Review

Biological Psychiatry

Oscillations and Neuronal Dynamics in Schizophrenia: The Search for Basic Symptoms and Translational Opportunities

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ABSTRACT

A considerable body of work over the last 10 years combining noninvasive electrophysiology (electroencephalography/magnetoencephalography) in patient populations with preclinical research has contributed to the conceptualization of schizophrenia as a disorder associated with aberrant neural dynamics and disturbances in excitation/inhibition balance. This complements previous research that has largely focused on the identification of abnormalities in circumscribed brain regions and on disturbances of dopaminergic mechanisms as a cause of positive symptoms and executive deficits. In the current review, we provide an update on studies focusing on aberrant neural dynamics. First, we discuss the role of rhythmic activity in neural dynamics and in the coordination of distributed neuronal activity into organized neural states. This is followed by an overview on the current evidence for impaired neural oscillations and synchrony in schizophrenia and associated abnormalities in gamma-aminobutyric acidergic and glutamatergic neurotransmission. Finally, we discuss the distinction between fundamental symptoms, which are reflected in cognitive deficits, and psychotic, accessory symptoms, the latter likely constituting a compensatory response for aberrant neuronal dynamics.

Keywords: Cognition, Development, Dynamics, Neural oscillations, Schizophrenia, Translational research

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The search for the pathophysiological substrates of schizophrenia (ScZ) remains one of the core challenges for psychiatric research (1). While a range of functional and structural abnormalities have been identified, a mechanistic understanding of the origins of neuronal and cognitive dysfunctions has remained elusive. As a result, little progress has been made with the development of novel treatments and biomarkers for early detection and diagnosis. Despite huge investments in drug discovery and impressive advances in the basic neurosciences, the efficacy of therapeutic interventions in ScZ has only marginally improved over traditional dopamine receptor D2 antagonists that were introduced 50 years ago (2). Moreover, current pharmacotherapy alleviates only the positive but not negative symptoms and the pervasive cognitive deficits, two domains that are closely related to the debilitating outcome of the disorder (3).

In the following, we would like to propose that progress in ScZ research and the development of novel treatments require a deeper understanding of abnormalities in circuit dynamics that give rise to fundamental disturbances in large-scale networks, which, in turn, are likely responsible for the disabling cognitive deficits constituting the core of ScZ (4).

In recent years, we seem to have witnessed a dramatic change in our views on brain functions, realizing that the brain is a highly active, self-organizing system whose functions emerge from extremely complex, high-dimensional, and mostly nonlinear dynamics (5). This notion suggests that the complex disturbances associated with ScZ might actually result from abnormalities in brain dynamics rather than from well-localized defects in particular brain regions.

In ScZ research, the analysis of the biological mechanisms underlying clinical symptoms and cognitive deficits had for a long time focused on the contribution of circumscribed brain regions, such as the prefrontal cortex (6). In contrast to this view, which was largely inspired by findings from clinical neuropsychology (7), current research suggests that anatomical alterations involve a large number of cortical and subcortical regions (8), highlighting that ScZ and perhaps other mental disorders are likely to constitute systemic disturbances involving essentially a disruption of the dynamics of neural processes in large-scale networks (9).

In this article, we review recent studies that emphasize the importance of neuronal dynamics in the organization of coherent perceptual and cognitive processes during normal brain functioning. Specifically, we provide an update on the hypothesis that neural oscillations are a fundamental mechanism for the coordination of distributed neural activity and that aberrant rhythmic activity in ScZ is likely to constitute a pathophysiological mechanism underlying the cognitive dysfunctions associated with the disorder (10–12). We review evidence that such abnormalities are compatible with alterations in excitation/inhibition (E/I) balance parameters, especially in disturbances of gamma-aminobutyric acid (GABA)ergic interneurons and *N*-methyl-D-aspartate (NMDA) receptors, with important implications for the development of novel diagnostic tools and

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treatments. In the final part, we address the relationship between oscillatory dynamics, cognition, and certain clinical symptoms, suggesting that cognitive dysfunctions constitute the primary disturbance that results from altered E/I parameters, while certain positive symptoms, such as delusions and hallucinations, are likely to constitute secondary phenomena resulting from attempts to cope with the cognitive consequences of aberrant dynamics in large-scale networks.

