



Review

# A unified theory for systems and cellular memory consolidation

Pramod K. Dash\*, April E. Hebert, Jason D. Runyan

*The Vivian L. Smith Center for Neurologic Research and the Department of Neurobiology and Anatomy, The University of Texas Medical School,  
P.O. Box 20708, Houston, TX 77225, USA*

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## Abstract

The time-limited role of the hippocampus for explicit memory storage has been referred to as systems consolidation where learning-related changes occur first in the hippocampus followed by the gradual development of a more distributed memory trace in the neocortex. Recent experiments are beginning to show that learning induces plasticity-related molecular changes in the neocortex as well as in the hippocampus and with a similar time course. Present memory consolidation theories do not account for these findings. In this report, we present a theory (the C theory) that incorporates these new findings, provides an explanation for the length of time for hippocampal dependency, and that can account for the apparent longer consolidation periods in species with larger brains. This theory proposes that a process of cellular consolidation occurs in the hippocampus and in areas of the neocortex during and shortly after learning resulting in long-term memory storage in both areas. For a limited time, the hippocampus is necessary for memory retrieval, a process involving the coordinated reactivation of these areas. This reactivation is later mediated by longer extrahippocampal connectivity between areas. The delay in hippocampal-independent memory retrieval is the time it takes for gene products in these longer extrahippocampal projections to be transported from the soma to tagged synapses by slow axonal transport. This cellular transport event defines the period of hippocampal dependency and, thus, the duration of memory consolidation. The theoretical description for memory consolidation presented in this review provides alternative explanations for several experimental observations and presents a unification of the concepts of systems and cellular memory consolidation.

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\* Corresponding author. Tel.: +1-713-500-5575; fax: +1-713-500-0621.

E-mail address: [p.dash@uth.tmc.edu](mailto:p.dash@uth.tmc.edu) (P.K. Dash).

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## 1. Introduction

Studies in human patients and animals have shown that explicit or declarative memory (e.g. episodic, semantic, spatial and contextual) is impaired by damage to the hippocampus [33,37]. These studies also demonstrate a time-limited role for the hippocampus in memory, which has been interpreted to indicate that the hippocampus provides a temporary storage of memory until a neocortical representation develops. The process of developing stable memory is referred to as consolidation, a phenomenon that has fascinated psychologists, biologists and clinicians for over 100 years [29]. Recently, consolidation at a systems level has been distinguished from consolidation at a cellular level [7]. Systems consolidation is the process by which memory becomes independent of the hippocampus. Cellular consolidation has been defined as the transition of memory from protein synthesis- and gene expression-dependence to independence [1,19]. A description of the mechanisms underlying the integration of cellular and systems memory consolidation would provide a better understanding of memory. In this review, we provide a short synopsis of the prominent theories for memory consolidation and present a theoretical description that unifies both systems and cellular consolidation models.

## 2. Consolidation models

In 1900, Muller and Pilzecker [21] proposed that the formation of permanent memory takes time and that, during this time, memory remains vulnerable to disruption. In 1957, Scoville and Milner [33] reported that the patient H.M., who was treated for epilepsy with a bilateral medial temporal lobectomy, showed profound amnesia for recent declarative memories with earlier memories remaining intact. The Standard Model for memory consolidation was developed in order to explain the occurrence of progressively worse amnesia for more recent memories compared to remote memories (i.e. temporally graded retrograde amnesia), following hippocampal damage as observed in patients and experimental animals. This model posits that memory is initially stored in the hippocampus using sparse non-overlapping representations. Over time, the hippocampus induces a distributed representation in the neocortex, after which the hippocampus is no longer required [15]. The time course for the development of this distributed neocortical representation is the key determinant for the duration of systems consolidation [17,18,36–38,44]. This model is

