What is Memory?

Cytoskeletal Signaling: Is Memory Encoded in Microtubule Lattices by CaMKII Phosphorylation?

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## Abstract

Memory is attributed to strengthened synaptic connections among particular brain neurons, yet synaptic membrane components are transient, whereas memories can endure. This suggests synaptic information is encoded and ‘hard-wired’ elsewhere, e.g. at molecular levels within the post-synaptic neuron. In long-term potentiation (LTP), a cellular and molecular model for memory, post-synaptic calcium ion (Ca2+) flux activates the hexagonal Ca2+-calmodulin dependent kinase II (CaMKII), a dodacameric holoenzyme containing 2 hexagonal sets of 6 kinase domains. Each kinase domain can either phosphorylate substrate proteins, or not (i.e. encoding one bit). Thus each set of extended CaMKII kinases can potentially encode synaptic Ca2+ information via phosphorylation as ordered arrays of binary ‘bits’. Candidate sites for CaMKII phosphorylation-encoded molecular memory include microtubules (MTs), cylindrical organelles whose surfaces represent a regular lattice with a pattern of hexagonal polymers of the protein tubulin. Using molecular mechanics modeling and electrostatic profiling, we find that spatial dimensions and geometry of the extended CaMKII kinase domains precisely match those of MT hexagonal lattices. This suggests sets of six CaMKII kinase domains phosphorylate hexagonal MT lattice neighborhoods collectively, e.g. conveying synaptic information as ordered arrays of six “bits”, and thus “bytes”, with 64 to 5,281 possible bit states per CaMKII-MT byte. Signaling and encoding in MTs and other cytoskeletal structures offer rapid, robust solid-state information processing which may reflect a general code for MT-based memory and information processing within neurons and other eukaryotic cells.

## Author Summary

Memory is understood as strengthened synaptic connections among neurons. Paradoxically components of synaptic membranes are relatively short-lived and frequently re-cycled while memories can last a lifetime. This suggests synaptic information is encoded at a deeper, finer-grained scale of molecular information within post-synaptic neurons. Long-term memory requires genetic expression, protein synthesis, and delivery of new synaptic components. How are these changes guided on the molecular level? The calcium-calmodulin dependent protein kinase II (CaMKII) has been heavily implicated in the strengthening of active neural connections. CaMKII interacts with various substrates including microtubules (MTs). MTs maintain cellular structure, and facilitate cellular cargo transport, effectively controlling neural architecture. Memory formation requires reorientation of this network. Could CaMKII-MT interactions be the molecular level encoding required to orchestrate neural plasticity? Using molecular modeling and electrostatic profiling, we show a precise matching between the spatial dimensions, geometry and electrostatics of CaMKII and MTs, and calculate the potential information capacity and bio-energetic parameters of such interactions. Results suggest signaling and encoding in MTs offers rapid, robust information processing with a large potential for memory storage, reflecting a general code for MT-based memory in neurons and other eukaryotic cells.

Memories May Not Live in Neurons’ Synapses: The finding could mean recollections are more enduring than expected and disrupt plans for PTSD treatments Mar 17, 2015 |By [Roni Jacobson](http://www.scientificamerican.com/author/roni-jacobson)

Do memories live outside neurons or within them? <http://www.scientificamerican.com/article/memories-may-not-live-in-neurons-synapses/>

As intangible as they may seem, memories have a firm biological basis. According to textbook neuroscience, they form when neighboring brain cells send chemical communications across the synapses, or junctions, that connect them. Each time a memory is recalled, the connection is reactivated and strengthened. The idea that synapses store memories has dominated neuroscience for more than a century, but a new study by scientists at the University of California, Los Angeles, may fundamentally upend it: instead memories may reside *inside* brain cells. If supported, the work could have major implications for the treatment of post-traumatic stress disorder (PTSD), a condition marked by painfully vivid and intrusive memories.

More than a decade ago scientists began investigating the drug propranolol for the treatment of PTSD. Propranolol was thought to prevent memories from forming by blocking production of proteins required for long-term storage. Unfortunately, the research quickly hit a snag. Unless administered immediately after the traumatic event, the treatment was ineffective. Lately researchers have been crafting a work-around: evidence suggests that when someone recalls a memory, the reactivated connection is not only strengthened but becomes temporarily susceptible to change, a process called memory reconsolidation. Administering propranolol (and perhaps also therapy, electrical stimulation and certain other drugs) during this window can enable scientists to block reconsolidation, wiping out the synapse on the spot.

The possibility of purging recollections caught the eye of David Glanzman, a neurobiologist at U.C.L.A., who set out to study the process in *Aplysia*, a sluglike mollusk commonly used in neuroscience research. Glanzman and his team zapped *Aplysia* with mild electric shocks, creating a memory of the event expressed as new synapses in the brain. The scientists then transferred neurons from the mollusk into a petri dish and chemically triggered the memory of the shocks in them, quickly followed by a dose of propranolol.

Initially the drug appeared to confirm earlier research by wiping out the synaptic connection. But when cells were exposed to a reminder of the shocks, the memory came back at full strength within 48 hours. “It was totally reinstated,” Glanzman says. “That implies to me that the memory wasn't stored in the synapse.” The results were recently published in the online open-access journal eLife.

If memory is not located in the synapse, then where is it? When the neuroscientists took a closer look at the brain cells, they found that even when the synapse was erased, molecular and chemical changes persisted after the initial firing within the cell itself. The engram, or memory trace, could be preserved by these permanent changes. Alternatively, it could be encoded in modifications to the cell's DNA that alter how particular genes are expressed. Glanzman and others favor this reasoning.

Eric R. Kandel, a neuroscientist at Columbia University and recipient of the 2000 Nobel Prize in Physiology or Medicine for his work on memory, cautions that the study's results were observed in the first 48 hours after treatment, a time when consolidation is still sensitive.

Though preliminary, the results suggest that for people with PTSD, pill popping will most likely not eliminate painful memories. “If you had asked me two years ago if you could treat PTSD with medication blockade, I would have said yes, but now I don't think so,” Glanzman says. On the bright side, he adds, the idea that memories persist deep within brain cells offers new hope for another disorder tied to memory: Alzheimer's.

***FURTHER READINGS AND CITATIONS*** [ScientificAmerican.com/apr2015/advances](http://scientificamerican.com/apr2015/advances)

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