Invited review

The organization of physiological brain networks

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• The brain can be represented as a complex network with functionally connected units at several levels that changes in neurological and psychiatric disease.

• Existing clinical neurophysiology techniques and network models to explain network properties are reviewed.

• In addition to the already established network models, we suggest a heuristic model including hierarchical modularity.

A B S T R A C T

One of the central questions in neuroscience is how communication in the brain is organized under normal conditions and how this architecture breaks down in neurological disease. It has become clear that simple activation studies are no longer sufficient. There is an urgent need to understand the brain as a complex structural and functional network. Interest in brain network studies has increased strongly with the advent of modern network theory and increasingly powerful investigative techniques such as “high-density EEG”, MEG, functional and structural MRI. Modern network studies of the brain have demonstrated that healthy brains self-organize towards so-called “small-world networks” characterized by a combination of dense local connectivity and critical long-distance connections. In addition, normal brain networks display hierarchical modularity, and a connectivity backbone that consists of interconnected hub nodes. This complex architecture is believed to arise under genetic control and to underlie cognition and intelligence. Optimal brain network organization becomes disrupted in neurological disease in characteristic ways. This review gives an overview of modern network theory and its applications to healthy brain function and neurological disease, in particular using techniques from clinical neurophysiology, such as EEG and MEG.

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1. Introduction

The brain can be seen as a complex anatomical and functional network. Theories that apply to complex networks in general, such as modern network theory and complex systems theory, are increasingly used in neuroscience to understand how normal brain function arises and what happens in disease. They provide a totally new perspective leading to some very new insights. This review gives an overview of the fundamentals and applications of modern network theory in the study of normal and developing brain function. In addition, we aim to explain how it is possible that various brain diseases can be understood in terms of failing network characteristics. The focus will be mainly on functional aspects of brain networks, but structural connectivity, animal studies, and modeling will also be discussed to provide a wider perspective. Since network studies are based upon a fundamental of functional connectivity, the neurophysiological basis of normal and disrupted synchronization is discussed first. Subsequently, the basic concepts and tools of modern network theory are introduced. The application of network theory is illustrated by studies in healthy subjects, and various disorders such as schizophrenia, depression, dementia, trauma and epilepsy with an emphasis on functional, and in particular neurophysiological approaches. Finally we suggest a general framework for the study of the organization of physiological brain networks.

2. The brain as a network

2.1. Representing the brain as a network

In 1906, Ramon Y Cajal and Camillo Golgi shared the Nobel Prize in Physiology or Medicine. Although they shared the prize, they did not share each other’s ideas (Jacobson, 1995; Rapport, 2005). According to Golgi, a defender of the reticular theory, the brain should be viewed as a large syncytium, or conglomerate, of directly connected neurons. Instead, Cajal, using the silver nitrate preparation developed by Golgi, interpreted his findings in support of the neuron theory that maintained that the brain consists of discrete neurons. In a sense, both turned out to be right: the brain is now considered to be a large network of about $10^{10}$ neurons, with each neuron communicating with about $10^4$ other neurons, mostly by synapses, but to a small extent also by gap junctions that directly connect the cytoplasm of two adjacent cells and may play an important role in physiological and pathological synchronization processes. Alternative views of the brain, stressing its diffuse and holonomic nature, have been proposed by Lashley (1923), Pribram and Carlton (1986), and more recently by Nunez (1995). Despite these suggestions, the concept of the brain as a large complex network of interconnected elements, at multiple scales, has obtained a dominant place in modern neuroscience (Nunez, 2010).

2.2. Anatomical and neurophysiological evidence for a network perspective

The concept of the brain as a complex network is increasingly supported by a wealth of neuroanatomical and neurophysiological data. Many different types of neurons have been recognized, and they connect in characteristic ways, from the level of micro or minicolumns (the smallest functional unit of the brain containing about 80–100 neurons) and macrocolumns (consisting of 60–80 minicolumns; for a recent review see: Buxhoeveden and Casanova, 2002) up to the level of local brain regions, lobes and functional brain systems. Izhikevich and Edelman (2008) included 22 different types of neurons in their model of the whole brain. Advanced techniques are now being used to dissect the precise anatomy at the smallest levels of the brain. Recently, using the micro-optical sectioning tomography (MOST) system, a major breakthrough was achieved in the detailed description of the connectivity of a mouse brain (Li et al., 2010). Major efforts to describe the microscopic anatomy of the brain are the Blue Brain Project and the Human Brain Project (Markram, 2006; Perin et al., 2011; www.humanbrainproject.eu). At higher levels of resolution, classic neuroanatomic techniques of tracing, successful in showing the network blueprint of the brain of macaques, and cats, are now replaced by modern imaging techniques, in particular high-field strength MRI in combination with DTI (diffusion tensor imaging) and tractography. These methods have revealed the large-scale patterns of brain connectivity from the level of voxels to the level of Brodmann areas (Hagmann et al., 2007, 2008; Gong et al., 2009a).

Since the early nineties of the last century, invasive neurophysiological studies in animals have been able to demonstrate communication, mostly by synchronization in the gamma band, between widely separated but connected brain regions (Eckhorn et al., 1988; Engel et al., 1991; Gray et al., 1989; König et al., 1995). Many of these findings have now been confirmed with EEG and MEG.
2.3. Networks are not enough: the need for a theoretical framework

The concept of the brain as a complex structural and functional network thus has a relatively long history, and a high face value given what we know about brain anatomy and neurophysiology. However, the notion of brain networks is too general to be optimally useful in understanding normal and disturbed brain physiology unless it is linked to a specific theory of networks. As indicated by Carter Butts: “To represent an empirical phenomenon as a network is a theoretical act.” (Butts, 2009). A complex network is more than the sum of the elements that constitute its building blocks; it is also more than the sum of all its pair-wise interactions. Complex systems have emergent properties that require exact mathematical theories for their proper understanding (Sporns, 2011a). In this respect, the development of modern network theory in the late nineties of the last century constitutes an important step forward. The introduction of powerful new mathematical models of complex networks such as the small-world networks and scale-free networks gave rise to a widespread and rapidly growing interest in network studies in many fields of science, ranging from physics, communication and transport systems to biological and sociological networks (Boccaletti et al., 2006). The development of modern network theory has greatly stimulated the interest in brain networks, and has enabled a more exact, quantitative study of the determinants of growth, learning, plasticity and failure in neural networks.

2.4. Networks in relation to complexity theory

While a network perspective is rapidly becoming a promising approach to understanding the complex nature of the brain, it is related to other scientific fields that deal with complex systems. Cybernetics, information theory and general system theory constitute early examples of attempts to define general mathematical frameworks for complex systems including neural networks (Shannon and Weaver, 1949; Simon, 1962; von Bertalanffy, 1969; Wiener, 1948). An excellent introduction to modern complexity science can be found in Melanie Mitchell’s book Complexity (Mitchell, 2009). The modern theory of dynamical systems, in particular chaos theory, has had a considerable influence on our understanding of complex behavior in deterministic but highly nonlinear systems. These ideas have influenced our concepts of brain function, in particular with respect to the predictability of epileptic seizures (Stam, 2005). Perhaps the most fruitful contribution of nonlinear dynamics has been the development of a general theory of synchronization processes, with considerable relevance for the study of communication between neurons and brain areas (Boccaletti et al., 2002).

Other important contributions have come from statistical physics and the theory of phase transitions. According to the theory of self-organized criticality, introduced by Per Bak, complex systems evolve autonomously to a critical state characterized by power laws (Bak et al., 1987). There is now increasing evidence that such phenomena may also be observed in the brain (Beggs and Plenz, 2003; Werner, 2007). The plenitude of complexity theories might suggest the lack of a unifying framework. However, modern network theory is a promising candidate for integrating many of the emerging concepts in complexity studies. Herbert Simon stressed that complex systems could be viewed in general as large collections of interacting elements displaying a hierarchical organization (Simon, 1962). Modern network theory is based upon graph theory as an exact mathematical formalism for the description of networks, including their hierarchical organization. In addition, it uses ideas from probability theory and statistical mechanics to deal with stochastic aspects of large networks, and finally it involves the theory of dynamical systems and synchronization for the study of processes taking place upon complex networks (Barrat et al., 2008). Therefore, modern network theory presents an attractive and versatile framework for the study of the organization of complex brain networks.

