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Neuronal Dynamics and Neuropsychiatric Disorders: Towards a Translational Paradigm for Dysfunctional Large-Scale Networks

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In recent years, numerous studies have tested the relevance of neural oscillations in neuropsychiatric conditions, highlighting the potential role of changes in temporal coordination as a pathophysiological mechanism in brain disorders. In the current review, we provide an update on this hypothesis because of the growing evidence that temporal coordination is essential for the context and goal-dependent, dynamic formation of large-scale cortical networks. We shall focus on issues that we consider as particularly promising for a translational research program aimed at furthering our understanding of the origins of neuropsychiatric disorders and the development of effective therapies. We will focus on schizophrenia and Autism Spectrum Disorders (ASDs) to highlight important issues and challenges for the implementation of such an approach. Specifically, we will argue that deficits in temporal coordination lead to a disruption of functional large-scale networks which in turn can account for several specific dysfunctions associated with these disorders.

Neuropsychiatric Disorders: the Grand Challenge for Brain Sciences

The understanding of the origins of neuropsychiatric disorders, such as schizophrenia, affective disorders (depression and bipolar disorder), Alzheimer 's disease (AD) and Autism Spectrum Disorders (ASDs), represents one of the most urgent and challenging areas of current scientific enquiry. In Europe alone, 38 % of the general population fall into one of these categories, thus creating an enormous need for medical and psycho-social intervention (Wittchen et al., 2011). Globally, disorders affecting the central nervous system constitute 13 % of the total burden of disease (Collins et al., 2011).

Despite the prevalence of neuropsychiatric disorders and the rapid advances in the basic neurosciences, there is only little progress in understanding the pathophysiology and the development of effective therapies. In schizophrenia, for example, recent studies have shown that since the introduction of second-generation antipsychotics, treatment efficacy has only marginally improved over traditional Dopamine D-2 antagonists which were introduced 50 years ago (Lieberman et al., 2005). Moreover, recent studies have raised the possibility that chronic antipsychotic treatment could be associated with loss of brain tissue (Ho et al., 2011). As a result, schizophrenia largely remains a chronic and debilitating condition which in up to 80 % of cases leads to life-long social and occupational impairments with an average reduced life expectancy of ~ 20 years due to medical complications (Tiihonen et al., 2009).

These data clearly highlight the need to reconsider approaches towards studying and treating mental disorders in order to improve therapies and outcome and eventually provide tools aimed at prevention of disorders. Strategies for the identification and development of new drugs have so far relied essentially on serendipitous discovery which was then followed by clinical testing. Over the last decade, however, we witness a paradigm shift that emphasizes the importance of applying findings from the basic sciences to formulate and test hypotheses on disease mechanisms. Insel (2009), for example, has advocated a "reverse translational" paradigm which involves identification of risk genes and then to study in

transgenic animals whether and how the abnormal gene patterns alter brain development and function (Figure 1).

For a number of reasons, we believe that this approach needs to be complemented by the development of a paradigm, which stresses the importance of neuronal dynamics and temporal coding. This is because novel measures of the brain´s structural and functional organization have highlighted the fact that cognitive and executive functions emerge from the coordinated activity of large-scale networks that are dynamically configured on the backbone of the fixed anatomical connections. The brain´s connectome has small-world properties (Bullmore and Sporns, 2009) which implies that even neuronal groups distributed across distant cortical areas can communicate with one another either directly or via only a small number of intervening nodes. The hypothesis that we would like to propose is that the formation of functional networks requires dynamic routing and coordination and that this is achieved by modulating the degree of coherence among the temporally structured responses of widely distributed neurons. If these dynamics are disrupted, so the hypothesis, pathological states emerge which give rise to neuropsychiatric syndromes.

In this review, we shall therefore focus on recently obtained evidence supporting the possibility that disturbances in the temporal dynamics in large-scale networks might be causally involved in neuropsychiatric disorders, such as schizophrenia and Autism Spectrum Disorders (ASD). In addition, we summarize evidence that emphasizes the strong dependence of temporal variables such as oscillations and synchrony on the subtle balance between excitation and inhibition (E/I balance). Moreover, we will highlight other likely causes for abnormal neural dynamics, such as developmental modifications of circuitry and transmitter systems, and provide recommendations for the design of novel treatments.

Neuronal Dynamics in Functional Large-Scale Networks

Until recently, efforts to understand the neural basis of cognitive processes have focussed on the analysis of individual brain regions and circuits. This paradigm has been highly successful but failed to address several central issues, such as the putative importance of interactions between distributed neuronal ensembles and the role of large-scale temporal coordination in cognitive and executive processes.

Beginning with the discovery of stimulus- and context-dependent changes in neural synchrony (Gray et al., 1989), evidence has been accumulated suggesting that the brain is a self-organizing complex system in which numerous, densely interconnected but functionally specialized areas cooperate in ever-changing, context- and task-dependent constellations. One reflection of such dynamic interactions are changes in the coherence of oscillatory activity in different frequency bands. Evidence obtained over the last two decades suggests that the precise synchronization of neural responses serves the dynamic coordination of distributed neural responses in both local and extended networks and is related to a wide range of cognitive and executive processes (Buzsaki and Draguhn, 2004; Uhlhaas et al., 2009a; Varela et al., 2001).

Important and distinct variables of these dynamic processes are the power and frequency of oscillatory activity in local circuits and the long-range synchronization of these temporally structured activities across brain areas (Varela et al., 2001). Engel and colleagues (Siegel et al., 2012) have proposed that local oscillatory processes, in particular at gamma-band frequencies, serve the generic cortical computations underlying local encoding of information while long-range synchronization in various frequency bands serves the effective coupling between more remote brain regions (Fries, 2005). Previous theoretical and empirical studies have indeed shown that functional interactions between brain regions are particularly crucial for cognitive processes and can occur in the absence of changes in local activity parameters, such as discharge rate and oscillation amplitude (Hipp et al., 2011; Lima et al., 2011). Recent advances in EEG and MEG-approaches have now allowed the non-invasive mapping of changes in the large-scale networks during perceptual and higher cognitive processes (Figure 2).

Support for the distinction between local oscillatory vs. long-range synchronization processes comes from studies that have examined the frequencies at which neuronal ensembles oscillate. Local processes tend to be associated with increased oscillations at gamma-band frequencies (25-200 Hz) while long-range interactions tend to involve a larger spectrum of frequency bands comprising theta-(4-7 Hz), alpha-(8-12 Hz) and beta-(13-25 Hz) frequencies (von Stein and Sarnthein, 2000). One

reason could be that larger networks cannot support synchronization with very high temporal precision because of long conduction times, lower frequencies putting less constraints on the precision of timing because the phases of increased and reduced excitability are longer (Kopell et al., 2000).

Recent theoretical (Vicente et al., 2008) and empirical work (Buschman and Miller, 2007), however, indicates that long-range synchronization can also occur at substantially higher frequencies (> 30 Hz) and that even zero phase-lag synchronization is compatible with conduction delays. It is therefore conceivable that the nesting of local high frequency oscillations in more global, lower frequency oscillations serves the binding of local processes into more integrated global assemblies. This possibility is supported by the growing evidence on the existence of cross-frequency coupling, the amplitude, frequency or phase of high frequency oscillations being modulated by slower oscillatory processes (Canolty et al., 2006; Canolty and Knight, 2010; Jensen and Colgin, 2007; Palva et al., 2005).

Neuron clusters can participate in several networks oscillating at different frequencies by engaging in partial coherence with both of them. This concatenation of rhythms has been observed in the hippocampus for gamma- and theta-band oscillations (Wang and Buzsaki, 1996), between different cortical laminae (Roopun et al., 2008) and for both low and high-frequency activity (Canolty et al., 2006; Jensen and Colgin, 2007; Palva et al., 2005).

Dynamic Formation of Functional Networks: Cellular and Network Mechanisms of Neural Synchrony

Much work has been devoted to the analysis of synaptic mechanisms and circuits that support the generation of oscillatory activity and its synchronization over short and long distances, respectively, which makes it possible to relate abnormalities of these dynamic phenomena to specific neuronal processes (Sohal et al., 2009; Traub et al., 2004; Vicente et al., 2008; Wang and Buzsaki, 1996).

During an oscillation cycle, neurons pass through a phase of enhanced and a phase of reduced excitability. During the former, the depolarizing phase, neurons become increasingly sensitive to excitatory input and emit spikes. During the following hyperpolarizing phase, they are exposed to massive inhibition by synchronously bursting inhibitory interneurons, emitno spikes and are little susceptible to excitatory inputs (Wang and Buzsaki, 1996; Whittington et al., 1995). Thus, by adjusting oscillation frequency and phase of anatomically connected cell clusters, effective coupling between these clusters can be enhanced by assuring that the respective excitatory inputs are synchronized and arrive at the peak of susceptibility while coupling can be virtually abolished if phase relations among the oscillating clusters are such that excitatory volleys arrive during the phase of low susceptibility (Fries, 2005; Womelsdorf et al., 2007).

