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Review article

The hippocampus and related neocortical structures in memory transformation

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ABSTRACT

Episodic memories are multifaceted and malleable, capable of being transformed with time and experience at both the neural level and psychological level. At the neural level, episodic memories are transformed from being dependent on the hippocampus to becoming represented in neocortical structures, such as the medial prefrontal cortex (mPFC), and back again, while at the psychological level, detailed, perceptually rich memories, are transformed to ones retaining only the gist of an experience or a schema related to it. Trace Transformation Theory (TTT) initially proposed that neural and psychological transformations are linked and proceed in tandem. Building on recent studies on the neurobiology of memory transformation in rodents and on the organization of the hippocampus and its functional cortical connectivity in humans, we present an updated version of TTT that is more precise and detailed with respect to the dynamic processes and structures implicated in memory transformation. At the heart of the updated TTT lies the long axis of the hippocampus whose functional differentiation and connectivity to neocortex make it a hub for memory formation and transformation. The posterior hippocampus, connected to perceptual and spatial representational systems in posterior neocortex, supports fine, perceptually rich, local details of memories; the anterior hippocampus, connected to conceptual systems in anterior neocortex, supports coarse, global representations that constitute the gist of a memory. Notable among the anterior neocortical structures is the medial prefrontal cortex (mPFC) which supports representation of schemas that code for common aspects of memories across different episodes. Linking the aHPC with mPFC is the entorhinal cortex (EC) which conveys information needed for the interaction/translation between gist and schemas. Thus, the long axis of the hippocampus, mPFC and EC provide the representational gradient, from fine to coarse and from perceptual to conceptual, that can implement processes implicated in memory transformation. Each of these representations of an episodic memory can co-exist and be in dynamic flux as they interact with one another throughout the memory's lifetime, going from detailed to schematic and possibly back again, all mediated by corresponding changes in neural representation.

1. Introduction

The nature of memory formation and long-term representation has been debated since the inception of the scientific investigation of memory in the 19th century. Through the work of Brenda Milner and her colleagues [1,2] on H.M. and other memory-impaired patients with medial temporal lobe excisions, the hippocampus assumed a central role in this debate [3]. Milner and her colleagues confirmed the pattern of relatively preserved remote, compared to recent, memories noted by Ribot [4] and others [5], a paradoxical effect that gave rise to standard consolidation theory (SCT) [6–10]. SCT builds on the supposition that memories, initially bound together by the hippocampus at encoding, are laid down as a hippocampal-neocortical ensemble (memory trace or engram), with the sparsely-coded hippocampal neurons referencing and activating the neocortical neurons to re-create the content of an experience [11,12]. This supposition, that memories are not stored in hippocampus as such, but arise from the interaction of hippocampal codes or representations with neocortical information, is common to all the models and theories that will be discussed in this review. SCT states as its central premise that the hippocampus serves this integrative or binding function only temporarily, mediating initial encoding, retention and retrieval, while promoting memory consolidation in the

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neocortex. Once consolidation is complete, retention and retrieval are supported by activation of these neocortical neuronal ensembles independently of the hippocampus. This consolidation process is meant to account for evidence of the observed temporal gradient following medial temporal lesions in which recent memories that did not have a chance to consolidate fully are lost.

For a half century, SCT dominated research on the neurobiological basis of memory and guided its theoretical development [8,10,13,14]. Evidence emerged, however, that challenged fundamental aspects of SCT [9]. Among the most noteworthy, it was found that a temporal gradient is not a universal feature of retrograde amnesia after hippocampal damage. Although semantic memory typically shows such a gradient, there are now many reports that episodic memory in humans [15–17] and episodic-like (context-specific) memory in animals [18] show a severe, temporally extensive or non-graded retrograde amnesia that can encompass a lifetime. As all declarative memories are treated alike by SCT, the distinction between episodic and semantic memory is particularly problematic.

At a more conceptual level, SCT, and most theoretical models of memory consolidation, operate on the assumption that consolidated memories are fundamentally similar, if not identical, to the initial memories – all that change are their neural representations. Memories, however, are dynamic, changing not only with age but also with experience as they interact with other memories and knowledge acquired before, and after, the episodic memories of interest were encoded; they can even be altered by the very act of retrieval [5,19–21]. By this view, it is not the *age* of the memory that matters, but its *nature* or quality [17] and, in accord with the principle of functional-neural isomorphism, changes at the psychological level are accompanied by corresponding changes at the neural level, and vice-versa [22,23].

As evidence on temporally-graded retrograde amnesia has been reviewed extensively elsewhere [8–10,15–18,24,25], we provide a brief summary here, emphasizing the most recent developments. We focus on the neural correlates that accompany memory transformation from shortly after acquisition to long afterwards, and track changes in both the neural correlates and corresponding changes in the qualitative nature of the memory, as they occur in humans and rodents. Our review leads to the proposal that representation of an episodic memory varies along the long axis of the hippocampus with fine, perceptual details represented in posterior regions (dorsal in rodents) and coarse, general aspects of the event, or gist, in anterior regions (ventral in rodents). The posterior and anterior regions interact, respectively, with perceptual systems in posterior neocortex, and schematic and semantic systems in anterior neocortex (Fig. 1) [26]. Although many anterior neocortical regions are implicated, such as the temporal poles, and lateral prefrontal cortex, as well as subcortical regions such as the amygdala, we concentrate on the medial prefrontal cortex (mPFC), the region most implicated in memory consolidation and transformation.[1]

2. Some definitions

It is widely accepted that there are two essential components to the consolidation process – a *cellular* component concerned primarily with early and rapid changes in the synaptic connections of local neuronal networks, among them the hippocampus and related structures, mediated by intracellular molecular mechanisms; and a *systems* component which is more prolonged and concerned with the reorganization of the memory trace and distributed representation throughout the neocortex and beyond the hippocampus. As noted by Sekeres et al. [29], "Cellular consolidation and systems consolidation tend to be studied separately but it is important to keep in mind that they are part of one continuous and dynamic process (p. 19)". This paper is concerned primarily with systems consolidation.

In humans, episodic memory refers to memory for a particular event and the personal experiences that accompany it. This often entails conscious recollection of the event. In non-humans, it is difficult to determine whether there is conscious awareness of a memory (but see 30,31); instead sensitivity to the context in which an event occurred is considered a defining feature of episodic-like memory in animals.

With respect to episodic memory, investigators recently have distinguished between different levels of resolution that have different neural correlates. On the one hand, fine-grained, perceptual, spatial and temporal elements contribute to highly *detailed memories* associated with a particular event (e.g., details of a recent birthday party). On the other hand, coarse-grained global, central features, in contrast to specific, local features, comprise the *gist*[2] of the event (e.g., summary of what happened at the birthday party). The term *schema* refers to 'knowledge extracted over multiple similar experiences [32–34]', capturing similarities *across* particular episodes. Thus, a gist representation may not be richly detailed but, nevertheless, be specific to a *single* episode (e.g. the recent birthday party), whereas a schema is a representation based on *multiple* similar episodes or memories (e.g., what happens at birthday parties in general) [23]. The term *semantic* refers to the conceptual aspects of an event (its definition, e.g., what 'birthday party' means) without specifying what typically transpires at such an event. The distinction amongst these terms will become important as we review the literature and consider how they apply to our evolving conceptualization of memory transformation. Investigation into the application of these constructs in animal research is just beginning [35,36], and we will note its development as we proceed through the paper.

3. Multiple trace theory: successes and limitations

The findings inconsistent with SCT created the need for new theories of memory consolidation. To account for the temporally extensive retrograde amnesia and for the differences between episodic and semantic memory, Nadel and Moscovitch [37] proposed their Multiple Trace Theory (MTT). The central notion of MTT is that episodic memories are always dependent on reactivation of memory traces through the hippocampus, whereas semantic memories rely primarily on the neocortex [38], unless the semantic information has personal significance in which case medial temporal structures are also recruited [39–43]. To account for different patterns of retrograde memory loss that had been reported to that point, Nadel and Moscovitch [37] postulated that each time a memory is reactivated, a new trace is formed [44,45] thereby creating multiple representations of that memory. The older the memory, the more opportunity there is for reactivation and formation of multiple traces, rendering remote memories more resistant to assault than recent memories, in proportion to the amount of tissue that was damaged – mild to moderate damage to the hippocampus should produce a temporally graded retrograde amnesia whereas extensive damage should lead to a non-graded, or temporally extensive, effect. According to MTT, these effects apply only to episodic or context-specific memories; semantic or context-general memories, on the other hand, are presumed to be derived by extracting information based on statistical regularities across the neocortical representations of the episodes, whether experienced externally or re-experienced internally (see below), and, once formed, are resistant to hippocampal damage.

