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Review article

# Gamma oscillations in the entorhinal-hippocampal circuit underlying memory and dementia

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## ABSTRACT

Gamma oscillations that occur within the entorhinal cortex-hippocampal circuitry play important roles in the formation and retrieval of memory in healthy brains. Recent studies report that gamma oscillations are impaired in the entorhinal-hippocampal circuit of Alzheimer's disease (AD) patients and AD animal models. Here we review the latest advancements in studies of entorhinal-hippocampal gamma oscillations in healthy memory and dementia. This review is especially salient for readers in Alzheimer's research field not familiar with *in vivo* electrophysiology. Recent studies have begun to show a causal link between gamma oscillations and AD pathology, suggesting that gamma oscillations may even offer a plausible future therapeutic target.

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### 1. Gamma oscillations in entorhinal cortex-hippocampus circuits of healthy subjects

The hippocampus and the entorhinal cortex (EC) play critical roles in the formation of declarative memory (Gomez-Isla et al., 1996; Scoville and Milner, 1957; Van Hoesen et al., 1991). The EC interfaces the hippocampus with a number of cortical regions, and most of the cortical input to the hippocampus comes from the EC (Cajal, 1911; Witter and Amaral, 2004). The medial part of

EC (medial entorhinal cortex, MEC) processes information about spatial memory (Steffenach et al., 2005), and contains spatially modulated cells including grid cells, head direction cells and border cells, which provide spatial information to place cells in the hippocampal CA1 (Moser et al., 2014). In contrast, the lateral entorhinal cortex (LEC) handles information for updating environmental cues, such as odors (Igarashi et al., 2014; Leitner et al., 2016; Li et al., 2017) or objects (Deshmukh and Knierim, 2011; Tsao et al., 2013). The information encoded within the EC is sent to the hippocampal CA1 through the temporoammonic (direct) pathway, and to the CA3 and dentate gyrus via perforant (indirect) pathway, providing information for memory to these regions (Witter et al., 2000).

Multi-channel (>32 channel) electrophysiological recording technique is a powerful method for investigating *in vivo* neuronal activities in the entorhinal-hippocampal circuit of behaving

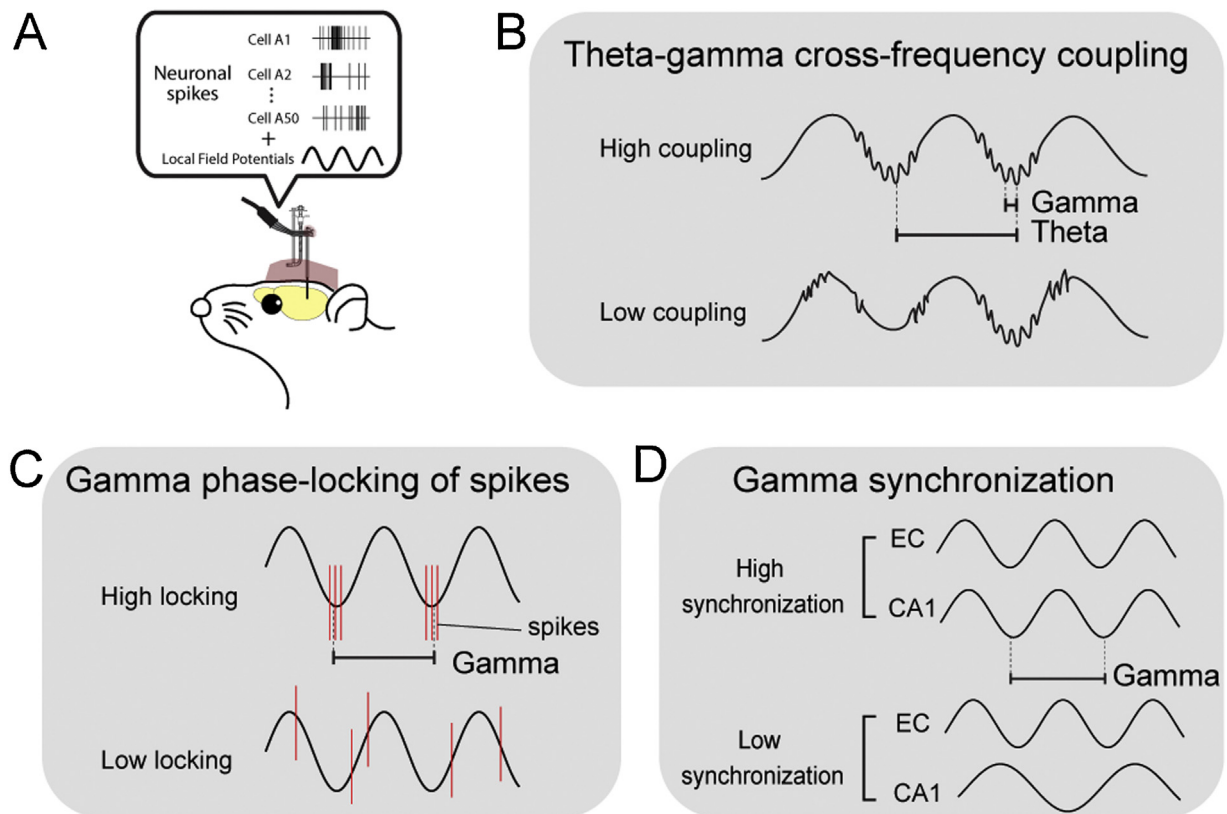
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**Fig. 1.** (A) Schematic diagram showing recordings of spike and local field potentials from behaving rodents. (B) Theta-gamma cross-frequency coupling. (C) Gamma phase locking of spikes. Red line shows spiking activity of neurons. (D) Gamma synchronization.