further based on experimental findings of memory interference [45]. Memories that are acquired within close temporal proximity to one another interfere with each other by competing for representational space. For example, AB–AC associative learning tasks show a decrease in retention for AB associations as AC associations are formed [2]. Consistent with this, computer modeling simulations have shown that a very rapid association between AC could drastically decrease the AB association [17,27]. Thus, models of consolidation usually incorporate different time courses for memory storage in the hippocampus when compared to cortical structures with the understanding that a gradual cortical memory storage would reduce interference [11]. This idea of a gradual development of neocortical representations provides an explanation for the time required for hippocampal independence. However, the AB–AC interference study was completed within minutes when hippocampal function is known to play a critical role in memory formation [2]. This suggests that interference can occur with competing hippocampal representations, calling into question the benefit of a gradual transfer of memory to the neocortex.

Teyler and DiScenna [43] proposed a variation of the Standard Model that states that long-term potentiation (LTP) in the hippocampus initially stores an experiential event as an index of the neocortical areas activated by this event. During memory retrieval, this hippocampal memory storage is necessary for reactivating the unique cortical areas involved in the original experiential event in the same spatio-temporal sequence. Over time, repeated hippocampal reactivation of the set of neocortical areas composing an experiential event, is proposed to be involved in establishing a cortically based memory trace that is capable of hippocampal-independent memory retrieval. Furthermore, more frequently recalled memories are stored in the cortex faster.

Another memory consolidation model, the Multiple Trace Theory (MTT), was proposed to explain observations of flat retrograde amnesia (the loss of both recent and remote memories equally) for episodic memory following hippocampal damage [23]. The MTT incorporates a key feature of the Standard Model in the idea that the hippocampal complex (hippocampus proper, subiculum, entorhinal and perirhinal cortices, and parahippocampus) rapidly encodes all information. However, the Multiple Trace Theory states that only non-episodic, or semantic information becomes hippocampal-independent over time. Episodic memory remains bound to the hippocampus. Episodic memory refers to memory of a personally experienced event, where as semantic memory refers to general knowl-

edge of the world (facts, names, etc.). According to this theory, each reactivation of a memory results in the creation of a new hippocampally stored memory trace. Over time, as more traces for a memory are created, the memory encompasses an increasingly larger hippocampal area. Therefore, a partial hippocampal lesion would not result in amnesia for older memories, but would give rise to a pronounced amnesia for recent memories. Complete hippocampal lesions would result in flat retrograde amnesia for hippocampal-dependent memories. However, animal studies have revealed that complete removal of the hippocampus in rats results in a temporally graded, rather than a flat retrograde amnesia for spatial and other hippocampal-dependent memories [40]. Consistent with this, it has been reported that patients with severe damage to the hippocampal region demonstrate a temporally graded retrograde amnesia for episodic and semantic, as well as spatial and non-spatial memory [42].

### 3. The C theory

Evidence is accumulating that molecular changes occur in the hippocampus and in the neocortex as a direct result of learning. In addition, some of these changes have been shown to be required for long-term memory. These data are not accounted for by previous consolidation theories that maintain that initial memory storage takes place solely within the hippocampus. In addition, these previous theories do not account for the apparent longer consolidation periods in species with larger brains. In contrast to the previous theories, the present C theory postulates that memory is stored simultaneously in hippocampal and neocortical areas during or shortly after learning. The initial learning event triggers genomic changes in neurons within hippocampal and neocortical areas resulting in long-term memory storage. During recall, as the hippocampus receives input from, and sends information to, many cortical

areas, it is able to serve as an initial memory coordinator for the reactivation of brain areas where components of memories are stored. The learning event also alters gene expression in the soma of cells with long projections connecting areas (cortical and/or subcortical) where components of memory are stored. These long projections will come to coordinate the retrieval of consolidated memories. However, until the gene products arrive at the synapses of these cells (which are likely to be tagged, see Box 1), the hippocampus continues to coordinate retrieval. In addition, activity in the hippocampus is required during this time perhaps to maintain the synaptic tag and/or to modify proteins as they arrive at tagged synapses. Therefore, the time required for the transport of proteins from the soma to the synapse would be proportional to the length of these longer projections, would correlate with the size of the brain, and would determine the duration of hippocampal-dependency.

