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Do gamma oscillations play a role in cerebral cortex?

Supratim Ray[1] and John H.R. Maunsell[2]

[1] Centre for Neuroscience, Indian Institute of Science, Bangalore 560012, India
[2] Department of Neurobiology, University of Chicago, 5812 South Ellis Avenue, MC0912 Chicago, IL 60637, USA

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

Corresponding author: Maunsell, J.H.R. (maunsell@uchicago.edu).
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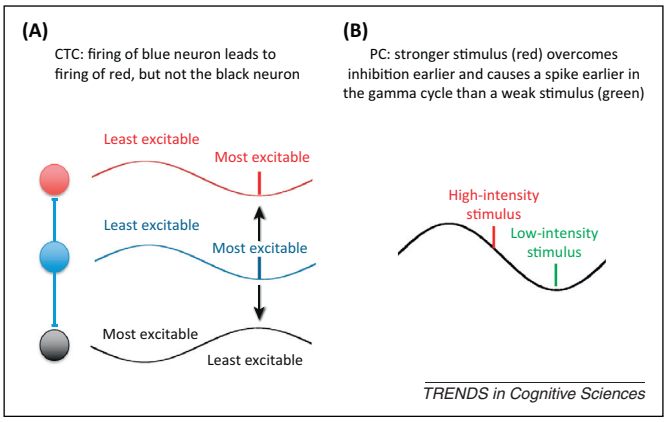

Figure 1. Functional roles of gamma. Two different proposals for how gamma is hypothesized to work. Both proposals rely on the fact that the excitability of the neuron varies within the gamma cycle and is maximal at the trough of the gamma rhythm measured extracellularly. **(A)** Communication through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