[1] The homologues between the human and rodent medial prefrontal cortex and their various subregions are not clear-cut [27,28]. In rodents, the anterior cingulate cortex (aCC), infralimbic and prelimbic frontal cortex refer to what is typically considered mPFC in humans. In this paper, we refer to these areas collectively as mPFC.

[2] In the past, we used the terms 'gist' or 'schematic memory' interchangeably to refer to the essential features of an event within a general context that excludes most of the local details. Because new empirical findings distinguish between gist and schemas, to avoid confusion between 'schematic memory' and 'schemas', we now exclusively use the term gist for this type of memory which refers to the general aspects of a specific event. The term 'schema' is reserved for what is common across different episodic memories.

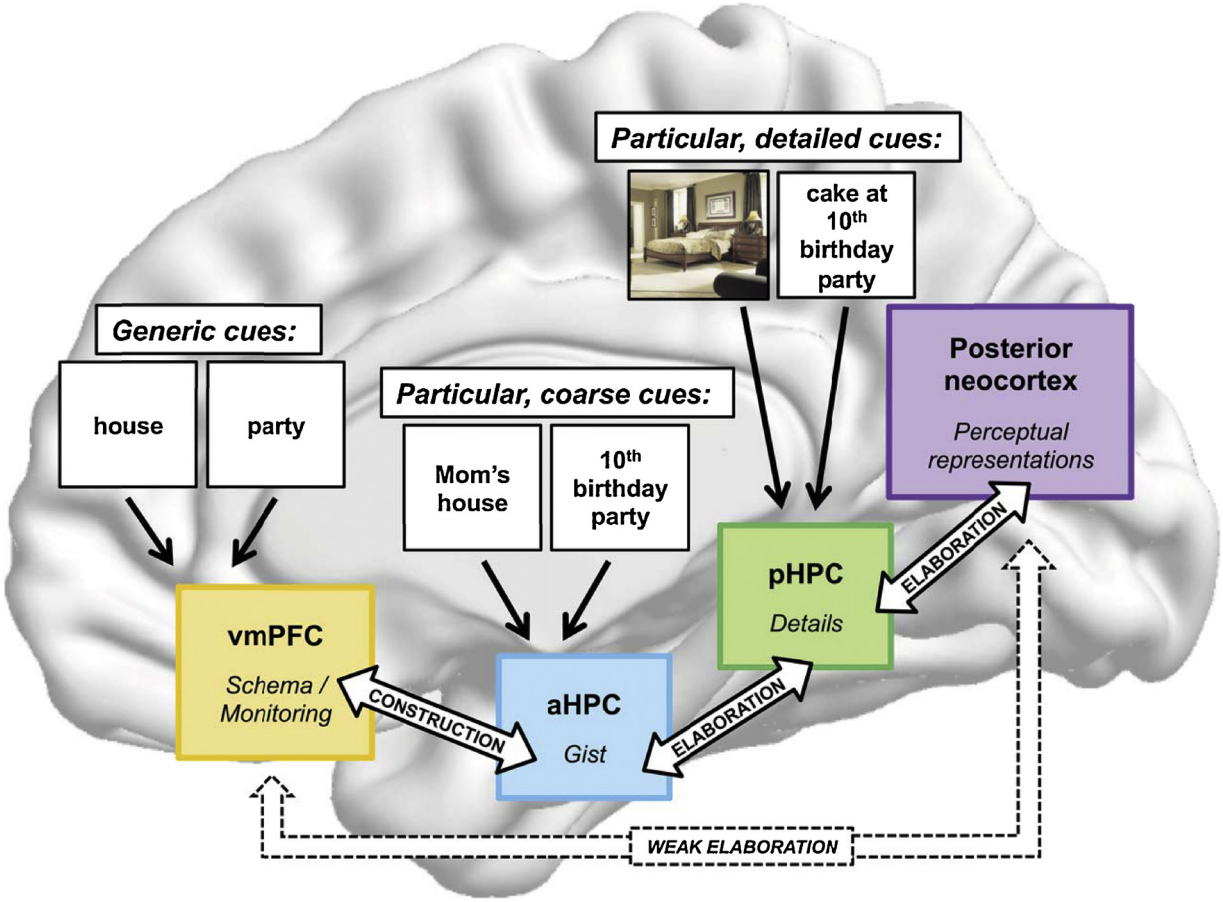

Fig. 1. Schematic of the representations mediated by hippocampus and medial prefrontal cortex and their interactions (from [26]).
Activations of the medial prefrontal cortex (mPFC), anterior hippocampus (aHPC), posterior hippocampus (pHPC), and the interactions among them, are influenced by the nature of the information the structures help represent, the type of cues used to elicit memories, and the goals of the memory task. Thus, generic cues will preferentially engage the ventral (v)mPFC and the schemas it represents; particular cues at a coarse level of detail will engage the aHPC and gist representation; and particular cues at a fine level of detail will engage pHPC and representation of details. This organization applies equally to memory for events and locations. In response to generic or particular cues, the initial phases of memory retrieval involve memory construction, which implicates interactions between vmPFC and aHPC, likely via entorhinal cortex [118]. Later phases in which the memory is fleshed out with details, involve a process of elaboration that recruits pHPC and interactions with posterior neocortex, including parietal and occipital regions involved in perceptual representations. If the cue is highly detailed, the pHPC may be engaged directly via a process of pattern completion. If the hippocampus is damaged, or memory is highly schematic, the vmPFC and posterior neocortical regions may interact directly to generate a less detailed representation [23].

The formation of sufficient multiple traces that can support the semantic, or context-general, version of the memory independently of the hippocampus takes time. Thus, following hippocampal lesions, semantic or context-general memory, in contrast to episodic memory, can be associated with a temporal gradient of as much as a decade in humans, and weeks to months in animals. The latter finding is consistent with both MTT and SCT [6–8,13,14].

In Contrast to SCT which maintains that memories remain constant as their neural representations reorganize with consolidation, implicit in MTT is the notion that an isomorphism exists between the nature of the memory and its neural correlate [8]. In other words, as the nature of the memory changes over time, the memory becomes associated with the development of different neural representations. Episodic memories are always linked to the hippocampus, whereas other forms of memory, e.g. semantic, are represented in other cortical structures. Crucial to this formulation is the notion that a memory's qualitative change is accompanied by a change in its neural correlates [8].

After publication of MTT, much research on consolidation in humans focused on determining whether the hippocampus is implicated in representing remote, yet detailed, episodic memories. The literature that speaks to this issue, which distinguishes MTT from SCT, has been reviewed extensively and will only be summarized here [15–18,24,25,46]. The evidence from people with hippocampal damage, dysfunction or deterioration generally favours MTT: episodic memories are impoverished, losing details specific to the episode but retaining non-specific, general information [17,22,23,47]. Proponents of SCT, however, argued that deficits in remote episodic memory are only evident when damage extends beyond the hippocampus [7,8]. It has also been claimed that patients' anterograde deficits prevent them from keeping track of their own narratives, so that they go on tangents when recalling remote memories, and their performance suffers. With appropriate guidance, performance improves to the point that their remote memory is not different from that of controls [48].

Both points can be disputed. The Autobiographical Interview (AI), developed by Levine et al. [49,50], is a structured memory interview that distinguishes between episodic and semantic aspects of memory narratives. The interview also provides specific probes that are meant to elicit more information should the narrative be curtailed or derailed. Such probes typically improved retrieval of episodic details for both patients and controls, but relative to controls, the patients continued to exhibit episodic memory impairment. With respect to lesion location, there are reports of patients with damage restricted to the hippocampus [51–53], to the fornix [54,55], and even to just the CA1 subfields [56] who, nonetheless, show severe and temporally extensive retrograde

amnesia. Also, the extent of the deficit seems not to be related to additional extra-hippocampal damage in the medial temporal lobe (MTL) [57,58] or other parts of neocortex. In this regard, it is especially telling that one patient [48] with extensive extra-hippocampal medial temporal damage was no more impaired than patients with restricted hippocampal lesions in retrieving remote, autobiographical memories when appropriate guidance was provided (see below for comparable evidence in rodents).