Experimental and theoretical evidence indicates that the networks of mutually interacting GABAergic interneurons are crucially involved as pacemakers in the generation of high-frequency oscillations in local circuits (Traub et al., 2004; Wang and Buzsaki, 1996). GABAergic interneurons, especially those expressing the calcium binding protein parvalbumin (PV), play a particularly important role in the generation of high-frequency oscillations because of their fast-spiking characteristics and the short time constants of synaptic interactions mediated by these cells (Bartos et al., 2007). In a landmark paper, Sohal and colleagues (2009) probed the influence of up- and down-regulation of PV-interneurons on gamma-band oscillations in mice. Inhibition of PV-interneurons led to an immediate suppression of 30-80 Hz oscillations while 10-30 Hz oscillations increased in power. In contrast, increasing PV-interneuron mediated feedback inhibition by boosting principal cell activity enhanced gamma-band power (Cardin et al., 2009).

Recent studies have also examined the specific role of glutamatergic inputs to PV-interneurons for the generation of coordinated network-activity. Carlen et al. (2011) examined the effect of deleting NMDA NR1-receptors on PV-interneurons applying an optogenetic approach. Mice with a reduced expression of NR1 subunits were characterized by increased spontaneous 36-44 Hz activity in somatosensory cortex compared to control animals while showing reduced gamma-band activity during sensory stimulation which was accompanied by dysfunctions in habituation, working memory and associative learning. Optic stimulation of PV-interneurons revealed diminished spike synchronization as well as increased spike latency and variance in spike timing. Similarly, Belforte et al. (2010) showed that NR1 deletion in GABAergic interneurons resulted in increased firing of pyramidal cells and reduced

synchronization of neuronal responses in slices, suggesting that NMDA-receptor hypofunctioning is associated with impaired temporal coordination of neuronal activity.

Further evidence that AMPA- and NMDA-receptor mediated activation of PV-interneurons is essential for the generation of oscillatory activity and its synchronization has been obtained in the hippocampus. Reduction of the GLuR-D receptor leads to a decrease of AMPA-mediated currents in PV-interneurons and reduced power of oscillations in the 20-80 Hz range which is accompanied by a deficit in working memory (Fuchs et al., 2007). In addition, selective ablation of the NMDA NR1-subunit in PV-interneurons is associated with a significant reduction of power, stability and rhythmicity of theta-oscillations and an enhancement of gamma oscillations in CA1 (Korotkova et al., 2010).

While the reciprocal connections between excitatory and inhibitory neurons determine the strength and duration of the oscillations and mediate local synchronization, long-range synchronization of spatially segregated cell groups has been attributed mainly to the action of excitatory pathways that target both excitatory and inhibitory neurons (Fuchs et al., 2001; Kopell et al., 2000). Specifically, modeling and experimental evidence suggests that generation of long-range synchronization is dependent on AMPA-type glutamate receptor (Fuchs et al., 2001).

Another and probably very important substrate for inter-regional synchronization are long-range inhibitory projections that originate from GABAergic cells and terminate selectively on inhibitory interneurons in the respective target areas. Such long-range inhibitory projections have been shown between the basal forebrain and the cortical mantel (Manns et al., 2000) between the two hemispheres (Buhl and Singer, 1989; Melzer et al., 2012), between septum and hippocampus (Jinno et al., 2007) and hippocampus and entorhinal cortex (Melzer et al., 2012). Given the pace-maker function of inhibitory networks, such direct coupling could provide a very efficient mechanism for the temporal coordination of distributed processes.

In addition to GABAergic and glutamatergic circuit dynamics modulatory systems play an important role in the gating of oscillations and synchrony. Thus, gamma oscillations and their synchronization depend critically on the activation of muscarinic acetylcholin-receptors (Rodriguez et al., 2004). Evidence is also available that dopamine and 5-HT modulate the prevalence of oscillations in different frequency bands (Demiralp et al., 2007; Dzirasa et al., 2009; Krause and Jia, 2005; Wojtowicz et al., 2009). However, a systematic investigation of the relevant receptor subgroups and mechanisms has only begun recently.

Neural Synchrony in Schizophrenia

Since our review in 2006 (Uhlhaas and Singer, 2006), there has been a significant expansion of studies on the role of abnormal oscillations and synchrony in schizophrenia. The overwhelming evidence points to a reduction of gamma-band oscillations during the execution of cognitive tasks (Uhlhaas and Singer, 2010). This has been demonstrated for a wide range of cognitive and perceptual paradigms, including working memory (Haenschel et al., 2009), executive control (Minzenberg et al., 2010) and perceptual processing (Ford et al., 2008; Hirano et al., 2008; Spencer et al., 2003; Uhlhaas et al., 2006) in both chronic and unmedicated patient populations (Minzenberg et al., 2010). The pattern of impairment is consistent with the view that gamma-band activity is constitutive for normal cortical functions (Fries, 2009) the disturbance of which leads to the disruption of a wide spectrum of cognitive deficits (Uhlhaas and Singer, 2010).

Schizophrenia is associated with a substantial genetic predisposition and there is evidence that disturbances of neural oscillations and synchrony are an endophenotype (Figure 3). Reduced auditory evoked gamma-band activity has been demonstrated in first-degree relatives of patients with schizophrenia as well as in unaffected, monozygotic twins with a high degree of heritability (Hall et al., 2011). Hong et al. (2008) examined evoked theta- and alpha-band oscillations during sensory-gating in patients with schizophrenia, their relatives and healthy controls. Theta- and alpha-band activity was significantly impaired in schizophrenia patients and first-degree relatives and the heritability of theta- and alpha-band gating abnormalities was estimated to be between 0.49 and 0.83 and was at least 4-fold higher than that of the P 50 event-related potential (ERP), suggesting that parameters defining oscillations and synchrony are ideal endophenotypes (Figure 3).

An important issue for the interpretation of deficits in task-related oscillations is the question whether there is a constitutive impairment of

mechanisms generating high-frequency oscillations or whether the deficit is apparent only during task performance. Recent studies point to the possibility that the pattern of spontaneously occurring gamma-band oscillations may differ from that associated with cognitive processing. Kikuchi et al. (2011) examined resting-state EEG-data in medication-naïve, first-episode patients with schizophrenia and healthy controls and found significantly elevated gamma-band power over frontal electrodes in patients. A similar finding was reported by Spencer et al. (2012) who showed significantly increased ~ 40 Hz baseline source-power in chronic patients with schizophrenia. Thus, it is unclear, at present, whether this elevated baseline activity is responsible for the relative reduction of stimulus induced oscillatory responses in the gamma-band range.

Neural Synchrony in Schizophrenia: Evidence for a Dysfunctional Balance between Excitatory and Inhibitory Mechanisms (E/I Balance)?

The data on spontaneous gamma-band activity suggests the possibility that circuits in schizophrenia patients can readily support the generation of high frequency oscillations, raising the interesting question why pronounced abnormalities occur in task-induced activity. Insights into possible causes of aberrant gamma-band activity in schizophrenia come from studies that have examined the effects of NMDA-receptor antagonists on neural synchrony. Administration of MK-801 in the PFC of awake rodents leads to an increased spiking activity in pyramidal cells (Homayoun and Moghaddam, 2007), presumably by a disproportionally strong reduction of efficacy of excitatory input to inhibitory interneurons. The resulting disinhibition then causes a shift in the E/I balance in favor of excitation of pyramidal cells (Homayoun and Moghaddam, 2007).

One consequence of increased cortical excitability is an upregulation of spontaneous high-frequency oscillations. Pharmacological and genetic manipulations leading to a downregulation of NMDA-receptor activity have consistently demonstrated an increase of gamma-band activity during rest (Carlen et al., 2011; Phillips et al., 2012; Pinault, 2008; Saunders et al., 2012) as well as an increased coupling between gamma-rhythms in layer III and V in visual cortex (Anver et al., 2011) (see Table 1). Manipulation of NMDA-subunits suggests that the GluN2A subunit may play a special role in the dysregulation of gamma-band activity (Kocsis, 2011) which is consistent with the fact that the GluN2A subunit is primarily expressed in PV-interneurons (Kinney et al., 2006).

Thus, the dysregulation of spontaneous gamma-band activity in schizophrenia patients and also in experimental settings following NMDA-receptor blockade supports the hypothesis of reduced NMDA-receptor functioning in schizophrenia (Kantrowitz and Javitt, 2010). However, in healthy volunteers acute administration of ketamine, an NMDA-receptor antagonist, has been reported to enhance not only resting state gamma-band but also stimulus induced gamma-band activity (Hong et al., 2010; Plourde et al., 1997). This finding needs further testing because in animal models, NMDA-antagonists lead to a decrease of gamma-band oscillations during cognitive tasks (Saunders et al., 2012).