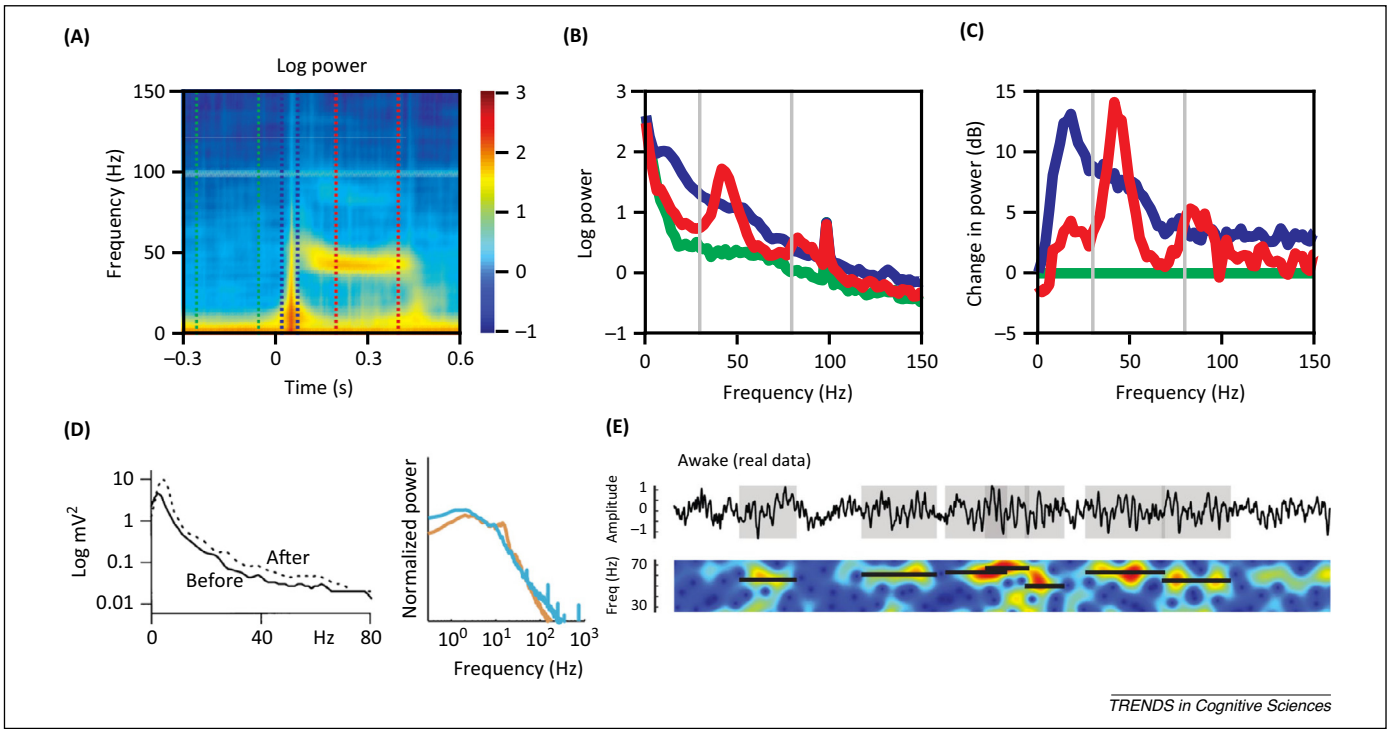

Figure 2. Low and inconsistent gamma power. **(A)** Time frequency power spectrum of the LFP. Time is relative to the onset of a stimulus that generates a salient gamma rhythm, observed at ~50 Hz starting about 100 ms after the stimulus onset. The green, blue, and red dotted lines indicate the baseline (−250 to −50 ms), early stimulus (25–75 ms), and late stimulus (200–400 ms) periods. **(B)** Power spectrum at baseline, early, and late stimulus periods. Gray lines show the gamma range (30–80 Hz). **(C)** Change in power from baseline, in decibels $\{10 \log[P(\omega)/P_{BL}(\omega)]\}$. It is computed by subtracting the log of baseline power (green trace shown in B) from the log of power during stimulus periods (red and blue traces in B). **(D)** Intracellular recordings from rat hippocampus before (solid line) and after (dotted line) tail pinching [58] (left) (reproduced with permission from John Wiley and Sons); simultaneous intra- (blue) and extracellular (orange) recordings from area S1 of rats [59] (right) (reproduced with permission from the Society for Neuroscience). **(E)** Raw local field potential (LFP) data recorded from the primary visual cortex of a monkey (top), and the corresponding time frequency power spectrum (bottom). The horizontal extent represents 1.5 s of recording. Black bars show the duration of gamma bursts, as described in [65]. Gamma is unstructured and occurs in bursts. Similar results are obtained with anesthetized monkeys, suggesting that these fluctuations are not because of fluctuation in some cognitive process such as attention (reproduced with permission from the Society for Neuroscience).

stimulus onset, in the sense that a distinct 'bump' in the power spectrum in the gamma range is either weak [61] or absent (green line in Figure 2B; Figure 1 in [56]) during spontaneous activity. One argument often put forward is that, even though there is no distinct bump in the power spectrum, there is non-zero power at gamma frequencies during baseline that could be used for computation. Another argument could be that gamma center frequency (bump) changes with time during the spontaneous period because it depends on the internal state of the animal, and is therefore not visible as a localized bump in the trial-averaged power spectrum. However, these arguments again implicitly assume that the neurons can filter in the gamma component in the signal to detect power in a particular frequency range, because the unfiltered signal has no overall periodicity which could be detected by a simple threshold operation. Second, in monkey V1, gamma appears only gradually after stimulus onset, becoming salient only after ~200 ms (Figure 2A,B), which could be either because gamma is absent in the initial period, or that it is present but is masked out by a much stronger onset-related transient. Considering that spiking responses begin ~30 ms after stimulus onset in V1, gamma becomes prominent only after most of the processing is already completed in V1. Indeed, many studies of gamma rhythm examine the rhythm hundreds of milliseconds after stimulus onset, ignoring at least the first ~200 ms post-stimulus to avoid 'response transients'. The sluggish growth of gamma rhythm raise questions regarding its role in visual processing, which is generally believed to proceed rapidly [62]. By contrast, it can be readily explained in terms of excitation–inhibition interactions [25,26].

Finally, recent studies that have looked at the reliability and consistency of gamma rhythms have reported that gamma is highly stochastic and lacks the attributes necessary to provide a clock or a communication channel (Figure 2E) [63–65]. Although part of this stochasticity could be due to changes in the behavioral state of the animal or variability associated with the estimation of power, and the proposed mechanisms could potentially operate even when gamma is not a perfect clocking signal [66], these mechanisms still require gamma to have enough power to generate time epochs in which the neurons are sufficiently depolarized to temporally coordinate their firing. Similarly, to work as an efficient feedforward communication channel between two cortical areas, it is desirable to have strong gamma power in the input layers (as shown in [61,67]), but recent studies have shown that gamma is weak in input layers compared to superficial layers ([68–70]; although in these studies recordings from different layers were not made simultaneously).

