

Episodic memory and cortico–hippocampal interactions

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There is a broad consensus that the hippocampal system plays a critical role in the encoding and retrieval of ‘episodic’ memories. Recent findings and computational modeling explicate the representational requirements of encoding episodic memories, and suggest that the idiosyncratic architecture of the hippocampal system and its interactions with cortical circuits are well-matched to the representational problems it must solve in order to support the episodic memory function. These findings also shed light on the nature of consolidation, identify the sorts of memories that must remain encoded in the hippocampal system for the long-term, and help delineate the semantic and episodic memory distinction.

Episodic memory refers to our ability to remember events and situations in our daily lives and acquire memories of specific events by reading a newspaper or watching a newscast [1]. A wide array of neuropsychological [2–5] and imaging [6] data suggests that the hippocampal system (HS) (see Fig. 1) plays a critical role in the encoding and recall of episodic memories (but see Ref. [7]). Behavioral data show that patients with bilateral HS lesions lose the ability to acquire novel episodic memories (anterograde amnesia), and also forget memories of specific events acquired over a period spanning decades prior to the damage (retrograde amnesia) [8–10]. Such patients, however, retain previously acquired semantic and procedural knowledge, exhibit recognition ability based on familiarity [11], continue to produce and understand language, demonstrate priming effects, and acquire novel categories and procedural skills. A link between the HS and episodic memory is also suggested by the neuropathology of Alzheimer’s disease; the HS is one of the first, and one of the most severely affected, areas in Alzheimer’s patients [12].

Several models have been proposed to explain how the HS subserves episodic memory function. These include system-level models that attempt to describe the functional role of the HS [3,4,9,13–19], as well as computational models that attempt to explicate *how* the HS realizes its putative function [20–34]. In conjunction with anatomical and physiological findings, this body of work suggests that at a macroscopic level the cortico–hippocampal interactions underlying episodic memory function may be described as follows (and see Fig. 1): our cognitive apparatus construes our experiences as a stream of events and situations. These construals are expressed as transient patterns of activity over high-level cortical circuits (HLCCs). HLCCs in turn project to the entorhinal cortex (EC) and give rise to activity in the HS. The transient activity injected into the EC propagates around the complex

loop consisting of the EC, the dentate gyrus (DG), CA3, CA2, CA1, the subiculum and the EC, and triggers synaptic changes in these structures that lead to the formation of an episodic memory trace. The activity arriving from CA1 and the subiculum into the EC constitutes the response of the HS. This re-entrant activity propagates back to HLCCs.

The proper functioning of the HS depends on its interactions with subcortical regions concerned with emotion, motivation, arousal and attention. These regions communicate the affective significance of the ongoing experience to the HS, and play a key modulatory role in memory formation [35,36].

Some models offer a different characterization of cortico–hippocampal interactions than the one given above. For example, one model describes the HS as an ‘orienting system’ that controls the search for cortical representations during memorization [23], others propose that the HS is a sequence predictor [29,30], and some others focus on the role of the HS in conditioning paradigms [22,24].

Hippocampus-based episodic memory system: some questions

The macroscopic description of cortico–hippocampal interaction given above does not specify the precise division of representational labor between the cortex and the hippocampus. It does not tell us what sort of neural circuits might be recruited in the HS to encode an event’s memory trace, and what might be their functional properties.

A prominent view holds that the HS acts as an ‘auto-associative’ memory [20,21,26–28]. The key representational attribute of such an encoding is that it supports pattern completion – the retrieval of complete patterns from partial cues. CA3 with its recurrent connections is typically assumed to be the locus of such an auto-associative memory.

