The Hippocampus and Memory Integration: Building Knowledge to Navigate Future Decisions

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Abstract Everyday behaviors require a high degree of flexibility, in which prior knowledge is applied to inform behavior in new situations. Such flexibility is thought to be supported in part by memory integration, a process whereby related memories become interconnected in the brain through recruitment of overlapping neuronal populations. Mechanistically, integration is thought to occur through specialized hippocampal encoding processes that integrate related events during learning. By recalling past events during new experiences, connections can be created between newly formed and existing memories. The resulting integrated memory traces would extend beyond direct experience in anticipation of future judgments that require consideration of multiple learned events. Recent advances in cognitive and behavioral neuroscience have provided empirical evidence for the existence of such a mechanism, with hippocampal encoding mechanisms—in coordination with medial prefrontal cortex—supporting memory integration. Emerging research suggests that abstracted representations in medial prefrontal cortex guide reactivation of related memories during new encoding events, thus promoting hippocampal integration of related experiences. Moreover, recent work indicates that integrated memories can impact a host of behaviors, from promoting spatial navigation and imagination to resulting in memory distortion and deletion.

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Introduction

Decades' worth of research documents the involvement of the hippocampus in rapidly encoding new episodes, which are then transferred (i.e., *consolidated*) to neocortex over time. However, memory is a dynamic phenomenon. The once widely accepted view that such consolidated memories are immune to modification has long since been refuted. Consolidated memories may be reactivated during new experiences, at which point they are susceptible to distortion, deletion, or updating (Nadel and Hardt 2011; McKenzie and Eichenbaum 2011; Nadel et al. 2012). Conversely, reactivated memories may also influence how new content is encoded (Zeithamova et al. 2012a; Gershman et al. 2013). Here, we review the recent work in cognitive and behavioral neuroscience that investigates the complex ways in which memories influence one another and change over time. One way by which such mutual influence may occur is through *memory integration*.

Memory integration refers to the idea that memories for related experiences are stored as overlapping representations in the brain, forming memory networks that span events and support the flexible extraction of novel information. For example, imagine you see a woman walking her dog in the park near your house (Fig. 1).

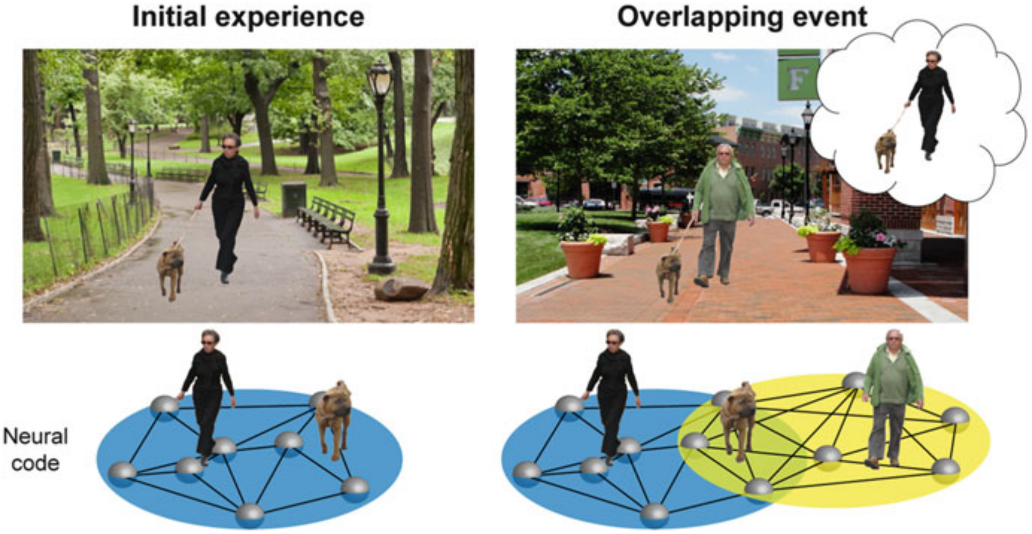


Fig. 1 Schematic depiction of related events that might lead to memory integration and their associated neural codes. One day while walking in the park, you encounter a woman and her dog (initial experience, *left*). Connections are formed among a group of simultaneously activated neurons, coding the woman–dog association (*blue network*). A few days later, you encounter the same dog in town, this time with a man (overlapping event, *right*). The dog (overlapping element) triggers reactivation of your initial experience in the park (woman–dog association). Such reactivation enables connections to be formed among neural representations of the woman, dog, and man, linking the related events across time (overlapping *blue* and *yellow networks*). The resulting integrated memories are hypothesized to support novel judgments that require consideration of both events; here, for instance, you may infer a relationship between the woman and the man despite never having seen them together. Figure adapted with permission from Schlichting and Preston (2015)

During this experience, you form a memory for the event that represents the relationship among the woman, the dog, and the park. The next day, you see the same dog out for a walk in town with a man. The familiar element (the dog) during this second experience may serve as a cue for hippocampal pattern completion, triggering the reactivation of your prior experience with the woman and dog. The new event (the man walking the dog in town) is then encoded in the presence of the reactivated information about your first experience with the dog. In this way, a link between the woman, the man, and the dog can be formed during encoding, despite the fact that you have never seen the woman with the man.

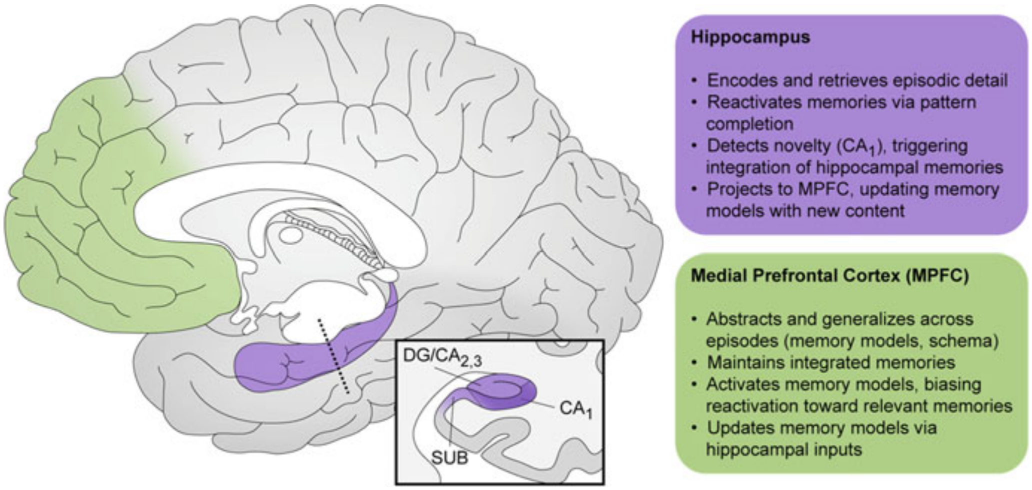
The notion that new encoding and prior knowledge interact with one another is by no means new (Bartlett 1932; Tolman 1948; Cohen and Eichenbaum 1993); yet, the neural mechanisms and behavioral implications of memory integration have only recently become the subject of empirical investigation. The field's growing interest in understanding these complex, real-world aspects of episodic memory has been realized thanks to the advent of elegant behavioral paradigms and advanced analysis methods for neural data. We first review evidence for the neural mechanisms that underlie memory integration. We then turn to a discussion of the range of behaviors that might be supported by integration, from flexible navigation to imagination and creativity. Finally, we set forth questions and considerations for future research.

Neural Mechanisms

Memory integration has been studied in both rodents and humans using highly controlled experimental paradigms in which subjects make decisions that span multiple learned experiences. In one example task, the associative inference paradigm (Preston et al. 2004), participants encode a series of overlapping events: AB followed later by BC, where 'AB' denotes a studied arbitrary association between items A and B. Participants are later tested on their memory for directly experienced information (AB, BC) as well as on their ability to make novel inferences (AC) that require consideration of two events. In this task, performance on the AC inference test serves as the critical behavioral index of memory integration. By recalling past (AB) events during new (BC) experiences, knowledge structures are formed that integrate the newly learned information into prior memories (Fig. 1). The resulting integrated memories would allow for direct extraction of novel inferences that cross event boundaries, thereby promoting performance on the AC test. In addition to a behavioral index of integration, such experimental designs allow researchers to index the neural processes specific to encoding of the second (BC) overlapping event, during which there is a unique opportunity to integrate across related memories. A number of similar paradigms have been used in the literature (Eichenbaum et al. 1996; Shohamy and Wagner 2008), all of which require participants to make novel decisions spanning learned pieces of information. For simplicity, in this section we refer to behaviors thought to index memory integration as *integration behaviors*; see section “Implications for Behavior” for a detailed discussion of the diverse set of behaviors potentially impacted by memory integration. In section “Mechanism Overview”, we provide an overview of the neural mechanisms underlying memory integration. We then describe examples of empirical evidence for these processes in sections “Evidence for a Hippocampal Role in Integration” and “Hippocampal-Medial Prefrontal Interactions”.

Mechanism Overview

Human and animal lesion work highlights the critical role of the hippocampus and an interconnected structure, the medial prefrontal cortex (Iordanova et al. 2007; DeVito et al. 2010b; Koscik and Tranel 2012; Ghosh et al. 2014; Warren et al. 2014), in memory integration (Fig. 2). Damage to either of these structures impairs the ability to combine information acquired during different episodes despite intact memory for the previously learned individual events (Bunsey and Eichenbaum 1996; DeVito et al. 2010b; Koscik and Tranel 2012). Work in rodents also demonstrates dynamic interactions between these structures during memory updating, perhaps reflecting the flow of information from hippocampus to MPFC (Tse et al.



Hippocampus

- Encodes and retrieves episodic detail
- Reactivates memories via pattern completion
- Detects novelty (CA_1), triggering integration of hippocampal memories
- Projects to MPFC, updating memory models with new content

Medial Prefrontal Cortex (MPFC)

- Abstracts and generalizes across episodes (memory models, schema)
- Maintains integrated memories
- Activates memory models, biasing reactivation toward relevant memories
- Updates memory models via hippocampal inputs

Fig. 2 Proposed roles of human hippocampus and MPFC in memory integration. Locations and hypothesized functions of regions critical for memory integration in the human brain. *Purple*, hippocampus; *green*, medial prefrontal cortex. Here, we intentionally provide a broad definition of MPFC due to high variability in the precise location of effects reported across studies. For instance, we include anterior cingulate cortex, which has been implicated in memory integration (Wang et al. 2012) and the formation of memory models (Roy et al. 2012). Inset, cross section through the hippocampus (*purple*) highlighting area CA_1 (*dark purple portion*). Approximate hippocampal subfield boundaries are indicated with thin *dashed lines*. Location of cross section along hippocampal axis is indicated with a thick *dashed line*. *MPFC* medial prefrontal cortex, *CA_1* Cornu ammonis field 1, *DG/$CA_{2,3}$* dentate gyrus and Cornu ammonis fields 2 and 3, *SUB* subiculum. Figure adapted with permission from Schlichting and Preston (2015)

2011). However, while these data underscore the importance of hippocampus and MPFC in memory integration, the precise mechanisms by which these regions contribute have only recently started to become clear.

One period during which memory integration may take place is when new learning experiences share content (e.g., a person, place, or thing) with existing memory traces (Fig. 1). Through this process, termed *integrative encoding*, memories are formed that integrate information across distinct experiences (Nadel and Hardt 2011; McKenzie and Eichenbaum 2011; Nadel et al. 2012) in anticipation of future use. This constructive, or prospective, nature of memory (Klein et al. 2002b; Buckner 2010; Addis and Schacter 2012) dates back to Tolman's concept of a "cognitive map" (Tolman 1948) and is reflected in modern memory theories including relational memory theory (Eichenbaum et al. 1999), multiple trace theory (Nadel and Moscovitch 1997), and schema theory (Bartlett 1932; van Kesteren et al. 2012). Memory integration has been proposed as a key mechanism underlying a host of flexible behaviors, including inferring novel relationships (O'Reilly and Rudy 2001; Shohamy and Wagner 2008; Zeithamova and Preston 2010; Zeithamova et al. 2012a), determining new routes through the environment (Gupta et al. 2010), and making adaptive decisions (Wimmer and Shohamy 2012). These ideas are also highly related to the influential temporal context model (Kahana 1996; Howard et al. 2005), in which items are bound to the learning context in which they occur. In this case, learning context may include related content that has been reactivated.