2.5. Relevance of brain networks for clinical neurophysiology

Normal brain functioning and its breakdown in neurological and neuropsychiatric disease cannot be properly understood without taking the network perspective into account. However, a general, informal notion of brain networks is no longer sufficient. Modern network theory is beginning to have an impact on our ideas about the way brain networks develop, how this development is organized and constrained by genetic and geometric factors, how the architecture of brain networks comes to display universal features such as hierarchical modularity and how this relates to cognitive function and intelligence. In addition, network theory influences notions of localization of brain function and global effects of local lesions. The idea that such different conditions as Alzheimer’s disease and epilepsy may both be explained in terms of “hub failure” clearly illustrates how network science is beginning to have an impact upon clinical concepts.

Clinical neurophysiology is the medical specialization that deals with diagnosis, monitoring, and prognosis of clinical neurological conditions using a variety of neurophysiological techniques. Modern network theory may be particularly relevant for clinical neurophysiology since two of its main techniques to study central nervous system function, the EEG and MEG, present an enormous and hardly explored potential to investigate how brain areas communicate, and how this communication fails in neurological disease. The fact that both EEG and MEG measure neural activity directly, and not indirectly such as is the case with fMRI BOLD, is a major advantage. Combining functional connectivity with modern network theory presents a unique opportunity for clinical neurophysiology. EEG and MEG are not only the most direct tools to measure brain function; they also can provide a window on the brain as a complex evolving network (Nunez, 2010).

3. Functional interactions

3.1. Time series and brain function

To gain an understanding how the brain is organized as a functional network, several elements are required: (1) we need to have a reliable measurement of the level of activity of the network ele-
ments; (ii) communication between network elements needs to be characterized and quantified; (iii) the full pattern of pair wise interactions between network elements needs to be integrated and analyzed within the framework of network theory; (iv) the interdependencies between functional and structural network levels need to be assessed. Here, we focus upon the first element. The other three aspects will be addressed in subsequent sections.

Neurons are the obvious structural and functional building blocks of the nervous system. Neuronal function is reflected in two different types of activity: (i) small fluctuations of the resting membrane potential of the dendrites induced by excitatory and inhibitory synapses; (ii) action potentials along the axon. A typical cortical pyramidal neuron may be covered by up to 1000–10,000 synapses, with the excitatory synapses predominantly located at the dendritic tree far away from the soma and the inhibitory synapses located closer to the nerve cell body. Activation of an excitatory synapse induces a brief depolarization of the membrane potential (excitatory post synaptic potential or EPSP) and activation of an inhibitory synapse causes a somewhat larger and longer lasting hyper polarization of the membrane potential (inhibitory post synaptic potential or IPSP). If the joint effect of all EPSPs and IPSPs on the dendritic tree, determined by spatial and temporal summation, causes the membrane potential near the axon hillock to exceed the threshold, an action potential is generated that will be propagated along the axon, but also backwards to the dendritic tree. Neurons influence other neurons by their action potentials, therefore the firing rate – number of action potentials per second – is an important parameter of neuronal activity. A major controversy in neuroscience concerns the question whether the relevant information is carried only by the firing rate, or also by the exact timing of action potentials. The fact that the exact timing of firing of pre and postsynaptic neurons may influence synaptic plasticity (a concept known as spike timing dependent plasticity or STDP) suggests that timing information may have to be taken into account (Abbott and Nelson, 2000).

While neuronal spiking is fundamental for inter neuronal communication, the most commonly used techniques to assess human brain function such as EEG, MEG, and fMRI do not measure action potentials directly. Both EEG and MEG reflect large-scale summed field potentials that are ultimately caused by EPSPs and IPSPs of cortical, mainly pyramidal neurons. Characteristically, the field potentials recorded with EEG and MEG show oscillations in a wide range of frequency bands, ranging from (sub) delta to gamma, high-frequency oscillations (HFO) and ripples (Buzsaki and Draguhn, 2004). The temporal resolution of EEG and MEG is essentially unlimited, which is of interest since both very low as well as very high frequency oscillations have been shown to have neurophysiological significance (Bragin et al., 2010; Van Someren et al., 2011). The functional significance of oscillatory activity in different frequency bands has long remained a mystery, and it has even been suggested that these oscillations might be mere epiphenomena (Niedermeyer and Schomer, 2011). There is now increasing evidence, however, that a phase relation exists between oscillatory field potentials and neuronal actions potentials (Eckhorn and Obermueller, 1993; Lee et al., 2005). This observation stresses that oscillatory brain activity contains information that is relevant for understanding local and interregional communication.

The BOLD signal reflects the presence of excess oxyhemoglobin in the smallest blood vessels near activated brain regions; it can be thought of as a low pass, integrated measure of neuronal spiking with a typical time scale of seconds. Studies combining EEG with fMRI are now beginning to reveal the complex relations between oscillatory band power and BOLD signals (Rosenkranz and Lemi- eux, 2010). In particular, a relation between the envelope of gamma band oscillations and BOLD time series has been suggested (Logothetis, 2002).

Time series techniques can be used to analyze the recordings of local brain activity by EEG, MEG and BOLD. The most common technique is spectral analysis, that represents signal power as a function of frequency. This approach is especially helpful to determine oscillatory components of the signal, such as a dominant peak due to the alpha rhythm, and power changes in certain frequency bands. Activation of specific brain regions is often associated with a decrease or increase of power in a particular frequency band; these changes can be captured with a technique called event-related desynchronization (ERD) or event-related synchronization (ERS) (Pfurtscheller and Lopes da Silva, 1999). Short-lasting, non-stationary changes in oscillatory brain activity can also be characterized with evoked or event-related potentials. In contrast to ERD and ERS, that measure induced power changes, evoked and event-related potentials only measure oscillatory changes that are exactly phase-locked to some event. Another effective technique to assess non-stationary aspects of oscillatory power is wavelet analysis. Oscillatory brain activity may show correlations on very long time scales. These correlations can be characterized by spectral analysis, the Hurst exponent, or detrended fluctuation analysis (Benayoun et al., 2010; Linkenkaer-Hansen et al., 2007; Stam and de Bruin, 2004). Finally, the non-random structure of
neurophysiological time-series analysis can also be characterized with techniques derived from nonlinear dynamics. Here, the time series is assumed to reflect a trajectory in a high-dimensional state space of the underlying dynamical system, and this trajectory can be characterized with measures such as the correlation dimension, Lyapunov exponents and entropy measures (for review see: Stam, 2005).

3.2. Functional and effective connectivity

In the previous section, we discussed how the activity of neurons or local brain regions can be measured and characterized with neurophysiological techniques and time series analysis. The next step is to consider how this information can be used to infer how communication between neurons and brain regions takes place (Fig. 1). An important concept for understanding communication in brain networks is synchronization. Unfortunately, synchronization is often used in neurophysiology in a rather informal way, referring to a vague notion of the level of cooperation between neurons. It is often assumed that band power of field potentials referring to a vague notion of the level of cooperation between neurons or local brain regions can be measured and characterized with measures such as the correlation dimension, Lyapunov exponents and entropy measures (for review see: Stam, 2005).

In physics, oscillations reflect this cooperation between neurons; however, it is often assumed that band power of EEG or MEG signal recorded at a particular electrode or sensor may depend upon many factors, and its interpretation in terms of (local) levels of neuronal synchronization is not straightforward (Daffertshofer and van Wijk, 2011). In physics, and in particular in dynamical systems theory, the notion of synchronization has been given a far more specific and quantitative interpretation, that goes back all the way to the groundbreaking work of the Dutch physicist Christiaan Huygens. Much of the work on synchronization has been based upon the notion of phase coupling between pairs of harmonic oscillators (Boccaletti et al., 2002; Rosenblum and Pikovsky, 2003). With the advent of nonlinear dynamics and chaos theory, the concept of synchronization has been broadened, and now includes any type of statistical interdependency between dynamical systems, even if they do not display regular oscillations and even if strict phase coupling is absent: so called generalized synchronization (Rulkov et al., 1995). These advances in the physics of synchronization influenced the possibilities for detecting and quantifying synchronization in neurophysiological data.

