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.

Keywords: Gamma; hippocampus; rhythms; oscillations; entorhinal cortex

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.

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 Ahmed and Mehta (2012) work appear to show a split between lower (~30-40 Hz) and higher (>60 Hz) gamma frequencies (see their Figure 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., 2014). 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 and colleagues (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 Bragin et al. study (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 Figure 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.

Several studies have suggested that slow gamma rhythms play an important mnemonic role in the hippocampal network. Place cell ensembles retrieve representations of upcoming locations when theta-modulated slow gamma (25-55 Hz) rhythms occur (Bieri et al., 2014). Additionally, Tort et al. (2009) found that coupling between theta phase and slow gamma (30-60 Hz) amplitude in CA3 increased as animals learned to correctly choose context-dependent stimuli in order to receive a reward. In this study, enhancement of theta-slow gamma coupling correlated with task performance and occurred prior to the point when animals made the correct selection, implying that theta-modulated slow gamma facilitated retrieval of the context-dependent memory. Shirvalkar and colleagues (2010) subsequently reported that co-modulation of theta and slow gamma (30-50 Hz) power was significantly higher in trials when animals successfully remembered the correct choice in a match-to-place task compared to trials when errors were made. A later study found that slow gamma (30-45 Hz) power increased toward the end of a fixation period in a delayed spatial alternation task, a point when memory retrieval may occur (Takahashi et al., 2014). A recent study showed that ~20-40 Hz coherence between lateral entorhinal cortex (LEC) and CA1 developed with learning of an odor-place association (Igarashi et al., 2014). The coherence occurred during odor sampling, as the odor presumably triggered recall of the associated place. Also, the development of ~20-40 Hz coherence between LEC and CA1 was paralleled by the development of odor-specific responses in LEC and CA1 cells. Together, these findings support the conclusion that slow gamma promotes the retrieval of stored memories.

However, other results do not support this hypothesis of slow gamma function. Trimper and colleagues (2013) recently reported increases in slow gamma (~40 Hz) coherence between CA3 and CA1 as rats explored novel objects, particularly objects that were later well-remembered. Memory encoding, not memory retrieval, would be expected to occur during

exploration of novel objects. In their Discussion, the authors suggested that the observed slow gamma coherence could reflect retrieval of memories of other objects that had previously been presented in the same locations. This interpretation remains to be tested, though. Similarly, Kemere et al. (2013) found that slow gamma (~20-55 Hz) power increased when animals explored a novel W-maze. However, fast gamma power also increased during exploration of the novel W-maze. Also, animals had been trained on a familiar W-maze previously. Thus, it is possible that animals retrieved their memory of the general context of the W-maze task as they explored the new maze, considering that they had to perform the task correctly in order to receive a reward. Whatever the case may be, it is clear that more experiments are needed to understand how these various slow gamma results fit together.

What is the current leading hypothesis of fast gamma function? One hypothesis is that fast gamma facilitates encoding of current spatial information. Fast gamma coordinates activity across MEC and CA1 (Colgin et al., 2009; Kemere et al., 2013), and MEC transmits information to the hippocampus about current spatial location (Brun et al., 2002; Fyhn et al., 2004; Hafting et al., 2005; Brun et al., 2008). The hippocampus would require this current location information during encoding of spatial memories. Some results provide support for this memory encoding during fast gamma hypothesis. Scopolamine, a drug that impairs memory encoding but not memory retrieval, reduced fast (~60-120 Hz) but not slow (~20-40 Hz) gamma rhythms (Newman et al., 2013). The ratio of fast gamma (~55-95 Hz) to slow gamma (~23-40 Hz) power in CA1 was significantly higher when mice used current place cues to navigate rather than relying on their memory of spatial sequences (Cabral et al., 2014). Ensembles of place cells preferentially represented recent locations, rather than predicting upcoming locations, during periods of fast gamma (~60-100 Hz) rhythms (Bieri et al., 2014). CA1 fast gamma (60-90 Hz) power was high at the start of a fixation period in a delayed spatial alternation task that included a light stimulus during the fixation period (Takahashi et al., 2014). The authors suggested that fast gamma likely occurred as the animal attended to the visual stimulus.