Conduction delays

Another difficulty with exploiting gamma rhythms for information processing is the relatively slow propagation of neuronal signals in cortex. Although fast-conducting

Box 1. Time frequency uncertainty principle

The time frequency uncertainty principle posits that it is impossible to characterize a signal with simultaneous precision in both the time and frequency domains. For example, if we want to know the frequency content of a 0.5 s signal, the frequency resolution is limited to 2 Hz (1/T Hz, where T is the length of the signal in seconds). A frequency resolution of 0.1 Hz can only be achieved by analyzing the full duration of a signal at least 10 s in length.

The cellular mechanisms described here for implementing CTC or PC, at first glance, appear to violate the fundamental time frequency uncertainty principle of signal processing. For example, suppose there are two neuronal assemblies, each associated with a gamma rhythm and firing action potentials at the trough of their respective gamma rhythm. Further, suppose that the two rhythms have frequencies of 40 and 42 Hz, such that the oscillation periods are 25.0 and 23.8 ms. The second assembly will start firing action potentials ~1.2 ms before the first, and therefore by observing the assemblies for 25 ms the two rhythms could be resolved. This seems to contradict the time frequency uncertainty principle, which states that to achieve a frequency resolution of 2 Hz the signals must be observed for 500 ms.

The apparent contradiction arises because we use a non-linear rule to dissociate the rhythms, namely that the value of the waveform must exceed a particular threshold to elicit a spike. This rule does not impose any other restriction on the nature of the signal – the two rhythms could have been triangular instead of sinusoidal to achieve the same result. However, for the neuron to use this rule, it is essential that there are no other frequency components in the signal that might distort the overall signal shape. On the other hand, sinusoids at 40 and 42 Hz are orthogonal when integrated over 500 ms (but not 25 ms, for which they are highly correlated). Therefore, if the computation extends over 500 ms, it is possible to retrieve the 40 (or 42) Hz component of any signal and use it for computation irrespective of whether other frequencies are present in the signal or not.

In short, the mechanisms by which gamma is hypothesized to play a role in cortical processing implicitly assume that most of the signal energy is concentrated in the gamma range, although that is never observed experimentally.

Box 2. Gamma bumps in power change spectra

Because power in the gamma range is much smaller than power at lower frequencies, the change in power is often shown instead of the raw spectrum. Specifically, instead of plotting $\log[P(\omega)]$, where $P(\omega)$ is the power spectrum, we plot the power change spectrum given by $\log[P(\omega)] - \log[P_{BL}(\omega)]$, where $P_{BL}(\omega)$ is the power spectrum obtained during prestimulus baseline period. However, the power change spectrum (Figure 2C) often shows a peak in the gamma range even in the absence of a gamma rhythm in the raw spectrum. For example, for the initial evoked response in Figure 2B (25–75 ms, blue trace), the raw power spectrum does not show a pronounced bump in the gamma range, but a striking bump is present in the change spectrum (Figure 2C). This happens because of the peculiar shape of the power spectrum during baseline period (green trace in Figure 2B): the slope of the baseline spectrum is very steep at low frequencies and becomes progressively shallower. The evoked power (blue trace), on the other hand, has a different slope such that the difference in power is largest in the gamma range, even when there is no clear peak in the evoked spectrum. This effect can be observed in other studies also (e.g., Figure 2 in [78]). The presence of a bump in change spectrum does not always imply the presence of rhythmicity in the signal.

axons can transmit spikes at tens of meters per second, there are substantial delays in the relay of signals within and between cortical areas (see e.g., Figure 2 and Table 1 in [71] for a detailed comparison of stimulus onset latency across several visual areas). In monkey visual cortex, the earliest responses of visual neurons in anterior inferotemporal cortex generally follow those in V1 by more than 50 ms [72,73]. Even within V1, the earliest spiking of neurons in the most superficial layers lags that in layer 4 by 10–15 ms [72,74]. Because every cortical area receives inputs from many brain structures that lie at many different distances (e.g., [75]), synchronizing inputs to arrive within a particular phase of a gamma cycle (i.e., within ~15 ms) presents a formidable problem.

None of the obvious solutions to this challenge are particularly attractive. CTC and PC lose much of their appeal if they apply only within local patches of cortex spanning a few hundred microns where timing might be relatively uniform. It seems unlikely that there is a central oscillator that coordinates gamma phase throughout the cortex. Conceivably, the problem of conduction delays could be met if each neuron received inputs only from neurons in different areas that shared the same gamma phase, but this would greatly reduce the flexibility of the proposed mechanisms and would put many constraints on the wiring of cortical and subcortical connections, in part because selecting a particular phase for inputs would necessarily dictate the phase for outputs to other areas. Furthermore, gamma rhythms in local populations do not have fixed frequency or phase (see below).