While synchronization in its various manifestations should be considered the fundamental physical concept for understanding correlations between neurophysiological time series, different notions have also become popular in the neuroimaging literature. Functional connectivity, first introduced by Aertsen et al. (1989), refers to the existence of any statistical interdependency between neurophysiological time series. Originally, this concept referred to recordings of neuronal spiking, but it is now also used for EEG, MEG and in particular fMRI (Lowe, 2010; Stevens, 2009). While functional connectivity is a model free concept, the notion of effective connectivity stresses asymmetric causal interactions between neural systems (Friston, 2002). The notion of effective connectivity is especially clear in the approach called dynamic causal modeling (DCM) introduced by Karl Friston (Penny et al., 2004). However, we should stress that both effective and functional connectivity could be defined in terms of synchronization theory, that is: in the language of interacting dynamical systems. As we will see, this is of particular importance if we want to obtain a formal understanding of communication processes taking place on complex networks (Arenas et al., 2008).

Many time series analysis techniques have been developed to characterize statistical interdependencies between two or more time series of neurophysiological activity. An excellent overview is the review by Pereda et al. (2005). A useful distinction is that between linear and nonlinear techniques. The most important linear measure of correlation between time series is coherence. It can be considered a generalization of the (time-lagged) correlation between time series. Coherence describes the strength of the correlation between two time series as a function of frequency; it depends upon the consistency of the phase difference as well as the power of the two time series (Nunez et al., 1997). To track correlations in non-stationary signals, coherence can also be based upon wavelet analysis (Lachaux et al., 2002). At least three categories of nonlinear synchronization measures can be distinguished. The first group consists of measures that quantify the consistency of the phase difference between two signals, discarding the influence of signal amplitude (Rosenblum et al., 1996). Phase synchronization analysis can be based upon a Hilbert transform of the data (Mormann et al., 2000) as well as wavelet analysis (Lachaux et al., 1999); both approaches are equivalent (Burns, 2004). A second group of measures is based upon nonlinear dynamics and quantifies generalized synchronization between attractors reconstructed from the time series (Arnhold et al., 1999; Hu and Nenov, 2004; Pecora and Carroll, 2000; Schiff et al., 1996; Schmitz, 2000). The synchronization likelihood is a relatively simple unbiased estimator of generalized synchronization (Stam and van Dijk, 2002; Montez et al., 2006). Finally, there is a group of nonlinear coupling measures such as event-synchronization and $h^2$ that cannot be easily characterized (Quian Quiroga et al., 2002b; Lopes da Silva et al., 1989).

The linear and nonlinear coupling measures mentioned above are generally symmetric, and do not provide information on causality or the direction of the influence. One approach to determine effective connectivity is based upon Granger causality, originally developed in economics (Granger, 1969). In the case of Granger causality, the future of time series $x$ can be predicted better, if not only its own past, but also the past of another time series $y$ is taken into account. If including the information of $y$ improves the prediction of $x$, $y$ is said to have a causal effect on $x$. An important technique to apply Granger causality in a frequency dependent way is the directed transfer function (DTF) (Blinowska, 2011). The direction of coupling can also be determined with techniques based upon phase synchronization. An important example is the phase slope index (Nolte et al., 2008). Measures of causal interactions have also been derived in a nonlinear dynamical systems context (Arnhold et al., 1999; Hu and Nenov, 2004; Pecora and Carroll, 2000; Schiff et al., 1996; Schmitz, 2000). Finally, the nonlinear correlation coefficient $h^2$ has also been used to derive a nonlinear directed coupling measure (Wendling et al., 2005).

In contrast to fMRI, neurophysiological techniques for determining the coupling between different brain regions suffer from the common source bias. If the activity recorded at two different electrodes or sensors is influenced by a single underlying source, the estimated correlations do not reflect true interactions between different neural systems. In the case of EEG, the activity recorded at the reference electrode can also influence the estimated correlations between different EEG channels (Nunez et al., 1997). These are serious methodological problems that cannot simply be solved by performing the connectivity analysis in source space instead of signal space. While source or Laplacian derivations may diminish these influences, they do not solve the problem completely, and they may obscure true long-distance interactions. Nunez et al. (1997) proposed a corrected version of the coherence to account for the influence of volume conduction in EEG. Nolte et al. (2004) suggested to use the imaginary component of coherence as a measure of coupling, that is not influenced by volume conduction. A disadvantage of the imaginary coherence is the fact that its magnitude is influenced by signal power as well as the magnitude of phase lag between the channels; therefore, increases or decreases cannot be interpreted easily. The only conclusion that is certain, is that the existence of a non-zero imaginary coherence cannot be explained by volume conduction. The phase lag index is based upon the idea of the imaginary coherence but it is not influenced...
by the signal amplitude nor by the magnitude of the phase lag (Stam et al., 2007b). The recently proposed weighted phase lag index WPLI is claimed to be less sensitive to noise, but re-introduces the dependency upon the magnitude of the phase difference (Vinck et al., 2011). Interestingly, coherence, imaginary coherence, phase coherence, WPLI and PLI are all intimately related to each other since they can all be computed from the Hilbert transform of the data (Stam et al., 2007b).

The availability of so many different measures of synchronization raises the question whether a rational choice can be made between them in terms of performance on real data. A few studies have attempted to compare a subset of measures with respect to their ability to correctly detect the presence of synchronization in a multivariate data set (Ansari-Asl et al., 2006; David et al., 2004; Quian Quiroga et al., 2002a). Unfortunately the results are not unequivocal. Performance of the measures seems to depend upon characteristics of the data set as well as characteristics of the method itself. In the case of complex synchronization measures based upon nonlinear dynamical systems theory, many parameters have to be taken into account (Montez et al., 2006). Performing the analysis in source space does not simplify matters, since each source reconstruction algorithm has its own assumptions that may influence correlations between source-based signals in unknown ways. At present, the most rational approach may be to use more than one technique, and to search for results that are as consistent as possible, irrespective of the technique that was used.

3.3. Fragile binding

Interregional synchronization, or functional/effective connectivity, conveys important information about healthy brain functioning. Here we briefly indicate what connectivity studies have shown even without a formal network perspective: below we will continue this discussion in the context of modern network theory. In healthy subjects the strength of interregional synchronization depends upon age. Long distance synchronization is relatively low at birth, and increases during development, possibly due to maturation and myelination of long distance association pathways (Barry et al., 2004; Gmehin et al., 2011; González et al., 2011; Thatcher et al., 2008). The strength of synchronization depends not only upon maturation and age, but is also strongly influenced by genetic factors (Chorlian et al., 2007; Posthuma et al., 2004; Van Beijsterveldt et al., 1998). How genetic factors can determine the strength of functional interactions between brain regions is not yet understood.

The level of interregional functional connectivity is different for different frequency bands and seems to be related to local band power as well as distance. According to some authors, long distance communication is mainly supported by synchronization in low frequency bands, while short distance local communication depends upon synchronization in beta and gamma frequency bands (Von Stein and Sarnthein, 2000). The strength of synchronization between different brain regions shows characteristic fluctuations that may not simply reflect noise effects, but could also be due to the rapid formation and dissolution of functional connections. This dynamic nature of synchronization, even during a resting-state, has been referred to as “fragile binding” (Stam and de Bruin, 2004). Two different models of synchronization dynamics have been suggested. According to the idea of microstates the brain manifests a succession of relatively stable states of a few hundred milliseconds duration connected by abrupt transitions (Lehmann et al., 2006). However, empirical studies show that the distribution of synchronization and desynchronization times is rather complex, pointing in the direction of a process with (self-organized) criticality (Beggs and Plenz, 2003; Breakspear et al., 2004; Stam and de Bruin, 2004; Gong et al., 2007). Interregional synchronization is also clearly influenced by behavioral state and cognition. During sleep, characteristic changes in synchronization occur in different sleep stages (Ferri et al., 2005). Tasks that involve working memory are associated with increased synchronization, especially in the theta band, and possibly also in the alpha band (Jensen et al., 2002; Klimesch, 1997; Sarnthein et al., 1998; Tesche and Karhu, 2000). Gamma band synchronization is now believed to be an important neurophysiological mechanism underlying binding, attention and even consciousness (Dehaene and Changeux, 2011; Fries et al., 2007; Jensen et al., 2007; Uhlhaas et al., 2011).

