

# Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology

## Review

Peter J. Uhlhaas<sup>1,2,\*</sup> and Wolf Singer<sup>1,3</sup>

<sup>1</sup>Department of Neurophysiology  
Max Planck Institute for Brain Research  
Deutschordenstrasse 46  
Frankfurt am Main, 60528  
Germany

<sup>2</sup>Laboratory for Neurophysiology and Neuroimaging  
Department of Psychiatry  
Johann Wolfgang Goethe University  
Heinrich-Hoffmann-Strasse 10  
Frankfurt am Main, 60528  
Germany

<sup>3</sup>Frankfurt Institute for Advanced Studies  
Johann Wolfgang Goethe University  
Max-von-Laue-Strasse 1  
Frankfurt am Main, 60438  
Germany

Following the discovery of context-dependent synchronization of oscillatory neuronal responses in the visual system, novel methods of time series analysis have been developed for the examination of task- and performance-related oscillatory activity and its synchronization. Studies employing these advanced techniques revealed that synchronization of oscillatory responses in the  $\beta$ - and  $\gamma$ -band is involved in a variety of cognitive functions, such as perceptual grouping, attention-dependent stimulus selection, routing of signals across distributed cortical networks, sensory-motor integration, working memory, and perceptual awareness. Here, we review evidence that certain brain disorders, such as schizophrenia, epilepsy, autism, Alzheimer's disease, and Parkinson's are associated with abnormal neural synchronization. The data suggest close correlations between abnormalities in neuronal synchronization and cognitive dysfunctions, emphasizing the importance of temporal coordination. Thus, focused search for abnormalities in temporal patterning may be of considerable clinical relevance.

### Introduction

Most of the brain's cognitive 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. Integration and segregation of neural activity needs to occur at various spatial and temporal scales, and these scales must be dynamically adjusted depending on the nature of the respective cognitive tasks.

In contrast to the large number of studies that investigated the role of synchrony in a wide range of cognitive and executive processes, relatively few investigations have examined the possible relevance of neural synchrony in pathological brain states, such as schizophrenia, epilepsy, autism, and Alzheimer's disease (AD).

Until recently, most of the investigations of electrophysiological correlates of pathological brain states concentrated on the analysis of power distributions in various frequency bands of resting-state electroencephalographic (EEG) activity, or on the search for abnormalities in averaged, event related potentials (ERPs) (John et al., 1988). Relatively few studies have examined task- and performance-related synchronization phenomena in a clinical context because the methods required for the determination of synchrony have become available only recently (e.g., Lachaux et al., 1999; Tass et al., 1998).

Therefore, we focus this review on studies that specifically investigated neural synchrony in association with circumscribed impairments in cognition in schizophrenia, epilepsy, autism, and AD. Furthermore, we review recent data on the relation between abnormal synchronization and motor deficits in Parkinson's disease (PD). In addition to the obvious medical relevance of this research, further insights into the underlying pathophysiological mechanisms are also likely to enhance our understanding of normal brain functions. Specifically, we hope that these correlations between neural synchrony and pathological brain states will shed some new light on the respective pathophysiological mechanisms and the role of synchrony in normal brain functions. We concentrate on noninvasive studies with EEG and magnetoencephalography (MEG), as these methods have the required temporal resolution to assess neural synchrony. In addition, because the database on neural synchrony established with these methods in disease-related studies is still sparse, we also review investigations based on magnetic resonance imaging (MRI) since they can provide evidence, albeit indirectly, on abnormalities of structural and functional connectivity between cortical areas that predict disturbances in large-scale synchronization.

### Distributed Processing and Neuronal Synchronization

Due to the distributed organization of sensory systems, the representation of sensory objects requires integration of responses across different cortical regions. The reason is that even basic features of an object are processed in parallel in different, specialized areas of the cortex. This intramodal integration must be complemented by mechanisms permitting binding of signals across different sensory modalities, since many objects encountered in the world are multisensory and possess, in various combinations, visual, auditory, haptic, and olfactory properties. In addition, at all levels of sensory processing, neuronal activity is shaped by top-down attentional mechanisms that dynamically select and bind sensory signals in a context-dependent way as a function of expectancies and a priori knowledge (Engel et al., 2001; Fries et al., 2001a). Finally, dynamic and flexible binding between sensory and motor areas is required to allow for the versatility of sensory-motor coordination (Roelfsema et al., 1997).

Transient synchronization of neuronal discharges has been proposed as one possible mechanism to

\*Correspondence: uhlhaas@mpih-frankfurt.mpg.de

dynamically bind widely distributed sets of neurons into functionally coherent ensembles that represent the neural correlates of a cognitive content or a motor program (Singer, 1999). This hypothesis first received experimental support from investigations on feature binding in vision (Gray et al., 1989). However, neural synchrony also seems relevant for large-scale integration of distributed neural activity since it occurs across distant cortical areas, such as, for example, across visual areas in the two hemispheres (Engel et al., 1991), and is modulated in a task- and attention-dependent way (Roelfsema et al., 1997). Furthermore, studies in human subjects combining noninvasive recording techniques such as EEG and MEG with advanced methods of time series analysis have revealed that neural synchrony is associated with cognitive functions that require large-scale integration of distributed neural activity. Examples are attention-dependent stimulus selection, multimodal integration, working memory, selective routing of activity, and conscious processing of stimuli (for a review see Singer, 1999; Schnitzler and Gross, 2005; and Varela et al., 2001). Synchronization in these studies was consistently associated with an oscillatory patterning of neuronal responses, most often in the  $\beta$ - (15–30 Hz) and  $\gamma$ - (30–80 Hz) frequency range. Subsequent research has indicated that such high-frequency oscillations are particularly effective in supporting precise synchronization of neuronal discharges (Fries et al., 2001b). 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 in the  $\beta$ - but also in the  $\theta$ - (4–8 Hz) and  $\alpha$ - (8–12 Hz) frequency range (Kopell et al., 2000; Schnitzler and Gross, 2005; von Stein and Sarnthein, 2000).

#### Measures of Oscillatory Activity and Synchrony

Recording methods that assess the activity of large populations of neurons, such as microelectrode recordings of local field potentials (LFPs) or EEG- and MEG-registrations, can only detect neuronal activity if it exhibits some degree of synchrony. Entirely uncoordinated activity would not be detectable because the currents of synaptic events, which are the major source of the measured signals (Mitzdorf and Singer, 1979), would cancel out.

In most cases, the signals recorded from neuron populations consist of oscillations that cover a broad frequency spectrum and are usually quantified by computing the relative power in distinct frequency bands. Until a decade ago, the most frequently applied technique for this spectral decomposition was the Fourier analysis. This classical method has recently been complemented by wavelet-based techniques (Bertrand et al., 1994) and multitaper analyses (Mittra and Pesaran, 1999), which are better adapted for the spectral decomposition of non-stationary time series.

In addition to analyzing the frequency spectrum of spontaneous oscillations, it is of interest to determine the time course of stimulus- or task-related oscillations. Two forms of stimulus-related oscillatory activity need to be distinguished: (1) evoked and 2) induced oscil-

lations (Tallon-Baudry and Bertrand, 1999). Evoked oscillations are strictly phase-locked to the onset of a stimulus and, therefore, can be measured by stimulus-triggered averaging of responses. Although these evoked oscillations are related to early, stimulus-driven encoding processes, they are state-dependent and can be modulated by top-down processes such as attention (Herrmann et al., 2004; Tiitinen et al., 1993). In contrast, induced oscillations appear in association with stimulus-triggered cognitive processes, but reflect self-paced temporal coordination of neuronal responses. They are not phase-locked with external events, and are therefore abolished by averaging. These induced oscillations typically occur in the  $\beta$ - and  $\gamma$ -frequency range and appear in association with a large variety of cognitive processes, ranging from the construction of coherent percepts (Tallon-Baudry and Bertrand, 1999) to focused attention (Fries et al., 2001a) and the preparation of movements (Murphy and Fetz, 1996).

Although the amplitude of LFP, EEG, or MEG signals correlates with the degree of synchrony of neuronal responses, there are numerous confounding variables that make it difficult to draw firm conclusions on synchrony by considering only amplitude measures. Among these are the size and the alignment of the dipole fields of the contributing neurons, the fraction of synchronously active neurons in the population of cells contributing to the signal, and, above all, the degree of precision with which the neuronal discharges are synchronized. The latter variable is particularly critical when neurons engage in high-frequency oscillatory activity. In this case, the precision of synchrony needs to be in the millisecond range in order to permit effective summation of synaptic currents and to yield a measurable signal. Therefore, methods have been developed which permit assessment of synchrony independently of amplitude (Lachaux et al., 1999; Tass et al., 1998; Zeitler et al., 2006). In essence, they determine separately for different frequency bands the precision and intertrial variance of phase relations between signals recorded simultaneously from different sites.

These measures need to be distinguished from measures of “coherence,” which determine the covariance of the amplitude of oscillations recorded from different sites for the various frequency bands (Andrew and Pfurtscheller, 1996). Both phase synchronization and coherence have been used to assess functional coupling among distributed neuronal populations (Rodriguez et al., 1999; Bressler et al., 1993).

Finally, measures for large-scale coordination of neuronal activity have also been derived from covariations of the amplitudes and latencies of hemodynamic signals in different brain regions (Friston et al., 1993). Although this method has very low temporal resolution and cannot assess the synchrony of evoked and induced oscillatory activity, it provides indications on functional connectivity and can contribute to the identification of the distributed networks supporting particular cognitive processes. Because clinical studies using measurements of phase synchronization to determine deficiencies in temporal coordination are still sparse, we also included in this review selected studies that applied coherence analysis to EEG and MEG signals and discuss fMRI data on functional connectivity.

### Neural Synchrony: Anatomical Substrate and Neurotransmitters

Studies involving lesions (Engel et al., 1991) and developmental manipulations (Löwel and Singer, 1992) indicate that neural synchronization in the high-frequency range ( $\beta$ - and  $\gamma$ -band) is mainly mediated by cortico-cortical connections that reciprocally link cells situated in the same cortical area, but also cells distributed across different areas and even across the two hemispheres. Accordingly, synchronization probability between neurons reflects the anatomical layout of excitatory cortico-cortical connections (Schmidt et al., 1997a, 1997b). Direct evidence for the synchronizing function of reciprocal cortico-cortical connections comes from the finding that section of the corpus callosum abolishes synchronization of induced oscillatory responses between neurons located in different hemispheres (Engel et al., 1991). These and related studies indicate that cortical mechanisms dominate in the generation and precise synchronization of high-frequency oscillatory activity in the  $\beta$ - and  $\gamma$ -frequency bands. In contrast, subcortical structures, and especially the thalamus, appear to dominate in the generation and synchronization of oscillatory activity in the lower frequency bands ( $\alpha$ ,  $\theta$ ,  $\Delta$ , and below) (Steriade, 2005; Llinas and Steriade, 2006). However, more research is needed to clarify how exactly cortical and subcortical mechanisms cooperate in the generation and synchronization of rhythmic activity in the various frequency bands.

