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# Actin dynamics and the evolution of the memory trace

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ABSTRACT

The goal of this essay is to link the regulation of actin dynamics to the idea that the synaptic changes that support long-term potentiation and memory evolve in temporally overlapping stages—generation, stabilization, and consolidation. Different cellular/molecular processes operate at each stage to change the spine cytoarchitecture and, in doing so, alter its function. Calcium-dependent processes that degrade the actin cytoskeleton network promote a rapid insertion of AMPA receptors into the post synaptic density, which increases a spine's capacity to express a potentiated response to glutamate. Other post-translation events then begin to stabilize and expand the actin cytoskeleton by increasing the filament actin content of the spine and reorganizing it to be resistant to depolymerizing events. Disrupting actin polymerization during this stabilization period is a terminal event—the actin cytoskeleton shrinks and potentiated synapses de-potentiate and memories are lost. Late-arriving, new proteins may consolidate changes in the actin cytoskeleton. However, to do so requires a stabilized actin cytoskeleton. The now enlarged spine has properties that enable it to capture other newly transcribed mRNAs or their protein products and thus enable the synaptic changes that support LTP and memory to be consolidated and maintained.

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## 1. Introduction

Shortly after Bliss and Lomo (1973) discovered long-term potentiation (LTP), Eva Fifková and her colleagues discovered that the induction stimulus that produced enhanced synaptic potentials also increased the size of dendritic spines (Fifková and Anderson, 1981; Fifková and van Harreveld, 1977; van Harreveld and Fifková, 1975). The change occurred rapidly and endured for at least an hour. A strong implication of this finding was that synaptic activity that produces LTP alters the structure and perhaps the function of dendritic spines. Fifková's subsequent research revealed the presence of actin filaments that formed a lattice structure in the dendritic spine head but that were organized in long strands in the spine neck and dendritic shaft. She speculated that the dynamic properties of actin could be essential to the modification of spine size and could play a major role in synaptic plasticity (Fifková, 1985). As her research foreshadowed, actin dynamics have proven to be central to synaptic plasticity and memory (e.g., Bosch and Hayashi, 2012; Fortin et al., 2012; Lamprecht, 2014).

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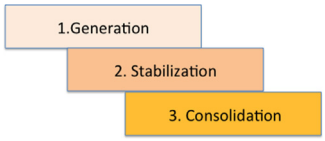


**Fig. 1 – The synaptic changes that support LTP and memory evolve in temporally ordered overlapping stages that can be distinguished by the unique set of molecular processes that regulate actin at each stage.**

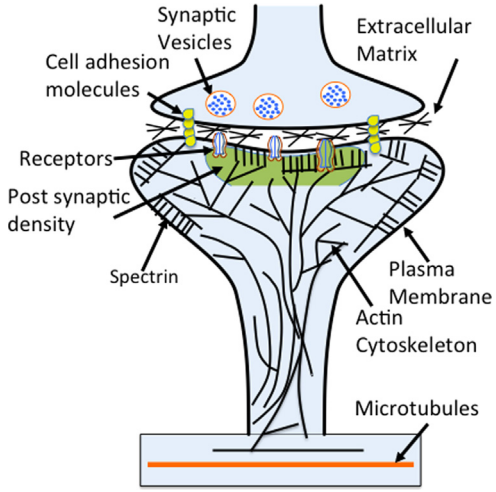


**Fig. 2 – Actin filament bundles are prominent in the spine neck and actin networks are prominent in the spine head and linked to the plasma membrane by *spectrins*. The actin-spectrin network forms a barrier that limits access to the postsynaptic density and the plasma membrane.**

Over a century ago William James (1890), the father of American psychology, proposed that the memory trace evolves in a set of overlapping stages that he called *after image*, *primary memory*, and *secondary memory*. A briefly lasting sensation (after image) is followed by a persisting representation of experience (primary memory) that forms part of a stream of consciousness that fades into the final stage (secondary memory)—the vast record of experiences that recede from consciousness but can later be retrieved.

Although the language has changed, much of modern research is guided by the idea that the memory trace and its synaptic basis also evolve in stages (McGaugh, 2003). Thus, memory researchers distinguish between short-term memory and long-term memory, and students of synaptic plasticity distinguish between various forms of LTP such as short-lasting LTP and long-lasting LTP or early-phase versus late-phase LTP. Implicit in such terminologies is the idea that (a) at different time points synapses that support memory or LTP may have a different molecular composition, and (b) this composition may be arrived at through different signaling pathways.

Lynch et al. (2007) provided a modern taxonomy that follows in the James tradition. Their framework assumes that synaptic changes that support LTP and memory evolve over three temporally ordered but overlapping stages referred to here as (a) generation, (b) stabilization, and (c) consolidation (Fig. 1). The purpose of this essay is to illuminate the contribution of actin dynamics to the synaptic changes that support LTP and memory by situating its regulation into this framework. Its goal is to show that different processes regulate actin dynamics at each stage and that the function of the actin cytoskeleton differs as these synaptic changes evolve toward stability.

To accomplish these goals, the organization of actin cytoskeleton in dendritic spines is briefly described and the regulation of AMPA receptor trafficking and actin dynamics will be identified as core targets of the biochemical processes that establish LTP. The two major sections that follow will discuss (a) the regulation of actin during different stages in the evolution of LTP and (b) actin dynamics and memory. A final section will speculate on how the function of the actin cytoskeleton changes at each stage and how a consolidated actin cytoskeleton in dendritic spines contributes to the maintenance of the synaptic changes in the face of molecular turnover.

## 2. Actin cytoskeleton in dendritic spines

Actin exists as a monomer (*globular, G actin*) that can interact at its head and tail (polymerize) with two other actin molecules to form *filamentous actin (F actin)*. *Cofilin* is a proximal regulator of actin polymerization. In its unphosphorylated state cofilin depolymerizes actin, but this property is inhibited when cofilin is phosphorylated.

Fifková's early description of the organization of actin in dendritic spines is still generally accurate. Actin filaments can organize into *actin bundles* and *actin networks*. For example, in the spine neck and dendrite, actin is organized in bundles—long strands that are cross-linked in parallel (Fig. 2). Parallel actin bundles support projections of the plasma membrane such as dendrites and spines. In contrast, in networks actin filaments are cross-linked in orthogonal arrays and are found primarily in the head region of the spine (Korobova and Svitkina, 2010).

Actin networks beneath the plasma membrane provide the structural basis of the cytoskeleton through association with the actin-binding protein *spectrin* (also called *fodrin*). This protein provides an interface between actin filament and the plasma membrane by its interaction with proteins in the plasma membrane. These networks are semisolid gels that can be viewed as creating a barrier to proteins, such as AMPA receptors and scaffolding proteins, which need to access the postsynaptic density (PSD) and plasma membrane. A functional synapse requires an established relationship between the pre and postsynaptic components. Actin also contributes to this stability by providing attachment sites for *cell adhesion molecules* such as *cadherins* and *integrins* that are present in the pre and postsynaptic components of the synapse.

## 3. AMPA receptor trafficking and actin regulation

In 1984 Gary Lynch and Michel Baudry proposed that enhanced synaptic excitatory potentials, recorded as LTP, were the result of postsynaptic calcium-dependent processes that expanded the pool of glutamate receptors in the PSD.