The Role of Oscillations and Synchrony in Cortical Networks and Their Putative Relevance for the Pathophysiology of Schizophrenia

Peter J. Uhlhaas[1–3], Corinna Haenschel[2,3], Danko Nikolić[2,4], and Wolf Singer[2–4]

[2]Department of Neurophysiology, Max-Planck Institute for Brain Research, Deutschordenstrasse 46, 60528 Frankfurt am Main, Germany; [3]Laboratory for Neurophysiology and Neuroimaging, Department of Psychiatry, Johann Wolfgang Goethe-Universität, Heinrich-Hoffman-Strasse 10, 60528 Frankfurt am Main, Germany; [4]Frankfurt Institute for Advanced Studies, Johann Wolfgang Goethe-Universität, Ruth-Moufang-Strasse 1, 60438 Frankfurt am Main, Germany

Neural oscillations and their synchronization may represent a versatile signal to realize flexible communication within and between cortical areas. By now, there is extensive evidence to suggest that cognitive functions depending on coordination of distributed neural responses, such as perceptual grouping, attention-dependent stimulus selection, subsystem integration, working memory, and consciousness, are associated with synchronized oscillatory activity in the theta-, alpha-, beta-, and gamma-band, suggesting a functional mechanism of neural oscillations in cortical networks. In addition to their role in normal brain functioning, there is increasing evidence that altered oscillatory activity may be associated with certain neuropsychiatric disorders, such as schizophrenia, that involve dysfunctional cognition and behavior. In the following article, we aim to summarize the evidence on the role of neural oscillations during normal brain functioning and their relationship to cognitive processes. In the second part, we review research that has examined oscillatory activity during cognitive and behavioral tasks in schizophrenia. These studies suggest that schizophrenia involves abnormal oscillations and synchrony that are related to cognitive dysfunctions and some of the symptoms of the disorder. Perspectives for future research will be discussed in relationship to methodological issues, the utility of neural oscillations as a biomarker, and the neurodevelopmental hypothesis of schizophrenia.

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[1]To whom correspondence should be addressed; tel: +0049-69-6301-83782, fax: +0049-69-6301-3833, e-mail: uhlhaas@mpih-frankfurt.mpg.de.

Neural Oscillations and Synchrony

A prominent property of neural networks is their tendency to engage in oscillatory activity. Hans Berger (1873–1941) was one of the first scientists to observe the brain's rhythms which he recorded in the form of electrical activity on the scalp of healthy, awake participants.[1] He also introduced the current nomenclature naming different rhythms by Greek letters. Rhythmic electroencephalographic (EEG) activity is commonly subdivided in 5 major frequency bands, the delta- (0–3 Hz), theta- (4–7 Hz), alpha- (8–12 Hz), beta- (13–30 Hz), and gamma-band (30–200 Hz). (We did not include oscillations in the delta-frequency range [0–3 Hz] in the review, as evidence on the functional role of delta oscillations is so far limited.)

Since the early discoveries of Berger and others, EEG has become a valuable tool for the study of brain functions as well as for clinical investigations of various neurological and psychiatric disorders. More recently, a method for recording the brain's magnetic activity noninvasively—magnetoencephalogram (MEG)—has been developed that has significantly improved the spatial resolution of extracranial recordings and, thereby, also the detectability of low-amplitude, high-frequency oscillations.

In the last 2 decades, the investigation of brain activity in EEG and MEG data has experienced an important paradigm shift because the focus has moved from the analysis of event-related averaging of neuronal responses (event-related potentials [ERPs]) to methods that investigate the power, the coherence, and the phase locking of nonaveraged oscillating signals. The reasons for this paradigm shift are in part technical; the access to computational power has increased, and the analysis techniques have proliferated.[2] However, the most important reason for this shift is conceptual: the discovery of synchronized, oscillatory in neuronal spiking activity led to novel hypotheses about the putative functions of the phenomenon,[3–5] and the testing of these hypothesis required the analysis of nonstimulus-locked internally generated temporal patterns.

Oscillations that reflect self-generated activity are referred to as induced oscillations and preclude evaluation of averaged responses and, therefore, require single-trial analyses because their latency varies from trial to trial.

Typically, the latency in which induced oscillations occur is within the time window of 150–400 ms. In contrast, evoked oscillations are strictly phase locked to the onset of the stimulus and are measured by stimulus-triggered averages of responses. Evoked oscillations typically occur within a latency window of 50–150 ms and have been related to early, stimulus-driven encoding processes.

An important link between oscillations and cortical computations was the discovery of the role of oscillatory rhythms in the beta/gamma range (20–80 Hz) in establishing precise synchronization of distributed neural responses. Gray and colleagues[6,7] showed that action potentials generated by cortical cells align with the oscillatory rhythm in the beta and gamma range, which has the consequence that neurons participating in the same oscillatory rhythm synchronize their discharges with very high precision. Thus, it is a central role of cortical oscillations in the beta/gamma range to enable neuronal synchronization.[4,5]

Self-generated oscillations and synchronization are highly dynamic phenomena and depend on numerous conditions, such as central states,[4,5,8] stimulus configuration,[6,7] or attention.[9] The occurring strength of synchrony is closely correlated with perceptual processes such as feature binding, subsystem integration, brightness perception, and interocular rivalry.[4] In addition, the strength of synchronization predicts whether an animal will give a correct response in an upcoming trial of a perceptual decision task,[10] suggesting its important functional role.

Synchronization patterns between pairs of neurons have a particular topology that exhibits the properties of small-world networks. Networks with "small-world properties" are characterized by a combination of local clustering of activity and a short path length as an index of global integration. The hubs of these networks—ie, neurons synchronized most strongly with the rest of the network—exhibit most prominently their cortical functions, ie, orientation selectivity in the early visual areas, suggesting a close relation between neuronal oscillations and synchrony on the one hand and the organization of network interactions on the other.[11]

Possibly the most important function of synchronized, oscillatory activity is the implementation of a mechanism that can exploit the relative phase of oscillations. Recent data show a systematic relation between the phase offset of synchronized spiking and stimulus properties,[12–14] suggesting that information is encoded in the relative firing times of the discharges of distributed neurons.

As the empirical data indicate, cells that are excited more strongly tend to fire earlier than those excited less strongly.[14] This offers a particularly efficient mechanism for encoding stimulus-related information, which can be either redundant or complementary to that already provided by the rate responses. Redundant information would provide more precision to the encoding process, and complementary would provide information additional to that coded by firing rates. Either way, an important advantage of such a temporal coding scheme is the processing speed with which participating neuronal structures may conduct computations.

The information about a neuron's firing rate can be assessed accurately only after observing this neuron's activity for some time (eg, 100 ms or more). In contrast, the information about the phase of an action potential is present instantaneously (ie, within a single cycle of a beta/gamma oscillation) and, hence, can be, at least in principle, also extracted within such a short period of time. Such accurate and readily available information can enhance numerous cognitive processes, ranging from object recognition to decision making.

