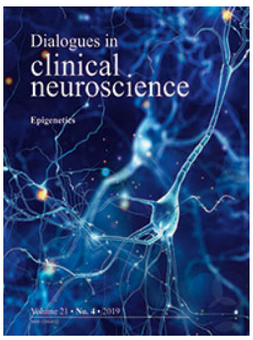

Dialogues in Clinical Neuroscience

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tdcn20

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To cite this article: Peter J. Uhlhaas & Wolf Singer (2013) High-frequency oscillations and the neurobiology of schizophrenia, Dialogues in Clinical Neuroscience, 15:3, 301-313, DOI: 10.31887/DCNS.2013.15.3/puhlhaas

To link to this article: https://doi.org/10.31887/DCNS.2013.15.3/puhlhaas

High-frequency oscillations and the neurobiology of schizophrenia

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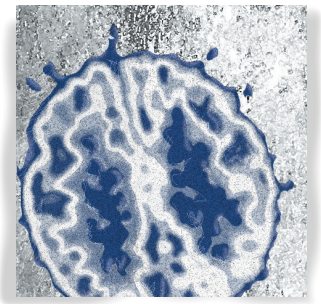

Neural oscillations at low- and high-frequency ranges are a fundamental feature of large-scale networks. Recent evidence has indicated that schizophrenia is associated with abnormal amplitude and synchrony of oscillatory activity, in particular, at high (beta/gamma) frequencies. These abnormalities are observed during task-related and spontaneous neuronal activity which may be important for understanding the pathophysiology of the syndrome. In this paper, we shall review the current evidence for impaired beta/gamma-band oscillations and their involvement in cognitive functions and certain symptoms of the disorder. In the first part, we will provide an update on neural oscillations during normal brain functions and discuss underlying mechanisms. This will be followed by a review of studies that have examined high-frequency oscillatory activity in schizophrenia and discuss evidence that relates abnormalities of oscillatory activity to disturbed excitatory/inhibitory (E/I) balance. Finally, we shall identify critical issues for future research in this area.

Dialogues Clin Neurosci. 2013;15:301-313.

Neural oscillations in large-scale networks

The majority of cognitive and perceptual functions are based on the coordinated interactions of large numbers of neurons that are distributed within and across different specialized brain areas. A fundamental, yet unresolved, problem of modern neuroscience is how this coordination is achieved. One possibility is that neural oscillations at low- (theta, alpha) and high- (beta/gamma) frequency ranges facilitate the transient formation of large-scale networks that represent the neural correlates of a cognitive content or a motor program.[1,2]

In recent years, oscillatory activity and related synchronization phenomena have received a renewed interest in cognitive neuroscience. This is because of the evidence that synchronization and phase locking gate communication among neurons[3] and thereby can support the dynamic configuration of functional networks.[2,4,5] While

Keywords: *oscillations; gamma; synchrony; cognition; schizophrenia; neurobiology*

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Selected abbreviations and acronyms

AMPA	*2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-y) propanoic acid*
E/I balance	*excitatory/inhibitory balance*
GABA	*γ-aminobutyric acid*
MEG	*magnetoencephalography*
NMDA	*N-methyl-D-aspartate*
PV	*parvalbumin*
SCZ	*schizophrenia*
TMS	*transcranial magnetic stimulation*

the first demonstrations of rhythmic activity were already obtained by investigators in the early 20th century,[6,7] evidence for a potential function was only established many decades later.

An important link between oscillations and cortical computations was the discovery that oscillatory rhythms in the gamma range (30 to 80 Hz) establish precise synchronization of distributed neural responses. Gray and colleagues[4] showed that action potentials generated by cortical cells align with the oscillatory rhythm in the gamma-band range. This has as a consequence that neurons participating in the same oscillatory rhythm synchronize their discharges with very high precision. Thus, high-frequency oscillations facilitate neuronal synchronization.

As a result of these discoveries, initial research focused on the relationship between gamma-band activity and perceptual processes (for a review see ref 8). However, it soon became clear that context and goal-dependent synchronization of neural oscillations was not restricted to visual responses and the gamma-frequency band but also occurred at lower frequencies (beta, alpha, theta)[9,10] and in a large number of brain structures in association with a wide range of cognitive and executive processes involving highly distributed processes in large-scale networks[1,2] *(Table I)*. More recently, these tight correlations between synchronized oscillations and higher cognitive functions prompted investigations of synchronization phenomena in pathological brain states.[11]

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[2] (for an overview of core concepts of neuronal dynamics see *Table II*). Support for the need to distinguish between local oscillatory versus long-range synchronization processes comes from studies that have examined the frequencies at which neuronal ensembles oscillate. Local processes tend to be associated with high-frequency oscillations above 30 Hz, the gamma band, while long-range interactions tend to involve syn-

	Theta (4-7 Hz)	Alpha (8-12 Hz)	Beta (13-30 Hz)	Gamma (30-200 Hz)
Anatomy	Hippocampus, prefrontal cortex, sensory cortex, limbic system	All cortical structures thalamus, hippocampus	All cortical structures, subthalamic nucleus, hippocampus basal ganglia, olfactory bulb	All cortical structures, hippocampus, retina, olfactory bulb, tectum, basal ganglia
Function	Memory, synaptic plasticity, top-down control long-range synchronization	Inhibition, attention, long-range synchronization	Sensory gating, attention perception, motor control long-range synchronization top-down control, consciousness	Perception, attention, memory, consciousness, synaptic plasticity, motor control

Table I. Neural oscillations in networks.

