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# Networks of neurons, networks of genes: An integrated view of memory consolidation

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**Abstract**

Investigations into the mechanisms of memory formation have abided by the central tenet of the consolidation theory—that memory formation occurs in stages which differ in their requirement for protein synthesis. The current most widely accepted hypothesis posits that new memories are encoded as neural activity-induced changes in synaptic efficacy, and stabilization of these changes requires *de novo* protein synthesis. However, the basic assumptions of this view have been challenged by concerns regarding the specificity of the effects of the protein synthesis inhibitors used to support the claim. Studies on immediate-early genes (IEGs), in particular *Arc*, provide a distinct and independent perspective on the issue of the requirement of new protein synthesis in synaptic plasticity and memory consolidation. The IEG *Arc* and its protein are dynamically induced in response to neuronal activity, and are directly involved in synaptic plasticity and memory consolidation. Although we provide extensive data on *Arc*'s properties to address the requirement of genomic and proteomic responses in memory formation, *Arc* is merely one element in a network of genes that interact in a coordinated fashion to serve memory consolidation. From gene expression and other studies, we propose the view that the stabilization of a memory trace is a continuous and ongoing process, which does not have a discrete endpoint and cannot be reduced to a single deterministic "molecular cascade". Rather, memory traces are maintained within metastable networks, which must integrate and update past traces with new ones. Such an updating process may well recruit and use many of the plasticity mechanisms necessary for the initial encoding of memory.


*Keywords:* Hippocampus; Arc; Immediate-early gene; Memory; Learning; Protein synthesis; Neocortex; LTP; Synaptic plasticity

## 1. Introduction

The theory of memory consolidation—that memory formation proceeds in stages and the stability and strength of newly formed memories increase with passage of time—has guided contemporary investigations into the neurobiological bases of learning and memory. The hypothesis originated from observations in human subjects in which interference introduced during a limited time after learning disrupted retention of learned information (Müller & Pilzecker, 1900). The term consolidation was adopted to describe the post-learning processes of memory stabilization. The idea was elaborated in later experiments when electroconvulsive shock administered to rodents at various time points post-training confirmed susceptibility of memory traces to interference at early, but not later, time points after learning (Duncan, 1949; Gerard, 1949). Thereafter, many investigations focused on identifying the molecular, cellular, and systems events and interactions, at successive time points post-learning, to address the mechanisms of memory consolidation (McGaugh, 2000).

Protein synthesis inhibitors (PSIs) became an important tool in the research on memory and consolidation since the seminal work of Agranoff, Davis, and Brink (1965) who administered the PSI puromycin into goldfish and demon-

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strated a time-limited impairment of long-term memory. The obvious inference from this study was that long-term memory requires *de novo* protein synthesis whereas short-term memory does not. This study and others (Davis & Squire, 1984; Flexner, Flexner, & Stellar, 1963; Goelet, Castellucci, Schacher, & Kandel, 1986) solidified the current and widely accepted model of memory consolidation, in which initially weak connections between newly recruited neurons become strengthened and stable in a *de novo* protein synthesis-dependent manner. The necessary cellular responses involved include activation of second-messenger systems, new RNA transcription, and protein synthesis. The mechanisms of stabilizing memory traces at the cellular level are referred to as "synaptic consolidation" (Dudai, 2004; Frankland & Bontempi, 2005). This is distinct from another form of consolidation, "systems" consolidation (Frankland & Bontempi, 2005), which denotes a reorganization of memory traces between brain regions. Although the terms "synaptic" and "systems" consolidation describe phenomena at different levels of analysis, the two processes may share similar mechanisms and occur in parallel. Reorganization of memory traces between brain regions ("systems") may require modifications of connections ("synaptic") within those networks. Here, we review the role of gene expression in memory with a focus at the "synaptic" consolidation level.

Some of the key support for the consolidation hypothesis came from studies examining the effects of PSIs on long-term memory. However, concerns about the technical issues and limits associated with the use of PSIs have been raised and brought on alternative explanations/hypotheses (Davis & Squire, 1984; Gold, 2006; Routtenberg & Rekart, 2005). For example, non-specific and toxic effects of PSIs (Gold, 2006; Routtenberg & Rekart, 2005; Rudy, Biedenkapp, Moineau, & Bolding, 2006) render uncertainties about whether the memory impairments observed in such studies are in fact due to direct inhibition of *de novo* protein synthesis. PSIs may not just inhibit new synthesis of proteins, but also induce kinase activation and apoptosis along with other unspecified effects (Rudy et al., 2006). As such, PSIs may selectively target active neurons made susceptible by their recent activity at the time of encoding and produce permanent alterations manifested as poor performance on retention testing (Rudy et al., 2006). Several studies reported a pharmacological "rescue" of PSI-induced amnesia and a lack of effects of PSIs on memory retention when training parameters were adjusted (reviewed in: Gold, 2006; Routtenberg & Rekart, 2005). These findings cast doubt on the requirement of *de novo* protein synthesis in memory consolidation. An alternative hypothesis proposes "post-translational protein modification (PTM)" of existing proteins as the only critical mechanisms for long-term memory (Routtenberg & Rekart, 2005). The PTM model suggests that modifications of proteins already present at activated synapses is necessary and sufficient for long-term memory, and that *de novo* transcription and translation merely serve a replenishment role. Another alternative suggests that *de novo* protein synthesis is critical in modulation, rather than consolidation, of memory, and it does not constitute the actual "substrate" of the memory trace (Gold, 2006). This suggestion explains the rescue of PSI-induced amnesia by pharmacological and training parameter manipulations. One must caution, however, that such pharmacological rescues of PSI-induced amnesia with drugs such as amphetamine result in an altered brain state, and do not necessarily speak to how the brain normally processes information to form memories. The central issue of discussion in this article is whether newly synthesized proteins play an "instructive" role in the form of enabling plastic processes, as opposed to a "permissive" role, in the form of replenishment.

Nonspecific global and noxious effects of PSIs do confound interpretations of studies using these agents, but they do not necessarily rule out the requirement of *de novo* protein synthesis for formation of long-term memory. While the discussion over the methodological limitations associated with use of PSIs could ensue endlessly, contemporary studies employing sophisticated molecular biology techniques offer alternative approaches to test the question of whether memory consolidation requires "instructive" protein synthesis induced by neuronal activity. Specifically, studies examining the role of dynamically expressed immediate-early genes (IEGs) and proteins in memory processes address the issue of requirement for genomic and proteomic responses to activity in formation of long-term memory. Whereas concerns about non-specific targets of PSIs have been raised to dispute the contribution of *de novo* translation to synaptic plasticity, IEG studies counter these arguments by showing memory impairments after selectively blocking expression of specific IEG proteins, thus minimizing global toxic effects. Here, we demonstrate that IEG studies provide an independent perspective on the validity of the memory consolidation hypothesis and support for the requirement of activity/experience-dependent genomic responses for long-term memory. We start with an overview of IEGs and show how their induction profiles and cellular functions serve synaptic plasticity mechanisms thought to be necessary for long-term memory. Then, we review studies examining one particular IEG, *Arc*, and how the findings provide support for the requirement of a genomic response in memory consolidation. Furthermore, we describe how IEG/*Arc* studies can transcend levels of analysis, from the molecular to systems levels, to form an integrated view of memory function. Finally, we discuss how gene expression studies stimulate the idea that orchestrated expression of multiple activity-regulated genes is critical for gating synaptic plasticity and the ability of neurons to encode and store new information. Based on gene expression and other studies, we propose a dynamic model of memory, which integrates molecular, cellular, and systems level interactions underlying long-term memory (Fig. 1).