NEURAL OSCILLATIONS AND COORDINATION DYNAMICS IN NORMAL BRAIN FUNCTIONS

Recent data highlight that cognitive and executive processes during normal brain functioning essentially emerge from the coordinated activity of distributed neuronal populations that are dynamically configured on the backbone of anatomical connections (13,14). The brain's connectome is characterized by an extraordinarily high degree of connectedness. Up to 70% of possible connections between cortical areas (nodes) are actually realized (15). This implies that even neuronal groups distributed across distant cortical areas can communicate with one another either directly or via only a small number of intervening nodes. From this perspective, cognition, consciousness, and its disturbances are not properties arising from isolated neuronal units but rather from the distributed and coordinated interplay of a large number of neuronal assemblies (14).

The dense connectome allows for virtually unconstrained interactions among any pair of neurons in the cortical mantel, either through direct connections or via a few switching nodes. To configure functional networks on the backbone of these anatomical connections or to flexibly associate neurons into assemblies for distributed coding and processing, mechanisms are required to dynamically gate signal flow between selected nodes (16). Numerous studies have used measures of temporal coherence for the identification of functional networks and provided ample evidence for the notion that cortical areas get dynamically bound into functional networks by synchronization in a task- and state-dependent way (17–21).

Synchronization of oscillatory responses has several functionally relevant consequences. It selectively enhances the interactions between the assembly members [see above and (22,23)], thereby increasing cohesion of the assembly. It focuses spikes to a narrow window of the oscillation cycle and thereby increases the likelihood for their further joint processing because synchronized excitatory postsynaptic potentials summate more effectively in target neurons than temporally dispersed inputs (24). This also facilitates segregation of responses originating from different assemblies. And finally, synchronization favors selective consolidation of connections among the assembly members and thereby their long-term cohesion because synaptic modifications follow a correlation rule (25–27).

Important and distinct variables of these dynamic processes are the power and frequency of oscillatory activity in local circuits and the long-range synchronization of these temporally structured activities across brain areas. Oscillatory processes, in particular at gamma-band frequencies, appear to serve some generic and basic cortical computations, while long-range synchronization occurs preferentially at lower frequencies, especially at theta/alpha/beta-frequencies, and serves the effective coupling between more remote brain regions (28,29). While this distinction provides a useful heuristic, it should be noted that certain long-range interactions, e.g., between homologue areas in the two hemispheres, can also occur by synchronization in the gamma frequency range (30).

E/I BALANCE AND OSCILLATORY DYNAMICS

Much work has been devoted to the analysis of synaptic mechanisms and circuits that support the generation of oscillatory activity and its synchronization over short and long distances, respectively, which makes it possible to relate abnormalities of these dynamic phenomena to specific neuronal processes (31–34), although regional differences may exist between brain areas in the generating mechanisms underlying rhythmic activity (35). Crucial variables are the time constants of ligand and voltage-gated ion channels, the balance between the efficiency of E/I balance (36), and the layout of long-range connections, both excitatory and inhibitory, that are held responsible for the synchronization of spatially segregated cell groups (30,37).

Experimental and theoretical evidence indicates that the networks of mutually interacting GABAergic neurons are crucially involved in the generation of high-frequency oscillations (38–40), while the reciprocal connections between excitatory and inhibitory neurons determine the strength and duration of the oscillations and mediate the local synchronization of cell groups. The long-range synchronization of spatially segregated cell groups has been attributed mainly to the action of excitatory pathways (30,31,41). However, recent evidence suggests that GABAergic long-range projections are more frequent than assumed previously and are likely to play an important role in long-range synchronization as well (37,42).

Recent optogenetic studies have further highlighted the important role of parvalbumin (PV) cells for the generation of gamma-band oscillations through demonstrating that inhibition of PV cells leads to an immediate suppression of 30 Hz to 80 Hz oscillations, while 10 Hz to 30 Hz oscillations increase in power. In contrast, increasing PV interneuron-mediated feedback inhibition by boosting principal cell activity enhanced gamma-band power (40). In addition, it was found that signal transmission is affected by gamma oscillations. Entrainment of gamma oscillations by rhythmic optogenetic activation of PV interneurons at 40 Hz specifically improved detection of weak tactile stimulation of the vibrissae, provided that sensory stimulation followed the induction of gamma oscillations by 20 to 25 milliseconds (42). This agrees with the notion that attention facilitates stimulus processing by enhancing gamma oscillations in sensory areas (16). It is also in line with the evidence that gamma oscillations reduce response variability and attenuate noise levels (43).

In addition to inhibitory and excitatory neurotransmission, there is also evidence for the potential contribution of monoamines, such as dopamine, to the modulation of high-frequency oscillations (44–47). However, further research is required to systematically address this relationship.

DISTURBANCES IN NEURAL OSCILLATIONS AND E/I BALANCE PARAMETERS IN ScZ

A considerable body of work with electroencephalography (EEG)/magnetoencephalography (MEG) over the last 10 years