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 acid (GABA)ergic 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

http://dx.doi.org/10.1016/j.biopsych.2014.11.019

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...
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 dynamically relevant consequences. It selectively enhances the power and frequency of oscillatory activity in local areas (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
has identified abnormalities in the amplitude and synchrony of neural oscillations at both low and high frequencies in ScZ (10), highlighting the possibility that cognitive deficits and certain clinical symptoms arise from a disturbance of neuronal dynamics (11,12). This hypothesis is consistent with the growing evidence that E/I balance parameters are fundamentally disturbed in the disorder (48–50) and contrasts with the classical view that considered abnormalities in dopamine signaling as the primary pathophysiological mechanism. Moreover, disturbances in E/I balance in ScZ are consistent with the comorbidity between some forms of epilepsy and psychosis (51). Figure 1.

Among the numerous signatures of brain dynamics, oscillations in the 40-Hz frequency range were initially considered to be of particular interest (52–56). Synchronized 40-Hz activity had been suggested by Gray et al. (57) as a correlate of perceptual binding in primary visual cortex. Since ScZ is characterized by impaired perceptual grouping operations in auditory and visual modalities (58), the evidence that the amplitude and synchronization of beta/gamma-band activity is reduced in ScZ provided important insights into the possible relationship between impaired sensory processing and abnormal rhythmic activity. Moreover, this view is consistent with data indicating that the abnormalities in PV1 interneurons are not confined to prefrontal cortices but extend to sensory areas (59) and the hippocampus (60,61), highlighting the importance of impairments in sensory processing and the possibility of a systemic disturbance in neuronal dynamics that could impact large-scale communication in distributed networks, such as between frontal and hippocampal ensembles (62).

Later work has extended this perspective by indicating that abnormalities in high-frequency oscillations are not confined to the 40-Hz frequency range but extend to frequencies above 60 Hz (higher gamma-band) (63–65). This is consistent with evidence from EEG/MEG studies and findings from invasive electrophysiology that high-frequency oscillations up to 120 Hz, as well as low-frequency oscillations in the theta (4–7 Hz), alpha (8–12 Hz), and beta (15–30 Hz) ranges also play

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**Figure 1.** Gamma-band oscillations in schizophrenia. Top panel: (A, left) Transcranial magnetic stimulation elicited high-frequency oscillations in control subjects and schizophrenia (ScZ) patients: single-pulse transcranial magnetic stimulation over four cortical areas was associated with peak frequencies between 20 Hz and 30 Hz in control subjects with prefrontal oscillations showing the highest peak frequency. In ScZ patients, the frequency of prefrontal oscillatory activity was strongly reduced. The individual natural frequency values of healthy control subjects and patients with schizophrenia are shown for four cortical areas. Horizontal lines indicate mean natural frequency values of each group for each cortical area. *p # .05; †p # .001. Right panel: The frequency of prefrontal cortex oscillations was inversely related to the level of positive symptoms on the Positive and Negative Syndrome Scale (PANSS) as well as to the reaction time of correct responses on a word memory task in patients with schizophrenia. Bottom panel: (B) High-frequency oscillations during perceptual organization in ScZ. Left panel: Time-frequency representations and topographies of gamma-band spectral power of magnetoencephalography data in response to Mooney faces for control subjects (top) and chronic ScZ patients (bottom). The gamma-band signal is expressed as relative power change in the poststimulus time window compared with baseline, averaged across all channels. The topographies (middle panels) display the results of a nonparametric analysis of variance indicating the main effects of group for both low (top) and high (bottom) gamma-band oscillations at the sensor level. Red colors indicate increased activity in control subjects, while blue colors suggest increased gamma-band power in schizophrenia patients relative to control subjects. The topographies depict corrected t values and the channels that form a statistically significant cluster are indicated (†p < .001; *p < .05). Right panel: Correlation between high gamma-band power and disorganization. The scatterplot shows the relationship between high (60 Hz to 120 Hz) gamma-band power in the 50-millisecond to 350-millisecond time window over positive channels and the disorganization component of the Positive and Negative Syndrome Scale. (A) Adapted with permission from Ferrarelli et al. (54). (B) Adapted with permission from Grutzner et al. (64).
important roles in cognitive and executive operations (66,67). These various oscillatory processes originate from distinct mechanisms (68) and subserve specific coordinating functions (for review, see (69)).

The abnormal dynamics in ScZ could be due to deficits in the local circuits required for the generation of oscillatory activity. In this case, one expects disturbances of GABAergic mechanisms because of the constitutive role of PV containing GABAergic interneurons in the generation of gamma-band oscillations (40). These alterations should be reflected in abnormalities of oscillatory activity, even under resting-state conditions. Alternatively, in or addition, abnormal dynamics could result from an inability to establish long-range synchrony. In this case, one expects alterations of long-range glutamatergic projections and behavioral deficits that might become manifest only in demanding cognitive tasks requiring coordination of large-scale networks. The latter scenario would be compatible with evidence implicating NMDA receptor hypofunctioning in ScZ (70), while a primary deficit in the generation of high-frequency oscillations would favor a deficit in the PV+ interneurons.

