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# Neural Synchrony in Schizophrenia: From Networks to New Treatments

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**Evidence is accumulating that brain regions communicate with each other in the temporal domain, relying on coincidence of neural activity to detect phasic relationships among neurons and neural assemblies. This coordination between neural populations has been described as "self-organizing," an "emergent property" of neural networks arising from the temporal synchrony between synaptic transmission and firing of distinct neuronal populations. Evidence is also accumulating that communication and coordination failures between different brain regions may account for a wide range of problems in schizophrenia, from psychosis to cognitive dysfunction. We review the knowledge about the functional neuroanatomy and neurochemistry of neural oscillations and oscillation abnormalities in schizophrenia. Based on this, we argue that we can begin to use oscillations, across frequencies, to do translational studies to understand the neural basis of schizophrenia.**

*Key words:* schizophrenia/neural synchrony/translational neuroscience

Traditionally, scientists have thought that information processing was revealed by changes in firing patterns of "smart" neurons dedicated to specific functional tasks within the processing stream. While conveying important information, such a conceptualization is relatively hard wired, failing to reflect the flexibility needed to cope with complex and changing environments.[1] In 1949, Hebb[2] suggested that activity in neural assemblies, by its very nature, introduces phasic relationships among neurons, which, in turn, give rise to oscillatory patterns of activation. Repeated activations increase the strength of the associations among neurons forming these assemblies, following the oft-quoted principle that "cells that fire together, wire together." Hopfield and Brody[3] (2001) later suggested that brief bursts of transient collective synchronization may mean that "many neurons now agree."

With increasingly sophisticated data collection and analysis, evidence is now accumulating that regions of the brain communicate with each other to integrate sensory information and to coordinate sensory-motor functions needed for learning.[4] As Fuster[5] noted, while much research has focused on prefrontal cortex (PFC), "none of its cognitive functions can be understood if taken out of a broad connectionist context." Functional brain imaging studies indicate that a one-to-one mapping between brain regions and specific cognitive functions is too simplistic. Not only does one task activate many areas but also one area is activated by many different tasks, in the temporally dynamic and integrated brain.

Communication between brain areas is reflected in patterns of synchronization and desynchronization of neuronal activity, eg, Singer,[1] Singer et al,[6] Varela et al.[7] The specific frequency of synchronous firing may identify neural populations as belonging to the same functional network, allowing the same neuron(s) to participate in different processes with other neurons.[8] Hence, synchronous oscillations in a wide range of frequencies are thought to play a crucial role in linking spatially distributed neuronal assemblies into functionally integrated and specialized networks. This coordination between neural populations has been described as "self-organizing," an "emergent property" of neural networks arising from the temporal synchrony between synaptic transmission and firing of distinct neuronal populations.[9] This synchronization has been shown to play a role in processes such as sensory registration,[10] perceptual integration,[11] and selective attention.[12] Furthermore, the synchrony of neural activity, rather than its amplitude, is more closely related to the overt behavior it drives.[13]

The temporal dynamics of neural activity in micro- and macroneural circuits, both in vitro and in vivo, can be captured by electrophysiological recording methods having a temporal resolution that matches the firing rate of neurons. Neural oscillations and their synchrony can be studied at multiple levels of brain organization: (1) with single unit recordings, ongoing firing of a single neuron can be characterized in terms of its frequency and its synchronization by antecedent stimulatory events; (2) with multiunit recordings, the synchronization of firing between neurons, particularly in relation to changing

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stimulus conditions, can reveal the elemental building blocks of temporally coherent microcircuitry; (3) local field potential recordings can capture the oscillatory frequencies and phases of localized neuronal populations (or "assemblies") and the extent to which these oscillations are synchronized with respect to antecedent stimuli and with respect to other spatially distant neuronal assemblies forming functional coherent macrocircuit constituents of neuronal networks; and (4) cortical surface electrode or scalp electrode electroencephalogram (EEG) recordings can capture the ongoing frequencies and phases of multiple oscillating neuronal networks, which despite their temporal and spatial summation, can be decomposed into specific frequencies whose phase can be shown to synchronize with respect to specific sensory, motor, and cognitive events, as well as to the oscillatory rhythms recorded from spatially (and cortically) distal electrode sites. Oscillations at a particular frequency can be assessed for power or phase coherence across space (ie, electrode sites) or time (ie, event-locked changes in the EEG).