3.4. Excessive connectivity

Synchronization in the healthy brain is a delicate process characterized by the rapid formation and disappearance of functional connections between different brain regions. This “fragile binding” can become disturbed in two different ways: excessive connectivity or disconnection. The most obvious example of a syndrome characterized by excessive synchronization would seem to be epilepsy (Lehnertz et al., 2009). At the neuronal level, epileptic phenomena are associated with paroxysmal depolarization shifts (Gorji and Speckmann, 2009). Recently, the significance of gap junctions as an important cause of hypersynchronization in epilepsy has also been pointed out (Volman et al., 2011). The classic interictal and ictal EEG patterns of epilepsy, such as spikes and generalized spike-wave discharges, are usually assumed to reflect excessive synchronization at the neuronal as well as the macroscopic level (Gorji and Speckmann, 2009). However, recent observations of the activity of individual neurons during seizures in humans suggest that a hypersynchronization-only concept of epileptic activity may be too simple (Truccolo et al., 2011).

Although some types of seizures, notably absence seizures characterized by generalized 3-Hz spike-wave discharges, may indeed reflect excessive synchronization compared to pre- and postictal states, this pattern may not hold for all seizures, and in particular not for partial seizures. Partial seizures may represent a complex sequence of increases as well as decreases of synchronization in different frequency bands during different stages of the seizure. In fact, the highest level of synchronization during partial seizures may be reached only at the very end of the seizure (Schindler et al., 2007). Pre-ictal changes in EEG synchronization have also been the topic of intense research, especially since papers by German and French groups suggested the possibility of seizure prediction (Lehnertz and Elger, 1998; Le van Quyen et al., 2001a; Martinerie et al., 1998). Of all EEG measures that have been tested for their performance in predicting seizures, measures of interregional synchronization turn out to be the most successful (Mormann et al., 2005). Surprisingly, the pre-ictal state may be characterized by a decrease rather than an increase in synchronization (Mormann et al., 2003). It has been suggested that this pre-ictal drop in synchronization might reflect a release of the ictal focus from the inhibitory influence of other brain regions (Le van Quyen et al., 2001b). In this respect, the interictal state should be distinguished from the pre-ictal state. There are indications that synchronization levels during the inter ictal state are abnormally high, not only compared to the pre-ictal state, but also to synchronization levels in healthy subjects. Increased synchronization in the theta band has been described in patients with different types of epilepsy, and may predict the risk of epilepsy even independently of the occurrence of epileptic spikes (Douw et al., 2010b).

Increased levels of synchronization are not limited to epilepsy. Although Parkinson’s disease is considered to be mainly a basal ganglia disorder, increased interregional synchronization in the alpha band has been found in early, untreated Parkinson’s disease.
3.5. Disconnection syndromes

While abnormally increased levels of synchronization in neurological disease may seem a bit counterintuitive, except in the context of epilepsy, the notion that destruction or loss of anatomical connections between brain regions would be reflected in diminished functional connectivity would seem more natural. A nice illustration of this idea is the loss of interhemispheric EEG coherence in children with agenesis of the corpus callosum (Koeda et al., 1995). The most obvious example of this idea is Alzheimer’s disease, a degenerative type of dementia characterized by a progressive and severe loss of neurons and connections between brain regions. An important concept is the idea that at least some types of cognitive dysfunction should be explained directly in terms of lost connectivity. Delbeuck et al. (2003) suggested referring to Alzheimer’s disease as a disconnection syndrome. Evidence for a loss of interregional synchronization comes from a large number of cases, increased levels of synchronization have also been reported, either at rest, or during the performance of cognitive tasks (Buldu et al., 2011; Jiang, 2005; Pijnenburg et al., 2004).

![Graph and adjacency matrix. Networks can be represented mathematically as graphs that consist of nodes (vertices) and connections (edges). In the left panel black dots correspond to nodes and lines between dots correspond to connections. This is an example of an undirected, unweighted graph. In the right panel the same graph is represented as an adjacency matrix. This is a square matrix with the same number of rows and columns as the number of nodes in the graph. Each matrix cell provides information on the presence (value 1; indicated by color red) or absence (value 0; indicated by color blue) of an edge between two vertices. Since this matrix corresponds to an unweighted, binary graph it is symmetric.](image)


3.6. Strengths and limitations of brain connectivity studies

Clearly, studies of functional interactions between brain regions can add important information to observations derived from local changes in brain activity only. As an obvious example, levodopa...
changes functional connectivity but does not affect local band power in Parkinson's disease (Stoffers et al., 2008a,b). Neurophysiological assessment of functional connectivity has the advantage of a high time resolution and a direct measurement of neural activity. Although functional interactions are constrained by anatomical connectivity, they are not identical to it (Adachi et al., 2011; Honey et al., 2009). Synchronization studies show fragile binding in healthy subjects and patterns of hyperconnectivity or disconnection in various neurological disorders. However, the patterns of synchronization changes in neurological disease are difficult to interpret. In particular the occurrence of increased as well as decreased synchronization (in different frequency bands and different brain areas) challenges our understanding of the underlying mechanisms, and demonstrates the need for a more consistent theoretical framework to study changes in network organization.

4. Network studies in brain research

4.1. Modern network theory

4.1.1. Graph theory, statistical physics and dynamical systems

While connectivity studies constitute a useful extension of local activation studies, the complexity of the data presents a challenge that is hard to face without a proper theoretical framework. One attempt to develop such a framework is modern network theory, also referred to as graph theory (Newman, 2010). While network theory and graph theory are sometimes referred to as if they were synonyms, they are not, and understanding how they are related may help to obtain a better idea what network theory is about, and how it might be helpful in dealing with connectivity data in neuroscience. Modern network theory is a highly interdisciplinary field of science, devoted to the study of complex networks. It is rooted in at least three different but connected branches of mathematics and physics: (i) graph theory; (ii) statistical mechanics of networks; (iii) dynamical systems theory.

Graph theory is a relatively old branch of discrete mathematics that deals with networks (Gross and Yellen, 2006). It originated with the work of Euler, in particular with his solution of the problem of the seven bridges of Königsberg. Typically, graph theory deals with relatively small networks that are represented as sets of network nodes (vertices) and network connections (edges) (Fig. 2). A network represented as a set of vertices and edges is called a graph. Different categories of graphs can be distinguished. Graphs where edges are either present or absent are called binary or unweighted; when a weight representing for instance the strength, length or importance of a connection is assigned to each edge the resulting graph is called weighted. When edges only indicate that a connection or relation exists between two vertices the graph is undirected. When edges indicate the direction of influence the graph is directed or a digraph. Many important theorems have been proven for graphs, in particular in relation to special cases such as fully connected graphs, Harary graphs, wheel graphs or trees, but this mathematical knowledge is mainly of interest in specific fields of science such as computer and communication science (Gross and Yellen, 2006). Classic graph theory could not deal with large networks with stochastic features.

The scope of graph theory was extended to realistic complex networks when models were introduced that aided the description and analysis of large networks with random components. The first example of such a model was the random graph model proposed by Erdős and Rényi (1959) (ER). In this model, an edge exists between any randomly chosen pair of vertices with a fixed probability $p$. While this may seem a very simple model, it turns out to have many surprising and important mathematical properties, such as the sudden emergence of a giant connected component for increasing values of $p$ and short path length. The ER random graph is not a realistic model of many real complex networks, but is often used as a null model for comparison. The breakthrough in the statistical approach to networks occurred with the publication of two papers.
in 1998 and 1999 (Barabasi and Albert, 1999; Watts and Strogatz, 1998). Watts and Strogatz (1998) introduced a model (WS) of a regular graph on a ring where each vertex is connected to its k neighbors (Fig. 3). With a rewiring probability p, an edge is chosen and reconnected to another randomly chosen vertex. For p = 0 this model corresponds to a regular graph or lattice characterized by high clustering (each vertex being connected to a few other vertices most of which are also connected to each other). In such a regular graph, it takes on average many steps to travel from one vertex to any other vertex on the graph, that is: a regular graph has a long path length. When p = 1 the graph is in fact a random graph, like the ER random graph. Such a random graph has a low clustering coefficient, but the average path length is now also very short. The really interesting behavior is seen for small but non-zero values of p: rewiring even a very small number of edges does not affect the high clustering, but results in a dramatic decrease of average path length. Such intermediate networks that combine high clustering with short paths lengths are called small-world networks.