The evidence from neuroimaging studies is even less equivocal, and decidedly favours the positions taken by MTT: detailed or vivid episodic memories activate the hippocampus no matter how long ago the memories were acquired [17,22,59,60], with the extent of activation being related to the episodic nature of the memory [47,61,62]. Moreover, hippocampal activation is accompanied by activation of a set of structures that include the retrosplenial, parahippocampal, inferior parietal, precuneus, anterior cingulate, lateral prefrontal cortex (lPFC), and ventromedial prefrontal cortex (vmPFC) which together form the autobiographical memory network [59,60,63,64].

Studies on animal models, particularly on rodents, are also consistent with the basic tenets of MTT. Using surgical lesions, optogenetic and inducible transgenic techniques, and a variety of memory paradigms, including contextual fear conditioning, water maze, cross-maze and socially-acquired food preferences, investigators found that detailed, context-specific memories were always dependent on the hippocampus; it was only as memories became less dependent on context (context-general) with time and experience, that hippocampal involvement diminished and memories could be retained and retrieved in its absence [17,25]. A notable advantage of animal research over its human counterpart is that the nature and time of experience, as well as the size and location of the lesion, can be precisely controlled. We review this evidence in more detail below.

Predictions arising from MTT have been confirmed in numerous studies involving humans and animals. By emphasizing the role of the hippocampus in representing detailed, context-specific information, MTT encouraged researchers to develop new testing procedures that distinguish more clearly between episodic and semantic memory in humans [47,49,50], and between context-specific and context-general memory in rodents [65,66]. Following this new approach, functional neuroimaging in humans and immediate early gene (IEG) expression studies in rodents revealed hippocampal activation during selective recall of remote memories that retained their detailed, context-specific features, no matter how long ago they were acquired. Semantic or schematic memories that lack such features are associated with reduced hippocampal, but increased, neocortical activation emerging over time, particularly in the mPFC in humans and rodents. As well, the existence of long-lasting, context specific memories, led investigators to examine hippocampal involvement in different cognitive functions that rely on the recruitment of hippocampus-dependent, often detailed, mnemonic representations, such as imagining the future, open-ended problem-solving, and decision-making [22].

Although MTT distinguished clearly between episodic and semantic memory, and suggested extraction of statistical regularity as one mechanism by which semantic memories can be derived from events, it did not take the dynamic aspect of memory into account, and the interplay that occurs between different forms of memory from acquisition to retrieval over long intervals [19,20]. In addition, MTT differentiated only between episodic and semantic memory, and did not consider qualitative changes with respect to a particular episodic memory. Building on MTT, Trace Transformation Theory (TTT) directly addresses the issue of memory change, even with respect to a single episode, by proposing a process of memory reorganization by which hippocampus-based memories are transformed with time and experience to neocortical representations. In line with the principle of functional-neural isomorphism [22], TTT also explicitly emphasizes changes in the relationship between psychological and neural representations in the course of memory transformation. Thus, although distinct, TTT was derived from MTT and endorses some of MTT's basic tenets. Among them is the principle that detailed episodic memories are dependent on the hippocampus in perpetuity and that semantic memories become relatively independent of the hippocampus with time and experience. Retrieval of episodic memories is accomplished in a context that is different from the initial one, and the resulting representations are re-encoded, which provides one of the foundations of memory transformation.

At the time MTT was developed (1997), the functional distinction among the various structures in the medial temporal lobe had not yet been well characterized. Consequently, MTT proposed that the extent and severity of retrograde amnesia was related to the size of the MTL lesion (see also 67). However, subsequent research failed to show a clear relation between the size and extent of hippocampal lesions, and severity of retrograde amnesia for detailed events [17,25]. We return to this problem at the conclusion of the paper.

4. Trace transformation theory (TTT)

TTT postulates that, with age and experience, detailed, episodic (context-specific) memories are transformed into variants of the original, which lack detail and context specificity, but retain gist and schematic features [17,22,25]. In the process, these transformed memories come to be represented in distributed neocortical networks from where they can be recovered without the involvement of the hippocampus. Like MTT, TTT maintains that detailed episodic or context-specific memories are always dependent on the hippocampus. When first proposed, TTT did not distinguish between gist and schemas, and their respective neural representations. As is noted below, however, such a distinction is central to our reformulation of TTT. Another tenet of TTT is that both the detailed, hippocampus-dependent memory and the schematic, cortical variant can co-exist and interact dynamically in a number of ways. The variant that is expressed, and the neural structures that are engaged, are determined by the demands of the task and the prevailing conditions. The different types of memory may also interact with each other as, for example, when schemas mediated by neocortical structures, facilitate access to gist, or detailed memories, mediated, respectively, by the anterior and posterior hippocampus, at retrieval (see below).

The process of transforming memories may depend, as MTT suggested, on repeated explicit retrievals of the initial memory (see 68) or implicit retrievals that occur as a result of replay during sleep or rest [24,69]. In fact, a single exposure to an event may be sufficient to trigger offline replay of a memory which supports both its consolidation, and the formation of distributed cortical representations from which gist and schemas are derived [14]. Similarly, Dudai has proposed that ongoing waves of synaptic consolidation act as 'subroutines of systems consolidation' [9,24] which may support the development of this distributed trace in the absence of explicit conscious retrieval.

Important evidence in support of TTT comes from cross-sectional and longitudinal studies showing that changes in the neural representation of memories are accompanied by corresponding qualitative changes in psychological representations. This evidence has been reviewed in recent publications [17,22,25]. Here we highlight some of the main findings, and focus on more recent studies, building and expounding on the theoretical formulations of Moscovitch, Winocur, Nadel, Robin and their colleagues.

5. Memory transformation in non-humans

In animals, tests of TTT have been conducted on several tasks, including contextual fear conditioning [70] and socially-acquired food preferences in rodents [71], and object recognition in primates [72]. The consistent finding in these early studies was that hippocampal lesions produce a temporally-graded effect in which remote memories are retained, whereas more recently acquired memories are lost.

Subsequent studies showed that the spared remote memories are mediated by extra-hippocampal structures including, in particular, the mPFC [73–76].

Results from the early studies were interpreted in accordance with SCT because of the implicit assumption that the identical memory was expressed at both time points. Winocur et al. [65] questioned this assumption by suggesting, in line with emerging evidence from the human literature, that remote memories are spared because they are transformed versions of recent memories that lost their precision or context-specificity. This interpretation was supported in studies in which rats acquired a contextual fear response or food preference, and then were tested at short and long intervals either in the original or a different context. At short intervals, rats' memory showed context-specificity for both learned responses, whereas at long intervals they generalized the response to other contexts. These findings suggest that, even in the intact brain, there is a gradual loss of context-specificity over time, accompanied by increased generalization of the memory. This generalized remote memory is supported by non-hippocampal cortical regions; animals that receive hippocampal lesions at extended delays following memory acquisition similarly express this generalized memory when tested in a context that differs from the conditioning context. These initial findings have since been replicated by other investigators [66]. In addition, when context-specificity seemed to be a pre-requisite for good performance, remote memories were as impaired as recent memories following lesions restricted to the hippocampus [17,25].

In follow-up work, Sekeres et al. [77] reasoned that patterns of brain activation associated with memory for a contextual fear response at short and long delays after learning should correspond to the type of memory that is retrieved. Using IEG expression of c-Fos, they found greater activation in the hippocampus, relative to the mPFC, at short delays when memory was context-specific, and the reverse at long delays when memory was transformed to a schematic version. Importantly, hippocampal activation was still evident even at long-delays, suggesting that the hippocampus may continue to contribute to remote memory performance through its interaction with the mPFC (see below).

Direct evidence of continued hippocampal involvement in memory representation after memories are presumably consolidated comes from gain-of-function studies using optogenetic activation [78,79]. Tonegawa and colleagues were able to identify and tag hippocampal cells associated with contextual fear conditioning in mice. By selectively reactivating these cells, they were able to elicit a fear response in animals that exhibited drug-induced retrograde amnesia [80], and in a mouse model of Alzheimer's Disease [81]. These findings provide strong support for the notion that the original neural ensemble, called 'engram cells' by Tonegawa and his colleagues [79], continue to be involved in memory storage and retrieval processes. Direct stimulation of this sparse population of cells is sufficient to express the fear response when naturalistic cues are ineffective. Similar findings were reported for non-aversive social memory such as recognition of a conspecific [82], suggesting that this phenomenon is not limited to fear memory.

Earlier work by Goshen et al. [83] had shown not only that hippocampal cells continue to be involved in the memory trace as long as four weeks after acquisition, but that they contribute directly to the expression of remote memory. They optogenetically inhibited the hippocampus or mPFC at short and long intervals following contextual fear conditioning. After a short interval, only hippocampal inhibition led to loss of the fear response. After a long interval, brief inhibition of either structure elicited this effect, suggesting that the two structures interact with one another to express remote memories.