In the following, we briefly review the knowledge about the neural basis, the functional neuroanatomy, and the neurochemistry of oscillations in the theta (4–7 Hz) and gamma (30–100 Hz) ranges. Based on this literature, we argue that we can begin to use oscillations, in all frequency ranges, to understand these neural bases of schizophrenia.

## Neural Basis of Oscillations

At a network level, theta (4–7 Hz) and gamma (30–100 Hz) activities appear to be universal properties of circuits that are gated by feedforward inhibition, ie, where there is glutamatergic excitation that is gated by γ-aminobutyric acid (GABA)–mediated inhibition.[14] Theoretically, intracerebral communication can occur at any frequency within the constraints of the biophysical properties of the network. The exact oscillation frequency in a microcircuit is not a fixed resonant property of cells; the same group of neurons produce alpha (8–12 Hz) or theta depending on activation strength of metabotropic glutamate receptors.[15] Also, GABAergic interneurons can phase the output of pyramidal cells, giving rise to oscillations in different frequencies.[16] Oscillation frequency may depend on the distance between the neuronal assemblies communicating with each other, conduction velocities of the axons connecting them, the kinetics of the receptors mediating neural transmission within the network, and the numbers of cycles needed for high-fidelity communication.[17]

## Function and Anatomy

Cortical gamma oscillations may derive from thalamic input or may be generated intrinsically within cortex. Theta is usually associated with hippocampal sources but is robust at the cortical surface. Theta and gamma can and do occur together, with theta modulating gamma and gamma often precipitating theta.[14,18] Investigators are attempting to understand the interplay of gamma and theta because they appear to reflect distinct aspects of information processing. Data from rodent hippocampus suggest that gamma carries the message and theta carries information about the order of the messages.[19] Hippocampal theta is also associated with processing of novel stimuli[19] and initiation of voluntary actions.[20] Although interacting theta/gamma oscillations have been most extensively studied in hippocampus, they are not unique to hippocampus. In fact, laminar layers of neocortex appear to contain different representations of neuronal oscillations, with neurons in middle layers tending to generate gamma and neurons in superficial layers tending to generate theta.[16] Interneurons firing at gamma frequencies in the cortex not only play a role in organizing the temporal features of oscillatory activity across microcolumns but also affect the phase relationships and synchrony of activity within a microcolumn.[21]

## Neurochemistry

The frequency of oscillatory activity not only is a biomarker for network activity but also signals distinct modes of network function. For example, pronounced increases in hippocampal and thalamic burst activity are associated with gamma and theta oscillations.[22,23] Burst activity, in turn, optimizes the probability of neurotransmitter release and may modulate gain within a neural network.[24] Further, neuronal activity in the theta range is optimal for N-methyl D-aspartate (NMDA) glutamate receptor–dependent forms of neuroplasticity,[25] while high-frequency stimulation (>100 Hz) produces a form of long-term potentiation dependent upon voltage-gated cation channels.[26] NMDA receptor antagonism disrupts prefrontal cortical network functionality, increasing the firing rate and reducing burst activity associated with gamma oscillations elsewhere.[27] Further, disruption of network function by deficits in NMDA receptor function involves a component of GABA dysfunction. NMDA receptor antagonists impair the engagement of inhibitory interneurons in hippocampus[28] and PFC[29]; drugs like ketamine model the deficits both in NMDA receptors and in GABA systems.[30,31] Neural oscillations in the beta band (13–30 Hz) have also been associated with networks of inhibitory interneurons, gated by GABA action,[32] and genetic linkage studies have linked activity in the beta frequencies to a $GABA_A$ receptor gene.[33]