The generation and synchronization of cortical  $\beta$ - and  $\gamma$ -oscillations involves several neurotransmitter systems. GABAergic neurons play a pivotal role in the primary generation of high-frequency oscillations and their local synchronization, whereas glutamatergic connections appear to control their strength, duration, and long-range synchronization (Traub et al., 2004; Wang and Buzsaki, 1996). Recent evidence indicates that cholinergic modulation plays a crucial role in the fast, state-dependent facilitation of high-frequency oscillations and the associated response synchronization (Rodríguez et al., 2004; Steriade et al., 1991; Wespapat et al., 2004). In addition to chemical synaptic transmission, direct electrotonic coupling through gap junctions between inhibitory neurons also contributes to the temporal patterning of population activity and, in particular, to the precise synchronization of oscillatory activity (Draguhn et al., 1998; Fukuda et al., 2006; Hormuzdi et al., 2001; Nase et al., 2003; Traub et al., 2001).

### Neural Synchrony in Schizophrenia

Schizophrenia is a severe mental disorder with an estimated life-time prevalence of 1%. The disorder is characterized by psychotic symptoms (delusions, hallucinations), negative symptoms (flattening of affect, apathy), and disorganization of thought and behavior. Cognitive dysfunctions are prominent throughout the course of schizophrenia and have been shown to be a better predictor for outcome than the overt symptoms, suggesting that cognitive deficits represent a core pathology of the disorder (Green, 1996). The pathophysiological mechanisms leading to the overt symptoms and deficits in cognition are, however, largely unknown.

Current theories of schizophrenia (Friston, 1999; Phillips and Silverstein, 2003) emphasize that core aspects

of the pathophysiology are due to deficits in the coordination of distributed processes that both involve multiple cortical areas and are associated with specific cognitive deficits. Some of the deficits concern functions, such as working memory, attention, and perceptual organization, that have been proposed to involve synchronization of oscillatory activity in the high-frequency band ( $\beta$  and  $\gamma$ ) (Phillips and Silverstein, 2003). Impairments in perceptual organization as are found in schizophrenia lead to very circumscribed deficits in experimental tasks. These deficits can produce superior performance relative to controls in tasks in which contextual information and dynamic grouping have a distractive effect. This underlines the specificity of the disease-related impairment of perceptual grouping functions (for a review, see Uhlhaas and Silverstein, 2005).

A substantial body of EEG studies supports the hypothesis that schizophrenia is related to impaired neural synchrony. Examination of auditory and visual steady-state responses to repetitive stimulation in patients with schizophrenia has revealed a specific reduction in the power of the stimulus-locked response in the  $\beta$ - and  $\gamma$ -frequency range, but not in the lower frequencies (Kwon et al., 1999; Krishnan et al., 2005). This could be due to reduced synchronization of stimulus-evoked high-frequency oscillations and/or an inability of neurons to follow high stimulation rates. Moreover, there is evidence for a reduction of evoked stimulus-locked oscillatory activity, again in the high-frequency range, following auditory and visual stimuli. Reductions in evoked oscillatory activity have been reported for tasks involving visual binding (Spencer et al., 2003, 2004), for backward-masking (Wynn et al., 2005) and in the auditory oddball-paradigm (Gallinat et al., 2004). Furthermore, there is also preliminary evidence for reduction of induced, non-stimulus-locked oscillations in the  $\gamma$ -band range during the processing of visual stimuli (Green et al., 2003; Haig et al., 2000). These results suggest selective deficiencies in the ability of cortical networks or cortico-thalamo-cortical loops to engage in precisely synchronized high-frequency oscillations.

In addition to these analyses of spectral power of evoked oscillatory activity, several studies have examined phase synchrony between distributed neuronal populations while patients performed cognitive tasks (Slewa-Younan et al., 2004; Spencer et al., 2003; Symond et al., 2005; Uhlhaas et al., 2006). In a recent study (Uhlhaas et al., 2006), we provided evidence for a close relation between impaired neural synchrony in schizophrenia and specific cognitive deficits (see Figure 1) using Mooney faces as stimuli. Mooney faces consist of degraded pictures of human faces where all shades of gray are removed, thus leaving only black and white contours. Schizophrenia patients exhibited a deficit in the perception of Mooney faces and reduced phase synchrony in the  $\beta$ -band, while the power of induced  $\gamma$ -band oscillations was in the normal range. This suggests that large-scale synchronization is crucially impaired in patients with schizophrenia, while local synchrony in the  $\gamma$ -band is largely intact. Indirect, but compatible, evidence for deficits in large-scale coordination in schizophrenia comes from fMRI studies that have reported reduced functional connectivity, i.e., reduced covariance of BOLD signals, for a wide range of cognitive tasks

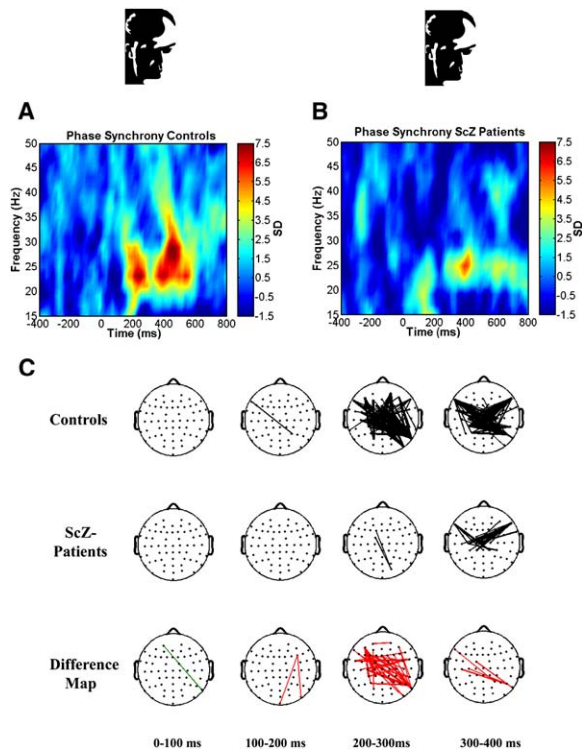


Figure 1. Neural Synchrony during Gestalt Perception in Schizophrenia

Group average of phase synchrony for all electrodes and for correct trials during a Gestalt perception task in controls (A and B). Phase-synchrony values are displayed in standard deviations (SD) in reference to the baseline. Phase synchrony during Gestalt perception in controls exhibited two maxima over an average frequency range of 20–30 Hz (A). The increase in phase synchrony between 200–300 ms has been related to the construction of coherent object representations (Rodriguez et al., 1999), 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 350–400 ms in the frequency range of 20–25 Hz (C). In addition, a second, weaker peak was found around 600 ms. Compared with controls, the reduction in phase synchrony in the frequency range of 20–30 Hz was significant [frequency range: 20–30 Hz, time interval: 200–280 ms,  $t(36) = 2.96$ ,  $p = 0.005$ ]. (C) shows the topography of phase synchrony between 20–30 Hz. Synchrony between electrodes is indicated by lines, which are drawn only if the synchrony value is beyond a two-tailed probability of  $p < 0.0005$ . Differences between groups are displayed in the bottom row. Black 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 200–300 ms indexes a deficit in the long-range synchronization during Gestalt perception in schizophrenia. Adapted from Uhlhaas et al., 2006, copyright 2006 by the Society for Neuroscience.

(Honey et al., 2005; Meyer-Lindenberg et al., 2005; Schlosser et al., 2003).

Impairments in the ability of distributed networks to establish precise synchronization of neuronal assemblies oscillating at high frequencies can have many reasons. These comprise both a host of local factors that determine the time constants of interactions within the oscillating microcircuits and the properties of long-distance connections that mediate interareal synchronization. Abnormalities have been identified for some of these candidate mechanisms in schizophrenia patients.

In vivo anatomical examination with diffusion tensor imaging (DTI) has revealed white matter anomalies that might be related to deficiencies in long-range synchronization (for a review see Kubicki et al., 2006). Cortico-cortical connections were reduced in the frontal, temporal, and parietal lobes, and between the two hemispheres. However, there is also evidence for locally increased connectivity that is related to productive symptoms, such as auditory hallucinations (Hubl et al., 2004). One interpretation of these seemingly paradoxical findings is that hyperconnectivity between higher- and lower-order cortical areas favors backpropagation to the respective primary sensory cortices of oscillatory activity generated in higher sensory areas during visual and auditory imagery, thus generating activation patterns that resemble those induced by sensory stimulation. This interpretation receives some support by the finding that hallucinations are associated with the following: (1) increased  $\gamma$ -oscillations in the corresponding sensory areas of the cerebral cortex (Lee et al., 2006); (2) long-range synchronization (Uhlhaas et al., 2006), and (3) increased hemodynamic responses (BOLD signal) in the respective primary sensory areas (Dierks et al., 1999). For several reasons, this increased BOLD signal is likely to reflect the entrainment of neurons in the primary areas into synchronized, high-frequency oscillations: first, it is improbable that neurons in primary sensory areas exhibit major increases in discharge rates in the absence of sensory stimulation. Second, top-down effects, such as those associated with focused attention, cause an entrainment of selected neuronal populations into well-synchronized  $\gamma$ -oscillations without enhancing the discharge rates (Fries et al., 2001a). Third, increases of the BOLD signal correlate much better with the entrainment of neurons into synchronized high-frequency  $\gamma$ -oscillations than with increases in discharge rates (Niessing et al., 2005).