Stimulus dependence of gamma

For gamma to play a functional role in communication or PC, it is desirable that the amplitude or frequency of gamma should not depend on the properties of the stimulus itself. However, gamma depends greatly and systematically on a variety of stimulus features [25] (Figure 3A–D) including size [56,76,77], contrast [31,78,79], noise [80], orientation [56,81,82], spatial frequency [83], speed [84–86], direction [87], and eccentricity [88,89]. It also depends on the properties of the brain, such as the resting level of GABA [90] or size of cortex [91]. More importantly, gamma power and frequency are often dependent on local stimulus features even when they clearly complicate the way gamma could be used for communication or PC. For example, if different parts of one stimulus have different contrasts, neuronal assemblies separated by as little as 400 μm in cortex oscillate at significantly different frequencies which are exclusively dependent on the local contrast [79] (Figure 3E). Similarly, when an oriented grating is replaced by a plaid, gamma is predicted to increase [92], but the opposite has been observed [88] (Figure 3F). Indeed, gamma is much stronger for gratings as compared to natural images [93], and inhomogeneities in a grating due to noise masking (Figure 3B), variable contrast (Figure 3E) or a second orthogonal grating (Figure 3F) all substantially reduce gamma (but see [94]).

In a recent paper, Roberts and colleagues [31] argued that, even though gamma peak frequency varies greatly with contrast, it varies in a consistent way in V1 and V2, such that CTC can occur. While this consistent frequency relationship could support CTC, and potentially allow 'multiplexing' of information based on frequency, implementing it under such dynamically changing conditions might require additional, complicated mechanisms. First, multiplexing or coding information based on frequency is