The C theory we are proposing has the following features:

- (1) long-term memory is stored in parallel in the neocortex and in the hippocampus (and perhaps other non-hippocampal structures) as a result of learning.
- (2) the hippocampus serves the role of an initial coordinator for memory retrieval until longer extrahippocampal connectivity has developed the capacity to take over this role.
- (3) (a) the event defining the period of hippocampal dependency is the transport time for gene products to travel in longer extrahippocampal connections from the soma to tagged synaptic sites. (b) Through its continued activity, the hippocampus contributes to the development of this hippocampal-independent memory retrieval.
- (4) specific spatial and feature-related information remains stored in the hippocampal complex even after the period of consolidation, as suggested previously [31].

Box 1. *Synaptic tagging*: Long-lasting changes in the strength of specific synaptic connections between neurons is thought to be a mechanism for encoding long-term memories. Long-lasting forms of synaptic plasticity have also been shown to require gene expression and protein synthesis. Since genes are expressed at the nucleus in the cell soma, the signals generated at a synaptic site must be transported to the nucleus and the gene products, in turn, are transported from the nucleus to the synapse. This raises the question of how gene products can be targeted to a specific synapse(s) and not to all the synapses of a neuron. Frey and Morris [8] first showed that once long-term plasticity has been induced at one pathway in a hippocampal slice, this long-term change can be “captured” at a second pathway with stimulation that would normally produce only short-lasting changes. Using a single bifurcated *Aplysia* sensory neuron that forms synapses with two motor neurons, Frey and Morris [8] and Martin et al. [16] independently demonstrated the synaptic “capture” phenomenon which led to the formulation of the “synaptic tagging” hypothesis. This hypothesis proposes that following the induction of long-lasting plasticity at a specific synapse (called the tagged synapse), gene products are synthesized and are delivered to all the synapses of a neuron, but are incorporated into only the synapse that has been “tagged” by previous synaptic activity. In addition, since gene products are transported to all the synapses of a neuron, a weak stimulation at a previously unstimulated synapse can utilize the gene products that are already present to induce long-lasting plasticity at this second synapse.

**Box 2. Rate of axonal transport:** Gene expression occurs in the cell somata (and for some genes in the mitochondria). The synthesis of proteins also occurs mainly in the cell somata. Although translation of selected proteins does occur in dendrites (and perhaps in axons), as a result of the transport of mRNA and ribosomes, the majority of newly synthesized proteins whose functions are needed at the synapse must be transported from the cell body to the axon terminal. While large organelles are carried by fast axonal transport in a bi-directional manner, cytosolic proteins are moved along axons by slow axonal transport [47]. Slow transport occurs only in the anterograde direction from the cell body to the axon terminal. The rate of slow axonal transport consists of at least two kinetic components [12,26]. The slow component moves at a rate of 0.2–2.5 mm/day. Proteins that make up the structural elements (e.g., the cytoskeleton) travel with slow kinetics. The fast component moves at 0.4–5.0 mm/day. Proteins using this mechanism include actin, actin-binding proteins, enzymes, etc. Thus, the distance between the cell soma and the tagged synaptic site where a specific protein is required is likely to be a rate-limiting step for long-term plasticity.

These features and supporting experimental evidence are discussed below.