Another prominent characteristic attributed to the HS-based memory system is that it serves as a ‘conjunctive code’ that binds together items comprising a memory [3,15,20,25,26,31,32]. This concept of a conjunctive code is related to notions such as ‘chunking’, ‘vertical associations’ [13] and ‘configural associations’ [17]. The formation of a conjunctive code is also assumed to occur in CA3, and many models impute both auto-associative and conjunctive properties to episodic memory traces. Typically, it is assumed that EC to CA3 pathways underlie the formation of conjunctive codes, and recurrent CA3 connections

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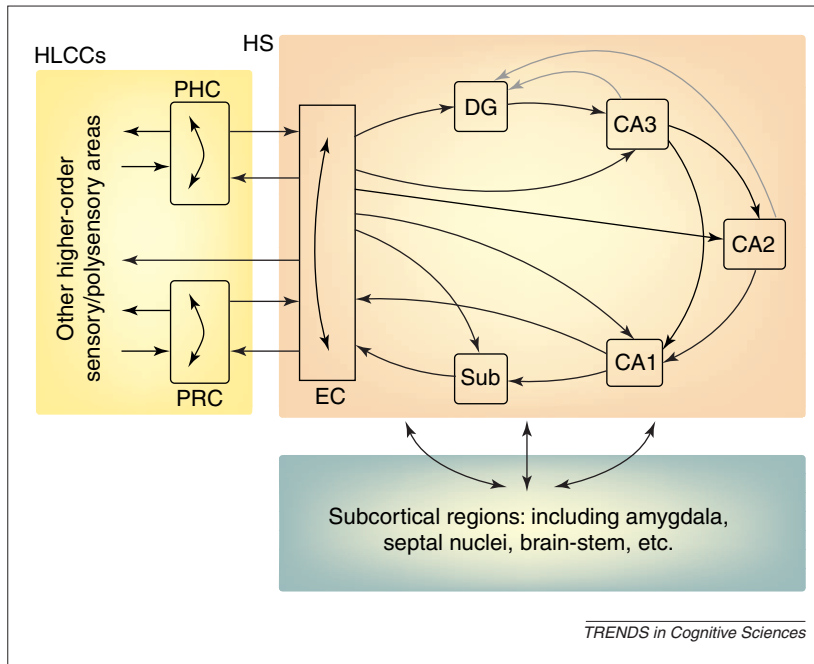


Fig. 1. A schematic of the major pathways interconnecting components of the hippocampal system (HS) and of the interactions between the HS and cortical (HLCCs) and subcortical areas [2]. The HS includes the entorhinal cortex (EC); the dentate gyrus (DG); Ammon's horn (hippocampus proper) consisting of fields CA1, CA2 and CA3; and the subiculum (Sub). EC is the principal portal between the HS and the cortex. Higher-order sensory and association areas project to the EC directly or via the perirhinal (PRC) and parahippocampal (PHC) cortices. Activity converging on the HS courses through the complex loop formed by HS pathways and returns to the cortical regions from where it originated. There also exist recurrent connections within DG, CA3, CA2 and, to a lesser extent, within CA1. The HS contains a variety of inhibitory interneurons that together with principal cells form local inhibitory circuits. The HS also receives afferents from subcortical regions and projects back to many of these regions. Other cortical areas related to the HS are pre- and para-subiculum (not shown).

impart auto-associativity to these codes. Some computational models also assign representational roles to other HS components [26–28,34].

A few modelers have suggested that the primary role of the HS is the encoding of relational representations [4,18]. As discussed below, events are inherently relational in nature, and this suggestion focuses attention on a crucial, though often overlooked, aspect of episodic memory. Though it has been pointed out that episodic memory traces must capture relational information, it has remained unclear *how* the HS realizes this function.

The cortico-hippocampal interactions described above do not specify the eventual disposition of episodic memory traces. Is the HS a temporary buffer that holds an event's memory trace until it is (re)coded within cortical circuits via a process of consolidation [3,20,25,27,31,37]? Or does an event's memory trace persist in the HS for as long as the event is remembered [9,38,39]? If the latter, then what is the role of HS-based memory traces in the updating of cortical representations?

An analysis of the architecture and local circuitry of the HS, coupled with recent work on computational modeling of episodic memory function [39], has shed light on some of the questions raised above concerning the functional properties of memory traces in the HS and their persistence in the HS.

These results explicate the representational requirements of encoding events and situations, identify a detailed neural circuit that satisfies these requirements and demonstrate that requisite circuits can be formed rapidly (within a second) in the HS as a result of long-term potentiation (LTP) [40].