The mechanisms underlying the generation of these spatiotemporal patterns associated with beta/gamma oscillations are likely to be similar to those responsible for the phase precession of pyramidal cell firing in the hippocampus relative to theta oscillations.[15,16] Cortical neurons not only generate such precise temporal information but also appear highly capable of reading out the same information when receiving inputs from earlier processing stages. The possible readout mechanisms have been discussed most commonly in the context of the varying spike latencies of the sensory inputs.[16–18]

In addition to the high-frequency oscillations in the beta- and gamma-band, oscillatory rhythms in the theta- and alpha-band also play an important role in cortical computations. Alpha activity (8–12 Hz) has been not only associated with an inhibitory function[19] but also with the long-distance coordination of gamma oscillations,[20] and theta activity has been proposed to support large-scale integration of subsystems serving the formation and recall of memories.[21–23] In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronized oscillations. Short-distance synchronization tends to occur at higher frequencies (gamma-band) than long-distance synchronization, which often manifests itself not only in the beta- but also in the theta- (4–8 Hz) and alpha- (8–12 Hz) frequency range.[23,24]

Thus, oscillations and their synchronization are important correlates of neuronal processing and provide valuable measures for the assessment of normal and pathological functions. (It is important to note that the remaining part of this review focuses on studies based solely on field recordings [EEG, MEG] rather than the activity of individual neurons. Consequently, it can never be directly resolved whether an increase in the power of these field recordings is due to the increase in the strength of synchrony or in the strength of oscillations.).

Theta Oscillations

Theta oscillations occurring in the frequency range of approximately 4–8 Hz represent one of the best-studied

rhythms in the mammalian brain (for a review, see Buzsaki,[21] Kahana et al,[25] and Lengyel et al[26]). In mammals, theta oscillations are particularly prominent in the hippocampus but occur also in extrahippocampal regions, such as the ento- and the perirhinal cortex, the prefrontal, somatosensory, and visual cortex, and superior colliculus.[27,28] In the hippocampus, theta oscillations are generated by an interplay of glutamatergic and gamma-aminobutyric acidergic (GABAergic) neurons.[29,30] In addition, GABAergic inputs are modulated by cholinergic inputs from the septum that possibly acts as a pacemaker for theta activity.[31]

Studies in rodents revealed a close relationship between the occurrence of theta oscillations in the hippocampus, locomotion, and the place-specific firing of hippocampal pyramidal cells (place cells).[15] These place cells have spatially selective fields and discharge when the animal is at the location corresponding to the receptive place fields.[32] In a seminal study, O'Keefe and Recce[15] reported that the phase of the place cell firing relative to the ongoing theta oscillations advances gradually as the rat passes through the cell's place field. This phenomenon, called phase precession, has been interpreted as a mechanism to increase the precision of spatial coding and to bind assemblies of place cells for the representation of movement trajectories.[21,16]

Spatial navigation, a process requiring evaluation and temporary storage of relations, is only one of the numerous functions of the hippocampus. A large body of evidence indicates that the special ability of the hippocampus to process relations is used in a much wider context and plays a crucial role in the formation and recall of episodic and declarative memory.[33,34]

Accordingly, theta oscillations have also been assigned functions in memory-related processes. (1) Manipulations that eliminate theta activity in the hippocampus produce deficits in spatial and nonspatial working memory (WM) tasks in rodents (for a review, see Gevins et al[35]); (2) theta oscillations correlate with WM load[35,36] and link neural assemblies in frontal and parietal cortices during the maintenance of items in WM[22]; (3) significant increases in theta power during encoding of information predict subsequent recall of information[37]; and (4) in human EEG data, a theta component that is largest over midline frontal regions (frontal midline theta) is enhanced in tasks involving WM and requiring focused attention.[35,36]

An involvement of theta activity in memory processes is also supported by the evidence that rhythmic stimulation in this frequency range (theta burst stimulation) is particularly effective in inducing long-term potentiation (LTP) and that LTP induction is highly sensitive to the phase between stimulation relative to the ongoing theta rhythm. Stimulation at the depolarizing peak of the theta cycle favors LTP while stimulation in the through causes depotentiation. Thus, both in vitro and in vivo data suggest that theta oscillations act as a windowing mechanism determining the threshold and polarity of synaptic modifications.[38–40]

Alpha Oscillations

Alpha oscillations, the frequency of which is centered around 10 Hz, were the first rhythm to be discovered by Berger in 1924.[1] Alpha activity is very prominent in the thalamus and can be sustained by isolated thalamic networks,[41] which led to the assumption that cortical alpha is driven by thalamic peacemakers (see Basar et al[42] for a review). However, da Silva et al[43] demonstrated that cortical alpha results from synergistic interactions within thalamo-cortical-thalamic reentrant networks (see Sauseng et al[44] for a review). In addition, alpha oscillations have also been recorded in subcortical areas, such as the hippocampus and the reticular formation.[42]

It is well established that alpha rhythms result from reciprocal interactions between excitatory and inhibitory neurons whereby the synchronization is in addition stabilized by gap junctions among inhibitory interneurons.[45,46] The susceptibility of these networks to engage in alpha rhythms is in turn modulated by cholinergic and serotonergic mechanisms and by glutamatergic afferents acting via metabotropic receptors.[47]

Alpha activity is most prominent over occipital cortex when the eyes are closed and subjects are in a relaxed state and has therefore been regarded as reflecting cortical idling.[48] Typically, opening the eyes results in an alpha blockade which has been linked to active stimulus processing.[44,49] It is currently under debate, whether alpha oscillatory activity is related to functional inhibition of task-irrelevant processing[44] or whether it is a direct and essential constituent of the active network (for a review, see Palva and Palva[20]). Results from studies investigating visuospatial attention[50–52] and WM,[44,53,54] especially when capacity limits are reached,[44] have been interpreted in favor of the inhibition hypothesis.

In contrast, evidence for an involvement of alpha activity in information processing has been provided by studies on mental imagery,[55] conscious somatosensory perception,[56] and WM tasks.[20] Furthermore, there is an evidence for a relationship between long-range coherence in the alpha-frequency band and perceptual and cross-modal binding.[54,57,58]

Several lines of research indicate a relationship between baseline alpha activity and the expression of ERPs. Low prestimulus alpha amplitudes are associated with larger P1 responses in a visual discrimination task and enhance good performance. By contrast, high prestimulus alpha is associated with enhanced P3 activity and enhanced retention in WM tasks.[44] The underlying assumption is that the sensory stimulus induces phase resetting of ongoing rhythmic activity in each trial and that averaging these phase-coherent rhythms produces the

ERP.[59,60] Another possibility is that the ERP reflects a transient response to the stimulus that is superimposed on the background EEG. The current literature suggests that these 2 mechanisms coexist (for a review, see Sauseng et al[44]).

Nevertheless, it is still a technical challenge to disentangle the ERP response from ongoing oscillations.[61] The available methods do not allow to distinguish conclusively between phase resetting and transient activity. Phase-coherent activity specifically in the lower frequency bands has been taken as evidence for the former model. However, the contrary may be true as well because transient bursts of neural activity may likewise result in similar phase-coherent activity. Thus, many of their physical characteristics may be overlapping and should not be used as criteria for the presence of either kind of activity (for a discussion, see Yeung et al[61]).

Beta Oscillations

Frequencies between 12 and 30 Hz are termed beta activity. Beta oscillations occur in all cortical areas and numerous subcortical structures including nonspecific thalamic nuclei, the hippocampus, the basal ganglia, and olfactory bulb.

