Effects of Patterned Stimulation of Mossy Cells during Fear Conditioning on Memory Retrieval and Dynamics of Dentate Gyrus Circuitry

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The hippocampus is a key brain region for learning and memory. The dentate gyrus (DG), the first relay station of the hippocampus, receives multimodal sensory inputs from cortical areas and participates in object recognition and contextual memory. The DG is composed of two types of glutamatergic neurons including the granule cells (GCs) and hilar mossy cells (MCs) and various types of local-circuit GABAergic interneurons (INs). The GCs receive cortical inputs and then excite the MCs, which directly feedback to excite GCs and indirectly inhibit GCs via activation of local INs. MC-mediated feedback excitatory loops are important circuit motifs of neuronal computation and are thought to support memory formation. However, chemogenetic experiments demonstrated that activation of dorsal MCs suppressed contextual fear memory. In contrast, optogenetic stimulation of MCs at physiologically relevant frequency during fear conditioning significantly enhanced memory retrieval.

Long-term potentiation (LTP) is considered a synaptic substrate for learning and memory. It is known that repetitive stimulation of MC axons induces LTP at MC-to-GC synapses, thereby increasing excitation/inhibition balance in GCs. Therefore, we hypothesized that repeated activation of MCs alters the circuit dynamics, including the plasticity of synapses onto GCs and input-output relationship of GCs and thereby enhances memory retention. To test our hypothesis, we will investigate whether photostimulation of MCs during contextual fear conditioning alters DG circuit dynamics including spontaneous and evoked local field potentials (LFP) and single GC activity in freely moving mice.