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Long-lasting memory from evanescent networks

Aryeh Routtenberg*
Department of Psychology, Feinberg School of Medicine (Chicago) in the Northwestern University Interdepartmental Neuroscience Program (NUIN), Cresap Neuroscience Laboratory, Swift Hall, Room 102, 2029 Sheridan Rd, Northwestern University, Evanston, IL. 60208, USA, Department of Neurobiology (Evanston), Feinberg School of Medicine (Chicago) in the Northwestern University Interdepartmental Neuroscience Program (NUIN), Cresap Neuroscience Laboratory, Swift Hall, Room 102, 2029 Sheridan Rd, Northwestern University, Evanston, IL. 60208, USA, Department of Physiology, Feinberg School of Medicine (Chicago) in the Northwestern University Interdepartmental Neuroscience Program (NUIN), Cresap Neuroscience Laboratory, Swift Hall, Room 102, 2029 Sheridan Rd, Northwestern University, Evanston, IL. 60208, USA

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.

*Tel.: +1 847 491 3628; fax: +1 847 491 3557. aryeh@northwestern.edu.

Keywords

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

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 pseudoredundancy 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 pseudoredundancy (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 impaired when the disrupting agent is given shortly after learning, but no impairment occurs when the same disruptive manipulation is given 1–2 h after learning. This has been demonstrated in a variety of learning situations with an array of animal species using different disrupting agents (McGaugh, 2000). Such results are taken to support a labile stage and then stable stage of memory formation (or, protein synthesis independent and then protein synthesis dependent stages).

We proposed that memory consolidation findings may be reinterpreted in the following way. The failure to disrupt 1–2 h after learning is a function of the rate of re-representation of the original trace as it is distributed to other brain loci in the dynamic network. This re-distribution elevates the threshold for disruption. Thus, memory surviving the disruptive agent is not due to its stabilization, but rather its distribution (Routtenberg and Rekart, 2005).

To expand on this idea: shortly after learning, residual traces are restricted to brain loci with low seizure threshold, such as hippocampus/amygdala, thus disrupting agents are highly effective. Trace dissemination and subsequent reduplication in other brain locations, for example cortical cell assemblies with a high threshold, would now render disruption of memory by manipulating subcortical structures less likely. Parallel processing suggested by the findings of Izquierdo et al. (1998) may be understood by the present model as a consequence of the time-dependent redistribution of the memory trace to different brain loci. This redistribution may also be inferred from studies in which cortical metabolic activity is increased 5 weeks but not 5 days after learning, while, in contrast, in the hippocampus this pattern is reversed (Maviel et al., 2004).

3. Is the PTM hypothesis capable of disproof?

I believe that there are empirical tests that can be made to evaluate the validity of the PTM hypothesis, at its different levels. Indeed, I would assert that this hypothesis is falsifiable, giving it inherent validity as a useful theory.

Recent empirical findings involving the direct manipulation of PTM in specific brain locales lead to the manipulation of long-lasting memory (Holahan and Routtenberg, 2007; Shema et al., 2007). Because failure to find such an effect would have seriously questioned PTM theory,

we might conclude that this test qualifies for the status of 'hard inference'. Moreover, these hypothesis-confirming findings raise the hope that our approach can pinpoint the brain locales that alternately hold and release networks that represent the memory.

4. Significance

Given the current state of the biology of memory, the proposal contained herein represents a set of heteroclitic ideas that have as their immodest goal no less than a paradigm shift in the way in which we view the mechanisms that are involved in memory representation.

For the proposed model to achieve a substantive theoretical foundation, a computational model must be constructed. I have written this paper in the hope of stimulating discussion of ways in which such a model, which is currently an intuitive, neurobiological one, can in the future be framed within a defined computational network. It is thus important to honor the distinction between the network and molecular levels of analysis, though the mechanisms studied depend on the interaction between these two levels. Thus, long-lasting memory is represented *within a network*, whereas the post-translational modification state of proteins regulates the individual synapses within that network.

5. Comparison with previous work

I have found that the computational-based models of Eve Marder, Larry Abbott, and Gerry Edelman all contain elements of the biologically inspired PTM model I propose, yet each has either a critical element that is not included or an assumption that does not fit well with the known biological facts marshaled in support of the PTM hypothesis. To give one illustration for each: The Marder model indicates the possibility in invertebrates to have the same output derived from any number of different network configurations (Prinz et al., 2004). This fits well with the 'degenerate code' of the PTM hypothesis. However, this model assumes a stable network derived from stable synaptic relationships, which I do not believe is the case in the vertebrate central nervous system. The Abbott model holds to a finite number of states within the synapse (Fusi et al., 2005), and while not discussing PTM mechanisms, the cascade model proposed could be readily adapted to that outlined for the PTM mechanism. Lacking in their formulation is any suggestion that these mechanisms coordinate with the ability of the memory system to form multiple representations. In the Edelman model, the sampling of different networks to represent the same memory is implemented in a network model (Izhikevich et al., 2004). However, the pseudoredundancy issue and the consequences for memory consolidation do not appear to be part of the implementation.

