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Cortical gamma responses: searching high and low

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Abstract

In this paper, a brief, preliminary attempt is made to frame a scientific debate about how functional responses at gamma frequencies in electrophysiological recordings (EEG, MEG, ECoG, and LFP) should be classified and interpreted. In general, are all gamma responses the same, or should they be divided into different classes according to criteria such as their spectral characteristics (frequency range and/or shape), their spatial-temporal patterns of occurrence, and/or their responsiveness under different task conditions? In particular, are the responses observed in intracranial EEG at a broad range of “high gamma” frequencies (~60–200 Hz) different from gamma responses observed at lower frequencies (~30–80 Hz), typically in narrower bands? And if they are different, how should they be interpreted? Does the broad spectral shape of high gamma responses arise from the summation of many different narrow-band oscillations, or does it reflect something completely different? If we are not sure, should we refer to high gamma activity as oscillations? A variety of theories have posited a mechanistic role for gamma activity in cortical function, often assuming narrow-band oscillations. These theories continue to influence the design of experiments and the interpretation of their results. Do these theories apply to all electrophysiological responses at gamma frequencies? Although no definitive answers to these questions are immediately anticipated, this paper will attempt to review the rationale for why they are worth asking and to point to some of the possible answers that have been proposed.

Keywords

Gamma band; High-gamma; Oscillations; Electrocorticography; Electroencephalography; Functional mapping; Induced responses; ERD/ERS

1. Introduction

Since the advent of EEG recordings in humans and animals, investigators have observed that functional brain activation is associated with suppression of resting EEG rhythms (e.g. alpha, mu, beta, etc) and the appearance of low voltage activity at faster frequencies (Adrian and Matthews, 1934; Berger, 1930; Jasper and Carmichael, 1935). Subsequent research on EEG activity at gamma frequencies (>30 Hz) related both spontaneous and evoked activity, particularly at 40-Hz, to cortical function in both animals and humans (Bressler and Freeman, 1980; Galambos et al., 1981; Loring and Sheer, 1984; Spydell et al., 1979). Interest in this activity was further intensified by experimental and theoretical work in the 80's and 90's suggesting a role for gamma oscillations in basic mechanisms of neural coding (Gray, 1999; Gray and Singer, 1989; Singer, 1993). In particular, LFP recordings in cat visual cortex showed that during appropriate visual stimulation, oscillatory neuronal firing

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Abbreviations: Electrocorticography (ECoG), electroencephalography (EEG), magnetoencephalography (MEG), local field potentials (LFPs)

in a frequency range of 40–60 Hz became synchronized between spatially separate columns in area 17 (Gray et al., 1989), between areas 17 and 18 (Eckhorn et al., 1988), and even between areas 17 of the two hemispheres (Engel et al., 1991). Because this synchronization was dependent upon global stimulus properties, it was proposed to serve a mechanism in perceptual grouping. More generally, synchronization at gamma frequencies was hypothesized to form a temporal code that dynamically “binds” spatially segregated neurons (e.g. with different retinotopic receptive fields) into assemblies representing higher-order, or global, stimulus properties (e.g. an object common to different receptive fields) (Singer and Gray, 1995; Von der Malsburg, 1995). As a corollary, synchronization was proposed to identify neurons belonging to different assemblies, solving the “superposition problem” of assembly coding (Gray, 1999). These hypotheses were linked with gamma oscillations by experiments (Murthy and Fetz, 1992; Sanes and Donoghue, 1993) demonstrating synchronization of single unit firing bursts with LFP gamma oscillations, suggesting that gamma oscillations facilitate and/or are facilitated by neuronal synchronization. The LFP gamma oscillations themselves are widely believed to depend on rhythmic and coherent firing in networks of inhibitory interneurons (Bartos et al., 2007; Buzsaki and Chrobak, 1995; Grenier et al., 2001).