When new event relates to prior experience, pattern completion mechanisms supported by the hippocampus reactivate the previously stored, overlapping memory (Zeithamova et al. 2012b; Preston and Eichenbaum 2013). Empirical support for reactivation of prior memories during overlapping learning experiences has recently been garnered using neural decoding of fMRI data (Fig. 3) (Kuhl et al. 2012; Zeithamova et al. 2012a; Gershman et al. 2013). With the related content reinstated in the brain, hippocampal area CA_1 (Fig. 2) is thought to compare prior memories with incoming information from the environment (Hasselmo and Schnell 1994). CA_1 may signal the presence of associative novelty (i.e., when new experiences violate memory-based predictions) and facilitate new encoding (Hasselmo et al. 1996; Larkin et al. 2014). Models of hippocampal subfield function have suggested that CA_1 novelty signals may influence neural dynamics via feedback connections to the medial septum, modulating acetylcholine levels and setting appropriate dynamics for learning (i.e., encoding rather than retrieval; Hasselmo and Schnell 1994; Hasselmo et al. 1996). The resulting integrated memories are highly structured, with shared elements coded similarly across experiences (McKenzie et al. 2013, 2014). One recent study (McKenzie et al. 2014) has shown that hippocampal CA field firing patterns for overlapping events reflect a hierarchy of features coded according to their behavioral relevance. This organization scheme could then be exploited to extract commonalities across episodes and support a host of behaviors, as discussed below.

Hippocampal mechanisms may be additionally influenced by operations in MPFC. While its specific role in memory is only starting to be uncovered, at least

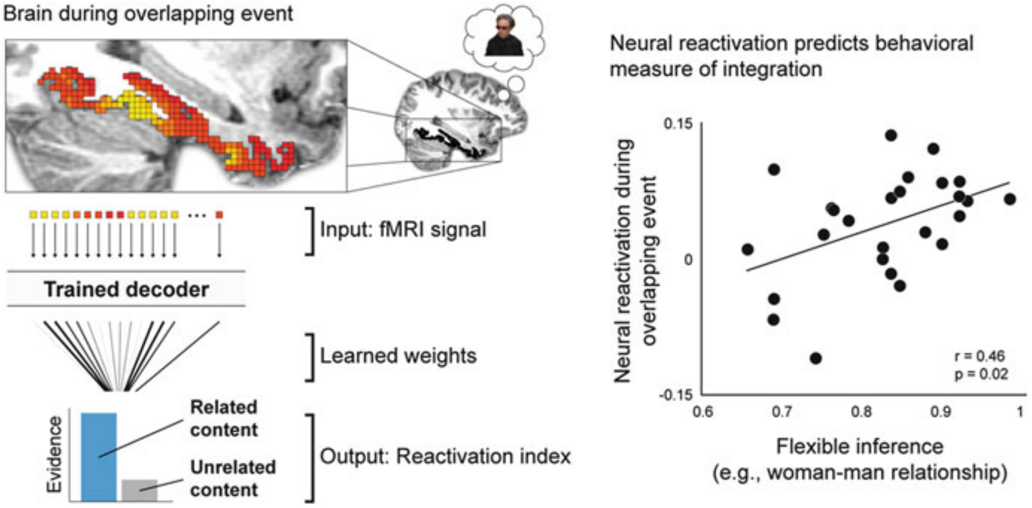


Fig. 3 Example use of neural decoding to quantify memory reactivation. *Left panel*, depiction of a neural decoding approach quantifying the degree of memory reactivation during learning. The neural pattern evoked during the overlapping event (man-dog from Fig. 1) is hypothesized to reflect reinstatement of the related—but not presently viewed—element (the woman). The fMRI signal is extracted for each voxel in a region of interest (here, ventral temporal cortex is used as an example). This information is then input into a neural decoder trained to recognize activation patterns associated with different kinds of stimuli (e.g., faces). Based on the weights for each voxel learned during training, the decoder outputs a value reflecting the degree to which the neural pattern reflects reactivation of the related versus unrelated content. These evidence scores can then be used as an index of reactivation. *Right panel*, reactivation during encoding of overlapping events predicts later flexible inference (woman-man association), a behavioral index of memory integration. Data are adapted with permission from Zeithamova et al. (2012a). Figure adapted with permission from Schlichting and Preston (2015)

two functions have been proposed for MPFC that are of relevance to the present discussion. First, MPFC is thought to represent mental models that guide behavior across a number of domains (Roy et al. 2012; Wilson et al. 2014). With regards to memory, some suggest that MPFC encodes interconnected information to form mental models based on mnemonic content (i.e., memory models) (Schacter et al. 2012; St. Jacques et al. 2013), which may include features such as behavioral relevance and appropriate response associated with a particular context (Miller and Cohen 2001; Euston et al. 2012; Kroes and Fernández 2012). This functionality may explain the involvement of MPFC in reinforcement learning, which has been hypothesized to reflect its coding of action-outcome associations. Anatomical features of MPFC may make it especially well suited to form such complex representations of goals or task rules, as it receives a broad range of input from sensory and limbic regions (Price and Drevets 2009).

A second possible function of MPFC is in biasing learning-phase retrieval toward the most behaviorally relevant memories, thereby influencing what will be integrated (van Kesteren et al. 2012; Kroes and Fernández 2012; Preston and Eichenbaum 2013). This may be conceptualized as the deployment of memory models to resolve conflict among related experiences. Memory models are thought to be activated when incoming information relates to existing knowledge. MPFC may then select specific task-relevant memories for reactivation (van Kesteren et al. 2012; Kroes and Fernández 2012; Wilson et al. 2014), perhaps via white matter projections to the medial temporal lobe (MTL) cortical structures that provide the major input to hippocampus (Cavada et al. 2000). Hippocampus may then bind reactivated content to current experience, resulting in an integrated trace. Following integration in hippocampus, memory models may be updated with new content as needed through direct hippocampal inputs to MPFC (van Kesteren et al. 2012). Through this process, MPFC may come to represent integrated memories that have been abstracted away from individual episodes (i.e., schema) over time (van Kesteren et al. 2012; Richards et al. 2014).

Of course, the possibilities we describe here are neither exhaustive nor mutually exclusive. Future research will be needed to fully understand the role of MPFC in memory integration, and assess whether its functionality might differ across subregions.

Evidence for a Hippocampal Role in Integration

Electrophysiological studies in rodents have shown hippocampal-mediated replay of prior event sequences in new spatial contexts (Karlsson and Frank 2009) and never-experienced spatial trajectories that represent a shortcut through a well-learned environment (Gupta et al. 2010; although note that novel routes represented a very small proportion of all replay events), consistent with the idea that memories extend beyond direct experience. Furthermore, in environments with overlapping elements, individual hippocampal neurons demonstrate experience-dependent generalized firing patterns that respond in multiple similar locations (Singer et al. 2010; McKenzie et al. 2013) or to the overlapping features themselves (Wood et al. 1999). Such generalized firing patterns suggest that hippocampal neurons develop representations that code the similarities between events. By representing features common to multiple events similarly, hippocampal codes can capture regularities shared across different experiences and, in doing so, may act as “nodes” that link distinct behavioral episodes (Fig. 1) (Eichenbaum et al. 1999).

Behavioral work in humans suggests that reactivating related memories immediately prior to a new learning experience increases the likelihood that new content will be integrated into existing memories (Hupbach et al. 2007). Using neuroimaging, researchers have also related the degree of reactivation of prior experience during encoding of new overlapping events to evidence for integration (Kuhl et al. 2010; Zeithamova et al. 2012a). In one study, the evidence for hippocampus-mediated reactivation of prior memories was associated with greater retention of the reactivated information (Kuhl et al. 2010), demonstrating that reactivating memories during new learning helps reduce forgetting of past events. In an associative inference paradigm, another study demonstrated that reactivation of existing knowledge during new learning of overlapping associations predicted superior integration behavior, suggesting that combining related memories during learning might underlie successful inferential reasoning (Fig. 3; Zeithamova et al. 2012a; see also Richter et al. 2015).

With relevant prior experience reactivated in the brain, hippocampus is then thought to bind or integrate current and prior experience (Shohamy and Wagner 2008; Zeithamova and Preston 2010; Zeithamova et al. 2012a). In one study (Shohamy and Wagner 2008), increases in hippocampal activation across the learning phase were associated with individual differences in integration behavior, even when accounting for performance differences on trained associations (Fig. 4a). Changes in hippocampal activation over learning in the associative inference task were also related to integration behavior across participants, even when accounting for differences in memory for single events (Zeithamova et al. 2012a). Moreover, interrogation of trial-by-trial neural engagement revealed that hippocampal activation during encoding of overlapping associations (BC), but not initially acquired associations (AB), differentiated between subsequently correct and incorrect inference judgments (AC; Fig. 4b-i) (Zeithamova et al. 2012a). Collectively, these findings highlight the importance of a hippocampal encoding mechanism whereby overlapping experiences are integrated into a network of related memories as they are learned.

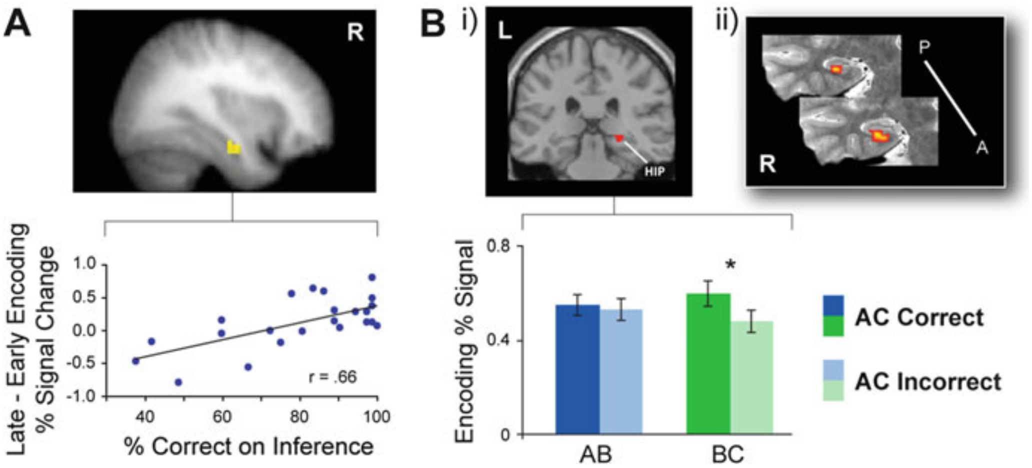


Fig. 4 Learning-phase integration signatures in hippocampus. (**a**) Activation in both left (not shown) and right hippocampus during encoding of overlapping associations was correlated with individual differences in inference performance. Specifically, increases in hippocampal activation from the early to late portion of the training phase were associated with superior performance on inferential probe trials. (**b**-i) In an associative inference task, right hippocampal activation during encoding of overlapping associations (BC) was greater for trials in which the corresponding inference judgment (AC) was later correct relative to trials on which the inference judgment was later incorrect. Hippocampal activation during initially acquired associations (AB) was not related to subsequent inferential performance. (ii) Using high-resolution fMRI, this signature was isolated to the CA_1 subfield of the hippocampus. Data are adapted with permission from: Shohamy and Wagner (2008) (panel **a**), Zeithamova and Preston (2010) (panel **b**-i), and Schlichting et al. (2014) (panel **b**-ii)

Integration is thought to be triggered by hippocampal comparator processes, with hippocampal area CA_1 signaling deviations between current events and reactivated content (i.e., associative novelty signaling; Lisman and Grace 2005). Empirical work in humans has supported the notion that area CA_1 signals deviations from prior experience, with engagement of this region increasing as the number of changes to a studied stimulus increase (i.e., with an increasing degree of mismatch; Duncan et al. 2012a). Activation in human CA_1 during the encoding of events that overlap with prior experiences has been shown to relate to a behavioral measure of memory integration (Fig. 4b-ii; Schlichting et al. 2014), consistent with the notion that novelty signals triggers the formation of links between new content and prior memories.