Measure	Definition
Neural oscillation	Rhythmic neural activity within a circumscribed frequency range
Spectral power	Reflects the amplitude of neural oscillations computed through a time-frequency transformation (TFT)
Phase	Phase is a way of quantifying the temporal relation between two oscillatory processes, eg, the temporal offset of the respective oscillation cycles
Phase synchrony	Measures the covariance of phase-values between two oscillatory signals disregarding amplitude
Local synchrony	A measure of local integration (~ 1 cm) which is typically reflected in fluctuations of the oscillation amplitude
Long-range synchrony	Synchronizations between widely separated brain regions (> 2 cm) as reflected, for example, in phase-synchrony
Cross-frequency coupling	Modulation of phase or amplitude of one oscillatory process by another oscillatory process

Table II. Key concepts of neuronal dynamics.

chrony in lower frequency bands comprising theta (4 to 7 Hz), alpha (8 to 12 Hz), and beta (13 to 30 Hz) frequencies.[12,13] One reason could be that larger networks cannot support synchronization with very high temporal precision as a result of long conduction times. This is because lower frequencies put fewer constraints on the precision of timing since the phases of increased and reduced excitability are longer.[14]

In addition, evidence is accumulating that networks oscillating at different frequencies can become associated by cross-frequency coupling.[15] Such interactions can take several forms and lead to correlated power/power fluctuations or phase-amplitude coupling.[16] In the latter case, the amplitude of a high-frequency oscillation is modulated by the phase of a slower rhythm. Thus, in a number of studies the power of gamma oscillations has been shown to be modulated by the phase of theta or alpha-band oscillations.[17,18]

Generation of high-frequency oscillations in large-scale networks

The formation of functional networks through synchronized oscillations at beta/gamma-band frequencies is critically depended upon the dynamics of excitatory and inhibitory networks (E/I-balance) that establish transient links between ensembles of neurons through the modulation of the level of neuronal responsiveness.[19] Recent insights into the cellular mechanisms underlying these dynamics and, more specifically, the generation of rhythms and the establishment of long-range synchrony, make it now possible to engage in a targeted search for pathophysiological mechanisms of diseases associated with abnormal neuronal dynamics such as schizophrenia (SCZ).

Previous experimental and theoretical work had already provided support for the notion that γ-aminobutyric acid (GABA)-ergic neurons play a pivotal role in the primary generation of high-frequency oscillations and their local synchronization,[20-22] whereas glutamatergic inputs appear to control their strength, duration, and long-range synchronization.[23]

GABAergic interneurons, especially those expressing the calcium binding protein parvalbumin (PV), play a particularly important role in the generation of high-frequency oscillations because of their fast-spiking characteristics and the short time constants of synaptic interactions mediated by these cells.[24] In a landmark paper, Sohal and colleagues[22] probed the influence of up- and downregulation of PV interneurons on gamma-band oscillations in mice. Inhibition of PV interneurons led to an immediate suppression of 30- to 80-Hz oscillations while 10- to 30-Hz oscillations increased in power. In contrast, increasing PV interneuron mediated feedback inhibition by boosting principal cell activity enhanced gamma-band power.[25]

Recent studies have also examined the specific role of glutamatergic inputs to PV interneurons for the generation of coordinated network activity. Carlen et al[26] examined the effect of deleting N-methyl-D-aspartate (NMDA) NR1 receptors on PV interneurons applying an optogenetic approach. Mice with a reduced expression of NR1 subunits were characterized by increased spontaneous 36- to 44-Hz activity in somatosensory cortex compared with control animals while showing reduced gamma-band activity during sensory stimulation. This change in neuronal dynamics was accompanied by dysfunctions in habituation, working memory, and associative learning. Optic stimulation of PV interneurons revealed diminished spike synchronization as well as increased spike latency and variance in spike timing.

Further evidence that 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-y) propanoic acid (AMPA) and NMDA receptor-mediated activation of PV interneurons is essential for the generation of high-frequency oscillatory activity, and its synchronization has been obtained in the hippocampus. Reduction of the GLuR-D receptor leads to a decrease of AMPA-mediated currents in PV interneurons and reduced power of oscillations in the 20- to 80-Hz range which is accompanied by a deficit in working memory.[27] In addition, selective ablation of the NMDA NR1 subunit in PV interneurons is associated with a significant reduction of power, stability, and rhythmicity of theta oscillations and an enhancement of gamma oscillations in CA1.[28]

While the reciprocal connections between excitatory and inhibitory neurons determine the strength and duration of the oscillations and mediate local synchronization, long-range synchronization of spatially segregated cell groups has been attributed mainly to the action of excitatory pathways that target both excitatory and inhibitory neurons.[14,29] Specifically, modeling and experimental evidence suggests that generation of long-range synchronization is dependent on AMPA-type glutamate receptor.[29]