Regardless of how they are elicited, oscillations in the different frequency bands are likely to involve interactions of excitation (pyramidal neurons) and inhibition (interneurons) and the corresponding interplay between glutamatergic and GABAergic neurotransmission.[34]

Dopamine modulates activity of both glutamatergic and GABAergic components of cortical (and cortical-striatothalamic) networks enabling the ventral tegmental area to play an important role in coordinating cortical networks.[35] Dopamine activates GABA neurons via D1 receptors and inhibits them via D2 receptors.[36] It also depresses excitability of glutamate pyramidal dendritic fields via D1/D5 receptors. D1 receptor activation promotes burst firing of pyramidal neurons in "up states"[37,38] and activity of prefrontal cortical networks in culture and contributes to experience-dependent "tuning" of networks.[39] D2 receptor activation is destabilizing and suppresses PFC burst firing.[40,41] Knowledge of the intricate interplay of these different neurotransmitter systems can ultimately promote understanding of oscillatory deficits in the different bands in schizophrenia.

## Relevance to Schizophrenia

Communication and coordination failures between different brain regions may account for a wide range of problems in schizophrenia, from psychosis to cognitive dysfunction.[42] The phenomenology of schizophrenia suggests a disturbance in integration of brain activity through loss of "inner unity"[43] or "cognitive coordination."[42] Abnormal oscillations have been reported in schizophrenia for both power and phase in gamma[11,44] and theta range, eg, Ford and Mathalon,[45] Koukkou et al.[46] Recent increased interest in gamma in schizophrenia was provoked by a confluence of findings: gamma oscillations are induced in PFC during working memory tasks[47] and schizophrenic patients perform poorly on working memory tasks (although the component process affected is unclear)[48] and have reduced gamma phase locking.[44] Interest in theta has been piqued by recent demonstrations of sustained theta power during target detection,[49–51] a task associated with event-related potential P300[52] and gamma power[53] deficits in schizophrenia.[52]

That gamma oscillations are abnormal in schizophrenia[44] is consistent with schizophrenia-related deficits in glutamate and GABA systems. Hypofunction of glutamatergic transmission at NMDA receptors is a leading hypothesis of schizophrenia.[54–56] Schizophrenia is also associated with a net reduction of GABA-mediated inhibitory modulation.[57,58] Postmortem studies suggest that abnormalities in connections between chandelier cells and pyramidal cells disturb GABA interneuron neurotransmission in schizophrenia.[59] In fact, gamma power deficits in schizophrenia could be produced by NMDA receptor dysfunction via its disruption of GABAergic interneuron activity.[44]

## Going Forward

We now have an opportunity to marry bench neuroscience with scalp-recorded EEG. For example, we know that neural networks of healthy volunteers prefer to oscillate at 40 Hz, but the neural networks of schizophrenia patients do not. We know neural synchrony can be measured in vitro and in vivo, and we can manipulate the in vitro preparations to learn about schizophrenia, perhaps using preference for 40-Hz stimulation as an outcome measure. If we find that GABA antagonists introduced to the petri dish produce the schizophrenia pattern (20 Hz $>$ 40 Hz), we can begin to understand how to "fix" the schizophrenia pattern. Because new algorithms give continuous values for both phase and power of oscillatory activity, we can make finely gradated distinctions of the outcome variables and make subtle adjustments to the neurochemical mix.

While neural synchrony abnormalities might become a model for one elemental dysfunction of schizophrenia, like other models, it might only reflect one aspect of the illness. For example, ketamine is a better model of the negative and cognitive, than the positive, symptoms of the illness.[30] However, as the in vivo studies go forward, we may learn that neural oscillations are a proxy for more complex behaviors and symptoms, and we may be able to use measures of synchrony as powerful endophenotypes for genetic studies and/or neurobiological targets of drug development efforts aimed at discovering novel treatments for neuropsychiatric disorders such as schizophrenia.

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