The latter result appears to be at odds with the well-established finding that remote memory for a generalized contextual fear response survives hippocampal lesions. To address this problem, Goshen et al. [83] inhibited the hippocampus for a prolonged interval to more closely approximate the effects of hippocampal lesions. In the presence of prolonged hippocampal inactivation, the contextual fear response was preserved. As a further test, Einarsson et al. [74] used lesions or pharmacological inactivation, which have a sluggish temporal dynamic that allows for functional recruitment of other cortical regions. They found that disruption of *both* the mPFC and the hippocampus, with either technique, impaired retrieval of the remote context memory, whereas disruption of just one region alone did not result in such impairment. Thus, temporal dynamics seem to be key in determining whether or not a deficit will emerge following hippocampal/mPFC inactivation.

It is necessary to add a caveat here. Some of these studies showed that optogenetic stimulation of cells tagged during encoding may be sufficient to elicit expression of the original memory, demonstrating that the original ensemble of neurons can continue to support a memory over time. Such stimulation, however, may not mimic the process that supports memory retrieval under normal physiological conditions. Therefore, while informing our understanding of how reorganized memory networks operate at the cellular level to a certain extent, these studies do not satisfactorily address how memory networks behave at the cellular level under natural conditions (see also review by Hardt & Nadel in this issue [84]).

The results from the optogenetic and pharmacological studies are consistent with TTT's tenet that the expression of remote memory is determined not only by the memory demands of the task but also by interactions between hippocampus and neocortical structures, such as mPFC. Furthermore, these studies suggest, as TTT postulates, that (1) the hippocampus may continue to be implicated in retention of context-specific memories, even when their expression is masked by the dominance of context-general representations mediated by neocortex [17,25], and (2) that context-specific memories can be reinstated under appropriate conditions.

The dynamic nature of the transformation process is further reflected in the *reconsolidation* phenomenon which contradicts a basic premise of SCT, namely, that once consolidated beyond the hippocampus, memories cannot be eliminated by removing or inactivating the hippocampus. Contrary to SCT, considerable evidence has shown that once a consolidated memory is reactivated, it can become labile and once again become susceptible to the effects of hippocampal disruption, unless it completes a process of 'reconsolidation' whereupon the memory is restabilized and strengthened [24,88–90]. Importantly, investigators of reconsolidation initially operated on the erroneous assumption that although the neural substrates changed, the nature of the memory remained constant throughout, from original learning, to storage, reactivation and reconsolidation. Here, too, Winocur et al. [90], in line with TTT, argued that changes in the neural substrate, from hippocampus-independent to hippocampus-dependent memory with reconsolidation are accompanied by corresponding changes in the qualitative nature of the memory itself. Consistent with this view, they confirmed, using contextual fear conditioning, that at a month's delay, memory performance was determined by context-general information mediated by extra-hippocampal structures: rats froze as much in a new context as in the original context. Re-exposing animals to the original conditioning environment, as required for reconsolidation to occur, reinstated the context-specific version of the memory, such that they froze much more when tested back in the original, rather than in the novel, context. This reactivated context-specific memory was dependent on the hippocampus, rendering the memory susceptible once again to disruption following hippocampal lesions. By contrast, a non-specific reminder merely activated the context-general memory represented in extra-hippocampal structures, such as mPFC.

That the initial context-specific memory could be reactivated indicates, as we have argued, that its neural substrate is still represented in the hippocampus at remote time points even as the context-general memory becomes represented in other cortical structures. As noted above, this interpretation is supported by results of studies using IEG

expression, transgenic mouse models, and optogenetics.

A recent optogenetic study by Kitamura et al. [91] supports this interpretation. Using a transgenic conditional labelling technique in mice, they were able to tag neurons active during the initial encoding of a contextual fear memory, and then re-tag neurons subsequently engaged during retrieval of the memory at both a recent (1 day) and a remote (approximately 2 weeks) time point in either the same conditioning context (Context-A), or in a novel context (Context-B). They found that inhibition of medial entorhinal cortex (MEC) terminal fibres projecting from hippocampus to mPFC resulted in reduced memory of a remotely learned contextual fear response, but did not affect memory when the response was recently acquired. These findings suggest that the MEC-mPFC pathway is important for the later retrieval of the remote, reorganized memory, but that this pathway is not necessary to support early memory retrieval, soon after encoding, at a time when it is primarily supported by the hippocampus (see also review by Hardt & Nadel in this issue [84]). They then showed that these MEC-mPFC neurons that become part of the remote memory network are recruited at remote recall only for the context-specific memory (Context A), but not for recalling the generalized memory in the novel context (Context B). These findings indicate that any non-tagged neurons recruited at the remote time point during Context-B recall are likely supporting recall of the non-specific, generalized memory. As mentioned earlier, however, there is a need for caution in interpreting studies using artificial forms of stimulation to understand neural memory network dynamics.

In accord with TTT, the animal studies we reviewed indicate that as a memory ages and becomes transformed into a schematic representation that is sufficient to support retrieval, specific contextual cues may be less effective in triggering the original memory trace. Despite not being *necessary* for context memory retrieval after a long delay, however, the hippocampal memory trace can be reactivated, either artificially via stimulation, or by appropriate contextual cues, and induce context-specific memory retrieval. Contrary to SCT, this finding shows that once consolidated and represented in extra-hippocampal structures, an initial hippocampus-mediated memory can be re-engaged.

Taken together, the evidence points to the existence of two memory representations: context-specific representations mediated by ensembles of hippocampal-neocortical neurons, and schematic or context-general representations mediated by ensembles of mPFC-neocortical neurons, possibly with the involvement of the hippocampus. The findings also underscore the need to consider interactions between the hippocampus and other brain regions, in particular the mPFC, in the transformation process and the expression of remote memories. We take up this issue and the more general question of how memories are transformed after examining the literature in humans.

6. Memory transformation in humans

As we noted in reviewing the evidence favouring MTT, neuroimaging studies focused on the neural substrates mediating remote, detailed memories in healthy adults. There is less evidence related to the structures implicated in memories that have been transformed either into gist-like or into schematic versions of the initially detailed memories, either in healthy people or in patients with hippocampal damage. To examine memory transformation and the structures that are implicated, we conducted a series of behavioural, lesion, and fMRI studies in which we assessed a combination of autobiographical memory and memory for naturalistic video clips. Using the AI, with its emphasis on distinguishing between details specific to the episode (internal details, particularly perceptual ones[3]) from those that are non-specific (external details), St-Laurent et al. [92,93] compared memory for remote autobiographical events and recently viewed video clips in healthy controls and in patients with MTL epilepsy (mTLE) that affected the hippocampus. For both types of material, they found that memory for external (semantic) details was relatively preserved in patients, as was memory for story elements that were central to plot coherence of the event or clip (gist). The patients' memory for perceptual details for both film clips and autobiographical memory, however, was clearly impaired. These findings indicate that not only was semantic or schematic memory preserved, but so was the gist of an event as captured by the central, story elements. As we noted earlier, the distinction between gist and schema will become important in the further development of our model of memory transformation.

In a subsequent fMRI study, St-Laurent et al. [93] found that mTLE patients' impoverished memory for perceptual details was associated with reduced activation in posterior neocortex which exhibited strong functional connections to posterior hippocampus [94,95]. This interpretation was bolstered by their finding that, in healthy controls, memory for perceptual details was associated with right hippocampal activation. That hippocampal activation was reduced, but not eliminated, in patients leaves open the possibility that this remaining activation may have mediated memory for gist.

To examine the nature of memory transformation more directly, Sekeres et al. [29], using the same video clips, first conducted a longitudinal, behavioural study in healthy controls, testing people immediately after clip presentation and at various intervals up to a week. They found that the central elements [96] of the events tend to be well-preserved over a one-week delay. By comparison, memory for many of the peripheral details which capture the non-essential aspects of the events, but which imbue memory with perceptual richness, is significantly reduced. At long delays, providing a reminder prior to retrieval disproportionately increased memory for peripheral, as compared to central, details.

