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Gamma oscillations in cognitive disorders

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Gamma oscillations (~25–100 Hz) are believed to play a role in cognition. Accordingly, aberrant gamma oscillations have been observed in several cognitive disorders, including Alzheimer's disease and Fragile X syndrome. Here, we review how recent results showing abnormal gamma rhythms in Alzheimer's disease and Fragile X syndrome help reveal links between cellular disturbances and cognitive impairments. We also discuss how gamma results from rodent models of Alzheimer's disease and Fragile X syndrome may provide insights about unique functions of distinct slow (~25–50 Hz) and fast gamma (~55–100 Hz) subtypes. Finally, we consider studies employing brain stimulation paradigms in Alzheimer's disease and discuss how such studies may reveal causal relationships between gamma impairments and memory disturbances.

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Introduction

Gamma oscillations are rhythmic fluctuations in local field potentials (LFPs) that span a broad range of frequencies (~25–100 Hz). Gamma oscillations are prominent across multiple brain regions including the hippocampus, where they are believed to play a role in attentional selection and memory operations [1]. Accumulating evidence suggests that the broad range of frequencies of oscillations that are described as gamma rhythms may actually be two functionally distinct rhythms, slow (~25–50 Hz) and fast (~55–100 Hz) gamma [2,3]. These different frequencies of gamma rhythms are thought to be locally generated by circuits involving some distinct and some overlapping classes of GABAergic interneurons [3]. Although slow and fast gamma are thought to be locally generated, gamma oscillators exhibiting similar frequencies in different brain regions can become coupled by anatomical connections between the regions.

Fast gamma rhythms in the hippocampus are coupled with fast gamma inputs from the medial entorhinal cortex [2], an area that processes current sensory information. Thus, it has been proposed that fast gamma promotes the transmission of current sensory information to the hippocampus during new memory encoding [3]. In agreement with this, hippocampal fast gamma dominates during exploration of novel object–place pairings [4], and hippocampal place cells represent recent locations and current trajectories during periods of fast gamma [5,6••]. Moreover, fast gamma has been shown to be dominant, relative to slow gamma, when mice attend to external landmarks to navigate to a goal location [7].

Conversely, slow gamma rhythms in hippocampal subfield CA1 are coupled with inputs from CA3 [2], a neighboring hippocampal subfield from which stored memories are thought to be retrieved [8–10]. In line with this proposed memory retrieval role of CA3, slow gamma has been hypothesized to promote memory retrieval by facilitating CA3 inputs to CA1 [3]. This hypothesis remains controversial, in part due to reports of enhanced slow gamma measures during exploration of novel objects [11] and places [12]. Still, other evidence supports a memory retrieval role for slow gamma. In familiar environments, hippocampal place cells were found to predict upcoming locations and trajectories when slow gamma was present in CA1 [5,6••]. Another study observed increases in the magnitude of slow gamma during correct performance of an associative memory task at a time when cue-evoked memory retrieval would be expected to occur [13]. Also, slow gamma power and coherence between CA3 and CA1 increases during sharp wave-ripples (SWRs) [5,14], high frequency (~150–250 Hz) events that arise in the hippocampus during inactive behaviors (e.g., waking rest, slow wave sleep, eating, grooming [15]). These results may support a memory retrieval function for slow gamma, given that sharp wave-ripples are thought to play a key role in memory retrieval [14–16].

Given the evidence suggesting that gamma rhythms are important for hippocampal memory processing, it is perhaps not surprising that several brain disorders that involve memory impairments are associated with disturbances in gamma rhythms. However, the question of whether gamma abnormalities are responsible for cognitive impairments, or instead are just a by-product of cellular and molecular disturbances that produce cognitive symptoms, remains unanswered. In this review, we will discuss recent evidence showing impaired gamma oscillations in two major disorders that affect memory: (1) Alzheimer's disease (AD); and (2) fragile X syndrome

(FXS). We discuss how reported impairments in gamma rhythms may relate to both cellular disturbances and memory impairments associated with these disorders. We also discuss novel therapeutic strategies that attempt to alleviate cognitive deficits in these disorders by restoring normal gamma activity. Experiments incorporating such strategies are expected to provide answers to the question of whether cognitive disturbances in brain disorders are explained by aberrant gamma rhythms.

