# Mechanisms of Memory Consolidation and Transformation

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**Abstract** Memory consolidation is a dynamic process occurring over the lifetime of a memory, yet the underlying mechanisms are not well understood. The hippocampus is considered to be a critical structure for the acquisition, initial storage, and retrieval of a memory, but there is considerable debate over the continuing role of the hippocampus in representing a memory as it ages. Studies in rodents and humans both point towards a reorganization of hippocampus-dependent memory traces in the cortex over time, but when and how long it takes these large-scale network changes to occur is uncertain. In this chapter, we address how a memory that is initially dependent on the hippocampus becomes represented in the cortex, independently of the hippocampus. We also discuss how the quality of the memory changes (transforms) as the trace reorganizes over time, with a focus on hippocampal-cortical interactions as described by Trace Transformation Theory (TTT), and consider the degree to which evidence related to the mechanistic basis of memory consolidation in rodents applies to complex human memory. We conclude that theories like TTT

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provide a new approach to thinking about consolidation as an ongoing and interactive process involving the hippocampus, mPFC, and other brain regions.

**Keywords** Memory · Consolidation · Transformation · Reconsolidation · Hippocampus · Medial prefrontal cortex · Episodic · Semantic · Context fear

**Abbreviations**

| | |
|---|---|
| **aCC** | Anterior cingulate cortex |
| **CREB** | Cyclic-AMP response element binding protein |
| **IEG** | Immediate early gene |
| **L-LTP** | Late phase long-term potentiation |
| **mPFC** | Medial prefrontal cortex |
| **MTL** | Medial temporal lobe |
| **MTT** | Multiple Trace Theory |
| **PFC** | Prefrontal cortex |
| **PRP** | Plasticity-related protein |
| **SCT** | Standard Consolidation Theory |
| **TGRA** | Temporally-graded retrograde amnesia |
| **TTT** | Trace Transformation Theory |
| **fMRI** | Functional magnetic resonance imaging |

## Introduction

The foundation for modern ideas of memory consolidation goes back over a century (Ribot 1882). Müller and Pilzecker (1900) provided the first experimental evidence that memories require a certain amount of time to become permanent, but other early researchers suggested that a memory trace does not simply become imprinted and fixed in its original form. Rather, it was proposed that the process is an evolving one and that with each subsequent recall or reactivation, the 'consolidated' memory is updated, eventually resulting in a modified version that is quite different from the original (Bartlett 1932). In 1903, Burnham had already summarized both the tension, and complementarity, between the two views. "*The fixing of an impression depends on a physiological process. It takes time for an impression to become so fixed that it can be reproduced after a long interval; for it to become part of the permanent store of memory considerable time may be necessary. This we may suppose is not merely a process of making a permanent impression upon the nerve cells, but also a process of association, of organization of the new impressions with the old ones*" (Burnham 1903, p. 128). This debate has dominated memory research for the past several decades, as researchers attempt to understand (1) how a memory trace forms, (2) how a memory trace changes over time, and (3) the physiological mechanisms underlying the change, or transformation, of a memory over time.

The process of consolidation is generally discussed in binary terms of (1) *cellular (or synaptic) consolidation*: rapid post-translational changes in local synapse efficiency and structural modifications of local neuronal networks in the hippocampus[1] following memory acquisition; and (2) *systems consolidation*: a prolonged process following acquisition during which the memory trace reorganizes and distributes in cortical regions beyond the hippocampus (see also Chapters by Nissen and colleagues). Cellular consolidation and systems consolidation tend to be studied separately but it is important to keep in mind that they are part of one continuous and dynamic process (see also Chapter by Genzel and Wixted).

Within the field of systems level memory consolidation, it is often said that memories 'transfer' out of the hippocampus into the cortex, or 'form representations' in certain brain regions, but researchers are often vague when defining these terms. It is unlikely that the physical substrate of a memory is transported from one brain region to another the way a piece of mail is delivered from one address to the next. So how does a memory trace that was initially dependent on the hippocampus become 'represented' in the cortex, independently of the hippocampus? How does the quality of the memory change (transform) as the trace reorganizes over time? Do the same molecular cascades that result in physical changes in the local neuronal network underlying cellular consolidation extend to systems consolidation in humans and other species? In this chapter, we address these issues, with a focus on hippocampal-cortical interactions as described by Trace Transformation Theory (TTT), and consider the degree to which evidence from the mechanistic basis of memory consolidation in rodents translates to complex human memory. Consideration of these issues will help identify questions that are still outstanding in the field of memory consolidation and transformation.

## How Does a Memory Trace Form? Mechanisms of Cellular Consolidation

For an experienced event to become stored as a long-term memory, it must form a physical 'memory trace' in the brain, in the form of synaptic connections within a set of neurons (Cajal 1894; Lorenté de No 1934; Hebb 1949, but see Gallistel and Matzel 2013). For this to occur, an experienced event must induce neuronal depolarization and an influx of intracellular $Ca^{2+}$, which initiates a downstream molecular cascade that results in transcription and translation of plasticity-related proteins (PRPs). These PRPs induce structural and functional changes in local neuronal networks, resulting in new, remodeled, or strengthened synaptic connections. Activity within these synaptic contacts leads to the development of a cell

[1]For this review, we will focus primarily on the type of memory that depends on the hippocampus for initial acquisition, including episodic memory in humans and episodic-like contextual and spatial memory in rodents.

assembly (Hebb 1949) of interconnected neurons known as a 'memory engram' (Semon 1923; Lashley 1950; Schacter et al. 1978; see Dudai 2012; Tonegawa et al. 2015; Josselyn et al. 2015 for review). These changes, which occur within minutes to hours of an experience, require a period of quiescence in order to stabilize. Interruption of this process via protein-synthesis inhibition, or interference from new learning events, can disrupt the stabilization process, leading to incomplete consolidation.