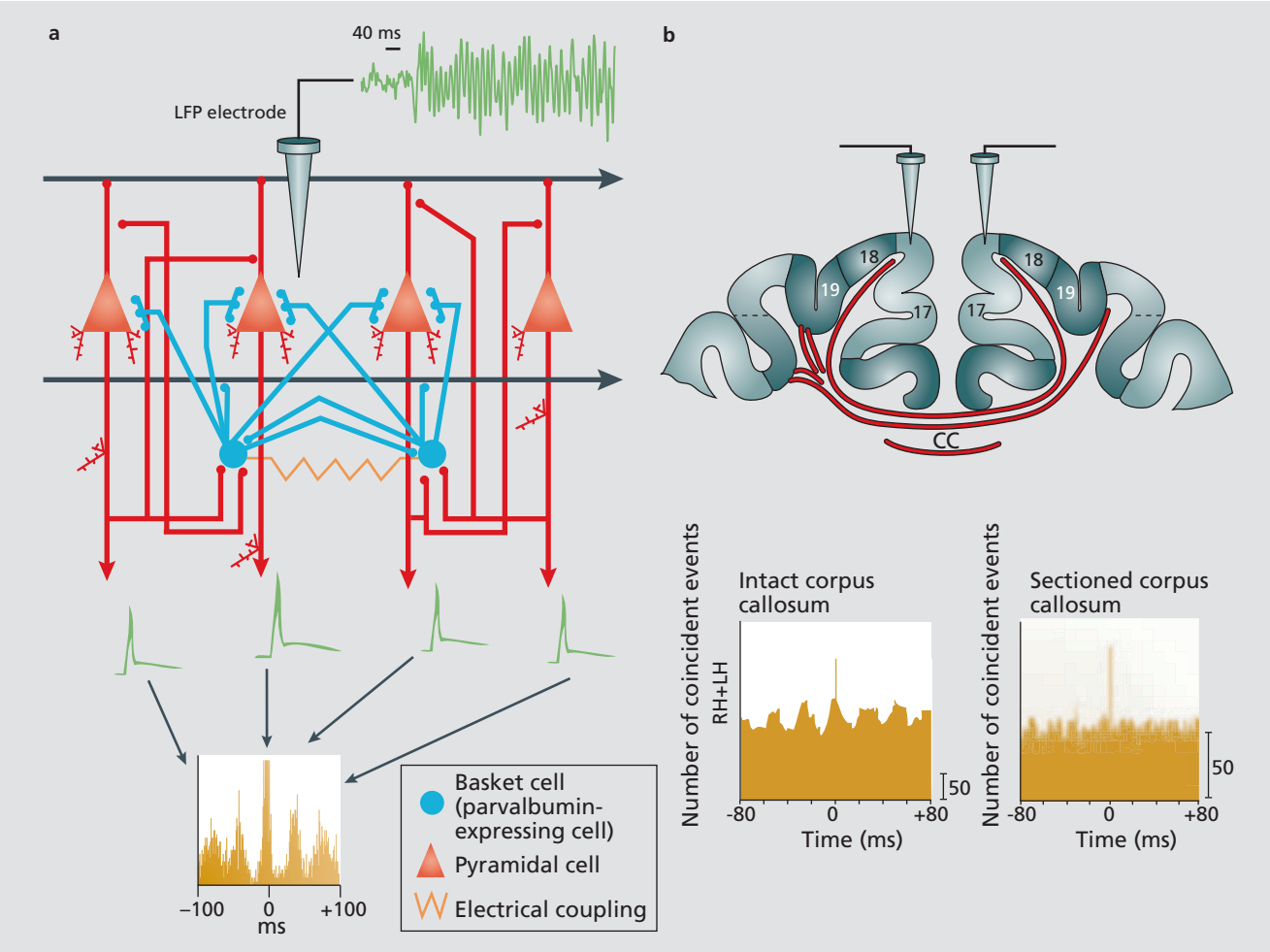

Figure 1. Mechanisms underlying the generation of gamma oscillations and synchrony. a) A neocortical circuit involved in the generation of gamma-band oscillations. Generation of synchronized neural activity in neocortical circuits is dependent on negative feedback inhibition of pyramidal cells by GABA (γ-aminobutyric acid)-ergic interneurons that express the Ca2+-binding protein parvalbumin. These receive glutamate receptor-mediated feedforward excitatory inputs, which makes them susceptible to changes in glutamatergic drive. Transient excitation of parvalbumin-expressing interneurons leads to a depolarization of many interneurons, which are themselves reciprocally interconnected through gap junctions and chemical GABAergic synapses. Electrical synapses are important for the synchronization of network activity because they rapidly propagate activity. Conversely, mutual inhibition through chemical synapses is a crucial determinant of the network frequency, as the duration of inhibitory postsynaptic potentials determines the dominant oscillation frequency. The resulting rhythmic inhibitory postsynaptic potentials can synchronize the firing of a large population of pyramidal neurons as the axon of an individual GABAergic neuron makes multiple postsynaptic contacts onto several pyramidal cells. This phasic inhibition leads to the synchronization of spiking activity that can be recovered with a cross-correlogram. A local field potential (LFP) recorded with an extracellular electrode reflects the average of the transmembrane currents that fluctuate at gamma-band frequency. Its extracranial counterpart can be reflected in electroencephalography (EEG) or magnetoencephalography (MEG) signals. b) Cortico-cortical connections mediate long-distance synchronization. The relationship between the integrity of the corpus callosum and interhemispheric synchronization of gamma-band oscillations in the cat visual cortex is illustrated. Recording electrodes were placed in the vicinity of the border of areas 17 and 18 of the right (RH) and left (LH) cortical hemispheres during stimulation with a light bar. In the bottom panels are cross-correlograms between responses from different recording sites in the LH and RH that indicate the degree of interhemispheric synchronization. When the corpus callosum was intact (left-hand panel), strong interhemispheric synchronization occurred with no phase lag between the LH and RH recording sites. Sectioning of the corpus callosum (right-hand panel) abolished interhemispheric synchronization while leaving synchronization within hemispheres intact. These data show that synchronization can occur over long distances with high precision and is crucially dependent on the integrity of cortico-cortical connections.

