Review

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Brain Rhythms Connect Impaired Inhibition to Altered Cognition in Schizophrenia

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ABSTRACT

In recent years, schizophrenia research has focused on inhibitory interneuron dysfunction at the level of neurobiology and on cognitive impairments at the psychological level. Reviewing both experimental and computational findings, we show how the temporal structure of the activity of neuronal populations, exemplified by brain rhythms, can begin to bridge these levels of complexity. Oscillations in neuronal activity tie the pathophysiology of schizophrenia to alterations in local processing and large-scale coordination, and these alterations in turn can lead to the cognitive and perceptual disturbances observed in schizophrenia.

Keywords: Brain rhythms, Cognition, Functional connectivity, Inhibitory interneurons, Schizophrenia, Temporal coding

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A quarter century after the discovery of reduced markers of gamma-aminobutyric acid (GABA)ergic interneurons in the brains of schizophrenia patients (1), inhibitory interneuron dysfunction has emerged as a central player in the etiology of schizophrenia. It has been tied to multiple neurotransmitter systems involved in the pharmacology of psychosis (2–5), as well as to the major genetic risk markers of schizophrenia (6–9). Inhibitory interneurons may be key because their development is targeted by a variety of schizophrenia risk genes (6,8–10), they are particularly vulnerable to environmental factors and oxidative stress (9,11), and their dysfunction may be either consequent or causal to other alterations (4,7,9,12–14).

Similarly, while schizophrenia is characterized by a variety of positive, negative, and cognitive symptoms, the latter have come to be recognized for their constancy and functional relevance (15). Deficits including alterations in executive function (16,17), sensory processing (18,19), and memory (20) are manifestations of an overall cognitive disorganization, which seems to be mediated by an underlying dysfunction of the coordination of neural activity (21–23).

It remains challenging to understand how the varied and specific manifestations of cognitive disorganization seen in schizophrenia arise from the varied and specific changes observed in schizophrenia-associated cell- and circuit-level neurobiology. We outline a framework for thinking about how these cellular level changes can be traced through mesoscale physiology to the level of the whole brain, to understand specific symptomatologies. Key to this multilevel analysis are temporal structures in the brain, including brain rhythms (2,24). Rhythmic alterations occur in schizophrenia and its animal models, accompany all neurotransmitter system manipulations that produce psychotic-like behavior (5,25–29), and are candidate endophenotypes of the disease (30). Rhythms are believed to play a key role in coordinating the activity of neuronal populations across multiple spatial and temporal scales (31–34) and are known to be associated with a wide range of cognitive and perceptual processes (35,36). Finally, inhibitory interneurons are central to the formation and maintenance of most brain rhythms (37–39), providing a conceptual link between the neurobiological and psychological manifestations of schizophrenia.

We review selected evidence from experimental and modeling work to sketch the following picture of schizophrenia dysfunction: changes at the cellular and molecular level—especially those affecting the function of inhibitory interneurons—alter the rhythmic coordination of neuronal activity. These alterations interfere with local processing, which is mediated by rhythmic activity. Perturbations of the oscillatory structure of local processing upset large-scale coordination of neuronal activity across brain regions. Finally, distorted local processing and large-scale coordination produce altered cognition.

CELLULAR, MOLECULAR AND CIRCUIT LEVEL CHANGES ALTER RHYTHMS

Different Rhythms Have Different Physiology

Spectral analysis of brain signals reveals multiple frequency bands (Figure 1), whose power, phase, and coordination are differentially related to task, state, and brain region (35,36). Brain rhythms reflect oscillations in population activity, but the local circuit structures giving rise to these oscillations vary widely (40), even between cortical layers, and under various conditions a single circuit or layer may express multiple rhythms.

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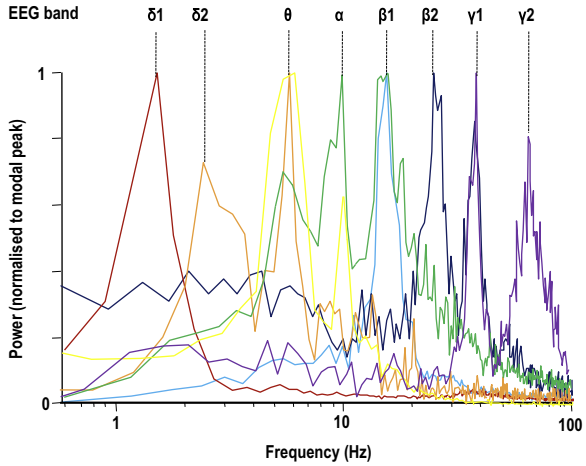