One specific transcription factor, cyclic-AMP response element binding protein (CREB), has been characterized as an essential 'memory gene' (Bourtchuladze et al. 1994) regulating the expression of many PRPs implicated in cellular consolidation, including growth factors, structural proteins, signal transduction proteins, and other transcription factors (see Alberini 2009; Sekeres et al. 2012b; Kandel et al. 2014 for review). The threshold for late-phase long-term potentiation (L-LTP), the electrophysiological correlate of long-term memory (Bliss and Collingridge 1993), is lowered in the presence of elevated CREB activity (Lonze and Ginty 2002). The enhanced neuronal excitability and plasticity induced by CREB-mediated transcription produces structural changes in neuronal morphology of activated cells, including growth of dendritic spines (the site of excitatory synaptic neurotransmission) (Barco and Marie 2011), and the formation of new synaptic connections (Martin and Kandel 1996). Prevention of these processes in the hippocampus during the post-acquisition phase disrupts subsequent consolidation at a systems level (Restivo et al. 2009b; Vetere et al. 2011; Cole et al. 2012). Conversely, enhancing the intrinsic excitability and availability of CREB in the CA1 or the dentate gyrus of the hippocampus allows for memory consolidation, even under weak learning conditions that do not otherwise support memory formation (Restivo et al. 2009a; Sekeres et al. 2010, 2012a).

For a weakly encoded memory to undergo cellular consolidation, it must be supported by de novo protein synthesis (Davis and Squire 1984). Due to the high intrinsic excitability and plasticity induced in neurons with elevated CREB function, enhancing intracellular CREB levels may similarly promote consolidation of a weakly encoded memory by artificially increasing the availability of PRPs during the post-encoding consolidation window (Barco et al. 2002). The synaptic tagging and capture hypothesis (Frey and Morris 1997, 1998) makes predictions that are consistent with these observations. It proposes that a weakly potentiated synapse can capture available PRPs produced by subsequent strong inputs to a nearby synapse. These newly available proteins provide the necessary plasticity factors required for synaptic remodeling and cellular consolidation of memories in the hippocampus (Wang et al. 2010; for review see Wang and Morris 2010). Similar phenomena, presumably dependent on the same underlying processes, have been observed in humans. Dunsmoor et al. (2015) showed that memory for neutral objects was enhanced if other objects from the same category were later paired with shock. This retroactive enhancement was observed only for weakly encoded items, and then only after a period of consolidation.

Together, these findings highlight the critical role of CREB in hippocampus-dependent memory consolidation. Similar enhancements have been

demonstrated in multiple brain regions in rodents, including the amygdala (Josselyn et al. 2001), insular cortex (Sano et al. 2014), and the retrosplenial cortex (Czajkowski et al. 2014). The high intrinsic excitability and plasticity induced in neurons with enhanced CREB function are thought to bias the selection of these neurons for memory encoding (Han et al. 2007). According to the memory allocation paradigm proposed by Silva et al. (2009), items presented in close succession may be encoded by overlapping populations of neurons. Due to the high excitability induced by the initial consolidation phase (Zhou et al., 2009), a subsequently presented item or context is likely to re-activate a large subset of this same population of excitable neurons, and thus, be linked during retrieval (Silva et al. 2009; Rogerson et al. 2014; Cai et al. 2016).

The neuronal allocation phenomenon may partially account for the temporal contiguity effect observed in humans, in which items experienced in close temporal proximity to each other during memory acquisition tend to be bound together at retrieval (Landauer 1975; Moscovitch 1992; Howard and Kahana 1999; Sadeh et al. 2015; see Davachi and DuBrow 2015 for review). Intracranial recordings from within the medial-temporal lobe revealed neuronal coding of temporal links between events and their reinstatement at retrieval (Gelbard-Sagiv et al. 2008; Paz et al. 2010; Manning et al. 2011). Together, this evidence supports the idea that an overlapping population of neurons may be recruited during encoding of contiguous items.

The protein synthesis-dependent processes observed in rodents may underlie human memory consolidation but, due to limitations in studying this phenomenon in vivo, cellular consolidation is not well characterized in humans. One functional magnetic resonance imaging (fMRI) study of episodic memory (Ben-Yakov and Dudai 2011) suggests that the immediate post-encoding period shows a spike in hippocampal activity following the offset of a short movie clip. These investigators proposed that the increase in hippocampal activity reflects the initiation of synaptic consolidation for the event, similar to that seen in hippocampal replay in rodents following spatial learning (Foster and Wilson 2006). Presenting stimuli during this phase interferes with the purported consolidation process and leads to poorer subsequent memory. This interpretation, however, is difficult to assess due the poor spatial resolution of fMRI, and the sluggish hemodynamic response underlying neural activity.

Another limitation in extending the cellular consolidation literature to human memory processing is that investigations of cellular consolidation in rodents typically involve single trial learning, such as tone or context fear conditioning, or conditioned taste aversion. One exception is spatial learning which occurs over multiple spaced trials. These types of learning are unlike those used in most human memory experiments, which typically involve many different trials in rapid succession, leaving no time for cellular consolidation processes to occur for individual trials. If a similar consolidation process occurs in humans, it is unlikely that the temporal dynamics would be so rapid that each item or trial within a multi-trial acquisition session undergoes its own consolidation process. From this perspective, the subsequently presented information could actually be seen as interfering stimuli

that render it difficult for any information to become consolidated at all. Similarly, in everyday life, humans rarely have an opportunity to rest quietly in the absence of any other stimuli while a newly acquired memory undergoes cellular consolidation and stabilizes. Despite this reality, somehow we manage to form strong and long-lasting memories. Precisely how this is accomplished in humans remains unclear.

One hypothesis relates to the architecture of the hippocampus. The hippocampus is thought to encode items in sparse, orthogonal synaptic connections which allow for unique representations (pattern separation) of distinct memories (Leutgeb et al. 2007; Bakker et al. 2008). Sadeh et al. (2013, 2016; see also Hardt et al. 2013) recently proposed that episodic memories that maintain a 'recollective' quality, are represented in such a way in the hippocampus, and as a result, are relatively resistant to interference from subsequently presented items. Information that is not represented in this manner, such as familiarity-based memories, will be more susceptible to interference. Familiarity-based memories, which are thought to be represented in the perirhinal cortex, lack the pattern separation capabilities of those controlled by the hippocampus. As a result, a subsequently presented similar item may activate the same synaptic contacts, resulting in disruption of the previously acquired item and its recall. Consistent with this view, memory loss in patients (Winocur and Weiskrantz 1976) and in animals (Winocur and Mills 1970; Winocur et al. 2012) with hippocampal dysfunction is exacerbated under conditions of high interference.