Until recently, it was difficult to reliably record high frequency responses in humans, due in part to limitations in EEG recordings and in part to low signal-to-noise ratios for this activity at the scalp surface. This began to change, however, as digital EEG systems were introduced with more powerful specifications and as researchers began to exploit the investigative potential of intracranial EEG recordings in patients undergoing epilepsy surgery. Prior to these developments, most reports of EEG gamma responses in humans were observed as components of phase-locked (evoked) or steady-state responses at, or in the neighborhood of, 40 Hz (Galambos et al., 1981). In addition, non-phase-locked 40-Hz activity was observed in some subjects during activation of motor cortex (Pfurtscheller et al., 1994; Pfurtscheller and Neuper, 1992), auditory cortex (Pantev, 1995), and visual cortex (Tallon-Baudry et al., 1997). However, few studies had considered the possibility of non-phase-locked responses at higher gamma frequencies. Brindley and Craggs (1972), while searching for components of local field potentials in monkey motor cortex that could be used to drive prosthetics, had found that if the signal was filtered between 80 Hz and 250 Hz and then rectified and smoothed, it was reliably correlated with the monkey's movements. Although the potential utility of this activity for controlling prostheses was recognized at the time, it was not exploited until much later (Leuthardt et al., 2004; Miller et al., 2009b). Furthermore, the significance of this finding with respect to cognitive neurophysiology was not fully appreciated nor was it further explored, perhaps because the aforementioned excitement about gamma oscillations had not yet taken hold.

In the 1980's and 1990's, as the surgical management of intractable epilepsy increasingly relied upon long-term, extra-operative monitoring with subdural electrocorticography (ECoG) to better localize seizure foci, clinicians and researchers began to explore ECoG as a potential tool for both functional mapping and cognitive neuroscience research. Although significant early progress was made in these studies by focusing on phase-locked response, i.e. event-related potentials (Halgren et al., 1995; McCarthy and Wood, 1987; Nobre et al., 1994), other studies began to investigate non-phase-locked responses (Crone et al., 1995; Crone et al., 1994). Interest in these responses was based in part on a growing appreciation for them in non-invasive EEG and MEG studies, where they were known as induced responses (Herrmann and Knight, 2001; Pantev, 1995) or as event-related desynchronization (ERD) and event-related synchronization (ERS) (Pfurtscheller, 1977, 1992). In addition, their lower sensitivity to temporal jitter was considered advantageous for functional tasks involving downstream cortical processing with more variable latencies (Herrmann et al., 2004). Furthermore, these studies were influenced by the aforementioned experimental and

theoretical accounts of gamma oscillations, which by then had gained substantial attention, and which did not assume phase-locking to a stimulus or event.

2. Experimental findings in humans

While exploring human ECoG as a tool for functional mapping and cognitive neuroscience, event-related, non-phase-locked responses to a variety of functional tasks were surveyed across a range of frequencies, including traditional alpha (8–13 Hz), beta (13–30 Hz), and gamma (> 30 Hz) frequencies. Using tasks designed to activate sensorimotor, auditory, visual, and language cortices (Crone et al., 1995; Crone et al., 1994), these studies observed spectral perturbations (e.g. ERD/ERS) that were generally in agreement with the findings of previous non-invasive EEG and MEG studies. However, an unexpected but consistent finding across these studies was that cortical activation was accompanied by a power increase in a broad range of frequencies that were substantially higher than the traditional 40 Hz gamma band. Because these responses were discovered in the context of searching for gamma oscillations in lower frequencies, without any knowledge of the studies by Brindley and Craggs (1972) over two decades earlier, they were provisionally called “high-gamma”, and their physiological significance was interpreted in the context of the burgeoning literature on gamma oscillations. However, as discussed later, investigations of high gamma responses have since revealed response properties that further distinguish them from “low” gamma oscillations and suggest potentially different interpretations with regards to their underlying neurophysiology.

Early accounts of ECoG spectral responses (Crone et al., 1998a; Crone et al., 1998b) focused on their localization within the relatively predictable somatotopic organization of sensorimotor cortex. This was done to validate these responses prior to their application to language cortex and other brain regions with less predictable functional anatomy. Compared to alpha power suppression (ERD) and “low gamma” power augmentation (ERS) during a visually cued motor task, augmentation of high gamma power (70–100 Hz in this case) appeared to be more discretely localized with respect to the expected anatomy and timing of cortical activation. In particular, high gamma responses were typically observed in fewer electrodes than responses at lower frequencies. Cortical stimulation at these sites usually interfered with movement of the same body part or caused involuntary movement of it. In addition, lower frequency responses appeared to have a slower temporal evolution, with more delayed latencies and longer durations, while high gamma responses had an abrupt onset and offset (Zygierewicz et al., 2005) that corresponded to the onset and offset of cued isometric muscle contractions, i.e. changes in muscle force. These basic properties of high gamma responses in sensorimotor cortex have been consistent across studies using a variety of motor tasks and signal analyses (Brovelli et al., 2005; Brunner et al., 2009; Dalal et al., 2008; Leuthardt et al., 2007; Miller et al., 2007; Ohara et al., 2000; Pfurtscheller et al., 2003). In addition, high gamma responses in sensorimotor cortex have since been shown to be of potential utility in the development of ECoG as a brain interface for controlling prosthetic devices (Gonzalez et al., 2006; Leuthardt et al., 2004; Miller et al., 2009b; Reddy et al., 2009).