Hippocampal-Medial Prefrontal Interactions

Recent evidence suggests that hippocampus interacts with MPFC to support memory integration in many circumstances (Fig. 2). One possible explanation for this region's involvement in encoding-phase memory updating lies in its pattern of anatomical connectivity: MPFC is directly connected to the hippocampus, receiving inputs primarily from the anterior portion of CA_1 (Barbas and Blatt 1995; Cavada et al. 2000). MPFC also has extensive connections with a diverse set of sensory, limbic, and subcortical structures (Cavada et al. 2000), suggesting that it might be important for combining across episodic memories, represented in the brain across distributed cortical and subcortical networks. Consistent with this idea, recent studies have observed encoding-phase engagement (Zeithamova et al. 2012a) and evidence for reactivation of prior memories in MPFC (Richter et al. 2015), demonstrating the importance of this region for memory integration during encoding. Moreover, enhanced functional coupling of hippocampus and MPFC has been shown when new learning can be integrated into prior knowledge (Schlichting and Preston 2016), consistent with the notion that MPFC interacts with hippocampus to promote integration. Integration behavior has also been linked to individual differences in the intrinsic functional connectivity (Gerraty et al. 2014) and structural connectivity (Schlichting and Preston 2016) of hippocampus and MPFC, highlighting that even static neural characteristics might render some individuals better suited for combining across related events.

Learning Factors Promoting Integration

A number of studies have investigated the learning factors that influence integration. For instance, while there is evidence that integration can occur in the absence of conscious awareness (Shohamy and Wagner 2008; Wimmer and Shohamy 2012; Henke et al. 2013; Munnelly and Dymond 2014), studies have shown that integration may be facilitated when subjects become aware of the task structure (either via instructional manipulations or spontaneously) (Kumaran and Melo 2013; Richter et al. 2015). In fact, one experiment (Kumaran and Melo 2013) demonstrated that such knowledge specifically benefitted judgments that spanned episodes with no effect on memory for the individual episodes themselves, suggesting that integration does not necessarily emerge with learning of the underlying experiences. One possibility is that awareness constrains MPFC control processes, which in turn biases hippocampal reactivation during learning toward task-relevant memories, allowing for integration across events.

It has been hypothesized that being reminded of related memories prior to a new learning experience also increases the likelihood of integration, as the reactivated memories become labile and readily updated. Consistent with this idea, behavioral work in humans (Hupbach et al. 2007) found more intrusions from a second learned list (List 2) when recalling the initial list (List 1) if participants had been reminded of List 1 before encoding List 2. This finding was recently replicated in rodents using "lists" of ordered feeder locations (Jones et al. 2012), with animals who learned two lists in the same relative to different spatial contexts producing more intrusions. Another study manipulated the degree of retrieval on a trial-by-trial basis within participants (Duncan et al. 2012b). That study similarly found superior integration performance for learning experiences that followed an old item (i.e., when retrieval was possible) versus those that followed a new item (when retrieval was not possible). These findings are consistent with the proposal that integration occurs via reactivation of prior memories; this work further highlights that reminding the learner of the prior related memory may encourage integration.

The strength of existing memories may be an additional factor mediating integration. In particular, stronger memories might be more readily reactivated during learning, thereby allowing for integration across memories. One neuroimaging study showed that offline processing of initial memories was associated with more evidence for reactivation and superior integration behavior during a subsequent learning experience, suggesting that memory strengthening during rest facilitates integration (Schlichting and Preston 2014). Integration signatures have also been preferentially observed when initial memories are well-learned at the time of the first overlapping event, as is the case in blocked learning (i.e., multiple AB learning opportunities occurring before any BC learning; Schlichting et al. 2015). These results suggest that strong prior memories may promote reactivation during learning, thereby allowing for integration across memories. This work underscores that integration may be especially likely when initial memories are well established prior to new learning.

Other factors hypothesized to impact integration include (1) the nature of the underlying memory representations, with more distributed as opposed to localized representations proposed to promote integration (Schiller and Phelps 2011); and (2) the degree of competition between new content and prior memories (i.e., whether or not the two memories can coexist), with integration preferentially occurring in cases when competition is minimal (Hupbach 2011).

Offline Processes Promoting Integration

Numerous empirical studies (Tambini et al. 2010; Jadhav et al. 2012; Deuker et al. 2013; Staresina et al. 2013) and theoretical accounts (Marr 1970; McClelland et al. 1995) highlight the importance of offline processes—such as reinstatement of recent experience and enhanced interregional communication—for episodic memory. It has been proposed that through hippocampal-neocortical interactions (McClelland et al. 1995; Nadel et al. 2000), memories are reactivated during periods of sleep and awake rest. Such reactivation (or *replay*) is thought to support the strengthening and transfer of memory traces from the hippocampus to neocortical regions for long-term storage (i.e., consolidation).

These mechanisms may also support the integration of memories across experiences (Kumaran and McClelland 2012). Recent theories suggest that hippocampus-mediated replay of event sequences during sleep (Hoffman and McNaughton 2002; Ji and Wilson 2007) provides a potential mechanism for constructing networks of related memories that anticipate future decisions and actions (Sara 2010; Diekelmann and Born 2010; Lewis and Durrant 2011)—a process referred to as *prospective consolidation* (Buckner 2010). Such theories propose that by reactivating memories during sleep, representations are recombined and recoded, resulting in rich networks of related memories that extend beyond initially encoded events (Kumaran and McClelland 2012). This process is thought to promote both the integration of new information into existing memories and abstraction across episodes in neocortical regions, particularly MPFC (Lewis and Durrant 2011). According to this view, stored memories are not veridical representations of events, but rather derived representations formed in anticipation of future use. Sleep-based replay of hippocampal memory traces, therefore, could enhance integration behaviors that tap knowledge about the relationships among events experienced at different times (Ellenbogen et al. 2007; Werchan and Gómez 2013; Coutanche et al. 2013). Consistent with this notion, one study (Ellenbogen et al. 2007) demonstrated that participants who slept following learning showed better integration behavior relative to a comparison group who remained awake.

In addition to sleep-based mechanisms that might promote integration, offline processes occurring during periods of awake rest have also been suggested to be important for memory. The mnemonic consequences of reactivation of recent experience has been demonstrated during awake rest using neurophysiological techniques in rodents (Jadhav et al. 2012) and, more recently, in humans using pattern information analysis of fMRI data (Deuker et al. 2013; Staresina et al. 2013). For instance, more delay period reactivation was observed for stimuli that were remembered relative to those that were forgotten in a subsequent test (Staresina et al. 2013). Moreover, studies have shown that the degree of hippocampal-neocortical functional coupling during rest periods following learning relates to later memory for the learned content (Tambini et al. 2010).

Recent evidence suggests that similar rest-phase mechanisms may promote the integration of memories that span related events (van Kesteren et al. 2010; Craig et al. 2015; Schlichting and Preston 2016), with integration-related neural signatures persisting into offline periods following encoding. For example, one study showed increased hippocampal-MPFC functional coupling during encoding conditions that necessitate schema reorganization and updating; interestingly, this pattern persisted during the post-encoding rest period (van Kesteren et al. 2010). These findings are consistent with the idea that neural patterns evoked during encoding are reactivated during offline rest periods, potentially reflecting early-phase consolidation mechanisms. Similar neural signatures have been reported following memory updating in an associative inference task, with the degree of hippocampal-MPFC connectivity enhancements during awake rest following an integration opportunity predicting individual differences in behavior (Schlichting and Preston 2016). While the precise effect of these rest-phase processes for memory integration is yet to be determined, it may be the case that memory reactivation and increased interregional coupling may strengthen connections among related memories, thereby further promoting the formation of integrated memory representations.

Neural Representations

Initial research suggests that one way in which the hippocampus supports behavioral flexibility is by integrating information across multiple experiences to establish links between related events, either during new learning or offline through replay of related experiences during sleep and rest. However, questions remain regarding the precise nature of the underlying hippocampal representations. Several theoretical and computational frameworks have proposed alternate accounts of the properties of memory representations that can support inference, which we describe here.

One hypothesized representational structure supporting integration is one in which new events are incorporated into existing memory traces to be parsimoniously represented in a single, composite memory representation (Fig. 5a). For instance, consider the simple example of two events that share a common element (AB, BC) as in the associative inference paradigm. When a new event occurs that contains an element overlapping with a previous event (e.g., BC after encoding AB), the overlapping element (B) can trigger pattern completion of the previously encoded memory (AB). According to this hypothesized representational structure, elements from the new, overlapping event (in this case, C) would be encoded into the existing, reactivated memory (AB) to form a single integrated representation that combines the two experiences (ABC). Because these integrated representations directly code the novel relationship between A and C along with the original experiences, this representational format provides a basis for the inferential use of memory, but has a notable cost in that details of the individual experiences may not be preserved (e.g., the knowledge that A and C were presented in two different temporal contexts).

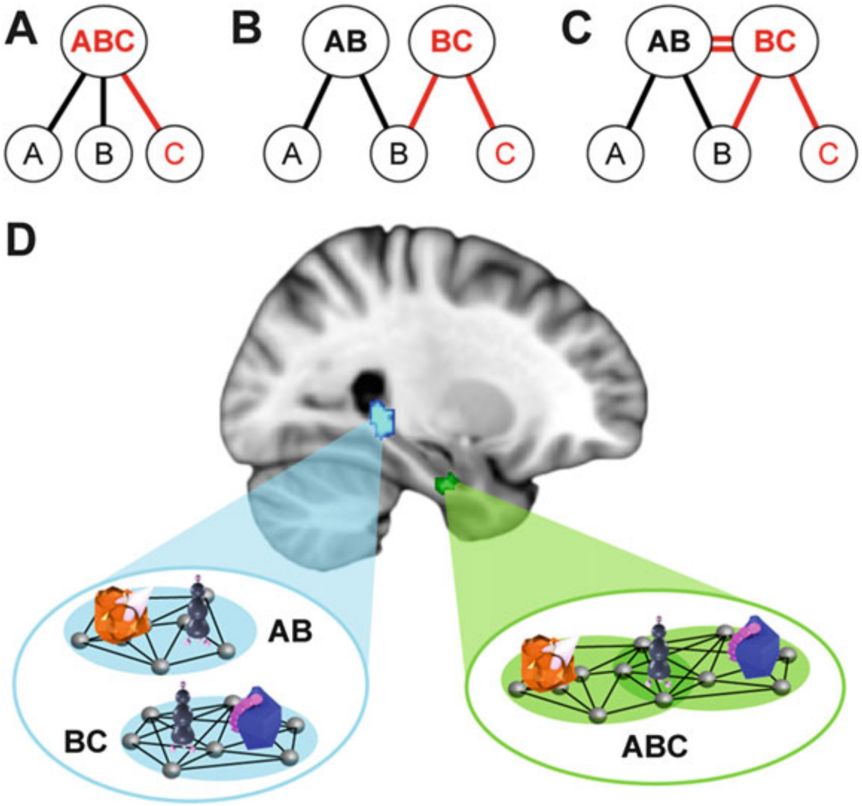


Fig. 5 Schematic depiction of alternative accounts of hippocampal representation in memory integration. Representations of overlapping events (here AB, BC in the associative inference paradigm) are shown using a simplified two-layer architecture. The *bottom* layer contains units for each event element; the *top* layer contains hypothesized patterns of hippocampal representation. (**a**) Single integrated representation for overlapping events. According to this hypothesized structure, new, overlapping event elements (C) are encoded into an existing, reactivated memory (AB) to form a single composite representation for the two related associations. (**b**) Pattern separated representations of individual events. In this view, a new event (BC) with partial overlap to a previous memory (AB) would recruit a distinct hippocampal representation that preserves the details of each individual experience. Links between the common element (B) and each of the individual experiences could be used to mediate inference at encoding or retrieval. (**c**) Relational representation of overlapping events. In this framework, separate representations are maintained for overlapping events (AB, BC) and direct links between those events (at the level of the hippocampus) code their relationship to one another. (**d**) Evidence for dissociable coding schemes for indirectly related (A, C) items in an associative inference task across the anterior-posterior axis of hippocampus. While posterior hippocampus showed that A and C items became more dissimilar following overlapping encoding (*blue cluster*), anterior hippocampus coded A and C items more similarly, particularly when memories were strong (*green cluster*). These findings suggest simultaneous separated and integrated representation of overlapping memories in posterior and anterior hippocampus, respectively. Panels (**a–c**) are as originally published in Zeithamova D, Schlichting ML, Preston AR (2012) The hippocampus and inferential reasoning: building memories to navigate future decisions. *Frontiers in Human Neuroscience* 6:70. doi:10.3389/fnhum.2012.00070. Panel (**d**) is adapted from Schlichting et al. (2015)