Although the data reviewed suggest a special relationship between NMDA-receptors on PV-interneurons and schizophrenia, it is important to note that NMDA-receptors are highly expressed on excitatory, especially pyramidal cells, while they are relatively sparse in PV-interneurons (Geiger et al., 1997; Wang and Gao, 2009). This raises the question of how reduced NMDA-receptor mediated excitatory currents can lead to an upregulation of gamma-band activity. One possibility is that this effect is related to the different EPSC kinetics of NMDA and AMPA-receptors. AMPA-mediated EPSPs in PV-interneurons have short time constants (fast kinetics) and are ideally suited to support gamma-band oscillations (Gonzalez-Burgos and Lewis, 2012) while the long time constants of NMDA-receptor mediated EPSCs could have a dampening effect on fast oscillations. This is consistent with the evidence that reduction of AMPA- but not NMDA-mediated drive impairs high-frequency oscillations (Traub et al., 1996). Further research is required to clarify this important issue.

Another non-exclusive possibility is that NMDA-receptor hypofunction impairs long-range synchrony and thereby reduces coordination of large scale networks. Cortico-cortical projections terminate preferentially in superficial cortical layers and distal segments of apical dendrites of pyramidal cells, which are rich in NMDA receptors (Monaghan and Cotman, 1985; Rosier et al., 1993). Thus, reduced NMDA receptor function may have a dual effect, an augmentation of local gamma activity and a liberation of local gamma oscillators from the coordinating action of long-range

connections. The result would be increased autonomy of local processors and reduced coordination of globally ordered states. Thus, positive symptoms could be the result of impaired communication between cortical regions (Hoffman and McGlashan, 1993). Indeed, there is preliminary evidence which suggests that local beta- and gamma-band oscillations are increased in patients with schizophrenia experiencing auditory hallucinations (Lee et al., 2006; Mulert et al., 2011).

In interpreting the effects of NMDA-receptor blockade, it is important to consider the differential effects of acute vs. chronic administration of NMDA-receptor antagonists (Jentsch and Roth, 1999) and further research has to compare the effects of acute vs. chronic NMDA-hypofunctioning on neural synchrony. This is because prolonged NMDA-receptor hypofunction is associated with reduced GABAergic neurotransmission which has been confirmed in several studies (Behrens et al., 2007; Zhang et al., 2008), suggesting that the alterations of GABAergic interneurons found in post-mortem studies of schizophrenia patients (Lewis et al., 2012) could be a consequence of a NMDA-receptor hypofunctioning.

However, it should be noted that altered neural synchrony can have many causes because several animal models of schizophrenia that involve quite different mechanisms are associated with aberrant synchrony and power of oscillatory activity (Table 1). Thus, it is unclear whether changes in the E/I-balance reflect a primary pathophysiological process or whether they are secondary consequences of altered network activity.

Neural Synchrony in Autism Spectrum Disorders

In our previous review (Uhlhaas and Singer, 2006), we interpreted ASDs as a syndrome in which the pattern of cognitive impairments and known physiological abnormalities made the involvement of aberrant neural synchrony an important and testable hypothesis (Uhlhaas and Singer, 2007). Yet at the time, very little direct evidence was available. By now, several EEG/MEG-studies have examined neural synchrony during cognitive functions and resting-state, supporting a role of altered neural synchrony in the pathophysiology of ASDs.

In children with ASDs, there is consistent evidence for a reduction of high-frequency oscillations during sensory processing. Similar to patients with schizophrenia, children and adolescents with ASDs are characterized by reduced entrainability of auditory circuits to stimulation at 40 Hz. This reduction is particularly pronounced in the left hemisphere (Wilson et al., 2007). Children with ASDs also show reduced phase-locking of beta- and gamma-band oscillations relative to normal children during illusory contour processing (Stroganova et al., 2011). Milne et al. (2009) presented Gabor patches of varying spatial frequency to 20 children with ASDs and 20 controls, assessing both ERPs and induced oscillations from EEG-data. In children with ASDs, alpha- and gamma-band power in or near the striate or extrastriate cortex was less modulated by variations in the spatial frequency of stimuli, suggesting reduced stimulus selectivity and/or entrainability of cortical circuits in visual areas. These alterations could in turn be responsible for the known impairments in perceptual binding (Dakin and Frith, 2005).

Alterations in large-scale functional networks may be furthermore relevant for early detection and diagnosis. Dinstein and colleagues (2011) examined interhemispheric functional connectivity in fMRI-data in toddlers with ASDs during sleep. Toddlers with ASDs exhibited significantly reduced connectivity between language areas of the two hemispheres relative to normally developing children and toddlers with language delay. Moreover, the degree of reduced interhemispheric connectivity correlated with verbal ability and severity of ASD-symptoms, highlighting the potential contribution of impaired large-scale interactions during the early pathogenesis of ASDs. These findings have to be interpreted cautiously, however, because amplitude and synchrony of neural oscillations undergo important developmental modifications (Uhlhaas et al., 2010). Hence, differences in neural synchrony during early development could also reflect differences in developmental trajectories between normally developing children and children with ADS. Therefore, it is important to also test abnormalities in adult populations with ASDs to clarify to what extent aberrant neural synchrony is pathognomonic for this syndrome.

In a recent study (Sun et al., 2012), we examined the possibility that gamma-band activity may be crucially involved in aberrant brain functioning in ASD (Figure 4). MEG-data were recorded from 13 adult participants with ASDs and 16 controls during the presentation of Mooney faces. Impaired perceptual organization in the ASD

group was accompanied by a reduction in both the amplitude and phase-locking of gamma-band activity in the 60-120 Hz frequency range. A beamforming approach identified distinct networks during perceptual organization in controls and participants with ASD. In controls, perceptual organization of Mooney faces involved increased 60-120 Hz activity in a fronto-parietal network while in the ASD group, stronger activation was found in visual regions. These findings highlight the possibility that impaired gamma-band activity, in particular the atypical modulation of high-frequency power in frontal-posterior networks, causes some of the complex disturbances of visual processing in ASD. This pattern of dysfunctional gamma-band activity is also consistent with anatomical and fMRI findings that suggest that fronto-posterior networks are differentially affected in ASD (Schipul et al., 2011).

Evidence also indicates dysfunctional resting-state oscillations in adult subjects with ASDs. Murias et al. (2007) examined resting-state EEG-data in 20 subjects with ASDs and found increased theta-activity in the left hemisphere and reduced long-range coherence in the low alpha band (8-10 Hz). Similar evidence for a shift towards increased local connectivity has been observed in the delta-band by Barttfeld and colleagues (2011), suggesting a dysbalance between local and global processing. This is consistent with pathophysiological theories that postulate increased connectivity in local and reduced connectivity in long-range circuits (Geschwind and Levitt, 2007).

Further evidence for abnormal gamma-band activity comes from studies in first-degree relatives of children with ASDs. Similar to the findings in children with ASDs, both the power and phase-locking of gamma-band oscillations to auditory 40 Hz stimulation are reduced in the left hemisphere in first-degree relatives (Rojas et al., 2011), suggesting that dysfunctions in sensory-driven gamma-band activity may represent an intermediate endophenotype.

E/I Dysbalance in ASDs

The pronounced alterations of gamma-band oscillations suggest that changes in the E/I balance of cortical networks may be a pervasive feature not only in schizophrenia but also in ASDs (Gogolla et al., 2009a; Rubenstein and Merzenich, 2003). Several lines of evidence support this possibility. ASD is associated with a high incidence of epilepsy (Tuchman and Rapin, 2002), altered expression of various GABA-receptor subtypes (Fatemi et al., 2002; Oblak et al., 2010) and dysfunctions in glutamatergic neurotransmission (Choudhury et al., 2011). Studies with larger samples, however, are required to further characterize the nature and extent of these changes.

Investigations of risk-factors and genes involved in the development of ASDs have revealed changes in PV-interneurons. Prenatal exposure to Valproic Acid (VPA), an anti-epileptic drug, leads to a 7-10 fold increase in relative risk for ASDs (Moore et al., 2000) and mice prenatally treated with VPA show a dramatic reduction of PV-interneurons in adulthood in the neocortex (Gogolla et al., 2009b). The reduction of PV-interneurons is consistent with a recent study that has examined the effect of pre-natal VPA exposure on gamma-band activity in mice (Gandal et al., 2010). VPA-exposed mice demonstrated selective behavioral alterations related to ASDs as well as reduced phase-locking of 30-50 Hz oscillations to auditory stimulation. Paralleling the findings from the animal model, children with ASDs showed a similar decrease in phase-locked gamma-band activity in both hemispheres. In addition, there is also evidence that VPA-exposure can lead to NMDA-receptor dysfunctions and aberrant long-term potentiation (LTP) because VPA-treated mice exhibit augmented susceptibility for LTP and enhanced expression levels of the GluN2A and GluN2B subunits (Rinaldi et al., 2007). However, examination of post-mortem tissue and blood samples has so far yielded conflicting evidence for the presence of abnormalities in glutamatergic neurotransmission in ASDs (Markram and Markram, 2010).

