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.

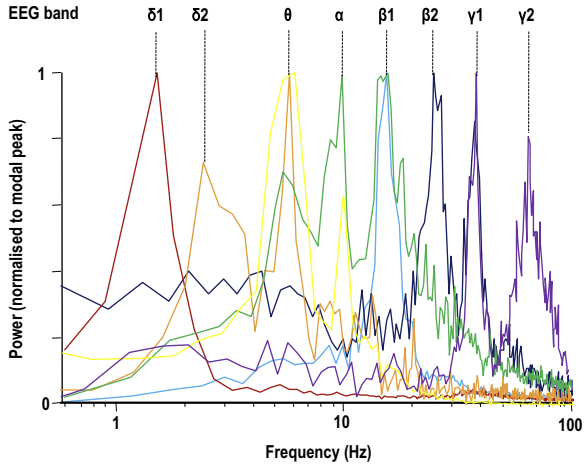

Figure 1. Multiple modal peak frequencies of persistent rhythms generated in isolated neocortex in vitro. All rhythms were generated in secondary somatosensory (parietal) cortical slices maintained in artificial cerebrospinal fluid (aCSF). Rhythms were recorded as local field potentials, resulting spectra (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

entrainment of the auditory steady-state response to a 40-Hz click stimulus (53).

***N*-methyl-D-aspartate Hypofunction.** Acute *N*-methyl-D-aspartate (NMDA) antagonism reproduces positive, cognitive, and negative symptoms of schizophrenia (12,14), and patients show reduced expression of NMDA receptor (NMDAR) messenger RNAs (68). In vivo, acute NMDAR blockade induces varied rhythmic and behavioral effects (24,69,70), intimately tied to the preferential effects of NMDAR blockade on different classes of inhibitory interneurons (4). Depending on these interneurons' properties and their roles in local circuits, NMDAR blockade may result in increased, decreased, or altered rhythmicity, as seen below in multiple studies of rodent electrophysiology.

- In rat prefrontal cortex (PFC), NMDA hypofunction seems to preferentially affect PV+ interneurons, reducing their level of tonic drive (3). Modeling has illuminated the mechanisms by which this gives rise to an increase, rather than the expected decrease, in γ power (71,72).
- In rodent hippocampus in vivo, NMDAR blockade results in both γ increases and θ decreases (73–75). Experimental and modeling work has shown how blockade of NMDARs on somatostatin-positive oriens lacunosum-moleculare interneurons may disinhibit PV+ interneurons, yielding increased γ via decreased θ rhythmicity (38,76,77).
- In entorhinal cortex (EC) slice, a slowing of γ oscillations is seen with NMDAR antagonism (78). Here, NMDA antagonism reduces drive to PV+ interneurons, unveiling a class of GABAergic interneurons having a slower decay of inhibition. These so-called goblet cells mediate the emergence of a slower γ rhythm.
- Recent thalamic slice work illuminates how NMDAR blockade acts on PV+ interneurons to give rise to increased δ rhythmicity (45). In contrast, acute NMDAR blockade in neocortex in vitro nearly abolishes locally generated δ activity (44), suggesting a shift in schizophrenia from coordinated, balanced thalamocortical δ activity to subcortically dominated δ activity.

Dopaminergic Disregulation. Mesolimbic hyperdopaminergia and mesocortical hypodopaminergia are leading causes of psychosis and negative/cognitive symptoms, respectively; may result from disinhibition in cortex and hippocampus (79); and may lead to regional differences in the effects of dopamine on brain rhythms. In a recent empirical and modeling study, amphetamine administration induced gamma decreases and increases in healthy and patient participants, respectively (80), changes replicated in a PFC model (80). In a hippocampal network model (81), dopamine had the opposite effect, reducing stimulus-induced gamma activity in putatively schizophrenic parameter regimes and increasing it in others.