The influential cognitive map theory (Tolman 1948; O'Keefe and Nadel 1978)—which first sparked interest in the flexible functions of the hippocampus—implicitly assumes such integrated representations. In the context of this theoretical framework, memory traces for newly learned individual events (i.e., recently traveled routes) are combined with memories of previously traveled routes to allow for the creation of an integrated map of the environment, including information about paths not traveled. As a cognitive map of an environment becomes established, it can be reactivated when an animal enters the same environment at a later point and updated with new experiences in that environment. When familiar routes to a goal are blocked, the cognitive map will enable navigation to the goal via an alternate route because information about this novel (i.e., never before traveled) route is included in a single representational structure of the environment.

In the context of non-spatial integration tasks, there is some evidence to support this hypothesized ABC representational structure. For example, one study showed that successful participants perform as quickly on integration judgments as on explicitly trained associations (Shohamy and Wagner 2008), suggesting similar representations for both directly learned and inferential associations. Moreover, informal assessment suggested that the majority of participants in this study failed to recognize the inferential probes as novel combinations of items, perhaps indicating that some contextual details of original experiences were lost. Returning to the dog-walking example, you may remember that the woman and man are a couple with a dog, but may not remember specific details about how you first encountered them. Future studies may provide a more detailed account of the circumstances under which memory for original experience may become degraded.

The loss of experiential detail is a significant downside to the single, composite representational structure linking elements of discrete events. Other computational perspectives propose a different representational structure for hippocampus, with pattern separation processes preserving distinct individual experiences and recurrent connections between the element and event representations allowing inference across experiences (Fig. 5b; Kumaran and McClelland 2012; McClelland et al. 1995). In our example, this representational structure would predict that a new event partially overlapping with a previous event (i.e., BC) would recruit a different hippocampal representation to make it distinct from the originally experienced event (AB). The two events would be linked through their individual connections to the shared event element (B). Because of the recurrent connections between individual element and event representations (ascribed to entorhinal cortex and hippocampus, respectively), such a hypothesized structure allows for preservation of event details while also supporting inferential judgments about the relationship between experiences. For example, when presented with a novel inferential probe (AC), each individual element (A and C) may serve as a partial cue leading to the reactivation of the originally experienced events (AB and BC). Activation of the common item (B) in both cases would lead to successful inference.

Results showing unique hippocampal responses during integration behavior itself (Preston et al. 2004; Zalesak and Heckers 2009; Zeithamova and Preston 2010) might reflect the use of such pattern separated inputs to support performance.

This representational structure can also explain recruitment of the hippocampus during encoding of overlapping events (Shohamy and Wagner 2008; Zeithamova and Preston 2010), which potentially reflects changes in the weights linking common elements to the individually experienced events. It is important to note that even such pattern-separated representations would be expected to change over time and become more generalized as follows (Kumaran and McClelland 2012). Reactivation of these memory representations during the consolidation process or during offline replay would result in more frequent reactivation of common elements and strengthening of their connections to event representations. In contrast, idiosyncratic elements unique to individual events would be reactivated less frequently and gradually lose their connections to event representations (Lewis and Durrant 2011). This process would lead to the gradual loss of episodic details in favor of abstracted representations that capture regularities across experiences (McClelland et al. 1995).

An alternate view that combines elements of both of these frameworks stems from relational memory theory (Cohen and Eichenbaum 1993). Relational memory theory proposes that the hippocampus maintains representations of individual events while also directly encoding relationships between separate experiences (Eichenbaum et al. 1999). In our symbolic representation of this theory, different hippocampal units are recruited to represent individual events, but a lateral connection exists at the second level, linking the representations of overlapping events together (Fig. 5c). Both pattern separation and pattern completion at the level of the hippocampus would contribute to the formation of such networks of related memories. For example, a new overlapping event (BC) would recruit a hippocampal representation distinct from the originally experienced event (AB). Simultaneously, the overlapping element (B) serves as a partial cue that reactivates the prior event (AB). Based on a Hebbian learning rule, the connection between the two hippocampal memory traces would be strengthened and an explicit link between the overlapping events would be formed. Like the representational structure above, such relational networks would support mnemonic inference while simultaneously preserving memory for individual experiences.

Different coding strategies may be preferred across subregions of the hippocampus. Prior work has implicated anterior hippocampus in processing relational information (Schacter and Wagner 1999; Kirwan and Stark 2004; Chua et al. 2007) and combining information across episodes (Preston et al. 2004; Addis et al. 2007; Barron et al. 2013), typically on the basis of activation enhancements during tasks that require consideration of multiple episodes. Mechanistically, anterior hippocampus might form generalized representations promoting behavioral flexibility using its broad place fields (Poppenk et al. 2013; Preston and Eichenbaum 2013; Strange et al. 2014). In contrast, posterior hippocampus, with its more finely tuned place fields, is thought to code event specifics. Consistent with this notion, rodent work has shown that while anterior hippocampal neurons respond similarly across related episodes, posterior hippocampal firing patterns are event-specific (Komorowski et al. 2013). Moreover, the ability to retrieve details has been differentially related to hippocampal volumes across the long axis, with smaller anterior and larger posterior regions being associated with superior recollection across individuals (Poppenk et al. 2013). These findings and others (Demaster et al. 2013) suggest dissociable functions along the hippocampal anterior-posterior axis in humans, with anterior generalizing across events and posterior representing event details (Poppenk et al. 2013). Anterior hippocampus also shares the strongest anatomical connections with MPFC (Barbas and Blatt 1995), making it a good candidate region for integrating across related experiences.

Despite the prominence of these theories, empirical evidence as to how elements of overlapping events are coded in human hippocampus has been demonstrated only recently (Collin et al. 2015; Schlichting et al. 2015). One study (Fig. 5d; Schlichting et al. 2015) scanned participants during viewing of individual items both before and after encoding of overlapping (AB, BC) associations to quantify how the representations of individual memory elements shift as a function of learning. In anterior hippocampus, indirectly related (A and C) items became more similar to one another following learning, consistent with integration across the related AB and BC events. In contrast, indirectly related items became more *dissimilar* in posterior hippocampus, suggesting separation of the overlapping events in this region. Similar findings were reported in another fMRI study (Collin et al. 2015) using a paradigm involving related events that could be combined to form narratives. Results revealed a gradient in the granularity of memory representations across the anterior-posterior axis of hippocampus, with individual events (small scale network) coded in posterior hippocampus and indirect relationships among related events (large scale network) represented only in anterior hippocampus. Neural codes also related to behavior, with only participants showing behavioral evidence of integration demonstrating a gradient in memory representation granularity. The results of both studies demonstrate that there are important regional differences in neural codes that allow for the simultaneous representation of integrated and separated memories within the hippocampus.

Implications for Behavior

Forming memories that integrate across related episodes is thought to confer a degree of mnemonic flexibility. For instance, by coding the relationships that span events, memories may be formed in anticipation of future decisions. In this section, we discuss the behavioral implications of memory integration across a number of cognitive domains. In section “Behavioral Benefits”, we focus on the various benefits conferred by integrated memories on behavior. However, memory integration may also yield undesirable mnemonic consequences, which we describe in section “Behavioral Consequences”.

Behavioral Benefits

Inferring Relationships

Inference is typically conceptualized as a logical, effortful process by which multiple memories are recombined to make a novel decision. In line with this intuition, initial studies of inference focused on hippocampal contributions to successful inference at the time of retrieval (Heckers et al. 2004; Preston et al. 2004; Zalesak and Heckers 2009; DeVito et al. 2010a). More recently, however, research attention has turned to the specialized hippocampal encoding mechanisms supporting the formation of integrated memories well suited to later decisions. Integrated memories may facilitate a host of novel judgments that require knowledge of the relationships among events, such as in associative inference, transitive inference, and acquired equivalence paradigms (Fig. 6; Zeithamova et al. 2012b; c.f. Kumaran 2012). These judgments tap memory flexibility, requiring participants to make novel inferences on the basis of trained associations; for simplicity, we group these behaviors under the term "inference." Because integrated memories code for the relationships among learned associations (Fig. 1), they may be reinstated and the new information directly extracted during an inference judgment itself (Shohamy and Wagner 2008).

Empirical evidence using neural decoding of cognitive states has demonstrated that an integration state can be differentiated from both pure retrieval and pure encoding states (Richter et al. 2015), suggesting that integration is neurally distinct from its underlying components. Evidence for an integration state in that study also predicted performance on the subsequent inference test both within and across participants, demonstrating that fluctuations in learning-phase integration impact subsequent behavioral flexibility. Recent work has also directly linked the degree of neural evidence for learning-phase reactivation of related memories to subsequent behavior (Kuhl et al. 2010; Zeithamova et al. 2012a; Richter et al. 2015). For instance, the degree to which previously encoded content is reactivated during new events has been shown to predict both subsequent memory for the reactivated content itself (Kuhl et al. 2010) and later inference (Fig. 3; Zeithamova et al. 2012a; Richter et al. 2015), consistent with the notion that reactivation supports memory strengthening and flexibility via integration. One study (Zeithamova et al. 2012a) also demonstrated that engagement of hippocampus and ventral MPFC related to later inference performance. Moreover, that study observed functional connectivity enhancements across learning repetitions, suggesting that memories bound in hippocampus may come to depend on MPFC as they are integrated and strengthened (Zeithamova et al. 2012a). Within the hippocampus, CA_1 engagement during overlapping events has been shown to predict subsequent inference (Schlichting et al. 2014). The degree to which learning-phase CA_1 patterns are reinstated during inference has also been shown to relate to speed and accuracy, consistent with ideas regarding this region's role in integration (Schlichting et al. 2014).