However, other studies yielded results that are not easily reconciled with a memory encoding function for fast gamma. In a study by Yamamoto et al. (2014), CA1 fast gamma (~65-100 Hz) power was significantly higher on the central arm of a delayed spatial alternation task than on the side arms. Moreover, performance on this task was significantly impaired when CA1 fast gamma was suppressed on the central arm by inhibiting MEC layer III inputs to CA1. The central arm portion of this type of task is not thought to be associated with memory encoding but rather with memory retrieval (Montgomery and Buzsaki, 2007) or working memory (Yamamoto et al., 2014). In the latter case, memory retrieval may occur in the start box before the animal enters the central arm (Ainge et al., 2007). Yamamoto and colleagues (2014) did not test the effects of inhibiting MEC layer III inputs to CA1, and thereby inhibiting fast gamma, at the reward sites. Thus, it is possible that task impairment would also occur if fast gamma was blocked at the reward sites, where memory encoding likely occurs. Such results would be consistent with a memory encoding role for fast gamma. In any event, the results from

Yamamoto et al. (2014) suggest that fast gamma may play a role in working memory. The afore-mentioned findings from Takahashi et al. (2014) could also be re-interpreted to support this hypothesis. Specifically, fast gamma power could have been high during the initial part of the fixation period because the animal was maintaining a memory of the previous trial in working memory. The working memory function hypothesis for fast gamma could also explain recent results from Schomburg et al. (2014). They reported increases in both slow gamma (~40 Hz) and fast gamma (~90 Hz) on the center arm of a delayed spatial alternation task. It is possible that slow gamma increased as animals retrieved their memory of the previous trial at the initial part of the center arm trajectory. Fast gamma may then have occurred during the remainder of the central arm trajectory as animals held this information in working memory.

In summary, the current hypotheses regarding fast gamma and slow gamma functions in memory processing require further testing. The hypotheses that fast gamma promotes memory encoding and slow gamma facilitates memory retrieval remain attractive in part because they are consistent with findings related to theta rhythms. Memory encoding and retrieval are thought to optimally occur at different phases of theta (Hasselmo et al., 2002; Kunec et al., 2005; Manns et al., 2007; Lever et al., 2010; Douchamps et al., 2013; Siegle and Wilson, 2014). Perhaps related to this, slow and fast gamma rhythms tend to occur on different theta phases (Colgin et al., 2009; Belluscio et al., 2012; Lasztoczi and Klausberger, 2014; Yamamoto et al., 2014; Schomburg et al., 2014), although there are discrepancies across studies with regard to what those phases are. The phase differences may be due to different methods, as suggested by Schomburg et al. (2014). Also, the preferred phase of fast gamma reported in Colgin et al. (2009) was likely distorted somewhat by epsilon (~100-150 Hz) activity, which largely reflects spiking (Belluscio et al., 2012), because the fast gamma band in Colgin et al. extended up to 140 Hz. Another possibility is that discrepancies across studies are related to differences in behavioral tasks, considering that coupling of gamma amplitude to theta phase has been related to task performance in several studies (see Colgin, 2014, for a review).