Representational requirements of encoding episodic memories

Let us identify some basic representational requirements of encoding an event. Consider the event in which John gives Mary a book in the library on Tuesday. This event is an instance of a specific sort of interaction involving John, Mary and a book that occurs in a particular location and at a particular time. John, Mary and a book fulfill specific 'roles' in this interaction; John does the giving, Mary does the receiving, and a book is the given object. Clearly, this event cannot be expressed as a mere association between John, Mary, a book, the library and Tuesday. At a bare minimum, this event's memory trace must encode some sort of 'relational structure' wherein the role *giver* is bound to (the concept) John, the role *recipient* is bound to Mary, the role *object* is bound to a book, the role *location* is bound to the library and the role *temporal-location* is bound to Tuesday. This relational information can be expressed succinctly as the following 'relational structure':

GIVE: <giver = John>, <recipient = Mary>, <give-object = a book>, <location = library>, <temporal-location = Tuesday>.

The above encoding involves two levels of bindings: (1) entities occurring in the event are bound to the roles they fill in the event, and (2) all role–entity bindings pertaining to the event are grouped together in order to distinguish them from role–entity bindings of other events. This encoding is more complex than one that only binds together and forms a 'conjunctive' representation of items involved in the event, or one that views an event as a feature vector.

The encoding of an event might also require the specification of parameter-values pertaining to sensorimotor schemas. The problem of encoding parameter–value bindings, however, is similar to that of encoding role–filler bindings.

Significance of role–entity bindings

The above observations suggest that the memorization of an event requires the encoding of role–entity bindings. But are a few bindings sufficient to capture an event's memory? Events extend over space and time. They are sensorially rich, and emotionally charged. Hence, it would seem that encoding an event's memory trace should require more than a few bindings. But as argued below, it is possible to reconstruct an event by activating the web of semantic, procedural and sensorimotor knowledge with the relevant role–entity bindings [39].

Direct and irrefutable evidence that the mind or brain can reconstruct an event from a small number

of bindings comes from the phenomena of language understanding. Consider the sentence, 'John bought a car.' Upon hearing this sentence we effortlessly understand the implied transaction, which might involve John visiting a car showroom, selecting a car, paying for the car and obtaining ownership of the car. Thus our mind (or brain) can construct a complex event given the four-word sentence 'John bought a car', even though the only explicit information contained in the sentence is that $\langle \text{buyer} = \text{John} \rangle$, $\langle \text{buy-object} = \text{a car} \rangle$ and that the event has occurred.

How does an impoverished four-word 'input' specifying only two bindings lead to an understanding of a complex event? A plausible answer seems to be that an elaborate understanding of the event emerges when the bindings specified in the sentence tap into and activate the complex web of conceptual knowledge in our mind (or brain). This web of knowledge includes, besides other things, semantic knowledge about different sorts of entities and their attributes, causal knowledge about the relationship between actions and their effects and schematized, embodied representations of generic actions.

The above conception of language understanding strongly resonates with proposals that understanding involves 'embodied mental simulations' [41–43] and 'reflexive inferences' to establish referential and causal coherence [44,45]. This body of work suggests that the temporal structure and dynamics of an event can be reconstructed by binding the roles and parameters of an appropriate action schema to suitable entities and values, and 'executing' the schema [41,46].

The language understanding analogy explains how a few bindings suffice to encode an event in episodic memory: as in the case of language understanding, a fleshed out representation of an event is reconstructed during recall by retrieving a small set of bindings pertaining to the event and activating the web of semantic and procedural knowledge with these bindings. What is different in the two cases is the source of bindings. In the case of language understanding, bindings are obtained from verbal input. In the case of remembering, they are retrieved from the event's episodic memory trace in the HS.

Retrieval as reconstruction via embodied mental simulations

The idea that memory recall involves a constructive process is very old [47] and has received support from psychologists [5] and, more recently, from imaging studies [48,49]. However, key additional insights obtained from the above analysis are as follows [39]:

- The seed underlying the reconstruction of a specific event is a small number of role–entity (and parameter–value) bindings.
- Such bindings, together with ancillary functional circuits enumerated in the following section, are encoded in the HS during the memorization of an event. This constitutes an event's 'episodic memory trace'.