Data on gene expression levels support changes in GABA- and NMDA-receptor mediated neurotransmission in ASDs. Voineagu et al. (2011) examined gene-expression levels in frontal and temporal cortices of cases with ASDs and found alterations in genes that are involved in the regulation of interneurons, suggesting that the phenotype of ASDs is mediated by abnormal GABAergic neurotransmission. Similarly, mutations of the MeCP2 gene, that has been linked to a variety of neuropsychiatric disorders, including Rett-syndrome, autism and childhood-onset schizophrenia, are associated with impaired GABAergic signaling in forebrain neurons and several behavioral features characteristic for ASDs, such as repetitive and impaired social behavior (Chao et al., 2010). Recently, Goffin et al. (2012)

furthermore showed that a mutation of the MeCP2 gene in mice leads to a reduction in amplitude and phase-locking of event-related oscillations at both low- and high-frequencies.

Maturation of E/I Balance and Neural Synchrony in ASDs and in Schizophrenia

The evidence reviewed suggests that there is substantial overlap between schizophrenia and ASDs with respect to deficits in neural synchrony and abnormalities in mechanisms supporting the generation of oscillations and synchrony. These indications for shared pathophysiological mechanisms are consistent with recent genetic data that have shown overlap between risk genes of both disorders (Guilmatre et al., 2009). However, there are also important differences between the two phenotypes, in particular in relation to the developmental periods at which the clinical symptoms emerge. ASDs are typically diagnosed during early childhood while schizophrenia typically manifests itself in late adolescence, raising the question which events determine these distinct time courses. In the following section, we will review recent evidence on fundamental changes in the E/I balance during development that might account for the distinct developmental trajectories of ASDs and schizophrenia and provide cues for the development of effective treatments.

Early Development of Cortical Circuits and E/I-Balance

GABAergic neurotransmission is critically involved in the development of early cortical circuits and undergoes important modifications that in turn are fundamental for the temporal patterning of neuronal activity. GABA is the main inhibitory transmitter in the adult brain but during early development, GABA has an excitatory, depolarizing effect due to an altered chloride equilibrium and plays a central role in regulating cortical development (Ben-Ari et al., 1989; Luhmann and Prince, 1991; Wang and Kriegstein, 2009).

PV-interneurons which underlie the generation of high-frequency oscillations in the adult cortex are particularly important for the regulation of the time course of development and plasticity (Hensch, 2005). Expression of PV-interneurons in the visual cortex of rodents begins near postnatal day (PD) 12 and matures around PD21 (del Rio et al., 1994). Gene-targeted deletion of the GABAergic synthetic enzyme GAD65 in mice abolishes developmental plasticity but this loss can be rescued at any age with benzodiazepines (Fagiolini and Hensch, 2000; Iwai et al., 2003). Thus, early abnormalities of GABAergic neurotransmission could have severe consequences for the experience dependent development of cortical circuits. This hypothesis is supported by evidence that inhibitory mechanisms impact on the structural organization of cortical circuits during normal development through modifications in the synchrony and amplitude of neural oscillations (Bonifazi et al., 2009).

Moreover, there is compelling evidence from studies on the development of connections in the visual system that correlated activity plays a crucial role in the selection of axonal projections (Katz and Shatz, 1996; Meister et al., 1991) for review see (Singer, 1995) and that neural synchrony undergoes important modifications during early developmental periods (Khazipov and Luhmann, 2006). Specifically, oscillatory entrainment between cortical and limbic structures at theta-frequencies, which is important for information transfer and higher cognitive functions, such as memory (Colgin, 2011), undergoes important maturation during the first postnatal weeks in mice (Brockmann et al., 2011). Similarly, gamma-band oscillations emerge during PD 0-7 and enable precise spatiotemporal thalamo-cortical synchronization in sensory systems which could - in analogy to pathway selection in the visual system - contribute to the formation of topographically distinct functional connections (Minlebaev et al., 2011).

From this perspective, it appears likely that genetic aberrations could cause early modifications in the E/I balance in ASDs and that the resulting disturbances of network dynamics jeopardize the self-organizing mechanisms required for the formation of canonical circuits and maps. In addition, also the experience dependent developmental processes would be impaired that are indispensable for the use-dependent fine tuning of networks and the generation of higher cognitive functions.

Adolescent Modifications in the E/I-balance as a Critical Factor for the Pathophysiology of schizophrenia

Recent data suggest that the E/I-balance continues to undergo important modifications during the transition from adolescence to adulthood which has consequences for the precision of temporal coordination and the dynamics of large-scale

cortical networks (Uhlhaas and Singer, 2011). These late developmental changes could be important for understanding neuropsychiatric disorders with late onset, such as schizophrenia (Uhlhaas, 2011).

While the number of GABAergic cells undergoes only small modifications during the adolescent period, axons of PV-containing basket and chandelier neurons seem to undergo modifications (Hoftman and Lewis, 2011). For example, there is evidence that the density of PV-positive axon terminals of basket cells increases during adolescence (Erickson and Lewis, 2002) and similar findings have been reported for the density of axon cartridges of chandelier neurons (Cruz et al., 2003).

Changes in GABAergic neurotransmission also comprise modifications in the subunit composition of GABA receptors. Hashimoto et al. (2009) described a decrease of GABAA receptor α2 subunits and an increase of α1 subunits with age in the monkey dorsolateral prefrontal cortex (DLPFC). This change is accompanied by marked alterations in the kinetics of IPSCs, including a significant reduction in the duration of miniature IPSCs in pyramidal neurons. The shift in GABAergic subunit expression could lead to an increase in the precision of temporal patterning as the time course of IPSPs is an important determinant for the frequency at which a network can oscillate (Wang and Buzsaki, 1996).

In addition, there are changes in excitatory and modulatory systems that lead to a modification of inhibitory processes, such as alterations of the dopaminergic modulation of prefrontal interneurons (Tseng and O'Donnell, 2007), and the reconfiguration of NMDA- and AMPA-receptors in fast-spiking (FS) interneurons. Wang and Gao (2009) examined the changes in cell-type specific development of NMDA-receptors in rat PFC. During brain maturation, NMDA-currents in FS-interneurons got reduced, leading to an increase of the AMPA/NMDA current ratio. Thus at PD 15-28, 72.7 % of FS-interneurons showed a prevalence of NMDA-mediated currents while during adolescence, this value is reduced to 26.1 %. This important findings requires further investigation because it is currently unclear if the reduction of NMDA-currents in FS-interneurons occurs throughout cortex and whether this change in AMPA/NMDA-ratio is related to the finding that psychotic symptoms through ketamine administration can only be elicited in adults but not children (White et al., 1982).

Developmental changes in the susceptibility of neural circuits to NMDA-receptor blockade are also indicated by data showing that certain physiological effects of NMDA-hypofunction are only observed in mature cortex but not during earlier developmental periods. For example, Zhang et al. (2008) treated rats for two days with Ketamine and observed reductions in both frequency and amplitude of mIPCS as well as a decrease in GAD 67 in adult rats but not in pubs at PD 35.

The reorganization of excitatory and inhibitory transmission during adolescence is paralleled by profound changes in neuronal dynamics and behavior. Single-unit recordings in the orbitofrontal cortex (OFC) of adolescent rats showed increased firing frequency and firing rate variability compared to adult rats (Sturman and Moghaddam, 2011), suggesting reduced neuronal inhibition in prefrontal circuits which could impact on the occurrence of precisely coordinated oscillations. This is supported by recent evidence that substantial changes in the amplitude of oscillations and their synchronization have been found to occur in the adolescent brain in humans (Uhlhaas and Singer, 2011). Specifically, modifications of cortical circuits during adolescence are accompanied by an increase in the power of gamma-band activity as well as an increase in long-range synchrony in the theta-, beta- and gamma-bands which were preceded by a transient destabilization of cortical networks in late adolescence (Uhlhaas et al., 2009b).

Neural Synchrony in Schizophrenia and ASDs: The Development of a Translational Paradigm for Psychiatry

In our review, we have attempted to summarize the advances in understanding aberrant neural synchrony in schizophrenia and ASDs and the potential role of dysfunctions in the E/I- balance. While we focused in our initial paper in 2006 (Uhlhaas and Singer, 2006) on the phenomenological changes in oscillations and their synchronization in several neuropsychiatric disorders, we believe that the advances made since then in the analysis of putative mechanisms are substantial enough to justify the search for novel cures and preventive efforts.

These novel data emphasize the close relations between, genetics, developmental changes in signaling cascades - especially those involving

inhibitory mechanisms and NMDA-receptors - abnormal brain dynamics and the disturbed cognitive functions in shared neuropsychiatric disorders. If temporal coordination of neuronal response patterns by synchronization and phase locking serves the transient and context dependent formation of functional networks, disturbance of these processes would be equivalent with functional disconnection and a disorganization of global brain states. Thus, considering psychiatric disorders as a reflection of disturbed temporal coordination of distributed brain processes – a disruption of globally ordered dynamic states - might be a promising avenue for further search of causes and therapeutic interventions.