More recently, evidence has emerged that long-range inhibitory projections that originate from GABAergic cells and terminate selectively on inhibitory interneurons in the respective target areas could constitute an important substrate for inter-regional synchronization.[30] Given the pace-maker function of inhibitory networks, such direct coupling could provide a very efficient mechanism for the temporal coordination of distributed processes.
In addition to GABAergic and glutamatergic circuit dynamics, modulatory systems play an important role in the gating of oscillations and synchrony. Thus, gamma oscillations and their synchronization depend critically on the activation of muscarinic acetylcholin-receptors.[31] Evidence is also available that dopamine and 5-HT modulate the prevalence of oscillations in different frequency bands.[32-35]

High-frequency oscillations in schizophrenia

Because of the close relations with underlying physiological parameters and evidence for the functional involvement of oscillatory networks in cognitive processes, there is increasing interest in the possibility that neural oscillations in SCZ may be informative for revealing the causes of cognitive deficits as well as establish potential links to the pathophysiology. Indeed, a large body of work has examined rhythmic activity during both spontaneous and task-related activity in SCZ patients with electroencephalography (EEG)/magnetoencephalography (MEG). Because of the prominent role of gamma-band activity in cognition during normal brain functioning, a particular focus has been on the investigation of high-frequency activity in patient populations.

Gamma band (30-100 Hz)

The overwhelming evidence points to a reduction of gamma-band oscillations during the execution of cognitive tasks in SCZ patients relative to controls.[36] Reductions in gamma-band amplitude have been demonstrated for a wide range of cognitive and perceptual paradigms, including working memory,[37] executive control,[38] and perceptual processing.[39,40] There is preliminary evidence that the decrease in gamma-band spectral power is independent of medication status.[38]
Recent studies have also examined the contribution of high (> 60 Hz) gamma-band oscillations to perceptual and cognitive deficits in schizophrenia. In a recent study by our group[41] *(Figure 2)*, impaired task performance during a perceptual organization task was accompanied by a widespread deficit in the power of gamma-band oscillations between 60 and 120 Hz. This deficit was associated with an effect size of d =1.26 which is in the range and above of effect sizes for event-related potentials (ERPs) that have been frequently investigated in SCZ, such as the Mismatch Match Negativity (MMN).[42] Similar results supporting the relevance of dysfunctions in oscillatory activity >60 Hz have been reported by Tsuchimoto et al[43] and Hamm and collegues[44] who examined high gamma-band activity during an auditory steady state (ASS) paradigm.
Of particular importance is the evidence that not only the amplitude but also the synchronicity of gamma oscillations is reduced in SCZ patients.[45,46] This is relevant because a large body of evidence suggests that the functional networks underlying perception, attention, and executive processes rely on dynamic coordination by phase locking of oscillatory activity originating in widely distributed cortical areas.[2,5] Accordingly, reduced long-range phase synchronization could lead to a functional disconnection syndrome which has been proposed by several theorists to constitute a core impairment in SCZ.[47]
A potentially informative way of probing the ability of neural circuits to support the generation of high-frequency oscillations is the application of TMS in combination with EEG. Ferrarelli et al[48] applied transcranial magnetic stimulation (TMS) over four cortical areas and analysed stimulus-evoked EEG-activity for peak-frequency, synchrony as well as amplitude of neural oscillations *(Figure 2)*. In controls, TMS pulses elicited robust activity in the 25- to 35-Hz frequency range over frontal electrodes while premotor, motor, and parietal cortex were characterized by beta-band activity. In SCZ patients, the peak frequency of evoked oscillations over frontal electrodes was characterized by a reduction of ~10 Hz compared with controls which correlated with both positive and negative symptoms as well as with neurocognitive impairments. In a previous study,[49] the same group demonstrated that TMS-elicited gamma-band oscillations propagated less beyond the area of stimulation in SCZ patients than in controls. One reason for this reduced spreading of activity could be impaired synchrony which should reduce propagation of neuronal activity.

Recent studies point to the possibility that the pattern of spontaneously occurring gamma-band oscillations may differ from that associated with cognitive processing and entrainment through TMS. Kikuchi et al[50] examined resting-state EEG data in medication-naïve, first-episode patients with SCZ and healthy controls and found significantly elevated gamma-band power over frontal electrodes in patients. A similar finding was reported by Spencer et al[51] who showed significantly increased ~40 Hz baseline source power in chronic patients with schizophrenia. However, a study with MEG which investigated resting-state activity in chronic SCZ patients could not confirm this finding.[52]

However, an important issue in regard to the interpretation of the elevated spontaneous high-frequency activity, and to task-related activity in general, is the question whether the changes during resting-state reflect an oscillatory process. An oscillation is characterized by a frequency-specific and narrow-banded modulation of spectral power,[53] while a broad band increase of high frequencies, at least in electrocorticography and perhaps also MEG recordings, is considered to reflect the sum of local synaptic events and action potentials and hence just the level of local cortical activation.[54]

Beta-band oscillations in SCZ

Oscillations in the 13- to 30-Hz frequency range have been associated with the formation of widely distributed functional networks in the context of polymodal sensory processing, sensory-motor coordination, and the maintenance of posture during normal brain functioning.[55] More recently, Engel and Fries[56] have suggested that synchronized beta-band activity serves the