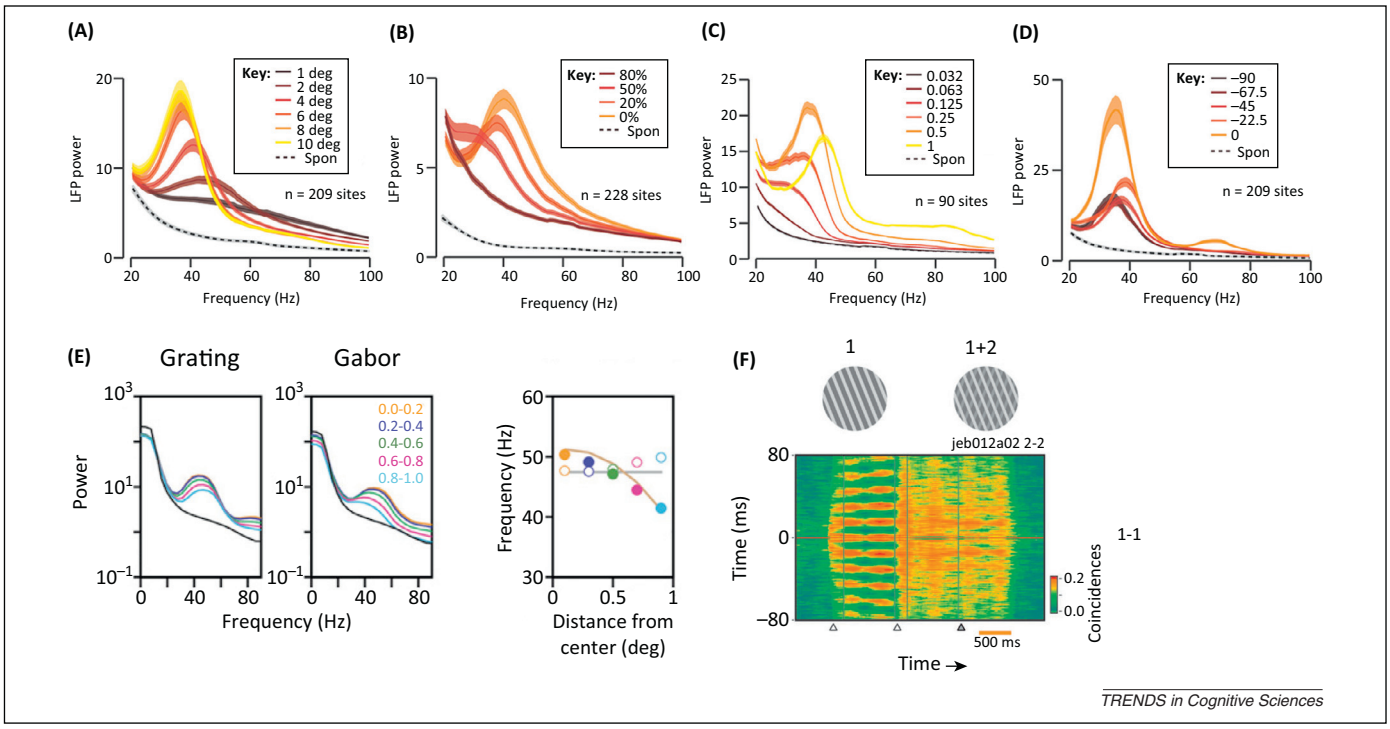

Figure 3. Stimulus dependence of gamma. (A–D) Power spectra during the presentation of stimuli of different sizes **(A)**, noise levels **(B)**, contrasts **(C)**, and orientations **(D)** [25] (reproduced with permission from the Society for Neuroscience). **(E)** Gamma frequency depends on local contrast. A large grating (left plot) or Gabor (middle plot) stimulus was presented while recording from an array of microelectrodes inserted in V1. Gamma oscillations were observed in all electrodes whose receptive fields were within the stimulus, but the center frequencies of these simultaneously recorded gamma oscillations depended on the stimulus type. For a grating, the center frequencies did not vary much (right plot, empty circles) but, for a Gabor stimulus, they varied significantly depending on the distance between the stimulus and receptive field centers that determined the local contrast (right plot, filled circles) [79] (reproduced with permission from Elsevier). **(F)** Sliding window autocorrelation analysis of the multiunit activity (MUA) reveals a strong gamma rhythm after the presentation of a grating, which is reduced when another grating in the orthogonal direction is superimposed [88] (reproduced with permission from Oxford University Press).

difficult due to the time frequency uncertainty principle (Box 1). To prevent mixing of information between two close frequency channels, signals must be integrated for a long duration, which would limit the processing speed. Further, for CTC to work under such conditions requires that the contrast level should *a priori* be known in all areas trying to communicate with each other. Therefore, once the local excitation (which depends on the contrast) reaches V1, information about the contrast must reach V2 via a second communication channel, which would subsequently set up a gamma rhythm in V2 that matches the rhythm in V1 so that other information can subsequently be sent across to V2. In particular, information regarding the stimulus contrast itself cannot be sent via CTC because the communication medium cannot be set up without the knowledge of the contrast. Although a stable phase relationship is crucial for CTC [13], Roberts and colleagues [31] did not report whether the phase difference between the V1 and V2 oscillations were consistent across contrasts or across different sites for a given contrast.

On the other hand, these results can be explained based on simple excitation–inhibition interactions. It is not particularly surprising that gamma frequencies in V2 would vary with contrast in a way similar to those in V1, because the two areas have similar response properties [95] and receptive field sizes [96], and V2 receives most of its excitatory drive from V1 [97,98]. If gamma frequency follows the overall level of excitation in a local region of cortex, gamma frequencies in V1 and V2 for grating stimuli can be expected to track contrast in similar ways.

Spike-related transients affect gamma phase estimation

In CTC or PC, gamma rhythms adjust the coordination or timing of a spike, and testing this hypothesis therefore entails a proper estimation of gamma phase with respect to the spike. This is a methodological problem that the experimenter faces. Further, these hypotheses assume that the spike itself does not change the properties of the gamma channel because this would cause the properties of the carrier to be modified depending on the content. However separating the carrier and content is difficult to achieve because they are generated by the same network (the neuronal network itself faces this problem as well). We focus here only on the first issue related to the estimation of gamma phase.

Earlier studies assumed that low-frequency components of brain signals are not related to spikes [99], but there is now growing appreciation that spike-related activity is present at low frequencies also, including the gamma band [77,100,101]. Specifically, because the spike-related transient is similar to a negative delta function, or an inverted pulse, it can be decomposed into a series of sinusoidal components that all have their trough aligned to the spike (essentially adding a sinusoidal component with a phase of 180° at all frequencies). This can potentially bias the estimation of phase of a genuine rhythm. Further, the magnitude of this artifactual phase shift would depend inversely on the amplitude of a genuine oscillation: low amplitude will lead to a greater shift towards 180° because the contribution of the spike transient will be proportionately greater [102] (Figure 4A,B).