Generation of beta-band oscillations has been linked to neurotransmitter systems including metabotropic glutamate as well as *N*-methyl D-aspartate (NMDA) receptors and GABAa receptor activity.[62,63] Of particular clinical relevance is the dopaminergic modulation of beta oscillations in the basal ganglia, the subthalamic nucleus, and the motor cortex.[64] In Parkinson disease, reduced dopaminergic control leads to the instability to desynchronize these beta oscillations that prevail in the rest condition and need to be replaced by gamma oscillations in order to enable the initiation of voluntary movements.[65]

This central beta oscillation has been related to the rolandic mu rhythm that is generated by the sensorimotor cortex and is most prominent at rest and attenuated or abolished by moving or observing biological movements.[66] There is evidence for enhanced synchronized beta-band activity prior to movements in sensorimotor cortex influencing descending motor commands to contralateral hand muscles.[67–69] Such corticomuscular coherence is the strongest during steady hold periods after movement but is abolished during the actual movement.[68]

In addition, beta activity has been implicated in a variety of cognitive tasks, such as learning in the mammalian olfactory bulb,[70] novelty detection in the auditory system,[71] sensory gating,[72,73] and reward evaluation.[74] It has been suggested that the common denominator of beta oscillations is to highlight a stimulus as novel or salient that warrants further attention.[72]

Furthermore, beta-band activity is involved in large-scale coordination of distributed neural activity. Kopell and colleagues[29] showed that beta oscillations support more effectively coherence over large distances than gamma oscillations because their synchronization is less susceptible to long conduction delays. Consistent with this hypothesis, Tallon-Baudry and colleagues[75] observed increased oscillatory activity in the beta-frequency range between 2 sites in inferior temporal cortex during the maintenance period in a WM task. Further evidence for a relationship between long-range synchronization and beta-band activity was reported by Schnitzler and Gross.[76] The authors investigated the neural networks underlying attention control in visual processing in the attentional blink task. The results revealed that communication within the fronto-parieto-temporal attentional network proceeds via transient long-range phase synchronization in the beta-band.

Gamma Oscillations

Rhythms >30 Hz are addressed as gamma oscillations and occur in virtually all brain structures, including the olfactory bulb and the retina. These oscillations cover a broad frequency band ranging up to 200 Hz. Gamma-band oscillations were first recorded by Adrian and Matthews[48] from the olfactory bulb following odor stimulation and have been later observed in the visual cortex following visual stimulation.

Generation of gamma-band activity is critically dependent upon several neurotransmitter systems. The networks of chemically and electrically coupled GABAergic neurons play a pivotal role in the primary generation of high-frequency oscillations and local synchronization[77–81] while more far-reaching glutamatergic connections appear to control their strength, duration, and long-range synchronization.[79] Cholinergic modulation via muscarinic receptors plays a crucial role both in the fast, state-dependent facilitation of gamma oscillations and associated response synchronization as well as in the control of use-dependent long-term modification of cortical dynamics that favor synchronization of responses in the gamma-frequency range.[82,83]

First indications for a functional role of gamma-band oscillations for information processing in cortical networks have been obtained in studies investigating the relations between stimulus-induced synchronization of gamma oscillations and feature binding in cat primary visual cortex (V1) by Gray and Singer[7] (see figure 1). This relationship was then confirmed in a series of studies with EEG and MEG that found robust support for the role of gamma oscillations in the grouping of stimulus elements into coherent object representations.[84,85]

Further research has found a close relationship between attention, oscillations, and synchrony in the gamma-band range. Fries and colleagues[86] recorded neurons in cortical area V4 while macaque monkeys attended to behaviorally relevant stimuli and ignored distracters.
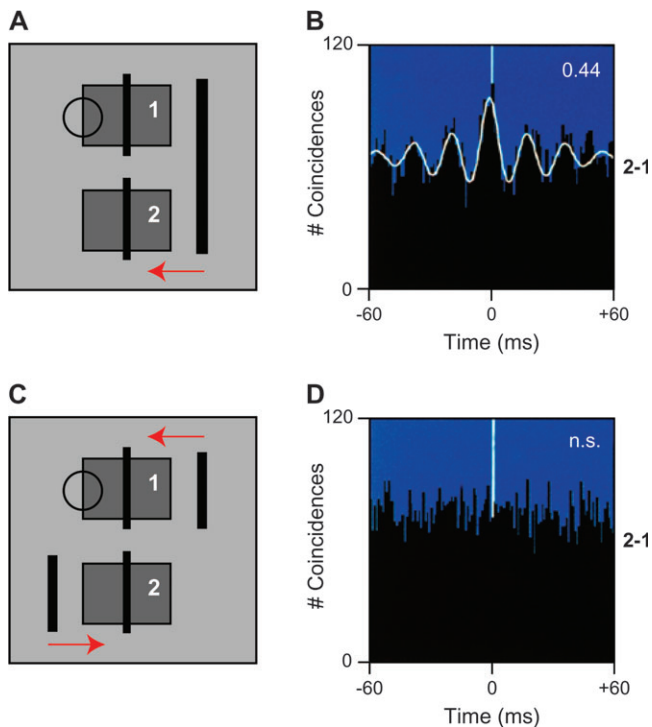
Fig. 1. Synchronous Gamma Oscillations and Perceptual Binding. Responses are recorded for a pair of multiunit (MUA) activity with nonoverlapping receptive fields in primary visual cortex of an anesthetized cat. In the 2 different visual stimulation conditions, the stimuli consisted either of a single long moving bar (A) or of 2 small bars moving in different directions (C). In both conditions, the receptive fields were stimulated near optimally and simultaneously, and consequently, no changes in neurons' firing rates were observed (results not shown). In contrast, neuronal synchronization between the 2 MUAs changed strongly, as estimated by the cross-correlation histograms (CCHs) in (B) and (D). The high center peak and the good fit of a Gabor function in (B) indicate that the stimulus in (A) evoked strong neuronal synchrony, while the flat CCH in (D) indicates lack of synchronization between the responses to stimuli in (C).

Neurons activated by the attended stimulus showed increased gamma synchronization (35–90 Hz) compared with neurons at nearby V4 sites activated by distracters. Consistent evidence for the relationship between attention and gamma-band activity both during visual and auditory perception has been also found in human EEG and MEG recordings.[87–89] Taken together, these findings suggest that gamma-band oscillations have a general computational role in dynamically selecting neurons that communicate information about sensory inputs effectively.

Gamma oscillations have been also implicated in higher cognitive functions, such as memory. Tallon-Baudry and colleagues[90] examined EEG-activity during a visual short-term memory task. Induced gamma-band activity was observed during the delay over frontal and parietal electrodes, indicating that gamma oscillations are involved in the maintenance of information in WM. Additional evidence for the role of gamma oscillations during

WM has been obtained from intracranial recordings[91] as well as from studies that examined the relationship between auditory WM and gamma oscillations in MEG data.[92] Finally, gamma oscillations may also be involved in long-term memory because there is a relationship between the amount of gamma-band activity during the encoding of information and the subsequent recall.[37,93,94]

Recent data suggest that synchronized gamma-band activity may also be related to consciousness. A large body of evidence suggest that consciousness has to be understood as a function of numerous interacting systems that require a mechanism that transiently synchronizes a number of widely distributed neural assemblies.[95] Melloni et al[96] examined EEG data in response to the processing of visible and invisible words in a delayed matching to sample task. Both perceived and nonperceived words caused a similar increase of local (gamma) oscillations in the EEG, but only perceived words induced a transient long-distance synchronization of gamma oscillations across widely separated regions of the brain.