Further candidate mechanisms for deficient synchronization in the high-frequency range are abnormalities in the rhythm-generating networks of inhibitory interneurons and abnormalities in the glutamatergic neurons mediating long-distance synchronization. Abnormalities in GABAergic inhibitory neurons (Lewis et al., 2005) and NMDA-receptor dysregulation (Moghaddam, 2003) have both been found in patients with schizophrenia. The possible role of NMDA-receptors in the pathophysiology of schizophrenia is supported by the acute effects of NMDA antagonists, such as ketamine or phencyclidine (PCP), on healthy volunteers. For example, subanaesthetic doses of ketamine produce an acute psychosis that includes many of the symptoms and characteristic cognitive dysfunctions of schizophrenia (Krystal et al., 1994). Hypofunctioning of the NMDA-receptor in schizophrenia is also compatible with the dopamine hypothesis of schizophrenia, as NMDA antagonists can induce dopamine dysregulation (Jentsch and Roth, 1999). Because the typical and atypical neuroleptics interfere with dopaminergic and serotonergic neurotransmission, respectively, abnormalities in these transmitter systems are thought to play a central role in the pathophysiology of schizophrenia. Whether these systems play a role in modulating neural synchrony has not been investigated yet.

There is preliminary evidence, however, indicating a relationship between dopaminergic neurotransmission

and neural synchrony. For example, studies that have examined the relationship between dopamine-mediated neurotransmission in PD and neural synchrony show that dopamine agonists decrease pathological  $\beta$ -oscillations in the subthalamic nucleus (STN) and increase  $\gamma$ -band oscillations in cortical and subcortical networks (Brown et al., 2001; Sharott et al., 2005). Moreover, dopaminergic dysfunctions could affect neural synchronization in schizophrenia via dopaminergic action on GABAergic interneurons (Seamans and Yang, 2004).

So far, direct evidence for a link between neural synchrony and neurotransmitter systems is available only for the cholinergic system (Rodriguez et al., 2004). Cortical networks can only engage in synchronized, high-frequency oscillations when muscarinic receptors are activated. Further studies need to clarify whether this finding can be related to the emerging evidence that deficits in cholinergic transmission may be involved in abnormal cortical information processing in schizophrenia (Sarter et al., 2005).

In summary, there is consistent evidence that neural synchrony is impaired in patients with schizophrenia. This impairment is particularly pronounced for oscillatory activity in the  $\beta$ - and  $\gamma$ -frequency ranges and for the synchronization of these high-frequency oscillations over longer distances. Because synchronization of oscillatory activity in this frequency range is associated with cognitive functions that are disturbed in schizophrenia patients, it is conceivable that the relation between impaired synchrony and the symptomatology of schizophrenia is not merely correlative. Data on anatomical connectivity and neurotransmitter systems in schizophrenia suggest several potential causes for impaired neural synchrony, but more focused studies are required to distinguish between cause and effect.

### Neural Synchrony in Epilepsy

Epilepsy designates a group of heterogeneous disorders of the nervous system that differ with respect to etiology and symptomatology. Traditionally, epilepsy has been assumed to result from abnormal, typically too high and too extended, neural synchronization. Penfield et al. (1954), for example, suggested that the high voltages recorded from epileptic cortex reflect hypersynchronous neural activity.

Etiologically, a wide range of factors can induce abnormal synchronization. These range from structural damage (encephalitis, craniocerebral trauma and tumors) to abnormal metabolic states (fever, sleep deprivation, alkalosis, etc.). Genetic predisposition also plays a role in epileptogenesis. Depending on etiology and disposition, seizures can be confined to restricted regions of the cortex (focal epilepsy). This leads to specific cognitive or motor symptoms, such as hallucinations, in the case of complex partial seizures within sensory areas, or myoclonia, if the focus is in motor areas. In contrast, in convulsive seizure disorders (grand-mal epilepsy), abnormal synchronization tends to spread over the whole neocortex, involving also subcortical structures, and leads to comatose states. In absence seizures, characteristic, highly synchronized low-frequency oscillations generated by thalamo-cortico-thalamic loops cause a breakdown of all higher cognitive functions (Niedermeyer, 2005). Together with the

evidence that synchronization of neural responses plays an important role in signal transduction and information processing (see Introduction), these well-established correlations between abnormal synchronization and the breakdown of neuronal functions are strong support for the hypothesis that temporal patterning of neural activity and a precisely regulated trade-off between correlated and decorrelated activation patterns are crucial for normal brain functions.

One of the hallmarks of epileptiform activity is abnormally high synchrony in extensive brain regions as reflected by large-amplitude fluctuations in the EEG both during and between seizures (Niedermeyer, 2005; Steriade, 2003). For example, during absence seizures, the sudden arrest of ongoing behavior and the impairment of consciousness are accompanied by the abrupt occurrence of synchronous, low-frequency, three-per-second spike-and-wave discharges (SWDs) in the EEG over a wide range of cortical areas. Meeren et al. (2002) showed in a genetic animal model of absence epilepsy that SWDs originate in the cortex and initiate oscillations in the thalamo-cortico-thalamic loop. These results are consistent with findings that cortical-spike wave seizures can still be recorded after ipsilateral thalamectomy (Steriade and Contreras, 1998), thus making it unlikely that seizure generation depends only on thalamic mechanisms.

Epilepsy is typically associated with a number of characteristic cognitive and behavioral phenomena. Complex partial seizures are frequently accompanied by auras that involve hallucinations in different modalities, unusual sensations, déjà vu experiences, emotional feelings, and recall of old memories (Medvedev, 2002). After partial complex, generalized tonic-clonic, and certain other types of seizures, loss of short-term memories and retrograde amnesia has been reported. Depending on the involved cortical regions, specific cognitive dysfunctions are observed. Temporal lobe epilepsy (TLE) is typically associated with memory impairment, while focal epilepsy over the language-dominant hemisphere can cause word finding and naming difficulties (Motamedi and Meador, 2003). These correlations suggest that abnormal temporal patterning of neural activity disrupts cognitive processes.

High-frequency oscillatory activity, especially in the  $\gamma$ -band, has been frequently observed in the EEG before and during epileptic events (for a review see Rampf and Stefan, 2006). Allen et al. (1992) and Fisher et al. (1992) reported activity in the  $\gamma$ -band before and at the onset of seizures. High-frequency oscillations (100–500 Hz) were also found in intracerebral recordings in patients with focal epilepsy near the time of the onset of the seizure (Jirsch et al., 2006). The presence of high-frequency oscillatory activity prior to the onset of ictal activity has also been observed in rodent models of epilepsy (Bragin et al., 1999).

Several studies examined phase synchrony during interictal, ictal, and preictal activity and have provided further insights into the role of neural synchrony in the generation of seizure activity. These studies challenged the notion that neural synchrony is generally increased in epilepsy. Evidence from hippocampal slices shows that bursts in CA1 pyramidal neurons are caused by neuronal activity that is synchronized with high

precision (<10 ms) in the  $\beta$ -band; however, during seizures, neuronal activity is no longer synchronous (Netoff and Schiff, 2002). Garcia Dominguez et al. (2005) analyzed MEG data from epileptic patients with generalized seizures in order to determine the extent of phase synchronization within and across distant cortical areas. The results revealed increased local synchrony in the  $\beta$ - and lower  $\gamma$ -band, whereas synchrony was normal, or even reduced, between distant regions. This is in agreement with the study by van Putten (2003), which showed that only enhanced local phase synchronization is a significant correlate of seizure activity.

Analyzing phase synchrony during preictal EEG activity has also challenged the notion that neural synchrony is generally increased. Le Van Quyen et al. (2003) examined phase synchrony with intracranial recordings from eight patients exhibiting neocortical focal epilepsy. In 77% of the seizures, there was a preictal decrease in synchrony in the  $\beta$ -band. This reduction of synchrony between different electrode sites sometimes occurred before the actual seizure and was characterized by recurrent spatial patterns that were close to the actual sites of the epileptogenic focus. This suggests that preictal desynchronization may facilitate seizure activity through isolating the pathologically discharging neurons of the epileptic focus from the controlling influence of the embedding network. It is thus conceivable that reduction of coherence and the associated reduction in coupling allows the focus to engage in supracritical synchronous activity, which then spreads into the surrounding networks.

Data from functional and anatomical imaging studies support this view. Waites et al. (2006) showed that during resting state, patients with TLE exhibit reduced functional connectivity between the brain areas involved in language generation. Likewise, in a recent DTI study, Dumas de la Roque et al. (2005) reported that patients with intractable partial epilepsy had reduced connectivity between cortical areas surrounding the electric focus, as well as reduced connectivity between more distant cortical areas.

Experimental and clinical data suggest that convulsive epilepsy is often associated with an imbalance between excitatory and inhibitory neurotransmitter systems, causing enhanced excitability. GABAergic interneurons play a critical role in maintaining this balance (Levitt, 2005) and accordingly, convulsive seizures can be suppressed or reduced by enhancing GABAergic transmission (Snead, 1992). However, in vitro data indicate that seizure activity can be precipitated by the administration of GABAergic drugs (von Krosigk et al., 1993). In animal models of absence seizures, GABA(B) receptor agonists increase spiking activity, whereas blocking of GABA(B) receptors reduces the number of spiking episodes (Marrosu et al., 2006). These heterogeneous effects of GABAergic drugs have to do with the multiple functional roles of inhibitory interneurons. On the one hand, their activity reduces network excitability; on the other hand, they contribute essentially to the oscillatory patterning and synchronization of neural activity (see above). As synchronization increases the impact of neural activity in target structures, enhanced GABAergic transmission may, in certain cases, facilitate seizures by inducing synchronous population dis-

charges that then spread very effectively across neighboring networks. In the case of absence seizures, GABA-mediated hyperpolarization is essential for the development of the synchronized, low-frequency oscillations because these depend on low-threshold  $\text{Ca}^{2+}$  channels that are only activatable when the membrane potential drops substantially below the average resting level (e.g., McCormick and Williamson, 1989; Huguenard and Prince, 1994; Ulrich and Huguenard, 1996). However, there is also evidence that abnormalities in GABAergic transmission alone may not be sufficient for epileptogenesis in mature cortex and that seizure activity is likely to depend, in addition, upon synergistic alterations of glutamatergic transmission involving NMDA-receptors (Khalilov et al., 2005).

Furthermore, gap junctions have been proposed to play an important role in the synchronization and propagation of epileptic activity (Carlen et al., 2000; Traub et al., 2001). In vitro data show that the generation of the high-frequency oscillations associated with preictal EEG activity is facilitated by direct electrotonic coupling of neurons via gap junctions (Draguhn et al., 1998). Accordingly, gap junction blockers have been shown to be effective in suppressing seizures in rat models of focal cortical epilepsy (Nilsen et al., 2006), in modifying the expression of rhythmical discharges, and in controlling the duration and propagation of individual seizures in vivo (Gajda et al., 2003).