6. Questions raised by the model

The present model raises a series of empirical questions:

1. Where are the initial encodings of the memory trace?
2. What is the time course of distribution of the trace once encoded?
3. Does the original site of encoding retain a residual of the trace?
4. To what distant locales is the original trace distributed?
5. What is the kinetics of this trace distribution, e.g., how many duplicated traces are there in 6 h?
6. How are these traces maintained?
7. What is the 'residual' that allows for resurrecting lifetime memories?

7. Re-interpretation of well-known memory-related phenomena: A new look at some venerable memory demonstrations

7.1. Reminiscence

The propensity in the aged for memories of youth to resist the ravages of time and newer memories to be more readily lost is oft-noted and bemoaned by young and old alike. Reminiscence may have a spontaneous, disconnected and repetitious quality, perhaps because it emerges from highly re-represented traces maintained by endogenous activity. These memories are further maintained by the act of reminiscence which would then lead to strengthening of these old memories. Because older memories are represented more extensively, the probability is that it is those that will be recovered, leading to yet more reminiscence. In this regard one can only imagine the extensive neural network distribution that would be involved in the representation of our own good name. Thus, each recall maintains the network by reactivating an approximation to the post-translational mechanisms that underlie the organization of long-lasting memory.

7.2. Shrinkage of amnesia

This clinical phenomenon is observed after head trauma in which the loss of memory for events prior to trauma begin to recover over time. The nature of the recovery is curious: the most distant events in time from the trauma re-appear first, and then memories recover backwards so that only those events close to the traumatic event itself are lost. Presumably the most distant memories, in contrast to the more recent ones, have already been re-duplicated and hence possess a more elaborate network. This may be explained in the present model as follows: as the non-specific trauma (diaschisis) subsides, the most duplicated or re-represented networks that were disrupted are more likely to be re-activated by internal endogenous activity and thus begin to function once again. Shrinkage of amnesia occurs because the degraded network begins to activate the traumatized network, re-adjusting the PTM of proteins in this system, such that the PTM state in these bruised neurons approaches pre-traumatic levels of organization.

7.3. Serial vs. parallel processing

Elimination of short-term memories while preserving long-term using region-specific neuromodulators and receptor antagonists (Izquierdo et al., 1998) may be interpreted within the context of the pseudo-redundant network proposed for the PTM hypothesis. Because such demonstrations are only seen when the chemical is applied centrally, only part of the network involved in short-term memory (call it A) is altered. Therefore, another part of the network working in parallel (call it B) to effect a longer term storage need not be playing a role in retrieval in short term memory, but only is recruited at some later time point. Thus, a local manipulation at A may cause disruption of short-term memory, without disrupting long-term, suggesting a parallel process in B with different kinetics.

7.4. The classic case of HM

Bilateral hippocampal extirpation in this patient caused a profound anterograde amnesia attributed to the loss of memory-forming hippocampus. Presuming that the initial coding and storage of information is within hippocampal circuitry, the anterograde amnesia may arise for the obvious reason that the structure is no longer present to perform its function. The preservation of long-lasting memories, or limited retrograde amnesia, may be understood within the PTM model, as the highly over-represented, and widely distributed endogenously rehearsed material, that the temporal lobe damage did not access. An interesting sidelight is that if hippocampus is important for maintaining and driving endogenous activity one would

predict a more profound loss of these older memories. In fact it has been noted that his memories are fading (B. Milner, personal communication).

7.5. Alzheimer's disease

The present theory may help understand the preserved functions observed in Alzheimer's disease patients. In particular, it has been shown in several dramatic instances where the person can play bridge but cannot identify the names of the cards or can improvise on a jazz tune without knowing the chord structure or the name of the tune. Presumably the high degree of representation permits this preserved learning, and thus some resistance to the ravages of the disorder. In our laboratory, it has been shown that there is a hypertrophy of connections that appears to occur in Alzheimer's disease within the hippocampus, giving rise to potentially inappropriate growth which would actively interfere with memory formation processes (Rekart et al., 2004).

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