Although a potential distinction between responses in high vs. low gamma frequencies was first reported in studies of sensorimotor cortex, this suspicion was deepened by the results of ECoG studies of auditory cortex (Crone et al., 2001a). As in studies of sensorimotor cortex, in comparison to non-phase-locked responses in lower frequencies, high gamma responses were observed in a smaller number of sites in posterior superior temporal gyrus (pSTG) critical for auditory discrimination. The temporal envelopes of these responses were again faster than those of lower frequency responses. In addition, high gamma responses in dominant pSTG were more robust during speech discrimination than during tone

discrimination, consistent with the critical role of this site in processing the more complex acoustic features of speech. However, this study also afforded a more detailed analysis of the reactivity of the power spectrum during cortical activation. This showed that in ECoG recorded from dominant pSTG, speech discrimination was consistently associated with power augmentation at high gamma frequencies (in this case >80 Hz). However, depending on the electrode site or even the subject, power in lower gamma frequencies could either be increased or decreased. Furthermore, power augmentation was evident across a wide range of frequencies that extended well beyond 100 Hz, without any clear or consistent upper boundary. The picture that began to emerge was that cortical activation is associated with power augmentation over a large range of frequencies and that the lower boundary of this power augmentation is quite variable. Sometimes this extends down to traditional gamma frequencies, e.g. 40 Hz, but sometimes it does not. This variability in the direction of power changes at lower gamma frequencies may be due to variability in the frequency range over which event-related power suppression (ERD) occurs. For example, if task-related power suppression at alpha/beta frequencies extends into low gamma frequencies, it may mask any power augmentation in this frequency range. The most consistent power augmentation, however, can be observed at high gamma frequencies though the lower boundary of this response may sometimes extend down to low gamma frequencies. Subsequent studies of auditory cortical physiology in both humans (Chang et al., 2010; Edwards et al., 2005; Edwards et al., 2009; Kaiser and Lutzenberger, 2005; Lenz et al., 2008; Trautner et al., 2006) and monkeys (Brosch et al., 2002; Steinschneider et al., 2008) have found non-phase-locked responses with the same or similar time-frequency characteristics. The aforementioned ECoG studies of sensorimotor and auditory cortices have provided important frames of reference to verify the functional anatomy of task-related high gamma activity and its relationship to other spectral responses. High gamma responses have also been observed with similarly good temporal, spatial, and functional correspondences in a variety of other functional anatomical domains, including somatosensory cortex (Gross et al., 2007; Hauck et al., 2007; Ihara et al., 2003; Ray et al., 2008c), visual cortex (Hoogenboom et al., 2006; Lachaux et al., 2005; Siegel et al., 2007; Tallon-Baudry et al., 2005; Tanji et al., 2005; Vidal et al., 2006), frontal eye fields (Lachaux et al., 2006); olfactory cortex (Miyanari et al., 2006), and language cortex (Brown et al., 2008; Canolty et al., 2007; Crone et al., 2001b; Edwards et al., 2010; Jung et al., 2008; Lachaux et al., 2007; Mainy et al., 2008; Sinai et al., 2005; Tanji et al., 2005; Towle et al., 2008). In addition, several studies have found greater task-related augmentation of broadband gamma activity when more attention is paid to the task (Brovelli et al., 2005; Jensen et al., 2007; Jung et al., 2008; Ray et al., 2008c; Tallon-Baudry et al., 2005; Vidal et al., 2006). In addition, this activity has been used to study various aspects of memory (Axmacher et al., 2006; Jacobs and Kahana, 2009; Lenz et al., 2008; Mainy et al., 2007).

