An emerging molecular and cellular framework for memory processing by the hippocampus

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The hippocampus plays a central role in memory consolidation, a process for converting short-term memory into cortically stored, long-lasting memory in the mammalian brain. Here, we review recent data and discuss the 'synaptic re-entry reinforcement' (SRR) hypothesis, which can account for the role of the hippocampus in memory consolidation at both the molecular and systems levels. The central idea of the SRR hypothesis is that reactivation of neural ensembles in the hippocampus during the consolidation period results in multiple rounds of NMDA-receptor-dependent synaptic reinforcement of the hippocampal memory traces created during initial learning. In addition, such reactivation and reinforcement processes permit the hippocampus to act as a 'coincidence regenerator', providing coordinated input that drives the coherent reactivation of cortical neurons, resulting in the progressive strengthening of cortical memory traces through reactivation of cortical NMDA receptors.

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Researchers have sought to understand the biological mechanisms underlying the formation of long-term memory for more than a century [1]. Studies of amnesiac patients and experimental animals have revealed two devastating consequences of hippocampal damage: loss of the ability to form new declarative memories (anterograde amnesia) and a disproportionate loss of recently formed memories (retrograde amnesia) [2–4]. These findings have led to the general notion that the hippocampus is necessary for the brain to convert short-term memory into long-lasting memory, a crucial process known as memory consolidation.

The search for the molecular and cellular mechanisms underlying learning and memory has made much progress in recent decades. The discovery of LTP marked a beginning for the molecular and cellular exploration of synaptic plasticity [5,6]. The role of NMDA-receptor-dependent synaptic plasticity in learning and memory has been explored using both second-generation (region-specific) and third-generation (region-specific and inducible) gene-knockout techniques. These experiments demonstrate that the CA1-hippocampal NMDA receptor, a major cellular coincidence detector, is required for formation of hippocampus-dependent spatial and non-spatial memories [7–9].

In parallel to the work of molecular neurobiologists, the systems-level processes underlying hippocampal memory formation and memory consolidation have been pursued by researchers through the use of *in vivo* electrophysiological recordings and neural-network modeling techniques [10–13]. These studies share in some form the general idea that, after initial learning, reactivation of hippocampal memory traces drives cortical plasticity.

Although much progress has been made, at both the computational and molecular levels, the two approaches to understanding learning and memory have largely proceeded in parallel. As such, a common molecular and cellular framework underlying memory consolidation has not previously emerged.

Can the 'single molecular cascade' hypothesis account for the formation of long-lasting memory in the mammalian brain?

The NMDA receptor has been established as a crucial molecular switch for synaptic plasticity [5,6,14]. Recent genetic 'gain-of-function' and 'loss-of-function' experiments have provided convincing evidence that the NMDA receptor does indeed serve as a cellular coincidence detector for memory formation [7–9,15–17].

At the molecular level, long-term memory is widely believed to be expressed ultimately in the form of synaptic structural changes resulting from a single molecular cascade (e.g. Ref. [18]). It is postulated that learning triggers a molecular cascade consisting of receptor activation, transient changes in levels of protein phosphorylation, new protein synthesis and gene expression. This 'single cascade hypothesis' has guided experimental designs and conceptual thinking in the past decades.

However, a single molecular cascade triggered within the hippocampus during learning might not be sufficient to account for the consolidation of long-term memory in the mammalian brain, for three reasons. First, hippocampus-mediated consolidation of long-term memories occurs over a time-scale of week(s) in rodents [19–22] and years in humans [23–25]. Second, although protein synthesis inhibitors seem to produce long-term memory deficits (often tested within a day or days of training), spontaneous recovery or reminder-induced recovery of memory over a time course of a week or weeks has been reported in animals initially thought to be amnesic [26–28] (reviewed in Ref. [29]). Third, synaptic structures in the adult