While difficult to measure in humans (50), such baseline gamma effects are accessible in animal models. Nonspecific dopamine agonists and dopamine-releasing drugs like amphetamine have modest effects on baseline gamma (5,26), but selective activation of D4 receptors increases gamma power in hippocampal slice (5) and in the PFC in vivo (28). These effects are also likely mediated by PV+ interneurons: these cells are particularly enriched with D4 receptors, and interneuron spiking activity and pyramidal cell inhibitory postsynaptic potentials show enhanced synchrony with field potentials following D4 activation (5).

RHYTHMS ASSIST IN LOCAL PROCESSING

The temporal structure rhythms imposed on neural dynamics can have dramatic effects on cells' ability to elicit responses in their downstream targets. The temporal proximity of spikes occurring within a single γ cycle enhances their ability to induce spiking and spike-timing dependent plasticity in downstream neurons (82,83). Also, multiple lines of evidence suggest that spike phase, relative to ongoing rhythms, contributes to the neural code (84–87). Indeed, cell assemblies may consist of distributed neuronal populations whose spiking is brought together in time by rhythmic phase-locking (88,89). Below, we elaborate on the ways rhythms can enable local processing (90) and how altered rhythmicity can lead to information processing deficits.

Frequency Segregates Information Streams and Directs Information Flow

When oscillations are paced by inhibition, periodic inhibitory volleys result in the rhythmic gain modulation of both the inputs to and the outputs from cells participating in the rhythm (40,91). Rhythmic population output directed to a rhythmic target population can be filtered out, depending on the frequency and phase relationships between the rhythms of the two populations (40,91). Thus, oscillations may support selective (frequency dependent) population interactions, such as alternating receptivity of cornu ammonis (CA)1 to CA3 and EC (92). A change in the endogenous γ frequency of EC, as observed with NMDAR blockade (78), could lead to altered information flow within these circuits.

The frequency of an inhibition-based rhythm depends, at least in part, on the degree of excitatory drive to the participating cells, but the sensitivity of this dependence can vary, subtly directing information flow. In rodent auditory cortex in vitro, the frequency of a layer 4 γ rhythm is highly sensitive to changing excitation; in contrast, a superficial γ is relatively insensitive to excitation (93). Output layer 5 follows the layer with the higher frequency; thus, the degree of excitation determines which superficial layer dominates (Figure 2). The NMDAR-dependent layer 4 γ may mediate the response to salient stimuli, bypassing layers 2 and 3 to directly drive layer 5 (93). Schizophrenia-associated changes may detrimentally affect this switching of information flow: both NMDAR-mediated excitation and the kinetics of GABAergic inhibition are critical for this phenomenon.

Rhythm Concatenation Allows Integration of Cell Assemblies

In rodent parietal cortex, a superficial layer γ rhythm (~40 Hz) and a deep layer β_2 rhythm (~25 Hz) combine to produce a slower β_1 rhythm (~15 Hz) (Figure 3) (94,95). In this slow β_1, which requires both fast perisomatic (PV+ interneuron-mediated) and slower dendritic (SOM interneuron-mediated) inhibition, inhibitory interneurons are no longer entirely driven by superficial pyramidal cells, allowing multiple γ-rhythmic cell assemblies to be active simultaneously and perhaps integrated (96).

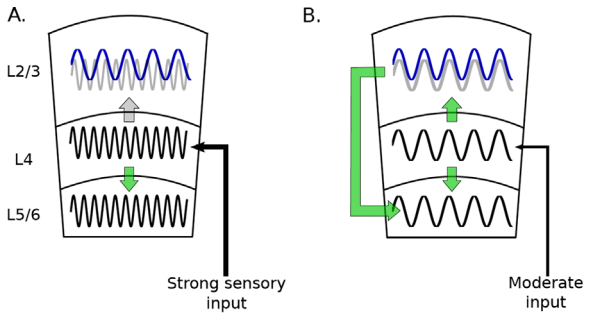

Figure 2. In rodent auditory cortex in vitro, the frequency of a layer (L)4 γ rhythm is highly sensitive to changing excitation. Under conditions of high excitation **(A)**, layer 4 exhibits a high frequency rhythm, which bypasses layers 2/3 to entrain output layer 5. Under conditions of moderate excitation **(B)**, layer 4 and layer 2/3 exhibit rhythms of the same frequency, and layer 5 is driven by both layers. Sinusoids depict gamma rhythms in each layer. The light gray sinusoid in L2/3 depicts oscillatory input from L4. Signal flow is depicted by green arrows. The size of the arrow denotes the relative strength of connection. [Reproduced with permission from Cannon *et al.* (40)].

