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Do gamma oscillations play a role in cerebral cortex?

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Gamma rhythm (which has a center frequency between 30 and 80 Hz) is modulated by cognitive mechanisms such as attention and memory, and has been hypothesized to play a role in mediating these processes by supporting communication channels between cortical areas or encoding information in its phase. We highlight several issues related to gamma rhythms, such as low and inconsistent power, its dependence on low-level stimulus features, problems due to conduction delays, and contamination due to spike-related activity that makes accurate estimation of gamma phase difficult. Gamma rhythm could be a potentially useful signature of excitation–inhibition interactions in the brain, but whether it also provides a mechanism for information processing or coding remains an open question.

Gamma rhythms in the brain

Electrical signals recorded from the brain often show oscillations spanning a broad range of frequencies, which are highly conserved across species and are associated with distinct cognitive states [1,2]. Gamma rhythm, which is an oscillation concentrated in a range of ~20 Hz with a center frequency between 30 and 80 Hz, has been consistently linked with high-level cognitive functions such attention [3–6], memory [7–9], and perception [10,11], which has led to proposals that gamma plays a role in cortical processing [12,13] and might be important for processes such as binding different attributes of a stimulus [14,15]. We review some of the proposed functional roles in a signal-processing framework, and argue that gamma rhythms are not well suited to playing any role in higher cortical functions. However, they could be a generic and potentially useful marker of relatively local, low-level cortical interactions involving excitation and inhibition.

Generation, functional roles, and alternative hypotheses

It is well established that inhibition, especially through parvalbumin-positive fast spiking basket cells, plays a crucial role in the generation of gamma rhythms [16–21]. A network of inhibitory interneurons that fires rhythmically can induce periodic fluctuations in the intracellular potential of pyramidal cells, such that the excitability of those cells varies within each cycle of the rhythm. The inhibitory network could generate the rhythm by itself or through periodic excitation arising from the pyramidal cell population (see [20] and references therein for a detailed discussion of cellular mechanisms). Several models have been proposed to explain this phenomenon [22–26]. In most of these models, gamma oscillations are generated due to excitation–inhibition interactions as a consequence of simple network dynamics and time constants associated with excitatory postsynaptic potentials and inhibitory postsynaptic potentials. We focus on two recent proposals that rely on rhythmic inhibition from an interneuronal network for specific signaling mechanisms.

One of these proposals is the communication through coherence (CTC) hypothesis. This hypothesis [27] proposes that when the activity of a neuronal assembly oscillates, the periodic fluctuations in excitability produce temporal windows for communication such that only coherently oscillating assemblies can communicate effectively (because their temporal communication windows are aligned), thereby allowing flexible long-range communication between neuronal assemblies [27–31], as illustrated in Figure 1A. Simple models based on reciprocally connected excitatory and inhibitory neurons can implement CTC [24,31–33]. There is experimental evidence both in favor of [4,29] and against CTC [34]. In the latter study, the authors showed an increase in pairwise synchrony of neurons in visual areas V1 (striate cortex) and V2 due to gamma, but the conduction delay between V1 and V2 was on the order of ~3 ms, whereas gamma rhythms in the two areas differed by ~90°, equating to about 5–8 ms [34]. These results are inconsistent with CTC (see Figure 7 and related text in [34] for a detailed discussion).

Another influential proposal focuses on phase coding (PC), or coding of sensory information in the timing of the spike relative to the phase of an ongoing oscillation. PC was first shown in the hippocampus of rats where the position of the spikes relative to theta oscillations (7–12 Hz) carried information about the position of the rat in the environment [35], and the concept of PC in the framework of inhibitory networks was proposed by Buzsáki and Chrobak [36]. It has recently been proposed that gamma oscillations might also be used for PC [37]. The proposal is as follows: because the inhibition is strongest at the peak of gamma cycle (measured extracellularly), strong incoming excitation can overcome the inhibition earlier and fire a spike earlier in the gamma cycle, whereas weak

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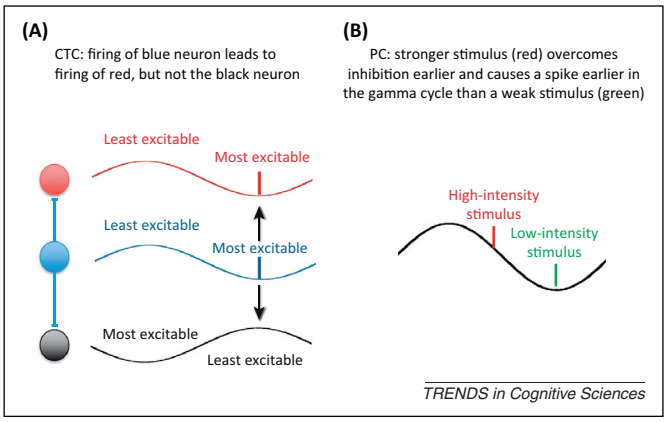

Figure 1. Functional roles of gamma. Two different proposals for how gamma is hypothesized to work. Both proposals rely on the fact that the excitability of the neuron varies within the gamma cycle and is maximal at the trough of the gamma rhythm measured extracellularly. **(A)** Communication through coherence (CTC) hypothesis. **(B)** Phase coding (PC) hypothesis.

excitation can only lead to a spike when the inhibition is weakest (at the trough of the gamma cycle). Thus, stimulus intensity can be encoded in the position of the spike with respect to the phase of gamma (Figure 1B).