In addition to the role of gamma-band oscillations in perceptual organization, attention, memory, and consciousness, gamma-band activity has also been related to other cognitive phenomena, including language processing and motor coordination (for comprehensive reviews, see Fries et al[4] and Singer[5]).

As has been discussed for theta oscillations, gamma oscillations are also involved in the gating of synaptic plasticity.[82] The mechanisms are similar, but because of the high frequency of gamma oscillations, the temporal resolution of the gating process is much higher and capable of distinguishing temporal offsets between pre- and postsynaptic activity in the range of milliseconds.

Neural Oscillations in Cortical Networks

In summary, cortical networks have a strong tendency to engage in oscillatory activity at multiple frequency bands. These oscillations provide a temporal frame for the timing of discharges and an option to use precise temporal resolutions for the encoding of information. The special case of synchrony is likely to be exploited for the definition of relatedness both in information processing and learning. In addition, synchronization seems to be used to increase the salience of signals, to facilitate their propagation across sparsely connected networks, and to assure selective routing. Moreover, systematic phase shifts between the discharges of individual neurons and population oscillations appear to be exploited for cortical computations. However, numerous questions concerning the functional roles and definition of oscillations are still unanswered.

One question relates to the validity of the current system of assigning oscillations into distinct frequencies. For example, theta oscillations in the rodent hippocampus

Table 1. Neural Oscillations in Cortical Networks

	Theta (4–7 Hz)	Alpha (8–12 Hz)	Beta (13–30 Hz)	Gamma (30–200 Hz)
Anatomy	Hippocampus, prefrontal cortex, sensory cortex	Thalamus, hippocampus, reticular formation, sensory cortex, motor cortex	All cortical structures, subthalamic nucleus, hippocampus, basal ganglia, olfactory bulb	All brain structures, retina, olfactory bulb
Neurotransmitters	GABA, glutamate, acetylcholine	Glutamate, acetylcholine, serotonin	Glutamate, GABA, dopamine	GABA, glutamate, acetylcholine
Function	Memory, synaptic plasticity, top-down control, long-range synchronization	Inhibition, attention, consciousness, top-down control, long-range synchronization	Sensory gating, attention, perception, motor control, long-range synchronization	Perception, attention, memory, consciousness, synaptic plasticity, motor control

Note: GABA, gamma-aminobutyric acid.

cover a wide range of frequencies that can vary with the behavioral state of the animal. Similarly, it is unclear whether oscillations in the beta- and gamma-band should be considered as strictly distinct rhythms or whether there is continuum between both frequencies that may relate to a common underlying physiological mechanism.

Moreover, it is conceivable that subbands within theta, alpha, beta, and gamma oscillations may serve differential mechanisms. Gamma oscillations cover a wide frequency range from 30 to 200 Hz, possibly containing different subclasses of rhythms. Vidal et al,[89] eg, recently reported gamma-band activity in 2 frequency bands in MEG-recordings during perceptual grouping, suggesting that grouping is associated with high (70–120 Hz) and attentional focusing with lower (44–66 Hz) gamma-band oscillations.

Another important conundrum is the interaction between oscillations of different frequencies. A characteristic of oscillations in cortical networks is that multiple frequency bands coexist, and there is evidence that interactions between oscillations at different frequencies are used for the encoding of nested relations (for a review, see Jensen and Colgin[93]).

Cross-frequency coupling has been observed between theta and gamma-rhythms during various cognitive tasks and in several brain areas. Specifically, modulation of gamma oscillations through the phase of the theta rhythm is associated with visual perception[97] and WM.[98] Lisman[99] proposed that the coupling between these 2 rhythms may represent a more general coding scheme for information processing.

In addition to the coupling between the phase of a particular frequency and the power of an oscillation, different principles of cross-frequency interaction are conceivable.[93] For example, phase-to-phase interactions have been observed between several frequency bands by Palva et al.[100] The authors tested cross-frequency coupling (n:m phase synchrony) in MEG data through examining phase synchronization between oscillations during a mental arithmetic task. Significant interactions between

alpha, beta, and gamma oscillations were observed that increased with task load and with pronounced interaction between gamma- and alpha-band oscillations (table 1).

Neural Oscillations and Schizophrenia

Further insights into neural oscillations and their relationship to cognitive processes may be gained by correlations between abnormal brain states, such as in schizophrenia, that are accompanied by cognitive abnormalities as well as by changes in neurotransmitter systems that are involved in the generation of oscillations and their synchronization.

Until recently, research into the role of aberrant oscillatory activity in the pathophysiology of schizophrenia has focused largely on the investigation of resting state EEG data. This research has produced consistent evidence for abnormalities in several frequency bands (for a review, see Boutros et al[101]). However, these data allow only limited insights into the relationship between dysfunctional cognitive processes and impaired oscillatory activity in schizophrenia. With the advent of advanced time-frequency analyses tools (for a review, see Le Van Quyen and Bragin[2] and Roach and Mathalon[102]), recent research has begun to examine task-related oscillatory activity in patients with schizophrenia. These data have revealed novel insights into the neural mechanisms underlying cognitive dysfunctions that may have important implications for the pathophysiology of schizophrenia.

Theta Oscillations

As reviewed above, theta oscillations have been implicated in episodic and WM and in the top-down control of cognitive functions. Schizophrenia is associated with impairments in all these domains, suggesting the possibility of abnormal theta activity. Preliminary evidence suggests that this is the case in patients with schizophrenia. Schmiedt et al[103] reported abnormal evoked theta activity during WM and cognitive control, ie, the ability to adjust

strategies flexibly in accordance with one's intentions and goals. WM was examined in an N-back task in 10 patients and 10 healthy participants. In addition, the authors manipulated cognitive control by monitoring simple actions during WM performance. In controls, theta activity was particularly prominent over frontal electrodes in the high cognitive control condition and increased with WM load. In contrast, patients with schizophrenia did not show an increase in evoked theta activity in either the difficult high control condition or with increased WM load.

Ford et al[104] investigated the role of long-range synchronization of theta oscillations between frontal and temporal lobes in the context of auditory hallucinations. EEG data were recorded in 2 conditions: Participants listened either to their own played back speech or were instructed to talk aloud. In normal participants and patients with schizophrenia without hallucinations, talking was associated with an increase in theta coherence between left frontal and temporal electrodes relative to the listening condition. In patients with schizophrenia with auditory hallucinations, this modulation was absent. The finding of increased theta coherence in controls and patients without hallucinations may reflect the action of a corollary discharge mechanism whereby frontal brain structures prepare temporal lobe areas for speech production. The lack of such a corollary signal has been proposed as a pathophysiological mechanism for auditory hallucinations.[105]

Alpha Oscillations

Neural oscillations in the alpha-band have been investigated predominantly in the resting EEG of patients with schizophrenia as well as in relation to ERP generation (see below). There is consistent evidence that patients with schizophrenia are characterized by diminished alpha power in the resting state EEG.[106–108] The diminished alpha activity in the resting EEG is difficult to interpret. It could be due to abnormal functions of the alpha generators, but because of the marked state dependence of alpha oscillations, it could also result from tonically enhanced arousal and/or neuroleptic treatment.

