Dysconnectivity, Large-Scale Networks and Neuronal Dynamics in Schizophrenia

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Abstract: Schizophrenia remains a daunting challenge for efforts aimed at identifying fundamental pathophysiological processes and to develop evidence-based effective treatments and interventions. One reason for the lack of progress lies in the fact that the pathophysiology of schizophrenia has been predominantly conceived in terms of circumscribed alterations in cellular and anatomical variables. In the current review, it is proposed that this approach needs to be complemented by a focus on the neuronal dynamics in large-scale networks which is compatible with the notion of dysconnectivity, highlighting the involvement of both reduced and increased interactions in extended cortical circuits in schizophrenia. Neural synchrony is one candidate mechanisms for achieving functional connectivity in large-scale networks and has been found to be impaired in schizophrenia. Importantly, alterations in the synchronization of neural oscillations can be related to dysfunctions in the Excitation-Inhibition (E/I)-balance and developmental modifications with important implications for translational research.

Introduction

Beginning with the concept of dementia praecox proposed by Emil Kraepelin [1], research into the physiological substrates of cognitive dysfunctions and clinical symptoms of schizophrenia has been predominantly pursued with the assumption that pathophysiological processes are to be found in alterations of circumscribed brain regions and circuits. Advances in functional and anatomical magnetic resonance imaging (MR/fMRI) have supported this hypothesis through providing a large body of work demonstrating changes in brain functioning as well anatomical parameters across cortical regions in schizophrenia. While this approach has yielded an impressive body of work, central questions regarding the pathophysiology have, however, remained unclear leading to a lack of progress in prevention and treatment [2].

In the following review, it is proposed that research into the pathophysiology of schizophrenia needs to be complemented by a focus on neuronal dynamics in large-scale networks. This is because novel measures of the brain´s structural and functional integrity have highlighted the fact that cognitive functions emerge from the coordinated activity of distributed neuronal processes [3]. The formation of such networks is achieved by increasing the coupling among neurons that are functionally relevant for a specific task while reducing the strength of nodes that are task-irrelevant [4]. This implies that communication within and between cortical areas occurs on a millisecond time-scale to achieve a transient binding of widely distributed neurons into dynamically configured functional networks [5].

One possible mechanisms to signal the relatedness of neurons is through the modulation of the synchrony of neuronal oscillations (neural synchrony) [6]. Neural oscillations at low (delta, theta, and alpha) and high (beta/gamma) frequencies are a fundamental mechanism for enabling coordinated activity during normal brain functioning as they establish precise temporal correlations between distributed neuronal responses. Oscillations in the beta/gamma range have been linked to synchronization in local cortical

networks whereas lower frequencies preferentially establish synchronization over longer distances [7]. However, recent work has shown that long-range synchronization can also occur at substantially higher frequencies (>30 Hz) and that even zero phase-lag synchronization is compatible with conduction delays [8].

Table 1 Neural Oscillations in Cortical Networks

	Delta (1-3 Hz)	**Theta** (4-7 Hz)	**Alpha** (8-12 Hz)	**Beta** (13-30 Hz)	**Gamma** (30-200 Hz)
Anatomy	thalamus, neocortex	hippocampus, sensory cortex, prefrontal cortex	thalamus, hippocampus, reticular formation, sensory cortex, motor cortex	all cortical structures, subthalamic nucleus, basal ganglia and olfactory bulb	all brain structures, retina and olfactory bulb
Function	memory, synaptic plasticity	memory, synaptic plasticity, top-down control and long-range synchronization	inhibition, attention, consciousness, top-down control and long-range synchronization	sensory gating, attention, motor control and long-range synchronization	perception, attention, memory, consciousness and synaptic plasticity

Neural oscillations at low- and high-frequencies occur in different cortical and subcortical brain regions. In addition to achieving in synchrony, neural oscillations have been also linked with distinct cognitive and sensory functions.

Further support for the role of neuronal dynamics in large-scale cortical networks comes from studies which have examined fluctuations of neuronal responses in the absence of sensory input. Multisite recordings revealed that on-going "spontaneous" activity is often highly structured, exhibiting oscillatory patterning in characteristic frequency bands and complex correlations that depend not only on stimulation conditions but also change as a function of central states, attention, expectancies and behavioural goals [9]. Much of the response variability of individual neurons appears to be caused by these self-generated activity patterns and hence is with all likelihood conveying information related to memories and expectancies rather than being the consequence of noise and system imperfection [10]. In agreement with the psychophysical evidence for active sensing and predictive coding, neuronal responses to sensory stimuli are more and more understood as the result of a

Bayesian matching operation between sensory evidence and internally generated predictions [11].