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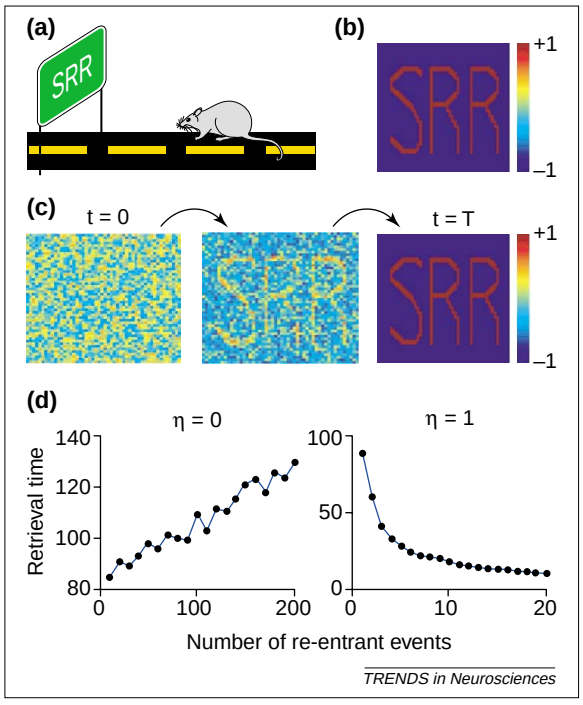

Fig. 1. The synaptic re-entry reinforcement (SRR) process provides a consolidation mechanism for both the strengthening and the maintenance of memories. (a,b) Memory acquisition occurs during awake behavior, providing sensory input that drives synaptic change in the brain. In the SRR-network model, a learned binary pattern, forming the letters 'SRR', is weakly stored in the network. When the pattern is retrieved, neurons will fire either maximally (+1) or minimally (–1) as shown. The color of each pixel represents the activity of a single neuron in the network. (c) During recall, neural activities are randomly initialized and the network evolves until the memory trace (the letters 'SRR') is retrieved. The strength of the memory trace is represented by the amount of time (T) taken for the network to settle to this attractor state. (d) Owing to decay processes, in the absence of SRR (η=0, γ=1; see Box 1) the memory decays with time, as indicated by the increasing length of time taken to settle to the attractor, or memory, state (left panel). In the presence of SRR, (η=1, γ=1), the time taken to reach the memory from a random initialization of the network decreases exponentially as a function of SRR events (right panel). The data shown are the average of ten simulations.

brain are not stationary and synaptic receptors and proteins are turned-over regularly. For example, a recent study using inducible-knockout techniques shows that synaptic NMDA receptors are degraded in approximately five days in the brain of freely behaving animals [9]. Thus, it is not clear whether structural changes resulting from a single molecular cascade can be sustained in the presence of such dynamic turnover processes for long enough to complete cortical memory consolidation.

SRR hypothesis for consolidating memory in the mammalian brain

If the single molecular cascade hypothesis is not sufficient to explain long-term memory formation in the brain, what is the molecular and cellular mechanism that allows the hippocampus to consolidate and process memories for long-term storage? Because the hippocampus is required for processing memory traces for week(s) after initial memory acquisition, we do not review here consolidation experiments in which drug treatments and memory retention tests were performed within 24 h of training (reviewed in Ref. [30]).

SRR and hippocampal memory consolidation

New insight into the molecular and cellular mechanisms of memory consolidation has come from recent experiments using an inducible, reversible and CA1-specific gene-knockout technique [9]. Shimizu *et al.* discovered that the formation of long-lasting memories was severely disrupted if the CA1-hippocampal NMDA receptor was knocked out selectively during the initial post-training week(s) [9]. By contrast, inducible knockout of the CA1-hippocampal NMDA receptor during the fourth week post-training had no effect on the retention or retrieval of one-month-old hippocampal memories. These results are consistent with lesion studies showing that the hippocampus becomes dispensable once memories have been sufficiently consolidated in the cortex [19].

Presuming the activation of the NMDA receptor in CA1 is not crucial for basal synaptic transmission, these observations have led us to the 'synaptic re-entry reinforcement' (SRR) hypothesis, according to which memory consolidation requires multiple rounds of NMDA-receptor-dependent synaptic modification to reinforce the synaptic changes initiated during memory acquisition. Such a process could counteract the turnover of synaptic receptors, making memory traces stronger and more stable, extending their durability and robustness within the hippocampus. This idea is illustrated in Fig. 1: a single memory stored in a neural network is either lost (owing to synaptic decay) or strengthened and maintained (by repeated rounds of Hebbian modification each time the memory is reactivated) (see also Box 1).

Post-learning processing of hippocampal memory traces

Through our computational model, we can explore in greater detail the impact of SRR on the consolidation process [31]. Of particular interest, we find that repeated reinforcement of synapses during the reactivation of memory traces could lead to a situation in which memory traces 'compete', such that the strengthening of one memory is always at the expense of others, which are either weakened or lost entirely [32] (Fig. 2). In other words, we predict that memory consolidation is a biased selection process.