Beta Oscillations

Oscillations in the beta-frequency range have been associated with long-range synchronization between neuronal assemblies in the context of polymodal sensory processing, sensory-motor coordination, the maintenance of limb positions, and WM. Uhlhaas et al[109] examined the extent of long-range synchronization deficits in 19 chronic patients with schizophrenia and 19 healthy controls during the perception of Mooney faces (see figure 2). Mooney faces consist of degraded pictures of human faces where all shades of gray are removed, leaving only black and white contours. Perception of Mooney faces requires the grouping of the fragmentary parts

into coherent images. EEG data were analyzed for induced spectral power and phase synchronization in the beta- and gamma-frequency range. Patients with schizophrenia exhibited a deficit in the perception of Mooney faces and reduced phase synchrony in the beta-band (20-30 Hz) while the power of induced gamma-band oscillations was in the normal range, suggesting a differential impairment in long-range synchronization during perceptual organization.

Ford et al[110] examined EEG activity within 150 ms preceding speech onset compared with prelistening and related this to the ERP activity following speech or listening. Results showed that beta intertrial coherence (ITC) was larger for prespeech compared with prelistening. The ERP component N1 was suppressed during talking compared with listening in controls but not in patients and here especially in those with a history of auditory hallucinations. Furthermore, there was a strong correlation between ITC and N1 suppression in controls but not in patients. The authors suggested that the ITC reflects the action of a forward model system that dampens auditory responsiveness to self-generated speech.

Krishnan et al[111] probed the ability of cortical networks to generate and maintain oscillatory activity with a steady-state visual evoked potentials (SSVEPs) paradigm in chronic patients with schizophrenia. SSVEP represents a basic neural response to a temporally modulated stimulus to which it is synchronized in frequency and phase. The authors presented flicker at 7 different frequencies of stimulation (4, 8, 17, 20, 23, 30, and 40 Hz). Results showed that patients with schizophrenia showed significantly reduced SSVEPs at 17, 23, and at 30 Hz of stimulation relative to controls. Contrary to earlier findings,[112,113] SSVEP deficits were not present in the lower (theta, alpha) frequency ranges.

Dysfunctions in SSEVPs in several frequency bands are consistent with pervasive dysfunctions in visual processing in schizophrenia that have been found at the phenomenological, physiological, and structural level (for a review, see Uhlhaas and Silverstein[114] and Uhlhaas and Mishara[115])

Gamma Oscillations

A series of studies has examined gamma-band activity in patients with schizophrenia, providing consistent evidence for the presence of abnormal gamma-band oscillations. Kwon et al[116] employed an auditory steady-state paradigm in 15 chronic patients with schizophrenia and 15 control participants to examine evoked gamma-band activity. Patients with schizophrenia showed reduced EEG power at 40 Hz but not at lower frequencies of stimulation. In addition, gamma-band oscillations in patients with schizophrenia were characterized by a delayed onset of phase synchronization and delayed desynchronization to click trains at 40 Hz.
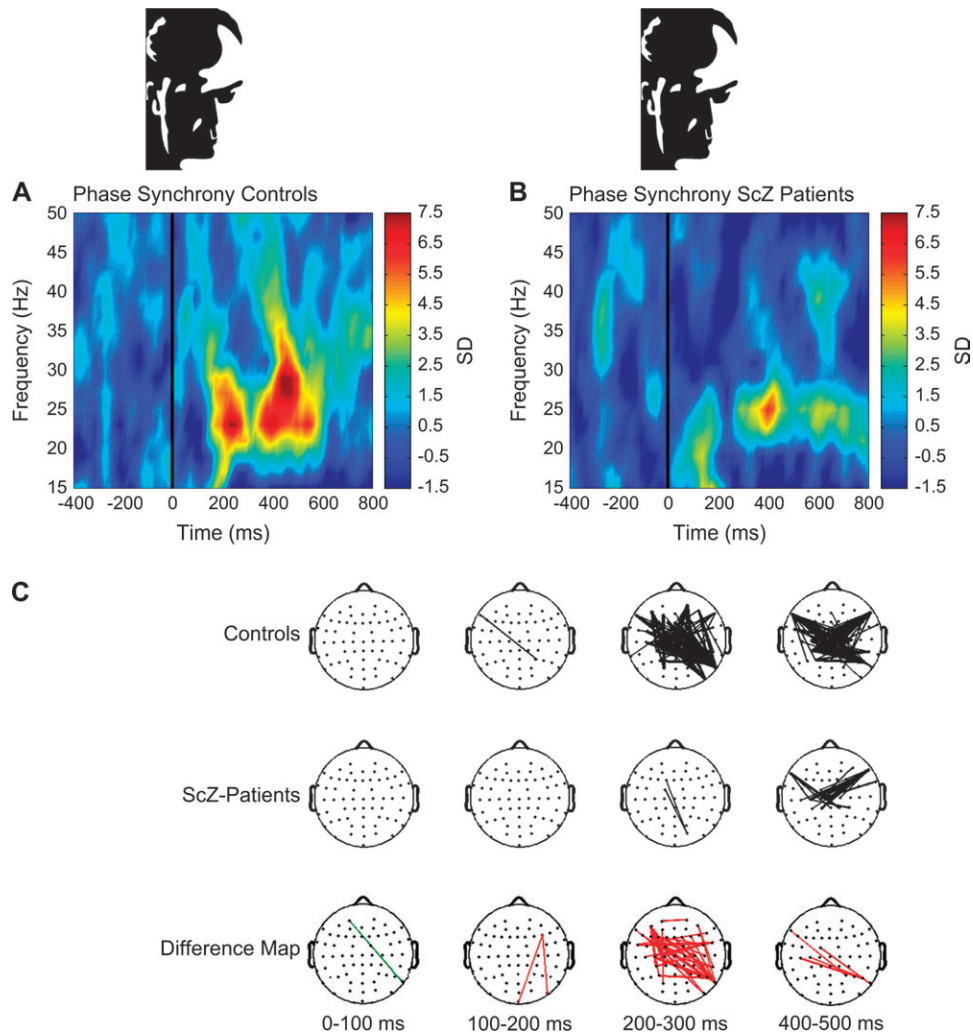
Fig. 2. Neural Synchrony During Gestalt Perception in Schizophrenia. Group average of phase synchrony for all electrodes and for correct trials during a Gestalt perception task in controls (A). Phase synchrony during Gestalt perception in controls exhibited 2 maxima over an average frequency range of 20–30 Hz (A). The increase in phase synchrony between 200 and 300 ms has been related to the construction of coherent object representations,[84] whereas the second peak indexes the preparation and execution of the motor response. In patients with schizophrenia (B), the onset of the first peak in the face condition was delayed and occurred between 350 and 400 ms in the frequency range of 20–25 Hz. In addition, a second, weaker peak was found around 600 ms. Compared with controls, the reduction in phase synchrony in patients with schizophrenia in the frequency range of 20–30 Hz was significant (frequency range: 20–30 Hz, time interval: 200–280 ms, $t(36) = 2.96$, $P = .005$). (C) This shows the topography of phase synchrony between 20 and 30 Hz. Synchrony between pairs of electrodes is indicated by connecting lines, which were drawn only if the synchrony value is beyond a 2-tailed probability of $P < .0005$. Differences between groups are displayed in the bottom row. Red lines indicate a decrease in synchrony in schizophrenia patients compared with controls. Green lines indicate increase in synchrony for patients with schizophrenia relative to controls. The decrease in phase synchrony between 200 and 300 ms indexes a deficit in the long-range synchronization during Gestalt perception in schizophrenia. Adapted with permission from Uhlhaas et al.[109] Copyright 2006 Society for Neuroscience.