The strength of the small-world model is that it explains the combination of high clustering and short paths encountered in many real complex networks. However, it does not explain another property of realistic networks. In ER and WS graphs the vertices all have about the same number of edges, that is: they have a narrow degree distribution. The degree distribution P(k) = k is defined as the probability that a randomly chosen vertex will have degree k. Surprisingly in many complex networks in nature this distribution corresponds to a so-called power law: P(k) \propto k^{-\gamma}, with \gamma a scaling exponent between 2 and 3. Barabasi and Albert (1999) were the first to suggest a simple algorithm for growing networks, where newly added vertices connect preferentially to existing edges with higher degrees (Fig. 4). The scale-free network of Barabasi and Albert (BA) is now considered one of the most important models to explain the presence of highly skewed power law degree distributions in many complex networks, such as the Internet and the World Wide Web (Barabasi, 2009). An important implication of such a degree distribution is the presence of so-called hubs, vertices with an exceptionally high number of connections.

Graph theory and statistical physics present two of the major pillars of modern network theory; the third is dynamical systems theory. Networks in general, and complex networks in particular, are mainly important because we are interested in the processes that take place on these networks (Barrat et al., 2008). For instance, we could assume that each vertex corresponds to a dynamical system, perhaps an oscillator, and each edge indicates which oscillators interact and how strong this interaction is. More generally, we can imagine that some transport of traffic, goods, or information is taking place on the graph. The important questions here are: how does the topology of the graph influence the dynamical processes on the graph? In particular, do topological properties

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predict the onset of synchronization, or the efficiency of information transport in the network? Of interest, Watts and Strogatz were investigating such questions about oscillator synchronization when they discovered their small-world model. Finally, perhaps the most challenging questions of all relate to mutual interactions between dynamics and topology: how do dynamical processes change the architecture of the networks, and how does altered network structure constrain dynamics?

4.1.2. Measures of complex networks

Modern network science, with its roots in graph theory, statistical physics, and nonlinear dynamics, has developed a large and still increasing number of measures that can be used to characterize large and complex networks (Table 1 and Fig. 5). We have already encountered a few of these measures, such as the clustering coefficient, the average shortest path, and the degree distribution. Often, new measures are developed when new models or new observations on real networks suggest that a particular feature of networks may be of interest and deserves exact quantification. An overview of currently used network measures can be found in several review papers and textbooks (Kaiser, 2011; Newman, 2010; Rubinov and Sporns, 2010). Here we briefly mention the most important categories.

The first category involves measures that characterize the presence and nature of structural building blocks and sub networks. The simplest example is in fact the clustering coefficient, which reflects the presence of triangles (complete subgraphs of three vertices) in networks. Triangles are important since they are directly related to the robustness and error tolerance of the network (Boccaletti et al., 2006). Triangles are the simplest example of motifs. Motifs are small subgraphs consisting of a few vertices connected in a particular way and possibly associated with a specific function. Motif analysis involves counting the prevalence of different motifs in a network and comparing the results with those for random networks (Milo et al., 2002). Exponential random graph analysis is a sophisticated statistical technique popular in the social network research, that also involves reconstructing complex networks from a set of simple motif-like building blocks (Simpson et al., 2011). One level up, it may be possible to distinguish clusters or modules, sub graphs with vertices that are more strongly connected to each other than to vertices outside their own module (Newman, 2006). Finally, modules can sometimes combine to form higher order structures, giving rise to a true hierarchical modularity (Ravasz, 2009).

A second category involves measures sensitive to the level of integration in a network. Global integration can be assessed with the average shortest path, the diameter (the longest shortest path), global efficiency (Latora and Marchiori, 2001, 2003) and the spectral radius (the largest eigenvalue of the adjacency matrix of the network) (Van Mieghem, 2011).

A third category involves measures of relative vertex importance. The most basic measure is the degree of vertex (the number of edges connected to a vertex), and the degree distribution $P(k)$. As we have seen, different types of complex networks may be distinguished on the basis of their degree distribution. Degree is thus a measure of the importance of a vertex in a network. This concept is referred to as centrality. The degree correlation indicates whether high degree vertices tend to connect preferentially to other high degree vertices (assortative mixing) or to low degree vertices (disassortative mixing) (Newman, 2003). Centrality is not always the same as degree, and other more sophisticated centrality measures have been developed as well. Betweenness centrality of a vertex is the number of shortest paths through that vertex divided by the total number of shortest paths (in a similar way it is also possible to define edge betweenness) (Wang et al., 2008). The eccentricity of a vertex is the length of its longest shortest path to any other vertex; the lower the eccentricity, the more central a vertex is in a network. Eigenvector centrality determines the importance of a vertex on the basis of its connections to other vertices, but also with respect to how those other vertices are...
network physiology data in the form of graphs. For structural data, this is relatively easier than for physiological data. Since the full information on the connectivity of the neuronal network of *Caenorhabditis elegans* is known, Watts and Strogatz were able to represent this nervous system as a graph by taking the neurons as vertices and connections between neurons as edges (Watts and Strogatz, 1998). For several animals, maps are available of the structural connections between macroscopic brain areas; this allows a representation as graphs by taking brain areas instead of neurons as vertices (Sporns et al., 2000; Stephan et al., 2000). Modern MRI studies in humans present two possibilities to models anatomical connectivity as graphs. Matrices of correlations in cortical thickness can be taken as surrogate measures of anatomical connectivity (He et al., 2007). More sophisticated techniques allow the reconstruction of anatomical networks in individuals (Tijms et al., 2011). Alternatively, DTI and tractography can be used to construct connectivity matrices at various levels of anatomical resolution (Hagmann et al., 2007, 2008; Iturria-Medina et al., 2007).

Representing neurophysiological data as a graph is less straightforward. We first describe the basic approach (Fig. 6). Then we mention some alternative possibilities and point out methodological caveats. Assume we have a recording of *n* channels of “high-density EEG” or MEG. After preprocessing, artefact removal and filtering, we can compute the strength of synchronization between all possible pairs of channels or sensors, using one of the techniques described in Section 3.2. The resulting information can be represented in the form of an *n* by *n* matrix, with each *n* by *i* matrix cell containing a real number reflecting the strength of synchronization between channel *i* and *j*. In graph theory, such a matrix is referred to as the adjacency matrix *A*. To represent this information in the form of a graph, we consider each of the *n* channels to be a vertex. We choose a threshold *T* such that if *a* *i* *j* > *T*, an edge is present between vertices *i* and *j*. If *a* *i* *j* < *T*, no edge is present between vertices *i* and *j*. If we indicate the presence of an edge by 1, and the absence by 0, we have converted the *n* by *n* channel EEG or MEG data into a binary matrix. Once the data are represented as a graph (with its equivalent adjacency matrix), in principle all measures available in network theory can be applied to the network. Clearly, this approach opens up new and potentially interesting ways to analyze functional as well as structural network data.

There are a number of variations to this basic scheme, and a few methodological problems. First, a strong point of the approach is that it can be applied to all sorts of data, structural, functional (EEG, MEG, fMRI BOLD time series, correlations in spike trains or calcium fluctuations). However, it is not always clear what should be considered a vertex, and what is an edge, especially in the case of functional data (Kaiser, 2011). EEG and MEG recorded in signal space do not have a simple relation to underlying sources, and therefore according to some authors might not qualify as bona fide vertices (Antiqueira et al., 2010). The alternative would be to do network analysis in source space rather than signal space; however, even this will not solve problems related to volume conduction and spatial sampling that might interfere with properties of the reconstructed networks (Bialonski et al., 2010). A further problem concerns the choice of a threshold. This can be based upon the significance of the synchronization, or a requirement that the resulting graph is connected. The same threshold can be used for all networks to be compared, or it can be adjusted individually to obtain networks with the same degree for all subjects and conditions (Stam et al., 2007a). In many cases, a range of thresholds is studied to avoid the rather arbitrary choice of a single threshold. Clustering coefficients, motif prevalence, and path lengths are often normalized by comparing the results with those of random networks with the same number of nodes, edges, and degree distribution (Achard and Bullmore, 2007). Unfortunately, comparison of networks with different numbers of vertices and edges remains...
problematic, even after normalization by random network data (van Wijk et al., 2010).