- During recall, an event's episodic memory trace becomes active and reinstates the event's bindings within cortical circuits.
- Upon being activated with the appropriate bindings, cortical circuits encoding action schemas, sensorimotor programs and semantic knowledge about entities, reconstruct an event via embodied mental simulations and reflexive inference.

Because role–entity bindings are critical for memorizing and reconstructing an event, an event's episodic memory trace should include functional circuits for encoding such bindings and reinstating them within cortical circuits in response to a matching cue. Properties of episodic memory, however, impose additional representational requirements on episodic memory traces.

Episodic memory traces must include binding-error detectors and binding-error integrators

An event's episodic memory trace must be responsive to highly partial cues, but at the same time, it should be capable of distinguishing between the memorized event and highly similar events. For example, the memory trace of the event, 'John gave Mary a book in the library on Tuesday' (*E1*) should match the partial cue, 'Did John give Mary a book?', but not the cue, 'Did John give Susan a book in the library on Tuesday?', even though the latter is highly similar to *E1*.

Given a cue, we might be reminded of an event that has an incompatible binding, but which is otherwise very similar to the cue. In case of such reminding, however, we are explicitly aware of the mismatch between the cue and the evoked memory. For example, we might be reminded of *E1* when asked, 'Did John give Susan a book in the library on Tuesday?'. But we would be aware that the cue specifies an incorrect recipient. Being reminded of a similar event, but with an explicit awareness of a mismatch, further highlights the pattern-separation property of episodic memory.

The requirement that an episodic memory trace must respond positively to partial cues and simultaneously reject any cue that specifies an incompatible binding, implies that an episodic memory trace must be capable of detecting binding errors as well as binding matches. A memory trace that detects only binding matches cannot satisfy these requirements because it cannot distinguish between an unspecified binding and an incorrect binding. For example, a memory trace of ($R: \langle r1 = a \rangle$, $\langle r2 = b \rangle$, $\langle r3 = c \rangle$) that only detects binding matches will treat an erroneous cue ($R: \langle r1 = a \rangle$, $\langle r2 = b \rangle$, $\langle r3 = d \rangle$) on a par with a partial, but matching, cue ($R: \langle r1 = a \rangle$, $\langle r2 = b \rangle$) because both cues contain the same number of matching bindings.

In view of the above discussion, an event's episodic memory trace should incorporate neural circuits capable of: memorizing bindings; detecting a mismatch between memorized bindings and bindings