Figure 1. Multiple modal peak frequencies of persistent rhythms generated in isolated neocortex in vitro. All rhythms were generated in secondary somatosensory (parietal) cortical slices maintained in artificial cerebrospinal fluid (aCSF). Rhythms were recorded as local field potentials, resulting spectra (from 60-second epochs of data) are plotted with powers normalized to modal peak. Delta1 (δ1, ~1.5 Hz) rhythms were generated in control slices spontaneously after >1 hour incubation in normal aCSF. Delta2 (δ2, 2–3 Hz) rhythms were generated by bath application of cholinergic agonist carbachol (2 μmol/L). Both delta rhythms had maximal amplitudes in layer (L)V. Theta (θ, 6–8 Hz) rhythms were recorded in layers II/III in the presence of the glutamatergic receptor agonist kainate (10 nmol/L) and occurred concurrently with δ2 rhythms in LV. Alpha (α, ~10 Hz) rhythms were generated following transient activation of cortex by pressure ejection of glutamate. Peak amplitude was in LV and was present concurrently with θ and β1 rhythms in LII/III and LIV, respectively. Beta1 (β1,13–17 Hz) rhythms were generated alone by partial blockade of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate receptors following tonic activation by kainate (400 nmol/L). Beta2 (β2, 22–27 Hz) rhythms were generated in LV by kainate (400 nmol/L) and always occurred concurrently with gamma1 (γ1, 30–50 Hz) rhythms in LII/III in this brain region. Gamma2 (γ2, 0–80 Hz) rhythms were also generated by kainate (400 nmol/L) but occurred in LV in aCSF with reduced chloride ion concentration. Additional peak frequencies at ≥100 Hz are generated by brief, intense periods of excitation but rarely meet criteria for persistence and so are not considered here. [Reproduced with permission from Roopun *et al.* (150)]. EEG, electroencephalogram.

Some general principles have been learned from work on the biophysical mechanisms underlying brain rhythms. Inhibitory interneuron diversity is crucial to the temporal dynamics of neural activity (37), and the kinetics of the intrinsic and synaptic currents of neurons are critical for determining the frequencies of network oscillations. For example, the time scale of the γ rhythm (~30–90 Hz) is determined by feedback inhibition from (predominantly parvalbumin-positive [PV+]) interneurons (41). Perturbations changing the decay time of inhibition can change the frequency of this rhythm (41). Other GABAergic interneurons mediate inhibition at different time scales, to different receptors, cell types, and positions on neurons. Rhythm frequency is also determined by time constants associated with interneuron-specific intrinsic currents (42–47). Due to this variety, inhibition plays different roles in different rhythms, by interacting differently with the multiple underlying voltage-dependent processes. Changes in inhibition can thus have a variety of effects on rhythms (see below), and an understanding of these effects necessarily involves computational modeling.

The Pathophysiology of Schizophrenia Affects Rhythms

Early research into electroencephalography alterations in schizophrenia found consistent increases in δ and θ power in patients (48). Recent studies have revealed an overall profile of enhanced and uncoordinated baseline γ power in schizophrenia, coupled with decreased synchronized γ and β across sites during tasks and presentation of sensory stimuli, and altered coordination of γ, β, and α rhythmicity (24,49–55).

Investigators have attempted to determine how various molecular and cellular level changes lead to these rhythmic disruptions; effects on inhibition are often key. Below, we describe results for schizophrenia risk genes and multiple neurotransmitter systems.

Schizophrenia Risk Genes. Many genetic markers of schizophrenia code for products affecting neuronal rhythms. The loci meeting genome-wide significance in the largest genome-wide association study of schizophrenia ever conducted (8) include genes coding proteins shown to directly affect neuronal oscillations, such as metabotropic glutamate receptor 3 (mGluR3 - δ, θ and β) (56,57), glutamate receptor 1 (GluR1 - δ-γ interactions) (58), hyperpolarization-activated cyclic nucleotide-gated channel (HCN - θ and α) (42,43,59), nicotinic acetylcholine receptor (nAChr - θ) (60), T-type calcium channels (δ) (45), and NR2A subunit-containing NMDA receptor (Nr2Ar - γ) (61). Further genome-wide associations concern genes that may be indirectly involved in rhythms, expressed in GABAergic interneurons, or regulate synaptic transmission or neurodevelopment (8,9).

Schizophrenia susceptibility genes also play roles in neuronal development and maintenance and oscillations. Disrupted in schizophrenia 1 mutations affect GABA and dopamine systems and appear to preferentially disrupt parvalbumin-interneuron cytoarchitecture and function (10,62). Neuregulin-1, the product of a schizophrenia susceptibility gene, increases the power of γ-band oscillations in hippocampal slices (5,63). Reduced dysbindin-1, as occurs with schizophrenia, is associated with reduced phasic activation of parvalbumin-interneurons and impaired auditory evoked γ band activity (6).

GABA Alterations. Widespread, diverse changes in GABAergic signaling are seen in schizophrenia, affecting almost all mechanisms governing the activation of interneurons, the release of GABA, and its postsynaptic effects (64). A widespread reduction in glutamic acid decarboxylase 67 (required for GABA synthesis) is seen, while changes in GABA receptor subunit expression enhance the impact of a given quantity of GABA (64). The changing role of GABAergic signaling during development may magnify and complicate the effects of these alterations (9). Potassium channel subunits essential for fast spiking and coincidence detection in interneurons are also reduced (65).

Changes in the amount, temporal fidelity (65), and kinetics of inhibition have varied rhythmic effects. Reduced calcium binding via parvalbumin enhances the repetitive release of GABA and consequently γ rhythm power (66). Reduced reuptake via specific GABA transporters allows the transmitter to remain in the synaptic cleft for longer, prolonging postsynaptic inhibition (67). A longer time scale of GABA inhibition can result in slowed γ rhythms and explains patient deficits in