Finally, the current review will also address the relationship between changes in neuronal dynamics and the neurodevelopmental profile of the disorder. The typical onset of schizophrenia during the transition from late adolescence to adulthood is a central feature of the disorder but the underlying mechanisms for the late manifestation have remained unclear [12]. Evidence is emerging to suggest profound modifications in excitation/inhibition (E/I) balance parameters which impact on the occurrence of neural synchrony during late brain development [13] with important implications for the emergence of psychosis as well as for the treatment and prevention of the disorder.

Disconnection and Dysconnectivity in Schizophrenia

A paradigm that has provided an alternative conceptualization of pathophysiological processes in schizophrenia and is able to accommodate critical features of large-scale cortical networks is the disconnection hypothesis. It was first proposed in 19th century highlighting that reduced interactions of brain regions could arise from abnormal axonal connectivity (for a review see [14]). The concept re-emerged with the seminal contribution of Friston and colleagues [15] who re-examined the evidence from the emerging fMRI-literature which indicated reduced functional interactions between brain regions identified through BOLD-signal correlations [16]. Importantly, the authors modified the original term *disconnection* (''dis'' = ''apart,'') to *dysconnectivity* to highlight that functional and anatomical connectivity is not generally reduced but may also involve abnormal increases in schizophrenia (dys = bad or ill).

Until recently, only fMRI-based connectivity measures allowed robust insights into the co-fluctuations and directed interactions between brain regions. However, with advances in cortex-wide mapping of electro/magnetoencephalographical-(EEG/MEG) data, the

examination of large-scale integration has now become feasible (see Table 1) [17]. EEG/ MEG approaches have a temporal resolution superior to that of fMRI and allow the assessment of neural events and their interactions in the millisecond time range. In addition to time, frequency is an important dimension available in EEG/MEG-recordings. Recent data indicate that distinct frequencies are involved in different computations as well as coordination at varying spatial scales [18]. Moreover, interactions between different frequencies enlarge significantly the coding space through establishing coherence between different rhythms with important consequences for cognitive processes [19].

Table 2 Measures of Large-Scale Interactions in Human Imaging Data

Measure	Imaging Measure	Alterations in Schizophrenia
Phase Synchrony: measures the covariance of phase-values between two signals through separating phase and amplitude components	EEG,MEG, fMRI	✔✔
Coherence: Estimates the covariance between two signals	EEG, MEG, fMRI	✔✔
Granger Causality: Estimates the directed influences between neuronal populations (effective connectivity)	EEG, MEG, fMRI	✔
Transfer Entropy: A model-free method to detect directed interactions between time series	EEG, MEG, fMRI	
Cross-frequency coupling: Modulation of phase or amplitude between different oscillations frequencies	EEG, MEG	✔
Oscillation Amplitude: A measure of local integration (~ 1 cm) which is an indirect measures of synchrony	fMRI, EEG, MEG	✔✔✔

✔ = preliminary evidence; ✔✔ = robust evidence; ✔✔✔ = strong evidence

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 [20], respectively, which makes it possible to relate abnormalities of these dynamic phenomena to specific neuronal processes [21]. In particular, experimental and theoretical

evidence indicates that the networks of mutually interacting GABAergic neurons are crucially involved as pacemakers in the generation of high-frequency oscillations in local circuits [22, 23]. Recent studies have also examined the specific role of glutamatergic inputs to PV-interneurons for the generation of coordinated network-activity. Thus, both N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have been shown to exert significant effects on gamma-band oscillations through modulating excitatory transmission on PV cells [24-26].

**Neural Synchrony and Dysconnectivity in Schizophrenia**

A large body of evidence has accumulated that points towards the role of oscillations and their synchronization in the pathophysiology of schizophrenia [27]. Importantly, alterations in neural synchrony parameters can be related to several core features of the disorder, such as the generalized cognitive deficits, the neurodevelopmental profile and cellular dysfunction.

