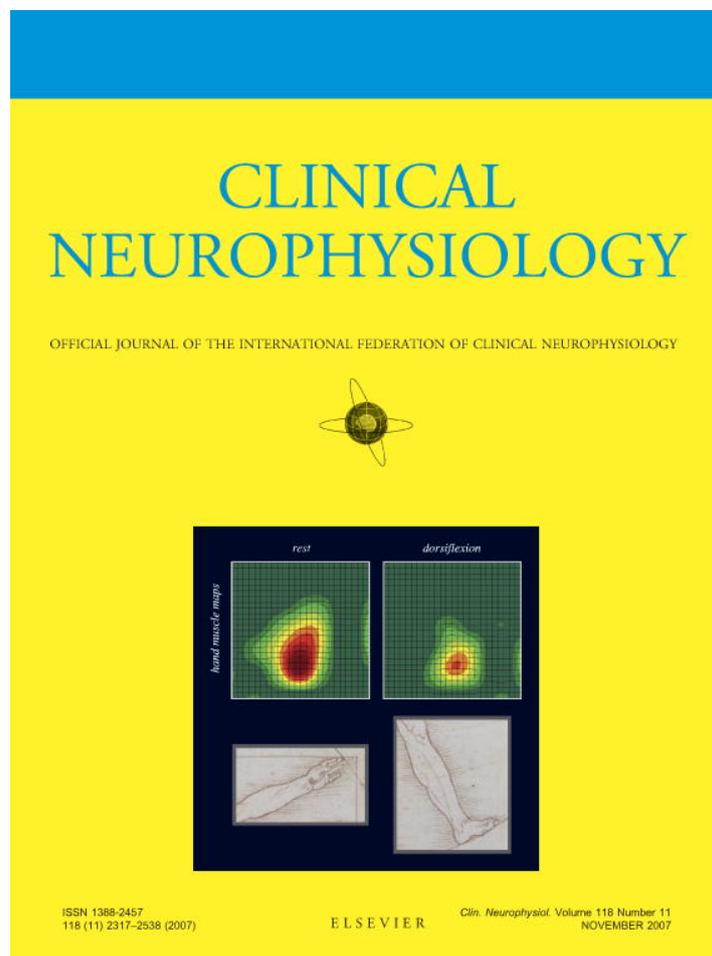


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Invited review

The application of graph theoretical analysis to complex networks in the brain

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Abstract

Considering the brain as a complex network of interacting dynamical systems offers new insights into higher level brain processes such as memory, planning, and abstract reasoning as well as various types of brain pathophysiology. This viewpoint provides the opportunity to apply new insights in network sciences, such as the discovery of small world and scale free networks, to data on anatomical and functional connectivity in the brain. In this review we start with some background knowledge on the history and recent advances in network theories in general. We emphasize the correlation between the structural properties of networks and the dynamics of these networks. We subsequently demonstrate through evidence from computational studies, *in vivo* experiments, and functional MRI, EEG and MEG studies in humans, that both the functional and anatomical connectivity of the healthy brain have many features of a small world network, but only to a limited extent of a scale free network. The small world structure of neural networks is hypothesized to reflect an optimal configuration associated with rapid synchronization and information transfer, minimal wiring costs, resilience to certain types of damage, as well as a balance between local processing and global integration. Eventually, we review the current knowledge on the effects of focal and diffuse brain disease on neural network characteristics, and demonstrate increasing evidence that both cognitive and psychiatric disturbances, as well as risk of epileptic seizures, are correlated with (changes in) functional network architectural features.

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1. Introduction

Traditionally, neuroscientists correlate ‘focal’ brain lesions, for instance brain tumors, with ‘focal’ clinical deficits. This approach gave important insights into the localization of brain functions; a classical example is the identification of the motor speech center in the lower left frontal cortex by the French neurologist Paul Broca at the end of the 19th century. Particularly during the last decades of the 20th century, this essentially reductionistic program led to significant progress in neuroscience in terms of molecular and genetic mechanisms.

Despite the impressive increase of knowledge in neuroscience, however, progress in true understanding of higher level brain processes has been disappointing. Evidence has accumulated that functional networks throughout the brain are necessary, particularly for higher cognitive functions such as memory, planning, and abstract reasoning. It is more and more acknowledged that the brain should be conceived as a complex network of dynamical systems, consisting of numerous functional interactions between closely related as well as more remote brain areas (Varela et al., 2001).

Evaluation of the strength and temporal and spatial patterns of interactions in the brain and the characteristics of the underlying functional and anatomical networks may contribute substantially to the understanding of brain

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function and dysfunction. A major advantage of this approach is that a lot can be learned from other fields of science, particularly the social sciences, that are also devoted to the study of complex systems. In the last decade of the 20th century, considerable progress has been made in the study of complex systems consisting of large numbers of weakly interacting elements. The modern theory of networks, which is derived from graph theory, has proven to be particularly valuable for this purpose (Amaral and Ottino, 2004; Boccaletti et al., 2006).