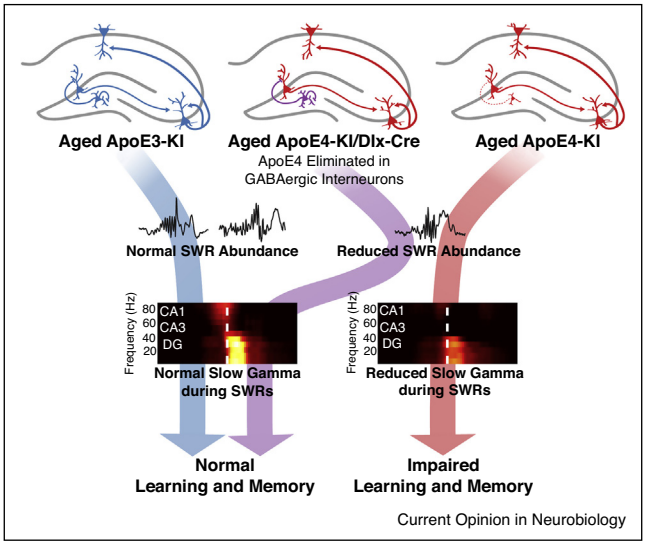
AD

AD is a progressive neurodegenerative disease that exhibits characteristic cellular and molecular pathologies in the brain, including the accumulation of amyloid-β (Aβ)-containing amyloid deposits in the extracellular space and formation of tau neurofibrillary tangles inside neurons [17]. The entorhinal cortex and hippocampus, key brain regions for spatial and episodic memory, are particularly vulnerable to cellular pathologies that characterize AD [18]. Accordingly, early cognitive symptoms of AD involve episodic and spatial memory impairments [19]. However, it remains unclear how cellular and molecular disturbances in AD affect coordinated activity across the distributed networks of neurons that subserve memory operations.

Recently, a novel hypothesis has been proposed to explain memory impairments in AD, namely that patients with AD are able to encode memories but are unable to later retrieve these memories [20••]. In accordance with this hypothesis, and the purported role of slow gamma in memory retrieval described above, disruptions in slow gamma rhythms have been observed in several rodent models of AD. We recently reported reductions in slow gamma power in CA1 of 3xTg mice navigating a familiar circular track [21•]. Also, CA1 place cell representations of space were unstable, and slow gamma coordination of CA1 place cell firing was decreased [21•]. It is possible that slow gamma impairments in these mice caused incomplete retrieval of stored spatial information from CA3 to CA1. Deficits in hippocampal slow gamma power and concomitant spatial memory impairments have also been observed in a mouse model of tau pathology [22]. However, in this study, reduced power was observed at fast gamma frequencies also, making it difficult to identify memory impairments selectively associated with slow gamma rhythms.

Decreased SWR-associated slow gamma has also been observed in multiple AD mouse models. A series of studies using mice that had undergone targeted replacement of endogenous mouse ApoE with the AD-linked human ApoE4 gene (ApoE4 KI mice) showed that manipulations that alleviated slow gamma impairments in ApoE4 KI mice rescued learning and memory deficits [23••,24]. Specifically, elimination of ApoE4 in GABAergic interneurons rescued SWR-associated slow gamma and abolished memory impairments in ApoE4 KI mice [23••,24], highlighting a role for interneuron abnormalities in slow gamma disturbances and linking disturbed slow gamma to memory impairments in AD (Figure 1). Also, Iaccarino *et al.* [25••] observed reduced SWR-associated slow gamma in the 5xFAD mouse model of AD [25••], a line with high levels of Aβ accumulation from an early age [26]. Furthermore, they demonstrated that rescuing slow gamma rhythms alleviated AD pathology. Specifically, optogenetic excitation of hippocampal fast-spiking parvalbumin-positive interneurons at slow gamma frequency (i.e., 40 Hz) attenuated Aβ production and promoted microglial engulfment of Aβ [25••].

Figure 1



Aged mice expressing the non-AD related ApoE3 allele show normal SWR abundance and SWR-associated slow gamma, and perform well in memory tasks. Conversely, aged mice expressing the AD-related ApoE4 allele have reduced SWR abundance, decreased SWR-associated slow gamma, and impaired learning and memory. Importantly, when the ApoE4 mutation is eliminated from GABAergic interneurons, SWR-associated slow gamma deficits are alleviated, and learning and memory impairments do not develop. This indicates that SWR-associated slow gamma is crucial for normal learning and memory in this aged AD model.
Source: Reproduced with permission from Ref. [23••].

The results of these studies suggest that lessening slow gamma disturbances may be a promising new strategy for treatment of memory impairments in AD. The studies discussed above demonstrate converging mechanisms in different models of AD, one modeling late-onset AD (ApoE4 KI mice) and others modeling familial AD (3xTg; 5xFAD mice). Both ApoE4 and Aβ are known to disrupt the excitatory/inhibitory (E/I) balance of neuronal networks by interfering with GABAergic transmission [27–29]. Moreover, memory impairments in both ApoE4 and Aβ AD mouse models can be attenuated by restoring interneuron function [24,30,31••]. Thus, it