Specifically, we propose that measures of temporal coordination are promising translational tools that are ideally suited to identify novel therapeutic targets. Because of the improved knowledge about the generating mechanisms of oscillations and their synchronization, this may further stimulate hypothesis-driven research into the pathophysiological origins of schizophrenia and ASD. While it is perhaps only now that such an ambitious endeavor can be attempted because of the substantial advances in basic neuroscience, we would like to note a number of important issues that we consider pertinent for the success of such a research program.

Emphasis on Dynamics in Large Scale Functional Networks

As a starting point in search for pathophysiological mechanisms we consider the level of large-scale dynamics in cortical circuits because no micro- or macroscopic lesion has been identified that is causally related to the development of major neuropsychiatric disorders. This perspective is consistent with recent evidence for alterations in the organization of the connectome in schizophrenia but also in ASD (Fornito et al., 2012; Shukla et al., 2011). Accordingly, these organizational changes of cortico-cortical connections could impact on the establishment of large-scale functional interactions that in turn could lead to cognitive deficits and clinical symptoms. This perspective furthermore predicts that impairments in any one of the multiple mechanisms that are involved in assuring the integration of local processes into globally ordered states can lead to similar disturbances of cognitive functions and agrees with the evidence for a multifactorial genesis of psychiatric disorders and the diverse risk factors that can lead to aberrant neural synchrony in animal models of schizophrenia (Table 1).

The validity of diagnostic categories in psychiatry is the subject of a long-standing debate and comparison between the phenomenology of classical disorder categories with spectral fingerprints (Siegel et al., 2012) characterizing the dynamics of complex, self-organizing systems may address this important issue. There is evidence for impairments in neural synchrony in bipolar disorder because auditory-steady state responses (O'Donnell et al., 2004) as well as long-range coherence (Ozerdem et al., 2010) are significantly impaired, paralleling findings in patients with schizophrenia (Kwon et al., 1999; Uhlhaas et al., 2006) which is consistent with a substantial overlap in biological vulnerability between the two syndromes (Hill et al., 2008). Yet, dysfunctional gamma-band activity may not extend to other disorders, such personality or mood disorders (Lenz et al., 2011).

We would like to note that the wide range of oscillation frequencies provides an additional parameter that can be used to delineate disorder-specific neuronal dynamics, which can then be used to identify the underlying physiological mechanisms. Estimates of neural synchrony might also be used to assign patients into novel disease categories. Fingerprints of neuronal dynamics, such as alterations in the frequency, temporal precision, phase locking and topology of neuronal oscillations, both during processing and resting state may provide novel criteria for differential diagnoses. Resting-state activity may be particularly suited for this purpose because it has been shown that spontaneous activity is not random but highly structured (Hipp et al., 2012) and that these structures are genetically heritable (Linkenkaer-Hansen et al., 2007), reflecting the coherent activation of functional networks that maintain representations of internal states (Deco et al., 2011).

Methodological Challenges

A crucial prerequisite for an approach which emphasizes large-scale neuronal dynamics are imaging tools that have sufficient temporal and spatial resolution. Until recently, studies investigating the spatial organization of large-scale cortical networks could only be conducted with MRI/fMRI because advanced source-analysis techniques for electrophysiological data which complement the excellent temporal resolution of EEG/MEG were not available. However, recent studies which have mapped oscillatory cortical

networks during cognitive and executive processes have demonstrated the feasibility of this approach (Chaumon et al., 2009; Grutzner et al., 2010; Jokisch and Jensen, 2007; Palva et al., 2010; Roux, 2012) (Figure 2).

So far, electrophysiological studies in schizophrenia and ASD have largely focused on obtaining amplitude estimates of spectral power at the sensor level. While the fluctuation of gamma-band power is an important variable that reflects changes in the E/I-balance, it nonetheless provides only limited insights into the dynamics of extended cortical circuits. This is demonstrated, for example, by the fact that local cortical circuits of schizophrenia patients may not have an intrinsic deficit to generate high-frequency oscillations. It is therefore conceivable that power-fluctuations reflect only the tip of the iceberg of aberrant network dynamics and that the pathognomonic factors are only revealed by considering the integration of local oscillators into coherently organized global brain states. This perspective is consistent with a long-standing hypothesis in schizophrenia research that clinical symptoms and cognitive deficits are the result of a dysconnection syndrome which emphasizes abnormal interactions between brain regions (Bleuler, 1911; Friston, 1998; Wernicke, 1906).

Thus, future studies should employ novel measures that allow for the testing of time and frequency sensitive neuronal interactions between cortical regions. Preliminary results obtained with scalp-recorded EEG-data have highlighted alterations in long-range synchronization at beta- and gamma-band frequencies (Spencer et al., 2003; Uhlhaas et al., 2006). However, because of the methodological problems and low spatial resolution of these approaches, we suggest that this promising approach should be complemented by source-reconstruction of EEG- and MEG-data which allow better insights into the dynamics and organization of extended functional networks (Palva and Palva, 2012).

Additional problems remain that deserve careful consideration when interpreting the EEG/MEG data for clinical and non-clinical applications. One issue is the contribution of eye movement related artifacts, the saccadic spike potentials (SSPs), which are produced by saccades and mircosaccades and mimick gamma oscillations in bandpass filtered EEG- and MEG-recordings (Carl et al., 2012; Yuval-Greenberg et al., 2008). Similarly, muscle artifacts can constitute another non-neuronal source of high-frequency activity that, if not carefully removed, can simulate power modulations in the gamma-band range (Whitham et al., 2007).

Finally, an important issue concerns the detection of an oscillatory process vs. the possibility of spectral changes due to spiking activity. Recent studies which have examined the involvement of high (> 60 Hz) gamma-band activity in cortical processes in MEG (Grutzner et al., 2010; Vidal et al., 2006) and intracranial electroencephalographic (iEEG) recordings in humans (Canolty et al., 2006; Crone et al., 2001) suggest that gamma-band activity extends to frequencies up to 200 Hz (Crone et al., 2011; Uhlhaas et al., 2011). It is questionable, however, whether broad-band spectral power increases actually reflect oscillatory processes. Unless the spectral analysis of this activity shows a clear "bump" in a particular frequency range, modulation of broad band activity that extends into to the gamma-band range is likely to reflect the sum of local synaptic events and action potentials and hence just the level of local cortical activation (Uhlhaas et al., 2011).

Challenges for Translational Research

Significant progress has been made in the identification of the mechanisms generating high-frequency oscillations in local circuits and this has sparked a large body of research on the effects that genetic, pharmacological and developmental manipulations have on PV-interneurons and gamma-band oscillations in animal models of schizophrenia and ASD. This work clearly demonstrates the feasibility of using aberrant network dynamics observed in patient populations as an endophenotype of disease mechanisms at the circuit level.

Nonetheless, if neuronal dynamics in large-scale cortical networks are pathognomonic for a particular disorder, then translational research needs to focus also on macroscopic analyses. In this context, one important question is how the dynamic regulation of effective coupling between spatially segregated cell populations is implemented during normal brain functioning and how synchronization is achieved over longer distances. As pointed out above, long-range synchronization has been assumed to be mediated predominantly by glutamatergic projections (Fuchs et al., 2001; Kopell et al., 2000). Yet, recent evidence suggests that GABAergic long-range projections are more frequent than assumed previously and are likely to

play an important role in long-range synchronization as well (Buhl and Singer, 1989; Jinno et al., 2007; Melzer et al., 2012). Finally, one needs to consider that higher-order thalamic nuclei, such as the pulvinar and the intra-laminar nuclei, which are all reciprocally connected with cortical areas, might play an important role in the temporal coordination of distributed cortical processes (Saalmann et al., 2012). These possibilities call for further research on mechanisms securing coherent brain states and could provide novel targets for treatment.

Such strategies need to be accompanied by the development of animal models with a stronger focus on changes in inter-areal synchronization. Recent evidence suggests that this is feasible and that relations exist between aberrant synchronization across prefrontal and hippocampal ensembles in rodents and observations in schizophrenia patients (Meyer-Lindenberg et al., 2005; Sigurdsson et al., 2010). However, investigations of neuronal dynamics in smaller brains, such as rodents, may not be fully generalizable. It is conceivable that the significant expansion of the neocortex in primates required strategies for large-scale coordination that differ from those of rodents. Therefore, testing of pathophysiological models in non-human primates may turn out to be indispensable.

Moreover, translational research into the causes of aberrant neural synchrony in schizophrenia and ASD may be critically aided by the simulation of neuronal dynamics. Recent advances in computational neuroscience have shown that properties of neural circuits can be captured by large-scale models which successfully predict, for example, the relationship between parameters of E/I-balance and the occurrence of gamma-band oscillations (Neymotin et al., 2011; Volman et al., 2011). Accordingly, computational neuropsychiatry (Montague et al., 2012) may become a critical component for a translational paradigm in the investigation of large-scale networks which could constitute an important link between the macroscopic level of neuronal dynamics captured by EEG/MEG-data on the hand, and the circuit level in animal models on the other.