4.2. Healthy subjects

Network studies of structural and functional brain networks have revealed a number of consistent characteristics. First, there is considerable evidence that brain networks are characterized by a combination of high clustering (the fraction of neighbors of a node that are connected to each other) and short average path lengths (the minimum number of edges to be travelled to get from one vertex to another). This has first been shown for functional networks with MEG and fMRI (Eguíluz et al., 2005; Stam, 2004; Stephan et al., 2000). Similar results have been obtained with structural MRI techniques, in particular cortical thickness correlations and DTI tractography (He et al., 2007; Hagmann et al., 2007,2008; Iturria-Medina et al., 2007; Gong et al., 2009a). Human brain networks should thus be classified as small-world networks. This is important since the strong clustering of small-world networks might support the segregation, and short path length might support the integration that are both assumed to be necessary for optimal information processing in networks (Sporns, 2011b; Stam, 2010). In addition to clustering, human brain networks also display structure at the larger scales of network motifs, and in particular network modules (Meunier et al., 2010; Sporns and Kötter, 2004). Structural and functional MRI studies have shown that human brain networks consist of around five to six modules, each corresponding with known functional subsystems (Gong et al., 2009a; He and Evans, 2010). These large-scale modules may be composed of smaller sub modules, suggesting a hierarchical organization of brain networks (Ferrarini et al., 2009; Gleiser and Spormaker, 2010; Meunier et al., 2010). It is interesting to see that the hierarchical organization of human brain networks is exactly the kind of organization that Herbert Simon predicted as optimal for any complex system (Simon, 1962).

Not all nodes or vertices in brain networks have the same significance. There is accumulating evidence that the degree distribution of human brain networks is highly skewed, with a relatively high prevalence of high-degree nodes or hubs (Eguíluz et al., 2005; Van den Heuvel et al., 2008). There is still some controversy whether human brain networks are truly scale-free with a power-law degree distribution. Some studies suggest that the degree distribution might be more properly modeled by an exponentially truncated power-law (Achard et al., 2006). This controversy is probably due, at least to some extent, to methodological issues, such as the as the level of resolution (ROIs versus voxels) used for the network analysis (Fornito et al., 2010). There is little doubt that the so-called default mode network, consisting of medial frontal, anterior and posterior cingulate cortex, precuneus and parietal cortex, constitutes a connectivity backbone that links the hubs with the highest degrees (Hagmann et al., 2008). The highly connected hubs of the default network are strongly correlated with intelligence, and may also be of central importance in consciousness (Douw et al., 2011; Li et al., 2009; Van den Heuvel et al., 2009; Sodu et al., 2011).

Network changes have also been described in relation to the physiological changes of consciousness related to sleep (Ferri et al., 2007, 2008). As we will discuss below, brain network hubs may not only play a central role in normal brain function, but also in some types of brain disease. The fact that high degree nodes in brain networks preferentially connect to each other suggests a positive degree correlation or assortative mixing (De Haan et al., 2009; Hagmann et al., 2008). A similar type of degree correlation is also found in social networks, whereas most other networks in nature tend to be disassortative (Newman, 2003). However, at the neuronal level, brain networks are disassortative rather than assortative (Bettencourt et al., 2007). This implies that the human brain is the only type of complex network known that displays opposite patterns of mixing at different spatial scales. At the cellular level, the brain is organized as a communication network, and at the macroscopic level the brain is organized as a social network. The origin and significance of this type of organization of brain networks are currently unknown.

The complex architecture of human brain networks arises during development and seems to be under strong genetic control. A large EEG study of children investigated at age 5 and 7 showed an evolution of a relatively more random to a more small-world like topology of functional brain networks (Boersma et al., 2011; Micheloyannis et al., 2009). In a follow up study, it was shown that the optimal small-world pattern of adult age is gradually replaced by a more random topology at higher ages (Smit et al., 2010). Thus, the evolution of brain network topology with respect to clustering and path length seems to follow an inverted u-curve. In addition, clustering coefficients and path lengths were shown to have a high heritability in twin studies (Smit et al., 2008). The evolution from random to small-world topology has been replicated in model studies (Siri et al., 2007). Another interesting finding is the difference in brain network topology in males and females, with higher connectivity and shorter path lengths in females (Boersma et al., 2011; Gong et al., 2009b; Schoonheim et al., 2011a).

4.3. Neuropsychiatric disease

Neuropsychiatric disease is a broad category of disorders, characterized by cognitive and psychiatric symptoms and a suspected but generally unknown neurobiological substrate. The need for objective diagnostic findings and the failure of structural imaging methods, in particular MRI, to show consistent patterns of abnormalities in neuropsychiatric disease presents a challenge for a more physiological and network based approach. One of the most prevalent and disabling psychiatric conditions is schizophrenia. Schizophrenia is not a simple Mendelian disorder, and complex genetic and developmental factors are assumed to play an important role (Kim et al., 2011). In particular, there is a suspicion that the normal development of long-range fronto-temporal connections is disrupted. Network studies provide some support for this thesis. In an early EEG study, functional brain networks of schizophrenic patients were shown to have lower normalized clustering and path length compared to healthy controls (Micheloyannis et al., 2006). An EEG study based upon network analysis of the level of nonlinear coupling also showed more random network topology in schizophrenic patients (Rubinov et al., 2009a). A few MRI studies showed rather subtle network changes in schizophrenia. Alexander-Bloch et al. (2010) reported a disruption of modular network structure in schizophrenia, with a preservation of global clustering and path length. Abnormal modular structure in schizophrenia has also been detected with EEG (Jalilzadeh and Knyazeva, 2011). Van den Heuvel et al. (2010) demonstrated very local network changes in frontal and temporal areas, with a preservation of global network properties. An overview of modern network research in schizophrenia is given in the review by van den Heuvel and Hulshoff Pol (2010). As we have discussed above, brain networks undergo systematic changes during development and such changes depend upon strong genetic influences as well as experience. If schizophrenia is indeed – at least to some extent – a genetic disorder of brain development subtle abnormalities of brain network topology in patients should be expected. These may be characterized by a relatively local fronto-temporal disturbance of normal network architecture.

Other neuropsychiatric conditions have not been studied extensively. In acutely depressed patients, global connectivity assessed with synchronization likelihood was lower and EEG functional...
network topology during sleep was more random compared to healthy controls (Leistedt et al., 2009). In a large fMRI study, depressed patients had lower normalized path length and increased node centrality of their functional brain networks compared to controls (Zhang et al., 2011). These changes are also consistent with a randomization of network topology in neuropsychiatric disease. Of interest, some of the altered node centrality measures correlated with disease duration and severity.

Structural and functional network changes, possibly under genetic control, have also been implicated in attention deficit hyperactivity disorder or ADHD (Konrad and Eickhoff, 2010). In a resting-state fMRI study, an increase of local and a decrease of global efficiency, suggesting abnormally regular networks, was reported in ADHD patients (Wang et al., 2009). Local changes in nodal efficiency mainly involved frontal, temporal and occipital areas. Community analysis of EEG networks, based upon a fuzzy synchronization likelihood, has been shown to be able to distinguish between ADHD patients and healthy controls (Ahmadlou and Adeli, 2011).

Functional network analysis of delta band EEG in autism spectrum disorder (ASD) revealed increased short-range fronto-lateral connectivity and a loss of long-range fronto-occipital connections (Barttfeld et al., 2011). These changes were accompanied by a lower clustering coefficient, longer path length, and increased modularity in ASD patients. An earlier EEG study also reported loss of global (alpha band) coherence and an increase in local (theta band) connectivity in ASD (Murias et al., 2007). In this study, no formal network analysis was applied. Graph theoretical analysis of structural brain networks in subjects with grapheme-color synesthesia showed a shift from global to more local processing (Hanggi et al., 2011).

4.4. Epilepsy

Epilepsy refers to a group of neurological conditions, characterized by the unexpected and unpredictable emergence of an abnormal dynamic state of the brain with excessive neuronal firing and synchronization. Epilepsy is one of the most prevalent and important neurological conditions. Because of its highly dynamic character, proper investigation of epilepsy requires tools with the highest possible temporal resolution such as EEG and MEG. How and why epileptic seizures arise in the brain is still essentially an enigma. Network theory can be of help here by studying changes in the organization of brain networks, that might lower the threshold for pathological synchronization and facilitate the spread of abnormal activity throughout the brain.

