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Do slow and fast gamma rhythms correspond to distinct functional states in the hippocampal network?

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ABSTRACT

For decades, hippocampal gamma was thought to be a single type of rhythm with a continuously varying frequency. However, an increasing body of evidence supports a new hypothesis regarding hippocampal gamma. The patterns traditionally defined as hippocampal gamma may actually comprise separate gamma subtypes with distinct frequencies and unique functions. The present review discusses the evidence for and against this new viewpoint. This review will also point out key questions that remain to be answered to validate the two-gamma hypothesis.

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1. Background

Until fairly recently, gamma rhythms in the hippocampus of freely behaving rodents received little experimental attention. There are several likely explanations as to why many hippocampal researchers may have disregarded gamma. One reason may be that gamma rhythms are overshadowed by larger amplitude patterns in hippocampal local field potentials, namely theta rhythms (Colgin, 2013, for a review) and sharp waves (Buzsaki, 1986). While theta and sharp waves have clear behavioral correlates, including active exploration for theta and immobility for sharp waves, gamma rhythms are observed during all behavioral states (Buzsaki et al., 1983). It is difficult to develop a testable hypothesis to explain a rhythm's function if the rhythm's occurrence is not limited to specific behaviors. Moreover, gamma rhythms are exceptionally variable with regard to both their amplitude and their frequency (from ~25 Hz to ~100 Hz). Effects of experimental manipulations on gamma amplitude and frequency can be difficult to detect because baseline measures of gamma amplitude and frequency continuously vary. Some sources of hippocampal gamma amplitude or power variations were explained in the relatively early days of hippocampal gamma research. Gamma power is maximal during theta-related behaviors, and the power of theta-associated gamma regularly fluctuates as a function of theta phase (Buzsaki et al., 1983; Bragin et al., 1995). These findings regarding gamma amplitude did not address, however, the occurrence of gamma during non-theta states (e.g., immobility). These findings also did not address variations in gamma frequency.

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2. One gamma rhythm with continuously varying frequency?

In an initial important study from the Buzsaki Lab, relatively fast gamma (~100 Hz) was associated with relatively fast theta (~10 Hz), and slower gamma (~50 Hz) was associated with slower theta (~6 Hz) (Bragin et al., 1995). This finding could indicate that gamma-generating circuitry speeds up as running speed increases, considering that theta frequency increases with running speed (Rivas et al., 1996; Slawinska and Kasicki, 1998; Jeewajee et al., 2008). This conclusion is consistent with recent findings showing that gamma frequency increases with running speed (Ahmed and Mehta, 2012). Increases in gamma frequency with increased running speed were accompanied by increases in the firing rate of interneurons. This corresponding interneuron effect may underlie gamma frequency increases considering that gamma rhythms involve inhibitory postsynaptic events (Soltesz and Deschenes, 1993; Penttonen et al., 1998; Pernia-Andrade and Jonas, 2014). These findings suggest that speed-modulated interneurons drive increases in gamma frequency as running speed increases to support faster transitions across gamma-modulated cell assemblies (Ahmed and Mehta, 2012).

However, some of the results shown in the work of Ahmed and Mehta (2012) appear to show a split between lower (~30–40 Hz) and higher (>60 Hz) gamma frequencies (see their Fig. 3). This supports the hypothesis that separate low frequency ('slow') and high frequency ('fast') gamma rhythms exist and that these different gamma subtypes are differentially affected by running speed. In line with this idea, the distribution of power in the gamma frequency range (i.e., 25–100 Hz) across different running speeds is best fit by two functions rather than a single function (Zheng et al., 2015). One function fits data in the slow gamma range, with slow gamma frequencies changing minimally as running speed increases. The other function fits the distribution of power in the fast gamma frequency range. In this case, frequencies increase as running speeds increase, as previously reported. These findings support the conclusion that slow and fast gamma states are more likely to occur during behaviors associated with low and high running speeds, respectively. Consistent with this conclusion, Kemere and colleagues also showed that slow gamma (~20–55 Hz) power in CA1 decreased with running speed, while fast gamma (~65–140 Hz) power increased with running speed (Kemere et al., 2013).

3. Two gamma rhythms entrained by different hippocampal inputs?

An early important study conducted by Bragin et al. (1995) employed current source density (CSD) analyses and concluded that there are two independent sources of hippocampal gamma: one in the entorhinal cortex (EC) and another intrinsic to the hippocampus. The dominant current sinks during gamma activity were observed in the middle molecular layer of the dentate gyrus, the termination zone for medial perforant path fibers. Moreover, CSD maps resembled CSD profiles for excitatory postsynaptic responses to medial perforant path stimulation. These findings suggest that the dominant generator of hippocampal gamma is the EC. Support for an entorhinal generator of hippocampal gamma was also provided by a CSD study in guinea pigs (Charpak et al., 1995). In the study of Bragin et al. (1995), EC lesions were also performed. After the lesions, the dominant current sinks in the molecular layer disappeared, and gamma currents arose in CA1 stratum radiatum, the termination zone for Schaffer collateral axons from CA3. This finding suggested that CA3 was a second site of hippocampal gamma generation. Interestingly, the average frequency of hippocampal gamma decreased after the entorhinal lesions, a finding that could have occurred as a result of diminished excitatory drive to the network. A later study from the same lab provided additional evidence for two hippocampal gamma oscillators, one in the dentate gyrus and one in the CA3-CA1 network. However, the peak frequency of these two gamma oscillators was reported to be similar, ~53 Hz (Csicsvari et al., 2003).

More recent findings shed light on the significance of the EC lesion effects reported by Bragin et al. (1995). Colgin et al. (2009) employed paired recordings from CA1 and two of its inputs and reported separate slow and fast gamma subtypes that were linked to inputs from the medial entorhinal cortex (MEC) and CA3, respectively. Slow (~25–50 Hz) gamma rhythms in CA1 were coupled with slow gamma in CA3, and fast gamma (~65–140 Hz) rhythms in CA1 were coherent with fast gamma in MEC (see also Kemere et al. (2013), their Fig. 3b, for a replication). Activity of CA3 neurons was significantly more correlated with the phase of slow gamma activity in CA1 than the phase of CA1 fast gamma. Also, layer III MEC neurons preferentially fired at a particular phase of fast, not slow, gamma rhythms in CA1. These findings support the hypothesis that distinct frequencies of gamma rhythms in the hippocampus are driven by different hippocampal inputs, namely CA3 and the EC.

Consistent with this hypothesis, a recent report (Schomburg et al., 2014) detected separate theta-modulated gamma components in stratum radiatum (SR) and stratum lacunosum-moleculare (S-LM) of CA1. The gamma activity in SR and S-LM displayed peak frequencies of ~40 Hz and ~90 Hz, respectively (see also Belluscio et al. (2012)). Moreover, another recent study provided support for the earlier entorhinal lesion results from Bragin et al. (1995): fast gamma (~80 Hz) power in CA1 was significantly lower in mice in which the direct projection from MEC layer III to CA1 was blocked optogenetically (Yamamoto et al., 2014). Taken together, all of these findings support the conclusion that the EC drives a fast (~60–100 Hz) variant of gamma in the hippocampus, while CA3 drives a slow (~30–50 Hz) gamma subtype.

4. Two gamma rhythms with separate functions?

But, does the existence of distinct gamma subtypes with different frequencies have implications for mnemonic operations in the hippocampal network? An increasing number of studies suggest that slow and fast gamma carry out specific functions. Yet, no consensus has been reached as to what those functions are.