It is important to note that although high gamma responses have been observed with the greatest clarity in ECoG and depth recordings, electrophysiological responses with the same or very similar spectral features have also been observed with MEG (Dalal et al., 2008; Gunji et al., 2007; Kaiser and Lutzenberger, 2005; Vidal et al., 2006) and even with scalp EEG (Ball et al., 2008; Ball et al., 2009; Darvas et al., 2010; Lenz et al., 2008). Because of the greater distances between cortical sources and extra-cranial sensors, these non-invasive techniques have lower sensitivity for high frequency activity and thus might not always reveal the full spectrum over which task-related power augmentation occurs. It is even possible, under some circumstances, that attenuation of higher frequencies may cause power augmentation to be observed in a narrower frequency range--at the low end of the high gamma range, than it would if it were observed with intracranial EEG. However, any epistemological uncertainty of EEG and MEG in this regard is outweighed by the risks associated with intracranial recordings and the potential drawbacks of studying normal neurophysiological responses in patients with intractable epilepsy. Nevertheless, these must

be considered when interpreting and comparing gamma responses in studies using these different recording techniques.

The apparent ubiquity and consistency of high gamma responses across such a wide variety of experimental tasks and cortical regions, has suggested that they are useful as a general electrophysiological index of cortical processing. This is of great practical significance for investigators attempting to explore less established functional-anatomic domains or those with greater inter-individual variability. More importantly, however, this suggests that the neurophysiological mechanisms responsible for task-related high gamma activity are somehow fundamental to neuronal function. Regardless of how important these mechanisms may be to the interpretation of experimental data, however, they are still largely unknown and are therefore subject to speculation, debate, and further investigation.

3. Mechanistic considerations and interpretations

From the preceding brief review of human experimental data, it would appear that high gamma responses are at least a very useful index of functional brain activation. But what neurophysiological mechanisms do they reflect and what is their significance vis-à-vis cortical function? If they are distinct from gamma oscillations at lower frequencies, how are they different and do these differences indicate different mechanisms? In particular, do high gamma responses have anything to do with the mechanisms previously proposed for gamma oscillations?

One of the most consistent characteristics of high gamma responses that must be taken into account when considering their possible neural mechanisms and/or role in cortical function, is the occurrence of task-related power augmentation over a relatively broad frequency range, e.g. ~60–200 Hz. The term “broadband” has been used as convenient shorthand for this characteristic. However, its usage in this context is not intended to mean that power augmentation is necessarily equal over all frequencies, though some have suggested this in its strictest sense (Miller et al., 2009a). Rather, it is merely intended here to highlight the difference between these responses and gamma responses that have been conceptualized and measured in much narrower frequency bands. Also implicit in this usage is the variable upper and lower boundaries of high gamma responses that make them difficult to define as a “band”. This difficulty complicates any attempt to assign a specific frequency band to these responses.

The relatively broad contour of high gamma frequency responses in the power spectrum have long been difficult to reconcile with theories that have been posited regarding the role of gamma oscillations in cortical function (Crone et al., 2001a; Crone and Hao, 2002; Crone et al., 1998a). In many recent animal studies, similar broad spectral responses have often been interpreted simply as gamma activity. However, the most influential and interesting theoretical mechanisms relating gamma activity to cortical function have assumed rhythmic oscillations that are expected to produce a peak in the power spectrum. One of these hypotheses, for example, proposes that the strength of cortical input, e.g. stimulus intensity, is coded by the relative phase at which output spiking occurs in the gamma cycle (Fries et al., 2007). Such a coding scheme appears to depend on rhythmic gamma oscillations at a relatively stable frequency. Such rhythmic oscillations have indeed appeared in experimental data as well-defined peaks in the EEG power spectrum. These peaks have usually been observed at low gamma frequencies (Engel et al., 2001; Fries et al., 2002), but some have also been observed in the high gamma range (>60 Hz) (Hoogenboom et al., 2006; Siegel et al., 2007). In many other studies, however, well-defined peaks are not seen in the spectral contours of responses at high gamma frequencies. This distinction between band-limited and broadband spectral contour could represent a more fundamental distinction between gamma

responses than the distinction between “high” and “low” gamma responses, i.e. based on arbitrary frequency ranges. If so, what does this say about the mechanisms responsible for what are commonly known as high gamma responses?

