Special Communication

Neural Oscillations and Synchrony in Brain Dysfunction and Neuropsychiatric Disorders
It's About Time

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Neural oscillations are rhythmic fluctuations over time in the activity or excitability of single neurons, local neuronal populations or "assemblies," and/or multiple regionally distributed neuronal assemblies. Synchronized oscillations among large numbers of neurons are evident in electrocorticographic, electroencephalographic, magnetoencephalographic, and local field potential recordings and are generally understood to depend on inhibition that paces assemblies of excitatory neurons to produce alternating temporal windows of reduced and increased excitability. Synchronization of neural oscillations is supported by the extensive networks of local and long-range feedforward and feedback bidirectional connections between neurons. Here, we review some of the major methods and measures used to characterize neural oscillations, with a focus on gamma oscillations. Distinctions are drawn between stimulus-independent oscillations recorded during resting states or intervals between task events, stimulus-induced oscillations that are time locked but not phase locked to stimuli, and stimulus-evoked oscillations that are both time and phase locked to stimuli. Synchrony of oscillations between recording sites, and between the amplitudes and phases of oscillations of different frequencies (cross-frequency coupling), is described and illustrated. Molecular mechanisms underlying gamma oscillations are also reviewed. Ultimately, understanding the temporal organization of neuronal network activity, including interactions between neural oscillations, is critical for elucidating brain dysfunction in neuropsychiatric disorders.

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Neural oscillations are rhythmic fluctuations over time in the activity or excitability of single neurons, local neuronal populations or assemblies, and/or multiple neuronal assemblies distributed across brain regions. Although trains of action potentials or spikes from single neurons can contribute to these rhythmic fluctuations, they mainly reflect inhibitory and excitatory postsynaptic currents. Neural oscillations manifest as cyclic changes in the voltages of local field potentials from patches of brain tissue and, via volume conduction, the voltages measured on the cortical surface (electrocorticogram) or the scalp (electroencephalogram [EEG]) and associated magnetic fields measured near the scalp (magnetoencephalogram). These voltage fluctuations would not be evident on spatial scales ranging from local field potentials to scalp EEGs if they were not synchronized in time and space across large groups of neurons (because electric fields that are randomly aligned, instead of synchronized, tend to cancel out). Synchronized oscillations may allow spikes from assemblies of neurons to have a greater effect on downstream targets than can be achieved by unsynchronized neurons,[1,2] and brain regions may be able to interact only when oscillating synchronously.[1,3] Synchronized neural oscillations are generally understood to depend on inhibition that paces assemblies of pyramidal (excitatory) neurons to produce alternating temporal windows of reduced and increased excitability.[1] This synchronization is achieved by the extensive networks of local and long-range feedforward and feedback bidirectional connections between neurons in the mammalian brain. Moreover, the temporal frequencies of neural oscillations, including ultraslow (<1 Hz), delta (1-3 Hz), theta (4-8 Hz), alpha (9-12 Hz), beta (13-30 Hz), gamma (31-80 Hz), fast (81-200 Hz), and ultrafast (201-600 Hz), are highly conserved across mammalian species despite substantial differences in brain size.[1] This observation supports the proposition that synchronization of rhythmic neural activity across a range of time scales is a fundamental organizing principle of the mammalian brain,[1] justifying translational research on neural oscillations between humans and other mammals. Ultimately, understanding the temporal organization of neuronal network activity, including the coordinated interactions between neural oscillations, is critical for elucidating how the brain works.

In general, neural oscillations can be described as a mixture of sine waves of different frequencies (cycles per second or hertz), peak amplitudes (power = amplitude squared), and phase (specific point in a sine wave cycle relative to its origin or another reference point, where a cycle is divided into 360 equal segments [degrees]) that overlay and summate in the raw time-series recordings. This framework gives rise to several analytic approaches and measures that are reviewed briefly herein and in more detail elsewhere.[4]