In conclusion, seizures are not only a consequence of heightened neuronal excitability such as results from an imbalance between excitatory and inhibitory mechanisms. Alterations of the mechanisms that support the oscillatory patterning and the synchronization of neuronal activity appear to be equally important. As synchronization enhances the coupling among distributed neuronal populations (Abeles, 1991; Bruno and Sakmann, 2006; Fries, 2005), reduced synchrony could contribute to the functional isolation of foci, allowing them to develop supracritical excitatory states, while synchronization could facilitate maintenance of supracritical excitatory activity in re-entrant loops and the spread of seizure activity. Both the reduced synchronization preceding some forms of epileptic activity and the enhanced synchronization associated with seizures proper go along with the disturbance of cognitive functions, supporting the notion that normal brain functions require not only appropriate adjustment of neuronal excitability, but also a subtle balance of synchrony.

### Neural Synchrony in Autism

Autism is a developmental brain disorder characterized by a triad of impairments that affect social interaction, verbal and nonverbal communication, and the repertoire of interests and activities (APA, 2000). Similar to recent work in schizophrenia (Uhlhaas and Silverstein, 2005; Phillips and Silverstein, 2003), theories that account for the pervasive cognitive dysfunctions associated with autism have highlighted a deficit in the integration of cognitive mechanisms (Frith and Happe, 1994; Hill and Frith, 2003). A number of studies have demonstrated superior performance in tasks requiring recognition of details and directing attention to small elements as, for example, in visual search and in the identification of hidden figures. This reduced ability to integrate

components into coherent representations is not confined to visual perception, but has also been found in the processing of auditory information, linguistic context, and social cues (for a review, see Happe and Frith, 2006).

Current theories and experimental data (Belmonte et al., 2004; Brock et al., 2002; Hill and Frith, 2003; Just et al., 2004; Polleux and Lauder, 2004) converge on the notion that dysfunctional integrative mechanisms in autism may be the result of reduced neural synchronization. Recent fMRI and EEG studies have supported this view. Just et al. (2004) examined functional connectivity by measuring the covariances of BOLD signals during sentence comprehension in high-functioning individuals with autism. The study showed systematic differences between groups with respect to the distribution of brain activation and functional connectivity. Compared to controls, subjects with autism were characterized by a marked reduction in functional connectivity throughout the cortical language system that was most pronounced during comprehension of sentences. In addition, individuals with autism showed reduced activation in the left inferior frontal gyrus (LIFG; also known as Broca's Areas), but enhanced activation in the left posterior superior temporal gyrus (LSTG) compared with the control group. This suggests that autistic subjects engaged more in extensive processing of the meaning of the individual words, as reflected in the activity in the LSTG, but reduced processing of syntactic and conceptual information.

A number of additional fMRI studies have supported the concept of reduced functional connectivity in autism. In a second study, Just et al. (2006) reported reduced functional connectivity between frontal and parietal areas during an executive task. Furthermore, there is evidence for reduced volume of the corpus callosum. fMRI studies of social cognition (Castelli et al., 2002), working memory (Koshino et al., 2005), and visuo-motor coordination (Villalobos et al., 2005) have further supported the notion that reduced functional connectivity may underlie a wide range of cognitive deficits in autism.

In analogy to the findings in schizophrenia patients, these data predict that autism should be associated with reduced neural synchrony. However, so far only a few studies have examined this possibility. Grice et al. (2001) analyzed induced  $\gamma$ -band activity in individuals with autism and in a matched control group during the perception of face stimuli. In controls, an increase in induced  $\gamma$ -power differentiated responses to face from no-face stimuli, while subjects with autism showed no difference between the two experimental conditions. Analysis of auditory steady-state responses indicates that, similar to patients with schizophrenia, there is a reduction in the power of the stimulus-locked responses in the  $\gamma$ -band range in autism (Wilson et al., 2006).

Several authors have recently proposed that cortical networks in autism may be characterized by an imbalance between excitation and inhibition, which leads to hyperexcitability and unstable cortical networks (Hussman, 2001; Rubenstein and Merzenich, 2003). This hypothesis is consistent with abnormalities in GABAergic and glutamatergic transmitter systems. Indications for reduced GABAergic inhibition have been derived from the evidence that autism is associated with mutations

of genes encoding subunits of the GABA(A) receptor, reduced expression of GAD 65 and GAD 67, and synthesis of abnormal isoforms of these enzymes (DiCicco-Bloom et al., 2006; Polleux and Lauder, 2004). Abnormal glutamatergic neurotransmission is supported by polymorphisms in genes that encode both metabotropic and ionotropic glutamate receptors (Carlsson, 1998; Polleux and Lauder, 2004), and a post mortem study has reported reduced AMPA-receptors in the cerebellum (Purcell et al., 2001). In addition, the serotonergic system may be dysregulated in autism (Polleux and Lauder, 2004). To date, it is unclear how these abnormalities relate to the cognitive deficits in autism, whether they play a role in the hypothesized disruption of integrative processes, and whether there are electrographic correlates of reduced large-scale synchronization in this disorder.

Anatomically, there is evidence for both hyper- as well as hypoconnectivity in autism. During early development (between 7–11 years), white matter increases significantly more in autistic than in normal children. In the same age group, gray matter is reduced in a number of regions, including the hippocampus and amygdala (Herbert et al., 2003). Evidence for a transient hypertrophy of white matter has also been found in previous studies (Courchesne et al., 2001), and this finding has later been complemented by results suggesting exaggerated pruning to subnormal levels, consistent with evidence for anatomical hypoconnectivity (Just et al., 2004; McCaffery and Deutsch, 2005). These anatomical results also predict reduced or otherwise abnormal synchrony, but more EEG and MEG studies with advanced techniques for the identification of synchrony are required to clarify this issue.

#### Neural Synchrony in Alzheimer's Disease

AD is the most common form of dementia, affecting approximately 11% of the world population older than 65 years of age (Hof and Morrison, 1999). AD is associated with a wide range of cognitive dysfunctions that typically start with characteristic memory impairment, followed by deficits in visuo-spatial and executive processes. These differential impairments in cognitive domains reflect the spread of cortical pathology from medial-temporal to parietal association areas (Braak and Braak, 1991; Pantel et al., 2004). Patients with AD show pronounced deficits while performing tasks that require interhemispheric transfer of information, executive processing, and episodic memory (for a review, see Delbeuck et al., 2003). In contrast, in early stages of the disease, automatic processing is intact. Delbeuck et al. (2003) have suggested that the profile of neuropsychological deficits is consistent with a disconnection syndrome.

A hallmark of the resting-state EEG in patients with AD is a relative increase in the  $\theta$  and  $\Delta$ -band activity that co-occurs with a reduction in activity in the  $\alpha$ - and  $\beta$ -band. The reduction in  $\alpha$ -band activity correlates well with the severity of the disease and the cognitive deficits (Jeong, 2004). These power changes in distinct frequency bands are associated with impaired synchrony. Patients with AD show reduced coherence of oscillations in the  $\alpha$ - and  $\beta$ -frequency band both for distant and nearby recording sites. More direct evidence comes from studies that have utilized more sensitive measures of synchrony.

Stam and colleagues (Stam et al., 2003, 2005, 2006) have analyzed EEG resting data using a measure of synchronization likelihood (SL) (Stam and van Dijk, 2002) that is sensitive to linear and nonlinear interdependencies between EEG channels. The results indicate that patients with AD show a reduction in  $\beta$ - as well as  $\alpha$ -band synchronization. Topographically, the reduction of synchrony is particularly pronounced for long-range synchronization (Babiloni et al., 2004; Stam et al., 2006). In addition to lowered synchronization in the  $\alpha$ - and  $\beta$ -band, patients with AD are also characterized by a reduction in  $\gamma$ -band synchronization in the resting state (Koenig et al., 2005).

Thus, there is substantial evidence for reduced neural synchrony during the resting state, but relatively little research has been performed so far to link reductions in neural synchrony directly to impaired cognition by analyzing task- and performance-related changes of synchronization. The only task-related study is the investigation by Pijnenburg et al. (2004). The authors examined neural synchrony in patients with AD during a working memory task. Patients with AD showed a reduction of  $\alpha$ - and  $\beta$ -band synchronization during maintenance of information in working memory compared with control subjects.

fMRI studies support this evidence of reduced coordination of neural activity in AD. By applying a working memory task, Grady et al. (2001) found reduced functional connectivity between prefrontal cortex and hippocampus and suggested that this reflects impaired coupling and may underlie the typical memory breakdown associated with the disease. Bokde et al. (2006) examined functional connectivity during a face-matching task in subjects with Mild Cognitive Impairment (MCI). Individuals with MCI have a higher risk of conversion to AD than cognitively normal subjects. Similar to the results by Grady and colleagues, MCI patients were characterized by a reduction in functional connectivity involving the fusiform gyrus (FG), the parietal lobes, and the dorsolateral prefrontal cortex (DLPFC). Interestingly, the groups did not differ in performance or activation. Also, the amplitudes of the BOLD signal were in the normal range, indicating that reduced functional connectivity might represent one of the earliest functional markers of AD.

The hypothesis that impaired neural synchrony underlies some of the cognitive deficits in AD is compatible with data suggesting that the degenerative processes caused by AD lead to a neocortical disconnection syndrome (Delbeuck et al., 2003). Neurofibrillary tangles (NFT) and neuritic plaques (NP) are particularly prominent in brain areas that give rise to long cortico-cortical tracts (Pearson et al., 1985). Accordingly, DTI studies (Naggara et al., 2006; Medina et al., 2006) disclosed disintegration of white matter fiber tracts. Furthermore, neural synchrony in the high-frequency range is expected to be reduced because AD leads to a pronounced degeneration of the cholinergic projections to the cerebral cortex that originate in the basal forebrain and have been shown to be a necessary prerequisite for the generation of  $\beta$ - and  $\gamma$ -band oscillations and response synchronization in this frequency range (Rodríguez et al., 2004). The evidence that muscarinic antagonists, such as scopolamine, induce a pattern of memory and cognitive deficits characteristic of elderly subjects

and shift EEG power toward lower frequencies (Ebert and Kirch, 1998) is compatible with this hypothesis.