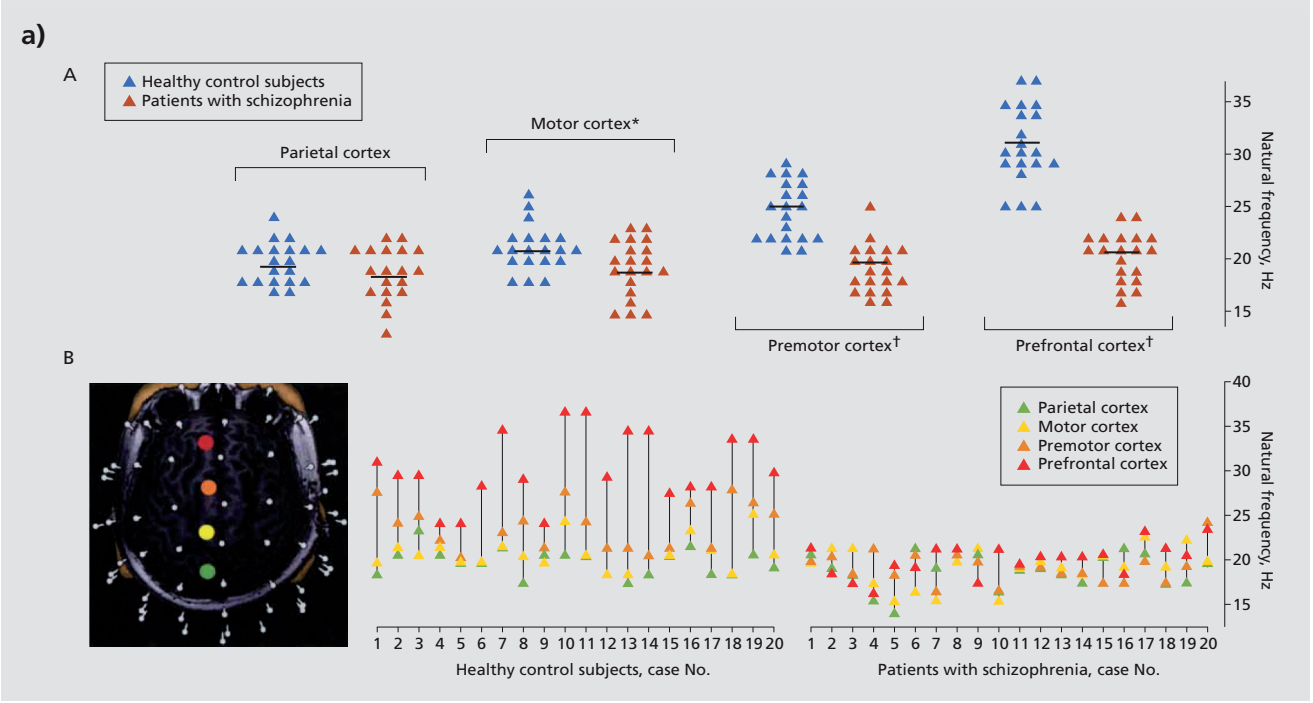

Figure 2. High-frequency oscillations in schizophrenia patients.

a) TMS-elicited high-frequency oscillations in controls and SCZ patients: single-pulse transcranial magnetic stimulation over 4 cortical areas was associated with peak frequencies between 20 and 30 Hz in controls 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 4 cortical areas. Horizontal lines indicate mean natural frequency values of each group for each cortical area. *$P \leq .05$; † $P \leq .001$. The frequency of prefrontal cortex oscillations was inversely related to the level of positive symptoms on the Positive and Negative Syndrome Scale (PANSS) (A) as well as to the reaction time of correct responses on a word memory task (B) in patients with schizophrenia.

Adapted from ref 48: Ferrarelli F, Sarasso S, Guller Y, et al. Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. *Arch Gen Psychiatry*. 2012;69:766-774. Copyright © American Medical Association 2012

maintenance of the actual sensorimotor or cognitive states.

In contrast to gamma-band activity, the role of beta-band oscillations has been less explored in SCZ. Uhlhaas et al[45] showed a pronounced impairment in long-range synchronization deficits in chronic SCZ patients during perceptual organization This is consistent with evidence highlighting the role of beta-band oscillations in establishing transient patterns of interactions across larger distances in oscillatory networks.[14]

Further evidence for an involvement of disturbed beta-band oscillations in cognitive deficits in SCZ was reported by Ford and colleagues.[57] The authors hypothesized that SCZ patients may fail to adequately predict the causes of sensory perception which could, for example, lead to self-generated speech acts being assigned to an external source as the result of a failure in the efference copy.[58] To investigate this hypothesis, Ford et al recorded EEG-activity prior to self-generated speech vs a perception condition during which self-generated utterances were played back to the participants. Results showed that the phase-locking of beta-band oscillations was larger in the prespeech than in the prelistening interval. In SCZ patients, however, beta-band synchrony in the prespeech condition was reduced relative to controls and this reduction was particularly pronounced in patients with a history of auditory hallucinations. The authors suggest that the synchronized beta-band activity reflects a forward model which dampens auditory responsiveness to self-generated speech. In SCZ patients, this forward model is impaired and, as a result, self-generated speech acts may be experienced as an externally generated percept.