A large number of studies have focused on amplitude changes of high-frequency oscillations which reflect integration at a local scale (~ 1 cm). Steady-state evoked potentials (SSEPs) are a basic neural response to a temporally modulated stimulus to which SSEPs are synchronized in frequency and phase which allow insights into the entrainment of local populations to an external rhythm. Several studies have examined auditory and visual SSEPs responses and found pronounced deficits to stimulation at gamma- but also at lower (theta and beta) frequencies [28-30].

In contrast to SSEPs, induced oscillatory activity reflects self-generated, non-phase locked activity which is important for large-scale interactions in extended cortical circuits. Evidence suggests that induced gamma-band activity is reduced during a wide range of cognitive and perceptual paradigms, including working memory, executive control and perceptual processing in both chronic and unmedicated patient populations, suggesting a generalized circuit dysfunction in schizophrenia [31, 32]. Finally, reduced auditory evoked

activity has been demonstrated in first-degree relatives of patients with schizophrenia as well as in unaffected, monozygotic twins with a high degree of heritability [33, 34], suggesting the neural synchrony parameters are endophenotypes.

While fluctuations of spectral-power are an important variable reflecting changes in E/I-balance parameters, neuronal dynamics in large-scale networks are more readily observed through the analysis of interactions between neurophysiological signals (Table 1). Preliminary results obtained with scalp-recorded EEG data have highlighted alterations in phase-synchronization at beta- and gamma-band frequencies [35, 36] (Figures 1). Phase synchronization is an effective mechanism for the integration of neural responses [37] and could therefore constitute a mechanisms for functional dysconnectivity of large-scale networks in schizophrenia. However, because of the methodological problems in the interpretation of phase-synchronization at the sensor/electrode level, this approach should be complemented by source reconstruction of EEG and MEG data. Recent studies have shown that this is feasible [38] and can be combined with estimates of large-scale integration [39].
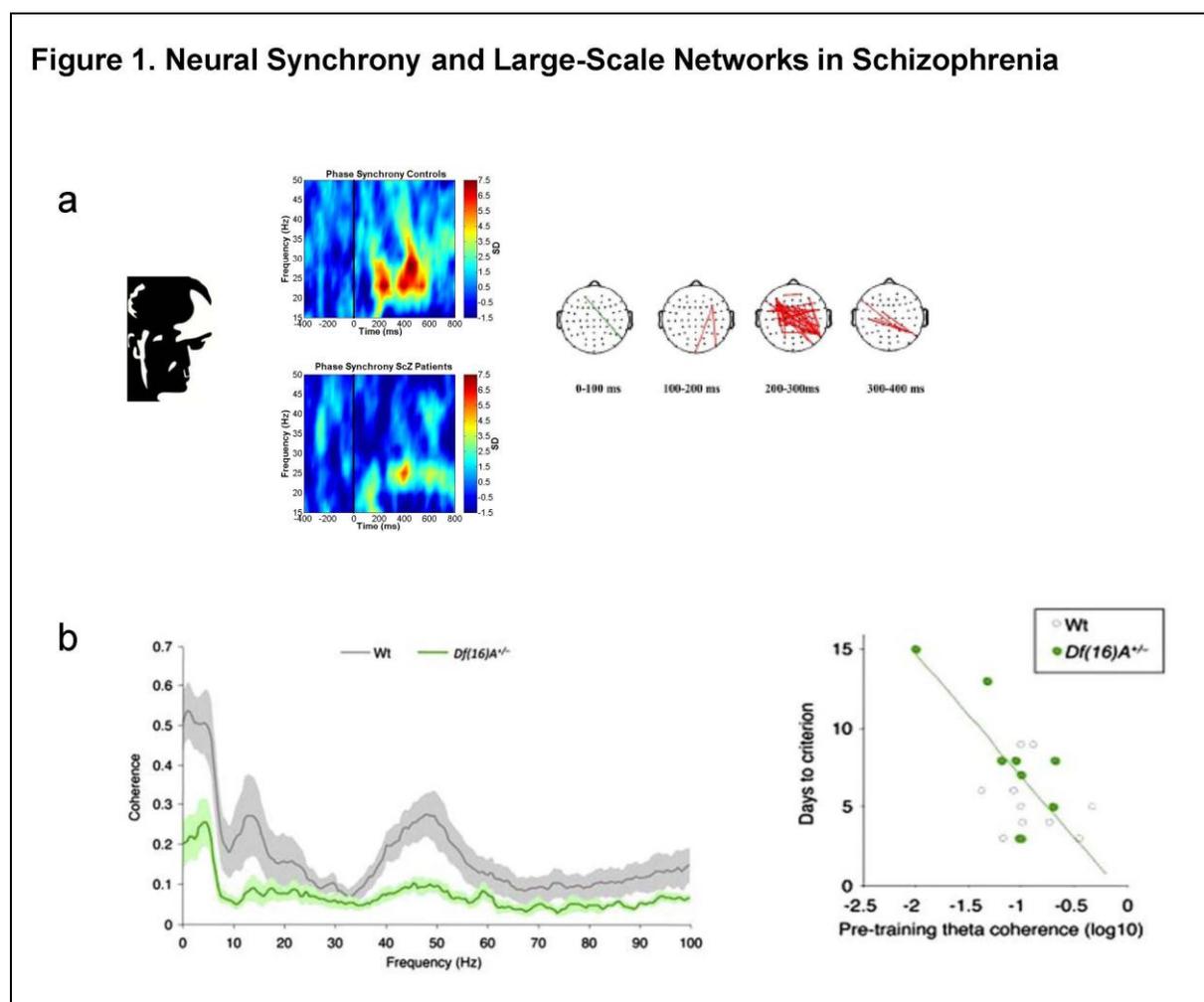
Figur 1 Neural Synchrony in Large-Scale Cortical Networks in Schizophrenia
a) Dysfunctional phase synchrony during Gestalt perception in schizophrenia. Mooney faces
were presented in an upright and inverted orientation and participants indicated whether a face was perceived. The top right panels show the average phase synchrony (indicated by the coloured scale) over time for all electrodes. In patients with schizophrenia, phase synchrony between 200–300 ms was significantly reduced relative to controls. In addition, patients with schizophrenia showed a desynchronization in the gamma band (30–55 Hz) in the 200–280 ms interval. The bottom panel shows differences in the topography of phase synchrony in the 20–30 Hz frequency range between groups. Red lines indicate less synchrony between two electrodes in patients with schizophrenia than in controls. Green lines indicate greater synchrony for patients with schizophrenia. SD, standard deviation. Adapted from Uhlhaas et al. [35].
b) Reduced hippocampal-prefrontal synchrony in Df(16)A$^{+/-}$ mice, which models a microdeletion on human chromosome 22 (22q11.2) that constitutes one of the largest known genetic risk factors for schizophrenia. Left panel: coherence between hippocampal and prefrontal field potentials during a spatial working memory task. Note reduced coherence in Df(16)A$^{+/-}$ mice. **$p < 0.01$; error bars and shaded regions represent mean $\pm$ SEM. Right panel: days taken to reach criterion versus theta coherence during habituation sessions for each animal. Animals with lower theta coherence before training take longer to learn the spatial working memory task. Green line, linear regression of data from Df(16)A+/− mice. Adapted from Sigurdsson et al. [47].