Implications for Treatment and Prevention

We believe that the data reviewed may already have implications for a targeted search of novel treatments and preventive efforts. Over the last 50 years, the pharmacological therapy of schizophrenia was based mainly on the dopamine hypothesis and made little progress (Lieberman et al., 2005). While effective in reducing the positive symptoms, the cognitive dysfunctions and negative symptoms, two major determinants for outcome and level of functioning, remained unchanged in the large majority of patients.

In view of the converging evidence for disturbed E/I-balance and the resulting changes in brain dynamics that are caused by alterations in GABAergic and glutamatergic neurotransmission, the search for drug targets should be intensified that restore E/I-balance. Evidence on the efficacy of this approach is still sparse with some studies showing modest benefits (Heresco-Levy et al., 2004) while other studies could not confirm efficacy in improving, for example, cognition in patients with schizophrenia (Buchanan et al., 2011).

Treatment strategies should also consider that circuit dysfunctions may undergo changes during the course of the disorder. Accordingly, different interventions may be required at different phases (Wood et al., 2011). Proton magnetic resonance spectroscopy (1-H MRS) has revealed, for example, that GABA and Glutamate concentrations are increased in unmedicated, first-episode patients but reduced in chronically medicated patients (Kegeles et al., 2012), suggesting that E/I-balance shifts during the course of the illness. Another possibility for therapeutic interventions is suggested by the protracted developmental trajectory of brain dynamics that undergoes marked changes in late adolescence. The manifestation of schizophrenia during the transition from late adolescence to adulthood is preceded by an extended period of mild psychotic symptoms and cognitive dysfunctions (Klosterkotter et al., 2001; Yung and McGorry, 1996) and improvement in therapeutic success will very likely involve early interventions that should ideally be initiated prior to the full manifestation of the clinical symptoms.

One crucial prerequisite for early intervention is the development of biomarkers that allow the identification of at-risk individuals prior to the outbreak of the full syndrome. However, search for biomarkers has so far focused mainly on anatomical and functional magnetic resonance imaging. These methods should be complemented by techniques capturing the fast dynamics of large-scale cortical networks since measures of temporal coordination may be better suited to detect early abnormalities in the development of global brain dynamics.

Finally, one might conceive of interventions that modulate brain dynamics by bio-feedback and electrical stimulation. There is increasing evidence that transcranial magnetic and transcranial direct current stimulation (TMS/tDCS) can be applied as tools to modulate neuronal oscillations and large-scale synchrony in a frequency specific way. Polania et al. (2012) showed that tDCS at theta-frequency can facilitate fronto-parietal synchrony and Vaadia (2012, personal communication) showed that monkeys can be trained to selectively enhance gamma-band oscillation in the motor cortex if they are rewarded for power increases of local-field potential oscillations recorded from motor cortex. The potential of these novel approaches for the remediation of cognitive deficits needs to be investigated further.

Conclusion

We have focused in this review on schizophrenia and ASD, but it is likely that alteration in brain dynamics play an important role also in other neurodegenerative disorders, such as Parkinson's Disease (PD), Alzheimer 's disease (AD), multiple sclerosis and certain affective disorders. Impaired neural synchrony has been demonstrated in some of these syndromes, suggesting the possibility that deficits in large-scale coordination may be causally related to the cognitive and executive deficits associated with these disorders.

Notwithstanding the conceptual and methodological challenges, we believe that neural oscillations and their synchronization are valid markers of large-scale coordination of distributed brain functions and therefore ideally suited for a translational paradigm aimed at deciphering the causes of brain disorders. As we have pointed out previously, the conditio sine qua non for a successful translation of data obtained from basic research to clinical observations is the appropriate lingua franca, i.e. a language shared between different disciplines. Synchrony parameters can readily be quantified and standardized in electrophysiological recordings from animal models, healthy human subjects and patients, allowing for a fruitful integration of basic and clinical research and for the testing of specific hypotheses.

The extension of translational paradigms to the analysis of the dynamics of large-scale cortical networks will likely advance our understanding of the origins of complex neuro-psychiatric disorders which remain a daunting challenge for science and society. In addition to the potential impact on the design of novel therapies, we also believe that such an extension will provide further insights into the functional significance of temporal coordination for normal cognitive functions and behavior. This is an important issue as most of the data on neuronal response properties and systems dynamics are only correlative in nature. Studying disease mechanisms is a powerful strategy to establish causal links between neuronal processes and functions.

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Figures

Figure 1. Traditional and Translational Paradigm in Psychiatry

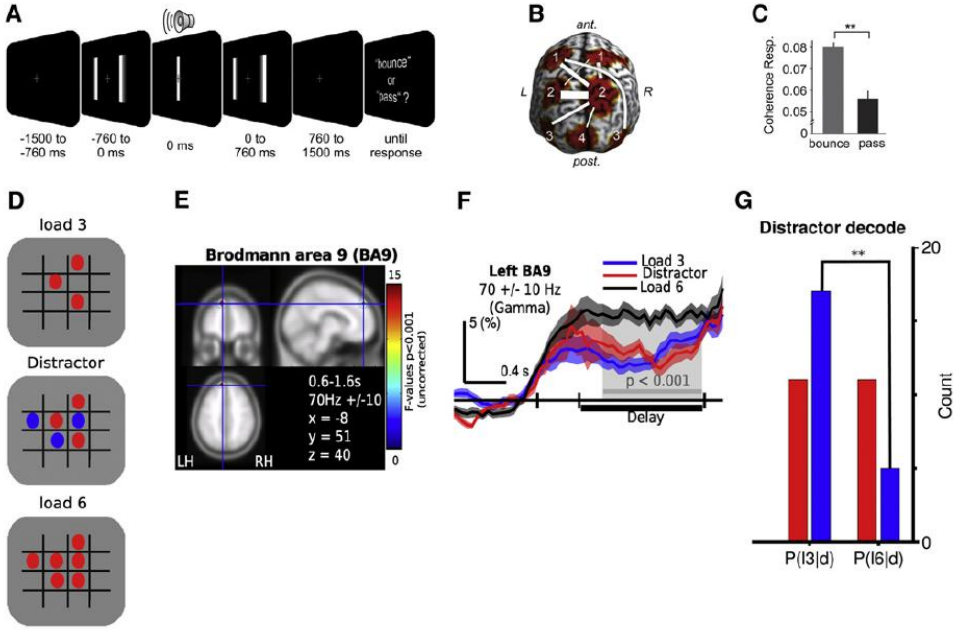

Figure 2. Advances in EEG/MEG-Approaches towards Identifying Large-Scale Functional Networks

Top Panel: Long-range beta/gamma-band synchrony in EEG-recordings predicts perception.

a) On each trial, participants fixated a central cross while two moving bars approached each other, overlapped, and diverged again (total duration, 1.52 s). At the moment of overlap (t = 0 s), a click-sound was played (duration, 0.02 s). The stimulus was either perceived as two bars passing each other (pass) or bouncing off each other (bounce).

b) Long-range beta-band coherence (15–23 Hz) between the fronto-parietal and visual cortex for bounce and pass percepts. Line-width represents relative coherence strength. 1, frontal cortex; 2, posterior parietal cortex; 3, lateral occipitotemporal cortex; 4, medial occipital cortex. Sources of oscillatory activity were reconstructed with a beamforming approach.

(D) Coherence response relative to prestimulus baseline within the beta-network (mean ± SEM) shows higher beta-band activity for bounce vs. pass percepts. Receiver operating characteristic (ROC) analysis revealed that, even on a single-trial level, the strength of beta-coherence significantly predicted the subjects' percept (permutation-test, $p < 0.0001$).

Adapted from Hipp, J.F., Engel, A.K., and Siegel, M. (2011). Oscillatory synchronization in large-scale cortical networks predicts perception. Neuron 69, 387-396.

Bottom Panel: Gamma-band activity in human prefrontal cortex codes for the number of items maintained during working memory. a) The visuo-spatial working memory task: On one third of the trials, participants were shown three red discs together with three blue discs (distractors) and participants were asked to memorize the positions of the red discs only and to ignore the positions of the blue discs. In the remaining trials, distractors were absent and either three or six red discs were presented. After a maintenance phase of 1.2 s, a test item was presented at a position identical (match) or different (non-match) to the sample array.

b) 60-80 Hz activity (0.6 to 1.6 s) across task conditions during the delay period for the left BA 9 displayed on axial, sagital and coronal sectional views of the MNI template brain. Functional maps display dependent F-values thresholded at $p < 0.001$ (uncorrected).

c) Time course of 60-80 Hz activity for peak voxels averaged across trials in BA 9. The light gray region corresponds to the temporal interval of significant differences between conditions ($p < 0.001$; corrected; post-hoc t-test). In BA 9, there was a significant increase of 60-80 Hz activity from 0.6 to 1.6 s during load 6 as compared to the load 3 and distracter conditions, while

activity during load 3 and the distracter was similar. No significant differences in 60-80 Hz power was observed in the intra-parietal lobule (IPL) between load 6 and the distractor condition.

d) Single trial decoding of 60-80 Hz delay activity with a linear classifier of distracter trials in BA 9 (blue) and IPL (red). Vertical axis is the count of participants for which single trial gamma-band source activity in the distracter condition was decoded as load three or as load six. Delay activity in BA 9 corresponding to distracter trials was decoded as load 3 with a probability of $p = 0.77$ ($p < 0.025$; corrected; two-sided Binomial-test), while in the IPL distracter trials had equal probability ($p = 0.5$) to be decoded as load three or load 6 (P = n. s.; two-sided Binomial-test). Adapted from Roux et al. (2012).