Reduced power and synchronization of gamma oscillations evoked by steady-state stimulation have now been confirmed in several studies.[117] These abnormalities were not confined to patients with a chronic disease history but were also found in first-degree relatives,[118] in adolescent patients with a psychotic disorder,[119] and first-episode patients with schizophrenia.[120] This dysfunctional evoked gamma-band activity is not an artifact of medication because similar deficits have been found in unmedicated, first-episode patients with schizophrenia tested with an oddball paradigm in a late latency range of 220–350 ms.[121]

Several studies have also reported abnormalities in induced gamma-band activity during auditory stimulation. Haig et al[122] examined induced spectral power during an auditory oddball paradigm in 35 medicated schizophrenics and 35 age- and gender-matched normal controls. For target trials, patients showed a significant decrease in poststimulus gamma oscillations in the left hemisphere and over frontal sites and an increase in

the right hemisphere and over parietooccipital sites. In the nontarget trials (at a different latency), patients with schizophrenia showed a widespread decrease in gamma power. In subsequent studies,[123,124] the authors also examined phase synchrony between electrode sites in first-episode and chronic patients with schizophrenia using the same paradigm. These studies revealed reduced gamma-band phase synchronization in both first-episode and chronic patients.

Impaired gamma-band activity has also been demonstrated during visual processing. Spencer and colleagues[125] analyzed EEG data during an illusory square task in chronic patients and healthy controls for evoked activity and phase synchrony. Chronic patients showed reduced evoked activity for the early gamma-band response as well as reductions in long-range synchronization in the 37- to 44-Hz frequency range. In a second article,[126] analyses of the evoked response revealed that gamma-band activity was phase locked to the reaction times in healthy participants. In contrast, in patients with schizophrenia evoked activity in the gamma-band was significantly reduced and was replaced by an increase in beta-frequency activity during the motor response.

Further studies have confirmed the presence of abnormal gamma-band activity during visual stimulation.[127–129] Wynn et al[129] examined evoked gamma-band oscillations during a backward masking paradigm in 32 patients with schizophrenia and 15 controls. Evoked gamma-band activity was significantly reduced in the right hemisphere for masked targets, whereas the oscillatory response to unmasked targets was intact. In an earlier article,[128] induced gamma-band activity was also found to be impaired during visual masking.

Abnormal gamma-band activity has also been related to disturbed corollary modulation of sensory processes. Ford et al[110] tested the hypothesis that impaired generation of efference copies (corollary discharges) might be related to impaired neural synchrony in patients with schizophrenia. EEG data were collected while participants performed a simple button press task. In controls, there was an increase in gamma-band phase locking approximately 100 ms prior to the motor response that was significantly reduced in patients with schizophrenia.

In addition to studies that have found abnormalities in gamma-band oscillations during sensory processing, there is also evidence suggesting a relation between abnormal gamma-band activity and impairments in higher cognitive processes, such as executive processes and WM (for a review, see Haenschel et al[130]). Cho et al[131] examined the relationship between executive processes and gamma-band oscillations in a cognitive control paradigm that required participants to inhibit a prepotent response. Patients with schizophrenia were characterized by a significant decrease of induced gamma-band power over frontal electrodes sites relative to controls during this cognitive control task. This impairment was significantly correlated with their reduced performance.

Impaired gamma-band activity has also been reported in a WM task[132] during the performance of mental arithmetic[133] and during the Wisconsin Card Sorting Test[134] providing further support for a relation between abnormal gamma-band oscillations and the disturbance of higher cognitive processes in schizophrenia.

Finally, there is evidence that abnormal gamma-band activity correlates with the severity and nature of psychopathological syndromes. Lee et al[135] demonstrated that enhanced phase synchrony in responses to targets in an oddball paradigm was positively correlated with increased positive symptoms while negative symptoms were associated with a decrease in gamma-band activity in a sample of chronic patients with schizophrenia. In contrast, Bucci et al[136] observed that induced gamma power and coherence were relatively preserved in patients with primary negative symptoms. Finally, Spencer et al[125] noted a relationship between the frequency of phase locking in the beta-frequency range and the severity of core symptoms of schizophrenia, suggesting that lower frequencies of the evoked oscillations are associated with more severe symptomatology.

Neural Oscillations, ERPs, and Cortical Noise

In addition to the analysis of task-related oscillations, several studies have examined the potential relationship between ERPs and oscillatory activity in schizophrenia. As pointed out above, recent experimental and theoretical evidence suggests that ERPs are partially generated by a reorganization of ongoing oscillations in the EEG.[61] Thus, the core assumption is that the background oscillations undergo a phase reset that contributes to the evoked components in response to a stimulus. Accordingly, impaired neural oscillations in schizophrenia could not only account for deficits in cognitive processes but could also explain some of the ERP abnormalities.

Jansen et al[137] used an auditory sensory gating paradigm to measure N100 and P200 ERP components and their relationship to phase synchronization in the 2- to 12-Hz frequency range. Results showed that patients with schizophrenia were characterized by reduced activity between 4 and 8 Hz for responses to the first stimulus. Furthermore, whereas N100 and P200 amplitudes correlated with phase synchronization in controls, this relationship was not present in patients with schizophrenia. Supporting evidence for a link between ERP components during sensory gating and reduced theta/alpha phase-synchronization was recently reported by Brockhaus-Dumke and colleagues.[138]

There is also evidence for a relation between abnormalities in high-frequency oscillation and altered ERPs in schizophrenia.[73,139,140] Hong et al[73] measured evoked gamma and beta activity following paired auditory clicks.

Table 2. Neural Oscillations and Schizophrenia

	Theta (4–7 Hz)	Alpha (8–12 Hz)	Beta (13–30 Hz)	Gamma (30–200 Hz)
Executive processes	Working memory, cognitive control, prefrontal noise	Prefrontal noise	Prefrontal noise	Cognitive control, working memory, mental arithmetic prefrontal noise
Sensory processes	Sensory gating, corollary discharge	Sensory gating, steady-state visual evoked potentials	Perceptual binding, sensory gating, corollary discharge, steady-state visual evoked potentials	Perceptual binding, auditory steady-state evoked potentials, corollary discharge, backward masking, auditory perception
Symptoms	Positive symptoms	—	Positive and negative symptoms	Positive and negative symptoms disorganization
Endophenotype	Prefrontal noise	Prefrontal noise	Prefrontal noise	Auditory steady-state evoked potentials
Effect in first episode				Auditory steady-state evoked potentials, auditory perception

Results showed that the reduced evoked beta-band amplitude to the first click contributed to the lack of P50 suppression to the second click in patients with schizophrenia. Johannesen et al[140] subdivided the patients according to the sensory gating inventory into a group with either large or normal perceptual disturbances. Results indicated that patients with large perceptual disturbances showed smaller P50 amplitudes and weaker gamma-band attenuation.