### 3.1. Long-term memory is stored in parallel in the neocortex and in the hippocampus (and perhaps other non-hippocampal structures) as a result of learning

Experimental findings of plasticity-related molecular changes in the hippocampus and neocortex following behavioral training support the idea of early cortical memory storage. The formation of long-term memory is dependent on both protein synthesis and gene expression [4,9]. These processes are initiated by the activation of cell signaling cascades such as the protein kinase A (PKA), the protein kinase C (PKC), calcium/calmodulin-regulated kinase (CaMKII) and the extracellular-signal regulated kinase (Erk) cascades. Trace fear-conditioning results in an immediate increase in Erk activity in the medial prefrontal cortex and an increase in Erk activity in the hippocampus at 1 h following training. Inhibition of Erk within minutes of training in either the medial prefrontal cortex or in the hippocampus blocks long-term memory for this task [32]. In addition, post-training inhibition of Erk in either the hippocampus or in the posterior parietal cortex soon after learning blocks long-term memory of a step-down inhibitory avoidance task [51,52]. Once activated, Erk translocates to the nucleus where it phosphorylates transcription factors including the calcium/cAMP response element binding protein (CREB). The phosphorylation of CREB has been shown to increase in the hippocampus, amygdala and parietal cortex shortly following fear conditioning in mice [41].

Phosphorylation and activation of transcription factors (e.g. CREB) induces the expression of downstream genes such as *bdnf*, activity-regulated cytoskeleton-associated protein (*arc*, also known as *arg 3.1*), *c-fos*, *zif-268* (also known as *zenk*, *egr-1*, *ngf-a*, *krox-24* and *tis8*) and *syntaxin1B*. The products of these and other genes are thought to be required for the formation of long-term memory. The cytoskeleton-associated protein *Arc* has been reported to be induced in both the hippocampus and parietal cortex soon after the exploration of a novel environment [50]. Furthermore, *c-fos* is induced in the hippocampus [49], retrosplenial cortex and

prelimbic cortex soon after radial maze training [48], and in the prelimbic and infralimbic areas of the medial prefrontal cortex shortly following fear conditioning [20]. These authors also demonstrated that infusions of antisense *c-fos* oligonucleotides into the medial prefrontal cortex before fear conditioning had no effect on acquisition but impaired the long-term retention of the cue-elicited fear response [20]. In addition to molecular changes, electrophysiological recordings and functional imaging studies show changes in cortical activation during the encoding and retrieval of memory [3,6,25]. These studies and others support the idea of early cortical memory storage as a result of behavioral training.

### 3.2. The hippocampus serves the role of an initial coordinator for memory retrieval until longer extrahippocampal connectivity has developed the capacity to take over this role

If long-term plasticity is occurring in parallel in the hippocampus and in the neocortex, why then is neocortical plasticity not sufficient for memory recall? As indicated above, recent experiments provide evidence that neocortical areas involved in a learning event store components of a memory soon after learning. The C theory proposes that before consolidation is complete, during recall, the hippocampus serves as a coordinator that enables the retrieval of all of the components from the different cortical areas that together constitute the memory. After consolidation, coordination of the various components of a memory is assumed by long extrahippocampal axonal projections between structures.

If the hippocampus is necessary for coordinating memory retrieval and neocortical structures store components of a memory before consolidation, then in the advent of hippocampal damage two things would be expected: (1) a loss in the ability to retrieve a memory and (2) that in the presence of multiple cues, memories stored in the neocortex could be accessed directly. In support of this, Tonegawa and colleagues demonstrated that transgenic mice with selective knockouts for NMDA receptors within the CA3 region of the hippocampus are incapable of retrieving

spatial memory when only one cue is present during retrieval testing. However, when all cues are provided, the mutants do not exhibit a deficit in memory retrieval compared to control animals [24]. Further, a functional imaging study demonstrated that reactivations of the hippocampus similar to that seen during paired-associated learning (learning to associate a face with a name) were observed when subjects viewed only the previously associated faces [35]. This sort of hippocampal reactivation could be essential in the retrieval of information stored at several neocortical sites. It has also been demonstrated in rats that an increase in *zif268* occurs in the CA1 field of the hippocampus during associative-memory retrieval 24 h following the learning event, but not 28 days following the learning event [10]. These studies and others are consistent with our suggestion that the hippocampus coordinates memory retrieval and that this role is time-limited.