Figure 1. Evoked and Induced Gamma Oscillations
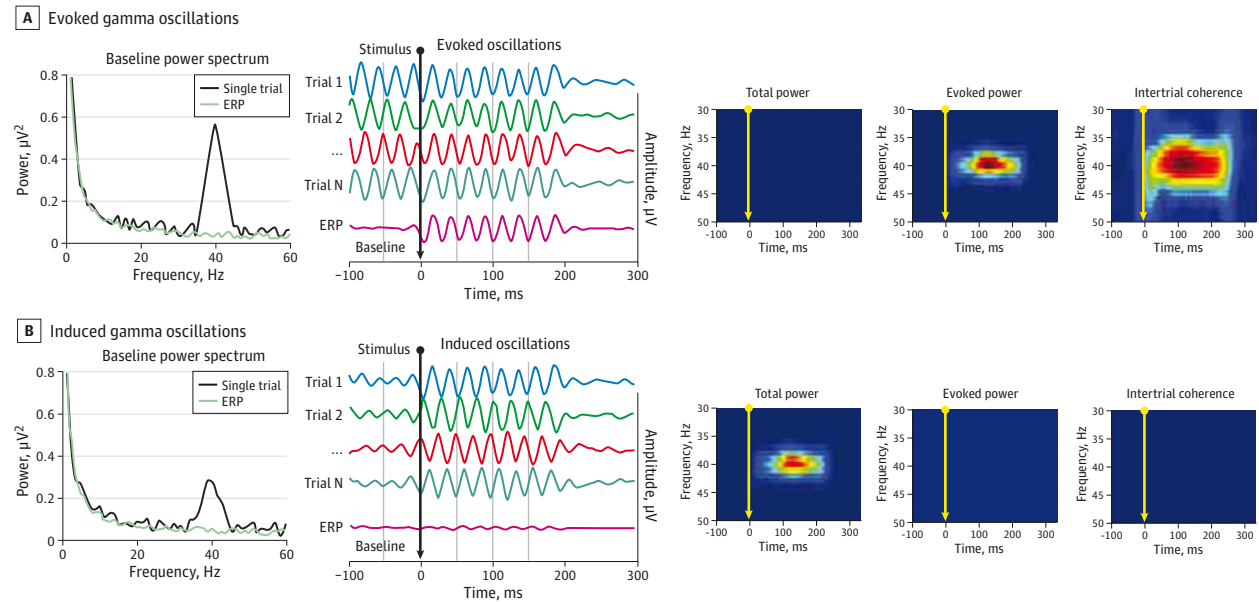
A, Evoked oscillations result when a stimulus resets the phase of ongoing oscillations or evokes new oscillations such that their phases are consistently aligned across trials. ERP indicates event-related potential. Evoked oscillations survive averaging across trials and are present in the ERP. They are reflected in evoked power and intertrial coherence. In this example, evoked oscillations are not reflected in total power estimates because their amplitudes did not increase relative to the prestimulus baseline. B, Induced oscillations result when a stimulus induces an increase in the amplitude of oscillations without resetting their phases across trials. Random phase of induced oscillations results in (1) no surviving oscillations when trials are averaged to generate the ERP; (2) no evoked power (calculated from the ERP); and (3) no intertrial coherence. In parts A and B, the power spectrum can be calculated for the prestimulus baseline electroencephalographic (EEG) intervals followed by averaging (single trial), or it can be calculated from the ERP baseline. The gamma oscillatory power evident in the single trials is lost during averaging over trials and is not present in the power spectrum of the ERP baseline. Because prestimulus baseline EEG oscillations are not time locked to events, their power is quantified as a power spectrum calculated over the entire time epoch (left panels).

Resting or Baseline Neural Oscillations

When spontaneous neural oscillations are recorded over time without intervening stimulus events, as in resting EEG or during baseline intervals between task trials (**Figure 1**), the principal quantitation approach is to decompose the time series data spectrally using a Fourier transformation, yielding estimates of power at each frequency.[4] Because the EEG in these time windows is not time or phase locked to specific events, oscillation phase information is not considered, and no baseline period exists from which to calculate a change in power. Moreover, when analyzing EEG epochs in the baseline periods preceding stimulus trials, power is estimated from individual trial epochs. This is because little or no baseline power survives averaging over trials in the resulting event-related potential (ERP) (Figure 1) owing to the random phase of the oscillations across trials. The power of specific frequencies can differ between individuals and groups (eg, baseline gamma power in Figure 1, A vs B). However, because absolute EEG power can vary by an order of magnitude between individuals, outliers should be excluded and/or the distribution normalized using an appropriate transformation (eg, logarithmic transformation).

