New theory challenges current view of how brain stores long-term memory

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How do you remember your own name? Is it possible ever to forget it? The memory trace, or engram, "feels" like it is stored permanently in the brain and it will never be forgotten.
Indeed, the current view of memory is that, at the molecular level, new proteins are manufactured, in a process known as translation, and it is these newly synthesized proteins that subsequently stabilize the changes underlying the memory. Thus, every new memory results in a permanent representation in the brain.

But Northwestern University neuroscientist Aryeh Routtenberg has presented a provocative new theory that takes issue with that view. Routtenberg, with doctoral student Jerome L. Rekart, outlined the new theory on memory storage in the January issue of the journal Trends in Neuroscience.

Rather than permanent storage, there is a "dynamic, meta-stable" process, the authors said. Our subjective experience of permanence is a result of the re-duplication of memories across many different brain networks.

For example, one's name is represented in innumerable neural circuits; thus, it is extremely difficult to forget. But each individual component is malleable and transient, and as no particular neural network lasts a lifetime, it is theoretically possible to forget one's own name.

This is seen in the most advanced stages of Alzheimer's disease, the

researchers stated.

The advantage of such a precarious storage mechanism is that it is a highly flexible system, enabling rapid retrieval even of infrequent elements, with great advantages over models of permanent storage, said Routtenberg, professor in the department of psychology and in the department of neurobiology and physiology, Judd A. and Marjorie Weinberg College of Arts and Sciences and a leading researcher in the Institute for Neuroscience, Northwestern University.

To achieve this high degree of flexibility, Routtenberg's new theory goes on to propose that the brain stores long-term memory by rapidly changing the shape of proteins already present at those synapses activated by learning.

While it is universally agreed that brain proteins are critical for memory storage, Routtenberg's hypothesis challenges the widely accepted, 40-year-old model that long-term memories are stabilized only once newly synthesized proteins are transported to recently activated synapses.

Indeed, this view is central to the theory of Eric Kandel, who in his Nobel Prize address reinforced the central position of this model in forming long-term memory.

So does memory form because you make more protein, as most neuroscientists believe, or because you change the shape of existing proteins, which are known to be strategically located to effect change within milliseconds of activation?

Part of the answer to this question lies in the fact that there are critical weaknesses in the prevailing view.

"There are enough instances of memory storage in the virtual absence of

protein synthesis to compel consideration of alternative models," said Routtenberg.

The authors noted that most of the evidence supporting the current view was obtained by studying the effects of certain drugs, called protein synthesis inhibitors, on memory, leading to the conclusion that synthesis was necessary. The authors outline specific evidence that calls those results into question.

For example, synthesis inhibitors that block the production of new proteins by more than 90 percent often cause no discernible memory impairments. Additionally, protein synthesis inhibitors cause a number of side effects that could lead to memory loss caused by something other than protein synthesis inhibition.

Routtenberg agrees with the view that it is the synapse that is modified in response to learning-associated activity, a position first articulated by Nobelist Ramon y Cajal a century ago. But the difference with the current theory is that he and Rekart do not believe that synaptic modification is brought about by recently synthesized proteins.

Routtenberg's theory, derived from a consideration of extensive, fundamental biochemical information, advocates that learning leads to a post-synthesis (or, post-translational) synaptic protein modification that results in changes to the shape, activity and/or location of existing synaptic proteins. In the Routtenberg-Rekart proposal, this is the only mechanism required for long-term memory.

To maintain some residue of this modification, Routtenberg proposes that the "spontaneous activity" of the brain actually acts to "cryptically rehearse" past events. So, long-term memory storage relies on a positive-feedback rehearsal system that continually updates or fine-tunes post-translational modification of previously modified synaptic proteins. It is

in this manner that this model allows for the continual modifications of memories.

In the Routtenberg-Rekart model, post-translational modifications within cells and synaptic dialog and endogenous activity between cells and networks work in concert to perpetuate and update memory representations.

A group of post-translational protein modifications that affect neuronal plasticity – present in activated pre-synaptic and post-synaptic elements and regulated by proteases, kinases and phosphatases – regulate the efficacy of the synapse in response to a learning event.

These modifications are, in turn, maintained via positive feedback between cells (dialog), which are regulated by synaptic excitation (e.g., via the neurotransmitter glutamate) or inhibition (e.g., via the neurotransmitter GABA).

Thus, the self-sustaining positive feedback system also carries built-in control mechanisms that would prevent runaway feedback leading to the detonation of one massive memory or "thermonuclear" engram.

Although Routtenberg's model may represent a radical departure from the current view of how long-term memories are stored, he believes that scientists need to articulate alternative models other than the prevailing one.

A more accurate description will help address issues of memory loss in mental retardation, aging and Alzheimer's disease. Indeed, new hypotheses can lead to the development of new chemical agents that would successfully target the chemical reactions necessary "We would assert that there is enough substance both in the concerns raised and in the post-translational modification/positive feedback model proposed to

energize the search for yet more plausible models of long-term memory storage, and to redirect and reinvigorate the quest to understand the brain substrates of information storage," Routtenberg said.

Source: Northwestern University