

Higher-order interactions between hippocampal CA1 neurons are disrupted in amnesic mice. Yan C, Mercaldo V, Jacob AD, Kramer E, Mocle A, Ramsaran AI, Tran L, Rashid AJ, Park S, Insel N, Redish AD, Frankland PW, Josselyn SA. Nat Neurosci. 2024 Jul 19. [Article](#).

Re-interpretation based on the IPL mechanism

Authors found that TAT-GluA23Y, an inhibitor of AMPA receptor (AMPA) endocytosis, partially rescued long-term memory deficits in mice with high levels of amyloid- β . The semblance hypothesis has put forward formation of (inter-postsynaptic (inter-spine) functional LINKS (IPLs) as the engram mechanism during learning and reactivation of these IPLs as the engram mechanism during memory retrieval generating first-person inner sensations. Endocytosis of AMPARs utilizes membranes segments from the lateral spine membranes to form endosomes. This will lead to a reduction in the size of the spine heads and lead to reversal of the IPLs formed during learning (**Fig.1**). By inhibiting AMPAR endocytosis, TAT-GluA23Y will maintain the spines in their maximum possible sizes that will facilitate IPL formation. Hence, even though amyloid- β within the extracellular space hinder IPL formation, TAT-GluA23Y can facilitate formation of more IPLs. This will enable partially rescue of long-term memory deficits in mice with high amyloid- β .

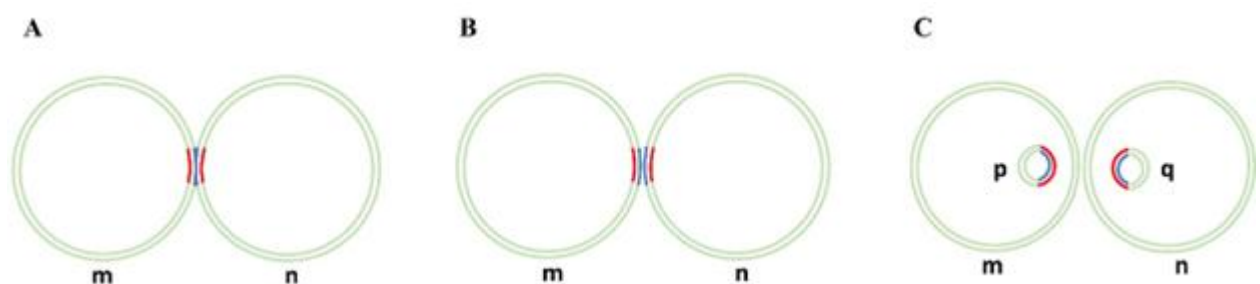


Figure 1. Figure showing how endocytosis will cause reduction in the size of the dendritic spine and reverse newly formed IPL. **A)** Cross section through two dendritic spines that are inter-LINKed to form a hemifused structure. **B)** Membrane segments invaginate from the spine membranes to form endosomes. In this process, the circumference of the spines reduces pulling the IPLs to separate. Here the hemifused

membranes reverse back to the stage of abutted membranes. **C)** When the endosomes are formed by using membrane segments from the spine membranes, IPLs completely reverse back to form independent spines. Note that endosome membranes are made of part of the membrane region that was forming the IPL in **Fig.A**. Red: inner membrane segments of the spines become outer membrane segments of the endosomes. Blue: outer membrane segments of the spines become inner membrane segments of the endosomes.

Authors also found that learning causes an increase in dendritic spine density and dendritic spine head diameter even in mice with high levels of amyloid- β . Based on the semblance hypothesis, increase in spine density can increase the probability for spines that belong to different neurons to form IPLs (this facilitates associative learning between stimuli that generates different motor outputs) or to form IPLs between different branches of the same neuron (this facilitates associative learning between stimuli that generate same motor output).

Finally, by comparing the accuracy of different classifiers trained on the neuronal Ca^{2+} data to decode freezing behavior, authors concluded that certain complex interactions between hippocampal CA1 neurons are necessary for normal memory. Based on the semblance hypothesis, these complex interactions between CA1 neurons of the same neuronal order occur due to the formation (during learning) and reactivation (during memory retrieval) of IPLs. Interconnections of several spines lead to the formation of islets of inter-LINKed spines (IILSs). The engram consists of relationships between the spines within the IILSs.