## How Does a Memory Trace Change Over Time? Reorganization and Distribution of the Memory Network

Systems consolidation is well studied in rodents and humans, but our understanding of the physiological mechanisms underlying this gradual process is limited. As noted above, the dynamic cellular consolidation process occurs within a narrow window following memory acquisition. Once this window closes, the memory trace stabilizes and is less susceptible to protein synthesis inhibition, pharmacological disruption, or interference from new learning (Nader and Hardt 2009). The memory trace then transitions into a much more prolonged process of systems consolidation, in which it begins to form new synaptic connections within neuronal networks throughout the brain (distributed memory traces) (Dudai 2012).

Leading modern theories of memory consolidation agree that the hippocampus and cortex both form traces upon memory acquisition (McClelland et al. 1995; Nadel and Moscovitch 1997; Squire 2004; Winocur and Moscovitch 2011). Where they differ is in whether the hippocampus has a continuing role in memory storage and retrieval as the cortical traces are consolidated over time. They also disagree on the nature of information represented within the cortical traces. For example, declarative memories, that can be consciously and explicitly recalled, are viewed

differently in discussions of memory consolidation. Declarative memory is traditionally subdivided into episodic (memory for a unique event occurring within a precise spatio-temporal context) and semantic (fact-based information related to an event, but lacking precise contextual details) components (Tulving 1972).

The Standard Consolidation Theory (SCT) treats both episodic and semantic memories equivalently in this regard. According to SCT, the hippocampus plays a time-limited role in the temporary storage of declarative memory (Squire 2004). Initially, memory is primarily supported by the hippocampus, but over time, the memory reorganizes and forms new traces in the cortex (see Chapter by Genzel and Wixted). As cortical representations strengthen, hippocampal involvement weakens. Eventually, the memory disengages from the hippocampus, and is represented, in its original form, in cortex (Alvarez and Squire 1994; McClelland et al. 1995; Frankland and Bontempi 2005). Early support for this position came from lesion studies of human medial temporal lobe (MTL) patients (Scoville and Milner 1957), monkeys (Zola-Morgan and Squire 1990), and rodents (Winocur 1990; Kim and Fanselow 1992; Squire 1992). Across species, a pattern of temporally-graded retrograde amnesia (TGRA) was observed in which memories acquired long before hippocampal damage were preserved, while memories acquired just prior to hippocampal damage were lost.

Upon further inspection, investigators noted that the preserved remote memories following MTL damage were qualitatively different from similarly aged memories in individuals with intact hippocampi (Nadel and Moscovitch 1997; Fujii et al. 2000; Corkin 2002; Rosenbaum et al. 2000, 2005). Surviving memories were more semantic in nature, and lacked perceptual, temporal, and contextual details—qualities that allow an individual to mentally re-experience a memory. There is a large body of neuropsychological evidence for TGRA for semanticized or schematic memory in MTL amnesic patients. Older semantic memories tend to be retained following MTL damage, but detailed autobiographical episodic memories tend to be lost regardless of how long ago they were formed. This suggests that the hippocampus is not required for the storage and retrieval of semantic memories (Steinvorth et al. 2005; St-Laurent et al. 2009).

The dissociation between preserved remote semantic memory and temporally extensive amnesia for episodic memory cannot be explained by SCT. In an attempt to reconcile shortcomings of SCT, Nadel and Moscovitch (1997) proposed the Multiple Trace Theory (MTT). This position holds that cortical memory traces are extractions of common elements, from repeated activations over time, which become integrated into existing schematic knowledge networks. Memory reactivations also allow for the formation of multiple, distributed traces of the precise contextual and perceptual details of the memory in the hippocampus. These details continue to depend on the hippocampus for their storage and retrieval.

Expanding upon MTT, Moscovitch (2007), Winocur and Moscovitch (2011) developed the Trace Transformation Theory (TTT), in which they theorized that the cortical version of the memory that develops over time is an extraction of the schematic, or gist-like features of the memory (see also Chapter by Cheng). As schematic memories lack many of the unique contextual and perceptual details

of the original experience, they may be recovered without the hippocampus. To retrieve episodically detailed information, however, the hippocampus is thought to be required, regardless of the age of the memory. Critically, TTT holds that, in the intact brain, the detailed, hippocampus-dependent version of the memory, and the generalized or semanticized cortical version of the memory, can co-exist. The original memory and the transformed memory representations are in dynamic flux or interaction, and the conditions at retrieval influence which version of the memory is expressed. If the schematic version is sufficient to support retrieval in a given situation, the cortical version will be engaged. If retrieval of more intricate contextual details is required, the hippocampus is recruited, but the cortical version may still be engaged. Thus, the *nature* of the targeted memory mediates the reliance on the hippocampus over time. Data from our group support this idea in both healthy humans and rodents (Sekeres et al. 2015, 2016b) in which recently acquired, perceptually detailed episodic memories (or context-specific memories in rodents) highly engage the hippocampus. As the memory ages and loses specificity and detail, hippocampal activity declines. Under these conditions, areas in the medial prefrontal cortex (mPFC) become increasingly active, suggesting a shift towards cortical activity as the memory generalizes (see also Chapters by Fernandez and by Genzel and Battaglia). In line with the predictions of TTT, as long as the retrieved memory retains perceptual detail (or context-precision in rodents), the hippocampus continues to be similarly active at both recent and remote time points.

Parallels to this pattern are found in the animal literature. As in MTL patients, rodents with hippocampal lesions show TGRA for context memory (episodic-like memory). Lesions performed soon after acquisition (i.e. 1 day) abolish the recently acquired memory, whereas hippocampal lesions performed long after acquisition (i.e. 1 month) spare the remote memory (Kim and Fanselow 1992). Similar to humans, when the retrieved memory was probed, it became clear that the hippocampus-independent version of the memory was qualitatively different from one that involves the hippocampus. When tested at short delays, control rats expressed fear memory in the original context, but not in a novel context (Winocur et al. 2007), whereas lesioned rats did not express the fear memory in either context; at long delays, however, lesioned rats exhibited fear in both contexts, suggesting that the memories at each delay differed fundamentally from each other. This observation (see also Wiltgen and Silva 2007; Goshen et al. 2011; Einarsson et al. 2014), led to the proposal that the hippocampus-independent version of the memory is a generalized memory which lacks context-specificity. Interestingly, Winocur and colleagues observed that control animals also exhibited this generalized memory when tested in the novel context after a long delay.