The first indications that network analysis might be helpful in understanding epilepsy, came from model studies. One study showed that changing the topology of simulated hippocampal neuronal networks from regular to small-world and then to random lowers the threshold for synchronization and gives rise to seizure-like activity and ultimately to epileptic bursting (Netoff et al., 2004). Percha et al. (2005) also suggested a relation between small-world topology and epileptic seizures. Another topological feature, that may be relevant for understanding seizures, is the degree-distribution, in particular the presence of hubs. Morgan and Soltesz (2008) showed that scale-free networks with hub nodes had the lowest threshold for the emergence and spreading of seizures. Healthy brain networks are probably characterized by a hierarchical modular structure, that could arise naturally during development and might subserve functional specialization (Rubinov et al., 2009b; Stam et al., 2010; Wang et al., 2011). Interestingly, modular structure might actually present a threshold for system-wide synchronization. Epileptic seizures could arise when the normal modular structure breaks down in brain disease (Kaiser and Hilgetag, 2010).

There is growing empirical support for the idea that changes in brain network topology might play a crucial role in epilepsy, as suggested by the model studies. Analysis of EEG depth recordings in patients suffering from temporal lobe seizures showed a transition from a more random to a more regular topology of functional brain networks during seizures (Ponten et al., 2007). The observation of abnormal regularization of functional brain networks during seizures has been confirmed by other studies, based upon electrocorticographic recordings (Kramer et al., 2008; Schindler et al., 2008). A similar pattern has been demonstrated with surface EEG and MEG during absence seizures (Gupta et al., 2011; Ponten et al., 2009). Several studies have shown that interictal functional networks in epilepsy patients may be characterized by increased connectivity, especially in the theta band, a shift to a more regular topology, changes in modular structure and prominent hub-like regions (Chavez et al., 2010; Douw et al., 2010b; Horstmann et al., 2010; Wilke et al., 2011). Inter-ictal network changes as well as cognitive impairment may also be related to the duration of the epileptic condition (van Dellen et al., 2009; Vlooswijk et al., 2011). MRI studies have also demonstrated abnormal brain network organization in epilepsy (Bernhardt et al., 2011; Liao et al., 2010; Vlooswijk et al., 2011; Zhang et al., 2011). These observations are clinically relevant since it has been shown, for instance, that removal of hub regions, identified with corticography during epilepsy surgery, is associated with a better outcome (Ortega et al., 2008; Wilke et al., 2011). Of interest, in the study of Ortega et al., the minimum spanning tree, based upon the corticographic time series, was used to identify the hub nodes. Characterization of interictal changes in connectivity could also improve the diagnostic yield of routine EEG (Douw et al., 2010a).

4.5. Dementia

Alzheimer’s disease is one of the most common causes of dementia in the aging population. It was also one of the first neurological conditions to be studied with the tools of modern network theory (Pievani et al., 2011). Functional network analysis of EEG filtered in the beta band showed changes in the path length in Alzheimer patients (Stam et al., 2007a). These changes correlated with a lower mini mental state score in the patient group. This study also showed the methodological problems associated with different ways for reconstructing networks from multi-channel EEG data, in particular using a fixed threshold or a fixed degree for all networks. In a later MEG study, resting-state functional brain networks in Alzheimer patients were characterized by a lower normalized clustering coefficient and path-length, especially in the lower alpha band (Stam et al., 2009). The network changes in Alzheimer patients could be replicated with a simple damage model that assumed preferential damage of hub-like network connections. A decrease of the normalized clustering coefficient and path-length in Alzheimer’s disease could be confirmed in a more recent EEG study (De Haan et al., 2009). This study revealed an opposite pattern of network changes in frontal lobe dementia (Fig. 7). All patients as well as healthy control subjects displayed positive degree correlations, but the degree correlations were significantly lower in Alzheimer’s disease and frontal lobe dementia. Functional connectivity of MEG during a working memory study was investigated in patients with mild cognitive impairment (Buldú et al., 2011). The average level of connectivity and a so-called outreach parameter were increased in the MCI group. These changes were interpreted in terms of higher energy expenditure and a tendency toward random structure in MCI patients. The increased synchronization likelihood during a working memory task in MCI is in line with the EEG study of Pijnenburg et al. (2004).

Network changes in dementia have also been shown with structural and functional MRI studies (Bokde et al., 2009; Filippi and
The first resting-state fMRI network study in Alzheimer’s disease (AD), frontotemporal dementia (FTLD) and control groups, the functional connectivity (synchronization likelihood, SL) based graphs are shown as headplots for different values of $K$. Lower $K$ values (higher threshold) result in a sparser network. On visual inspection, it is obvious that there are inter-group differences. From: De Haan W et al. Functional neural network analysis in frontotemporal dementia and Alzheimer’s disease using EEG and graph theory. BMC Neurosci 2009;10:101. (Copyright by the authors under the license agreement that the work can be freely distributed when fully cited.)

There is increasing evidence from these studies, that different types of dementia might be characterized by specific patterns of network changes (Zhou et al., 2010). This observation suggests that network analysis could be of clinical use in the differential diagnosis of dementia (Pievani et al., 2011; Zamrini et al., 2011).

One of the most challenging questions at this moment is whether the network changes in Alzheimer’s disease can be related to specific underlying mechanisms. One of the classic neuropathological hallmarks of Alzheimer’s disease is the deposition of amyloid beta. Deposition of amyloid beta in the brain is not random but follows a specific pattern with the highest concentrations in multimodal association areas. There is a considerable overlap be-

Agosta, 2011). The first resting-state fMRI network study in Alzheimer’s disease reported a significant decrease of the clustering coefficient, interpreted as a signature of local connection loss (Supekar et al., 2008). In contrast, a more recent study showed normal clustering coefficients but decreased normalized path length (Sanz-Arigita et al., 2010) (Fig. 8). In this study, the average level of connectivity, quantified as the synchronization likelihood of the resting-state BOLD time series, was the same in both groups, but Alzheimer patients had a relatively high connectivity level in frontal areas, and a relatively lower connectivity level in parietal and occipital areas. This anterior to posterior disconnection was also observed in another fMRI study (Wang et al., 2007).
5. Toward a theory of brain networks

5.1. From local activation to network organization

In this review, we have argued for the need and potential usefulness of studying the brain from the perspective of a complex organized network (Fig. 9). The underlying question is simple and daunting at the same time: why is our brain so complex? If we assume that our brain is the result of a long evolutionary process we can expect that its complex organization is not random but rather reflects some kind of optimal solution to multiple, possibly conflicting, constraints. The question then becomes whether a network perspective can provide an explanation, even if only tentatively, of the origins and functional significance of the organization of brain networks.

The study of the function of elementary units of the brain, from the level of neurons and microcolumns all the way up to macroscopic brain regions, is a necessary first step for understanding brain function (Section 3.1). Much of the progress in neuroscience in the past few decades is related to a better understanding of the conditions underlying local activation of functional brain units. However, it is also obvious that the activity of functional units of the brain makes little sense (literally as well as metaphorically) if it cannot be communicated to other units of the brain. The function of the brain is more than the sum of the firing rates of its neurons. Thus, it is of the utmost importance to understand how pairs of functional units interact and exchange information. This realization underlies the rapidly increasing interest in studies of “functional connectivity” and related concepts (Section 3.2). A major focus in this kind of studies is the development of reliable measures of pair-wise interactions. However, when this approach is applied to the study of interactions in systems with large numbers of elements, its limitations become apparent. Often, it is very difficult to make sense out of the multitude of increases and decreases of functional connectivity levels that are observed in different behavioral states and neurological disorders. The point is, that the functional architecture of the brain cannot be understood as the sum of a large number of pair-wise interactions (Section 3.6).

The point of modern network theory is that a kind of systems perspective is needed to understand how communication is organized in a brain, consisting of a large number of interacting elements (von Bertalanffy, 1969). A network perspective introduces concepts such as clustering, modularity, path length and degree distribution, that do not make sense, and in fact do not even exist, at the level of pair-wise interacting brain regions or neurons (Section 4.1). Such high level concepts and measures, based upon these concepts, can help to identify organizational themes in brain net-
works, and common patterns in the way these networks are disrupted in disease.