Finally, there is evidence for alterations in glutamatergic neurotransmission, which may also affect neuronal synchronization in AD. Snyder et al. (2005) demonstrated that NPs produce a persistent depression of NMDA-evoked currents in cortical neurons. Moreover, neurons from a genetically modified mouse model of AD expressed reduced amounts of NMDA-receptors. These findings suggest that AD-related alterations of cellular functions can cause depression of NMDA-receptor-mediated synaptic transmission. A more direct link between AD and impaired neural synchrony has been reported by Stern et al. (2004). Increased expression of amyloid precursor protein in transgenic mice produced an increased jitter in the timing of evoked action potentials in intracellular recordings from neocortical pyramidal neurons. These findings suggest the possibility that accumulation of AD-related proteins has specific effects on neural excitability and synaptic transmission that impair neural synchrony and, hence, also the propagation and temporal coordination of activity.

Taken together, these data suggest that the cognitive disturbances associated with AD may not solely be due to the loss of neurons, but also due to impairments in the temporal coordination of distributed neuronal activity. So far, studies have concentrated on neural synchrony in the lower frequency bands, especially in the  $\alpha$ -band, and more investigations are required to examine the expected deficits of long-range synchrony in the higher frequency bands.

### Neural Synchrony in Parkinson's Disease

Neural synchronization is not only relevant for cognitive functions; it also plays a major role in the temporal patterning of motor-related activity. For example, there is evidence for enhanced synchronized  $\beta$ -band activity prior to movement preparation and during visuo-motor coordination (Murphy and Fetz, 1996; Roelfsema et al., 1997). However, during the execution of movements this  $\beta$ -band synchronization disappears and gives way to synchronized  $\gamma$ -band oscillations (Schoffelen et al., 2005). These movement-related synchronization phenomena have been found in a widely distributed network comprising premotor and parietal areas of the neocortex, the cerebellum, the striatum, and subthalamic nucleus. Because we have focused this review on relations between synchrony and cognitive functions in selected brain disorders, we do not attempt to give a comprehensive overview of the numerous studies that have examined relations between oscillatory activity patterns, such as the  $\mu$  or Piper rhythm, and motor processes. Instead, we review recent evidence on correlations between abnormal synchronization and movement disorders in PD.

This neurodegenerative disorder is due to the loss of dopaminergic neurons in the substantia nigra and causes changes in the patterning of neural activity in the basal ganglia (BG). Among the cardinal symptoms of PD are impaired motor activity, such as akinesia (inability to initiate movement and slowness of movement), rigidity (stiffness of muscles), and tremor. Evidence indicates that the pathophysiological mechanisms responsible for the akinesia and the tremor differ (Brown, 2003).



Table 1. Selected Neurobiological Elements of Cognitive Dysfunction

Disorder	Neural synchrony	Cognitive dysfunctions	Anatomical connectivity	Neurotransmitters
Schizophrenia	consistent evidence for a reduction of local- and long-range synchronization	perception, executive processes, memory, attention, social cognition	evidence for reduced anatomical connectivity	glutamate, GABA, dopamine
Epilepsy	increase in local synchrony; evidence for a reduction in long-range synchronization	specific cognitive deficits in relationship to seizure focus	reduced connectivity between seizure focus and surrounding cortical areas	GABA, glutamate
Autism	reduced functional connectivity; preliminary evidence for impaired neural synchrony	perception, executive functions, social cognition, attention, memory	increased connectivity during early development, but possibly hypoconnectivity in mature cortex	GABA, glutamate, serotonin
Alzheimer's disease	reduced neural synchrony during resting state; evidence for reduced functional connectivity	working memory, perception, attention, executive processes	reduction in anatomical connectivity	acetylcholine, glutamate
Parkinson's disease	increase in neural synchrony in the basal ganglia, but also between subcortical-cortical structures	especially motor functioning, but also perception, working memory, attention, executive functions	unknown	dopamine

Traditionally, BG dysfunctions were explained in terms of alterations in neural firing rates that underlie the spectrum of movement disorders (Hutchinson et al., 2004). However, recent research has emphasized a specific relation between large-scale synchronization of oscillations in the  $\beta$ -frequency band and akinesia (for a review, see Boroud et al., 2005; Brown, 2003; and Schnitzler and Gross, 2005).

Increases in  $\beta$ -band activity in PD have been reported in the STN, globus pallidus externus (Gpe), and internus (Gpi) in single-unit activity and LFPs (Boroud et al., 2005). Moreover, noninvasive EEG and MEG recordings have yielded complementary data on increased long-range synchronization in the  $\beta$ -range between these structures and activity over cortical motor areas. This led to the hypothesis that enhanced synchronization in the  $\beta$ -band is responsible for the associated akinesia. This hypothesis is supported by the evidence that, in normal subjects, initiation of movements is associated with inhibition of  $\beta$ -rhythms in the STN and a burst of  $\gamma$ -oscillations. The duration of this  $\beta$ -suppression increases with the complexity of the intended movement, and the latency of  $\beta$ -suppression predicts the onset of movement; the earlier the suppression, the shorter the movement latency. In agreement with this hypothesis, therapeutic interventions reducing the akinetic symptoms have all been shown to reduce the enhanced synchronization in the  $\beta$ -band and to facilitate  $\gamma$ -oscillations. This holds for pharmacological treatments that enhance endogenous dopamine levels, for the stereotactic lesioning of the STN, and for the very effective electrical stimulation of the STN at high frequencies (>100 Hz) (Brown et al., 2001; Sharott et al., 2005).

As expected, a direct relation exists between oscillatory neuronal activity and the tremor in PD. Levy et al. (2000) examined the discharge patterns of STN neurons in PD patients with limb tremor who underwent functional stereotactic mapping. In patients who exhibited limb tremor during the recording session, neurons showed oscillatory activity that was coherent with the frequency of the tremor. Related results have been obtained with MEG recordings that have disclosed an

extended tremor-related network exhibiting oscillatory activity that was harmonically related to the tremor frequency (Timmermann et al., 2003).

#### Neural Synchrony and Pathological Brain States

The evidence reviewed suggests that schizophrenia, autism, epilepsy, AD, and PD are characterized by changes in neural synchrony that are likely to play an important role in the pathophysiology of the disorders (see Table 1 for a summary). There is consistent evidence across studies that disorders in schizophrenia, autism, and AD are associated with a reduction of neural synchrony that involves both local as well as long-range synchronization. In addition, the cognitive functions that are impaired have all been shown to be associated with neural synchronization, suggesting that abnormal synchrony could be one of the causes of the cognitive dysfunctions. The conditions in epilepsy and PD are more complex, as in these cases enhanced synchrony is responsible for some of the symptomatology.

The impairments of neural synchrony observed in schizophrenia, autism, and AD are consistent with current theories that emphasize a disconnection syndrome as the underlying pathophysiological mechanism. According to these theories, cognitive dysfunctions as well as the overt symptoms of these disorders arise from a dysfunction in the coordination of distributed neural activity between and within functionally specialized regions of the cerebral cortex. Reduced neural synchronization can be a consequence of disconnection, but it can also be the cause of impaired coupling between brain areas because synchronization of neural responses is essential for their propagation across sparsely connected networks (Abeles, 1991). At present, it is difficult to differentiate between these possibilities.

In contrast, epilepsy and PD are characterized by a large variety of abnormalities in the temporal patterning of neural activity, involving changes in the frequency of oscillatory activity and increases as well as decreases in synchronization. Each of these abnormalities is associated with specific impairments of cognitive or motor functions, supporting the notion that normal brain

functions depend to a crucial extent on the appropriate adjustment and coordination of temporally structured activity. This fine-tuning appears to involve selection of oscillation frequencies as well as a delicate balance between synchronization and desynchronization of interacting cell assemblies.

### **Neural Synchrony and Pathological Brain States: Implications for Normal Brain Functioning**

A wide range of cognitive functions requires the coordination of distributed neural activity, and current theories highlight neural synchrony as a putative mechanism for this coordination. The findings summarized in this review provide further support for this hypothesis by demonstrating a correlation between abnormal synchronization and specific cognitive deficits in a variety of neuropsychiatric disorders.

These data also suggest that deficits of mainly large-scale integration correlate with cognitive impairments. In schizophrenia (Uhlhaas et al., 2006), AD (Bokde et al., 2006; Stam et al., 2006), and autism (Just et al., 2004), large-scale integration was found to be more impaired than local synchronization, as reflected by the amplitude of local oscillatory activity and BOLD activation. Furthermore, cognitive dysfunctions were particularly pronounced for tasks requiring interactions between widely distributed brain areas, such as integration of polymodal stimulus attributes, dynamic perceptual grouping, working memory, and executive processes (Delbeuck et al., 2003; Minschew et al., 1997; Phillips and Silverstein, 2003). This agrees with the proposals of several authors that complex cognitive processes, such as attention, memory, dynamic grouping, and awareness require large-scale integration of activity (Fries, 2005; Schnitzler and Gross, 2005; Varela et al., 2001).

### **Future Perspectives of Research on Neural Synchrony in Pathological Brain States**

The data reviewed here suggest that measures of neural synchronization may be of importance for the diagnosis of neuropsychiatric disorders. As measurements of neuronal synchrony are noninvasive and quantifiable in an objective way that is largely immune to observer bias, advanced methods of time series analysis may provide valuable diagnostic tools for the assessment of disease progression and efficiency of therapeutic interventions. For example, analysis of phase synchronization has been applied to the EEG data of patients with epilepsy, and the results suggest that seizures can be predicted based on changes in synchronization (Le Van Quyen et al., 2003). Aberrant large-scale integration of neural activity may also turn out to be a predictor of incipient AD. The study by Bokde et al. (2006) showed that the covariance of BOLD responses during a face-matching task was a more sensitive measure for impaired brain functioning in patients with MCI than behavioral performance or the amplitude of regional brain activation, suggesting that reduced functional connectivity might represent one of the earliest markers of changes in brain functioning in AD. Prospective longitudinal studies of phase synchronization with EEG, and preferably MEG, methodology are required to examine whether changes of synchrony in the high-frequency bands can be used as an early predictor of AD.

Impaired neural synchrony may also guide further research into the pathophysiological mechanisms underlying neuropsychiatric disorders. For example, there is increasing interest in the role of GABAergic neurotransmission in schizophrenia and autism. These efforts have already led to the investigation of therapeutic effects of GABAergic modulators in these disorders. We believe that further research into neurotransmitter systems and other mechanisms involved in the generation of oscillatory activity and its synchronization could ultimately help develop more precise pharmacological interventions for these disorders.