There are indications in the literature that the context-specific memory may co-exist with the transformed generalized memory. For example, Winocur et al. (2009) used a reactivation paradigm (i.e. briefly replacing the rat back in the conditioning chamber) to show that a stable consolidated memory may be returned to a labile state during which it is susceptible to disruption (see also Nader et al. 2000; Sara 2000; Debiec et al. 2002; see also Chapter by Kessler, Blackwell and Kehyayan). Winocur et al. (2009) found that the brief reminder experience

reinstated (1) context-specificity and (2) hippocampal-dependency to the fear memory. Following reactivation, lesions to the hippocampus abolished memory for the fear response in both contexts, but did not impair retrieval of a non-reactivated remote memory, suggesting that the cortical representation of the memory continues to support retrieval of the remote memory. Together, these observations were taken as strong support for the notion within TTT that the context-general, hippocampus-independent memory dominates at a remote time point, but the context-specific memory continues to remain represented in the hippocampus. The latter can be re-engaged following reactivation, suggesting the two representations can co-exist. These findings, it should be noted, are not compatible with SCT, which argues that once represented in the cortex, the memory can no longer be returned to a hippocampus-dependent state.

Studies of rodents point to the anterior cingulate cortex (aCC) of the mPFC as a region that is involved in remote memory (Bontempi et al. 1999; Restivo et al. 2009b; Einarsson and Nader 2012). Increased expression of the immediate early gene (IEG) c-Fos, a commonly used marker of neuronal activity, (Greenberg and Ziff 1983) is observed in the aCC following retrieval of remote context memory. Conversely, inactivation of the aCC at a remote time point results in decreased freezing during context memory testing (Frankland et al. 2004), and decreased IEG expression in the aCC (Goshen et al. 2011). Interestingly, Einarsson et al. (2014) found that pharmacological inactivation of both the aCC and the hippocampus disrupted retrieval of the context memory, whereas inactivation of either aCC or hippocampus alone did not impair retrieval, suggesting that, at the remote time point, either structure can support the memory representation. Together these findings suggest that contextually-detailed memories continue to rely on the hippocampus, whereas over time a generalized memory trace develops in the aCC which can also support memory retrieval under certain conditions.

In humans, as in rodents, damage to the mPFC impairs episodic memory. There is no evidence, however, to suggest that it affects remote memories more than recent ones, though no-one has investigated this systematically. Deficits also extend to semantic memory, as might be expected if the mPFC is implicated in representing gist and schemas. Here, too, there is some dispute as to whether episodic memory is affected more than semantic memory (Gilboa et al. 2002; Dalla-Barba and La Corte 2015). Damage to mPFC in humans, however, does not lead merely to a loss of memory as one might infer on the basis of animal studies, but also to confabulation, a severe form of memory distortion in which the individual reports patently false memories, without any intention to deceive (Moscovitch 1989, 1995a, b; Gilboa et al. 2002; Nieuwenhuis and Takashima 2011; Hebscher et al. 2015). There is debate in the literature as to the nature of the deficits underlying this disorder, but a storage failure is not among the leading candidates (Ghosh et al. 2014). Instead, the deficits seem to result from corrupted or over-inclusive schemas which impair memory encoding and search, likely combined with poor monitoring of retrieved memories, resulting in failure to satisfy the criteria or goals of the memory task (Moscovitch and Winocur 2002; Gilboa et al. 2006; Ciaramelli and Ghetti 2007;

Moscovitch et al. 2016). These deficits may also impair the individual's ability to inhibit competing memories that are not relevant for the task at hand (Schnider 2008).

Reconciling the human studies with the rodent data, the most parsimonious explanation is that mPFC is implicated in processing or representing schemas, which guide perception, memory encoding and retrieval, and also provide a template against which retrieved memories can be compared to ensure that only plausible responses are emitted. Although in humans, damage to such a mechanism can manifest itself as confabulation, in non-humans, lacking verbal report, the deficit will just be one of impaired memory. In both cases, the deficit will appear when memory search and retrieval are primarily schema-dependent and strategic. When cues are sufficiently strong to specify the target memory, no deficits will be evident. This explanation may account for the relatively good performance on recognition or cued recall tasks under some conditions in humans, and on recently learned tasks in rodents, where the cues or contexts are at their most potent and specific, as compared to when the memory is more distant (Moscovitch et al. 2016).

## A Case for the Transformation of Spatial Memory

Since O'Keefe and Nadel (1978) published their seminal book "The Hippocampus as a Cognitive Map", one type of spatial memory was postulated to depend on the hippocampus's ability to form and maintain a cognitive map, namely an allocentric (viewpoint-independent) representation that captured the configuration of the environment (O'Keefe and Nadel 1978; Morris et al. 1982; Morris 1984). Spatial memories that are non-allocentric, but dependent on egocentric coordinates, routes or specific landmarks, could be formed and retained without the hippocampus.

Given the wealth of evidence supporting cognitive map theory, it was surprising to discover that, with sufficient time and practice since acquisition, humans with hippocampal damage exhibit accurate allocentric spatial memories of familiar neighborhoods. This observation was first noted in MTL lesion patients with extensive episodic memory impairment (Milner et al. 1968; Zola-Morgan et al. 1986; Beatty et al. 1987; Teng and Squire 1999; Rosenbaum et al. 2000; Corkin 2002). Patients could navigate normally in their neighborhoods and pass tests of mental navigation that were diagnostic of cognitive maps, such as finding the next shortest route to a goal when the shortest one was blocked, or the shortest route "as the crow flies" between two locations (vector mapping). Navigation along major routes was normal, though it was impaired along smaller, side streets (Maguire et al. 2006). They could even draw accurate maps of their neighborhoods and floor maps of their homes (Beatty et al. 1987), though they were not as detailed as those of controls (Rosenbaum et al. 2000, 2004). Later, functional neuroimaging studies of healthy young adults corroborated the conclusion that performance on these tests of mental navigation did not activate the hippocampus if the memory was acquired over a year ago and had become a familiar environment, but did activate the

hippocampus if the memory was more recent (Rosenbaum et al. 2005; Hirshhorn et al. 2012). Further investigation suggested that this preserved spatial ability relied on a schematized topographical representation, not unlike a skeletal cognitive map, that could be supported by extra-hippocampal representations. Detailed, perceptually-rich internal representation of the environment, even if acquired long ago, continued to require the hippocampus (Rosenbaum et al. 2000, 2004; Hirshhorn et al. 2012).