Several biases could be involved in determining which memory traces are preserved and which are not. First and foremost, the mechanism by which memories are reactivated will determine which are strengthened. It is not yet well-known what drives the reactivation of hippocampal neurons. In our

Box 1. Computational modeling of the 'synaptic re-entry reinforcement' process

To examine the effect of the 'synaptic re-entry reinforcement' (SRR) process on memory consolidation, we have constructed a simple neural network model by extending the fully connected, classical Hopfield model [a] to include continuous learning dynamics [b]. The network evolves according to the following dynamic system:

$$\tau_u \frac{du_i}{dt} = -u_i + \sum_j w_{ij} V_j + I_i \quad \text{[Eqn 1]}$$

$$\tau_w \frac{dw_{ij}}{dt} = -\gamma w_{ij} + \eta V_i V_j \quad \text{[Eqn 2]}$$

$$V_i = \tanh(\beta u_i) \quad \text{[Eqn 3]}$$

u_i - membrane potential of neuron I
V_i - firing rate of neuron I (varies from –1 to +1)
w_{ij} - synaptic weight connecting neurons i and j (w_{ij}=w_{ji})
$-\gamma w_{ij}$ - synaptic decay term, to account for processes such as turnover of synaptic proteins
$\eta V_i V_j$ - to model NMDA-receptor-dependent plasticity as Hebbian learning
I_i - external inputs to the network during training (I_i=0 during reactivation)

The basic experiment performed with this network is as follows. During initial learning, strong inputs (I_i) drive the network until a pattern of neural activity is reached with each V_i equal to either +1 or –1. The Hebbian learning term in Eqn 2 causes this pattern of activity to be stored as a fixed point of the network dynamics. During the reactivation period, the network is randomly initialized in the absence of external inputs (I_i=0). The network evolves until reaching a fixed point of the dynamical system, the attractor state, corresponding to stored memory traces.

For a more detailed account of the computational modeling, see Ref. [c]. Matlab code for all simulations presented here can be obtained at http//www.molbio.princeton.edu/labs/tsien.

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model, we consider random reactivation of the hippocampal network. However, it would be interesting to consider sequence learning, in which the reactivation of a given memory is modulated by the reactivation of other memory traces preceding it, in a learned sequence. Second, a particular memory trace might be favored for long-term storage based on its importance to the animal. If a large amount of time is spent investigating a particularly interesting cue during a training event, while others are less fully explored, we would expect that cue to be more strongly stored in the network during training – perhaps making it more likely to be subsequently reactivated and consolidated. Alternatively, if danger or reward becomes associated with a particular cue, a stronger memory trace might be created. Finally, differences in the frequency with which memory traces are either consciously or subconsciously recalled could be another factor biasing the selection of which memories are consolidated. For example, in our model, if one particular memory trace is recalled and, thus, strengthened by the SRR process, then during subsequent consolidation and under the random reactivation paradigm presented this memory trace would be consolidated preferentially.

SRR and consolidation of cortical memory

Shimizu *et al.* also proposed that the general principle of the SRR process can serve as a cellular means for the hippocampus to transfer and convert short-term memories into cortically stored, long-term memory in the brain [9]. During the consolidation period, the hippocampus could serve as a coincidence regenerator for the coordinated reactivation of cortical neurons, activating cortical NMDA receptors and strengthening intercortical connections through SRR. This would allow cortical neurons previously corresponding to different sensory modules to be reactivated simultaneously, leading to the strengthening of the connections between them. Indeed, recent observations show that the correlations between hippocampal–cortical neurons emerging during learning can be subsequently measured during sleep [33]. Once these cortical connections are fully consolidated and stabilized, the hippocampus itself becomes dispensable for the retrieval of the 'old memory'. Therefore the hippocampus, by forming its reinforced memory traces, could act as a coincidence-regenerator to provide coherent input, inducing reinforcement of synaptic connections between cortical neurons via cortical SRR.

In the absence of SRR in the hippocampus, hippocampal memory traces do not remain intact. As a result, it would be difficult for the hippocampus to maintain its ability to provide coherent output to drive the cortical neurons to reactivate coherently after initial memory acquisition. This makes the NMDA-receptor reactivation between these cortical connections less likely, thus preventing the consolidation and binding of cortical memories spanning multiple sensory modules (Fig. 3).