This hypothesis is consistent with recent evidence that beta-band oscillations mediate mainly top-down activity,

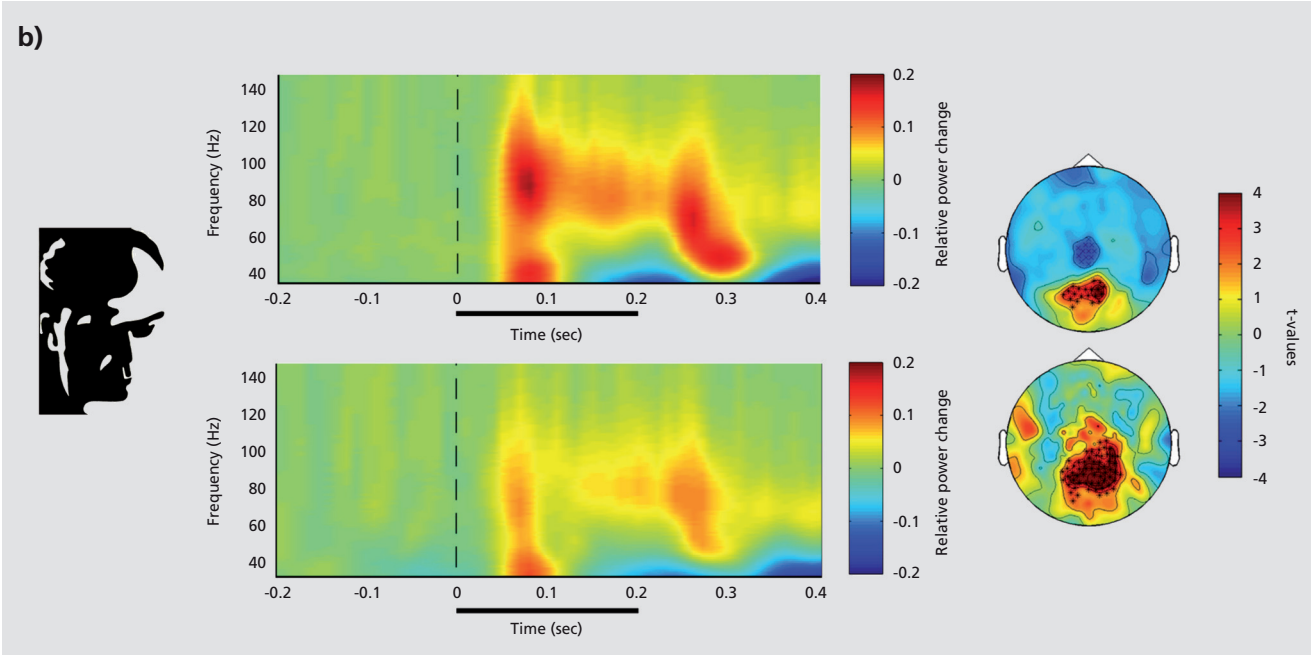

Figure 2. Continued

b) High-frequency oscillations during perceptual organization in SCZ. Left panel: Time-frequency representations and topographies of gamma-band spectral power of magnetoen-data in response to Mooney faces for controls (top) and chronic SCZ patients (bottom). The gamma-band signal is expressed as relative power change in the post-stimulus time window compared with baseline, averaged across all channels. The topographies (middle panels) display the results for a nonparametric ANOVA 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 controls while blue color suggests increased gamma-band power in schizophrenia patients relative to controls. The topographies depict corrected t-values and the channels that form a statistically significant cluster are indicated (*, $P< 0.001$; x, $P< 0.05$). Right panel: Correlation between high gamma-band power and disorganization. The scatter-plot shows the relationship between high (60 to 120 Hz) gamma-band power in the 50- to 350-ms time window over positive channels and the disorganization component of the positive and negative syndrome scale.

Adapted from ref 41: Grützner G, Wibral M, Sun S, et al. Deficits in high-frequency (>60 Hz) gamma oscillations during visual processing in schizophrenia. *Front Hum Neurosci*. In press. Copyright © Frontiers Research Foundation

and hence are critically involved in the prediction of upcoming sensory events while gamma-band oscillations, at least in sensory cortices, are involved in feedforward signaling.[59] This distinction is supported by the differential laminar expression of beta and gamma-band oscillations, respectively.[60] In vitro and in vivo recordings show that gamma-band activity is prominently generated in superficial layers 2/3 of the cortex,[61] the main origin of feed forward connections, whereas beta oscillations are mainly found in infragranular layers,[62] from which feedback projections originate preferentially.

High-frequency oscillations and the neurobiology of schizophrenia

Significant progress has been made in the identification of the mechanisms generating high-frequency oscillations in local circuits, and this has generated in turn research on the effects of genetic, pharmacological, and developmental manipulations of high-frequency oscillations.[63] The results of these studies support the view that neural oscillations are ideally suited as a measure to establish links between genes, physiology, and behavior in SCZ, and eventually may contribute to the identification of pathophysiological mechanisms.

E/I balance parameters

Recent work has focused on the alteration of mechanisms that influence E/I-balance parameters as one possible cause for deficits in high-frequency oscillations. In this context it is noteworthy that the messenger RNA for the enzyme GAD 67 which synthesizes GABA is reduced in several cortical areas in SCZ patients.[64] Moreover, this decrease is accompanied by reduced expression of the GABA membrane transporter 1 (GAT1).[65] Further evidence for a dysfunction in GABAergic transmission comes from magnetic resonance spectroscopy (1H-MRS) studies which have shown abnormal GABA levels in SCZ patients,[66] especially at illness onset.