This way of thinking about remote spatial memory in humans was consistent with novel findings of spared remote spatial memory in rodents with hippocampal lesions. Winocur and colleagues reared rats in a 'village' environment for several months prior to lesioning the rats' hippocampus. Such prolonged pre-morbid experience allowed for the development of a map of the environment from multiple perspectives, similar to the way individuals learn the layout of their home and neighborhood. Hippocampal lesions performed after the development of this map did not impair the rat's ability to navigate along highly familiar routes in the village (Winocur et al. 2005b). This paralleled the finding in MTL lesion patients. When major spatial cues within the environment were re-configured, or when previous routes were blocked, however, lesioned rats exhibited significant spatial memory impairments. This suggests that rodents were relying on a schematic representation of the environment that differed from that of controls; they lacked a detailed, cohesive allocentric representation which would allow them to adapt and re-map to accommodate changes in the environment (Winocur et al. 2010). Together, these findings support the idea that both contextually-detailed and schematic components of spatial memory may develop for well-learned spatial environments, and support the position that spatial memory undergoes a similar transformation as other episodic memories during systems consolidation. In line with TTT, non-transformed spatial memories always depend on the hippocampus, and a result, remain vulnerable to disruption following hippocampal damage (Winocur et al. 2005a, 2013). Despite the similarities with respect to detail, there is a discrepancy between the human and animal findings in that humans with hippocampal lesions, unlike rats, seem able to adjust better to spatial changes, such as blocking routes. Future research will determine whether the nature of the underlying extra-hippocampal representation differs between rats and humans, or whether this difference in performance arises because humans' greater intelligence enables them to compensate better than rats in operating on an impoverished, and fundamentally different, representation than the one mediated by the hippocampus.

IEG expression studies in rodents showed that the aCC emerges as a key extra-hippocampal region supporting remote spatial memory (Bontempi et al. 1999; Frankland et al. 2004; Maviel et al. 2004; Teixeira et al. 2006). Reports of reduced hippocampal activity in rodents during remote spatial memory retrieval was initially taken as support for SCT (Frankland and Bontempi 2005). Recent evidence, however, is consistent with the TTT as indicated above. The evidence suggests that the remote spatial memory that is represented is different from the initial memory represented in the hippocampus; by comparison to the detailed memory in the hippocampus, the memory that develops in the mPFC is more schematic (Tse et al.

2007, 2011; Richards et al. 2014). As with context memory, it is not a 'transfer' of the memory trace that takes place, but rather, the development of a distributed network in the cortex consisting of multiple traces of the schematic elements of the spatial memory which, in the absence of the hippocampus, can support retrieval of the schematic spatial memory.

Studies of the effects of mPFC lesions on spatial memory in humans are rare. In the one reported study, participants were asked to travel from one familiar location to another, but erred in doing so, and sometimes got lost. The deficit seems to have arisen from an inability to keep distracting or intruding spatial information at bay, such as following inappropriate routes triggered by cues in the environment while navigating to a destined location, rather than from a loss of remotely learned spatial information (Ciaramelli 2008). As result, the patient is sidetracked from the intended path.

## Evidence for Systems Consolidation and Memory Transformation in the Healthy Rodent Brain

The fact that context-specificity of a memory and hippocampal dependence can be restored by reminders speaks to the dynamic interaction between the hippocampus and extra-hippocampal structures in memory retention and retrieval. It also suggests that some vestige of the original specific memory is likely retained by the hippocampus, and contributes to remote memory performance. Evidence in support of this interpretation comes from investigations using fast temporal and precise spatial resolution to identify engram cells thought to be the physical storage site of a specific memory (Tayler et al. 2013; Denny et al. 2014; Josselyn et al. 2015; Tonegawa et al. 2015). Previous studies with rapid optogenetic inactivation of tagged engram cells suggest that the hippocampus may be the default retrieval structure, but when it is unavailable, the cortical version of the memory is expressed (Goshen et al. 2011). These studies provide strong support for the idea that, in the healthy brain, a specific context memory may continue to be supported by specific cell assemblies. Although, over time, the memory network may reorganize and distribute in the cortex, activation of the original cell assembly can result in expression of the context memory (Goshen et al. 2011; Liu et al. 2012; Ramirez et al. 2013). While these cells continue to play a critical role in the storage and retrieval of the memory, stimulation of these cell assemblies alone likely does not activate the entire memory trace. Rather, stimulation may induce activity in other parts of the network, which together support retrieval of the memory.

Recent evidence in mice supports this position. Using an inducible transgenic mouse model, Denny et al. (2014) were able to tag hippocampal neurons active during acquisition of a context fear memory. Selectively silencing, via optogenetic inhibition, this neuronal network at the time of remote memory retrieval abolished the freezing response, indicating impaired memory for the conditioning context (Denny et al. 2014). In light of the previous discussion regarding distributed

memory representations, it is puzzling that the extra-hippocampal neuronal assembly would not be sufficient to support retrieval of the context memory in the absence of the hippocampal engram cells. These results suggest that in the healthy brain, rapid inactivation of a normally functional part of the memory network disrupts the coordination of the entire network. In the case of hippocampal lesions, or slow-acting pharmacological inhibitors, the long temporal lag between inactivation and retrieval may allow the network sufficient time to adapt and to compensate for the hippocampal disruption (Goshen et al. 2011). From this perspective, so long as it exists, the original hippocampal neuronal assembly formed during encoding may be the default region which coordinates the rest of the memory network, supporting retrieval of the original, detailed version of the memory (Lee et al. 2016). When this original neuronal assembly is no longer accessible, if the brain has sufficient time to compensate, other components of the memory network can come online to support retrieval. The retrieved version, however, may be a more generalized representation.