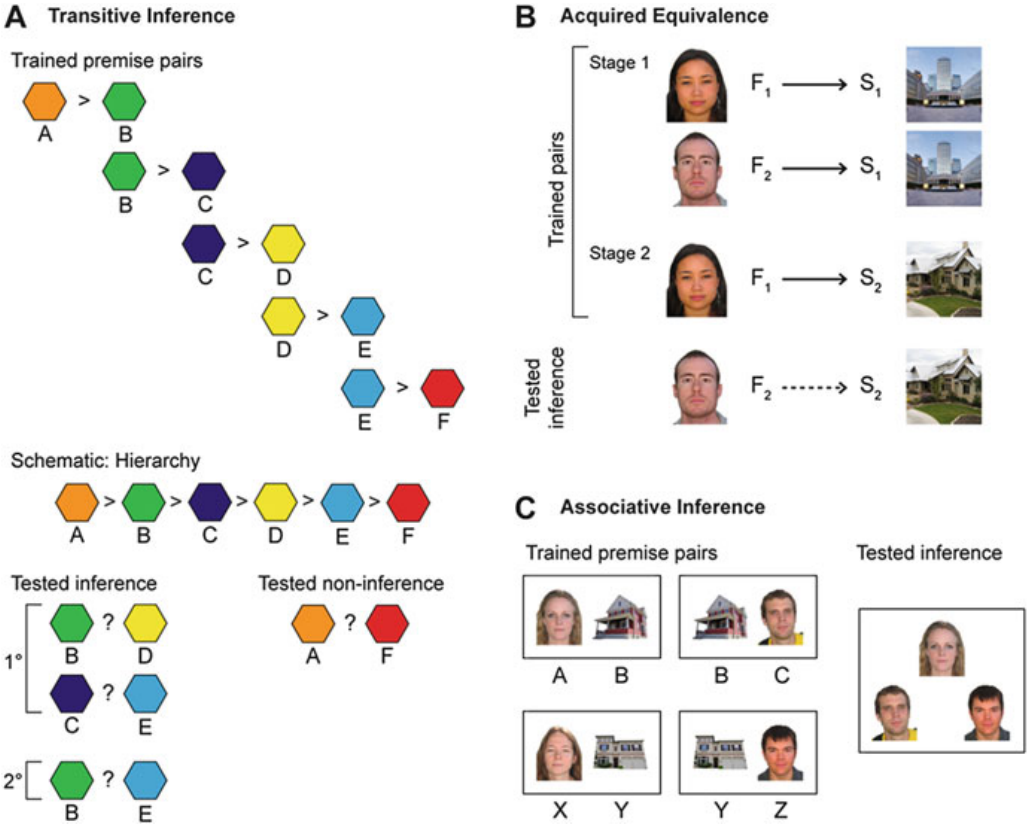


Fig. 6 Inference tasks. (**a**) Transitive inference task with six elements. A set of overlapping training pairs forms an ordered hierarchy of relationships. Participants learn each individual training pair via feedback (e.g., A > B) and are then tested on novel inference and novel non-inference judgments. Items in inferential probe trials may be separated by one element in the hierarchy (e.g., B ? D, indicated as 1°) or two elements (e.g., B ? E, indicated as 2°). Novel non-inferential probes test knowledge of the relationship between the end items of the hierarchy (A ? F). (**b**) Acquired equivalence task. In stage one of training, participants are trained via feedback to associate two faces (F_1 and F_2) with a particular scene (S_1). In stage two, participants learn to select a second scene (S_2) when cued with one of the faces (F_1). Inference is then measured as the proportion of trials on which participants choose S_2 when cued with F_2. The schematic depicts trained stimulus–response relationships (*solid black arrows*) and inferential relationships (*dashed black arrows*). (**c**) Associative inference task. Participants learn an overlapping set of associations (here, face–house associations), in which two stimuli (a man and a woman) are associated with a common third item (a house). Novel inference trials evaluate knowledge for the indirect relationship between items (who lives together in the same house). Figure as originally published in Zeithamova D, Schlichting ML, Preston AR (2012) The hippocampus and inferential reasoning: building memories to navigate future decisions. *Frontiers in Human Neuroscience* 6:70. doi:10.3389/fnhum.2012.00070

Recent work has also shown that inference is impaired in patients with lesions to ventral MPFC (Koscik and Tranel 2012). Furthermore, novel inference judgments are selectively facilitated following sleep (Ellenbogen et al. 2007; Werchan and Gómez 2013), emphasizing the importance of offline processes in integration.

Spatial Navigation

Perhaps the most familiar and widely studied form of memory integration stems from Tolman's seminal work on cognitive maps (Tolman 1948). Tolman proposed that navigation relies on the coherent representation of spatial layouts, which can flexibly give rise to new inferences about the relative locations of landmarks in the environment (Tolman 1948). One mechanism by which cognitive maps may be formed is by representing both recent past and future experience in the hippocampus at the same time. One rodent study demonstrated such simultaneous coding of retrospective and prospective paths leading up to a choice point in a continuous T-maze (Catanese et al. 2014), consistent with the notion that the hippocampus forms an ongoing representation of space including both past and future routes (see also e.g., Johnson and Redish 2007). Another recent report (Wu and Foster 2014) suggests that rather than separately representing the temporal structure of multiple traversed paths, the hippocampus integrates across overlapping routes to accurately codes the overall spatial topology of the environment. This type of representational scheme might support the ability to generate novel paths when, for instance, there is an obstacle blocking a learned route.

Recent work in humans has demonstrated a relationship between hippocampal volumes and the ability to infer novel spatial relationships among a set of trained landmarks (Schinazi et al. 2013), consistent with the idea that the hippocampus constructs integrated spatial maps. Behavioral studies have further found sleep- (Coutanche et al. 2013) and rest- (Craig et al. 2015) related increases in spatial relational inference performance. For instance, participants who passively rested for 10 min following route learning through a virtual environment had better memory for the spatial layout relative to participants who engaged in a 10-min distractor task (Craig et al. 2015). Importantly, the memory test tapped the formation of a cognitive map by assessing knowledge of routes that had never been directly experienced. Similar behavioral benefits have been reported in a group of participants who slept relative to a group who remained awake (Coutanche et al. 2013), indicating that early phase consolidation processes engaged during offline periods may facilitate the construction of cognitive maps.

Work in rodents demonstrates that the firing patterns of hippocampal CA_1 neurons predict future routes (Pfeiffer and Foster 2013). In one study, hippocampal trajectory events predicted rats' immediate future behavior as they navigated to a previously learned goal location in a familiar open arena. Trajectory events were more consistent with future than with previously traveled routes (Pfeiffer and Foster 2013), suggesting a role for hippocampal processing in planning future navigation through a familiar environment. Interestingly, trajectories can represent even novel future paths (although this is rare; Gupta et al. 2010; Pfeiffer and Foster 2013), suggesting that the hippocampus—perhaps guided by MPFC (de Bruin et al. 1994)—may support flexible navigation by simulating and evaluating possible trajectories in the context of current goals.

It is of note that uncertainty remains in the literature about precisely how the hippocampus encodes cognitive maps. For instance, it has been proposed that CA cells code the transition among locations ("transition cells"). Thus, the relationship between the memory integration mechanisms described here and the emergence of a cognitive map remain unclear at this point, and will be an important avenue of future investigations.

Mapping Social "Space"

The role of the hippocampus in integration is thought to be domain-general, with recent work extending this idea into studying social relationships. For example, one study (Kumaran et al. 2012) taught participants both social and non-social hierarchies in a transitive inference paradigm. Results showed that while fMRI activation and volume of the amygdala was specifically related to performance on the social hierarchy, the hippocampus represented the hierarchical structure for both social and non-social scenarios. In another recent experiment (Tavares et al. 2015), participants performed a role-playing task comprising a series of interactions with fictional characters. Over the course of the experiment, characters moved across social space due to changes in their power over and affiliation with the participant. Hippocampal engagement was modulated by the position of the character in social space, suggesting that the hippocampus codes for characters' relative positions as a function of their social attributes (i.e., power and affiliation). Hippocampal activation was also correlated with behavioral measures of social skills across participants, consistent with the notion that hippocampal representations of social space may explain some variability in real-world social behaviors. Taken together, these studies suggest that hippocampal integration mechanisms may aid us in forming a cognitive map of social space.

Decision Making

Integrated memories may also influence non-mnemonic decision making. For example, one recent fMRI study (Wimmer and Shohamy 2012) suggests that the hippocampus supports the transfer of monetary value across related experiences through additional recruitment of reward regions. Participants first learned a series of arbitrary S_1S_2 associations. They then learned that half of the S_2 stimuli predicted a monetary reward (S_2+). During the critical decision phase, participants chose between two S_1 stimuli, only one of which was indirectly associated with a monetary reward (S_1+) through its association with a rewarded S_2. Value transfer was operationalized as the tendency to choose S_1+ over S_1-; importantly, though neither S_1 stimulus had been directly associated with a reward, one was indirectly predictive of monetary gain via S_2+. The researchers showed greater reactivation of prior related knowledge during encoding of new reward information for stimuli that showed more evidence of subsequent preference shifts toward S_1+.

Hippocampal-striatal functional coupling was also associated with value-related preference changes (Wimmer and Shohamy 2012), suggesting that hippocampus may interact with domain-specific regions (e.g., striatum in value learning tasks) in service of integration.

Consistent with a domain-general role for hippocampus in memory integration, rodent work (Blanquat et al. 2013) found that the hippocampus is necessary for updating a known goal location with new value information. These updated memories may then be transferred to neocortex, as MPFC was necessary for retaining the updated knowledge to support performance on the next day (Blanquat et al. 2013). Thus, integrated memories incorporating value information may be maintained as memory models in MPFC that will later bias behavior. We note that this role for MPFC is likely also domain-general given its documented involvement in a number of tasks lacking an explicit value component.

Schemas

Schemas are knowledge frameworks that capture regular patterns in the environment by abstracting information across experiences (Bartlett 1932) and represent features common to multiple different events while discarding idiosyncratic details. For example, a "restaurant schema" may contain commonly experienced elements such as sitting at a table, ordering from a menu, and paying the bill, but not one-time elements such as the waiter spilling water on you. We suggest that while the specific paradigms typically used to study memory schema are quite different from the associative learning tasks that are the focus of this chapter, these bodies of work share important features and the behaviors may be supported by a common neural mechanism. Like memory integration, building upon an existing knowledge structure (schema) to incorporate new information in particular has been shown to involve both hippocampus and MPFC.

Schemas guide behavior by providing a set of expectations for a given experience. Like integrated memory representations, schemas also contain information derived from multiple events that may support inferential decisions. Specifically, schemas represent relationships among elements commonly associated with certain types of situations, despite the fact that these elements have not necessarily been experienced together. Moreover, encoding new events in the context of a reactivated schema may provide an additional mechanism for inferential reasoning. For example, a person may come to your table at the end of your meal and inquire about the quality of the food and service. In the absence of an introduction, you may infer that this person is the owner or manager of the restaurant because your restaurant schema contains information about who is likely to ask for feedback about your dining experience.

Recent attention has focused on the behavioral benefits conferred by memory schema. For instance, research in rodents has demonstrated that reactivation of an existing task schema (in this case, a well-learned spatial layout) allowed for rapid acquisition of new flavor–place associations in a single trial (Tse et al. 2007, 2011).

Without an existing schema, such associative learning required repeated training across multiple weeks. Importantly, rats with hippocampal lesions failed to show facilitated learning of new information in the presence of reactivated schemas, highlighting a critical role for this region in the rapid incorporation of new information into existing knowledge frameworks. Echoing these results, a number of human studies have reported behavioral benefits in learning and memory when new information can be incorporated into an existing schema (Kumaran 2013; van Kesteren et al. 2013, 2014).

Rodent (Tse et al. 2011) and human (van Kesteren et al. 2010, 2013, 2014) work suggests that both MPFC and hippocampus are engaged during learning of schema-related information (i.e., schema updating). Recent empirical data indicate that one factor that may influence the relative engagement of MTL and MPFC is the degree of consistency between new information and existing schema. Specifically, one study (van Kesteren et al. 2013) demonstrated that MPFC engagement was more predictive of subsequent memory for information congruent with existing schema, perhaps reflecting direct encoding of new content into prior knowledge. Note that this idea contrasts with standard views of consolidation, which propose that hippocampal memories are transferred to neocortex after long time periods; however, recent work suggests the possibility of neocortical encoding of new information independent of the hippocampus (Sharon et al. 2011; see however Smith et al. 2014; Warren and Duff 2014). Conversely, MTL engagement was more predictive of successful encoding of incongruent information. Application of a schema to a new scenario has also been shown to primarily recruit hippocampus (Kumaran et al. 2009; de Hoz and Martin 2014). For example, one fMRI study (Kumaran et al. 2009) found that while engagement and connectivity of hippocampus and ventral MPFC was enhanced during generation of a task schema, the application of schema to guide behavior in a novel but similarly structured task selectively recruited hippocampus.