Besides pathological brain states such as AD, schizophrenia, epilepsy, autism, and PD, neural synchrony is also of relevance for several other disorders that have not been reviewed here. One case is multiple sclerosis (MS) because it is to be expected that axonal damage and demyelination interfere with the temporal coordination of neuronal activity. In particular, long-distance synchronization is likely to be impaired by prolongation of conduction times as has been recently demonstrated by Cover et al. (2006).

Future studies could also consider the use of measures of neural synchrony rather than just the power of EEG or MEG signals as biofeedback signals. Evidence indicates that biofeedback can be used to modify brain states in neuropsychiatric disorders (Serman and Egner, 2006). So far, the therapeutic effects of this approach have been variable, but it is conceivable that more advanced measures of the temporal coordination of distributed activity will be more effective in helping the patients bring aberrant activity under voluntary control.

### **Conclusion**

Theoretical considerations and experimental results suggest that synchronization of neuronal activity within and across different brain regions is a fundamental property of cortical and subcortical networks and serves a variety of functions in cognitive processes (for reviews, see Fries, 2005; Singer, 1999; and Varela et al., 2001). The data reviewed here suggest, in addition, that neuronal synchrony is altered in a number of pathological brain states, such as schizophrenia, epilepsy, autism, AD, and PD, and that these alterations in neural synchrony may account for some of the cognitive and motor dysfunctions associated with these diseases. Some of the disease-related alterations of anatomical conditions and neurotransmitter systems interfere directly with mechanisms that support synchronization of neuronal responses. These correlations between changes in neuronal substrate, synchrony, and cognitive performance support the hypothesis that temporal coordination of distributed neuronal activity through precise synchronization plays an important role in normal brain functions. Furthermore, these correlations suggest that a focused search for abnormalities in the temporal patterning and coordination of neuronal responses may be of potential clinical relevance both for the diagnosis and eventually for the treatment of those disorders as well.

### **Acknowledgments**

This research was supported by the Max Planck Society.

## References

- Abeles, A. (1991). *Corticonics: Neural Circuits of the Cerebral Cortex* (Cambridge: Cambridge University Press).
- Allen, P.J., Fish, D.R., and Smith, S.J. (1992). Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. *Electroencephalogr. Clin. Neurophysiol.* *82*, 155–159.
- APA (American Psychiatric Association). (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (Washington, D.C.: American Psychiatric Association).
- Andrew, C., and Pfurtscheller, G. (1996). Event-related coherence as a tool for studying dynamic interaction of brain regions. *Electroencephalogr. Clin. Neurophysiol.* *98*, 144–148.
- Babiloni, C., Ferri, R., Moretti, D.V., Strambi, A., Binetti, G., Dal Forno, G., Ferreri, F., Lanuzza, B., Bonato, C., Nobili, F., et al. (2004). Abnormal fronto-parietal coupling of brain rhythms in mild Alzheimer's disease: a multicentric EEG study. *Eur. J. Neurosci.* *19*, 2583–2590.
- Belmonte, M.K., Allen, G., Beckel-Mitchener, A., Boulanger, L.M., Carper, R.A., and Webb, S.J. (2004). Autism and abnormal development of brain connectivity. *J. Neurosci.* *24*, 9228–9231.
- Bertrand, O., Bohorquez, J., and Pernier, J. (1994). Time-frequency digital filtering based on an invertible wavelet transform: an application to evoked potentials. *IEEE Trans. Biomed. Eng.* *41*, 77–88.
- Bokde, A.L., Lopez-Bayo, P., Meindl, T., Pechler, S., Born, C., Faltraco, F., Teipel, S.J., Moller, H.J., and Hampel, H. (2006). Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. *Brain* *129*, 1113–1124.
- Boroud, T., Brown, P., Goldberg, J.A., Graybiel, A.M., and Magill, P.J. (2005). Oscillations in the Basal Ganglia: The good, the bad, and the unexpected. In *The Basal Ganglia VIII*, J.P. Bolam, C.A. Ingham, and P.J. Magill, eds. (New York: Springer), pp. 3–24.
- Braak, H., and Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol. (Berl.)* *82*, 239–259.
- Bragin, A., Engel, J., Jr., Wilson, C.L., Fried, I., and Mathern, G.W. (1999). Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. *Epilepsia* *40*, 127–137.
- Bressler, S.L., Coppola, R., and Nakamura, R. (1993). Episodic multi-regional cortical coherence at multiple frequencies during visual task performance. *Nature* *366*, 153–156.
- Brock, J., Brown, C.C., Boucher, J., and Rippon, G. (2002). The temporal binding deficit hypothesis of autism. *Dev. Psychopathol.* *14*, 209–224.
- Brown, P. (2003). The oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov. Disord.* *18*, 357–363.
- Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., and Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* *21*, 1033–1038.
- Bruno, R.M., and Sakmann, B. (2006). Cortex is driven by weak but synchronously active thalamocortical synapses. *Science* *312*, 1622–1627.
- Carlen, P.L., Skinner, F., Zhang, L., Naus, C., Kushnir, M., and Perez Velazquez, J.L. (2000). The role of gap junctions in seizures. *Brain Res. Brain Res. Rev.* *32*, 235–241.
- Carlsson, M.L. (1998). Hypothesis: is infantile autism a hypoglutamatergic disorder? Relevance of glutamate - serotonin interactions for pharmacotherapy. *J. Neural Transm.* *105*, 525–535.
- Castelli, F., Frith, C., Happe, F., and Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain* *125*, 1839–1849.
- Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., et al. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology* *57*, 245–254.
- Cover, K.S., Vrenken, H., Geurts, J.J., van Oosten, B.W., Jelles, B., Polman, C.H., Stam, C.J., and van Dijk, B.W. (2006). Multiple sclerosis patients show a highly significant decrease in alpha band inter-hemispheric synchronization measured using MEG. *Neuroimage* *29*, 783–788.
- Delbeuck, X., Van der Linden, M., and Collette, F. (2003). Alzheimer's disease as a disconnection syndrome? *Neuropsychol. Rev.* *13*, 79–92.
- DiCicco-Bloom, E., Lord, C., Zwaigenbaum, L., Courchesne, E., Dager, S.R., Schmitz, C., Schultz, R.T., Crawley, J., and Young, L.J. (2006). The developmental neurobiology of autism spectrum disorder. *J. Neurosci.* *26*, 6897–6906.
- Dierks, T., Linden, D.E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., and Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron* *22*, 615–621.
- Draguhn, A., Traub, R.D., Schmitz, D., and Jefferys, J.G. (1998). Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro. *Nature* *394*, 189–192.
- Dumas de la Roque, A., Oppenheim, C., Chassoux, F., Rodrigo, S., Beuvon, F., Dumas-Duport, C., Devaux, B., and Meder, J.F. (2005). Diffusion tensor imaging of partial intractable epilepsy. *Eur. Radiol.* *15*, 279–285.
- Ebert, U., and Kirch, W. (1998). Scopolamine model of dementia: electroencephalogram findings and cognitive performance. *Eur. J. Clin. Invest.* *28*, 944–949.
- Engel, A.K., Konig, P., Kreiter, A.K., and Singer, W. (1991). Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* *252*, 1177–1179.
- Engel, A.K., Fries, P., and Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* *2*, 704–716.
- Fisher, R.S., Webber, W.R., Lesser, R.P., Arroyo, S., and Uematsu, S. (1992). High-frequency EEG activity at the start of seizures. *J. Clin. Neurophysiol.* *9*, 441–448.
- Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.* *9*, 474–480.
- Fries, P., Reynolds, J.H., Rorie, A.E., and Desimone, R. (2001a). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* *291*, 1560–1563.
- Fries, P., Neuenschwander, S., Engel, A.K., Goebel, R., and Singer, W. (2001b). Rapid feature selective neuronal synchronization through correlated latency shifting. *Nat. Neurosci.* *4*, 194–200.
- Friston, K.J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr. Scand.* *395*, 68–79.
- Friston, K.J., Frith, C.D., Liddle, P.F., and Frackowiak, R.S.J. (1993). Functional connectivity: the principal component analysis of large data sets. *J. Cereb. Blood Flow Metab.* *13*, 5–14.
- Frith, U., and Happe, F. (1994). Autism: beyond "theory of mind". *Cognition* *50*, 115–132.
- Fukuda, T., Kosaka, T., Singer, W., and Galuske, R.A. (2006). Gap junctions among dendrites of cortical GABAergic neurons establish a dense and widespread intercolumnar network. *J. Neurosci.* *26*, 3434–3443.
- Gajda, Z., Gyengesi, E., Hermes, E., Ali, K.S., and Szente, M. (2003). Involvement of gap junctions in the manifestation and control of the duration of seizures in rats in vivo. *Epilepsia* *44*, 1596–1600.
- Gallinat, J., Winterer, G., Herrmann, C.S., and Senkowski, D. (2004). Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin. Neurophysiol.* *115*, 1863–1874.
- Garcia Dominguez, L., Wennberg, R.A., Gaetz, W., Cheyne, D., Snead, O.C., III, and Perez Velazquez, J.L. (2005). Enhanced synchrony in epileptiform activity? Local versus distant phase synchronization in generalized seizures. *J. Neurosci.* *25*, 8077–8084.
- Grady, C.L., Furey, M.L., Pietrini, P., Horwitz, B., and Rapoport, S.I. (2001). Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease. *Brain* *124*, 739–756.
- Gray, C.M., Koenig, P., Engel, A.K., and Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* *23*, 334–337.