θ-γ Nesting Coordinates and Sequences Cell Assemblies

In the hippocampus, multiple time scales of inhibition lead to nested γ and θ frequency rhythms (Figure 4) and the multiplexing of spatial representations into θ sequences: series of cell assemblies activated sequentially, each during one of the multiple γ cycles contained in a θ cycle (38). θ-γ nesting may serve encoding by bringing the firing of place-encoding cells together in time in a way that optimizes plasticity (82). Both γ and θ rhythms are perturbed in schizophrenia, and these rhythms' multiplexed coordination is decreased with NMDA hypofunction in rodents (73,74) in a manner consistent with decreased inhibition onto PV+ interneurons (38,77).

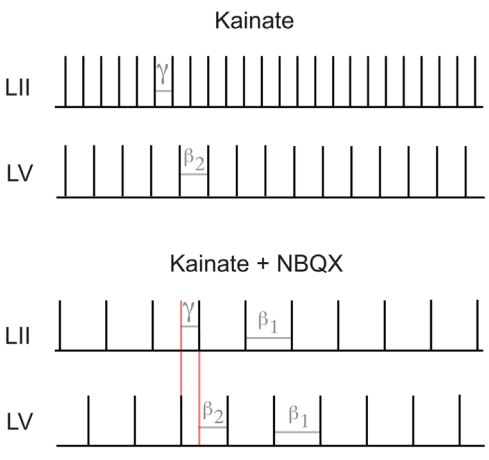

Figure 3. In rodent parietal cortex in vitro (and in computational models), a superficial layer γ rhythm (~40 Hz) and a deep layer β_2 rhythm (~25 Hz) are observed under conditions of high excitation, as with kainate application (top). When high excitation is followed by low excitation, as when kainate application is followed by application of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and kainate receptor blocker NBQX (bottom), these rhythms combine to produce a slower β_1 rhythm (~15 Hz). A single period of this slow β_1 rhythm is a concatenation of a single period of the superficial layer γ and a single period of the deep layer β_2. The emergence of this β_1 requires plasticity. [Reproduced with permission from Kramer *et al.* (95)].

RHYTHM PATHOLOGIES LEAD TO PATHOLOGIES OF COORDINATION

Abnormalities of structural and functional connectivity are well documented in schizophrenia (23,97). While altered structural connectivity can result in functional connectivity changes, the latter can also precede and cause the former (98); genetic markers suggest both may occur in schizophrenia (9,99–101).

The functional meaning of the statistical relationships often used to determine functional connectivity depends on their underlying mechanisms. By establishing transiently phase-locked ensembles of cells, controlling the direction of information flow between neuronal populations and allowing cross-talk on multiple channels defined by different frequencies (31,102), brain rhythms mediate dynamic interactions that contribute to measures of functional connectivity (34,103,104). Below, we discuss how multifaceted and location-specific rhythmic changes contribute to altered functional connectivity in schizophrenia.

θ Rhythm Dysfunction Leads to Impaired Hippocampal-Prefrontal Connectivity

Evidence strongly implicates abnormalities in hippocampo-prefrontal connectivity in the pathophysiology of schizophrenia (105,106). Disruption of the θ rhythm—which seems to coordinate hippocampal and prefrontal neuronal activity (107–109)—may be responsible: a genetic mouse model of schizophrenia exhibits reduced hippocampo-prefrontal θ-band coordination (110); similarly, both acute and genetically induced NMDAR hypofunction result in decreased θ coherence and increased δ coherence between hippocampus and prefrontal cortex in anesthetized mice (111).