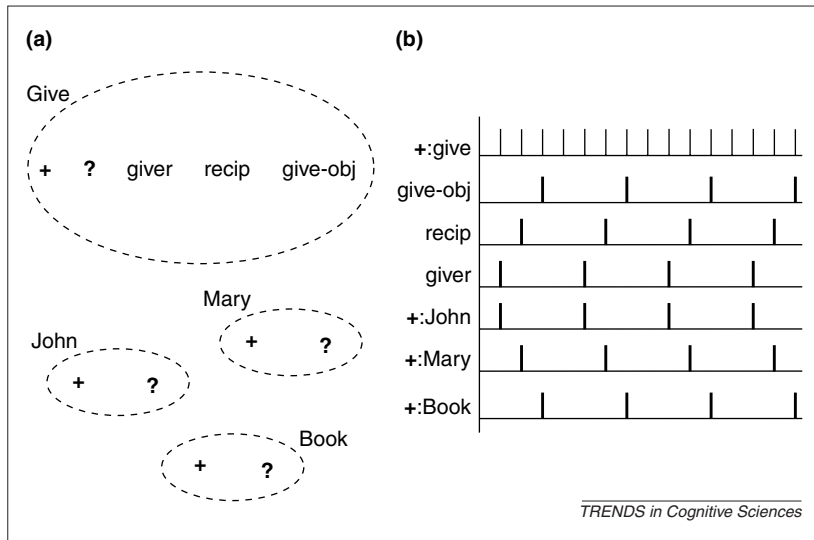


Fig. 2. (a) The encoding of relational information in high-level cortical circuits (HLCCs) is mediated by 'focal-clusters'. The focal-cluster for relation *give* is enclosed within the ellipse named *Give*. Each label within the ellipse denotes a cell ensemble. It is assumed that *give* has roles *giver*, *recipient* and *give-object*, encoded by ensembles *giver*, *recip* and *give-obj*, respectively. Roles *spatial-location* and *temporal-location* have been glossed over for simplicity. Each focal-cluster also includes ensembles labeled ? and +. The activation of + signifies that the active instance of the relation is being affirmed by some cognitive process and the activation of ? signifies that some cognitive process is posing a query about the active instance. Entities such as John also have focal-clusters associated with them (distinctions between 'a book' and 'books' are being glossed over, but have been discussed [45]). Focal-clusters serve as anchors for encoding perceptual, semantic and episodic information. Grouping of cell ensembles within a focal-cluster indicates the functional cohesiveness of these clusters, but does not signify physical proximity. (b) The activity-based encoding of the event, 'John gave Mary a book'. Role-entity bindings are expressed by the synchronous firing of bound role and entity ensembles. Each spike signifies the synchronous firing of cells in the appropriate ensemble.

specified in a cue; detecting a match between a cue and the memorized event based on the activity of the above-mentioned circuits; and reinstating the event's bindings within cortical circuits in response to a matching cue.

Cortical representations and activity-based encoding of events

How might the relational structure of an event be expressed as a transient pattern of activity within HLCCs? A possible solution is suggested by work on a neurally plausible model of relational information processing [44]. This work suggests that dynamic role-entity bindings of an event are expressed in HLCCs by the 'transient synchronization' of bound role and entity ensembles (see Fig. 2) [44,50–52]. The grouping together of all role-entity bindings pertaining to a single event arises from the fact that all the role ensembles pertaining to a relational schema (e.g. *give*) are components of a larger, structured ensemble of cells associated with the relation. This structured ensemble of cells is referred to as a 'focal-cluster' [39,44,45]. Similar focal-clusters are also associated with entities.

Regions in the anterolateral temporal lobe and ventromedial temporal cortex, especially the perirhinal cortex (PRC), play an important role in encoding and accessing knowledge about entities or objects [53,54]. Hence, it is likely that focal-clusters of entities are located in these regions. Focal-clusters

of relational schemas are likely to be located in (1) the parahippocampal cortex, which receives input from parietal and prefrontal areas, and (2) other cortical areas that project to the EC. In addition, some focal-clusters of entities and relations may be located in the EC.

Encoding of episodic memory traces in the HS

Consider an event E given by: $(R: \langle r1 = a \rangle, \langle r2 = b \rangle)$. The transient activity-based representation of E in HLCCs would be analogous to the rhythmic activity shown in Fig. 2b. The computational model, SMRITI [34,39], demonstrates that the propagation of such an activity through the HS can *automatically* lead to the rapid (within a second) formation of an episodic memory trace in the HS as a result of LTP. This memory trace is a rather complex neural circuit comprising all the functional subunits discussed in the section on representational requirements of encoding episodic memory, but SMRITI shows that the formation of this complex circuit is the direct consequence of the idiosyncratic architecture, local circuitry and plasticity of the HS. A schematic of this trace is depicted in Fig. 3.

A statistical analysis using plausible system parameters (e.g. number of cells in various HS regions, the density of HS projections and the ratio of principal cells to interneurons) shows that a large number of physically dispersed 'copies' of each functional unit are formed during an event's memorization [39]. This redundancy and physical dispersion make the memory trace robust against cell loss. Furthermore, the impact of shared and ill-formed functional units is minimal. Each subsequent reactivation of a memory trace recruits additional copies, thereby further strengthening the memory trace [9,39].

Episodic memory consolidation

Biological and psychological data suggest that rapid memory acquisition is followed by a slow consolidation process that makes the memory trace less prone to disruption and forgetting. What is the nature of this consolidation? A prevailing view is that episodic memory consolidation involves a recoding process that transfers episodic memory traces from the HS to the cortex [3,20,25,31,37]. This view, however, has been challenged on the grounds that it does not offer a satisfactory account of experimental data [9,33,38].