The potential relevance of abnormal cross-frequency interactions has only been investigated recently. Spencer et al. [40] reported a reduced modulation of gamma-band SSEPs in the auditory cortex in schizophrenia through the phase of delta-oscillations while Liddle et al. [41] observed decreased interactions between alpha- and gamma-band activity

during a somatosensory task. However, more recent results could not support impaired cross-frequency interactions between high and low frequency oscillations during auditory SSEPs [42]. Accordingly, this remains an important area for future research.

Neural Synchrony and Translational Research

Neural synchrony parameters are ideally suited for translational research into the mechanisms of cognitive dysfunctions and clinical symptoms. This is because neural synchrony parameters can readily be quantified and standardized in electrophysiological recordings from animal models and in non-invasive EEG/MEG-recordings which facilitates integration between basic and clinical research.

Recent work has focused on the alteration in the E/I-balance parameters as one possible cause for deficits in neural synchrony. Pharmacological and genetic manipulations leading to a downregulation of NMDA-receptor activity have consistently demonstrated a pronounced impact on gamma-band oscillations, especially on spontaneous activity [24, 43]. In addition, deficits in PV-cells have been shown to be profoundly altered in patients with schizophrenia [44] and recent data established links between reductions in GAD 67 and reduced gamma-band activity in vitro-preparations [45] and in computational models [46]. However, it should be noted that altered neural synchrony can have many causes because several animal models of schizophrenia that involve quite different mechanisms are associated with aberrant synchrony and power of oscillatory activity [21]. Thus, it is unclear whether changes in the E/I-balance reflect a primary pathophysiological process or whether these are secondary consequences of altered network activity.