In summary, the current evidence thus suggests that reductions in gamma and beta activity contribute to P50 impairments, whereas reductions in theta and alpha activity contribute to N100 and P200 impairments.

Abnormal oscillatory activity has been hypothesized as a source of noise impeding the function of prefrontal circuits in schizophrenia. To examine this hypothesis, Winterer et al[141] measured the increase in response variability of the event-related oscillatory activity in an auditory oddball paradigm in patients with schizophrenia (N = 65), their unaffected siblings (N = 115), and healthy subjects. The results showed enhanced broadband, nonstimulus-locked activity (0.5–45.5 Hz) over frontal and central electrodes in patients with schizophrenia and in unaffected siblings. Furthermore, the extent of noise was negatively correlated to the performance in an N-back WM task. According to Winterer et al, this abnormal high noise level in prefrontal circuits is due to a lack of stimulus-induced phase resetting of ongoing oscillations (table 2).

Neural Oscillations, Cognition, and Schizophrenia

The data reviewed so far suggest that oscillations in the theta-, alpha-, beta-, and gamma-frequency ranges are crucially involved in a wide range of cognitive functions. Although investigations of task-related oscillations and synchrony in pathological conditions have a short history, there is growing evidence for a close relation between psychopathology and abnormal brain dynamics.

Thus, further research on the role of oscillations and synchrony in the pathophysiology of schizophrenia is warranted.

Current theories of schizophrenia have emphasized that core aspects of the pathophysiology arise from a disconnection syndrome between and within cortical areas of the brain.[142–144] Deficits in neural oscillations may represent the functional correlate of disconnectivity in cortical networks and thus underlie the characteristic fragmentation of mind and behavior in schizophrenia. Functional disconnection between neural assemblies may furthermore reflect anatomical disconnectivity, such as white matter anomalies (see Kubicki et al[145] for a review). Studies involving lesions[146] and developmental manipulations[147] indicate that gamma-band activity and its synchronization are at least in part mediated by corticocortical connections that not only link reciprocally the cells situated in the same cortical area but also the cells distributed across different areas and even across the 2 hemispheres.

Although much of the available evidence emphasizes abnormalities of oscillations in the gamma-frequency range, abnormal task-related oscillatory activity has also been observed in theta-, alpha-, and beta-bands, suggesting that schizophrenia is associated with a widespread deficit in the generation and synchronization of rhythmic activity. Overall, the evidence suggests that schizophrenia is associated with a reduction of oscillatory activity which has been derived from amplitude measures of spectral activity in EEG and MEG studies. The amplitude of these signals represents neural activity that arises from the synchronous and periodic discharges of thousands or millions of neurons and the associated synaptic events and increases with the number of synchronously active neurons and with the precision of synchrony.

Thus, several factors could underlie the reduction of neural oscillations in schizophrenia. Reduced amplitudes could reflect reduced numbers of participating neurons (for a review, see Glantz et al[148]), reduced synaptic

connectivity,[149] and/or reduced synchrony. The latter could be the result of abnormalities in the rhythm-generating networks of inhibitory interneurons[150] or deficits in the pathways mediating long-distance synchrony such as disturbances in glutamatergic transmission[151] and/or abnormalities in the myelination or topology of long-distance corticocortical or cortico-thalamo-cortical connections.

However, other factors may also contribute to reduced amplitude of oscillations in schizophrenia. Neural oscillations and their synchronization are critically dependent upon central states of the nervous systems, such as the level of arousal and attention.[8,9] Accordingly, alterations in these state variables could also influence task-related neural oscillations, but the influence of these factors has so far not been systematically examined.

A more direct measure of synchrony than spectral power is the degree of phase locking between oscillations because it is independent of signal amplitudes.[152] Phase locking can be computed for single electrodes if responses are time locked to stimuli or between electrodes providing a measure of local- and long-range synchronization, respectively (see Roach et al[102]). Several studies that have employed synchrony measures have found reliable deficits in both local- and long-range synchronization in patients with schizophrenia[110,125,143] with some studies, suggesting that phase-locking measures provide a more sensitive measure toward alterations in oscillatory activity than power estimates.[143] These findings highlight the possible importance of precise synchronization of oscillatory activity in schizophrenia as a crucial pathophysiological mechanism rather than the overall amount of oscillatory activity.

Neural Oscillations and Schizophrenia: A Perspective

While the available evidence provides already robust support for the involvement of altered oscillatory activity in the pathophysiology of schizophrenia, we would like to raise a number of issues that we consider critical for further progress in this field of research.

The search for the pathophysiological mechanisms underlying the signs and symptoms of schizophrenia has implicated a large number of biological mechanisms, yet the precise causes of this devastating disorder have remained elusive. This is in part due to the heterogeneity of the disorder that is likely to involve multiple biological pathways. Another problem is that our understanding of the mechanisms through which cortical networks accomplish complex cognitive and executive processes is still at the very beginning.

The current interest in the relationship between neural oscillations and the pathophysiology of schizophrenia is based on the evidence that the putative functions of oscillations support those cognitive and executive functions that are most affected in schizophrenia. These functions have in common that they require large-scale integration of subsystems. Because the neuronal mechanisms responsible for the generation of oscillatory activity and its synchronization have been studied extensively both in vivo and in vitro, it is now possible to start focused search for abnormalities in these mechanisms (see Roopun et al[153]) and to explore new avenues for the treatment of this disorder (see Gonzalez-Burgos and Lewis[154]). Eventually, because of their quantifiability, abnormalities in oscillatory activity might become a valuable diagnostic marker and then also serve as endophenotype for genetic studies.

While these prospects are encouraging, we believe that several issues need to be considered that may be critical in the search for the electrographic correlations of schizophrenia.

Methodology

In contrast to conventional analyses of ERPs, eg, there are currently no general guidelines and standards regarding the analyses of task-related oscillations and their synchronization. Analyses of oscillations are dependent upon several parameters, such as the choice of size of the width of the analysis windows, the assessment of pre-task baseline activity, the methods to assess spectral densities, phase locking, and coherence. Last but not least, even details such as the definition of reference electrodes in EEG recordings need to be standardized to guarantee replicability and comparison of results.