Rhythmic Dynamics Mediate Switching Between Cortical and Limbic Control of Basal Ganglia Networks

The striatum has long been implicated in the pathophysiology of schizophrenia, with distinct roles for its dorsal and ventral

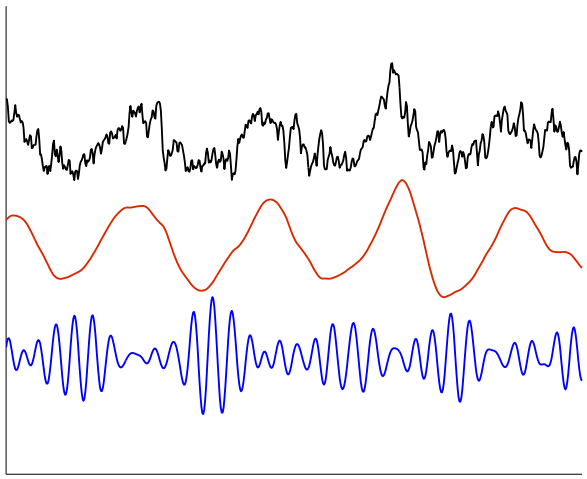

Figure 4. θ-γ nesting in a rodent hippocampal local field potential recording (top). γ rhythms (45–55 Hz bandpass, bottom) appear only at certain phases of the underlying θ rhythm (5–10 Hz bandpass, middle), allowing for multiplexing of cell assemblies into θ sequences.

extents (112). In the ventral striatum, schizophrenia-associated abnormalities may decrease hippocampal θ modulation (113,114). In rat dorsal striatum, dopamine agonism changes low-frequency phase modulation of high-frequency power from the δ to the θ band (115), suggesting coordination with hippocampus rather than PFC (109). This is intriguing, given the dorsoventral gradient of functional hypoconnectivity to hyperconnectivity with frontal cortex observed in the striatum in schizophrenia (116): in ventral striatum, decreased hippocampal input may be tied to increased cortical input, while similar mechanisms may have opposite effects in dorsal striatum, contributing to an altered interplay between cortical and limbic influences on striatum (117).

Gamma frequency may also play a role in determining the flow of information into ventral striatal circuits, in a manner similar to that observed in CA1. Both a slow (~50 Hz) γ coherent with limbic networks (e.g., piriform cortex) and a fast (~80–100 Hz) γ coherent with frontal cortex are observed in rat ventral striatum (118). Both amphetamine and apomorphine switch γ frequency in striatum from slow to fast (118). In schizophrenia, hyperdopaminergia may thus contribute to inappropriate cortical dominance of ventral striatal input.

Cortico-Thalamo-Hippocampal Network Dysfunction Leads to Impaired Rhythmic Coordination During Sleep and Waking

Thalamic activity and thalamocortical connectivity are implicated in many NMDA-hypofunction induced changes observed in the rodent prefrontal cortex (119,120), and a positive feedback loop between δ-frequency rhythmicity in the thalamus and hyperactivity in hippocampal networks has been suggested to trigger the psychotic break (121). Increased δ-frequency rhythmicity and subsequently altered cortico-thalamo-hippocampal connectivity during waking may mirror sleep disturbances in schizophrenia. In schizophrenia patients, α-frequency sleep spindles are less prevalent (122,123) and less coordinated across the cortex (123) than in control subjects. In a developmental mouse model of schizophrenia, the coordination between spindles, δ-frequency slow waves, and very high frequency ripples is disrupted, even as each oscillation remains measurably intact (124). This disturbed coordination is related to impaired propagation of slow waves across the cortex (124).

Top-Down Signaling Requires β Coordination

Recently, experimental and modeling results have converged to indicate roles for the β and γ rhythms in top-down and bottom-up signaling, respectively. Deep cortical layers, whose anatomical projections are mainly top-down (125), produce α and β rhythms (126,127), while superficial cortical layers, whose anatomical projections are mainly bottom-up (125), produce a γ rhythm (41,126,127). Measures of Granger causal influence between primate visual areas suggest feedforward influences are carried mainly in the θ and γ bands, while feedback influences are carried mainly in the β band (128). Recent modeling has indicated how top-down β signals may provide gain-modulation of bottom-up γ signals (129): β-frequency rhythms targeting deep layers are able to effectively recruit deep layer circuits having β resonance; these deep layer networks, when engaged in a β rhythm, enhance gamma power