The aim of this paper is to review applications of network theories to neuroscience in general, and clinical neurophysiology in particular (a more technically oriented review can be found in Stam and Reijneveld (Stam and Reijneveld, 2007)). After a brief historical introduction, we will summarize the basic characteristics of networks in general, and some important results on the relation between network properties and dynamical processes in these networks. Subsequently we will discuss applications of network theories in experimental neuroscience, both neuro-anatomical and neurophysiological. In the last section of this review, we will determine the effect of interventions or brain disease on neural network properties, in the light of patients with disturbed brain function, e.g. cognitive disturbances, epilepsy, and psychiatric disorders.

2. Network theories

2.1. Historical background

The modern theory of networks has its roots both in mathematics and sociology. In 1736 the mathematician Leonard Euler solved the problem of ‘the bridges of Königsberg’. This problem involved the question whether it was possible to make a walk crossing exactly one time each of the seven bridges connecting the two islands in the river Pregel and its shores. Euler proved that this is not possible by representing the problem as an abstract network: a ‘graph’. This is often considered as the first proof in graph theory. Since then, graph theory has become an important field within mathematics, and the only available tool to handle network properties theoretically.

An important step forward occurred when ‘random’ graphs were discovered (Solomonov and Rapoport, 1951; Erdos and Renyi, 1960). In random graphs, connections between the network nodes are present with a fixed and equal likelihood. Many important theories have been proven for random graphs. In particular it has been shown that properties of the graphs often undergo a sudden transition (‘phase transition’) as a function of increasing likelihood that edges are present. However, despite the success of random graph theory, most real-world networks, particularly those found in social or biological systems, have properties that cannot be explained very well by classic random graphs. These properties include the high clustering and power law degree distributions. One empirically observed phenomenon in many real networks is the fact

that the ‘distances’ in sparsely and mainly locally connected networks are often much smaller than expected theoretically. This phenomenon was probably first observed by the Hungarian writer Frigyes Karinthy in a short story called ‘Chains’. In this story he speculates that in the modern world the distance between any two persons is unlikely to be more than five persons, a phenomenon later studied and described in more detail by Stanley Milgram, and referred to as the ‘small world phenomenon’, or ‘six degrees of separation’ (Milgram, 1967).

2.2. Recent advances

The publication of a landmark paper in 1998 by Watts and Strogatz (Watts and Strogatz, 1998) provided a simple and elegant way of modeling small world networks. These authors proposed a very simple model of a one-dimensional network. Initially each node (‘vertex’) in the network is only connected to its ‘ k ’ nearest neighbors (k is called the degree of the network), representing a so-called ‘regular’ network. Next, with likelihood ‘ p ’, connections (‘edges’) are chosen at random and connected to another vertex, also chosen randomly. With increasing p , more and more edges become randomly re-connected and finally, for $p = 1$, the network is completely random (Fig. 1). Thus, this simple model allows the investigation of the whole range from regular to random networks, including an intermediate range.

The intermediate range proved to be crucial to the solution of the small world phenomenon. In order to show this, the authors introduced two measures: the clustering coefficient ‘ C ’, which is the likelihood that neighbors of a vertex will also be connected, and the path length ‘ L ’ which is the average of the shortest distance between pairs of vertices counted in number of edges. Watts and Strogatz showed that regular networks have a high C but also a very high L . In contrast, random networks have a low C and a low L . So, neither regular nor random networks explain the small world phenomenon. However, when p is only slightly higher than 0 (with very few edges randomly rewired) the path length L drops sharply, while C hardly changes (Fig. 2). Thus networks with a small fraction of randomly rewired connections combine both high clustering and a small path length, and this is exactly the small world phenomenon to be explained. The authors demonstrated the existence of such small world networks in the nervous system of *Caenorhabditis elegans*, a social network of actors, and the network of power plants in the United States. Furthermore, they showed that a small world architecture might facilitate the spread of infection or information in networks (Watts and Strogatz, 1998).

