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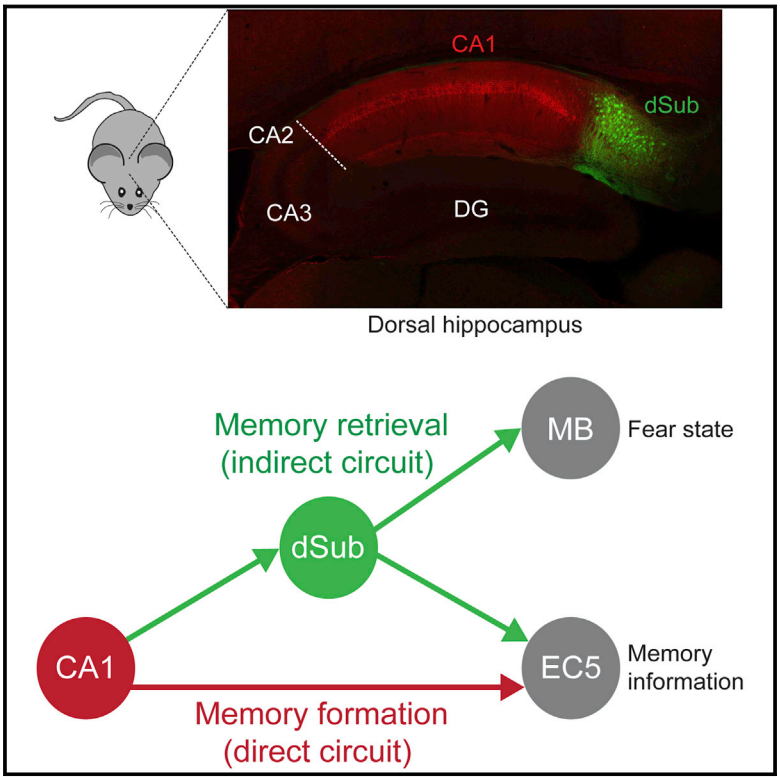
Distinct Neural Circuits for the Formation and Retrieval of Episodic Memories

Graphical Abstract



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In Brief

Episodic memories are formed and retrieved through distinct hippocampal pathways.

Highlights

- dSub and the circuit, CA1 → dSub → EC5, are required for hippocampal memory retrieval
- The direct CA1 → EC5 circuit is essential for hippocampal memory formation
- The dSub → MB circuit regulates memory-retrieval-induced stress hormone responses
- The dSub → EC5 circuit contributes to context-dependent memory updating

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Distinct Neural Circuits for the Formation and Retrieval of Episodic Memories

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SUMMARY

The formation and retrieval of a memory is thought to be accomplished by activation and reactivation, respectively, of the memory-holding cells (engram cells) by a common set of neural circuits, but this hypothesis has not been established. The medial temporal-lobe system is essential for the formation and retrieval of episodic memory for which individual hippocampal subfields and entorhinal cortex layers contribute by carrying out specific functions. One subfield whose function is poorly known is the subiculum. Here, we show that dorsal subiculum and the circuit, CA1 to dorsal subiculum to medial entorhinal cortex layer 5, play a crucial role selectively in the retrieval of episodic memories. Conversely, the direct CA1 to medial entorhinal cortex layer 5 circuit is essential specifically for memory formation. Our data suggest that the subiculum-containing detour loop is dedicated to meet the requirements associated with recall such as rapid memory updating and retrieval-driven instinctive fear responses.

INTRODUCTION

It is generally thought that formation and retrieval of a memory are accomplished by activation and reactivation of memory-holding cells (engram cells), respectively, by a largely common set of neural circuits that convey relevant sensory and processed information. However, this hypothesis has not been well studied. One of the best neural systems to prove this issue is the medial temporal lobe (MTL), including the hippocampus (HPC) and entorhinal cortex (EC), which plays crucial roles in episodic memory (Eichenbaum et al., 2007; Squire, 1992). Numerous studies have identified specific and crucial roles of individual HPC subfields and EC layers to the overall mnemonic function (Deng et al., 2010; Hasselmo and McClelland, 1999; Hitti and Siegelbaum, 2014; Moser et al., 2014; Nakazawa et al., 2004). However, the essential function of one HPC subfield, subiculum (Sub), is poorly known. The mammalian HPC formation is organized primarily as a unidirectional circuit, where information transferred from the EC's superficial layers to the dentate gyrus (DG) is processed successively in CA subfields: CA3, CA2, and CA1. Dorsal CA1 (dCA1) sends its primary projections directly to medial EC layer 5 (EC5) or indirectly via dorsal subiculum (dSub) (a detour circuit). One of the interesting differences between the direct and indirect HPC output pathways is that in the latter, dSub projects not only to EC5, but also to many cortical and subcortical brain regions (Ding, 2013; Kishi et al., 2000).

Using functional magnetic resonance imaging of human subjects, several studies have suggested that the DG and CA subfields are selectively activated during episodic memory formation, whereas subiculum (Sub) is active during the recollection of an episode (Eldridge et al., 2005; Gabrieli et al., 1997). In rodents, ibotenic acid lesions of the CA1 subfield or Sub caused impairments in the acquisition of place navigation (Morris et al., 1990). However, since human imaging studies provide only correlative, rather than causal, evidence and rodent lesions are not well targeted to a specific hippocampal subregion—especially given the close proximity of CA1 and dSub—it has not been possible to identify the essential function of Sub in episodic memory. Furthermore, previous studies did not address the potential purpose of the parallel diverging and converging dCA1 to medial EC5 and dCA1 to dSub to medial EC5 circuits in memory formation versus retrieval.

In the present study, we addressed these issues by creating a mouse line expressing Cre recombinase specifically in dSub neurons. Combined with circuit tracing and optogenetic manipulations during behavioral paradigms, we found differential roles of dSub projections in hippocampal memory retrieval and retrieval-induced stress hormone responses. We demonstrate that dSub and the circuit, CA1→dSub→EC5, are selectively required for memory retrieval, while the dSub to mammillary bodies (MB) circuit regulates stress hormones following memory retrieval. In contrast, the direct CA1→EC5 circuit is essential for hippocampal memory formation, but not recall. Our study reveals a functional double-dissociation between parallel hippocampal output circuits that are important for memory formation versus memory retrieval.