- Green, M.F. (1996). What are the functional consequences of neuro-cognitive deficits in schizophrenia? *Am. J. Psychiatry* 153, 321–330.
- Green, M.F., Mintz, J., Salveson, D., Nuechterlein, K.H., Breitmeyer, B., Light, G.A., and Braff, D.L. (2003). Visual masking as a probe for abnormal gamma range activity in schizophrenia. *Biol. Psychiatry* 53, 1113–1119.
- Grice, S.J., Spratling, M.W., Kamiloff-Smith, A., Halit, H., Csibra, G., de Haan, M., and Johnson, M.H. (2001). Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *Neuroreport* 12, 2697–2700.
- Haig, A.R., Gordon, E., De Pascalis, V., Meares, R.A., Bahramali, H., and Harris, A. (2000). Gamma activity in schizophrenia: evidence of impaired network binding? *Clin. Neurophysiol.* 111, 1461–1468.
- Happe, F., and Frith, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J. Autism Dev. Disord.* 36, 5–25.
- Herbert, M.R., Ziegler, D.A., Deutsch, C.K., O'Brien, L.M., Lange, N., Bakardjiev, A., Hodgson, J., Adrien, K.T., Steele, S., Makris, N., et al. (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain* 126, 1182–1192.
- Herrmann, C.S., Munk, M.H., and Engel, A.K. (2004). Cognitive functions of gamma-band activity: memory match and utilization. *Trends Cogn. Sci.* 8, 347–355.
- Hill, E.L., and Frith, U. (2003). Understanding autism: insights from mind and brain. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 281–289.
- Hof, P.R., and Morrison, J.H. (1999). The cellular basis of cortical disconnection in Alzheimer disease and related dementing conditions. In *Alzheimer Disease*, R. Terry, R. Katzman, K.L. Bick, and S. Sisodia, eds. (New York: Lippincott Williams and Wilkins), pp. 197–229.
- Honey, G.D., Pomarol-Clotet, E., Corlett, P.R., Honey, R.A., McKenna, P.J., Bullmore, E.T., and Fletcher, P.C. (2005). Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain* 128, 2597–2611.
- Hormuzdi, S.G., Pais, I., LeBeau, F.E., Towers, S.K., Rozov, A., Buhl, E.H., Whittington, M.A., and Monyer, H. (2001). Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. *Neuron* 31, 487–495.
- Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., Maier, S.E., Schroth, G., Lovblad, K., and Dierks, T. (2004). Pathways that make voices: white matter changes in auditory hallucinations. *Arch. Gen. Psychiatry* 61, 658–668.
- Huguenard, J.R., and Prince, D.A. (1994). Intrathalamic rhythmicity studied in vitro: nominal T-current modulation causes robust antio-scillatory effects. *J. Neurosci.* 14, 5485–5502.
- Hussman, J.P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *J. Autism Dev. Disord.* 31, 247–248.
- Hutchinson, W.D., Dostrovsky, J.O., Walters, J.R., Courtemanche, R., Boroud, T., Goldberg, J., and Brown, P. (2004). Neuronal oscillations in the basal ganglia and movement disorders: Evidence from whole animal and human recordings. *J. Neurosci.* 24, 9240–9243.
- Jentsch, J.D., and Roth, R.H. (1999). The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 20, 201–225.
- Jeong, J. (2004). EEG dynamics in patients with Alzheimer's disease. *Clin. Neurophysiol.* 115, 1490–1505.
- Jirsch, J.D., Urrestarazu, E., LeVan, P., Olivier, A., Dubeau, F., and Gotman, J. (2006). High-frequency oscillations during human focal seizures. *Brain* 129, 1593–1608.
- John, E.R., Prichep, L.S., Fridman, J., and Easton, P. (1988). Neuro-metrics: computer-assisted differential diagnosis of brain dysfunctions. *Science* 239, 162–169.
- Just, M.A., Cherkassky, V.L., Keller, T.A., and Minshew, N.J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain* 127, 1811–1821.
- Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K., and Minshew, N.J. (2006). Functional and anatomical cortical underconnectivity in Autism: Evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cereb. Cortex*, in press.
- Khalilov, I., Le Van Quyen, M., Gozlan, H., and Ben-Ari, Y. (2005). Epileptogenic actions of GABA and fast oscillations in the developing hippocampus. *Neuron* 48, 787–796.
- Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R., and Jelic, V. (2005). Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* 26, 165–171.
- Kopell, N., Ermentrout, G.B., Whittington, M.A., and Traub, R.D. (2000). Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. USA* 97, 1867–1872.
- Koshino, H., Carpenter, P.A., Minshew, N.J., Cherkassky, V.L., Keller, T.A., and Just, M.A. (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage* 24, 810–821.
- Krishnan, G.P., Vohs, J.L., Hetrick, W.P., Carroll, C.A., Shekhar, A., Bockbrader, M.A., and O'Donnell, B.F. (2005). Steady state visual evoked potential abnormalities in schizophrenia. *Clin. Neurophysiol.* 116, 614–624.
- Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers, M.B., Jr., and Charney, D.S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiatry* 51, 199–214.
- Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., and Shenton, M.E. (2006). A review of diffusion tensor imaging studies in schizophrenia. *J. Psychiatr. Res.*, in press.
- Kwon, J.S., O'Donnell, B.F., Wallenstein, G.V., Greene, R.W., Hirayasu, Y., Nestor, P.G., Hasselmo, M.E., Potts, G.F., Shenton, M.E., and McCarley, R.W. (1999). Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch. Gen. Psychiatry* 56, 1001–1005.
- Lachaux, J.P., Rodriguez, E., Martinerie, J., and Varela, F.J. (1999). Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208.
- Le Van Quyen, M., Navarro, V., Martinerie, J., Baulac, M., and Varela, F.J. (2003). Toward a neurodynamical understanding of ictogenesis. *Epilepsia* 44 (Suppl 12), 30–43.
- Lee, S.H., Wynn, J.K., Green, M.F., Kim, H., Lee, K.J., Nam, M., Park, J.K., and Chung, Y.C. (2006). Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. *Schizophr. Res.* 83, 111–119.
- Levitt, P. (2005). Disruption of interneuron development. *Epilepsia* 46 (Suppl 7), 22–28.
- Levy, R., Hutchinson, W.D., Lozano, A.M., and Dostrovsky, J.O. (2000). High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J. Neurosci.* 20, 7766–7775.
- Lewis, D.A., Hashimoto, T., and Volk, D.W. (2005). Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* 6, 312–324.
- Llinas, R.R., and Steriade, M. (2006). Bursting of thalamic neurons and states of vigilance. *J. Neurophysiol.* 95, 3297–3308.
- Löwel, S., and Singer, W. (1992). Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* 255, 209–212.
- Marrosu, F., Santoni, F., Fa, M., Puligheddu, M., Barberini, L., Genugu, F., Frau, R., Manunta, M., and Mereu, G. (2006). Beta and gamma range EEG power-spectrum correlation with spiking discharges in DBA/2J mice absence model: role of GABA receptors. *Epilepsia* 47, 489–494.
- McCaffery, P., and Deutsch, C.K. (2005). Macrocephaly and the control of brain growth in autistic disorders. *Prog. Neurobiol.* 77, 38–56.
- McCormick, D.A., and Williamson, A. (1989). Convergence and divergence of neurotransmitter action in human cerebral cortex. *Proc. Natl. Acad. Sci. USA* 86, 8098–8102.
- Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J.D., Moseley, M., Fleischman, D., Bennett, D.A., Leurgans, S., Turner, D.A., and Stebbins, G.T. (2006). White matter changes in mild cognitive