### *3.3. The event defining the period of hippocampal dependency is the transport time for gene products to travel from the soma to tagged synaptic sites*

A necessity for axonal transport of proteins over a considerable distance between cortical→cortical or cortical→subcortical structure(s) could dictate the period of systems consolidation. Studies performed in rat hippocampal slices and in *Aplysia* sensory-motor neuron co-cultures show that long-lasting plasticity is not cell-wide, but is instead synapse-specific [8,16]. Changes in synaptic strength may be needed to coordinate the retrieval of components of memory stored in different areas. This suggests that gene products expressed in the cell nucleus travel to the involved synapses in order to participate in long-lasting plasticity needed for memory retrieval. Martin et al. [16] and Frey and Morris [8] have proposed that only synapses that are tagged during the induction of plasticity are able to utilize these proteins (see Box 1). Thus, the rate of transport of proteins within long projections between structures involved in memory storage may give rise to the temporal constraints for memory consolidation (see Box 2). Since extrahippocampal projections may not be able to mediate the coordination of memory retrieval until the gene products arrive at tagged synaptic sites in the areas storing information, consolidation could then be viewed as the time period during which the hippocampal complex is needed for memory retrieval before arrival of the proteins at these tagged synapses.

This raises the question of how the hippocampus is able to mediate memory retrieval during the period of systems consolidation. Due to the structural proximity of pre- and post-synaptic cells within hippocampal subfields, long-term plasticity takes hours and not days or weeks allowing hippocampal projections to mediate retrieval. This possibility would also pertain to plasticity within proximal projections in neocortical structures storing components of a memory. Alternatively, plasticity within these structures may occur post-synaptically and, therefore, proteins would

only need to be transported a short distance to reach the site of plasticity.

Experimental findings indicate that the duration of consolidation appears to increase in relation to the size of the brain. For example, retrograde amnesia studies suggest that the period of consolidation is shorter in rodents as compared to monkeys and is shorter in monkeys as compared to humans. Rodent experiments have shown consolidation periods of a few weeks, where primate experiments by Zola-Morgan and Squire [54] have shown consolidation periods up to 6 weeks, and consolidation in humans can extend for decades. In addition, task-related differences in the consolidation period have been observed within a given species. In a food preference task using rats, a consolidation period of as little as 5 days has been reported [53]. In contrast, hippocampal-lesioned rats showed a temporally graded retrograde amnesia for context-specific fear memory for up to 14 days after conditioning [13]. The reported consolidation periods can be explained by the present theory in that the development of plasticity within projections between involved areas is the rate-limiting step in consolidation. It has been shown that, depending on the task, different cortical structures can contribute to information storage. Therefore, the rate of the development of activity-dependent changes in long projections involved in memory retrieval would be proportional to the length of these projections and this length would be dependent on which structures are involved in a specific task. Therefore, the probability of memory consolidation increases as gene products are transported to and incorporated in the most distant synapses. This implies that certain aspects of a memory may be consolidated before others, based on variation in the distance between involved structures.

Studies using human patients show a variable period of consolidation depending on the type of memory tested. Two patients (R.B. and G.D.) with bilateral lesions limited to the CA1 field of the hippocampus show retrograde amnesia for declarative memory spanning a few years [28]. However, it has also been shown in human patients that the duration of consolidation for autobiographical events (detailed episodic memory) can extend for decades, or even for the lifetime of the patient (for a review, see Ref. [22]). It is believed that with the availability of new information pertaining to a memory representation, episodic memories are updated continuously, which may explain the wide range of consolidation periods observed in humans. Taken together, these studies illustrate that the time-course for memory consolidation can vary depending on the species and task utilized.