Another mechanism which is crucial for the generation of high-frequency oscillations and influences the E/I-balance is the AMPA- and NMDA-receptor-mediated activation of PV interneuron. Dysfunctions of NMDA-receptor mediated transmission in SCZ have been suggested by genetic linking studies[67] as well as by the effects of pharmacological NMDA-receptor blockade on cortical dynamics and cognition. In healthy controls, ketamine, an antagonist of the NMDA receptor, elicits the full range of psychotic symptoms and impairments in cognitive processes.[68] Furthermore, blockade of NMDA receptors in animal models has been shown to induce aberrant high-frequency oscillations in extended cortical and subcortical networks[69] which is consistent with the preliminary evidence for an elevation of resting state high-frequency activity in EEG data from patient populations.[50]

Anatomy

Abnormal cortico-cortical connections are a likely cause for the impaired long-range synchronization observed in SCZ patients. Studies involving lesions and developmental manipulations indicate that gamma-band activity and its synchronization are mediated by cortico-cortical connections. These long-range, predominantly excitatory pathways, not only link reciprocally cells situated in the same cortical area but also cells distributed across different areas and even across the two hemispheres[70] *(Figure 1)*. Accordingly, abnormalities in the number and organization of anatomical connections should impair long-range synchronization. Early evidence from in vivo and post-mortem studies suggests that white matter volume and integrity are altered in patients with schizophrenia.[71] This evidence is further supported by the more recent findings that revealed alterations in the organization of the connectome in SCZ.[72]

Genetics

SCZ is associated with a genetic predisposition and there is evidence that high-frequency oscillations also exhibit genetically determined fingerprints that are highly specific for individual subjects.[73] It is thus of particular interest that auditory evoked gamma-band activity is not only reduced in SCZ patients but also in first-degree relatives,[74] as well as in unaffected, monozygotic twins,[75] suggesting that high-frequency oscillations qualify as an endophenotype.

Following this line of reasoning, several animal models have been examined for the effects of risk genes on E/I balance parameters and changes in high-frequency oscillations. "Disrupted-In-Schizophrenia-1" (*DISC1*) is a gene whose chromosomal translocation is associated

with an increased incidence of major mental disorders, including SCZ.[76] Hikida and colleagues[77] generated a transgenic mouse with a dominant-negative (DN) truncated *DISC1* and examined several anatomical parameters. DN-DISC1 mice were characterized by a selective reduction of PV immunoreactivity, PV being a Ca++-scavenger with preferential location in fast-spiking GABAergic-neurons that play a major role in the generation of high frequency oscillations.

Another SCZ-susceptibility gene, Neuregulin-1 (*NRG-1*), has been shown to increase the power of gamma-band oscillations in hippocampal slices.[78] This enhancement is mediated through the activation of ErbB4 receptors on PV interneurons. Finally, *DTNBP1* is a gene that encodes the protein dystrobrevin-binding protein 1 (dysbindin-1) and has been found to be reduced in SCZ patients.[79] Reduced dysbindin-1 expression in mice caused reduced phasic inhibition of PV cells which in turn was associated with impaired auditory evoked gamma-band activity.[80]

The relationship between genetic risk factors and long-range synchronization was examined in a study by Sigurdson et al.[81] The authors measured the synchronization between the hippocampus and the prefrontal cortex during a working memory (WM) task in Df(16)A1/– mice which provide a genetic model for the microdeletion on human chromosome 22 (22q11.2). The 22q11.2 microdeletion is one of the strongest genetic risk factors for SCZ.[82] Df(16)A1/– 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 SCZ impacts directly on large-scale interactions which in turn could underlie the cognitive deficits associated with the disorder.

Perspectives for high-frequency oscillations in schizophrenia

The available evidence suggests that SCZ is associated with aberrant high-frequency oscillations which could potentially explain core features of the disorders, such as the pronounced impairments of cognitive functions. Importantly, available evidence also establishes close relations between alterations in E/I balance parameters and oscillatory activity. These novel data emphasize the close relations between genetics, signaling cascades—especially those involving inhibitory mechanisms and NMDA receptors—and abnormal brain dynamics. Because of the improved knowledge about the mechanisms generating high- frequency oscillations, this provides a valuable basis for hypothesis-driven analysis of the pathophysiological origins of SCZ that may eventually lead to novel and targeted treatments. Because it is perhaps the right time to engage in such an ambitious endeavor, we would like to discuss a number of important issues that we believe are worth to be considered in the context of such a research program.

Towards a systems-oriented understanding of neuronal dynamics

So far, electrophysiological studies in SCZ have largely focused on obtaining amplitude estimates of spectral power at the sensor level. While the fluctuation of gamma-band power is an important variable that reflects changes in the E/I balance, it nonetheless provides only limited insights into the dynamics of extended cortical circuits. Thus, future studies should employ novel measures that allow for the testing of time and frequency sensitive neuronal interactions between cortical regions. Preliminary results obtained with scalp-recorded EEG data have highlighted alterations in long-range synchronization at beta- and gamma-band frequencies.[45,46] However, because of the methodological problems and low spatial resolution of these approaches, we suggest that this promising approach should be complemented by source-reconstruction of EEG and MEG data which allow better insights into the dynamics and organization of extended functional networks.

Further research into neural oscillations should also take into account the possibility that the impairments in high-frequency oscillations are related to alterations in low-frequency bands, in particular in the theta and alpha frequency ranges, which have been less explored so far. There is increasing evidence that neural oscillations exhibit cross-frequency coupling, suggesting that populations of neurons oscillating at different frequencies interact with each other, forming nested assemblies.[15] Such coupling has been proposed to be responsible for correlated amplitude fluctuations of oscillations in different frequencies and for the modulation of the amplitude of a fast oscillatory process by the phase of a low-frequency oscillation.[17,18]

The potential relevance of abnormal cross-frequency interactions has only been investigated recently. Spencer

et al[83] reported a reduced modulation of gamma-band somatosensory evoked potentials (SSEPs) in the auditory cortex in schizophrenia through the phase of delta oscillations, while White et al[84] observed decreased interactions between alpha- and gamma-band activities during a somatosensory task. However, more recent results could not support impaired cross-frequency interactions between high and low frequency oscillations during auditory SSEPs.[85] Accordingly, this remains an important area for future research.