animals (Fig. 1A). The recorded data are normally filtered out as spike activity and slower local field potential (LFP) activity. The most prominent activities observed in the LFP recordings are theta oscillations and gamma oscillations (30–100 Hz). Theta oscillations are 4–12 Hz oscillatory activity generated mainly by the input from the medial septal nucleus. Gamma oscillations in contrast, are local activity derived from the transmembrane current of a population of periodically synchronized neurons (Buzsaki et al., 2012; Einevoll et al., 2013). In healthy rodents and humans, the hippocampus and EC exhibit prominent gamma oscillations that emerge at specific phases of theta oscillations (a phenomenon called “*theta-gamma cross-frequency coupling*”; Fig. 1B) (Bragin et al., 1995; Buzsaki et al., 1983; Canolty et al., 2006; Chrobak and Buzsaki, 1998; Colgin et al., 2009; Mormann et al., 2005; Soltesz and Deschênes, 1993). Because oscillatory membrane current of neurons also contributes to spike generation, spike timing normally coincides with specific phases of gamma oscillations (“*gamma phase locking*” of spikes; Fig. 1C). Computational models suggest that cross-frequency coupling offers an effective mechanism for inter-regional information transfer, because slower theta oscillations can spread to wider areas and synchronize local gamma generators in individual regions (Lisman, 2005; Lisman and Idiart, 1995). In the entorhinal-hippocampal circuit, theta oscillations are thought to coordinate the activity of gamma generators within the entorhinal cortex and hippocampus, whereas these gamma generators coordinate spike timing of neuronal populations in each region. Because of the coordination of multiple gamma oscillators by a common theta rhythm, gamma oscillations in the entorhinal cortex and hippocampus often show synchronization (here we refer as “*gamma synchronization*”; also referred to as “*gamma coupling*”; Fig. 1D). Theta-gamma cross-frequency coupling, gamma phase-locking of spikes and gamma synchronization are indexes commonly used for evaluating the

strength of the neuronal activity coordination by gamma oscillations.

Several studies have demonstrated that strengthening of theta-gamma cross-frequency coupling or gamma synchronization parallels with increased memory formation. The strength of theta-gamma cross-frequency coupling in the hippocampus is correlated with the task load of a working memory in human (Axmacher et al., 2010). In rats, the degree of theta-gamma coupling in the hippocampus is correlated with the amount of task demands (Tort et al., 2009). In the rat EC, strengthening of theta-gamma cross-frequency coupling also occurs during olfactory association learning. In our previous study, we recorded neural activities in the LEC and hippocampal CA1 while rats learned an odor-place association task and asked whether oscillatory coupling in the LEC and CA1 developed during task learning (Igarashi et al., 2014) (Fig. 2A). Prior investigation reports that the acquisition of odor-place association requires an intact hippocampus (Day et al., 2003), which takes ~3 weeks. We found that LFP activity in both LEC and CA1 exhibited strong oscillations in the 20–40 Hz band (slow gamma band) during sampling of the odor cues. Recording during the task learning showed that cross-frequency coupling between the theta oscillations and the 20–40 Hz band became strengthened gradually over the learning in both the LEC and CA1. The theta-gamma coupling paralleled with gradual strengthening of gamma synchronization between the CA1 and LEC (Fig. 2B). Furthermore, spiking activity of neurons in both the LEC and hippocampus developed phase-locking to slow gamma oscillations as learning progressed. These results suggest that the coordination of EC-hippocampus circuit is supported by synchronized gamma oscillations between the LEC and CA1, together with the cross-frequency coupling in the individual areas. These studies strongly suggest that the coordination of neuronal activities by gamma oscillations in the EC-hippocampus

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