- impairment and AD: A diffusion tensor imaging study. *Neurobiol. Aging* 27, 663–672.
- Medvedev, A.V. (2002). Epileptiform spikes desynchronize and diminish fast (gamma) activity of the brain. An “anti-binding” mechanism? *Brain Res. Bull.* 58, 115–128.
- Meeren, H.K., Pijn, J.P., Van Luijckelaar, E.L., Coenen, A.M., and Lopes da Silva, F.H. (2002). Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *J. Neurosci.* 22, 1480–1495.
- Meyer-Lindenberg, A.S., Olsen, R.K., Kohn, P.D., Brown, T., Egan, M.F., Weinberger, D.R., and Berman, K.F. (2005). Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch. Gen. Psychiatry* 62, 379–386.
- Minshew, N.J., Goldstein, G., and Siegel, D.J. (1997). Neuropsychologic functioning in autism: profile of a complex information processing disorder. *J. Int. Neuropsychol. Soc.* 3, 303–316.
- Mitra, P.P., and Pesaran, B. (1999). Analysis of dynamic brain imaging data. *Biophys. J.* 76, 691–708.
- Mitzdorf, U., and Singer, W. (1979). Excitatory synaptic ensemble properties in the visual cortex of the macaque monkey: a current source density analysis of electrically evoked potentials. *J. Comp. Neurol.* 187, 71–83.
- Moghaddam, B. (2003). Bringing order to the glutamate chaos in schizophrenia. *Neuron* 40, 881–884.
- Motamedi, G., and Meador, K. (2003). Epilepsy and cognition. *Epilepsy Behav.* 4 (Supp2), 25–38.
- Murphy, V.N., and Fetz, E.E. (1996). Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. *J. Neurophysiol.* 76, 3949–3967.
- Naggara, O., Oppenheim, C., Rieu, D., Raoux, N., Rodrigo, S., Dalla Barba, G., and Meder, J.F. (2006). Diffusion tensor imaging in early Alzheimer’s disease. *Psychiatry Res.* 146, 243–249.
- Nase, G., Singer, W., Monyer, H., and Engel, A.K. (2003). Features of neuronal synchrony in mouse visual cortex. *J. Neurophysiol.* 90, 1115–1123.
- Netoff, T.I., and Schiff, S.J. (2002). Decreased neuronal synchronization during experimental seizures. *J. Neurosci.* 22, 7297–7307.
- Niedermeyer, E. (2005). Epileptic Seizure Disorders. In *Electroencephalography: Basic Principles, Clinical Applications, And Related Fields*, Fifth Edition, E. Niedermeyer and F. Lopes Da Silva, eds. (Philadelphia: Lippincott Williams and Wilkins), pp. 505–621.
- Niessing, J., Ebisch, B., Schmidt, K.E., Niessing, M., Singer, W., and Galuske, R.A. (2005). Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309, 948–951.
- Nilsen, K.E., Kelso, A.R., and Cock, H.R. (2006). Antiepileptic effect of Gap-junction blockers in a rat model of refractory focal cortical epilepsy. *Epilepsia* 47, 1169–1175.
- Pantel, J., Schonknecht, P., Essig, M., and Schroder, J. (2004). Distribution of cerebral atrophy assessed by magnetic resonance imaging reflects patterns of neuropsychological deficits in Alzheimer’s dementia. *Neurosci. Lett.* 361, 17–20.
- Pearson, R.C., Esiri, M.M., Hiorns, R.W., Wilcock, G.K., and Powell, T.P. (1985). Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. *Proc. Natl. Acad. Sci. USA* 82, 4531–4534.
- Penfield, W., Jasper, H., and McNaughton, F. (1954). *Epilepsy and the Functional Anatomy of the Human Brain* (Boston: Little Brown).
- Phillips, W.A., and Silverstein, S.M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav. Brain Sci.* 26, 65–82.
- Pijnenburg, Y.A., van der Made, Y., van Cappellen van Walsum, A.M., Knol, D.L., Scheltens, P., and Stam, C.J. (2004). EEG synchronization likelihood in mild cognitive impairment and Alzheimer’s disease during a working memory task. *Clin. Neurophysiol.* 115, 1332–1339.
- Polleux, F., and Lauder, J.M. (2004). Toward a developmental neurobiology of autism. *Ment. Retard. Dev. Disabil. Res. Rev.* 10, 303–317.
- Purcell, A.E., Jeon, O.H., Zimmerman, A.W., Blue, M.E., and Pevsner, J. (2001). Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. *Neurology* 57, 1618–1628.
- Rampf, S., and Stefan, H. (2006). Fast activity as a surrogate marker of epileptic network function? - A review. *Clin. Neurophysiol.*, in press.
- Rodriguez, E., George, N., Lachaux, J.P., Martinerie, J., Renault, B., and Varela, F.J. (1999). Perception’s shadow: long-distance synchronization of human brain activity. *Nature* 397, 430–433.
- Rodriguez, R., Kallenbach, U., Singer, W., and Munk, M.H. (2004). Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *J. Neurosci.* 24, 10369–10378.
- Roelfsema, P.R., Engel, A.K., Konig, P., and Singer, W. (1997). Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature* 385, 157–161.
- Rubenstein, J.L., and Merzenich, M.M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.* 2, 255–267.
- Sarter, M., Nelson, C.L., and Bruno, J.P. (2005). Cortical cholinergic transmission and cortical information processing in schizophrenia. *Schizophr. Bull.* 31, 117–138.
- Schlosser, R., Gesierich, T., Kaufmann, B., Vucurevic, G., Hunsche, S., Gawehn, J., and Stoeter, P. (2003). Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. *Neuroimage* 19, 751–763.
- Schmidt, K.E., Goebel, R., Lowel, S., and Singer, W. (1997a). The perceptual grouping criterion of colinearity is reflected by anisotropies of connections in the primary visual cortex. *Eur. J. Neurosci.* 9, 1083–1089.
- Schmidt, K.E., Kim, D.S., Singer, W., Bonhoeffer, T., and Lowel, S. (1997b). Functional specificity of long-range intrinsic and interhemispheric connections in the visual cortex of strabismic cats. *J. Neurosci.* 17, 5480–5492.
- Schnitzler, A., and Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nat. Rev. Neurosci.* 6, 285–296.
- Schoffelen, J.M., Oostenveld, R., and Fries, P. (2005). Neuronal Coherence as a mechanism of effective corticospinal interaction. *Science* 308, 111–113.
- Seamans, J.K., and Yang, C.R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog. Neurobiol.* 74, 1–58.
- Sharott, A., Magill, P.J., Harnack, D., Kupsch, A., Meissner, W., and Brown, P. (2005). Dopamine depletion increases the power and coherence of beta-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. *Eur. J. Neurosci.* 21, 1413–1422.
- Singer, W. (1999). Neuronal synchrony: A versatile code of the definition of relations? *Neuron* 24, 49–65.
- Slewa-Younan, S., Gordon, E., Harris, A.W., Haig, A.R., Brown, K.J., Flor-Henry, P., and Williams, L.M. (2004). Sex differences in functional connectivity in first-episode and chronic schizophrenia patients. *Am. J. Psychiatry* 161, 1595–1602.
- Snead, O.C., III. (1992). Evidence for GABAB-mediated mechanisms in experimental generalized absence seizures. *Eur. J. Pharmacol.* 37, 343–349.
- Snyder, E.M., Nong, Y., Almeida, C.G., Paul, S., Moran, T., Choi, E.Y., Nairn, A.C., Salter, M.W., Lombroso, P.J., Gouras, G.K., and Greengard, P. (2005). Regulation of NMDA receptor trafficking by amyloid-beta. *Nat. Rev. Neurosci.* 8, 1051–1058.
- Spencer, K.M., Nestor, P.G., Niznikiewicz, M.A., Salisbury, D.F., Shenton, M.E., and McCarley, R.W. (2003). Abnormal neural synchrony in schizophrenia. *J. Neurosci.* 23, 7407–7411.
- Spencer, K.M., Nestor, P.G., Perlmuter, R., Niznikiewicz, M.A., Klump, M.C., Frumin, M., Shenton, M.E., and McCarley, R.W. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc. Natl. Acad. Sci. USA* 101, 17288–17293.
- Stam, C., and van Dijk, B.W. (2002). Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. *Physica D* 163, 236–251.
- Stam, C.J., van der Made, Y., Pijnenburg, Y.A., and Scheltens, P. (2003). EEG synchronization in mild cognitive impairment and Alzheimer’s disease. *Acta Neurol. Scand.* 108, 90–96.

- Stam, C.J., Montez, T., Jones, B.F., Rombouts, S.A., van der Made, Y., Pijnenburg, Y.A., and Scheltens, P. (2005). Disturbed fluctuations of resting state EEG synchronization in Alzheimer's disease. *Clin. Neurophysiol.* *116*, 708–715.
- Stam, C.J., Jones, B.F., Nolte, G., Breakspear, M., and Scheltens, P. (2006). Small-world networks and functional connectivity in Alzheimer's disease. *Cereb. Cortex*, in press.
- Steriade, M. (2003). *Neuronal Substrates of Sleep and Epilepsy* (Cambridge: Cambridge University Press).
- Steriade, M. (2005). Cellular substrates of brain rhythms. In *Electroencephalography: Basic Principles, Clinical Applications, And Related Fields*, Fifth Edition, E. Niedermeyer and F. Lopes Da Silva, eds. (Philadelphia: Lippincott Williams and Wilkins), pp. 505–621.
- Steriade, M., and Contreras, D. (1998). Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus. *J. Neurophysiol.* *80*, 1439–1455.
- Steriade, M., Dossi, R.C., Pare, D., and Oakson, G. (1991). Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc. Natl. Acad. Sci. USA* *88*, 4396–4400.
- Sterman, M.B., and Egner, T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Appl. Psychophysiol. Biofeedback* *31*, 21–35.
- Stern, E.A., Bacskai, B.J., Hickey, G.A., Attenello, F.J., Lombardo, J.A., and Hyman, B.T. (2004). Cortical synaptic integration in vivo is disrupted by amyloid-beta plaques. *J. Neurosci.* *24*, 4535–4540.
- Symond, M.P., Harris, A.W., Gordon, E., and Williams, L.M. (2005). "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am. J. Psychiatry* *162*, 459–465.
- Tallon-Baudry, C., and Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends Cogn. Sci.* *3*, 151–162.
- Tass, P., Rosenblum, M.G., Weule, J., Kurths, J., Pikovsky, A., Volkmann, J., Schnitzler, A., and Freund, H.J. (1998). Detection of n:m phase locking from noisy data: application to magnetoencephalography. *Phys. Rev. Lett.* *81*, 3291–3294.
- Tiitinen, H., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., and Naatanen, R. (1993). Selective attention enhances the auditory 40-Hz transient response in humans. *Nature* *364*, 59–60.
- Timmermann, L., Gross, J., Dirks, M., Volkman, J., Freund, H.J., and Schnitzler, A. (2003). The cerebral oscillatory network of parkinsonian resting tremor. *Brain* *126*, 199–212.
- Traub, R.D., Whittington, M.A., Buhl, E.H., LeBeau, F.E., Bibbig, A., Boyd, S., Cross, H., and Baldeweg, T. (2001). A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. *Epilepsia* *42*, 153–170.
- Traub, R.D., Bibbig, A., LeBeau, F.E.N., Buhl, E.H., and Whittington, M.A. (2004). Cellular mechanisms of neuronal population oscillations in the hippocampus in vitro. *Annu. Rev. Neurosci.* *27*, 247–278.
- Uhlhaas, P.J., and Silverstein, S.M. (2005). Perceptual organization in schizophrenia spectrum disorders: empirical research and theoretical implications. *Psychol. Bull.* *131*, 618–632.
- Uhlhaas, P.J., Linden, D.E.J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., and Rodriguez, E. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J. Neurosci.* *26*, 8168–8175.
- Ulrich, D., and Huguenard, J.R. (1996). Gamma-aminobutyric acid type B receptor-dependent burst-firing in thalamic neurons: a dynamic clamp study. *Proc. Natl. Acad. Sci. USA* *93*, 13245–13249.
- van Putten, M.J. (2003). Nearest neighbor phase synchronization as a measure to detect seizure activity from scalp EEG recordings. *J. Clin. Neurophysiol.* *20*, 320–325.
- Varela, F., Lachaux, J.P., Rodriguez, E., and Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* *2*, 229–239.
- Villalobos, M.E., Mizuno, A., Dahl, B.C., Kemmotsu, N., and Muller, R.A. (2005). Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. *Neuroimage* *25*, 916–925.
- von Krosigk, M., Bal, T., and McCormick, D.A. (1993). Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* *261*, 361–364.
- von Stein, A., and Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *Int. J. Psychophysiol.* *38*, 301–313.
- Waites, A.B., Briellmann, R.S., Saling, M.M., Abbott, D.F., and Jackson, G.D. (2006). Functional connectivity networks are disrupted in left temporal lobe epilepsy. *Ann. Neurol.* *59*, 335–343.
- Wang, X.J., and Buzsaki, G. (1996). Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* *16*, 6402–6413.
- Wespapat, V., Tegnigkeit, F., and Singer, W. (2004). Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *J. Neurosci.* *24*, 9067–9075.
- Wilson, T.W., Rojas, D.C., Reite, M.L., Teale, P.D., and Rogers, S.J. (2006). Children and adolescents with Autism exhibit reduced MEG steady-state gamma responses. *Biol. Psychiatry*, in press.
- Wynn, J.K., Light, G.A., Breitmeyer, B., Nuechterlein, K.H., and Green, M.F. (2005). Event-related gamma activity in schizophrenia patients during a visual backward-masking task. *Am. J. Psychiatry* *162*, 2330–2336.
- Zeitler, M., Fries, P., and Gielen, S. (2006). Assessing neuronal coherence with single-unit, multi-unit, and local field potentials. *Neural Comput.* *18*, 2256–2281.