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Neural Synchrony in Schizophrenia

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Basic neuroscience research suggests that neural assemblies communicate with each other in the temporal domain and rely on the coincidence of neural activity to detect phasic relationships between groups of neurons. Clinical neuroscience research suggests that communication and coordination failures between different brain regions may account for a wide range of problems in schizophrenia, from psychosis to cognitive dysfunction. This theme issue presents: an overview of time-frequency analyses that are used by clinical neuroscientists studying neural oscillations in schizophrenia; a comprehensive review of the literature on schizophrenia and neural asynchrony; data supporting dysfunction of both the GABA and glutamate systems in contributing to neural synchrony dysfunction in schizophrenia; and an example of how neural activity oscillating at different frequencies can form a code, which when disrupted could account for various symptoms of the illness. These papers illustrate approaches to translational neuroscience that will increase our understanding of schizophrenia and provide neurobiological endpoints for developing novel treatments.

Key words: schizophrenia/neural oscillations/EEG/theta/beta/gamma

For four decades, event-related potential (ERP) studies have provided a method for examining brain dysfunction in schizophrenia. These studies have shown that patients with schizophrenia have reduced amplitude of specific ERP components, such as the mismatch negativity[1] and the P300[2], revealing deficits in short-term auditory memory and attentional resources, respectively. For most investigators doing these studies, the electroencephalographic (EEG) data from which ERPs are derived were of little interest, essentially being viewed as the background noise in which the ERP components were embedded. Averaging the EEG epochs allowed the relatively small ERP components to emerge from the EEG noise, which tended to cancel out as more trials were averaged. However, in the last decade, a paradigm shift has been occurring involving a realization that the EEG is not simply brain noise unrelated to experimental events. Rather, the EEG contains signals that reflect the synchronized oscillations of neuronal assemblies engaged in information processing, and changes in the magnitude and phase of these oscillations at specific frequencies are systematically related to experimental events. This fresh perspective on EEG coincides with advances in basic neuroscience that have documented the mechanisms that give rise to neuro-oscillations and the roles that these oscillations play in interneuronal communication. All of these developments have converged on the hypothesis that dysfunction of neuro-oscillations may be a core pathophysiological process in schizophrenia. In this issue, we take stock of these developments and bring the hypothesis of deficient neural synchrony to the forefront of the collective consciousness of the schizophrenia research community.

The proliferation of EEG time-frequency analyses in the biological psychiatry community has been fueled by the availability of the computing power needed to make these calculations, the growing realization that synchronization of neural firing increases the efficiency and integrity of communication between cortical areas, and the awareness that problems experienced by schizophrenia patients might result from failures of different brain regions to communicate and coordinate with each other in the temporal and frequency domains. As Roach and Mathalon[3] note, the confluence of these 3 factors has breathed new life into the relatively old technology of EEG. However, the increasing availability of computational tools for time-frequency analysis of EEG, and the proliferation of studies reporting findings based on these tools, is associated with a widening gap between the findings themselves and the ability of the larger schizophrenia research community to understand the analytical methods on which these findings are based. Roach and Mathalon take a step toward narrowing this gap by providing an overview of time-frequency analysis methods that aims to make the computational algorithms used in these analyses understandable to the nonexpert. This presentation makes clear that the term ''neural synchrony'' has been operationalized in

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a variety of different ways in schizophrenia research. Roach and Mathalon then present an analysis of EEG data from an auditory task, showing that patients with schizophrenia have reduced synchronization of gamma oscillations evoked 50 ms following tone presentations, consistent with a growing literature implicating deficient gamma-band synchrony in schizophrenia.

Uhlhaas et al.[4] discuss the role of neural oscillations in communication between brain areas and point out that quick communication is most effectively done through the detection of the coincidence of phase angles of neural activity, rather than firing rates. They argue that "Possibly the most important function of synchronized, oscillatory activity is the implementation of a mechanism that can exploit the relative phase of oscillations." Uhlhaas et al. review the growing literature on oscillations in schizophrenia and report deficits across a wide range of frequencies. They provide a thorough and very useful description of the different frequency bands and what is known about their functional significance. They note that "In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronized oscillations. Short distance synchronization tends to occur at higher frequencies (gamma-band) than long-distance synchronization, which often manifests itself in the beta- but also in the theta- (4–8 Hz) and alpha- (8–12 Hz) frequency range." Importantly, oscillations are not merely a *reflection* of neural activity, but *are* the neural activity, as they "have a general computational role in dynamically selecting the neurons that communicate information about sensory inputs effectively."

Armed with the knowledge that phasic information is essential for quick and effective communication within the brain, and that it is abnormal in schizophrenia, we turn to Gonzalez-Burgos and Lewis[5] to explain which cell types might be involved in phase-sensitive communication. The authors distinguish between pyramidal cells and fast-spiking parvalbumin-containing γ aminobutyric acid (GABA) interneurons. These GABA neurons need far less glutamate to excite them than pyramidal neurons; because of their postsynaptic electrical resonance properties, these GABA neurons prefer to oscillate in the gamma range, with pyramidal neurons preferring the theta range; because they synapse on the perisomatic region of pyramidal cells, these GABA neurons synchronize the firing of pyramidal cells. Thus, these GABA neurons influence both theta and gamma oscillations, key to intracerebral communication. Gonzalez-Burgos and Lewis conclude that "As basic research studies continue to provide insight into the role of GABA neuron-mediated inhibition in cortical network oscillations, an important challenge for future studies is to clearly identify whether GABA transmission-related changes in schizophrenia represent a cause, consequence, compensation or confound in the disease process."

While Gonzalez-Burgos and Lewis focus on the role of GABA in neural oscillations and its disruption in schizophrenia by studying postmortem tissue, Roopun et al.[6] focus on the glutamate system in animal models. They note that some aspects of the neural synchrony abnormalities reported in schizophrenia can be reproduced by acutely or chronically manipulating glutamatergic synaptic communication mediated by N-methyl D-aspartate (NMDA) receptors. They discuss the broad range of effects the NMDA receptor antagonist, ketamine, has on gamma (30–80 Hz) and beta2 (20–29 Hz) rhythms and address both the regional specificity and frequency specificity of its effects. They note that this complex pattern of effects resulting from manipulations of the glutamate system is similar to the changes in cortical dynamics seen in schizophrenia—with contrasting effects seen in different brain regions and for different frequency bands. They suggest that GABAergic dysfunction in schizophrenia may be secondary to deficits in NMDA receptor–mediated excitatory synaptic activity.

In the final paper of this series, Lisman and Buzsaki[7] present an excellent example of how neural oscillations in the theta and gamma bands can and do work together to form a neural code. They present evidence for how this coding scheme provides a way for multiple neural ensembles to represent an ordered sequence of items. In the hippocampus, this coding scheme is utilized during "phase precession," a phenomenon that can be interpreted as the recall of sequences of items and places from long-term memory. The same coding scheme may be used in certain cortical regions to encode multi-item short-term memory. As the sequencing of events and experiences is essential for maneuvering in our environment and monitoring the sources of our self-generated experiences, it is quite possible that abnormalities in theta and gamma oscillations, and their interaction, could underlie avolition and apathy experienced by people with schizophrenia, as well as the experience of inner dialogues sounding like voices from outside.

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