Because of the scientific climate in which high gamma responses were initially observed in human ECoG, they were initially interpreted within a conceptual framework that attempted to explain broadband high gamma responses from the experimental and theoretical perspective of narrow-band gamma oscillations (Figure 1). In particular, it was argued that for the broadband responses to arise from band-limited network oscillations, power changes would have to arise from the summation of oscillatory activity from multiple spatially overlapping neural assemblies, each oscillating at different, perhaps overlapping or more broadly-tuned frequencies (Crone and Hao, 2002; Crone et al., 1998a). Implicit in this provisional and speculative “model” is the notion that neuronal assemblies, i.e. networks of neurons or neuronal aggregates, representing different stimulus features, different aspects of behavioral output, and/or different task-related computational streams, rhythmically oscillate in parallel at different resonant frequencies, and that high gamma responses with a broad spectral shape are observed when a large number of these assemblies and their oscillations are averaged both in time and space. Also implicit in this model is that gamma oscillations, narrow band or not, can occur at high gamma frequencies. Although some support for this possibility may be found in the results of computational models of cortical networks (Bartos et al., 2007; Frund et al., 2009), most models of cortical gamma oscillations have not focused on such high frequencies (Jefferys et al., 1996; Kopell et al., 2000). Also implicit in this model is the prediction that if activity from the constituents of the aforementioned assemblies could be recorded in isolation, more band-limited oscillations would be observed at high gamma frequencies and that these oscillations might then be functionally segregated. Experimental testing of this prediction, however, would presumably require arrays of microelectrodes, and even then the contributions of different assemblies to LFPs at each recording site might be difficult to disambiguate. It might also be difficult to manipulate experimental conditions such that assemblies oscillating at different frequencies are preferentially engaged. In addition to spatial averaging of cortical responses, temporal averaging of responses at different frequencies may also contribute to the broad spectral shape of high gamma responses. The amplitude of activity at high gamma frequencies is very low, and although a change in this activity can be detected in single trials, reliable estimates of its power spectrum may require averaging over many trials of a task. It is difficult to ensure that all experimental conditions are held constant over these trials, and even if they can be, the neural assemblies and oscillatory dynamics sufficient to accomplish a task may vary from trial to trial.

A very different explanation for the broadband spectral contour of high gamma responses was proposed (Miller et al., 2007) in a paper reporting ECoG spectral responses in sensorimotor cortex during a variety of motor tasks. In this paper ECoG spectral responses were segregated into broad low frequency (8–30 Hz) and high frequency (70–100 Hz) bands, and a model of spectral responses to cortical activation was proposed in which suppression of resting band-limited oscillations at low frequencies is superimposed on broadband power augmentation not only in high gamma frequencies, but across *all* frequencies, including low frequencies where the aforementioned power suppression masks power augmentation. In a subsequent paper (Miller et al., 2009a), additional details and supporting data have been presented for this model of spectral responses that reflect a power law and thus do not emphasize any specific frequency range. In addition to attempts to define an exponent for this power law, a model of its generation has been proposed, based on random, uncorrelated synaptic inputs to cortical neurons (Miller, 2010). This model does not allow any role for narrow-band or even band-limited gamma oscillations in the generation of high gamma responses and suggests that these responses reflect random noise

in synaptic membrane potentials rather than any special mechanisms playing a role in neural coding. If true, this model would tend to limit the interpretive power of these responses though it would not diminish their practical significance and utility. This model produces membrane activity consistent with a power law, but the lack of correlation in the inputs to neurons implies a low degree of network connectivity. Another potential limitation of this model is that it is based on the shape of power spectra estimated for relatively large temporal windows (seconds) averaged across trials. A peak would be expected in these spectra if gamma oscillations were stable over these timeframes, but if oscillatory responses were brief and had varying latencies, durations, and/or frequencies, they could potentially be averaged to a power law shape. In this case, the observed power law might reflect random variability in the scale of networks and their resonant frequencies.

Yet another possible explanation for broadband high gamma responses in some, but not likely in all circumstances, is that they are the time-frequency representations of transient responses. Regardless of the methods used for signal analysis, there is an unavoidable tradeoff in the time-frequency representation of a time series such as EEG, and the energy of brief transients is distributed over a broad frequency range. This appears as a broadband spectral response, particularly when there is a sudden change in signal energy, as for example when recordings are made in sensory cortex at the onset or offset of a strong stimulus in the same modality. If the latencies of these transients are sufficiently variable, they may disappear from phase cancellation when averaged in the time domain, but survive when averaged in the frequency domain. This possibility must be kept in mind when interpreting very brief high gamma responses in sensory cortices, particularly when these responses extend across a wider frequency range than is typical of high gamma responses.

