding and retrieval of within-domain associative recognition memory influences perirhinal cortex activity more than between-domain associative recognition influences activity. Second, they must determine whether the MTL-activating effects of familiarity and recollection, explored separately, are distinct for different kinds of association. The DD view predicts that perirhinal cortex familiarity-related effects should be greater for within-domain than for between-domain associations. Third, imaging needs to examine where specific components are processed and represented in extra-MTL neocortex, and whether psychologically and/or neurally closer representations converge for memory processing within the perirhinal (or possibly parahippocampal) cortex rather than within the hippocampus. This work should determine how well pre-hippocampal convergence of components for memory processing corresponds to the within–between distinction.

Although there have been many functional neuroimaging studies of associative recognition [40–61] and source memory [34,35,59,62,63], no studies have systematically pursued these three kinds of research by comparing within- and between-associative memory. Nearly all the studies have focused on examining whether hippocampal activation is greater for recollecting particular kinds of association relative to item recognition alone. For example, hippocampal encoding activation predicted successful source memory rather than merely word [34,35] or object–picture recognition [45]. At retrieval, face cueing of name recall and face–name recognition activated the hippocampus equivalently, although recall did activate the hippocampus more than face recognition alone [59]. This suggests that recognition of between-domain face–name associations depends strongly on hippocampally mediated

Box 4. Questions for future research

- Can objective criteria be found that identify when new intra-item memory representations, such as representations of new compound words or unknown machines, have been created? It is particularly important to discover how much learning is necessary before this happens with what were within-domain or between-domain associations.
- What kinds of encoding facilitate the formation of direct links between components that do not depend on mediators, and do these kinds of encoding enhance familiarity and pre-hippocampal MTL neural activity?
- If between-domain associative familiarity exists, does it depend on the same MTL structures as item familiarity or is it mediated by the hippocampus, as would be expected if familiarity takes different forms (see Ref. [72])?
- Are the MTLs necessary for binding together high-level perceptual representations as well as memory representations? If so, how closely does their role in perceptual binding parallel their role in binding memory representations? Also, if the MTLs help mediate high-level representations of faces, scenes and visual objects, do they have a similar role with any other kinds of high-level representations [73,74]?
- How can the extent of associative memory processing of within- and between-domain components best be measured in the neocortex generally and in the pre-hippocampal MTLs? Will the combined use of tractography and effective connectivity approaches help?
- How does the MTL interact with extra-MTL structures to mediate familiarity and recollection for different kinds of association?
- Are the MTLs involved in mediating unaware associative memory [75–78]? If so, which brain regions are directly responsible for the memory feelings that are characteristic of declarative memory?

recollection. A similar study [49] compared face–face recognition of directly learned pairs with face–face pairs that were linked indirectly through a 'house' stimulus. Consistent with the DD view, hippocampal activity was greatest for indirect pair recognition where recall of the house was essential for successful recognition, whereas recognition in the direct condition was familiarity dependent. Similarly, when a sentence-encoding routine was used for learning word pairs, making recognition recollection dependent, strong hippocampal activation was produced by recognition of intact pairs [41].

These studies do not have strong implications for the validity of the DD view, which predicts that hippocampally mediated recollection is available for both between- and within-domain associations. It is unclear, without specifying the encoding and recognition conditions carefully, how much recollection will be used, so there is no unqualified expectation that recollection dependence will always be greater for between-domain associative recognition than for within-domain associative recognition. Indeed, recollection might sometimes be as great for item recognition as for associative recognition (see Ref. [43] for a contrary view). Also, the level of hippocampal activation depends on the control condition with which successful associative recognition is compared. Because associative recognition is assumed to include item recognition, the aim is to identify the activations that are related to the additional associative recognition alone. However, if the comparison condition involves successfully rejecting recombination foils, then, when subjects use recall-to-reject extensively, this might include as much recollection as accepting an intact pairing. A more appropriate comparison is failure to recognize an intact pair, provided that recognition of the individual items is familiarity based. What should be left to produce the activations is recollection of encoding context, cued by the association, and/or familiarity for the association *per se*. Several studies of encoding activations have come close to achieving this goal. One study found that production of subsequently successful face–name recognition activated the hippocampus (and possibly entorhinal cortex) more than unsuccessful face–name recognition [60]. A further study found that successful word–word encoding also activated the hippocampus and entorhinal cortex but that the activation spread into the perirhinal cortex [42]. This suggests that perirhinal cortex activation was produced by successful encoding of word–word associations but not face–name associations, which is consistent with the DD view. Encoding of object pairs, a different kind of within-domain association, also activated the perirhinal cortex in another study [48]. However, the control procedure did not exclude the possibility that the activation could have related to a single object rather than to associative encoding.

Two studies have produced a different pattern of results [50,61] that could seem problematic for the DD view. Both studies found more hippocampal activations, rather than deactivations, for novel object–object, face–object and object–location recombined pairs than for studied pairs. Köhler *et al.* [50] found that novel objects activated the perirhinal cortex more than studied ones, consistent with other fMRI studies (e.g. Refs [39,48,64,65]) and monkey single-unit recording work [66]. However, neither study [50,61] found perirhinal cortex deactivation for intact object–object associations, as the DD view predicts. The conflict might be soluble. Encoding encouraged spatial processing of objects in different locations, which could have reduced the formation of direct object links that would have produced perirhinally mediated familiarity memory. Also, test objects were often located differently at the study and test stages, and this could have reduced associative familiarity. The hippocampal deactivations that were found for recognized associations suggest that spontaneous encoding of the novel associations was particularly striking and could have reversed the old–new associative activations that have been reported in other studies (e.g. Refs [42,60]). Finally, it is important to note that the DD view predicts perirhinal cortex effects because familiarity-based memory is produced, although no study has yet measured associative familiarity in the scanner.

Concluding comments

Currently, psychological, lesion and functional imaging evidence is broadly consistent with the DD view, but no studies have directly contrasted the predictions of the different views. A central set of issues concerns whether within-domain associations support associative familiarity more than between-domain associations do, and how much this is influenced by encoding instructions and retrieval test formats. How much familiarity for different kinds of unitized and non-unitized association is dependent solely on pre-hippocampal MTL structures also needs resolving. Investigation of these issues would be greatly facilitated by the use of the familiarity-only procedure (Box 2).

The factors that determine how much different kinds of associative memories support various kinds of recollection also need systematic exploration, using cued recall or direct measures of recollection (Box 2). As with familiarity, investigation is also needed into whether hippocampal mediation is common to all kinds of recollection and how, if at all, the MTL cortices (e.g. parahippocampal cortex) contribute.

Finally, exploration is required into the neocortical representation of different associative components, and whether the relative distance between these representing regions influences memory-processing convergence in the MTL structures. If degree of pre-hippocampal convergence varies, then how much an associative memory supports familiarity should vary along a continuum rather than be dichotomously determined. Information converges in the MTLs where it undergoes memory-related and possibly perception-related associative processing. Currently, evidence suggests that different MTL structures mediate memory for different kinds of association in different ways as a function of where information converges. Future research must rigorously test these ideas (Box 4).

Acknowledgements

We thank Christine Denby for her contributions to the preparation of Figure 1 and Wael El-Deredy, Donna Lloyd, Ellen Poliakoff and Dimitris Tsivilis for their helpful comments on the revised draft.

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