One theory (van Kesteren et al. 2012) of schema-dependent learning suggests that with increasing congruency, MPFC becomes increasingly able to bias reactivation toward related memories. Increasing congruency would also be associated with decreasing novelty, which may result in diminished reliance on hippocampal integration triggered by area CA_1. In such cases, MPFC memory models may guide reactivation and be updated directly, thus bypassing hippocampal involvement. In contrast, when an existing memory model is weak or nonexistent, MPFC would play no role in guiding memory retrieval. In this case, new content would be encoded by hippocampus. Across multiple related experiences (i.e., when forming a new schema), MPFC may come online (Zeithamova et al. 2012a), reflecting the emergence of guided reactivation and the abstraction across experiences. However, in many cases, new events are likely to be neither entirely novel nor identical replications of prior experience. These events will instead share a moderate level of congruency with existing memory models, and would thus be expected to involve both MPFC and hippocampus.

While one important characteristic typically ascribed to schemas is the loss of idiosyncratic details that code the differences among events, it remains unknown whether the same is true of integrated memory representations. Anecdotal evidence from the acquired equivalence paradigm suggests that some event details may also be lost during integration, as participants failed to recognize inferential probe trials as novel pairings of stimuli (Shohamy and Wagner 2008). This finding suggests that details about directly experienced events may sometimes be lost in favor of an abstracted, generalized framework that codes consistencies among distinct stimulus-response relationships. However, whether a similar loss of detailed event information is typical in other inference paradigms, especially those that utilize rapid acquisition procedures (e.g., single-trial learning), is not known. More research is needed to understand how the processes supporting inference are related to those implicated in the formation and use of schemas. Consideration of how task dynamics influence the type of representational structure formed may provide important insights into how the hippocampus codes overlapping event information and interacts with MPFC to support mnemonic flexibility. Moreover, it is noteworthy that the operational definition of "schema" varies across species (e.g., spatial layouts in rodents versus movie knowledge in humans) and across studies within a species (e.g., movie knowledge versus semantic knowledge in humans). Future work should seek to bridge the gap between animal and human work to better specify the conditions and mechanisms that support the building, updating, and use of memory schemas.

Learning and Associative Facilitation

Recent work suggests that new learning can be promoted by integrating new information into existing knowledge structures. This phenomenon is highly related to findings in the schema literature showing a behavioral benefit to encoding schema-congruent information (described in section "Schemas"). However, here we make no assumptions about the level of detail retained in the existing knowledge structure; prior memories need not be generalized.

The observation that prior knowledge can boost learning is by no means new; classic studies have shown that prior knowledge is beneficial to new learning under some circumstances (Bransford and Johnson 1972). For example, one such classic study showed a memory advantage for new responses paired with well-learned old stimuli (i.e., stimuli previously learned with a different response), a phenomenon known as associative facilitation (Underwood 1949). These observations appear robust across species, with existing knowledge of a spatial layout shown to facilitate acquisition of new related associations in rodents (Tse et al. 2007), for example. Such facilitation may also extend to novel judgments that require the simultaneous consideration of multiple memories (e.g., inferences).

Behaviorally, memory integration has been shown to have a protective effect on memory; instructing participants to integrate is associated with better memory for both the initial and newly encoded content (Anderson and McCulloch 1999; Forcato et al. 2010; see however Richter et al. 2015). Neuroimaging studies using the associative inference paradigm have shown that memory integration mechanisms may underlie associative facilitation (Schlichting and Preston 2014, 2016). Participants first formed strong memories for (AB) face-object pairs across four study-test iterations in a pre-training phase. They then encoded new object-object associations in a single exposure, half of which overlapped with (BC) and half of which did not overlap with (XY) prior knowledge. Importantly, overlapping and non-overlapping pairs were matched in terms of content type (two objects) and number of exposures (one per pair); thus, any differences in neural or behavioral signatures are attributable to the presence or absence of prior related knowledge. Results showed that the degree of evidence for memory reactivation during a rest period following AB pre-training predicted individual differences in the ability to later encode the new overlapping associations. Moreover, neural signatures during rest predicted engagement of face-sensitive regions at task, suggesting that offline memory processing promotes reactivation during the new learning phase (Schlichting and Preston 2014). Successful overlapping pair encoding was also associated with engagement of the hippocampal-MPFC circuit (Schlichting and Preston 2016). These findings suggest that the same memory integration mechanisms that support the ability to make novel inferences spanning events may also facilitate the encoding of new, related information.

Creativity and Imagination

Memory integration may also underlie the ability to recombine prior memories to construct new ideas and imagine future scenarios (Schacter et al. 2012). Consistent with this notion, recent work (Duff et al. 2013) has demonstrated that hippocampal damage results in impaired performance on creativity tasks in which participants generate novel responses on the basis of existing knowledge. MPFC may also support performance in such tasks; one fMRI study (Takeuchi et al. 2012) showed that individual differences in resting state functional connectivity of MPFC with posterior cingulate cortex predicted creativity.

Hippocampus and MPFC are also engaged during imagination (Martin et al. 2011; Barron et al. 2013), particularly when imagined scenarios are rich in episodic detail. One human fMRI study showed enhanced connectivity between hippocampus and MPFC during imagination of future scenarios that were later remembered (Martin et al. 2011), consistent with the notion that these regions are important for creating and maintaining integrated memories—even those representing imagined events. Another study (Barron et al. 2013) required participants to construct mental representations of novel foods from two familiar ingredients. Using an fMRI adaptation paradigm, researchers found that imagining novel foods engaged the same neuronal populations as did the ingredients in both hippocampus and MPFC, reflecting retrieval and recombination of prior memories during mental construction. The ingredient items themselves also came to recruit overlapping neuronal populations, perhaps reflecting integration of the simultaneously reactivated memories (Fig. 5). Interestingly, the degree of representational overlap of the ingredients in hippocampus and MPFC tracked across participants with subjective value of the imagined foods, suggesting that integration may be enhanced according to behavioral relevance (here, for high value items).

Behavioral Consequences

While we focus primarily on the positive outcomes associated with memory integration, a few noteworthy studies have highlighted its negative behavioral consequences. For example, integration may lead to the formation of false memories (i.e., through overgeneralization) (Cabeza et al. 2001; Warren et al. 2014), memory misattributions (Hupbach et al. 2007; Jones et al. 2012; Gershman et al. 2013; St. Jacques et al. 2013), and interference (Chan and LaPaglia 2013).

Both MTL and MPFC have been implicated in the formation of false memories. Neuroimaging studies have reported similar MTL engagement during recognition of both studied items ("true" memories) and unstudied lures ("false" memories) (Cabeza et al. 2001; Slotnick and Schacter 2004; Abe et al. 2008), suggesting that integrated hippocampal representations might underlie the tendency to incorrectly identify conceptually similar items as having been studied. Interestingly, these effects appear somewhat specific to anterior aspects of both hippocampus and MTL cortex (Cabeza et al. 2001; Abe et al. 2008; McTighe et al. 2010), while more posterior MTL regions (e.g., parahippocampal cortex) typically differentiate true from false memories based on activation (Cabeza et al. 2001; Okado and Stark 2003; Kim and Cabeza 2007a, b). These results are broadly consistent with the notion that anterior hippocampus in particular is well suited to integrate across related memories, perhaps at the cost of memory specificity. Ventral MPFC has also been implicated in constructing generalized memory representations; patients with ventral MPFC lesions show reduced false memories relative to healthy control participants for words that were never seen but are thematically related to a studied word list (Warren et al. 2014).

Integration may also explain the phenomenon of memory misattribution, in which an episodic experience is incorrectly attributed to a different encoding context than the one in which it occurred (e.g., as measured by intrusions). Misattributions may result when prior knowledge is reactivated and updated with the current experience to the detriment of memory accuracy. One fMRI study (Gershman et al. 2013) used neural decoding to quantify the reinstatement of the context associated with prior memories (List 1) during new learning (List 2). Results showed that greater evidence for reactivation of the List 1 context was associated with more misattributions of List 2 words to List 1. Another study (St. Jacques et al. 2013) showed that when participants reactivated a prior experience during new encoding, engagement of both hippocampus and ventral MPFC was associated with later memory misattributions, consistent with a role for these regions in linking experiences across time.

Memory integration mechanisms may also lead to interference or forgetting. When a memory is retrieved during a new learning experience, that memory becomes malleable and susceptible to change as a function of the current experience. One possible outcome of learning-phase reactivation is integration—that is, prior memories are updated to incorporate the new information. However, learning-phase reactivation can also lead to forgetting of the initial memory under some conditions (Walker et al. 2003; Forcato et al. 2007; Chan and LaPaglia 2013). For example, one behavioral study had participants watch a movie of a crime, which served as the initial memory. Later, participants listened to a narrative describing the crime that included misinformation: the crime was committed with a different weapon than the one depicted in the movie. Critically, reactivation of the initial memory prior to hearing the narrative resulted in forgetting of the initial, "true" memory of the crime (Chan and LaPaglia 2013). By design, the newly learned information in that study directly competed with or replaced the prior knowledge. Thus, whether memories for the original events are "overwritten" or simply updated to incorporate the new information may depend largely on the degree to which the two memories are compatible (Hupbach 2011).

It is notable that in the hippocampus, forgetting has typically been attributed to passive decay rather than interference due to the strong hippocampal tendency to pattern separate (Hardt et al. 2013). However, recent work suggesting that hippocampus—particularly its anterior portion—can form integrated codes that span related memories (Collin et al. 2015; Schlichting et al. 2015) calls this view into question. That is, memory integration predicts that even hippocampal memories may be forgotten when related content is incorporated into existing memory traces (i.e., through interference).

Conclusions

In summary, extensive evidence indicates that the hippocampus and its interactions with MPFC promote memory integration processes that support flexible cognition. Hippocampus does so by building memory representations that code not only associations within individual events, but also relationships spanning multiple episodes. In this way, the function of the hippocampus is not merely to enable the retrospective use of memory; rather, hippocampal function is "intrinsically prospective" (Klein et al. 2002a), aimed at constructing representations that can be used to successfully negotiate future judgments and actions. Integration tasks thus provide a powerful tool for studying the adaptive nature of memory and how the computational properties of the hippocampus allow memories to be reconstructed into prospectively useful formats.

The findings described here collectively suggest the importance of hippocampal encoding processes in linking related experiences. Integrated memories may support a host of flexible behaviors, from navigating our environment to imagining our future. Importantly, hippocampus does not work in isolation; rather, it communicates with other cortical regions to facilitate reactivation of memories, encoding of new memories, and updating of existing representations to incorporate new information. In doing so, it plays a key role in the extraction of knowledge across learning events.