5.2. A heuristic model of complex brain networks

The concept of a graph provides a general framework for dealing with all sorts of networks and allows studying the organization of the brain using novel concepts and measures (Fig. 10). The concepts and measures derive their meaning from the fact that they are defined in the context of specific structural models of complex networks. The introduction of random graphs bridged the gap between small, deterministic graphs, and large networks that require a statistical description (Erdős and Rényi, 1959). The ER model explains some important aspects, but fails to explain the phenomenon of clustering. The small-world model solves this problem but cannot explain the diversity of node properties, observed in real networks. The scale-free model of Barabasi and Albert does explain node diversity and the existence of hubs or highly connected nodes, and has a very short path length, but unfortunately also a vanishing clustering coefficient.

The problems we are faced with can be described as follows: currently, we have two powerful models, the WS model (that contains the ER model as a special case) and the SF (scale-free) model, both of which explain some of the properties of real brain networks (notably: clustering, short paths and degree diversity). The first problem is that of the relationship between the two models. Neither model can be reduced to the other; some properties can only be explained by one model, and not by the other. In other words: we need them both, but they do not go well together. The second problem is that a number of network properties have been detected that are clearly present in structural and anatomical networks, but cannot be explained by either model. The two most obvious examples are (hierarchical) modularity and degree correlations. These two problems present an important challenge for a network theory of the brain.

To overcome these problems, and to guide future studies, we present a heuristic model of complex brain networks (Fig. 10). The heuristic model assumes an abstract “network space” defined by three corners and three axes. The first, horizontal axis, is a representation of the WS model. The left corner is occupied by the regular lattice network, the right corner by the random ER network, and intermediate networks between the lattice and random network correspond to small-world configurations. The horizontal axis indicates the balance between order and randomness. The vertical axis with the SF network in the upper right corner indicates the level of node diversity. While interpolation between ER and SF networks is not commonly used, it is easy to see how this could be done, for instance by randomly rewiring the edges of the SF network with a probability p. The degree diversity kappa (\(\langle k^2 \rangle/\langle k \rangle\)) could be a useful measure to locate a network between the extremes of ER and SF. The third diagonal axis connects the lattice in the lower left corner to the SF network in the upper right corner. According to Ravasz and Barabási (2003), networks that are intermediate between a lattice and a scale-free network display hierarchical modularity (hierarchical modular network, HMN). This can be quantified by the exponent of the power law relation between C(k) and k (with C the clustering coefficient and k the degree). In networks with hierarchical modularity, the clustering coefficient is inversely correlated with the degree.

The heuristic model of “network space” suggests that the HMN presents a very special case. This type of network is not only intermediate between the lattice and the SF network, but, if we project its position on the X axis, also between the lattice and the ER model, and if we project it on the Y axis, between the ER and the SF network. In fact, the HMN combines properties of a lattice, a random and a scale-free network as a kind of compromise. It combines high clustering with short path lengths and high degree diversity. In addition, it displays hierarchical modularity and could be linked to positive degree correlations (Newman, 2003, 2006).

The concept of HMN is very attractive, since it suggests how the fundamental properties of network models might be related. Furthermore, HMNs are the only network model that explain all major properties (clustering, short paths, degree diversity, modularity and assortativity) observed in real structural and functional networks. There are indications that modular structure can evolve naturally in networks that use optimization algorithms such as simulated annealing (Kirkpatrick et al., 1983) to deal with multiple conflicting constraints (Pan and Sinha, 2007; Rubinov et al., 2009b; Stam et al., 2010; Yuan and Zhou, 2011). Furthermore, hierarchical modularity has been shown to explain critical dynamics as well as oscillations of neural activity, both of which are assumed to play a key role in neuronal information processing (Kaiser et al., 2010; Rubinov et al., 2011; Wang et al., 2011). Since HMNs present a compromise between many network properties and may evolve naturally in networks dealing with multiple constraints, it is seductive to conceive of HMNs as optimal configurations functioning as attractors in “network space”. However, it should be stressed that at present, in contrast to the ER, WS and SF models, we do not have a simple, universal mathematical model of HMNs. The discovery of such a model could offer substantial support for the heuristic model presented here.

5.3. Development, aging and neurological disease in network space

Can we use our heuristic model of complex brain networks to make sense out of the many network studies described in this review? We will address this question with respect to development, aging and various types of neurological disease. The central idea of the heuristic model is that hierarchical modular networks present an optimal state characterized by high clustering, short paths, degree diversity, hierarchical modularity and assortativity. In this view, network changes are either towards or away from this optimal state. Furthermore, the three corners in “network space” can characterize distinct patterns of network changes.

In general, network studies of brain development are in agreement with the notion of a movement toward an optimal HMN organization (Boersma et al., 2011; Fair et al., 2009; Micheloyannis et al., 2009; Yap et al., 2011). Here we should note that changes from either a lattice or a random network to a small-world network could be translated to changes in the direction of a HMN network; in fact, the heuristic model predicts that node diversity should increase at the same time. Studies differ with respect to the starting point of the network trajectory. EEG studies suggest that network development may start in the lower right corner, whereas MRI-based studies indicate that networks may be more lattice-like early in development (Boersma et al., 2011; Fair et al., 2009; Yap et al., 2011). Evolution toward a hierarchical modular structure, irrespective of the initial state, is supported by model studies (Siri et al., 2007). Network changes in aging may be explained by a movement away from the HMN pattern toward either a more random or a more lattice like structure (Smit et al., 2010). Loss of modular structure has also been observed in aging (Meunier et al., 2009).

The heuristic model suggests that brain disease at the network level always implies a movement away from the optimal HMN state. Depending upon the trajectory through “network space”, different patterns may be discerned. First, network disease could result in a straightforward movement to the lower right corner. This network randomization is a pattern that has been observed in many different types of brain disease, ranging from Alzheimer’s disease, brain tumors, depression to schizophrenia (De Haan et al., 2009; Leisteldt et al., 2009; Micheloyannis et al., 2006; Rubinov et al., 2009a; Stam et al., 2009). Network randomization seems to
be a characteristic of relatively severe and advanced brain disease. Second, in some other conditions brain networks seem to move away from the HMN toward the lower left corner. This type of change would be characterized by a shift from global to local connectivity, and a pathological increase in “network regularity”. This pattern of brain network changes has been observed in developmental disorders (Battfleld et al., 2011; Hänggi et al., 2011; Wang et al., 2009) as well as in the early stages of various neuropsychiatric conditions (Buldú et al., 2011; Pijnenburg et al., 2004; Schooneheim et al., 2011b). Third, in some situations brain disease may be characterized by the abnormal activation of hubs, or the emergence of new pathological hub-like brain areas. This would correspond to a movement to the upper right corner. Excessive activation of hub nodes has been associated with epileptic brain regions (Chavez et al., 2010; Douw et al., 2010b; Horstmann et al., 2010; Wilke et al., 2011; Zhang et al., 2011). In addition, excessive hub activation could be a temporary state in other neurological disorders, followed by a more general network randomization.

While different trajectories in network space might characterize different stages or patterns of disease, if the disease is long lasting and severe, the natural endpoint seems to be the random network in the lower right corner. This suggests that the random network could be thought of as an “attactor” for pathological networks, just like the HCN could be an attractor for healthy brain networks.

5.4. Future challenges

The additive value of network analysis of the brain is that it allows us to go beyond local activation and pairwise-wise interaction studies, and define higher order concepts relevant for normal and abnormal brain function. One challenge is to develop better measures of brain network characteristics, and use these measures to integrate information from multiple imaging modalities such as EEG, MEG, structural and functional MRI. However, even more urgent is the need for new and better models that can fill the gap between the existing small-world and scale-free models. A simple mathematical model of hierarchical networks could be an important step forward. A deeper understanding of complex brain networks also requires the identification of the most relevant constraints that confront developing brain networks, as well as the algorithms that are used to deal with them. In particular, the role of space and geometric constraints may be important factors (Henderson and Robinson, 2011; Kaiser and Hilgetag, 2004). It may be helpful to think of the complex architecture of brain networks in terms of solutions; the main task then becomes to identify the problems these networks are trying to solve. Finally, the ultimate challenge for network studies in a clinical context, and in particular in clinical neurophysiology is whether this approach will have an impact not only on our understanding of pathophysiological mechanisms, but also on clinical diagnosis and treatment.

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