The finding that retrograde amnesia in hippocampal patients often extends to events occurring several decades prior to hippocampal insult poses a problem for the 'consolidation as transfer' hypothesis [8–10,33]. Under this hypothesis, the temporal extent of retrograde amnesia should be no more than the time required to transfer an episodic memory trace from the HS to the cortex. Therefore, under the 'consolidation as transfer' hypothesis, the temporal extent of retrograde amnesia implies that

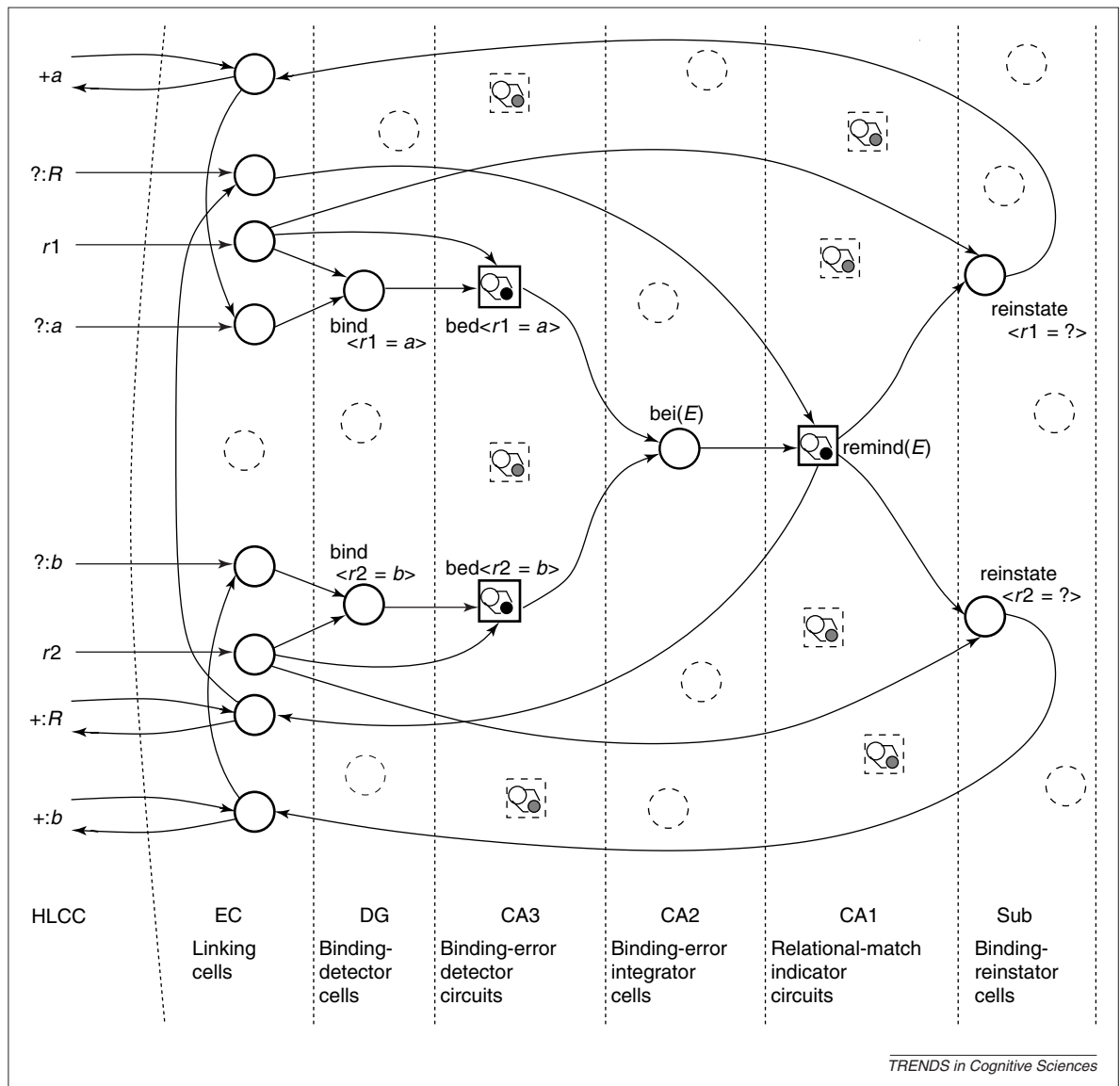


Fig. 3. A schematic of the distributed circuit formed during the memorization of event E given by $(R: \langle r1 = a \rangle, \langle r2 = b \rangle)$. This circuit is formed as a result of long-term potentiation (LTP). Bold circles and squares refer to cells and local circuits, respectively, recruited during the memorization of E , and links refer to connections whose synapses undergo LTP during the memorization. Dashed circles and squares signify other cells and circuits. Cells for linking cortically located focal-clusters of relations and entities to the HS are recruited in the entorhinal cortex (EC); binding-detector cells encoding role–entity bindings are recruited in the dentate gyrus (DG); circuits that serve as binding-error-detectors ('bed' circuits) are recruited in hippocampal region CA3; cells that integrate the outputs of bed circuits are recruited in CA2; relational-match-indicator circuits ('remind' circuits) that signal a match between E and ongoing hippocampal activity (e.g. a cue) are recruited in CA1; and 'binding-reinstator' cells that reinstate bindings of E in cortical circuits during recall are recruited in the subiculum (Sub). Remind circuits and binding-reinstator cells are hooked up to linking cells in EC.

the transfer of an episodic memory trace to the cortex requires decades. Although there is a rationale for long-lasting information transfer from episodic memory traces to cortical semantic structures [37], such a long-lasting process of episodic memory transfer is unmotivated and unnecessary on computational as well as biological grounds.

Persistence of episodic memory traces in the HS

Computational and architectural considerations also lead to the prediction that an event's episodic memory trace must persist in the HS for as long as the event is remembered as a specific episode [39]. This prediction is based on (1) the observation that only the HS appears to have the necessary convergence of high-level multi-modal inputs *and* (2) the remarkable match between the idiosyncratic architecture of the HS and the specialized neural circuitry required to encode relational items such as episodic memories (compare Figs 1 and 3). Representational properties of relational items that might necessitate HS participation in their memorization and long-term maintenance have been discussed elsewhere [39].

Recent studies of CA1-specific knockout mice indicate that N-methyl-D-aspartate (NMDA) receptors in CA1 continue to play a critical role in memory consolidation even a week after memory acquisition [55]. This suggests that synaptic plasticity *within* the HS is crucial for memory consolidation and hence, memory consolidation