NMDA antagonists in both animal models and humans lead to a pronounced increase in gamma-band oscillations (71), in particular when spontaneous activity is examined (70,72), suggesting that the rhythm-generating mechanisms are intact but not sufficiently constrained by glutamatergic pathways. It is still a matter of debate whether the effects are consistent with current observations in ScZ patients. Some studies suggest that resting-state activity is elevated and gamma-band activity at baseline (73,74), while others could not confirm these findings (63,64,75).

In general, rhythmic activity is characterized by a modulation of spectral amplitude within a circumscribed frequency band, which in the case of gamma oscillations, is most prominent during stimulus-related activity. In addition, one observes both during resting-state activity and stimulus-induced responses broadband high-frequency activity that lacks a clear peak in the spectrogram (76). It is still unclear whether this broadband activity results from a superposition of high-frequency oscillatory activity with differing frequencies and/or from the summation of uncorrelated synaptic potentials and neuronal discharges. Accordingly, further studies are required to clarify the nature of alterations in spontaneous high-frequency activity in ScZ and its relationship to deficits in task-related neural oscillations before firm conclusions on mechanisms can be drawn from changes in high-frequency broadband activity.

In addition to abnormalities of high-frequency oscillations, alterations have also been demonstrated for lower frequencies in the theta/alpha frequency range during sensory processing and working memory tasks (77-79). An important question is whether these abnormalities are secondary to gamma-band dysfunctions or whether they represent independent abnormalities. As inhibitory interactions are constitutive for most oscillatory processes (68), it could well be that some basic disturbance of GABAergic transmission also affects oscillations in lower frequency bands.

Alternatively, oscillatory processes in different frequency bands could influence one another as suggested by the phenomenon of cross-frequency coupling (CFC). During spontaneous activity, the phase of alpha-band oscillations modulates closely the amplitude of broadband gamma activity (80,81), a phenomenon addressed as phase to amplitude coupling (82). Accordingly, it is possible that abnormalities in E/I balance parameters also lead to disturbances of alpha-gamma band interactions.

Preliminary evidence suggests that changes in CFC are associated with ScZ (83). Similar to the analysis and interpretation of fluctuations in resting-state oscillations, it should be noted that there are several important analytical and methodological caveats to be taken into account for the analysis of CFC [see our recent review (84)]. Thus, before computing CFC indices, one needs to identify clear peaks in a time-resolved power spectrum and to select appropriate bandwidths for the definition of the instantaneous phase. Finally, a key issue is to distinguish whether CFC is due to common drive by external or internal input or whether the correlation is due to a causal interaction between rhythms. Thus, CFC parameters derived from paradigms with strong evoked activity are likely to be inappropriate (Figure 2).

NEURAL OSCILLATIONS, COORDINATION DYNAMICS, AND THE SEARCH FOR BASIC SYMPTOMS

An improved understanding of the contribution of oscillatory dynamics to the pathophysiology of ScZ is likely to require a renewed focus on the distinction between fundamental versus secondary symptoms of the disorder. Although this distinction is at the heart of the ScZ concept and has been emphasized among others by Bleuler (85), Meehl (86), Huber (87), and colleagues (88), current research practice largely identifies patient populations on the basis of positive symptoms. This approach has been criticized because it may impede identification of core aspects associated with ScZ, such as the disturbances in self-experience and the subjectively experienced impairments in cognition and perception (89).

The latter have been emphasized by the basic symptoms approach in which subtle, subjectively experienced subclinical disturbances in thinking, speech, and affect reflect the biological vulnerability for ScZ. In this framework, the gradual transition toward full positive symptoms is considered as an adaptive response in which coping strategies are developed to render the aberrant cognitive experiences coherent. The idea is that these adaptive responses manifest themselves as positive symptoms as a result of cognitive schema and appraisal processes, which are imposed on abnormal sensory processes through top-down mechanisms (87,90,91).

Conceptualizing ScZ as a disorder of neuronal dynamics in which aberrant oscillations and their synchronization constitute the primary and fundamental pathophysiology has a long history and is consistent with previous formulations that have highlighted that the core neurobiological impairments do not arise from dysfunctions in circumscribed brain areas but are due to dysfunctional interactions between and within cortical and subcortical regions. For example, Bleuler (85) highlighted that the essential disorder lies in the interplay between various mental faculties, constituting the primary disturbance of cerebral pathology in the disorder. Moreover, Meehl (86)
highlighted the possibility that the genetic predisposition for schizophrenia leads to a defect in neural integration that constitutes the basic biological vulnerability or schizotaxia.

From this perspective, disturbances in E/I balance parameters during brain development give rise to abnormal dynamics and disturbed temporal coordination that, in turn, lead to cognitive deficits that provide the underlying vulnerability from which the more complex manifestations of the disorder emerge. Cognitive impairments across several domains are detectable several years before the onset of psychosis (92), which typically emerges during late adolescence/early adulthood. One possibility therefore is that the onset of clinically manifested symptoms during this developmental period is due to the ongoing changes in oscillatory dynamics and the underlying neurobiological mechanisms responsible for coherent mental states. This perspective is consistent with current thinking that perceptual and cognitive impairments are the earliest signposts for an at-risk mental state (93), while subthreshold and full psychotic symptoms emerge only later during the development (84).