## Limitations to Rodent Models of Memory Consolidation

To date, few studies have attempted to characterize the brain-wide remote memory network in rodents (Bontempi et al. 1999; Wheeler et al. 2013). Studying the mechanistic basis of consolidation in animals using IEG expression as a marker of neuronal activity is a time-consuming and labor intensive process, and therefore it is more practical to study changes at the neuronal level within a limited number of regions (but see Vousden et al. 2015 and Ye et al. 2016 for novel brain-wide imaging approaches). Importantly, in the analyses reported in these papers, the hippocampus emerges as a crucial hub linking several regions even when the memory is remote. While the mPFC is a major hub in the remote memory network, in rodents, it is only one node of a larger retrieval network involving regions, including the hippocampus and posterior cingulate cortex, that have been identified in the human recollection network (Rugg and Vilberg 2013; Wheeler et al. 2013). Further research is needed to understand how damage to key nodes of this network changes activity and functional connectivity during recent and remote memory retrieval (see Vetere et al. 2015 for preliminary investigation silencing key nodes of the rodent functional connectome). Although novel gene expression techniques, in vivo $Ca^{2+}$ imaging, and high resolution fluorescence microscopy in rodent models provide valuable insight into neural dynamics of consolidation, they are limited in their ability to visualize brain-wide changes in activity over *multiple retrieval events within the same animal*. fMRI approaches in humans allow us to overcome this drawback, and emphasize the importance of considering changes in the overall retrieval network over time. This approach also allows for a more nuanced investigation of changes to the quality of memory as remote memory networks reorganize.

## Evidence for Systems Consolidation and Memory Transformation in the Healthy Human Brain

Prior to the development of intact brain neuroimaging, our knowledge of the role of the hippocampus and the mPFC in human memory was based largely on loss-of-function lesion studies in patients. As noted earlier, beginning with H.M., studies of the effects of MTL lesions suggested that remote memories were spared, but memories acquired just before the lesion and subsequent to it were impaired (Scoville and Milner 1957; Penfield and Milner 1958). More careful observation indicated that only semantic memories and gist-like memories of autobiographical events followed that pattern, whereas richly-detailed, episodic memories were impaired across the lifetime (Sanders and Warrington 1971; Nadel and Moscovitch 1997; Moscovitch et al. 2005, 2006, 2016). These findings in patients, however, are complicated by the fact that damage often extended to adjacent medial temporal regions (Squire and Bayley 2007; Squire and Wixted 2011), contributing to the debate over the continuing role of different MTL regions in remote memory.

Modern functional neuroimaging techniques allow the use of multivariate analyses to identify changes in brain-wide patterns of activity underlying memory encoding and retrieval over time. In the healthy individual, hippocampal activity declines after 1 week as episodic memory recollection fades (Viskontas et al. 2009), but remote autobiographical episodic memories which retain their vividness and perceptual detail continue to be associated with high hippocampal activity (Addis et al. 2004; Gilboa et al. 2004; Sheldon and Levine 2013). Vividly retrieved remote autobiographical memories are also correlated with increased activation of prefrontal cortical regions, particularly the ventromedial prefrontal cortex, supporting it as a candidate region for remote episodic memory processing in humans (Bonnici et al. 2012). Testing autobiographical memory is a valuable way of assessing the nuanced quality of human memory, but verifying the accuracy of memory details remains a problem. To address this limitation, researchers have used functional neuroimaging during encoding and retrieval of film clips of everyday events (Ben-Yakov and Dudai 2011; St-Laurent et al. 2014, 2016) as a means of inferring how brain networks change as the quality of naturalistic episodic memory changes over time (Furman et al. 2012; Sekeres et al. 2015, 2016b). This approach retains control over the conditions during encoding, as well as the ability to assess the accuracy of memory content.

Behavioral studies have confirmed that perceptual, contextual, and central schematic elements that together make up human episodic memories decline at different rates over time, with perceptual and contextual details declining more rapidly (Thorndyke 1977; Bahrick 1984). As the hippocampus is critical for the representation of those perceptual and contextual details, our group used memory for film clips to determine how the network of brain activity changes as different elements of episodic memory are lost over time (Sekeres et al. 2016a). A fMRI study of healthy young adults revealed how the retrieval network reorganizes as the quality and content of memory for events in the film clips changes (transforms) over

the course of one week. In line with the predictions of TTT, we found that (1) immediately after encoding, retrieval of perceptually-detailed memory for events in the film clips highly engaged the hippocampus; (2) memory for perceptual details declines over time, whereas memory for the central story elements is retained. This is accompanied by a reduction of hippocampal activity and an increase in mPFC activity during retrieval of the 7 day old memory; (3) vivid and perceptually detailed retrieval of the film clips highly engages the hippocampus at both immediate and 7d delayed time points. Vivid retrieval of the 7 day old memory, however, was also supported by strong activity in the mPFC, consistent with the idea that the memory becomes distributed and supported by a cortical network over time, but also continues to depend on the hippocampus for retrieval. It remains unclear if the mPFC is playing a supportive or redundant role during retrieval of the vivid memory. These results provide further support for the idea that both the hippocampally-dependent detailed version of a memory, and the cortically-dependent schematic version can co-exist (Sekeres et al. 2015, 2016b). In the latter regard, the evidence is consistent with that obtained in rodents. It may be that these parallel representations interact with each other when intact, but also build in compensatory representations that can be accessed by different cues and can operate under different task demands.

Dudai and colleagues used a short documentary to test time-dependent changes in the quality of naturalistic episodic memory. In line with our findings, they found that the hippocampus continued to be recruited during accurate recall of memory details in the weeks and months following encoding; as recognition accuracy for events in the film decreased over time, hippocampal activity also decreased, though accuracy was still correlated with the extent of hippocampal activation (Mendelsohn et al. 2010; Furman et al. 2012). Together, these findings provide converging evidence for the time-dependent reorganization of the memory network which shifts towards frontal activity as the memory ages and loses precision. The quality, rather than the age, of the retrieved memory appears to mediate hippocampal engagement.