SRR throughout the brain

Although the SRR process was initially proposed to describe the consolidation of hippocampus-dependent memory traces [9], the same process might occur in other brain regions involved in hippocampus-independent long-term memory formation. For example, a recent study reports that post-training pharmacological blockade of the NMDA receptor prevents the consolidation of fear-extinction learning in the amygdala [34]. Further, another study has shown that impaired cortical LTP appears to be correlated with late-stage deficits in cued fear memory consolidation [35]. Therefore, the SRR process could potentially present a general molecular and cellular framework for memory consolidation in the mammalian brain.

When and how does SRR occur? Is there a role for sleep?

What might trigger the SRR process and when does SRR take place? It is conceivable that one triggering

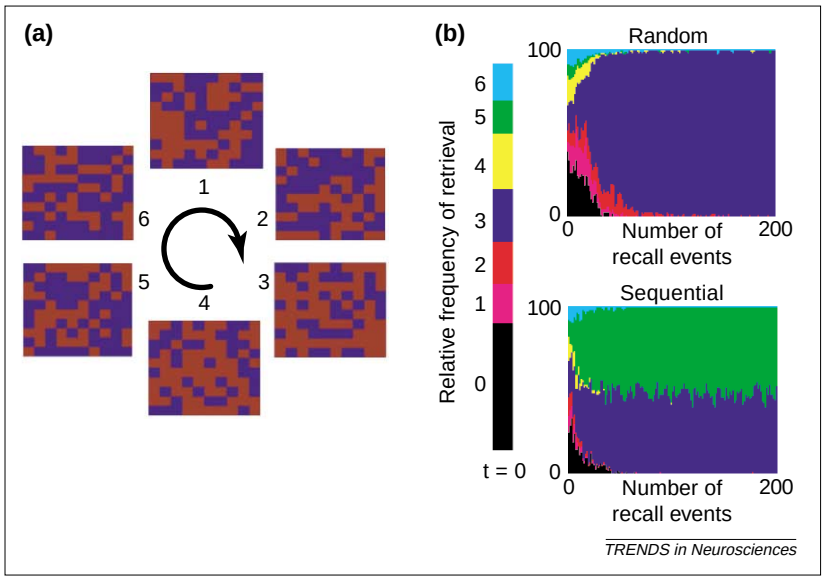

Fig. 2. Effect of synaptic re-entry reinforcement (SRR) on the consolidation of multiple memory traces in a recurrently connected network. (a) During training, binary patterns are presented to the network in a cyclic, sequential manner, clockwise from one to six. (b) Selective consolidation of memory traces based on reactivation strategy. The vertical height of each color in the left-hand multicolor bar represents percentage of initial conditions leading to the eventual reactivation of that memory trace (or a 'junk' attractor shown in black, '0') immediately after training. This illustrates the t=0 points of the right-hand panels, which show how the relative strengths of the memory traces evolve in time as the network undergoes consolidation driven by two different reactivation schemes. Upper right panel: the network is periodically reactivated at random and allowed to settle into one of the memory states while the ongoing learning dynamics (SRR) continues. This results in competition between patterns, in which only one memory, exemplified by memory number 3 in blue, is eventually stored in the network. Lower right panel: rather than random reactivation, the network is initiated alternately near to attractor states corresponding to memories 3 and 5, represented in blue and green, respectively. As a result, both memory traces remain stable, illustrating the effect of reactivation strategy on the stability of memories in the network