5. Link between gamma rhythms and synaptic plasticity?

‘Theta burst stimulation’ patterns (i.e., bursts of 100 Hz stimulation delivered at theta frequency) resemble theta-modulated fast gamma rhythms and are optimal for inducing long-lasting increases in synaptic strength that are believed to underlie memory encoding (i.e., long-term potentiation (LTP); Larson et al., 1986; Larson and Lynch, 1986). This resemblance naturally leads to the hypothesis that theta-modulated fast gamma rhythms are involved in memory encoding, a hypothesis that has been suggested previously for theta-modulated gamma in general (Jensen and Lisman, 2005). In line with this hypothesis, the fast gamma period (~10-15 ms) falls within the critical time window for inducing increases in synaptic strength (i.e., ≤ 20 ms; Bi and Poo, 1998). Also, there are some indications that cells in superficial layers of entorhinal cortex fire repetitively at fast gamma frequencies (Chrobak and Buzsaki, 1998) across successive theta cycles (e.g., Climer et al., 2014). Thus, it is plausible to hypothesize that entorhinal inputs to hippocampus during exploratory behaviors are capable of inducing LTP.

There is also evidence suggesting that slow gamma (40 Hz) stimulation induces LTP when paired with postsynaptic depolarization (Buonomano, 1999). However, slow gamma stimulation in this study was delivered continuously, not timed by theta periods. There is little *in vivo* evidence that hippocampal principal cells fire at gamma frequencies for extended periods of time (i.e., >200 ms, as in the Buonomano, 1999 study). Identifying LTP induction patterns that are physiologically realistic is important, in part because not all forms of LTP are identical. For example, signaling pathways involved in LTP differ for natural (i.e., theta burst stimulation) and unnatural (i.e., tetanic stimulation) stimulation protocols (Zhu et al., in press). Nevertheless, the question of how slow gamma activation patterns relate to synaptic plasticity remains open and warrants further study.

6. Slow and fast gamma during quiescent states and sleep

Any explanation of the functional significance of slow and fast gamma must also address the occurrence of slow and fast gamma during quiescent and sleep states. Previous findings suggesting that slow and fast gamma coordinate the flow of activity in the hippocampal network (Colgin et al., 2009) evoke hypotheses regarding slow and fast gamma during different states of sleep and waking. Sharp waves involve propagation of activity from CA3 to CA1 (Buzsaki 1986; Colgin et al., 2004), suggesting the hypothesis that slow gamma occurs during sharp wave-related states, including awake immobility and slow-wave sleep (Buzsaki 1986). Theta rhythms occur during REM (Buzsaki et al., 1983), and activity flows from EC superficial layers to the hippocampus during theta (Chrobak and Buzsaki, 1994). Thus, a plausible hypothesis is that fast gamma occurs in the hippocampus during REM sleep. In line with the first hypothesis, recent studies revealed that slow gamma power increased in CA3 and CA1 during sharp wave-ripples (Carr et al., 2012) and decreased during REM (Schomburg et al., 2014). Fast gamma (60-120 Hz) power, on the other hand, has been reported to increase in CA1 and MEC during REM sleep (Schomburg et al., 2014), consistent with our unpublished observations (Figure 1). These findings are in line with the hypothesis that slow gamma promotes CA3 inputs to CA1 and fast gamma facilitates EC inputs to CA1 during both sleep and waking states.

7. Key questions for future study

If slow and fast gamma are separate network states in the hippocampus, as the arguments above suggest, then one would expect the two states to have separate mechanisms of generation. A likely possibility is that different classes of interneurons are involved in slow and fast gamma generation. Consistent with this idea, Lastoczi and Klausberger recorded interneurons of unknown classification in CA1 stratum radiatum and lacunosum-moleculare and found that some coupled with 20-45 Hz gamma and others with 60-100 Hz gamma (Lastoczi and Klausberger, 2014). Recent findings raise the possibility that CA3-activated interneurons could drive slow gamma, while also inhibiting fast gamma-generating circuitry. OLM interneurons in CA1, which are activated by inputs from CA3, were shown to inhibit EC input to CA1 while also disinhibiting input from CA3 (Leao et al., 2012). These findings raise the question of whether

interneurons that receive entorhinal input could operate in a similar manner, driving fast gamma while also inhibiting slow gamma. Experiments that silence select classes of interneurons and determine effects on slow and fast gamma will shed light on this question and the question of which interneuron classes are critically involved in slow and fast gamma generation.