## What Are the Mechanisms of Systems Consolidation?

Investigations over the past several decades have significantly advanced our understanding of the molecular mechanisms supporting cellular consolidation (Kandel et al. 2014). Comparatively little work of this nature has focused on mechanisms underlying systems consolidation, and remodeling of the distributed memory network.

One mechanism possibly implicated in remodeling is reconsolidation, a process, as described above, in which memory reactivation makes the memory trace temporarily labile, and vulnerable to disruption or alteration, and in need of further consolidation (re-consolidation) if it is to be retained (Misanin et al. 1968, Nader et al. 2000; Sara 2000). The few available studies in rodents suggest that

similar molecular mechanisms are involved in this process as in initial consolidation. Debiec et al. (2002) were the first to demonstrate that remote memory undergoes a similar protein-synthesis dependent systems reconsolidation process in the hippocampus. Here, an infusion of the protein-synthesis inhibitor anisomycin into the hippocampus following reactivation of a remote context memory disrupted the restabilization of the memory, and abolished freezing when re-tested in the context. In the absence of reactivation, however, anisomycin had no effect on the subsequent retrieval of the context memory.

Several recent studies involving rodents have investigated the possibility of *enhancing* systems consolidation and using the same PRPs that boost cellular consolidation. Shema et al. (2011) found that virally increasing PKMζ, a protein implicated in the maintenance of LTP (Ling et al. 2002), in the insular cortex 6 days after conditioned taste aversion training (at a time when the window for protein-synthesis dependent cellular consolidation has closed) enhanced subsequent memory even though the memory had not undergone reactivation. It is surprising that, in the absence of direct reactivation, increasing PKMζ would enhance the retrieval of a consolidated memory; it is possible, however, that enhancing cortical plasticity at this time facilitated systems consolidation, which is presumed to be an ongoing process that, over time, continues to form multiple memory traces in the cortex.

To directly test how enhancing PRPs during initial consolidation may have enduring effects on systems consolidation, Sekeres et al. (2012a) virally over-expressed the transcription factor CREB in the dentate gyrus of the mouse hippocampus prior to context fear conditioning. This served to potentiate plasticity during the initial cellular consolidation phase. One month later, the memory was tested in the original context, and in a novel context. Importantly, using this transient viral expression technique, CREB levels were elevated during memory acquisition (within the window for cellular consolidation), but had returned to basal endogenous levels several days later. When tested one month later, mice conditioned with high hippocampal CREB continued to show robust, context-specific memory, suggesting that increasing plasticity during acquisition facilitated the cellular consolidation of the context memory. It is likely that these neurons were re-engaged during remote memory testing, leading to the retrieval of persistent, context-specific remote memory.

This finding does not argue against the development of schematic, or context-general memory traces in the cortex, but suggests that the hippocampus-dependent version of the memory dominates at retrieval. Similarly, in line with Debiec et al.'s report (2002) of protein synthesis-dependent systems reconsolidation, over-expression of CREB in the hippocampus just prior to reactivation of a remote context memory enhanced reconsolidation of context-specific fear memory. This suggests that not only can a reminder bring a generalized remote memory back to a hippocampus-dependent, context-specific state, but the same molecular mechanisms underlying initial cellular consolidation also support systems consolidation and reconsolidation. Future studies are needed to determine the downstream effects (i.e. synaptic remodeling) that support this facilitation of systems consolidation.

In the absence of explicit retrieval or reactivation, which may re-initiate synaptic consolidation or reconsolidation processes throughout the brain, how does a physical trace of a memory form in the cortex? One proposed mechanism is the 'active consolidation in sleep' hypothesis. This position proposes that offline hippocampal reactivation or replay during slow wave sleep or rest (Diekelmann et al. 2011; see Atherton et al. 2015 for review) results in multiple traces distributed throughout the hippocampus and cortex. This replay or reactivation initiates new waves of synaptic consolidation that gradually support physical changes in the morphological neuronal network structure (including dendritic growth and the formation or remodeling of dendritic spines). It also promotes changes in synaptic strength and efficiency in neurotransmission within the cortical neuronal networks. Consistent with TTT, studies in humans suggest that these sleep-dependent changes can be accompanied by a transformation of the initial memory trace from one that is context-specific to one that is more schematic, retaining the gist but not the context (Cairney et al. 2011; Lewis and Durrant 2011, see Chapters by Schönauer and Gais as well as Rauss and Born).

These ongoing or recurrent waves of synaptic consolidation can be considered 'subroutines of systems consolidation' (Dudai 2012; Dudai et al. 2015), and require that the memory be reactivated in order to undergo systems consolidation across a distributed network. Accordingly, not all memories will undergo systems consolidation or transformation. A memory that is never, or rarely, reactivated will not have undergone sufficient waves of synaptic consolidation to allow the formation of multiple distributed traces in the cortex. This is not to say that a memory undergoes the synaptic consolidation process every single time it is reactivated or replayed, as there are boundaries limiting the conditions that will initiate the reconsolidation process, such as novelty, and the strength and the age of the memory (Dudai 2012; Finnie and Nader 2012), as well as the context in which the memory is reactivated (Hupbach et al. 2008).

This explanation does provide an attractive mechanism for MTT and TTT, and is also in line with the growing evidence that memories, especially contextually-bound memories, continue to be represented in their original neural ensembles. This does not argue against the parallel development of other traces in mPFC (see also Chapters by Fernandez as well as Genzel and Battaglia). These cortical traces are likely not randomly formed, but rather, integrate into existing schematic memory networks represented in the mPFC, updating the general knowledge network. Accordingly, newly acquired memories that are consistent with existing schemas may be rapidly consolidated in the mPFC, where they may be supported independently of the hippocampus (Tse et al. 2007; van Kesteren et al. 2012, 2013; Richards et al. 2014; Ghosh and Gilboa 2014).