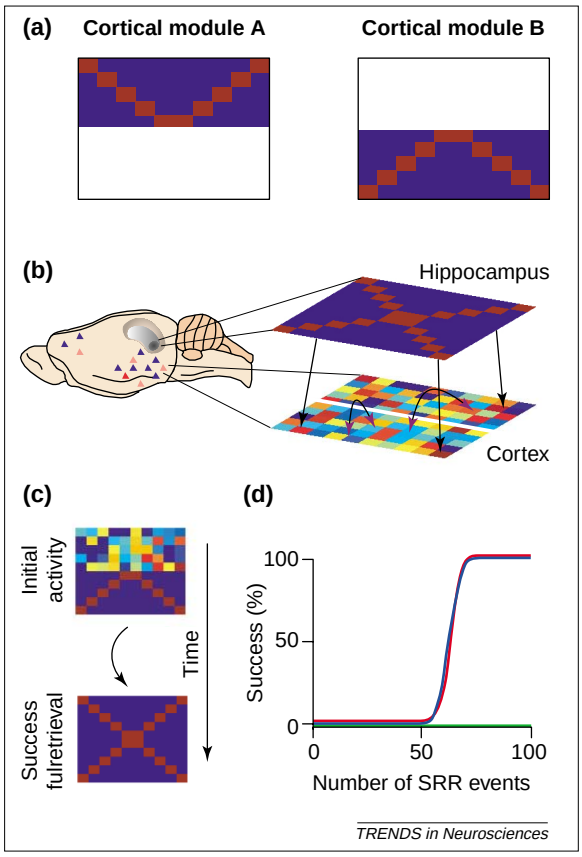

Fig. 3. Synaptic re-entry reinforcement (SRR) within the hippocampus is required in a temporally restricted manner to drive cortical memory consolidation. (a) During learning, cortical modules A and B are activated and provide input driving hippocampal neurons. (b) During consolidation, the hippocampus (grey) reactivates and further strengthens the stored memory trace by SRR. Coherent hippocampal reactivation provides coordinated reactivation of cortical modules, resulting in the SRR-based strengthening of synaptic efficacies, primarily between cortical modules A and B, as well as within each module. (c) Cortical consolidation is measured by the time taken to retrieve the memory trace in module A, triggered by the reactivation of the memory trace in module B, or vice versa. The frequency with which the cortical network recovers the full memory is recorded. (d) The blue curve demonstrates that the ability of the cortical network to retrieve the full pattern improves with each SRR event. The green curve shows that turning off the SRR process in the hippocampus after initial memory acquisition results in an inability to consolidate the memory in cortex. The red curve shows that turning off the SRR process within the hippocampus at a later stage (after 50 SRR events in our model) has no effect on the ability of cortex to retrieve the cortical memory traces that have already been consolidated.

mechanism could be conscious recall. This is consistent with our own experience: if a particular event is recalled more frequently, it will be remembered more efficiently and for longer. Another triggering mechanism could be the subconscious reactivation of the hippocampus and/or cortex, which could be achieved during sleep. An increasing amount of evidence suggests a role for sleep in memory consolidation (reviewed in Refs [36–40]). Moreover, learning-induced correlations in the firing of hippocampal place cells have been reported to reappear during sleep [39,40]. Such coordinated reactivation of these neurons suggests the existence of a natural condition in which the NMDA receptor might be reactivated, thus reinforcing the synaptic connections between them.

Degradation of out-dated hippocampal memory traces after consolidation – adult dentate neurogenesis as a means for memory clearance?

It is thought that the hippocampus could have limited storage capacity [41]. It has been speculated that the continued accumulation of outdated memory traces in the hippocampus might gradually overload the system, eventually disabling hippocampal function in memory consolidation.

Intriguingly, the dentate gyrus of the hippocampus has ongoing and robust adult neurogenesis in many mammalian species, ranging from rodents to monkeys and humans. Because of the lack of identification of crucial genes controlling adult neurogenesis, its functional consequence largely remains speculative. Recently, Feng *et al.* have found that the forebrain-specific knockout of the gene encoding presenilin-1, mutations of which are responsible for the vast majority of cases of early-onset Alzheimer's disease, resulted in a pronounced deficiency in enrichment-induced neurogenesis in the dentate gyrus [42]. Behavioral experiments suggested that adult neurogenesis in the dentate gyrus might play a role in the clearance or destabilization of outdated hippocampal memory

traces after cortical memory consolidation, thereby saving the hippocampus from overload.

Although more experiments are needed to test further the adult neurogenesis and memory destabilization hypothesis, it is interesting to note that these adult-born neurons are short-lived, typically with a life-span of three weeks in rodents [43,44]. This temporal duration correlates well with the time-scale of the hippocampal dependence of some forms of declarative memory, such as contextual-fear memory. Furthermore, it is feasible that such addition and removal of adult-born neurons in the upstream location of the hippocampal circuitry make it ideal to amplify the 'destabilization' effect within the entire hippocampus, thus altering the 'attractor' states corresponding to memories previously stored in the network and, in time, destabilizing them.

Conclusions

In summary, we have discussed the SRR-based consolidation hypothesis, attempting to bridge the gap between the understanding of hippocampal-dependent memory consolidation at the molecular level versus the network level. The general principle of SRR can be used to describe the NMDA-receptor reactivation-mediated consolidation of memories within the hippocampus, as well as in the hippocampal–cortical and cortical–cortical circuitry.

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