Adapting this paradigm to an fMRI study, Sekeres et al. [77] and Bonasia et al. [97] found that at encoding and at immediate recall of the clips, the anterior-posterior extent of the hippocampus as well as the mPFC were activated. At a week's delay, posterior hippocampal activity was diminished, whereas activation of the mPFC increased, consistent with the observation that participants rely less on the peripheral, perceptually detailed information, and more on gist information to support their memory of the event, as TTT predicts. Importantly, when events were vividly recalled after a week, activation of the hippocampus was comparable to that observed at immediate testing. This hippocampal involvement was accompanied, nonetheless, by increased activation of the mPFC which suggests an ongoing process of transformation that contributes to the formation of schemas that support recovery of these details [98–101].

As noted earlier, there is growing evidence that the mPFC is implicated in the formation and instantiation of prior knowledge as represented by schemas [34,102,103]. These schemas are actively involved in encoding new events and in their retrieval. Using the data from Sekeres et al. [77], Bonasia et al. [97] showed that schema-congruent clips, namely those whose elements are related to common scenarios that were consistent with pre-existing schemas, such as of a family dinner or birthday party, engaged the mPFC more than incongruent clips at both encoding and immediate and delayed retrieval. With respect to the hippocampus, the reverse held – memory for schema-incongruent clips engaged the hippocampus more than that for schema-congruent clips both at encoding and delayed retrieval. It is important to note that there was little evidence of hippocampal activation during retrieval of schema-congruent clips at a week's delay, suggesting that participants relied primarily on mPFC-mediated schematic information to retrieve the memory. Additionally, the mPFC and MTLs each demonstrated functional connectivity with parietal areas during retrieval [104], but only for typical *or* atypical events, respectively.

In other longitudinal studies using film clips to test naturalistic

[3] There are many kinds of internal details. Here we focus primarily on perceptual details. Later, we refer to these internal details as "peripheral" elements since they are not crucial to the story line. We refer to those elements that are crucial as "central" elements [96].

event memory, Furman et al. [105] presented participants with long narrative film clips, and tested their memory for the clips at various intervals ranging from hours to months. Although performance decreased, they found stable anterior hippocampal activation on tests of recall, but a decrease in hippocampal activation over time on recognition memory. Importantly, their remote recognition memory was still significantly correlated with the residual activity in the hippocampus. Furman et al. [105] concluded that the hippocampal representation was pruned and consolidated during the interval, yet supported retrieval of the 'crux of the event', which we interpret as its gist.

Taking another approach, Bonnici et al. [99,100] used multivariate pattern analysis to track representations of autobiographical memories that remained detailed and contextually specific over a two-year period and compared them with equally detailed memories that were ten years old. They showed that despite being detailed, representations of these memories increased in mPFC and posterior hippocampus over a two-year period to a level found during retrieval of ten-year old memories, whereas representations in the anterior hippocampus remained relatively stable, as in Furman et al. [105].

In a meta-analysis of studies on autobiographical memory in young and older adults, Viard et al. [62] reported findings consistent with these data on the differential role of the anterior and posterior hippocampus in retrieval of autobiographical memory. They noted that the posterior hippocampus is implicated in perceptually-detailed re-experiencing of the past. Retrieval cues associated with the gist of the event, such as were used in the study by McCormick et al. ([98], see below), activated the anterior hippocampus. Last, there was greater activation in anterior hippocampus in older (over 55 years), than in young, adults, consistent with older adults' greater reliance on gist as a result of their compromised ability to re-experience the past in great detail [50].

7. Comparison of human and non-human studies

Overall, the results from human and non-human studies align well with one another. In both, detailed, context-specific memories are shown to depend on the hippocampus in interaction with posterior neocortex. As memories age, there is a loss of perceptual details while general details, in the form of gist and schema information, are preserved. A similar pattern is seen following hippocampal lesions or dysfunction. Such preserved, general memories depend on the mPFC in interaction with the hippocampus and other structures in healthy controls. Following hippocampal damage, the memories depend more heavily on mPFC and its relatively weak interaction with posterior neocortex. Importantly, in both intact rodents and healthy humans, reminders can reinstate context-specific memories, a phenomenon which, in rodents, has been shown to depend, once again, on the hippocampus. Comparable neuroimaging studies have not yet been conducted in humans (but see [106]).

The fact that results from human and non-human studies have much in common suggests that similar memory transformation processes occur across species. In human fMRI studies, whole brain analyses can identify crucial regions in memory transformation, and their interaction through functional connectivity analyses. Such procedures are prohibitively time intensive in rodent studies (see [76,107,108]), but in those that were conducted, the hippocampus emerged as a crucial hub linking several regions in the remote memory network, consistent with MTT and TTT. It is unlikely that the technology for tagging single brain cells, and subsequently activating or inhibiting them, as in optogenetics, will soon be achieved in humans. On the other hand, there is evidence that applying transcranial stimulation to different brain regions, and assessing the effects with functional connectivity analysis, may enable the determination of those areas that are implicated in memory transformation in humans [109].

Recent investigations of specialization within the long axis of the hippocampus provide important insights into the neural mechanisms underlying its role as a hub in the transformation process. These investigations have revealed differences in functional organization between the anterior (ventral in rodents) and posterior (dorsal in rodents) regions, related to receptive field size, the distribution of hippocampal subfields, and their connections to other brain regions. Based on these differences, investigators (see [95]) have suggested that the posterior hippocampus (pHPC) is suited for coding (representing) fine grained, local features of an event which underlie rich perceptually-based memory representations (details), whereas the anterior hippocampus (aHPC) codes more coarse-grained, global aspects of an event, which support representations of gist memory. Thus, as in the example of the birthday party (see Fig. 1 and the section on definitions), the pHPC is biased to support memory of the specific details of the event (e.g., the appearance of the cake, decorations in the room and their location, which music was playing). In contrast, the aHPC codes for more general information related to that particular event (e.g., it was my brother's birthday and we gathered in the living room). The respective functional connections of the pHPC and aHPC with other brain regions enable the organization of these aspects of memory: the pHPC is strongly connected to posterior neocortical structures implicated in perception such as ventral temporal cortex, precuneus, retrosplenial cortex and posterior cingulate cortex, whereas the aHPC is connected to the anterior temporal lobe, mPFC and amygdala, which, respectively, are associated with semantic memory, schemas (see definitions), and emotion [95,110,111].

Our examination of changes in memory representation with time has shown that memory for perceptual details is associated with activation of the pHPC and its posterior neocortical connections, whereas memory for gist is associated with aHPC activation in conjunction with anterior structures, such as the mPFC [77,92]. As memories are transformed from detailed to more gist-like representations, there is a shift in activation from posterior hippocampus and neocortex, to anterior hippocampus and neocortex, particularly the mPFC. In the next section, we use these observations to inform and update our model of memory transformation.

8. How are memories transformed? The role of the long axis of the hippocampus in interaction with posterior and anterior neocortex

8.1. Evidence in humans

Various theoretical models of memory, along with supportive data, provide insight into the neural interactions that underlie the transformation process [17,22–24,34,36,102,112–115]. Our view is that the process of transformation is determined initially by the types of representations mediated by the anterior and posterior hippocampus in interaction with mPFC and posterior neocortical structures, respectively, at the time of encoding. According to our formulation, activity in these inter-connected structures and their corresponding cognitive correlates form the foundation of the transformation process. Discoveries of dissociable functions along the long axis of the hippocampus point to a mechanism for the initial representation of events that provides the building blocks for the subsequent neural changes that are fundamental to the transformation process on the one hand, and for retaining detailed memories of those events, on the other [9,22,24,36,95].

Work on rodents and humans indicates that structural differentiation along the axis of the hippocampus from high to low granularity enables the representation of corresponding memories that differ in detail. The pHPC, through its reciprocal interactions with posterior neocortex, mediates the representation of rich, perceptual details of an event. In contrast, the aHPC, in interaction with anterior neocortical structures, mediates the representation of the global features, gist or general context of the event. Among the structures with which the aHPC interacts are the anterior lateral temporal cortex which mediates semantic information, the amygdala whose contribution supplies some of the emotional tone of the entire event, and the mPFC. The mPFC is

implicated in the higher level representation of gist-related information by its interaction with aHPC, as well as the creation and instantiation of schemas which represent common elements among exemplars within a class of events (see Fig. 1). These schemas can be used at encoding to interpret events, and at retrieval to control and monitor their recovery [116]. By virtue of its role in representing schemas [33], the mPFC provides a template that enables the anticipation and interpretation of events at encoding [116]. Similarly, at retrieval, schema instantiation directs strategic memory search [117] and provides a template for subsequent monitoring to ensure that the retrieved memory is consistent with the goals of the task [32,34]. In humans, regions of the mPFC and related orbito-frontal cortex are implicated in subsequent control processes that determine the cognitive and behavioural outcomes [118,119].