What controls the switch between slow and fast gamma states? During theta-related behaviors, the fast gamma state occurs more often than the slow gamma state (Colgin et al., 2009; Belluscio et al., 2012). Thus, it is possible that fast gamma is the default state during active exploration. Perhaps there is a region in the brainstem or diencephalon that projects to the hippocampus and causes the network to switch from fast gamma to slow gamma. The supramammillary nucleus (SUM) is a potential candidate to initiate the switch. The SUM projects to the hippocampus and entorhinal cortex (Pan and McNaughton, 2004, for a review), and SUM neurons have been reported to exhibit ~37 ms interspike intervals (Kocsis and Vertes, 1994), which matches the period of slow gamma. However, the relationship between SUM and the hippocampus during slow gamma remains to be tested.

How do slow and fast gamma relate to different populations of gamma-modulated place cells found in CA1 (Senior et al., 2008)? Slow and fast gamma phase distributions for place cell spikes were reported to be different (Colgin et al., 2009), raising the possibility that the two populations reported by Senior and colleagues (2008) represent slow and fast gamma-modulated cells. In line with this idea, place cells reportedly tend to fire on the trough of fast gamma and the rising phase of slow gamma (Colgin et al., 2009). Additionally, place cells that fire on the rising phase of gamma in Senior et al. (2008) fire more tightly locked to theta phase when gamma is present, whereas gamma trough-preferring cells precess across the range of theta phases when gamma is present. These results at first appear similar to effects of slow and fast gamma on theta phase precession reported by Bieri et al. (2014). However, Bieri et al. showed that place cells tend to fire early in their place field during slow gamma. In contrast, cells in Senior et al. that prefer the gamma rising phase fire mostly in the second half of the place field. Thus, the question of how the two populations of gamma-modulated cells reported by Senior et al. relate to slow and fast gamma-modulated cells remains unanswered.

Are slow and fast gamma limited to the hippocampus or do they represent different processing states throughout the brain? Accumulating evidence points to the latter. Separate slow and fast gamma rhythms have been reported in the olfactory bulb (Kay, 2003). Fast gamma (65-100 Hz) in the olfactory bulb occurred during active intake of olfactory stimuli and during exploratory behaviors, whereas slow gamma (35-65 Hz) tended to occur during alert immobility. Separate slow (45-55 Hz) and fast (70-85 Hz) gamma rhythms have also been reported in the ventral striatum, where they occur during different components of a spatial decision task (van der Meer and Redish, 2009). Also, a recent study in the visual cortex of macaque monkeys found that fast gamma (~60-80 Hz) rhythms are involved in bottom-up processing, while slower beta (~14-18 Hz) rhythms mediate top-down processing (Bastos et al., 2014). The beta frequencies observed in this study were lower than the slow gamma frequencies seen in the above-described

studies. However, the studies described above involved rodents, not monkeys. It is possible that the beta rhythms seen in monkeys during top-down processing are analogous to slow gamma observed in rodents, with lower frequencies perhaps allowing for longer conduction delays (Kopell et al., 2000) in the larger primate brain (Zheng and Colgin, in press).

8. Conclusions

It is imperative to continue testing the two-gamma hypothesis and to provide answers to the many questions that remain. The above-described data support the conclusion that the hippocampus takes in and processes information differently depending on gamma state, similar to how theta and sharp wave-ripples represent distinct processing states in the hippocampal network. If this is the case, then future studies will need to take this into consideration when evaluating and interpreting hippocampal results.

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FIGURE CAPTIONS

Figure 1: Theta-modulated fast gamma rhythms in MEC during REM sleep. A color-coded cross-frequency coherence plot is shown on the left. Note how theta phase (x-axis) modulates the power of fast gamma (y-axis). An example recording of theta-modulated fast gamma rhythms is shown on the right.

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Figure 1