4. Experimental data from animals

Ultimately, experiments in animals will be needed to fully understand the neurophysiological mechanisms associated with high gamma responses and to determine whether these share anything in common with the neural mechanisms posited to date for gamma oscillations. Most studies of gamma oscillations in animals, however, have either not focused on high gamma responses or have not distinguished them from low gamma responses. In some of these studies, it is possible that the dominance of low gamma oscillations was due to species differences (Jeschke et al., 2008; Lenz et al., 2008). In still other studies, broadband gamma responses have been apparent in the power spectrum, but these responses also included low gamma frequencies, and they were simply interpreted as gamma responses. Regardless of the terminology and any disagreement about what constitutes a frequency band, a small number of studies have found high correlations between high gamma responses similar to those observed in human ECoG and increases in population firing rates (Belitski et al., 2008; Liu and Newsome, 2006; Manning et al., 2009; Ray et al., 2008a). These studies have provided valuable support for the utilitarian value of high gamma responses as an index of cortical activation.

In a recent study of microelectrode recordings from macaque SII cortex during tactile stimulation, broadband high gamma responses were observed with spectral profiles identical to those recorded in human iEEG (Ray et al., 2008a; Ray et al., 2008b). Detailed time-frequency analyses of these responses using matching pursuits revealed that they were temporally tightly linked to neuronal spikes. However, the experimental methods did not permit their precise generating mechanisms to be determined (Ray et al., 2008b). Nevertheless, LFP power in the high gamma range was strongly correlated, both in its temporal profile and in its trial-by-trial variation, with overall firing rate increases in single units recorded with the same electrodes (Ray et al., 2008a). One possible interpretation of these findings, along the lines of the previous discussion of time-frequency representations

of transients, is that high gamma responses arise from the summation of transients in membrane potentials that are tightly associated with action potentials. Although it is possible that energy from action potentials appears in the high gamma range in LFP recordings from microelectrodes, action potential currents are much less likely to contribute significant energy to ECoG and especially to EEG signals (Nunez, 1981).

Whether the underlying signals giving rise to ECoG high gamma responses are oscillations or transients, activity in such a high frequency range is much more likely to be recorded at the mesoscale of subdural electrocorticography if there is some degree of synchronization across a population of neural generators. In an attempt to relate the high gamma responses in animal LFP with those recorded in human ECoG (Ray et al., 2008a), high gamma responses recorded at the cortical surface with macroelectrodes were simulated using high gamma waveforms decomposed with matching pursuits from animal LFP. Using a simple model of volume conduction and summation of the LFP waveforms, firing patterns in the underlying cortical population were varied. Although increases in firing rate and increases in neuronal synchrony both resulted in broadband high gamma power increases, the modeled high gamma ECoG responses were much more sensitive to increases in neuronal synchrony than to increases in firing rate (Ray et al., 2008a). Based on this admittedly simplistic model, it is possible that high gamma responses index neuronal synchronization to some extent even if the underlying firing pattern is not a band-limited oscillation. In theories proposing mechanistic roles for gamma oscillations in cortical function, their role is usually to enhance the synchronization of neuronal firing in assemblies of neurons. Similar mechanisms have been proposed for theta oscillations, and there is experimental evidence for phase-modulation at theta frequencies of both band-limited gamma oscillations in scalp EEG (Demiralp et al., 2007) and broadband high gamma responses in ECoG (Canolty et al., 2006). Synchronization of neural firing may itself constitute a temporal coding strategy for cortical computation that complements rate coding and plays a role in higher cortical functions such as attention (Fries et al., 2001; Steinmetz et al., 2000). Although subthreshold membrane oscillations, whether in gamma or other frequencies, provide a mechanism for synchronizing neuronal firing, synchronization may occur by other means (Niebur, 2002; Niebur and Koch, 1994), and regardless of the mechanisms responsible for synchronization, it is intriguing to consider the possibility of a macroscopic electrophysiological index of synchronization in the activity of neuronal populations. Without more evidence for this, however, the safest interpretation at this point is that high gamma responses are correlated with increases in overall population firing rates.