Phase-synchrony between neuronal ensembles has also been investigated in animal models which mimic the observation of functional dysconnection in EEG/MEG-data. Sigurdson et al. [47] (Figure 1) measured the synchronization between the hippocampus and

9

the prefrontal cortex during working memory (WM) in Df(16)A$^{+/-}$ mice which provide a genetic model for the microdeletion on human chromosome 22 (22q11.2). The 22q11.2 microdeletion is one of the largest known genetic risk factors for schizophrenia [48]. Df(16)A$^{+/-}$ mice were characterized by impaired WM-performance which was closely correlated with reduced phase-locking of theta-band oscillations between prefrontal and hippocampal cells, suggesting that the genetic risk for schizophrenia impacts directly on large-scale interactions which in turn could underlie the cognitive deficits associated with the disorder.
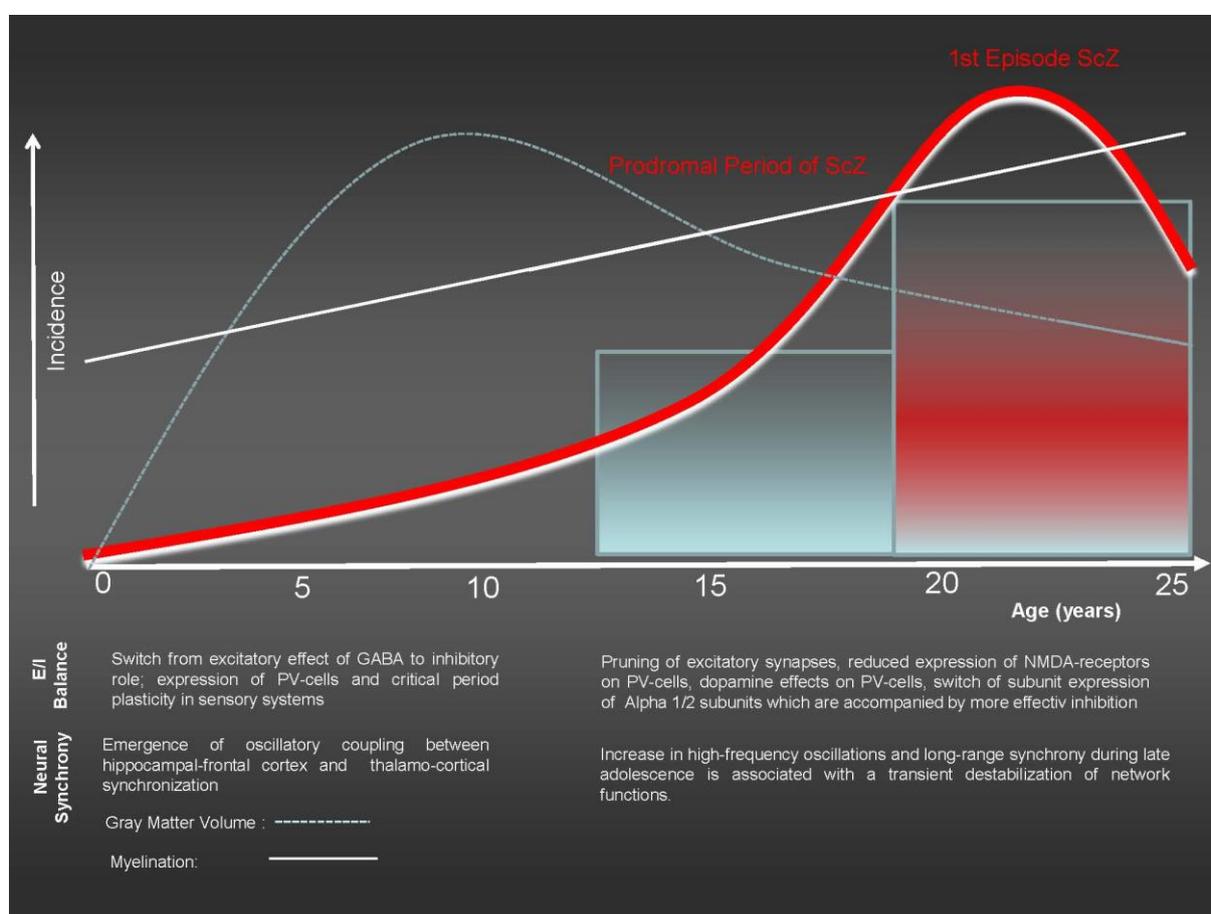

Figur 2 Brain Maturation, Changes in E/I Balance, and the Manifestation of Schizophrenia.
Insights into the pathophysiology of schizophrenia are to be gained from a stronger focus on developmental changes of E/I balance parameters during critical adolescence which coincides with the manifestation of schizophrenia.