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References

Abe N, Okuda J, Suzuki M et al (2008) Neural correlates of true memory, false memory, and deception. Cereb Cortex 18:2811–2819. doi:10.1093/cercor/bhn037

Addis DR, Schacter DL (2012) The hippocampus and imagining the future: where do we stand? Front Hum Neurosci 5:173. doi:10.3389/fnhum.2011.00173

Addis DR, Wong AT, Schacter DL (2007) Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia 45:1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016

Anderson MC, McCulloch KC (1999) Integration as a general boundary condition on retrieval-induced forgetting. J Exp Psychol Learn Mem Cogn 25:608–629. doi:10.1037/0278-7393.25.3.608

Barbas H, Blatt GJ (1995) Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. Hippocampus 5:511–533

Barron HC, Dolan RJ, Behrens TEJ (2013) Online evaluation of novel choices by simultaneous representation of multiple memories. Nat Neurosci 16:1492–1498. doi:10.1038/nn.3515

Bartlett F (1932) Remembering: a study in experimental and social psychology. Cambridge University Press, Cambridge

Blanquat PDS, Hok V, Save E et al (2013) Differential role of the dorsal hippocampus, ventro-intermediate hippocampus, and medial prefrontal cortex in updating the value of a spatial goal. Hippocampus 23:342–351. doi:10.1002/hipo.22094

Bransford JD, Johnson MK (1972) Contextual prerequisites for understanding: some investigations of comprehension and recall. J Verbal Learn Verbal Behav 11:717–726

Buckner RL (2010) The role of the hippocampus in prediction and imagination. Annu Rev Psychol 61:27–48. doi:10.1146/annurev.psych.60.110707.163508

Bunsey M, Eichenbaum H (1996) Conservation of hippocampal memory function in rats and humans. Nature 379:255–257. doi:10.1038/379255a0

Cabeza R, Rao SM, Wagner AD et al (2001) Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci U S A 98:4805–4810. doi:10.1073/pnas.081082698

Catanese J, Viggiano A, Cerasti E et al (2014) Retrospectively and prospectively modulated hippocampal place responses are differentially distributed along a common path in a continuous T-maze. J Neurosci 34:13163–13169. doi:10.1523/JNEUROSCI.0819-14.2014

Cavada C, Compañy T, Tejedor J et al (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10:220–242

Chan JCK, LaPaglia JA (2013) Impairing existing declarative memory in humans by disrupting reconsolidation. Proc Natl Acad Sci U S A 110:9309–9313. doi:10.1073/pnas.1218472110

Chua EF, Schacter DL, Rand-Giovannetti E, Sperling RA (2007) Evidence for a specific role of the anterior hippocampal region in successful associative encoding. Hippocampus 17:1071–1080. doi:10.1002/hipo.20340

Cohen NJ, Eichenbaum H (1993) Memory, amnesia, and the hippocampal system. The MIT Press, Cambridge, MA

Collin SHP, Milivojevic B, Doeller CF (2015) Memory hierarchies map onto the hippocampal long axis in humans. Nat Neurosci 18:1–5. doi:10.1038/nn.4138

Coutanche MN, Gianessi CA, Chanales AJH et al (2013) The role of sleep in forming a memory representation of a two-dimensional space. Hippocampus 23:1189–1197. doi:10.1002/hipo.22157

Craig M, Dewar M, Harris MA, Della Sala S (2015) Wakeful rest promotes the integration of spatial memories into accurate cognitive maps. Hippocampus. doi:10.1002/hipo.22502

de Bruin JPC, Sànchez-Santed F, Heinsbroek RPW et al (1994) A behavioural analysis of rats with damage to the medial prefrontal cortex using the morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation. Brain Res 652:323–333

de Hoz L, Martin SJ (2014) Double dissociation between the contributions of the septal and temporal hippocampus to spatial learning: the role of prior experience. Hippocampus 24:990–1005. doi:10.1002/hipo.22285

Demaster DM, Pathman T, Lee JK, Ghetti S (2013) Structural development of the hippocampus and episodic memory: developmental differences along the anterior/posterior axis. Cereb Cortex 24:3036–3045

Deuker L, Olligs J, Fell J et al (2013) Memory consolidation by replay of stimulus-specific neural activity. J Neurosci 33:19373–19383. doi:10.1523/JNEUROSCI.0414-13.2013

DeVito LM, Kanter BR, Eichenbaum H (2010a) The hippocampus contributes to memory expression during transitive inference in mice. Hippocampus 20:208–217. doi:10.1002/hipo.20610

DeVito LM, Lykken C, Kanter BR, Eichenbaum H (2010b) Prefrontal cortex: role in acquisition of overlapping associations and transitive inference. Learn Mem 17:161–167

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126. doi:10.1038/nrn2762

Duff MC, Kurczek J, Rubin R et al (2013) Hippocampal amnesia disrupts creative thinking. Hippocampus 23:1143–1149. doi:10.1002/hipo.22208

Duncan K, Ketz N, Inati SJ, Davachi L (2012a) Evidence for area CA1 as a match/mismatch detector: a high-resolution fMRI study of the human hippocampus. Hippocampus 22:389–398. doi:10.1002/hipo.20933

Duncan K, Sadanand A, Davachi L (2012b) Memory's penumbra: episodic memory decisions induce lingering mnemonic biases. Science 337:485–487. doi:10.1126/science.1221936

Eichenbaum H, Schoenbaum G, Young B, Bunsey M (1996) Functional organization of the hippocampal memory system. Proc Natl Acad Sci U S A 93:13500–13507

Eichenbaum H, Dudchenko PA, Wood E et al (1999) The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23:209–226

Ellenbogen JM, Hu PT, Payne JD et al (2007) Human relational memory requires time and sleep. Proc Natl Acad Sci U S A 104:7723–7728. doi:10.1073/pnas.0700094104

Euston DR, Gruber AJ, McNaughton BL (2012) The role of medial prefrontal cortex in memory and decision making. Neuron 76:1057–1070. doi:S0896-6273(12)01108-7

Forcato C, Burgos VL, Argibay PF et al (2007) Reconsolidation of declarative memory in humans. Learn Mem 14:295–303. doi:10.1101/lm.486107

Forcato C, Rodríguez MLC, Pedreira ME, Maldonado H (2010) Reconsolidation in humans opens up declarative memory to the entrance of new information. Neurobiol Learn Mem 93:77–84. doi:10.1016/j.nlm.2009.08.006

Gerraty RT, Davidow JY, Wimmer GE et al (2014) Transfer of learning relates to intrinsic connectivity between hippocampus, ventromedial prefrontal cortex, and large-scale networks. J Neurosci 34:11297–11303. doi:10.1523/JNEUROSCI.0185-14.2014

Gershman SJ, Schapiro AC, Hupbach A, Norman KA (2013) Neural context reinstatement predicts memory misattribution. J Neurosci 33:8590–8595. doi:10.1523/JNEUROSCI.0096-13.2013

Ghosh VE, Moscovitch M, Melo Colella B, Gilboa A (2014) Schema representation in patients with ventromedial PFC lesions. J Neurosci 34:12057–12070. doi:10.1523/JNEUROSCI.0740-14.2014

Gupta AS, van der Meer MAA, Touretzky DS, Redish AD (2010) Hippocampal replay is not a simple function of experience. Neuron 65:695–705. doi:10.1016/j.neuron.2010.01.034

Hardt O, Nader K, Nadel L (2013) Decay happens: the role of active forgetting in memory. Trends Cogn Sci 17:109–118. doi:10.1016/j.tics.2013.01.001

Hasselmo ME, Schnell E (1994) Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: computational modeling and brain slice physiology. J Neurosci 14:3898–3914

Hasselmo ME, Wyble BP, Wallenstein GV (1996) Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. Hippocampus 6:693–708. doi:10.1002/(SICI)1098-1063(1996)6:6<693::AID-HIPO12>3.0.CO;2-W

Heckers S, Zalesak M, Weiss AP et al (2004) Hippocampal activation during transitive inference in humans. Hippocampus 14:153–162. doi:10.1002/hipo.10189

Henke K, Reber TP, Duss SB (2013) Integrating events across levels of consciousness. Front Behav Neurosci 7:68. doi:10.3389/fnbeh.2013.00068

Hoffman KL, Mcnaughton BL (2002) Sleep on it: cortical reorganization after-the fact. Trends Neurosci 25:1–2

Howard MW, Fotedar MS, Datey AV, Hasselmo ME (2005) The temporal context model in spatial navigation and relational learning: toward a common explanation of medial temporal lobe function across domains. Psychol Rev 112:75–116. doi:10.1037/0033-295X.112.1.75

Hupbach A (2011) The specific outcomes of reactivation-induced memory changes depend on the degree of competition between old and new information. Front Behav Neurosci 5:33. doi:10.3389/fnbeh.2011.00033

Hupbach A, Gomez R, Hardt O, Nadel L (2007) Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. Learn Mem 14:47–53. doi:10.1101/lm.365707

Iordanova MD, Killcross AS, Honey RC (2007) Role of the medial prefrontal cortex in acquired distinctiveness and equivalence of cues. Behav Neurosci 121:1431–1436. doi:10.1037/0735-7044.121.6.1431

Jadhav SP, Kemere C, German PW, Frank LM (2012) Awake hippocampal sharp-wave ripples support spatial memory. Science 336:1454–1457. doi:10.1126/science.1217230

Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–107

Johnson A, Redish AD (2007) Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. J Neurosci 27:12176–12189. doi:10.1523/JNEUROSCI.3761-07.2007

Jones B, Bukoski E, Nadel L, Fellous J-M (2012) Remaking memories: reconsolidation updates positively motivated spatial memory in rats. Learn Mem 19:91–98. doi:10.1101/lm.023408.111

Kahana M (1996) Associative retrieval processes in free recall. Mem Cognit 24:103–109. doi:10.3758/BF03197276

Karlsson MP, Frank LM (2009) Awake replay of remote experiences in the hippocampus. Nat Neurosci 12:913–918. doi:10.1038/nn.2344

Kim H, Cabeza R (2007a) Differential contributions of prefrontal, medial temporal, and sensory-perceptual regions to true and false memory formation. Cereb Cortex 17:2143–2150. doi:10.1093/cercor/bhl122

Kim H, Cabeza R (2007b) Trusting our memories: dissociating the neural correlates of confidence in veridical versus illusory memories. J Neurosci 27:12190–12197. doi:10.1523/JNEUROSCI.3408-07.2007

Kirwan CB, Stark CEL (2004) Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus 14:919–930. doi:10.1002/hipo.20014

Klein SB, Cosmides L, Tooby J, Chance S (2002a) Decisions and the evolution of memory: multiple systems, multiple functions. Psychol Rev 109:306–329. doi:10.1037//0033-295X.109.2.306

Klein SB, Loftus J, Kihlstrom JF (2002b) Memory and temporal experience: the effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. Soc Cogn 20:353–379

Komorowski RW, Garcia CG, Wilson A et al (2013) Ventral hippocampal neurons are shaped by experience to represent behaviorally relevant contexts. J Neurosci 33:8079–8087. doi:10.1523/JNEUROSCI.5458-12.2013

Koscik TR, Tranel D (2012) The human ventromedial prefrontal cortex is critical for transitive inference. J Cogn Neurosci 24:1191–1204. doi:10.1162/jocn_a_00203

Kroes MCW, Fernández G (2012) Dynamic neural systems enable adaptive, flexible memories. Neurosci Biobehav Rev 36:1646–1666. doi:10.1016/j.neubiorev.2012.02.014

Kuhl BA, Shah AT, DuBrow S, Wagner AD (2010) Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. Nat Neurosci 13:501–506. doi:10.1038/nn.2498

Kuhl BA, Bainbridge WA, Chun MM (2012) Neural reactivation reveals mechanisms for updating memory. J Neurosci 32:3453–3461. doi:10.1523/JNEUROSCI.5846-11.2012

Kumaran D (2012) What representations and computations underpin the contribution of the hippocampus to generalization and inference? Front Hum Neurosci 6:157. doi:10.3389/fnhum.2012.00157

Kumaran D (2013) Schema-driven facilitation of new hierarchy learning in the transitive inference paradigm. Learn Mem 20:388–394. doi:10.1101/lm.030296.113

Kumaran D, McClelland JL (2012) Generalization through the recurrent interaction of episodic memories: a model of the hippocampal system. Psychol Rev 119:573–616. doi:10.1037/a0028681

Kumaran D, Melo HL (2013) Transitivity performance, relational hierarchy knowledge and awareness: results of an instructional framing manipulation. Hippocampus 23:1259–1268. doi:10.1002/hipo.22163

Kumaran D, Summerfield JJ, Hassabis D, Maguire EA (2009) Tracking the emergence of conceptual knowledge during human decision making. Neuron 63:889–901. doi:10.1016/j.neuron.2009.07.030

Kumaran D, Melo H, Duzel E (2012) The emergence and representation of knowledge about social and nonsocial hierarchies. Neuron 76:653–666. doi:10.1016/j.neuron.2012.09.035

Larkin MC, Lykken C, Tye LD et al (2014) Hippocampal output area CA1 broadcasts a generalized novelty signal during an object-place recognition task. Hippocampus 24:773–783. doi:10.1002/hipo.22268