Studies on reconsolidation in humans are few, and predominantly behavioral, though the results have neurobiological implications and are consistent with the above hypotheses (see Chapter by Kessler, Blackwell and Kehyayan). Schiller and her colleagues (2010) have shown that reactivating a fear-conditioned response can promote extinction of the fear response if the extinction procedure is administered

during a temporal window of about 6 h after reactivation, when the reactivated memory is labile.

Other studies, however, have shown that memory reactivation and subsequent reconsolidation also can lead to alteration of the existing memory trace, rather than its elimination. Hupbach, Nadel and their colleagues showed that reactivating memory for a set of objects alters that memory if another set of objects is presented shortly after reactivation. The memory for the initial items is not reduced, but the new items are incorporated into it, leading participants to (mistakenly) recall the new items along with the old. In this way, reconsolidation can serve as a mechanism for memory updating at retrieval. Importantly, Hupbach et al. (2008) noted that such updating only occurs if memories are reactivated in the initial spatial context.

Chan et al. (2009) showed that reactivating a memory of an event, makes individuals more prone to the misinformation effect, namely the incorporation of false information, delivered after the event, into an eyewitness account. Such alterations of an existing memory can occur even if the memory had been acquired days earlier (Chan and LaPaglia 2013). These observation are reinforced by studies of reconsolidation, updating, and false memory conducted by St. Jacques and Schacter (2013) using a novel paradigm in which participants toured a museum while wearing a camera that recorded the event. At test, they were presented with photos taken during their tour, along with photos taken from a different tour of the same museum. Subsequent recognition memory was better for those photos that matched highly reactivated memories, but importantly, reactivation also increased false memories of the novel photos. A follow-up fMRI study (St. Jacques et al. 2013), showed that highly reactivated true memories were associated with increased activity in the retrosplenial, parahippocampal and inferior temporal cortices. These areas are associated with contextual reinstatement, particularly involving spatial context and scene construction, and are consistent with Hupbach et al. (2008) findings. Importantly, false recognition of the novel photos was associated with activation of the anterior hippocampus and vmPFC, regions identified by TTT as implicated in memory transformation (Winocur et al. 2010; Winocur and Moscovitch 2011; Kroes and Fernández 2012).

## Timeline of Systems Consolidation

Studies in rodents and humans both point towards a reorganization and distribution of the memory network over time, but *when* and *how long* it takes these large-scale network changes to occur is uncertain. One major limitation to this field of study is the broad temporal range over which systems consolidation can occur (Varela et al. 2016). Using fMRI in humans, we see evidence that large-sale reorganization of declarative memory networks can be detected only 24-hrs following associative memory acquisition (Takashima et al. 2009; Ritchey et al. 2015), and one week following encoding of complex episodic memory for film clips (Sekeres et al. 2015, 2016b). Other naturalistic studies find that reorganization of the autobiographical

memory network follows a similar pattern extending over a much longer period of months and years (Nieuwenhuis and Takashima 2011; Maguire 2014). Moreover, if we take the time-dependent effects of damage to the hippocampus as a marker of systems consolidation, it seems that the process could last years. It is likely that the reorganization of memory networks begins early, and continues over the lifetime of the memory. This process may be dependent on memory reactivation, but there is evidence that similar network changes may be detected for very old memories that had not been recently reactivated (Bonnici et al. 2012).

In rodents, hippocampal neurons activated during context memory acquisition are reactivated when the context memory is retrieved 2 days later; however, fewer hippocampal cells show this overlap when the memory is retrieved 2 weeks later, supporting the idea of a pruning of activated hippocampal engram cells and a reorganization and broadening of the memory network over time (Tayler et al. 2013). It is likely that this two-week old memory has already begun the transformation process, and has formed traces in the mPFC. As a result, fewer of the original hippocampal neurons will be engaged as the extra-hippocampal regions mediating the reorganized memory trace become increasingly active during remote memory retrieval.

Several studies have investigated how preventing morphological modifications to memory networks at various stages during systems consolidation affects remote memory in rodents. Formation of a remote memory is associated with dendritic spine growth in the aCC, which is prevented if the hippocampus is lesioned one day after memory encoding (Restivo et al. 2009b). This suggests that the cortical plasticity supporting remote memory formation may be driven by interactions with the hippocampus occurring early in the consolidation process (Vetere et al. 2011). If spine growth is suppressed in the hippocampus, recent context memory consolidation is similarly impaired (Cole et al. 2012). There is evidence for the development and clustering of dendritic spines on pyramidal motor neurons following motor task learning (Xu et al. 2009; Fu et al. 2012), and Tonegawa and colleagues have proposed that a similar spine clustering may support the development of the engram following episodic memory acquisition (Govindarajan et al. 2006). To date, very little is known about the dynamics of plasticity mechanisms in humans, and while this spine growth and remodeling has not been studied in vivo, it suggests one potential neural mechanism supporting changes in large-scale memory networks in the human brain.

## Conclusion: Transforming the Concept of Consolidation

The term ‘consolidation’ is commonly used to describe the process by which memories become represented in the brain and available for retrieval, but it is clear from the dictionary definition of the term consolidation, ‘to make firm’, that it is a misnomer. Cellular consolidation, systems consolidation, and reconsolidation are all part of a dynamic, non-linear process. A recent review by Dudai and colleagues

proposed that consolidation is an outdated term usefully employed to describe a range of memory-related processes, but should possibly be reconsidered. "*The term consolidation… is well-rooted in the memory literature and therefore deserves not to be reconsolidated even in systems level discussion, but research… indicates that in the memory dictionary, its translation is ongoing transformation, not fixation*" (Dudai et al. 2015, pg. 28). Research in the field of memory consolidation and transformation has scratched the surface in determining how memory 'traces' are formed, transformed and 'represented' throughout the brain. The terminology and ideas behind these concepts will likely become more refined as the development of genetic technology, *in vivo* functional neuroimaging, and computational modeling advance our understanding of the mechanisms of systems level memory consolidation. Whatever these new developments reveal, it is clear that there is no returning to traditional notions that memory consolidation marks the end of hippocampal processing after memories become represented permanently in extra-hippocampal structures. Rather, theories like TTT provide a new direction for thinking about consolidation as an ongoing and interactive process in the hippocampus and mPFC, and also across broader memory networks in the brain.

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