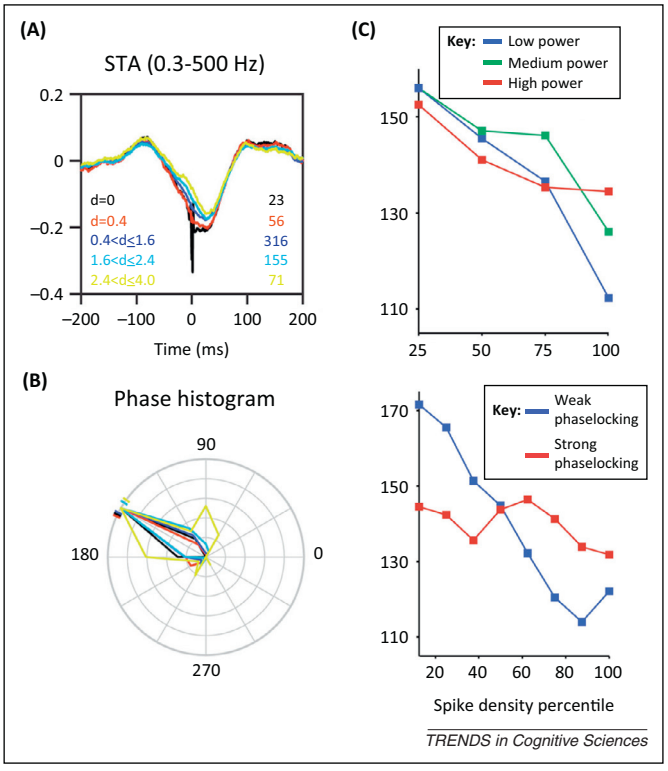

Figure 4. Phase shift due to spike transients. **(A)** Spike-triggered local field potentials (stLFP) recorded with LFPs recorded from electrodes at various distances ('d' mm) away from the spike electrode. Black trace (d = 0) corresponds to the case when spikes and LFPs are recorded from the same electrode [102] (reproduced with permission from the Society for Neuroscience). **(B)** Phase of the 5 Hz component of the LFP with respect to the spike. The trough of the rhythm occurs at 180°. The phase shifts towards the trough when the spike transient is larger [102] (reproduced with permission from the Society for Neuroscience). **(C)** Evidence of gamma PC [104]. The phase of gamma with respect to the spike is plotted as a function of stimulus intensity, here measured as spike density percentile. Phase of 180° corresponds to the trough of the rhythm. At low intensities, spikes tend to occur near the trough but, as the intensity increases, the phase shifts to lower values, in accordance with the phase coding hypothesis. However, repeating this analysis separately for trials with high or low power (upper panel), or with neurons that phase locked strongly or weakly (lower panel) showed that phase-shifting is more pronounced when gamma power or phase locking are weak, for which the estimation of phase is likely to be biased towards 180° owing to the spike transient (reproduced with permission from the Society for Neuroscience).

Typically spikes and local field potentials (LFPs) are taken from different electrodes to address this issue, but, because the firing of nearby neurons is correlated [103], the spike transient can often be observed in the LFP even when the LFP from a distant electrode is used (Figure 4A,B). For example, a recent study has shown evidence of gamma PC [104], but the phase shift was salient only when gamma was weakly phase locked: during strong phase locking the phase shift was almost abolished (Figure 4C), suggesting a possible shift introduced by a relatively stronger spike transient in the case of weak gamma locking.

Concluding remarks

In summary, we raise several signal-processing issues regarding gamma oscillations. First, they have low power, typically less than 10% of the total signal power, are absent during baseline, and are too weak to serve any role during the first ~200 ms after stimulus onset. Special filtering techniques are needed to use these signals for coding, for which there is little evidence. Second, long conduction delays pose serious issues in matching gamma phase across distributed brain areas. Third, gamma is highly stimulus-dependent, and its properties are well described by simple models of excitation–inhibition interactions. Finally, spike-related activity has sufficient power in the gamma range to bias the phase of the extracellularly recorded signal, which makes its estimation difficult (unlike the first three issues, this issue affects only the experimenter, but it must be dealt with properly before testing any hypothesis involving gamma). However, even if gamma plays no role in cognitive processing, it could still be a potentially useful marker of excitation–inhibition interaction and might serve as a powerful diagnostic tool [105–107].

Whether gamma rhythms play a role in signal processing will not be easy to establish, or to dismiss. Progress is likely to be aided by deeper consideration of the challenges faced by any neuronal gamma-based processing mechanism, and more direct exploration of whether the degree of synchrony observed in physiological experiments is consistent with the sort of robust mechanisms on which perception and cognition are likely to depend.

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