A study by McCormick et al. [98] is illustrative of the retrieval process. Using functional connectivity analyses, they found that during the initial search and construction phase of retrieving autobiographical memories, which is thought to depend on instantiating schemas and retrieving gist [120], the mPFC interacted closely with the left and right aHPCs. During the subsequent elaboration phase, when the participant elaborated on details of the event, there was a shift in connectivity from anterior hippocampus and mPFC, to posterior hippocampus and posterior neocortex [see also 121].

Damaging the hippocampus should bias activation toward the mPFC. That is what McCormick et al. [101] found in a subsequent study of patients with left unilateral temporal lobectomy, confirming and extending the findings first reported by Addis et al. [122] and complementing those of St-Laurent et al. [92,93] reported above. In contrast to controls, mPFC activation in patients was correlated with activation in other prefrontal and lateral temporal cortices during the construction phase, and in visual-perceptual cortices during the elaboration phase, without aHPC and pHPC acting as intermediaries. Together, these findings suggest that impoverished autobiographical memory recall in mTLE patients is a consequence of reduced activation of bilateral hippocampal networks and greater reliance on anterior neocortical contributions to memory retrieval. Though mPFC is functionally connected to posterior neocortex, it is less able than the pHPC to recruit the pattern of neural activity needed to reinstate a perceptually rich memory.

The above studies show the importance of *pre-existing* schemas in memory formation and transformation at retrieval. A number of recent experiments show how new schemas are built at encoding and contribute to both processes. Milivojevic et al. [123] used The Sims 3 videos of life-like animated events and presented clips which could be integrated into a narrative (schema) or not depending on whether a linking clip was presented or withheld. The presentation of the linking clip led to an insight that triggered the integration of disparate memories into a coherent narrative (schema formation) that was accompanied by changes in neural representation. Specifically, the linking clip and the subsequent integration led to increased neural similarity among linked events in the posterior hippocampus, mPFC and other nodes in the autobiographical memory network, and increased neural dissimilarity in pHPC among unlinked events. Clips unrelated to the narrative structure were pruned out, a process signalled by a mismatch response in the aHPC. Consistent with our hypothesis of interaction between schema formation mediated by mPFC and global context representation mediated by aHPC, the strength of the mismatch response in aHPC was related to the change in neural similarity responses in the mPFC.

A subsequent study by Collin et al. [124] supported this interpretation of a global-local gradient along the long axis of the hippocampus. Using the same clips and the narrative insight task, they found that in the pHPC, neural similarity was observed only between clips that were presented together (A-B or B-C but not between them). In the mid-portion of the hippocampus, neural similarity was observed between presented pairs that shared a common clip (A-B was similar to B-C, but neither was similar to A-C which were not presented together but whose association was inferred), and in the aHPC between events that were never presented together, such as A–C, but were integrated through linking via a common clip, (A–B, B–C and A–C were similar to one another).

These studies using film clips are formally similar to studies of associative inference that use unrelated pictures (A–B, B–C) with overlapping or common elements (B) to promote associations between items that were never presented together, such as A–C in the above examples [125,126]. Here, too, associative inference between A–C is dependent on the interaction between aHPC and mPFC [36,127]. Using representational similarity analyses, Schlichting et al. [128] showed that in the pHPC and anterior mPFC memories are represented distinctly, especially if they share a common element, whereas in the aHPC and posterior mPFC memories that share a common element are more similar to one another, suggesting that they are integrated. Such integration is facilitated if the initial A–B pairing is well-established. The latter finding is consistent with Liu et al.'s [103] observation that pre-experimental prior knowledge of faces facilitates the formation of associative memory between faces and houses, a process related to functional connectivity between the aHPC and mPFC at encoding [103], and between the hippocampus, anterior temporal lobe (ATL), and fusiform face area during post-encoding rest [129].

None of the above studies, however, examined the effect of such integrative processes over long retention intervals where there is opportunity for greater memory transformation. Using a face-location association task [130,131], Sweegers and Talamini [132] had participants link faces to locations. Some faces, which shared common features and formed a category, were always linked to a particular location (RULE condition) and thus contained regularities in face placement, whereas other faces were randomly assigned to a location (NO RULE), thus containing no regularities in placement. If one considers regularities to conform to a schema for faces, then one would expect, according to our transformation hypothesis, that the difference in hippocampus-mPFC connectivity between the RULE and NO RULE conditions, would increase with time as detailed representations are transformed to gist-like ones in interaction with schemas. Indeed, that was the case, though it was the mid-region of the hippocampus that was implicated, rather than the aHPC.

Similar results were reported by Tompary and Davachi [133] using trial unique associations that shared features with other trials (e.g. A–B, C–B, D–B; W–Z, X–Z, Y–Z). Memory for these associations was tested immediately and a week later by presenting the non-overlapping member of the pair. Using multi-variate pattern analysis (MVPA), they examined the similarity in neural representations between memory for items that shared an overlapping association (A with C, and W with X) and for those that did not (A with W, and C with X). Consistent with our transformation hypothesis, they found that the greater similarity among overlapping relative to non-overlapping memories increased with time in mPFC, which was related to connectivity between aHPC and mPFC for the remote, but not recent, memories. Interestingly, pHPC also showed an increase in similarity for the overlapping memories with time, though no decrease for non-overlapping memories, suggesting that this region is sensitive both to extracted regularities among memories over time, while also maintaining detailed representations of unique associations. This finding fits well with Bonnici et al.'s [99] observation that the pattern of activation in pHPC can distinguish among remote autobiographical memories. By contrast, the pattern of activity for aHPC showed no change in similarity for overlapping items over time, but a decrease in similarity for non-overlapping memories, consistent with our hypothesis that aHPC is sensitive to the global, shared properties of a memory while pruning those properties that are unique.

These findings are broadly consistent with those of an earlier study by Ritchey et al. [134], who presented sentences with unique objects associated with overlapping locations (the room in which the objects were located – e.g., chair in living room, mug in living room) or non-

overlapping locations (pencil in kitchen). Recognition memory, accompanied by recollection and familiarity judgements, was tested immediately or after a day. Recollection-related activity declined after a day in pHPC but remained stable in aHPC. MVPA analysis revealed that aHPC coded for the overlapping location (global context), and that after a delay, this coding was related to successful retention of context information. These finding support the interpretation that aHPC is implicated in coding the overlapping context, which helps form the gist of the experience, which in turn would aid in recovering information about items associated with that context (see [98]).

The interaction between schema formation, memory and time is highlighted in a heroic experiment by Sommer [135] who showed how *new* schemas are built, and contribute to memory formation and transformation. He created a human analogue of Tse et al.'s [136] animal paradigm (see below) in which participants first learned 10 different schemas, each defined by 20 different locations on a computer screen. Participants then learned to associate different objects with 12 of these locations and rehearsed them for up to 302 days. They were tested at short (1, 2 days), intermediate (91, 92, 105 days) and long delays (310, 312 days). Performance and neural activity was compared to a control condition in which memory was assessed for a target that was associated with a novel set of locations that had not been learned (non-schema condition).

The results, like the study, are complex, but generally consistent with TTT. Briefly, given the location within a learned schema as a retrieval cue, participants' performance at short delays was supported by recollection (context-dependent memory), which was progressively diminished as the delay increased, at which point they relied on high confidence familiarity (context-independent memory). Along with this functional change in memory, there were corresponding changes in the neural structures mediating the memory, with a reduction in aHPC activity accompanied by an increase in mPFC, indicating schema-guided memory retrieval at short delay. At longer delay there was increased activity in ventro-lateral PFC (vlPFC), a structure implicated in semantic memory. Importantly, schema-related mPFC activation and memory-related aHPC involvement, as well as functional connectivity between them, re-emerged at intermediate and long intervals when participants encoded novel associations that were related to the previously-acquired schemas.

Immediate retrieval of these associations was related to functional connectivity between mPFC and pHPC, with activity in pHPC dropping when tested a day later. When tested 15 days later, there was a decrease in activation in both aHPC and pHPC, with an accompanied increase in vlPFC activity.