Neural oscillations as a biomarker

Increasing evidence suggests that alternations in high-frequency activity may not be specific to SCZ. Impairments in neural synchrony have been demonstrated in bipolar disorder because auditory steady-state responses[86] as well as long-range coherence[87] are significantly impaired, paralleling findings in patients with schizophrenia.[45,88] This is consistent with a substantial overlap between the two syndromes with respect to biological vulnerability.[89] Yet, dysfunctional gamma-band activity may not extend to other disorders, such as personality or mood disorders.[90]

We would like to note that the wide range of oscillation frequencies provides a rich parameter field that can likely be exploited to delineate disorder-specific neuronal dynamics. If successful, such frequency specific markers could then be used to identify the underlying physiological mechanisms and perhaps be used to assign patients to novel disease categories. Fingerprints of neuronal dynamics, such as alterations in the frequency, temporal precision, phase locking, and topology of neuronal oscillations, both during processing and resting state, may provide novel criteria for differential diagnoses. Resting-state activity may be particularly suited for this purpose because it has been shown to be highly structured,[91] genetically determined,[92] and to most likely reflect the coherent activation of functional networks that maintain representations of internal states.[93]

Implications for treatment and prevention

The data reviewed may already have implications for a targeted search of novel treatments and preventive efforts. In view of the converging evidence for disturbed E/I balance and the resulting changes in high-frequency oscillations that are caused by alterations in GABAergic and glutamatergic neurotransmission, it might be rewarding to search for drug targets that restore E/I balance. Evidence on the efficacy of this approach is still sparse with some treatments showing modest benefits[94] while others failed to improve, for example, cognition in patients with schizophrenia.[95]

Treatment strategies should also consider that circuit dynamics may undergo changes during the course of the disorder. Accordingly, different interventions may be required at different phases.[96] Proton magnetic resonance spectroscopy (1-H MRS) has revealed, for example, that GABA and glutamate concentrations are increased in unmedicated, first-episode patients but reduced in chronically medicated patients,[66] suggesting that E/I balance shifts during the course of the illness. Another possibility for therapeutic interventions is suggested by the protracted developmental trajectory of brain dynamics that undergoes marked changes in late adolescence. The manifestation of schizophrenia during the transition from late adolescence to adulthood is preceded by an extended period of mild psychotic symptoms and cognitive dysfunctions[97,98] and improvement in therapeutic success will very likely involve early interventions that should ideally be initiated prior to the full manifestation of the clinical symptoms.

Finally, one might conceive of interventions that modulate brain dynamics by biofeedback and electrical stimulation. There is increasing evidence that transcranial magnetic and transcranial direct current stimulation (TMS/tDCS) can be applied as tools to modulate neuronal oscillations and large-scale synchrony in a frequency specific way. Polania et al[99] showed that tDCS at theta-frequency can facilitate frontoparietal synchrony, and Engelhard et al[100] showed that monkeys can be trained to selectively enhance gamma-band oscillations in the motor cortex if they are rewarded for power increases of local-field potential oscillations recorded from this area. The potential of these novel approaches for the remediation of cognitive deficits needs to be investigated further. ❑

Acknowledgments: This work was supported by the Max Planck Society and the LOEWE Grant 'Neuronale Koordination Forschungsschwerpunkt Frankfurt'.

Oscilaciones de alta frecuencia y neurobiología de la esquizofrenia

Las oscilaciones neurales en los rangos de baja y alta frecuencia constituyen una característica fundamental de las redes a gran escala. La evidencia reciente ha indicado que la esquizofrenia está asociada con la amplitud anormal y la sincronía de la actividad oscilatoria, en particular, a altas frecuencias (beta/gama). Estas alteraciones se observan tanto durante la actividad neuronal espontánea como en la relacionada con tareas, lo que puede ser importante para la comprensión de la fisiopatología del síndrome. En este artículo, se revisa la evidencia actual del deterioro de las oscilaciones de las bandas beta/gama y su participación en las funciones cognitivas y algunos síntomas de este trastorno. En la primera parte, se entrega una actualización sobre las oscilaciones neuronales durante las funciones normales del cerebro y se discuten los mecanismos subyacentes. A continuación se revisan los estudios que han examinado la actividad oscilatoria de alta frecuencia en la esquizofrenia y se discute la evidencia que relaciona las alteraciones de la actividad oscilatoria con el deterioro del balance excitatorio/inhibitorio (E/I). Finalmente se identifican los temas críticos para el futuro de la investigación en esta área.

Oscillations à haute fréquence et neurobiologie de la schizophrénie

Les oscillations neuronales de basse et de haute fréquences sont une caractéristique fondamentale des réseaux de grande échelle. D'après des données récentes, l'amplitude et la synchronisation de l'activité oscillatoire sont anormales dans la schizophrénie, en particulier aux hautes fréquences (bêta/gamma). Ces anomalies sont observées lors de l'activité neuronale de repos et de travail, ce qui peut être important pour comprendre la physiopathologie de ce syndrome. Nous analysons dans cet article les preuves actuelles de l'altération des oscillations gamma/bêta et de leur rôle dans les fonctions cognitives et certains symptômes de la maladie. Dans la première partie, nous proposons une mise à jour sur les oscillations neuronales lors de l'activité normale du cerveau et nous en étudions les mécanismes. Puis nous examinons les études qui ont analysé l'activité oscillatoire à haute fréquence dans la schizophrénie et nous discutons les preuves reliant les anomalies de l'activité oscillatoire à la perturbation de l'équilibre excitation/inhibition (E/I). Enfin, nous identifions les points cruciaux de la recherche à venir dans ce domaine.

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