Lewis PA, Durrant SJ (2011) Overlapping memory replay during sleep builds cognitive schemata. Trends Cogn Sci 15:343–351. doi:10.1016/j.tics.2011.06.004

Lisman JE, Grace AA (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46:703–713. doi:10.1016/j.neuron.2005.05.002

Marr D (1970) A theory for cerebral neocortex. Proc R Soc Lond B Biol Sci 176:161–234

Martin VC, Schacter DL, Corballis MC, Addis DR (2011) A role for the hippocampus in encoding simulations of future events. Proc Natl Acad Sci U S A 108:13858–13863. doi:10.1073/pnas.1105816108

McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 102:419–457. doi:10.1037//0033-295X.102.3.419

McKenzie S, Eichenbaum H (2011) Consolidation and reconsolidation: two lives of memories? Neuron 71:224–233. doi:10.1016/j.neuron.2011.06.037

McKenzie S, Robinson NTM, Herrera L et al (2013) Learning causes reorganization of neuronal firing patterns to represent related experiences within a hippocampal schema. J Neurosci 33:10243–10256. doi:10.1523/JNEUROSCI.0879-13.2013

McKenzie S, Frank AJ, Kinsky NR et al (2014) Hippocampal representation of related and opposing memories develop within distinct, hierarchically organized neural schemas. Neuron 83:202–215. doi:10.1016/j.neuron.2014.05.019

McTighe SM, Cowell RA, Winters BD et al (2010) Paradoxical false memory for objects after brain damage. Science 330:1408–1410. doi:10.1126/science.1194780

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202. doi:10.1146/annurev.neuro.24.1.167

Munnelly A, Dymond S (2014) Relational memory generalization and integration in a transitive inference task with and without instructed awareness. Neurobiol Learn Mem 109:169–177. doi:10.1016/j.nlm.2014.01.004

Nadel L, Hardt O (2011) Update on memory systems and processes. Neuropsychopharmacology 36:251–273. doi:10.1038/npp.2010.169

Nadel L, Moscovitch M (1997) Memory consolidation, retrograde amnesia, and the hippocampal complex. Curr Opin Neurobiol 7:217–227

Nadel L, Samsonovich A, Ryan L, Moscovitch M (2000) Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10:352–368

Nadel L, Hupbach A, Gomez R, Newman-Smith K (2012) Memory formation, consolidation and transformation. Neurosci Biobehav Rev 36:1640–1645. doi:10.1016/j.neubiorev.2012.03.001

O'Keefe J, Nadel L (1978) The hippocampus as a cognitive map. Clarendon, London

O'Reilly RC, Rudy JW (2001) Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol Rev 108:311–345. doi:10.1037//0033-295X.108.2.311

Okado Y, Stark C (2003) Neural processing associated with true and false memory retrieval. Cogn Affect Behav Neurosci 3:323–334. doi:10.3758/CABN.3.4.323

Pfeiffer BE, Foster DJ (2013) Hippocampal place-cell sequences depict future paths to remembered goals. Nature 497:74–81. doi:10.1038/nature12112

Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013) Long-axis specialization of the human hippocampus. Trends Cogn Sci 17:230–240. doi:10.1016/j.tics.2013.03.005

Preston AR, Eichenbaum H (2013) Interplay of hippocampus and prefrontal cortex in memory. Curr Biol 23:R764–R773. doi:10.1016/j.cub.2013.05.041

Preston AR, Shrager Y, Dudukovic N, Gabrieli JDE (2004) Hippocampal contribution to the novel use of relational information in declarative memory. Hippocampus 14:148–152. doi:10.1002/hipo.20009

Price JL, Drevets WC (2009) Neurocircuitry of mood disorders. Neuropsychopharmacology 35:192–216. doi:10.1038/npp.2009.104

Richards BA, Xia F, Santoro A et al (2014) Patterns across multiple memories are identified over time. Nat Neurosci 17:981–986. doi:10.1038/nn.3736

Richter FR, Chanales AJH, Kuhl BA (2015) Predicting the integration of overlapping memories by decoding mnemonic processing states during learning. Neuroimage. doi:10.1016/j.neuroimage.2015.08.051

Roy M, Shohamy D, Wager TD (2012) Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn Sci 16:147–156. doi:10.1016/j.tics.2012.01.005

Sara SJ (2010) Reactivation, retrieval, replay and reconsolidation in and out of sleep: connecting the dots. Front Behav Neurosci 4:185. doi:10.3389/fnbeh.2010.00185

Schacter DL, Wagner AD (1999) Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9:7–24

Schacter DL, Addis DR, Hassabis D et al (2012) The future of memory: remembering, imagining, and the brain. Neuron 76:677–694

Schiller D, Phelps EA (2011) Does reconsolidation occur in humans? Front Behav Neurosci 5:24. doi:10.3389/fnbeh.2011.00024

Schinazi VR, Nardi D, Newcombe NS et al (2013) Hippocampal size predicts rapid learning of a cognitive map in humans. Hippocampus 23:515–528. doi:10.1002/hipo.22111

Schlichting ML, Preston AR (2014) Memory reactivation during rest supports upcoming learning of related content. Proc Natl Acad Sci U S A 111:15845–15850. doi:10.1073/pnas.1404396111

Schlichting ML, Preston AR (2015) Memory integration: neural mechanisms and implications for behavior. Curr Opin Behav Sci 1:1–8. doi:10.1016/j.cobeha.2014.07.005

Schlichting ML, Preston AR (2016) Hippocampal-medial prefrontal circuit supports memory updating during learning and post-encoding rest. Neurobiol Learn Mem. doi:10.1016/j.nlm.2015.11.005

Schlichting ML, Zeithamova D, Preston AR (2014) CA1 subfield contributions to memory integration and inference. Hippocampus 24:1248–1260. doi:10.1002/hipo.22310

Schlichting ML, Mumford JA, Preston AR (2015) Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. Nat Commun 6:8151. doi:10.1038/ncomms9151

Sharon T, Moscovitch M, Gilboa A (2011) Rapid neocortical acquisition of long-term arbitrary associations independent of the hippocampus. Proc Natl Acad Sci U S A 108:1146–1151. doi:10.1073/pnas.1005238108/-/DCSupplemental. www.pnas.org/cgi/doi/10.1073/pnas.1005238108

Shohamy D, Wagner AD (2008) Integrating memories in the human brain: hippocampal-midbrain encoding of overlapping events. Neuron 60:378–389. doi:10.1016/j.neuron.2008.09.023

Singer AC, Karlsson MP, Nathe AR et al (2010) Experience-dependent development of coordinated hippocampal spatial activity representing the similarity of related locations. J Neurosci 30:11586–11604. doi:10.1523/JNEUROSCI.0926-10.2010

Slotnick SD, Schacter DL (2004) A sensory signature that distinguishes true from false memories. Nat Neurosci 7:664–672. doi:10.1038/nn1252

Smith CN, Urgolites ZJ, Hopkins RO, Squire LR (2014) Comparison of explicit and incidental learning strategies in memory-impaired patients. Proc Natl Acad Sci U S A 111:475–479. doi:10.1073/pnas.1322263111

St. Jacques PL, Olm C, Schacter DL (2013) Neural mechanisms of reactivation-induced updating that enhance and distort memory. Proc Natl Acad Sci U S A 110:19671–19678. doi:10.1073/pnas.1319630110

Staresina BP, Alink A, Kriegeskorte N, Henson RN (2013) Awake reactivation predicts memory in humans. Proc Natl Acad Sci U S A 110:21159–21164

Strange BA, Witter MP, Lein ES, Moser EI (2014) Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci 15:655–669. doi:10.1038/nrn3785

Takeuchi H, Taki Y, Hashizume H et al (2012) The association between resting functional connectivity and creativity. Cereb Cortex 22:2921–2929. doi:10.1093/cercor/bhr371

Tambini A, Ketz N, Davachi L (2010) Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 65:280–290. doi:10.1016/j.neuron.2010.01.001

Tavares RM, Mendelsohn A, Grossman Y et al (2015) A map for social navigation in the human brain. Neuron 87:231–243. doi:10.1016/j.neuron.2015.06.011

Tolman EC (1948) Cognitive maps in rats and men. Psychol Rev 55:189–208. doi:10.1037/h0061626

Tse D, Langston RF, Kakeyama M et al (2007) Schemas and memory consolidation. Science 316:76–82. doi:10.1126/science.1135935

Tse D, Takeuchi T, Kakeyama M et al (2011) Schema-dependent gene activation and memory encoding in neocortex. Science 333:891–895. doi:10.1126/science.1205274

Underwood BJ (1949) Proactive inhibition as a function of time and degree of prior learning. J Exp Psychol 39:24–34

van Kesteren MTR, Fernández G, Norris DG, Hermans EJ (2010) Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci U S A 107:7550–7555. doi:10.1073/pnas.0914892107

van Kesteren MTR, Ruiter DJ, Fernández G, Henson RN (2012) How schema and novelty augment memory formation. Trends Neurosci 35:211–219. doi:10.1016/j.tins.2012.02.001

van Kesteren MTR, Beul SF, Takashima A et al (2013) Differential roles for medial prefrontal and medial temporal cortices in schema-dependent encoding: from congruent to incongruent. Neuropsychologia 51:2352–2359. doi:10.1016/j.neuropsychologia.2013.05.027

van Kesteren MTR, Rijpkema M, Ruiter DJ et al (2014) Building on prior knowledge: schema-dependent encoding processes relate to academic performance. J Cogn Neurosci 26:2250–2261. doi:10.1162/jocn

Walker MP, Brakefield T, Hobson JA (2003) Dissociable stages of human memory consolidation and reconsolidation. Nature 425:616–620. doi:10.1038/nature01951.1

Wang S-H, Tse D, Morris RGM (2012) Anterior cingulate cortex in schema assimilation and expression. Learn Mem 19:315–318. doi:10.1101/lm.026336.112

Warren DE, Duff MC (2014) Not so fast: hippocampal amnesia slows word learning despite successful fast mapping. Hippocampus 24:920–933. doi:10.1002/hipo.22279

Warren DE, Jones SH, Duff MC, Tranel D (2014) False recall is reduced by damage to the ventromedial prefrontal cortex: implications for understanding the neural correlates of schematic memory. J Neurosci 34:7677–7682. doi:10.1523/JNEUROSCI.0119-14.2014

Werchan DM, Gómez RL (2013) Generalizing memories over time: sleep and reinforcement facilitate transitive inference. Neurobiol Learn Mem 100:70–76. doi:10.1016/j.nlm.2012.12.006

Wilson RC, Takahashi YK, Schoenbaum G, Niv Y (2014) Orbitofrontal cortex as a cognitive map of task space. Neuron 81:267–279. doi:10.1016/j.neuron.2013.11.005

Wimmer GE, Shohamy D (2012) Preference by association: how memory mechanisms in the hippocampus bias decisions. Science 338:270–273. doi:10.1126/science.1223252

Wood ER, Dudchenko PA, Eichenbaum H (1999) The global record of memory in hippocampal neuronal activity. Nature 397:613–616. doi:10.1038/17605

Wu X, Foster DJ (2014) Hippocampal replay captures the unique topological structure of a novel environment. J Neurosci 34:6459–6469. doi:10.1523/JNEUROSCI.3414-13.2014

Zalesak M, Heckers S (2009) The role of the hippocampus in transitive inference. Psychiatry Res Neuroimaging 172:24–30. doi:10.1016/j.pscychresns.2008.09.008

Zeithamova D, Preston AR (2010) Flexible memories: differential roles for medial temporal lobe and prefrontal cortex in cross-episode binding. J Neurosci 30:14676–14684. doi:10.1523/JNEUROSCI.3250-10.2010

Zeithamova D, Dominick AL, Preston AR (2012a) Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. Neuron 75:168–179. doi:10.1016/j.neuron.2012.05.010

Zeithamova D, Schlichting ML, Preston AR (2012b) The hippocampus and inferential reasoning: building memories to navigate future decisions. Front Hum Neurosci 6:70. doi:10.3389/fnhum.2012.00070