Event-Related Neural Oscillations

When neural oscillations are recorded during tasks in which stimuli are presented over many trials, several event-related measures can be calculated.[4] First, single-trial EEG epochs time locked to stimulus on-

sets can be averaged, yielding an ERP (Figure 1). Second, using time-frequency decomposition methods (eg, Morelet wavelets), one can estimate the change in EEG power relative to the prestimulus baseline for various frequencies as a function of time after the stimulus. These changes can be averaged over trials to yield total power[4] (Figure 1). When a stimulus induces an increase in the amplitude of oscillations without resetting their phases across trials, the magnitude of the resulting induced oscillations is termed *induced power*, which is only evident in the total power estimate (Figure 1, B). Third, the same computational methods can be used to quantify the degree to which the phase of poststimulus oscillations is consistent across trials, a measure known as *intertrial coherence*. When a stimulus resets the phase of ongoing oscillations or evokes new oscillations such that their phases are consistently aligned across trials, the result is termed *evoked oscillations* (Figure 1, A). These phase-locked oscillations survive averaging over trials and are evident in the ERP (Figure 1, A). Indeed, evoked oscillations may underlie aspects of ERPs. Fourth, stimulus-evoked changes in oscillation magnitude can be calculated from the ERP, a measure termed *evoked power* (Figure 1). Evoked power can result from pure-phase resetting of ongoing oscillations by a stimulus in the absence of stimulus-induced increases in power on individual trials (Figure 1, A).
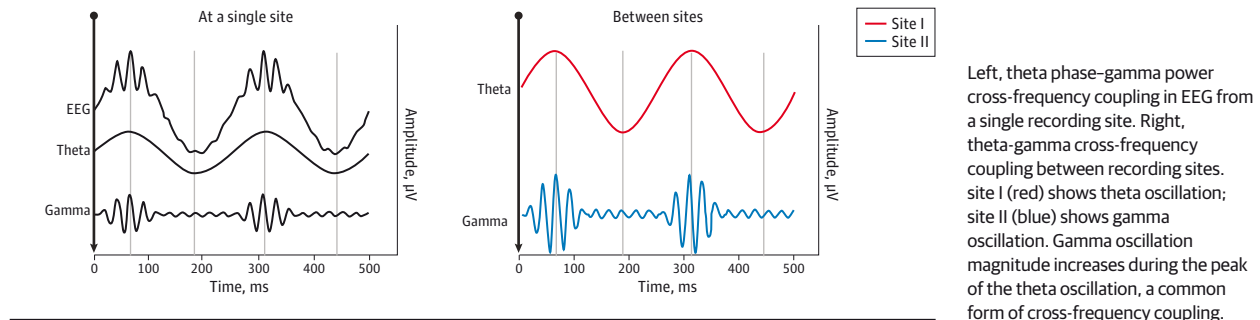
Cross-Site Oscillation Coherence

The degree to which oscillations from 2 recording sites are correlated or coherent may reflect aspects of neural connectivity.[1] Sev-

Figure 2. Cross-Site Gamma Phase Coherence
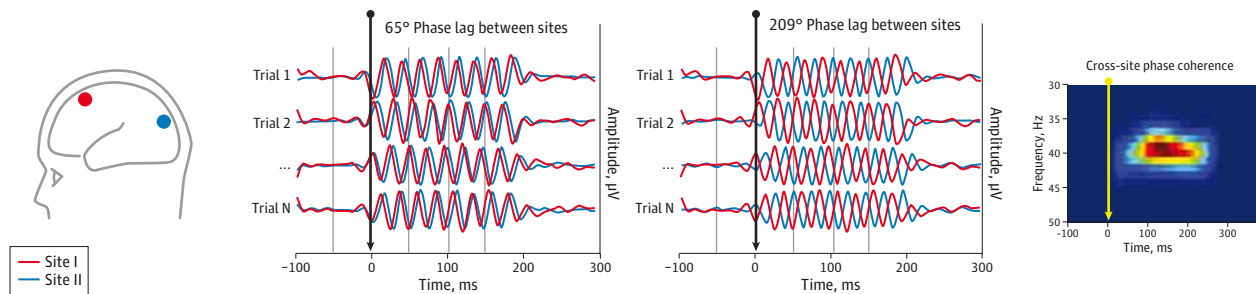
On the left side, 2 hypothetical cortical sources of gamma oscillations, a frontal source (site I [red]) and a parietal source (site II [blue]). In the middle, an overlay of oscillations from sites I and II for each single-trial electroencephalographic (EEG) epoch. The middle left shows relatively short phase lag (65°) between oscillations from sites I and II. The middle right shows relatively long phase lag (209°) between oscillations from sites I and II. On the right side, cross-site phase coherence reflects consistency of phase lag between sites I and II across trials. Gamma-phase coherence across sites is equivalent regardless of whether the phase lag between the gamma oscillations from the 2 sites is short or long. Furthermore, despite high phase coherence between sites over trials, the phases of the oscillations across trials at each site are not consistent (ie, low intertrial coherence).