Summary and Perspectives

Research into neural synchrony has contributed towards the conceptualization of schizophrenia as a disorder of neuronal dynamics in large-scale networks with important implications for efforts to decipher pathophysiological mechanisms. While previously, the search for pharmacological targets has largely focused on the dopamine system, recent research has focused on drug targets which impact on glutamatergic and GABAergic neurotransmission [49, 50]. In the light of their crucial role in the assuring E/I balance, this approach should be intensified further and may lead to more effective treatments.

In addition, several issues may be addressed in future studies to further the understanding of the potential role of neural synchrony in the pathophysiology of schizophrenia. One concerns the relationship between the late maturation of E/I-balance parameters, neural synchrony and the manifestation of the disorder (Figure 2). Evidence has accumulated that points towards important modifications in neurotransmitter-systems supporting high-frequency oscillations during adolescence [51-53]. Furthermore, developmental data on neural synchrony has highlighted that cortical circuits during late brain maturation are accompanied by profound modifications in the amplitude and synchrony at theta-, beta-, and gamma-frequencies [54]. Together these findings raise the interesting possibility that late developmental modifications of large-scale networks in schizophrenia is abnormal which could lead to a disintegration of coordinated network activity and consequently psychosis during the transition from adolescence to adulthood [13]. To further test this hypothesis, more detailed research is required which examines changes in the E/I-balance parameters during normal development as well as the modifications in large-scale network in subjects at high-risk for the development of schizophrenia. Such research could be important for developing biomarkers for early detection as well as novel treatment approaches aimed at the prevention of schizophrenia.

In addition to a stronger developmental focus, insights into the functional relevance of neural synchrony towards the explanation of cognitive and clinical symptoms may be gained through the integration of neural synchrony parameters within the predictive coding framework. A core deficit in schizophrenia may reside in a dysfunction in corollary discharge mechanisms which could underlie impairments in the differentiation between self and non-self-generated actions [55]. From this perspective, schizophrenia patients may fail to adequately predict the causes of sensory perception [56] which could, for example, lead to self-generated speech acts being assigned to an external sources as the result of a failure in the efference copy [57].

Corollary discharge mechanisms require a millisecond coordination between expected and unexpected neuronal events and preliminary evidence indicates that this process may be mediated by gamma-band activity during normal brain functioning [58]. Moreover, recent theoretical and empirical work has highlighted that sensory predictions are a fundamental feature of normal brain functioning [11] which are implemented through low-level oscillatory mechanisms [59]. This raises the possibility that abnormal sensory predictions as a result of aberrant neural synchrony could parsimoniously explain both central clinical symptoms as well as the pervasive deficits in cognitive and perceptual processes in schizophrenia.

To achieve further insights into the mechanistic role of dysfunctional neural synchrony, improved electrophysiological methods are required that allow the reliable assessment of large-scale interactions. In EEG/MEG-data, separating high-frequency oscillations due to neuronal vs. non-neuronal mechanisms [60] as well as the reconstruction of spatial reconstruction of source activity has been challenging. However, reconstruction of cortex-wide oscillatory networks with EEG/MEG combined with measures that assess ongoing interactions between brain regions is now feasible [17] which could yield unprecedented insights into neuronal dynamics in large-scale networks. Additional important

steps toward clinical use of such measures are the identification of paradigms with robust test-retest reliability as well as translational applications in animal models.

Addressing these points will hopefully contribute towards advancing our understanding of the causes of schizophrenia and eventually lead to improved evidence-based interventions. Given the lack of progress in recent decades in targeting cognitive dysfunctions and improving the overall outcome of patients with schizophrenia, an interdisciplinary dialogue involving basic and cognitive neuroscience as well as clinical research is required. Importantly, the insights gained from this endeavor may not only reduce the tremendous human and social costs associated with schizophrenia but may bring about important insights into the fundamental contribution of neural dynamics in large-scale networks during brain functioning in general.

Acknowledgments

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