In addition to standardization of analyses routines, new methods that allow more precise measurements of oscillations and their synchronization are crucial. Measurement of synchronized, oscillatory activity in scalp EEG and MEG data is contaminated by volume conduction and muscle artifacts that can mimic neural synchrony. One solution is the transformation of EEG and MEG data into source space.[155,156] Besides more precise estimation of synchronous, oscillatory activity, this technique has the additional advantage of substantially improving the spatial resolution of EEG and MEG measurements. Several techniques have been developed to achieve this goal. They allow the measurement of synchronization between sources that have yielded new insights into the relationship between synchronous, oscillatory activity and cognitive processes.[76,156]

The majority of studies on schizophrenia have so far concentrated on high-frequency oscillations but because of the interdependence of high- and low-frequency activity, the latter deserve equal attention, as well as the relations between the different frequency bands. As discussed above, theta oscillations are crucially involved in learning, memory, and executive processes, and there is extensive evidence that these processes reflect core domains of pathology in schizophrenia.

Oscillations as a Biomarker for Disturbed Network Activity in Schizophrenia

The search for biomarkers that provide an objective and quantifiable index of network activity is an important target of schizophrenia research.[157] Biomarkers may potentially provide an objective measure toward the diagnosis, detection, and therapeutic response of a clinical syndrome. Moreover, identification of specific biological pathways will be crucial toward the development of targeted, pharmacological intervention that adjusts altered neural oscillations in neuropsychiatric disorders.

Neural oscillations may be particularly suited for this purpose because much is already known about the underlying neurotransmitter systems involved in the generation of oscillations. Manipulation of neurotransmitter systems in in vitro experiments (see Roopun et al[153]), eg, allow a direct test of the involvement of specific receptor systems in the generation of abnormal rhythmic activity that provide critical tests for pathophysiological mechanisms in schizophrenia.

However, there are concerns regarding the specificity of altered neural oscillations that may reduce their potential utility as a biomarker for schizophrenia. Abnormal oscillations are associated with a wide range of neuropsychiatric syndromes, such as autism, Alzheimer disease, and epilepsy,[143] suggesting that abnormal rhythmic activity may represent a core feature of neuropsychiatric disorders that involve changes in cognitive functions. The overlap between abnormal neural oscillations in schizophrenia and other clinical syndromes is consistent with the fact that numerous putative biomarkers in schizophrenia have also been found to be abnormal in other psychiatric syndromes.[157] Although overlap between existing nosological entities is plausible, there are distinct differences between Alzheimer disease, schizophrenia, and autism, with respect to the developmental profile, their phenomenology, and the associated cognitive dysfunctions.

In order to identify the similarities and differences between the abnormal patterns of rhythmic activity associated with schizophrenia and other major psychiatric syndromes, we suggest that future studies should compare data from schizophrenia patients with other clinical populations. While it is conceivable that the present methods still lack the sensitivity to detect subtle differences in neural oscillations between different syndromes, we believe that novel methodological approaches adapted from the field of nonlinear dynamics, such as the analyses of cross-frequency interactions and advanced source-analyses techniques, may achieve this goal.

Neurodevelopment, Neural Oscillations, and Schizophrenia

There is consensus in the literature that schizophrenia is likely the result from an abnormal development of cortical networks, possibly involving an early pre- or perinatal insult associated with later bifurcations of maturational events that lead to the emergence of psychosis during the transition from adolescence to adulthood.[141,158]

It is conceivable that abnormal oscillations and deficient synchrony are not solely the consequence of developmental disturbances but are also one of the causes of abnormal development of neuronal networks. Oscillations and the concomitant generation of synchronized neuronal activity play a crucial role in the activity-dependent self-organization of developing networks. The development and maturation of cortical networks critically depend on neuronal activity, whereby synchronized oscillatory activity plays an important role in the stabilization and pruning of connections.[159] It is to be expected that these essential developmental processes become impaired when rhythm- and synchrony-generating mechanisms are dysfunctional. We face a classical vicious circle.

Imprecise synchrony leads to imprecise connectivity that can only support imprecise temporal dynamics. It is thus conceivable that the marked increases of beta and gamma synchronization that normally occurs toward the end of adolescence cannot be achieved. This would agree with the fact that schizophrenia manifests itself preferentially toward the end of adolescence, when the temporal precision of synchronous high-frequency oscillatory activity normally reaches adult levels.

Abnormal oscillations can in principle affect all stages of brain development. During prenatal and early postnatal development, the cerebral cortex exhibits self-generated synchronized oscillatory activity that is believed to be essential for the shaping of cortical circuits (for a review, see Khazipov and Luhmann[160]). Accordingly, abnormal neural oscillations during early development may be one critical factor that leads to abnormal cortical networks that in turn lead to subtle changes in cognitive and motor functions that have been reported in children who are at risk for the development of schizophrenia.[161]

Furthermore, there is emerging evidence that neural oscillations undergo substantial changes during normal adolescent development that may be related to the emergence of psychotic symptoms. In a recent study, we were able to show that well-synchronized, oscillatory activity in the theta-, beta-, and gamma-band emerges relatively late during the transition from adolescence to adulthood,[162] suggesting that late adolescence is a critical development period during which the temporal patterning of brain activity reaches adult levels. These data are consistent with late maturational changes in signaling systems that are involved in the generation of neural oscillations, such as GABAergic interneurons[137] and NMDA-dopamine interactions.[163] Moreover, in this developmental period, one also observes changes in myelination patterns and the ratio between gray and white matter, suggesting ongoing reorganization of circuitry.[164]

Because of the evidence that synchronous oscillatory activity plays a crucial role in the selection and pruning of developing cortical connections, further research is required in animal models and in at-risk subjects that closely examine the putative contribution of abnormal development of neural synchrony in schizophrenia. The hypothesis needs to be examined that early pre- or postnatal developmental errors initiate a vicious circle that jeopardizes the self-organizing developmental process required for the expression of normal connectivity patterns. The assumption is that genetic or epigenetic disturbances of the mechanisms responsible for the generation of temporally structured activity patterns (oscillations in the different frequency bands and their synchronization) impede the activity-dependent specification of developing circuitry which in turn leads to abnormal temporal patterns. One possibility is that this vicious developmental circle leads to a decompensation of the system once developmental processes come to an end and can no longer compensate through self-organizing processes for the accumulation of connection errors.

Summary

The review has highlighted that neural networks tend to engage in synchronized oscillatory activity in the theta-, alpha-, beta-, and gamma-frequency ranges that support a wide range of cognitive functions. Specifically, neural oscillations facilitate synchronization which may in turn serve as tag of relatedness for the formation of distributed assemblies that underlie coherent action and cognition. Moreover, an oscillatory patterning of activity allows the exploitation of phase space for the encoding of information.

As the data indicate schizophrenia appears to be associated with abnormal oscillatory activity in a wide range of frequencies and with disturbed large-scale synchronization of oscillations. Moreover, these are consistently associated with core cognitive dysfunctions and symptoms of the disorder, suggesting a close, perhaps even causal, relation. If so, this has important implications for the understanding of pathophysiological mechanisms and diagnosis and, hopefully, also for the treatment of the disorder.

In order to increase the utility of neural oscillations and synchrony as a biomarker in schizophrenia, standardization and further development of EEG and MEG analysis techniques are essential. Comparison with other neuropsychiatric syndromes might furthermore identify commonalities and differences in biological pathways that will be crucial for the advancement of targeted, pharmacological interventions. Finally, the neurodevelopmental hypothesis of schizophrenia is consistent with the involvement and possible dysfunction of neural oscillations in early development of cortical circuits and with the delayed manifestation of the disorder in late adolescence.

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