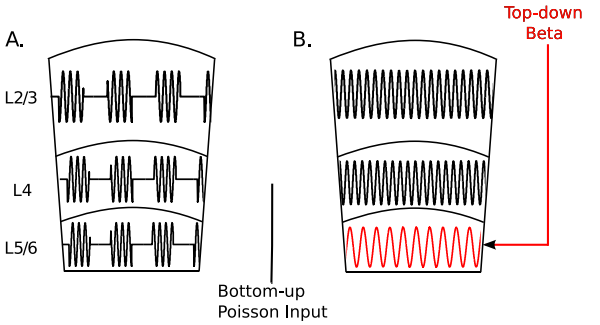

Figure 5. A dramatization of the effects of top-down beta signals in a computational model of a cortical column. Both model columns receive background Poisson inputs (at a rate of 50 Hz) to layer (L)2/3, and bottom-up Poisson inputs (at a rate of 100 Hz) to layer 4. In the absence of top-down beta **(A)**, these inputs lead to intermittent gamma, appearing at alpha frequency. In the presence of top-down beta inputs to layer 5 **(B)**, persistent gamma is seen in the superficial layers. Effects have been exaggerated for clarity; see Lee *et al.* (129) for actual computational data.

in the input layers, more effectively transmitting signals up the cortical hierarchy (Figure 5) (129). Both top-down signaling and β coherence are disturbed in schizophrenia (49,130).

COGNITION (AND ITS DYSFUNCTION) EMERGES FROM (RHYTHMIC) COORDINATION (AND ITS DYSFUNCTION)

There is broad agreement that normal cognition emerges from the coordinated activity of spatially distributed neuronal ensembles. Below, we discuss how rhythm-associated impairments in local processing and large-scale coordination contribute to the cognitive and perceptual aberrations seen in schizophrenia. We organize our discussion around the relevant domains of the MATRICS-National Institute of Mental Health consensus cognitive battery (Matrics Assessment Inc., Los Angeles, California) (131), a tool intended to accelerate the search for treatments of cognitive dysfunction in schizophrenia, then depart from this framework to discuss how positive symptoms may arise from some of the same rhythmic impairments as cognitive deficits.

Attention and Vigilance Depend on Rhythmic Gain Control of Sensory Signals

Schizophrenia patients are impaired at tasks that require continuous monitoring of stimulus streams and appropriate responses to cued stimuli (131). The preferential processing of salient stimuli is one component of vigilance that may be rhythm-dependent. In the auditory cortex in schizophrenia, NMDA hypofunction may alter the response to salient stimuli by attenuating the layer 4 γ rhythm (93). Schizophrenia patients also show deficits in the enhancement of rare stimuli and the suppression of repeated stimuli, phenomena tied to insufficient β power (132,133).

Working Memory Relies on Rhythmic Coordination Across Functional Networks

Altered rhythms at multiple frequencies have been related to working memory deficits in schizophrenia (20,134). The coupling of prefrontal and hippocampal networks via the θ rhythm is implicated in memory processing (86,109,135), and working memory deficits in a genetic mouse model of schizophrenia

have been related to deficits in hippocampo-prefrontal θ coordination (110).

Verbal and Visual Learning and Memory Are Impaired at Multiple Levels of Processing

Schizophrenia patients show impairments in recall of visual and verbal information independent of working memory (131). Encoding and recall depend on low-level perceptual mechanisms, the recognition and encoding of salient stimuli, and the maintenance of memory systems through sleep-dependent memory consolidation and synaptic homeostasis.

Impairments in Gestalt perception (49) and multimodal integration (136–139) seen in schizophrenia may be rhythm-dependent. Patient errors in Gestalt perception have been correlated with decreased β-band (49) and altered γ-band (52) phase coherence. Models suggest that the parietal β_1 rhythm is NMDA dependent (95) and may mediate multimodal integration (96). In schizophrenia, NMDA hypofunction combined with altered inhibition may weaken β_1 expression, contributing to deficits in multimodal integration.