Recent studies in developmental cognitive neuroscience have provided novel data on the importance of late brain maturation that could provide potentially a conceptual framework for the onset of psychosis with important implications for early diagnosis and targeted interventions. Developmental findings on neural oscillations have highlighted that cortical circuits during late brain maturation are accompanied by profound modifications in the amplitude and synchrony at theta, beta, and gamma frequencies (95). These data suggest that the oscillatory dynamics that underlie the coordination of distributed neuronal processes in large-scale networks are only fully functional during late brain maturation. Development of neural oscillations during adolescence is consistent with important modifications in E/I balance parameters, such as the profound modifications in GABAergic neurotransmission (96), NMDA receptors (97), and dopamine-interneuron interactions (98).

One possibility therefore is that the interaction between neural circuits with an existing altered E/I balance and dysfunctional neuronal dynamics and the developmental modifications in these parameters during adolescence lead to critical fluctuations in large-scale, neuronal dynamics (99). The development of certain positive symptoms, such as delusions and hallucinations, could represent an adaptive response aimed at attributing significance to the abnormal states resulting from disturbed dynamic coordination of distributed networks. One of the functions of the dopaminergic system is to reward consistent brain states such as are likely to be associated with the eureka effect that accompanies solutions of perceptual tasks and the confirmation of predictions (100). One might expect an upregulation of dopaminergic signaling if such states are rare. This could, in turn, have the consequence that normally neutral external and internal experiences are judged as meaningful or salient, which is a hallmark of positive symptoms (90). The transition from adolescence to adulthood could be a critical period in such a scenario, since it is only during this late developmental phase that dopamine signaling is fully matured (101,102).

**IMPLICATIONS FOR TRANSLATIONAL RESEARCH**

The interpretation of ScZ as a disorder resulting from a two-stage process, a primary disturbance of the temporal coordination of large-scale network functions that lead to cognitive disturbances and a secondary process that eventually causes the positive symptoms, highlights the importance of research that examines at-risk populations. This is because the modifications of neuronal circuits through ongoing developmental processes and the adaptive changes in large-scale networks, as well as the effects of antipsychotic medication on brain structure (103) and function (104) are likely to impede the identification of those pathophysiological processes that are at the origin of the disorder.
Moreover, as the current treatments available do not reverse circuit dysfunctions, once clinical symptoms reach current diagnostic thresholds, development of biomarkers for targeted early intervention are crucial. EEG/MEG approaches may be ideally suited for this goal, as the wide range of parameters extractable from data reflecting brain dynamics provides a large search space for the delineation of disorder-specific abnormalities. In addition, one distinct advantage of neural oscillations as measured with EEG/MEG over magnetic resonance imaging/function magnetic resonance imaging is the availability of measures describing the amplitude and synchrony of rhythmic activity that can be obtained from animal models of ScZ as well as from human participants. Further delineation of the dynamic features of brain activity associated with the pathophysiology of ScZ could potentially reveal specific fingerprints (28,105) that, together with other diagnostic information such as cognitive impairments (106), could help to identify subclasses of the disorder and ultimately to develop individual/personalized treatments. However, although a large body of work exists on spectral abnormalities in ScZ and related disorders, it still needs to be confirmed that indices of oscillation amplitude, synchrony, phase locking, and cross-frequency coupling constitute clinically useful biomarkers.

Given the importance of basic impairments in information processing in ScZ and the involvement of E/I balance parameters in the generation of coordinated neuronal activity, it is likely that novel treatment targets will have to focus on GABAergic and glutamatergic neurotransmission to improve the disabling consequences of cognitive dysfunctions in ScZ. Although several recent studies have provided mixed support for this hypothesis (107,108), it is conceivable that this is due to the fact that such studies were conducted in chronically medicated ScZ populations. Recent studies also indicate that trials with novel compounds for the treatment of ScZ that are tested in such populations may fail because of long-term changes in the dopamine system following chronic antipsychotic drug therapy (109).

Finally, findings that perceptual and cognitive impairments are the earliest signposts for an at-risk mental state highlight the importance of targeted neurobiological and psychological interventions. Indeed, there is evidence from animal models that have identified novel targets shown to be effective in preventing, for example, dysfunctions in PV cells and associated cognitive deficits during brain development (110,111). In addition, preliminary evidence suggests that cognitive training during this period may protect neural circuits from developing signatures of cognitive deficits in ScZ in animal models (112), which is consistent with the potential effectiveness of cognitive behavioral therapy in reducing the development of psychotic symptoms through strengthening reality testing in at-risk populations (113).

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Max-Planck Society. PJU has received research support from Lilly.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Sep 27, 2014; revised Oct 29, 2014; accepted Nov 21, 2014.

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