It is reassuring for TTT that despite great differences in stimulus and task parameters, the general patterns of activation in the hippocampus, mPFC, and posterior neocortex, and the interactions among them, are comparable across experiments (but see [137]). The picture that emerges is consistent with TTT. Forming schemas, whether by inserting conceptual or thematic links, as in Milivojevic et al.'s study, or by having overlapping elements among stimulus events, involves interactions between mPFC and usually aHPC. Once formed, the mPFC-mediated schemas interact with novel information at encoding to facilitate formation of new memories that are dependent initially on the aHPC and pHPC, with the aHPC coding for global (gist) aspects of a memory, and the pHPC, coding for local aspects (details). At retrieval, the pattern of activation of mPFC, aHPC, and/or pHPC that is observed depends on which aspects of the memory are retrieved. Typically, as memories are transformed with time, there is a reduction in memory for local, event unique aspects (details) of the memory, and greater reliance on global, gist-related and schema-related aspects, with concomitant reduction in activation of pHPC and increased reliance on aHPC, but especially on mPFC (see Fig. 1). Representational similarity in these structures reflect these changes, with increasing similarity in mPFC and typically, but not always, increased similarity among related stimuli in aHPC. These changes are accompanied by a decrease in similarity among unrelated stimuli as befits structures that code for schemas and gist, and act as templates for distinguishing related from unrelated stimuli, and emitting an error or mismatch signal for the latter [123]. Insofar as some memories are highly detailed, their distinctiveness will be retained and reflected in pHPC with changes in degree of similarity among unrelated items that may vary with the amount of detail that is retained.

The one puzzling finding, however, relates to reports of increases in representational similarity in pHPC among related events [123,133]. If pHPC codes for details, and not gist, why should this occur? We propose that this occurs precisely because pHPC codes for details, and the relations among them. With respect to stimuli with overlapping elements, one can expect that such elements, being common among stimuli, are likely to decay less with time, as compared to non-overlapping elements. Thus they will form a larger proportion of the memory representation and lead to greater similarity among those memories [133]. When details become thematically related by the introduction of a linking event, then how those details are coded also changes, making their coding more similar to one another and leading to greater neural similarity.

8.2. Evidence in rodents

A similar picture emerges from studies on rodents. Here, the distinction between details, gist and schema at the neural and behavioural levels, and related control processes, are emerging with some encouraging results that are broadly consistent with the human literature. McKenzie et al. [138] and Komorowski et al. [35] trained rats in different contexts (test chambers) with rewards situated in different locations within those chambers. Inactivation of the ventral hippocampus (homologue of anterior in humans) at retrieval led to deficits in distinguishing one test chamber from the other (gist, or general context), whereas inactivation of the dorsal hippocampus (homologue of posterior in humans), only led to deficits in remembering rewarded locations within a particular chamber (local details). Clearly a dynamic interaction between both regions is needed to represent and express both global and local features of the memory. Recent work by Eichenbaum [139] and his collaborators [35,138], and Guise and Shapiro [140] showed that the mPFC interacts with the hippocampus to enable rats to exercise control over which test chamber is chosen. These findings are consistent with our idea, derived from work with humans, that the mPFC is needed for instantiating the appropriate schema against which memories can be compared. Afterwards, related structures in orbito-frontal cortex are recruited to control memory-related responses.

Tse et al. [136,141] showed that building schemas implicates the mPFC and can facilitate associative learning that is mediated by the hippocampus. They had rats learn a schema defined as a set of smell-location associations within an arena (open field). Given a particular scent cue, rats learned to retrieve a reward at the associated location. Once the schema was learned, a new location associated with a new smell was introduced in the arena. Rats learned the new smell-location association quickly. Initially dependent on the hippocampus, this new association became independent of it, and reliant on the mPFC, more quickly than memory for new smell-location associations not related to the schema. Tse et al. [141] concluded that schema-related learning accelerates memory consolidation (transformation) such that the new learning is integrated rapidly into the schemas represented in the mPFC.

The importance of mPFC-hippocampal interactions shortly after learning to support the formation of short-term and remote memories is highlighted in studies on socially acquired food preferences by Lesburguères et al. [142]. They showed that inactivating either the hippocampus or mPFC with the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) shortly after learning impaired retention. Inactivation at long delays was effective only when mPFC was targeted, indicating that the memory had been transformed into one that now was dependent on the mPFC and was relatively independent of the hippocampus.

Although Tse et al. [136] and Lesburguères et al. [142] did not explore the nature of the mPFC memories to determine if they were schematic versions of the original, other studies on contextual fear conditioning and socially-acquired food preference clearly indicate that the consolidated or transformed memories were schematic [17,25,66,113]. In those studies, performance shortly after acquisition depended on reinstating the context in which the memories were initially acquired (context specific), whereas, at longer delays, context specificity was lost so that performance indicative of memory retrieval was observed even in new contexts.

The increased recruitment of mPFC neurons over long intervals may be related to Kitamura et al.'s [91] (see above) observation in their optogenetic studies with mice. They found that during initial learning of contextual fear conditioning, input from the hippocampus and entorhinal cortex was instrumental in forming new prefrontal memory networks. Although not initially viable, with time and continued support from these structures, the prefrontal cells matured and contributed to memory performance. Once the prefrontal cells were viable, the influence of hippocampal cellular activity receded. These studies support the view that mPFC-hippocampal networks are required for the formation of enduring associative memory [142] and for mediating related control processes at encoding and retrieval (see 117,143,144).[4]

In addition to direct connections between the hippocampus and mPFC, interactions between these structures during the transformation process may be facilitated by indirect connections via the entorhinal cortex [91]. Insel and Takehara-Nishiuchi [114] working with rats, and Fuentemilla et al. [145], with humans, have shown that synchronization between activity in aHPC and entorhinal cortex is greater during learning, and between entorhinal cortex and mPFC is greater during memory consolidation/transformation. In addition, Insel and Takehara-Nishiuchi [114] and Morrissey et al. [115] found that ensembles of cells in the entorhinal cortex stably represent the experimental, conditioning context regardless of moment to moment fluctuations in the environment, suggesting that the entorhinal cortex is involved in representing gist-like information. By comparison, as transformation progresses, "cells in the mPFC become less selective for the perceptual features unique to each association… and more selective for common relational features" indicative of schemas [115].

With respect to our model, we interpret these findings as showing that the entorhinal cortex helps to capture the gist of an event, whereas the mPFC is involved in capturing schemas that abstract what is common across events. The entorhinal cortex may enable the translation of signals related to gist from the aHPC and transmit them to mPFC for assimilation into an appropriate schema.

9. Conclusions, limitations and questions

An episodic memory consists of a multifaceted representation that includes details, gist and general knowledge (schemas and semantic information) about the remembered event. The long axis of the hippocampus serves as a hub for representing episodic memory, with pHPC interacting with posterior neocortex to represent perceptually rich details, and aHPC representing a memory's gist as a result of its interaction with anterior neocortex, particularly the mPFC which mediates schemas (See Fig. 1). The updated TTT incorporates these ideas to explain how a complete version of an episodic memory that represents details, gist and schema may be transformed, with time and experience, to one in which some of these components are lost or unavailable while others are retained or emphasized, and allows for their respective expression in appropriate ways. As memories age and details are lost while gist is retained, there is a shift in memory representation from pHPC to aHPC and, from there, via entorhinal cortex, to mPFC, and related structures in anterior neocortex. When gist is also lost, as it sometimes can be even in healthy people, and only schemas remain, memories are mediated by mPFC without hippocampal engagement. Providing healthy individuals with appropriate cues can help recover the gist, and even details of an event, whereas such recovery is unlikely or impossible in patients and animals whose relevant structures are damaged or lost (see below). If details are retained, however, memories continue to engage the posterior (and anterior) hippocampus in perpetuity, but also increasingly engage the mPFC as memories become remote. The model also helps to account for the effects of selective damage to one of its constituents on episodic memory (see Fig. 1).

Another important aspect of TTT is that both the memory details and gist mediated by the pHPC and aHPC, respectively, and schemas mediated by mPFC, can all co-exist and interact dynamically. The type of memory that is expressed and the neural structures that are engaged are determined by a variety of factors that include the nature of retrieval cues, strategic retrieval processes available to the subject, immediate and delayed post-encoding processes, and task demands [17,25,26].

A number of predictions that follow from our model have not been fully or systematically tested. For example, extensive damage to both anterior and posterior hippocampus, with sparing of the mPFC should leave the individual bereft of even the gist of episodic memories, with sparing of only schematic memories of past events, or semanticized memories of episodes. It is interesting to note that this description fits with what has been observed in H.M. [146,147] and in other well studied amnesic patients with hippocampal damage [148,149], including K.C. [150].[5] (See [8,57,183] for reports of spared remote episodic memory in patients with extensive damage restricted to the hippocampus).