Hippocampal circuits are implicated in the entry of salient (i.e., novel and reward-predictive) information into long-term memory (140,141). By changing the direction of information flow within hippocampal circuits (78,92), NMDA hypofunction may impair detection and encoding of salient stimuli.

Finally, coordinated non-rapid eye movement sleep rhythms are thought to mediate the transformation, consolidation, and transfer of episodic memories from hippocampus to neocortex; patients show deficits in the overnight consolidation of procedural memories relative to control subjects (142), and overnight improvement on a procedural task is positively correlated to spindle number and density in patients (123).

Reasoning and Problem Solving Require Intact Rhythmic Coordination

Many high-level cognitive tasks, such as set shifting—the ability to switch between sets of rules determining behavioral response to a cue—and pattern completion, are impaired in schizophrenia (131). The coordinated function of prefrontal, thalamic, hippocampal, and basal ganglia networks is involved in decision making, reward-seeking behavior, and cognitive flexibility (17,117,143), and set-shifting impairments in schizophrenia (17) and NMDA hypofunction (144) are consistent with altered rhythmic connectivity in these networks (17). Recent work suggests that θ-rhythmic activity may be a signature of the coordination of multiple sources of information during decision points in complex goal-directed behavior (145). In schizophrenia, regional alterations in θ rhythmicity may decrease θ coherence across brain regions and impair decision making.

Psychoses are Manifestations of Rhythmic Dysfunction

While cognitive symptoms are primarily associated with reduced task-related oscillatory power and coherence in