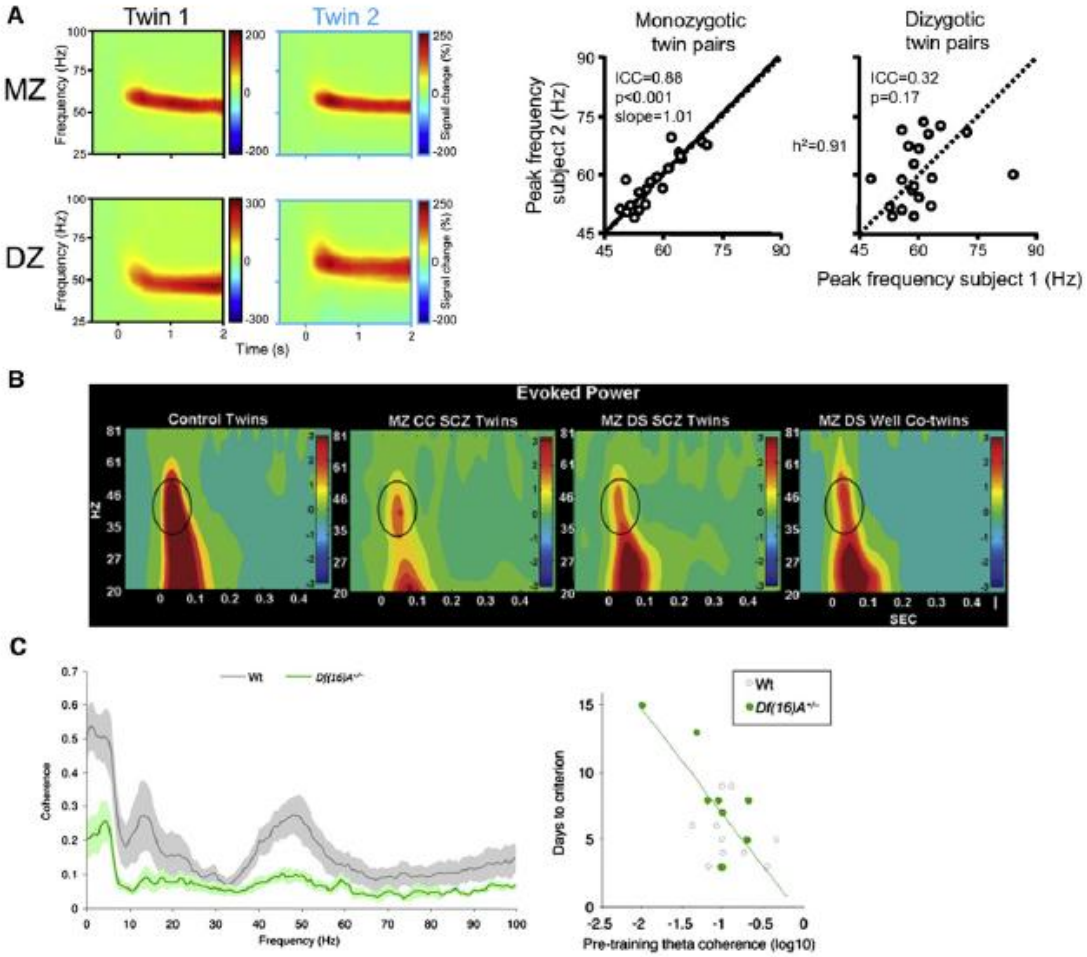

Figure 3. Genetics, Neural Oscillations and Schizophrenia

Strong genetic determination of the peak frequency of high frequency oscillations.

a) Left panel: Visually induced gamma-band activity in MEG-Data in a monozygotic (MZ) and a dyzygotic (DZ) twin pair. Time-frequency representations (TFRs) of activity in the gamma-band range relative to prestimulus baseline levels in two twins of a MZ pair, averaged across 74 parieto-occipital MEG sensors. Time 0 s denotes stimulus onset. Right panel: Correlation between gamma-peak frequencies in MZ twins (A) and DZ twins (B). Each data point represents the peak frequency of one twin versus that of his or her co-twin (random axis assignment). Slope values are estimated by random permutations of x- and y-values. The data suggest a heritability of the gamma-band frequency of 91%. Adapted from van Pelt, S., Boomsma, D.I., and Fries, P. (2012). Magnetoencephalography in twins reveals a strong genetic determination of the peak frequency of visually induced gamma-band synchronization. J Neurosci 32, 3388-3392.

Evoked oscillatory activity in schizophrenia patients and their unaffected co-twins. b) EEG time-frequency analyses of evoked gamma-band power during an auditory oddball task for responses to the standard stimuli at electrode Cz in healthy twins, MZ twins concordant with schizophrenia, MZ twins discordant with schizophrenia and unaffected co-twin members. Impaired evoked gamma-band power was significantly associated with schizophrenia and unaffected co-twins exhibited significantly reduced 30-60

Hz power as well compared with controls, highlighting the genetic contribution towards impairments in high-frequency oscillations in the disorder. Adapted from Hall MH, Taylor G, Sham P, Schulze K, Rijsdijk F, Picchioni M, Toulopoulou T, Ettinger U, Bramon E, Murray RM, Salisbury DF (2011). Schizophr Bull 37 778-87.

c) Reduced hippocampal–prefrontal synchrony in Df(16) A+/– mice which models a microdeletion on human chromosome 22 (22q11.2) that constitutes one of the largest known genetic risk factors for schizophrenia. Left panel: Coherence between hippocampal and prefrontal field potentials during a spatial working memory task. Note reduced coherence in Df(16)A+/– mice **P < 0.01; error bars and shaded regions represent mean ± s.e.m. Right panel: Days taken to reach criterion versus theta coherence during habituation sessions for each animal. Animals with lower theta coherence before training take longer to learn the spatial working memory task. Green line, linear regression of data from Df(16)A +/– mice. Adapted from Sigurdsson, T., Stark, K.L., Karayiorgou, M., Gogos, J.A., and Gordon, J.A. (2010). Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature 464, 763-767.

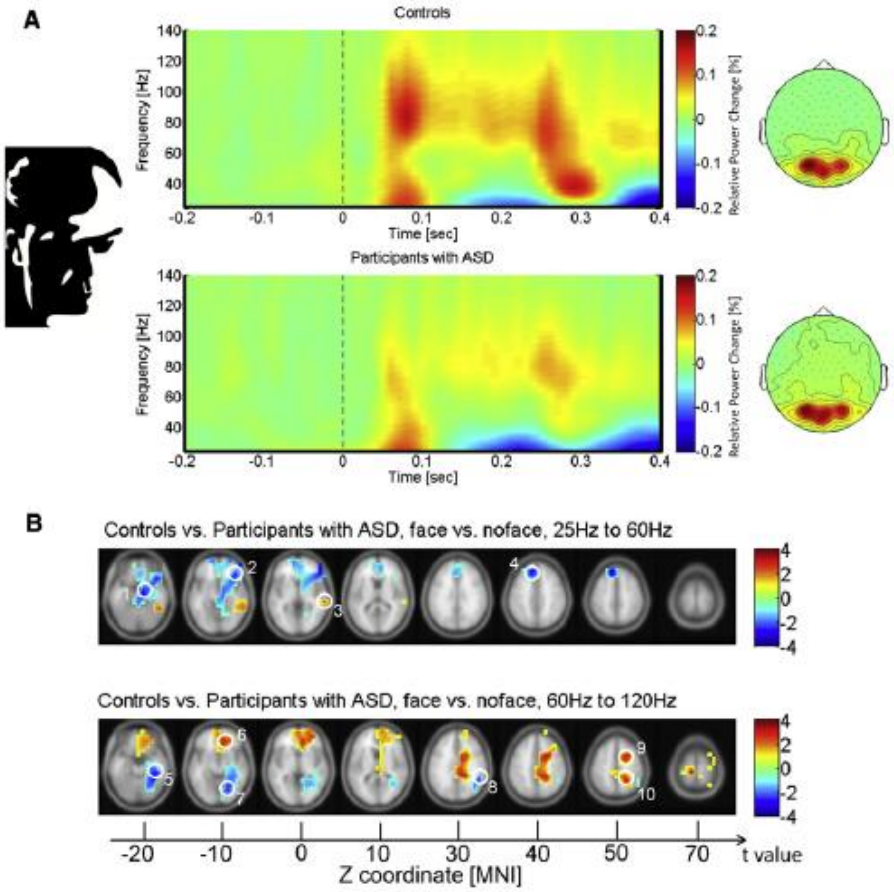

Figure 4. Gamma-Band Activity in Autism Spectrum Disorders

a) Time-frequency distributions and topographies of gamma-band spectral power during the perception of a Mooney face (left) for controls (top) and participants with ASD (bottom). The gamma-band signal is expressed as relative power change in the post-stimulus time window compared to baseline, averaged across all channels and all subjects in each group. The topographies are averaged across the post-stimulus interval (0–400 ms) and for frequencies between 25 and 120 Hz.