Damage to the mPFC should also lead to impaired remote and recent memory, not because details and gist are lost or impoverished, as occurs after damage to the hippocampus, but because schemas play a role in perception at encoding, and in search, monitoring and control at retrieval. By and large, the evidence supports these ideas [22,34]. In humans, mPFC damage leads to confabulation, a disorder that arises from poor schema instantiation that biases perception, and that likely contributes to poor stategic search, monitoring and control [116,118,119]. The model, however, also predicts that if cues are highly specific, the memories may be retrieved directly via the hippocampus, bypassing the indirect route via the mPFC. There is some suggestion that this is the case [151,152], but these issues have not been investigated systematically.

In rodents, reliance on the mPFC emerges over time [73,74,153,154] but there is evidence that early communication between the hippocampus and mPFC is required for the formation of the remote mPFC memory network [142]. Lesioning or blocking dendritic spine growth in the hippocampus shortly after context fear memory acquisition prevents the formation of the remote context memory, and also disrupts subsequent remodeling of dendritic spine growth in the mPFC [75,155]. Early inactivation of the mPFC does not impact memory retrieval (but see 142), but if the reorganized remote memory network is allowed to develop, later inactivation of the mPFC impairs subsequent memory retrieval [73,84,156]. It is surprising that in the presence of a functional hippocampus, the hippocampal memory trace would not come online to support retrieval, but, as has been discussed, activation of that memory trace may largely depend on the cues present at the time of retrieval. It seems that, in the absence of sufficiently salient environmental cues, or direct stimulation of these traces, the default remote memory retrieval route operates via the mPFC. If the

[4] In these early papers, Moscovitch & Winocur formulated a conceptual (*working-with-memory)* model that focussed on the dynamic interaction between the hippocampus and the prefrontal cortex. The present model extends this view by characterizing the two structures as working closely together in the formation and long-term representation of new memories, and in their later retrieval.

[5] KC had extensive hippocampal damage that extended to extra-hippocampal structures.

mPFC is unavailable, retrieval performance suffers (but see 74).

Many questions remain about the interactions among the different constituents supporting episodic memory. In the studies we reviewed, there are variations on the extent to which the aHPC and pHPC are implicated in memory transformation, but, as indicated above, we do not yet have a good idea of what accounts for the variation. Our proposal is related to granularity of representation along the long axis, but other hypotheses are emerging, among them that the pHPC is dedicated more to representing space, by virtue of its connectition to parahippocampal cortex, and the aHPC, to representing items and concepts, by virtue of its connections to peri-rhinal cortex [184,185]. Another is that the aHPC is implicated in scene or event construction [157–161]. A third proposal, that shares characteristics with both of these as well as with TTT, is that the extent to which the pHPC and aHPC are recruited, depends, respectively, on the integration of perceptual and spatial details on the one hand, and the open-endedness and conceptual aspects of the task, on the other [121]. Testing these and other hypotheses against one another will advance our knowledge and refine our models.

As we noted, recent studies suggest that the entorhinal cortex may be especially important in relaying information between the hippocampus, particularly its anterior region, and the mPFC, and vice versa. Exactly what the nature of this information is, and how it is used to guide the formation of schemas, is not known. Nor is it known whether the same pathways serve as a conduit of schematic information from mPFC to hippocampus to guide encoding and retrieval. As with regard to aHPC and pHPC, there are at least two pathways in entorhinal cortex, the medial carrying spatial information and the lateral carrying object information, that may influence both transformation, and encoding and retrieval processes [163,164].

The nucleus reuniens of the thalamus is another structure that will need to be integrated into developing models of systems consolidation and transformation [154]. Its role seems to be the moment to moment synchronization or coordination of activity between mPFC and hippocampus, enabling activation of the type of memory needed to meet task demands [162,165].

Such moment to moment variations in coupling between the different regions of the hippocampus and its related structures suggest that they form Process Specific Alliances (PSA) [166]. PSAs are small networks that are assembled quickly to perform a particular cognitive operation, and rapidly disassemble once the operation is complete, leaving the constituents free to enter into other alliances as needed [22,166]. Thus, during early stages of memory retrieval, mPFC and anterior hippocampus form one PSA, which is disassembled during memory elaboration to form a PSA between anterior and posterior hippocampus, and pHPC with posterior neocortex. Given the rapidity of the process, timely communication among distant regions is essential for good performance. Neural oscillations among structures can serve this purpose [116,166,167], making research into their operation crucial for revealing the neural underpinnings of episodic memory and its transformation.

As we noted earlier in the paper, no clear relation has been found between the size of hippocampal lesions and the extent and severity of retrograde amnesia. The effects of lesion size played a prominent role in the development of MTT, though not in its subsequent iterations or in the development of TTT. Given the knowledge we've gained about the anatomical and functional organization of the hippocampus, the effects of the size of hippocampal lesions cannot be addressed without taking into account the recent developments on specialization along the long axis of the hippocampus, and on the role of dentate gyrus, subiculum and hippocampal subfields in memory formation, retention and retrieval. These developments suggest that the regions or subfields that are affected may be more of a determining factor than the size of lesion. Considering the interconnection of each of these areas with one another, it is possible that even a small lesion in a crucial location, such as CA1 subfields [56,168], may lead to severe and extended retrograde amnesia, whereas a comparable or even larger lesion in another region may spare it. Similar considerations may operate at encoding, and during post-encoding processes. Drawing on some of this emerging evidence [186], and incorporating it into a new version of TTT, may provide some insight into the mechanisms and processes implicated in formation, retention, and especially transformation of episodic/context specific memories.

We also know very little about what determines the time it takes for transformed memories to become independent of the hippocampus and rely only on other structures. In part, the time course may be determined by the paradigms and tests that are used to measure it, and the type of transformation the memory undergoes. If reduction of hippocampal activation in fMRI studies is used as an index, the time course for memory transformation can be very rapid, and evident within hours or days. If memory preservation after hippocampal damage is the index that is used, then hippocampal independence of transformed memories may not be achieved for years [8,9,15–18,22,25]. Investigations of memory transformation at the molecular and cellular level should also contribute to our understanding of these variations in time course, as they may set boundary conditions for the time course of transformation processes.

A related question is whether all declarative or explicit memories are initially episodic, and dependent on the hippocampus, and that it is only through a process of transformation that they become semantic or schematic (e.g. [13,14])? Recent studies have shown that this not true in all cases. Through a process of "fast mapping" [171] mediated by perirhinal cortex, semantic memories can be formed rapidly and independently of episodic memory and the hippocampus[172–174]. Such memories can be retained for a long time though under some conditions they are more prone to interference than comparable memories formed via the hippocampus [175], as predicted by McClelland et al. [13].

Our notions of details, gist and schema, are not as developed or as well-differentiated as we would like. As is evident from our review, the term schemas is applied to many different representations from the central structure of events and narratives [29,97,123], to common, repeated elements among isolated or associated stimuli [36,125–129], to regularities or central tendencies abstracted from events [176,177] and to overlearned associations that provide a structure for encoding, retention and retrieval of related memories [135,136,141]. Some progress has been made in defining schemas and distinguishing among its different manifestations [154] but our impression is that we have yet to reach a consensus. If that is true of schemas, which has a long history in memory research, it certainly is true of gist which is a relatively new concept as applied to memory [187,188]. For the moment, some rule-of-thumb approaches seem to suffice, and the concept will gain in precision with research.

Related to this problem is the possibility that transformation itself may take different forms that rely on different structures. We do not as yet know whether the mechanisms underlying transformations that result from forgetting [169,170] are similar to those that result from distortion, regularization (extraction of statistical regularities), and assimilation of memories to pre-existing schemas [9,10,22,24].

Although we have made important advances, there is still much to be learned about the neural basis of memory transformation. The focus of our review has been on the hippocampus and mPFC, yet it is well known that episodic/context-specific memory depends on the interaction of a variety of regions [59,60,104,178,179], only a handful of which were mentioned in this paper. It is likely, therefore, that these other regions also have a hand in memory transformation, but their contribution has hardly been explored. In addition, the large majority of studies have examined relatively static events, whereas episodes unfold in time. We know little about the transformation of temporal and sequential information with time and experience [180–182]. These gaps in our knowledge are even wider when considering transformation of non-episodic memories. We anticipate that the gaps will narrow in the future and hope that TTT, and future transformations of it, can continue to stimulate the research needed to narrow the gaps.

Contributions of the authors

All the authors contributed equally to researching the literature and writing the manuscript.

Conflict of interest

The authors report no conflicts of interest.

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