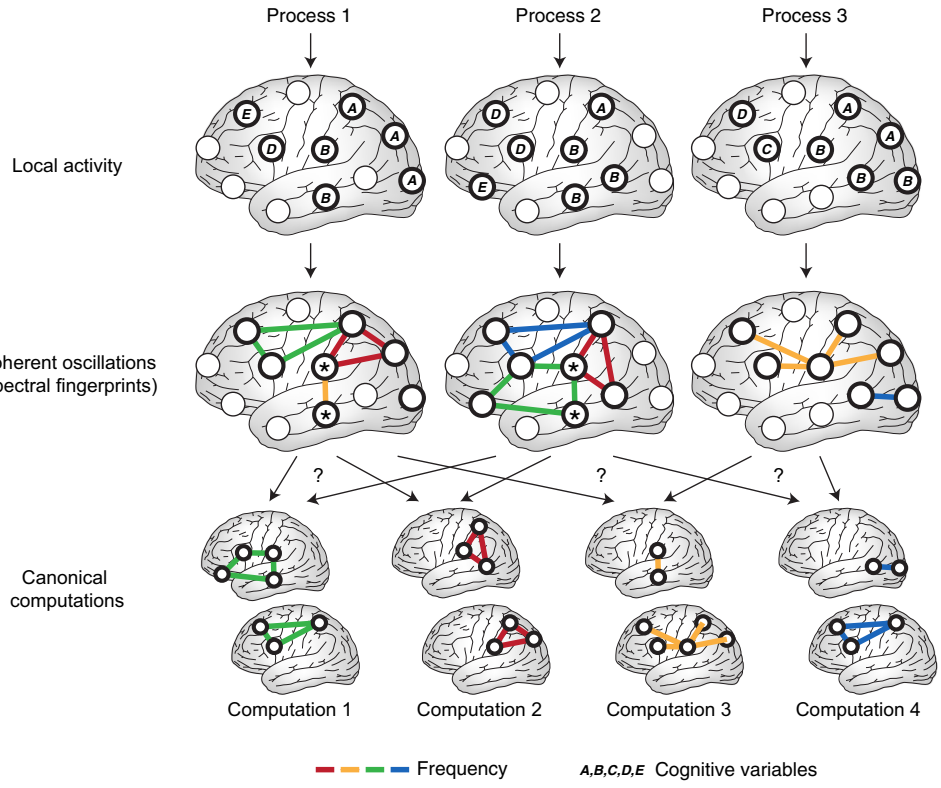

Figure 6. Schematic illustration of how coherent oscillations provide spectral fingerprints for regrouping of cognitive processes (A–E). Top: Studies of neuronal activity in individual brain regions (circles) elucidate the activation of different regions (bold circles) and the encoding of various cognitive variables (Roman numerals) during different cognitive processes. Several cognitive variables (for example, different sensory features) are simultaneously encoded in each region, but for simplicity, only one variable is depicted per region. Note that the pattern of local activity and encoding can be similar between processes. Middle: Coherent oscillations allow for the characterization of the interactions between different brain regions (colored lines) during different cognitive processes. The frequency of these oscillations (indicated by the colors) allows the corresponding network interactions to be classified and, thus, for the cognitive processes to be regrouped. For simplicity, only interactions in one frequency range are depicted between pairs of regions. The two regions marked by asterisks illustrate that different frequency-specific interactions (yellow versus green lines) can dissociate cognitive processes that show identical effects at the level of local activity (compare with the marked regions in A). Bottom: The different frequencies of coherent oscillations may allow for the identification of corresponding canonical computations that underlie cognitive processes. [Reproduced with permission from Siegel *et al.* (34)].

patients (24,49,51–53,133,134), psychosis is associated with increased spontaneous rhythmicity at multiple frequencies (146) and increased sensory-induced gamma (50). Animal models also show increased spontaneous cortical and hippocampal gamma (5,61–63).

Both reduced task-related and increased spontaneous oscillations have been proposed as mechanisms of auditory verbal hallucinations (147). In patients, fronto-temporal delta, theta, and beta coherence relaying the predicted sensory outcomes of motor execution are diminished (148). The absence of this efference copy or corollary discharge may lead to misattribution of the sensory consequences of speech production and planning to external sources, resulting in auditory hallucinations (148). Alternatively, instabilities in sensory cortical areas may lead to spontaneous activation producing a coordinated percept only in individuals with preserved gamma synchrony (147). Intriguingly, gamma synchrony, while reduced in schizophrenia, is positively correlated with the severity of hallucinations in patients (52).

More generally, altered cortical, thalamic, and hippocampal rhythmicity and coordination may result in unbalanced input to basal ganglia structures such as the ventral tegmental area (121) and the ventral striatum (116,117), leading to the emergence of the chief pathophysiology of psychosis, dopaminergic dysfunction (121).

CONCLUSION

From the current literature on schizophrenia and brain rhythms, the causal links of the pathophysiology of schizophrenia—from cellular and molecular biology, through processing in local circuits and large-scale coordination of brain activity, to cognition and perception—are becoming discernible. Temporal dynamics, mediated by the activity of diverse populations of inhibitory interneurons (37) and indexed by rhythms and their coordination, provides key ties among these levels of organization.

This explanatory framework has broad applicability: inhibitory dysfunction, impaired oscillations, and cognitive deficits are not unique to schizophrenia, and comparative approaches, while still rare (146,149), are feasible and important. It also has great translational potential: electrophysiological signals are recorded in vitro and in vivo across the animal kingdom, and oscillatory phenomena are robust, heritable, and—increasingly—modifiable.

The web of causality in schizophrenia is tangled because, within a given frequency, brain rhythms play multiple, nonoverlapping, task-specific cognitive roles (34). As shown above, the functional significance of a given rhythm depends on its particular biophysics, on how and why it structures activity in local and large-scale networks (40,90). Thus, biophysical modeling is key to parsing the functions of brain rhythms.

The repetitive patterning of cortical networks suggests that the brain combines and iterates certain canonical mesoscale computations to perform cognitive tasks. Rhythms, which sculpt population behavior and appear in nearly all cognitive tasks, may be signatures of these mesoscale computations (34). Attempts to associate rhythms with psychologically intuitive task components may not be fruitful (34). Instead, allowing the functions of rhythms to emerge from their biophysics and their deployment (Figure 6) (31,34,102) may better illuminate both the successful performance of cognitive tasks and the failures that result when mesoscale computations are disrupted by disease.

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