Figure 3. Theta Phase–Gamma Power Cross-Frequency Coupling

Left, theta phase–gamma power cross-frequency coupling in EEG from a single recording site. Right, theta-gamma cross-frequency coupling between recording sites. site I (red) shows theta oscillation; site II (blue) shows gamma oscillation. Gamma oscillation magnitude increases during the peak of the theta oscillation, a common form of cross-frequency coupling.

eral coherence measures have been developed that reflect the correlation of the magnitudes and/or phases of oscillations at specific frequencies between sites[4]; these measures can be calculated for resting or baseline spontaneous oscillations and for event-related oscillations. Magnitude-squared coherence reflects both magnitude and phase consistency, whereas phase coherence reflects only phase synchrony between sites[4] (**Figure 2**). Phase coherence is high if the phase difference between oscillations at 2 sites is consistent across trials even when the phase at individual sites is inconsistent across trials (Figure 2). This sensitivity to the consistency of the cross-site phase lag across trials, rather than the consistency of the phase across trials, distinguishes cross-site phase coherence from the intertrial coherence calculated from a single site. Moreover, the phase coherence of synchronized oscillations between sites is equivalently high irrespective of whether the phase lag between them is small or large (Figure 2). A methodological challenge for EEG and/or magnetoencephalography is the spurious cross-site coherence that can arise when oscillations from a single source are volume conducted to both sites. Approaches have been proposed to mitigate this challenge, but controversies remain.[4]

Cross-Frequency Coupling

Neural oscillations can be organized hierarchically such that the phase of slower oscillations modulates the amplitude, frequency, or phase

of faster oscillations, a phenomenon generally termed *cross-frequency coupling*.[1,4,5] For example, the magnitude of gamma oscillations in the cortex and hippocampus systematically varies with the phase of hippocampal theta oscillations in rodents,[1] and similar theta-gamma coupling has been observed in humans.[1,5] Such temporal coupling of gamma oscillations with the phase of slower oscillations may constitute the fundamental element of a syntactic code for temporally chunking information arising from distinct neuronal assemblies,[1] as described during the encoding of items in short-term memory or spatial locations while moving through the environment.[1] In principle, different oscillation frequencies may exhibit coupling across all combinations of phase, power, or frequency.[1,5] However, coupling involving increased gamma oscillation magnitudes during the peaks of coincident theta oscillations within or between recording sites (**Figure 3**) is the most intensively studied example to date.[1,5]

Focus on Gamma Oscillations

Gamma oscillations have generated particular interest for many reasons. The duration of a gamma cycle corresponds to the 10- to 30-millisecond window of temporal integration for postsynaptic neurons and for spike-timing dependent synaptic plasticity and also corresponds to the time constants of γ-aminobutyric acid (GABA-A) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)

Figure 4. Parvalbumin (PV) Interneuron–Pyramidal Neuron Microcircuit Underlying Neuronal Gamma Oscillation
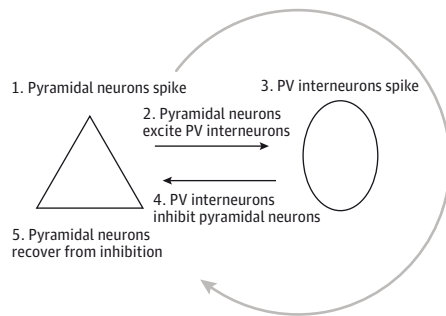
Active pyramidal neurons excite PV interneurons, causing PV interneurons to spike and leading to inhibitory synaptic potentials in pyramidal neurons, silencing them. When this inhibition wears off, pyramidal neurons spike again, leading to reexcitation of the PV interneurons and starting a new cycle.

receptors.[1] These observations have contributed to the hypothesis that gamma oscillations organize information flow between brain regions.[1,3] Gamma oscillations are also major drivers of the blood-oxygen level–dependent signal measured by functional magnetic resonance imaging.[6] Gamma oscillations are implicated in functions ranging from early sensory processing to higher-order cognition in rodents and humans.[7]