5. Conclusions

More experimental work will be needed to determine the relationship between high gamma responses and other gamma responses, including the relative salience of broadband responses vs. band-limited responses, i.e. oscillations, and the relative contribution to high gamma responses from increases in firing rate vs. increases in synchrony. Moreover, it remains to be determined whether these electrophysiological responses reflect mechanisms integral to information coding and the functioning of cortical networks, or simply arise from time-frequency analyses of increased population activity. At this point, therefore, we believe it is most prudent to remain agnostic on these questions until more experimental data is available from both human and animal studies and from computation modeling of neural networks. We also believe it is important to acknowledge that any of the aforementioned mechanisms could potentially contribute to high gamma responses observed in experimental data. Nevertheless, even if high gamma responses simply reflect, for example, increases in overall population firing rates, their significance and utility are unlikely to be diminished. There is already ample experimental evidence from invasive recordings in humans and animals that high gamma responses reflect neural activity that is tightly related to cortical

function and can be exploited for functional mapping (Crone et al., 2009), for cognitive neuroscience experiments (Jacobs and Kahana, 2010), and for interfacing the brain with computers and prostheses (Schalk, 2010). In addition, there is growing evidence that these responses can be measured noninvasively, i.e. with MEG and even scalp EEG, opening up a vast potential for future studies in normal subjects. Thus, debate will likely continue about how these responses should be interpreted, particularly with respect to the neural mechanisms responsible for cortical function, and about what they should be called, i.e. high gamma, low gamma, broadband gamma, band-limited gamma, or just plain gamma.

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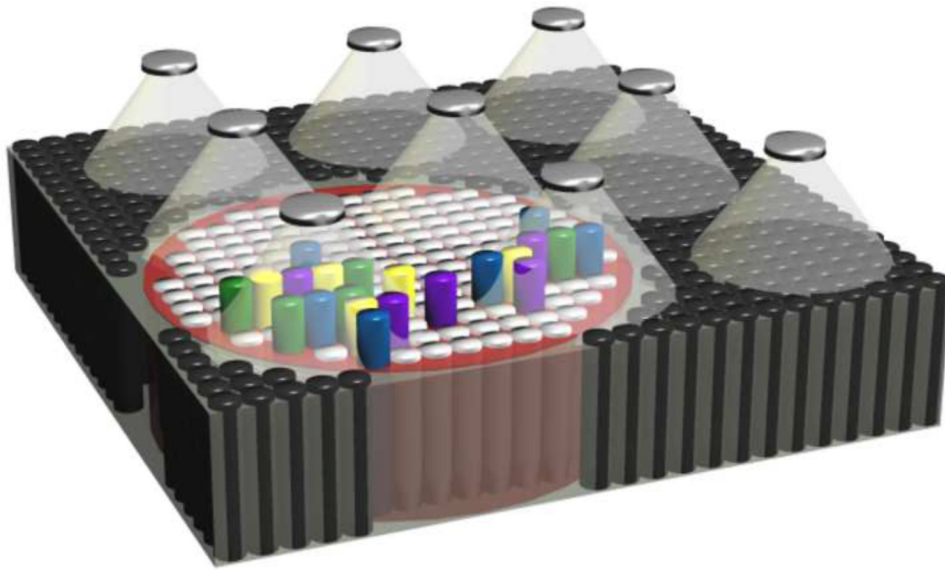


Figure 1.

Conceptual schematic illustrating a possible mechanism explaining the broad range of frequencies involved in high gamma responses recorded with electrocorticography. An electrode array is positioned over a slab of cortex (scaling distorted for illustration purposes) with inverted cones “illuminating” cortical regions contributing the most to signals recorded at each electrode. Cylinders in cortex represent assemblies of neurons with strong functional connectivity, e.g. macrocolumns or groups of tightly interconnected columns. Black (and white) cylinders represent neuronal assemblies that are not currently engaged in task-related cortical processing. Different colored cylinders represent assemblies that are engaged in different aspects of cortical processing (e.g. processing different object features) and have different resonant frequencies at which synchronous neuronal firing and associated membrane potential oscillations occur. Membrane potential oscillations with different center frequencies collectively contribute to signals recorded by ECoG macroelectrodes and their summation produces a broadband shape to high gamma responses in the power spectrum. This would require more oscillations than can be illustrated here unless their bandwidths at half power were quite wide (low Q). Unrelated to the mechanisms discussed in the text, red-highlighted circular area indicates a region of cortex with event-related desynchronization (ERD, power suppression) in alpha/beta frequencies, reflecting a thalamocortical gating mechanism in a larger zone of cortex that permits or facilitates cortical processing related to the current task. Reproduced with permission from Elsevier (Crone and Hao, 2002).