b) Source power in the high gamma-band (60-120 Hz) for the interaction between condition (face vs no-face condition) and group (participants with ASD vs controls). Red clusters represent stronger activation under the two conditions in controls, whereas blue clusters represent stronger activation under the two conditions in participants with ASD. In the high gamma band, controls were characterized by enhanced activity relative to the ASD group in a fronto-parietal network during perceptual organization. This hypoactivity in the ASD group was accompanied by increased source activity in posterior regions, including the lingual gyrus,

parahippocampal gyrus, and supramarginal gyrus. A reversed pattern of activation differences was found for the low gamma-band range. Note that p values are calculated by cluster-based statistical analysis. 1, parahippocampal gyrus; 2, IFG; 3, MTG; 4, MeFG; 5, parahippocampal gyrus; 6, MeFG; 7, lingual gyrus; 8, supramarginal gyrus; 9, MFG; 10, precuneus.

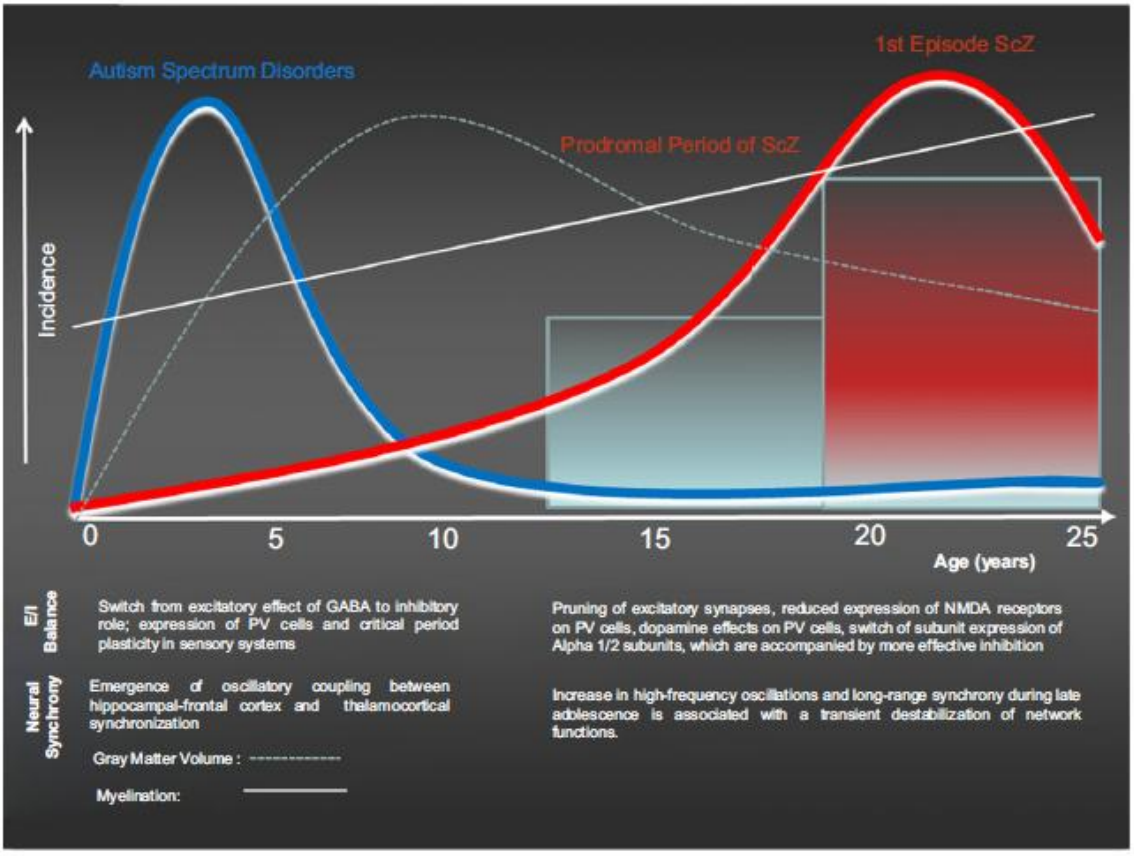

Figure 5. Brain Maturation, Changes in E/I-balance and the Manifestation of ASD and Schizophrenia

Insights into the pathophysiology of ASD and schizophrenia are to be gained from a stronger focus on developmental changes of E/I-balance parameters during critical developmental windows which coincide with the manifestation of these disorders during early childhood (ASD) and late adolescence (schizophrenia).

Uhlhaas, P. J., Singer, W. (2012) Neuronal Dynamics and Neuropsychiatric Disorders: Towards a Translational Paradigm for Dysfunctional Large-Scale Networks. Neuron 75(6), 963-980.

Table 1. Animal Models of Schizophrenia and Neural Synchrony

Study	Animal Model	Anatomy/Parameter	Result
Developmental Models			
Lodge et al. (2009)	Methylazoxymethanol acetate (MAM) G17 model in rats	Evoked gamma and theta power in PFC and HP	↓ gamma power to a conditioned tone
Steullet et al. (2010)	Oxidative Stress in young adult mice	Kainate-induced beta/ gamma power in CA3	↓ gamma power in ventral hippocampus
Pharmacology			
Anver et al. (2011)	NMDA-receptor antagonists in rats	Gamma-power/phase-coupling in V1/2 slices	↑ phase-coupling of gamma-activity in layer III to layer V
Carlén et al. (2012)	PV-Cre/NR1f/f mice	Baseline and induced gamma power in somatosensory cortex	↑ baseline gamma power; ↓ induced gamma power
Cunningham et al. (2003)	$LPA1^{-/-}$ mice; Acute ketamine model	Kainate-induced gamma power (superficial/deep medial entorhinal cortex (mEC) and HP	↓ gamma power in superficial mEC in $LPA1^{-/-}$ mice and after ketamine
Dzirasa et al. (2009)	DAT-KO mice (hyperdopaminergia); NR1-KD mice (NMDA receptor hypofunction)	HP – PFC gamma and theta phase-synchrony; cross frequency phase coupling	DAT-KO: ↑ HP-PFC gamma phase synchrony NR1-KD: ↓ gamma phase synchrony
Hunt et al. (2011)	Acute ketamine-model in rats	LFP gamma/high-frequency activity (HFA 130–180 Hz) power in HP and NAc	↑ gamma power in NAc; ↓ HP ↑ HFA in NAc
Kittelberger et al. (2012)	Acute and chronic NMDA-antagonists in rats	Theta/gamma-power in frontal cortex and HP	↑ gamma-power in HP in acute model ↓ gamma/theta-power in chronic model
Kocsis (2012)	NMDA-antagonists in rats	Gamma power; theta-gamma cross-frequency coupling (CFC) (frontal and occipital cortex)	↑ spontaneous gamma power; ↓ theta-gamma CFC for nonselective and NR2A-specific NMDA-receptor antagonists
Phillips et al. (2012)	MAM E17 rats treated with NMDA-receptor antagonists (PCP, ketamine, MK-801, SDZ 220,581)	Spontaneous gamma power/HFA over visual and motor cortex	↑ gamma-power and HFA with NMDA-receptor antagonists; stronger effects in MAM rats over motor cortex
Pinault (2008)	Acute ketamine; MK-801 in rats	Spontaneous gamma power in fronto-parietal cortex	↑ gamma power
Saunders et al. (2012)	Acute NMDA-antagonists (Ketamine, MK-801) in mice	Spectral power and intertrial coherence (ITC) (5–10 Hz; 35–80 Hz) in CA3	↑baseline gamma power ↓ evoked gamma and ITC (5–10 Hz) to auditory stimuli
Risk Genes			
Carlson et al. (2011)	$Dys1^{-/-}$ mice (reduced dysbindin-1)	Spectral power and phase-locking during auditory processing (5–100 Hz)	↓evoked gamma power; deficit in late gamma-suppression in HP
Risahn et al. (2009)	NRG-1 in WT rats, WT mice and $ErbB4^{MHC\text{-}ErbB4\,-/-}$ mice	Kainate-induced gamma (20–80 Hz) power in HP	NRG-1: ↑ gamma power in WT rats/mice, no increase in $ErbB4^{MHC\text{-}ErbB4\,-/-}$ mice;
Sigurdsson et al. (2010)	$Df(16)A^{+/-}$ mice	Theta/gamma power and phase-synchrony (PFC-HP)	↓ phase-synchrony (PFC/HP) during working memory