The existence of gamma oscillations and their modulation with specific stimuli and behaviors does not necessarily imply a role in cortical processing because basic cortical processes such as control of gain [38], changes in interneuronal correlation [39], normalization [40,41], learning [42], and working memory [43] all rely on excitation–inhibition interactions. Cognitive processes such as attention, which has been associated with an increase in normalization strength [44–46] and reduction in interneuronal correlations [47,48], should therefore also modulate gamma power and frequency [49]. Indeed, almost anything that changes the overall level of activity in a local region of cortex might be expected to result in incidental changes in the strength of gamma oscillations.

A mechanism involving periodic fluctuations in intracellular potential to provide a temporal structure in the firing of the neuronal population is plausible from a physiological perspective, and could potentially be a useful way for communication across brain areas. However, testing hypotheses such as CTC or PC against a null hypothesis that gamma plays no role (and hence is only a reflection of excitation–inhibition interactions) involves first establishing a quantitative framework based on communication and information theory in which the efficiency of communication or coding depends on the properties of gamma [50–52]. Because most neurophysiological studies only describe correlations between behavior and neuronal activity (in case of gamma, often a tiny change in power or coupling with changes in behavior or stimulus), it is difficult to discern whether the observed gamma oscillations are strong and reliable enough to play a role in cortical processing. Optogenetic manipulations [18,19,53,54] and transcranial alternating current stimulation [55] have recently been used to test whether gamma plays a functional role, generating mixed results. However, these approaches must be interpreted with caution because gamma generated using optogenetic manipulation or transcranial current stimulation might be very different from gamma generated under physiological conditions (e.g., compare Figure 1c in Cardin *et al.* [18] with Figure 2 below). We focus here exclusively on various signal processing aspects related with the proposed functional roles, and highlight several issues that could constrain the mechanisms by which these rhythms could be used in cortical processing.

Low and inconsistent power

Proposals such as CTC and PC are easy to implement when the signal energy at the frequency of interest is much higher than other frequencies [50,51], which can be the case for low-frequency rhythms such as alpha or theta (Box 1). However, all biological rhythms have a 1/f power form, such that the signal power typically falls off with the inverse of the frequency. Figure 2A shows the time frequency power spectrum under very favorable conditions for producing gamma oscillations. Figure 2B shows the power versus frequency for three time intervals (shown in dotted lines in 2A), whereas Figure 2C shows the change in power from prestimulus baseline (green line; subtraction is done on a log scale so each plot shows the log ratio of power). Even under favorable conditions, power at peak gamma frequency is ~10% of the power at lower frequencies (other studies have shown similar results – see e.g., Figure 1 in [56].) The relative weakness of gamma oscillations means that they cannot be detected by a simple threshold mechanism because the amplitude of the signal is dominated by lower-frequency components, irrespective of gamma. Because the absolute magnitude of gamma power is small, many reports show a change in power from a prespecified baseline (Figure 2C) instead of the absolute power (Figure 2B), which, apart from downplaying the issue of relative power, can show a peak in the gamma range even when the raw power spectrum fails to show any concentration of power in the gamma range (Box 2).

Many studies focus on the coupling between spikes and oscillations in the gamma range (often measured using a metric such as spike-field coherence, SFC) instead of raw gamma power because the ability of a rhythm to entrain the spikes at a particular phase is crucial. However, it is important to note that SFC is often very small in the gamma range (see e.g., Figure 2 in [4] or Figure 3 in [57], and note the different scales for low and high-frequency plots). The magnitude of the phase locking of spikes is crucial if phase is to provide useful information, but it is sometimes not emphasized in neurophysiological studies.

The low power of gamma rhythm measured extracellularly would not be a concern if it were more salient in the intracellular signal – because the excitability of a neuron is largely determined by its transmembrane potential. However, intracellular recordings also have a 1/f form [58] (Figure 2D), and intra- and extracellular recordings are often highly correlated [59]. Further, even if a neuron is able to extract the gamma component by filtering out other frequencies (perhaps in a particular location within the cell), the phase of the filtered gamma would be different from the extracellular gamma because all biologically plausible filters shift the phase of the signal they process [60].

Apart from low gamma power, the power spectra in Figures 2A–C show additional issues related to gamma rhythm. First, gamma rhythm is weak or absent before