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Review

Long-lasting memory from evanescent networks

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Abstract

Current models of memory typically require a protein synthetic step leading to a more or less permanent structural change in synapses of the network that represent the stored information. This instructive role of protein synthesis has recently been called into question [Routtenberg, A., Rekart, J.L. 2005. Post-translational modification of synaptic proteins as the substrate for long-lasting memory. Trends Neurosci. 28, 12–19]. In its place a new theory is proposed in which post-translational modifications (PTMs) of proteins already synthesized and present within the synapse calibrate synaptic strength. PTM is thus the only mechanism required to sustain long-lasting memories. Activity-induced, PTM-dependent structural modifications within brain synapses then define network formation which is thus a product of the concatenation of cascaded PTMs. This leads to a formulation different from current protein synthesis models in which neural networks initially formed from these individual synaptic PTM-dependent changes is maintained by regulated positive feedback maintains. One such positive feedback mechanism is 'cryptic rehearsal' typically referred to as 'noise' or 'spontaneous' activity. This activity is in fact not random or spontaneous but determined in a stochastic sense by the past history of activation of the nerve cell. To prevent promiscuous network formation, the regulated positive feedback maintains the altered state given specific decay kinetics for the PTM. The up or down state of individual synapses actually exists in an infinite number of intermediate states, never fully 'up', nor fully 'down.' The networks formed from these uncertain synapses are therefore metastable. A particular memory is also multiply represented by a 'degenerate code' so that should loss of a subset of representations occur, erasure can be protected against. This mechanism also solves the flexibility–stability problem by positing that the brain eschews synaptic stability having its own uncertainty principle that allows retrieval from a probabilistic network, so that a retrieved memory can be represented by a selection of components from an essentially infinite number of networks. The network so formed, that is the retrieval, thus emerges from a hierarchy of connectionistic probabilities. The relation of this new theory of memory network formation to current and potential computational implementations will benefit by its unusual point of initiation: deep concerns about the molecular substrates of information storage.

Keywords: Post-translational modification; Hebb synapse; Cryptic rehearsal; Memory; Lifetime memories; Neural network

Contents

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1. Introduction — Statement of the problem

Storing memories of ongoing, everyday experiences requires a high degree of plasticity, but retaining these memories demands protection against changes induced by further activity and experience (e.g., Abraham and Robins, 2005). In the present post-translational modification (PTM) model of long-lasting memory (Routtenberg and Rekart, 2005), further activity is thought to rehearse existing memories rather than interfere with them (in contrast to the Fusi et al., 2005). Synaptic strength in this model cannot be binary, which is good for storing, but not retrieving, but is rather a continuous function with an infinite number of states, hence it is metastable. We have constructed a model in which each synapse has a cascade of PTM states with different levels of plasticity. Thus, PTMs may be viewed as continually in transition, a protein–protein concatenation determined by multiple PTM mechanisms forming a supramolecular complex, with an oscillating PTM based on the synaptic lattice of interacting proteins. In brief, essential features of the PTM hypothesis are the need for metastability of networks to maintain an open architecture and incorporate new information into existing schema. This is achieved by exploiting ongoing synaptic flexibility yet attaining from the proposed degenerate code the remarkable achievement of long-lasting memory.

It is generally believed that short-term memory sets into motion the plasticity of synaptic connections which can be rendered stable over time due to a protein synthesis dependent mechanism that requires tagging and that then leads to structural stability and thus a substrate representation of long-term memory. In our recent review (Routtenberg and Rekart, 2005) we have suggested a different position: that protein synthesis is not the instructive mechanism that mediates long-term memory but rather serves instead a permissive, replenishment role. Post-translational modifications (PTMs) maintained by positive feedback driven by the brain's endogenous activity serves the instructive function underlying long-lasting brain information storage. Under such conditions hard-wired synapses are not formed in memory-associated networks, rather there are synaptic 'probabilities' that are maintained by the network in which the synapses are embedded.

How is it possible to have a long-term memory in which component synapses remain labile and the networks are never stabilized. That is, how to define maintaining a network without explicit rehearsal, without a permanent structural modification or a stabilized synapse?

Level 1 Answer: If the permanence of memory emerges from the extensive distribution and re-duplication of the trace, the degenerate code, then the PTM view of synaptic change can permit positing a dynamic synapse with no need for a stabilized one. Long-lasting memory is represented by a set of multiple networks whose underlying component synapses are in a labile state. No single network memory trace is critical to memory maintenance; thus the neural code for a particular memory is 'degenerate' in the sense that one memory is represented by different networks. This borrows the terminology of the triplet base code for amino acids in which more than one base sequence can code for the same amino acid. Returning to memory, this is pseudo-redundancy because the multiple neural representations are not identical though they are similar enough to protect against memory loss even when more than half of the total network is lost.

Level 2 Answer: A central role is given to the number of representations of any particular memory. A particular memory can be recalled from any one of a number of multiple network representations after the initial event has occurred. In order for long-lasting memory to survive in this model, a particular memory is represented by an ever-increasing number of networks which protect against memory loss by this pseudo-redundancy (pseudo- because each individual network is not identical, hence the degenerate code). To enable the flexible re-assortment of different networks to form either the same or different memories, an open architecture design is enabled by network metastability.

Based on available evidence, the input event is first represented in subcortical structures such as the amygdala and/or hippocampus. Over the course of hours, cortical representations of this original subcortical network are formed remaining part of hippocampal or amygdaloid circuitry. Then, the subcortical machinery is released from its ties with cortex, permitting cortex to reduplicate traces, depending on the criticality of the memory, and to develop multiple 'degenerate' networks, while the hippocampus and amygdala continue, in parallel, their work of encoding new memories of contextual or emotional content, respectively. Evidence to support this model is growing; some of it will be reviewed in a later section of this paper.

2. Re-interpretation of memory consolidation

The quintessential element of memory consolidation is its time-dependent nature (McGaugh, 2000). Memory is readily