Mechanisms Underlying Gamma Oscillations

A class of inhibitory interneurons, identified by their expression of the calcium-binding protein parvalbumin (PV) and/or their fast-spiking electrophysiologic properties, are critical for generating gamma oscillations.[2] Parvalbumin interneurons may contribute to gamma oscillations through 2 mechanisms.[8] First, PV interneurons are reciprocally connected with excitatory pyramidal neurons (**Figure 4**). Thus, when pyramidal neurons are active, they will excite PV interneurons, causing PV interneurons to spike. Spikes in PV interneurons then lead to inhibitory synaptic potentials in pyramidal neurons, silencing them. When this inhibition wears off, pyramidal neurons are able to spike again, leading to reexcitation of the PV interneurons and starting a new cycle of the gamma oscillation. In this scheme (Figure 4), termed *pyramidal neuron–interneuron network gamma* (PING), a gamma cycle (lasting 10-30 milliseconds) con-

stitutes the time needed for pyramidal neuron spikes to elicit spikes in PV interneurons (a few milliseconds) plus the time for PV interneuron–mediated inhibitory currents in pyramidal neurons to decay (about 5-20 milliseconds). Parvalbumin interneurons are also interconnected, providing a second mechanism for gamma generation. If a population of PV interneurons receives somewhat homogeneous excitatory input, many will spike. In fact, PV interneurons are connected by electrical synapses, which enhance their tendency to spike together. Once a group of PV interneurons spikes, they inhibit each other and are then unable to spike again until this inhibition wears off. Because the kinetics of inhibitory currents are similar across PV interneurons, they will tend to spike again at the same time, initiating a new gamma cycle. This mechanism is termed the *interneuron network gamma* (ING). Thus, in addition to the functions outlined above, gamma oscillations represent an important barometer for healthy PV interneuron function.

Spontaneous Gamma Oscillations in Schizophrenia

Based on theoretical considerations and empirical evidence, dysfunction in the generation and/or coordination of neural oscillations is increasingly implicated in the pathophysiology of psychiatric disorders.[1,2] Hirano et al[9] have reported that patients with schizophrenia have reduced auditory evoked–gamma phase synchrony, which is consistent with the findings of prior studies,[4] as well as increased gamma power during the baseline intervals between task stimuli. Gamma oscillations during task baselines may reflect neural noise in the sense that they do not appear to participate in processing the stimulus at hand. Indeed, this noise interpretation is supported by their inverse relationship with subsequent stimulus-evoked gamma synchrony.[9] Rodent studies have shown that disruptions in PV interneurons similarly increase spontaneous gamma power,[2] suggesting that PV interneuron abnormalities in schizophrenia[10] may underlie their increased baseline gamma power.[9] This increase in gamma power was not present in the spontaneous EEGs recorded from patients during rest,[9] which underscores the need to consider how task context may influence gamma oscillations during baseline intervals between task stimuli and dissociate it from the spontaneous gamma oscillations recorded during task-free rest periods. This distinction warrants further attention, because it has not been emphasized in prior animal and human studies focused on spontaneous neural oscillations.

REFERENCES

1. Buzsáki G, Watson BO. Brain rhythms and neural syntax: implications for efficient coding of cognitive content and neuropsychiatric disease. *Dialogues Clin Neurosci*. 2012;14(4):345-367.

2. Sohal VS. Insights into cortical oscillations arising from optogenetic studies. *Biol Psychiatry*. 2012;71 (12):1039-1045.

3. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci*. 2005;9(10):474-480.

4. Roach BJ, Mathalon DH. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophr Bull*. 2008;34(5): 907-926.

5. Canolty RT, Knight RT. The functional role of cross-frequency coupling. *Trends Cogn Sci*. 2010;14 (11):506-515.

6. Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RA. Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science*. 2005;309(5736):948-951.

7. Bosman CA, Lansink CS, Pennartz CM. Functions of gamma-band synchronization in cognition: from single circuits to functional diversity across cortical

and subcortical systems. *Eur J Neurosci*. 2014;39 (11):1982-1999.

8. Tiesinga P, Sejnowski TJ. Cortical enlightenment: are attentional gamma oscillations driven by ING or PING? *Neuron*. 2009;63(6):727-732.

9. Hirano Y, Oribe N, Kanba S, Onitsuka T, Nestor PG, Spencer KM. Spontaneous gamma

activity in schizophrenia [published online January 14, 2015]. *JAMA Psychiatry*. doi:10.1001 /jamapsychiatry.2014.2642..

10. Lewis DA. Inhibitory neurons in human cortical circuits: substrate for cognitive dysfunction in schizophrenia. *Curr Opin Neurobiol*. 2014;26:22-26.