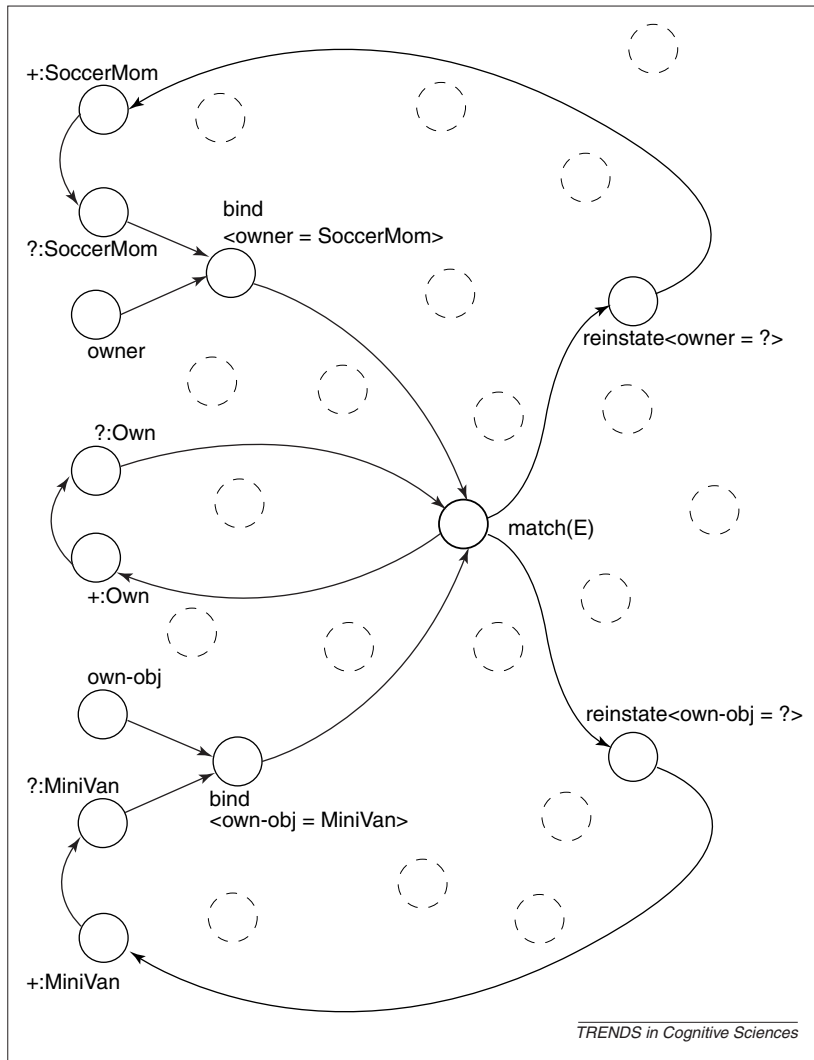


Fig. 4. Schematic of a cortical circuit encoding the taxon-fact, 'Soccer moms are likely to own minivans'. A taxon-fact encoding is simpler than an episodic memory trace, and consists only of 'binding-detector' cells, 'match' cells (soft-conjunction of bindings) and 'binding-reinstator' cells. A taxon-fact responds based on overall similarity. Any single cortical area is unlikely to receive converging inputs from the full spectrum of relations and entities, including those required for encoding spatio-temporal context. Hence, taxon-facts are unlikely to include 'source' information about where and when the fact was acquired [5].

involves the consolidation of episodic memory traces within the HS.

Information transfer from the HS to cortical semantic structures

The persistence of episodic memory traces in the HS does not preclude information transfer from the HS to cortical circuits encoding semantic knowledge [9,33,39]. One example of such a transfer would be the gradual formation of new and the fine-tuning of existing 'taxon-facts' in the cortex [39,45]. Unlike episodic-facts that encode specific events, taxon-facts encode distillations or statistical summaries of multiple events (the name is inspired by the taxon-locale distinction [14]). An example of a taxon-fact is shown in Fig. 4.

Over a lifetime, HS-based episodic memories are repeatedly activated while reminiscing, problem

solving and during sleep [56,57], and trigger reflexive inferences and mental simulations in cortical representations. The resulting cortical activity can lead to the fine-tuning of synaptic strengths and, in effect, to the modification of prior and conditional probabilities encoded in cortically expressed semantic structures such as taxon-facts [44,45].

Several researchers have suggested that HS-based episodic memory traces contribute to the fine-tuning of cortical semantic representations [25,27,37], and in the process get transferred to cortical circuits. By contrast, the HS to cortex transfer suggested by some authors [9,33,39], and argued for above, is one in which episodic memory traces of *memorable* events persist in the HS – even after they have contributed to cortical semantic representations.

HS and the acquisition of semantic memory

An episodic memory trace can be reinstated multiple times in HLCCs. This can facilitate the incorporation of the event's information content into semantic structures. Consequently, an intact HS should greatly facilitate the acquisition of semantic memory. But an intact HS should not be essential for acquiring semantic knowledge: the construal of any experience is expressed as a pattern of activity over HLCCs. This activity can cause incremental synaptic changes within HLCCs. Over time, and with repetition, these changes can accumulate and lead to qualitative changes in semantic structures. Thus, it would be possible, though extremely difficult, to acquire semantic knowledge without a functioning HS [39,58,59].

Conclusion

Recent work on computational modeling of episodic memory, coupled with an analysis of the architecture and local circuitry of the HS, helps explicate the representational requirements of encoding episodic memories, and suggests that there is a remarkable match between the architecture of the HS (form) and these representational requirements (function). These findings shed light on the division of labor between the HS and cortical circuits and suggest that the HS may be the long-term repository of episodic memory traces.

Questions for future research

- What neural mechanisms underlie consolidation and the forgetting of episodic memory?
- What is the role of sleep in consolidation and forgetting?
- How does neurogenesis impact memory formation?
- If the HS is essential for encoding complex relational items, it should play a critical role in supporting short-term (working) as well as long-term (episodic) memory of such items [60]. Is this the case?
- How do prefrontal circuits implicated in working memory, planning and executive function interact with HS-based episodic memory?

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