### *3.4. Through its continued activity, the hippocampus contributes to the development of this hippocampal-independent memory retrieval*

The C theory proposes that continued hippocampal activity is either necessary for the maintenance of the synaptic tag, which is normally transient, or that within

these long projections between structures, newly arriving proteins at tagged synapses will be modified by hippocampal-cortical activity, completing the consolidation process. Further, if memory representations in the hippocampus and the cortex are activated simultaneously following training, one of the outcomes could be to induce further plasticity in a bi-directional manner both in the neocortex and in the hippocampus. Thus, a loss of NMDA receptors or other molecules in the hippocampus could also result in a loss of subsequent plasticity (i.e. the robustness of a memory), rather than a complete loss of memory. Consistent with this, it has been reported that post-training deletion of NMDA receptor subunits in the hippocampus after training impairs long-term memory [34].

### 3.5. Specific spatial and feature related information remains stored in the hippocampal complex even after the period of consolidation, as suggested previously

The Multiple Trace Theory states that for context-rich episodic memory hippocampal representations are maintained, perhaps permanently [31]. A study by Teng and Squire [42] reports that old spatial memories about neighborhoods are intact following hippocampal damage. However, this patient, R.B., remembered only general, but not detailed, information regarding the landmarks in his California neighborhood. A second patient, K.C., also showed impaired memory for the detailed features of his environment. K.C. had difficulty in identifying specific features on outline maps of Ontario and Canada, where the patient was from [30]. The C theory proposes that spatial-specific or feature-related information is maintained in the hippocampal formation, providing detailed memory consistent with the type of information loss observed in patients R.B. and K.C.

Recently, it has been reported that injection of the protein synthesis inhibitor anisomycin into the hippocampus shortly after recall of a consolidated memory can result in loss of simple forms of memory [5]. However, protein synthesis inhibition does not disrupt hippocampal place field selectivity for recalled familiar contexts, but does disrupt place field selectivity for newly exposed contexts, arguing that reconsolidation may not occur for more complex memories [55]. The present theory proposes that each time a memory and its feature-specific information is retrieved, the hippocampal memory representation is reactivated. This triggers molecular events that store these retrieval-related changes in the hippocampus, in addition to causing activity-dependent cortical modifications. Therefore, inhibition of protein synthesis in the hippocampus during recall would result in a loss of this updated information. However, we propose that the cortical information should remain intact when protein synthesis is blocked in the hippocampus during recall. Therefore, memory cues or other such manipulations would aid in retrieving the information stored in non-hippocampal structures. Consistent with this, following inhibition of hippocampal protein synthesis after recall by exposure to

the training context, the contextual memory can be revived if cued by exposure to the unconditioned stimulus in a novel context [56]. Additionally, patients with hippocampal damage can benefit from recognition and contextual cues during memory recall, suggesting that the cortical information remains intact [14]. In further support of intact cortical information storage, when shown the first few letters of previously studied words, hippocampal-damaged patients are capable of correctly identifying as many words as normal patients [39]. However, if these letters are not used to prime memory recall, then the hippocampal-damaged patients demonstrate a deficit in word recall.

## 4. Experimental tests for the C theory

Some of the properties of memory consolidation proposed here are experimentally testable. First, this theory would be supported by additional experiments specifically testing for simultaneous molecular changes in the neocortex and in the hippocampus following training, along side experiments testing for deficits after immediate, or early blockade of these molecular changes. Second, experiments showing that damage to extrahippocampal structures that mediate memory retrieval results in an impairment of consolidated memory, similar to findings by Vale-Martinez et al. [46], would further validate this theory. Finally, the present theory posits that there is a defined time for the duration of memory consolidation for a learning event, which is determined by the rate of slow axonal transport. This limit cannot be shortened by stimulation of the cortical network in a manner that emulates hippocampal activity. In contrast, if traditional models for memory consolidation were correct, then repeated stimulation of cortical networks would decrease the time period required for systems consolidation. The present theory indicates that systems consolidation could be viewed as a prolonged cellular consolidation within long projections, thus providing a unification of the concepts of systems and cellular consolidation.

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