A second major discovery was presented in 1999 by Barabási and Albert (Barabási and Albert, 1999). They proposed a model for the growth of a network where the likelihood that newly added edges connect to a vertex depends upon the degree of this vertex. Thus, vertices that have a high degree (large number of edges) are more likely

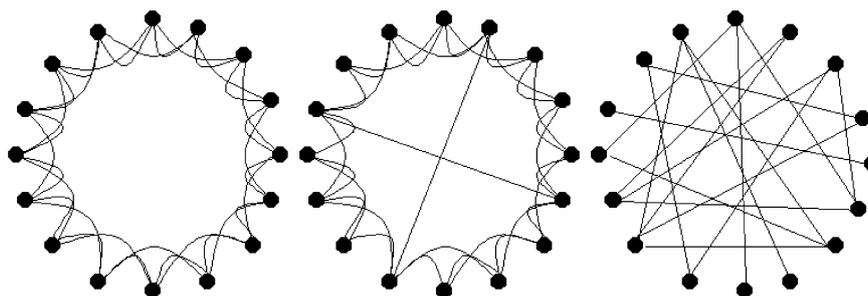


Fig. 1. Different types of networks. Regular network in which all cells are only coupled to their nearest neighbors (left). Small world network in which small numbers of connections are broken and rewired in order to make long-distance connections at random locations (middle). Random network with more long-distance connections (right), the network loses the property that most connections are local.

to get even more edges. This is the network equivalent of ‘the rich getting richer’. Networks generated in this way are characterized by a degree distribution which can be described by a power law: $p(k) = k^{-1/a}$. Networks with a power law degree distribution are called ‘scale free’. It has been shown that many social and technological networks, such as for instance collaborative networks of scientists, the World Wide Web, and networks of airports, are likely to be scale free (Newman, 2003).

3. Basics of modern network theory

The discovery of small world networks and scale free networks set off a large body of theoretical and experimental research, which has led to increasing knowledge on various aspects of network properties in the last decade. Before we move on to the application of network theories to experimental neural networks, and healthy and diseased brain, we will provide some basic knowledge on several aspects of network properties. As mentioned before, more detailed mathematical descriptions can be found in Albert and Barabási (Albert and Barabási, 2002) and Stam and Reijneveld (Stam and Reijneveld, 2007).

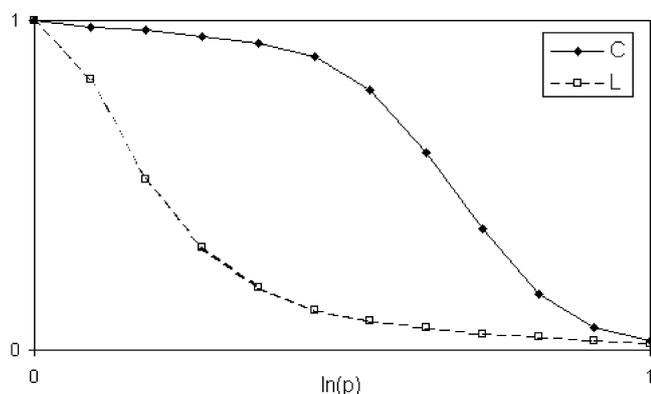


Fig. 2. Graph illustrating the fact that when p is only slightly higher than 0 (which represents a completely regular network with $p = 0$, high C , high L) and thus a few edges are randomly rewired, the path length L drops sharply, while C hardly changes. At the other end of the graph a completely random graph ($p = 1$, low C , low L) is represented.

3.1. Core measures

The degree distribution, clustering coefficient, and path length are the core measures of graphs. The degree distribution can be described as the likelihood $p(k)$ that a randomly chosen vertex will have degree k . The clustering coefficient C is an index of local structure. It is the likelihood that neighbors of a vertex will also be connected to each other, and have been interpreted as a measure of resilience to random error (if a vertex is lost, its neighbors remain connected). The path length L is a global characteristic; it indicates how well integrated a graph is, and how easy it is to transport information or other entities in the network (Fig. 3).

On the basis of the abovementioned three measures, four different types of graphs can be distinguished: (i) regular or ordered; (ii) small world; (iii) random (see Fig. 1); (iv) scale free. We should stress that neither regular, small world, nor random networks are scale free. Scale free networks can have very small path lengths of the order of $\ln \ln(N)$, but the clustering coefficient may also be smaller than that of small world networks (Cohen and Havlin, 2003).

3.2. Additional measures

3.2.1. Motifs, degree correlation and betweenness

In addition to clustering coefficients, path lengths, and degree distributions, other measures have been introduced to characterize properties of a network. ‘Motifs’ are simple sub-graphs consisting of a small number of vertices connected in a specific way (Milo et al., 2002; Artzy-Randrup et al., 2004; Sporns and Kotter, 2004). Triangles are a simple type of motif. Larger, more complex types of motifs have also been described. Alternatively, one could view motif analysis as a kind of generalization of the clustering coefficient. Another measure is the ‘degree correlation’, indicating whether the degree of a vertex is influenced by the degree of another vertex to which it connects. Graphs with a positive degree correlation (vertices with high degrees connecting preferably to other vertices with high degrees) are called assortative; in the case of a negative

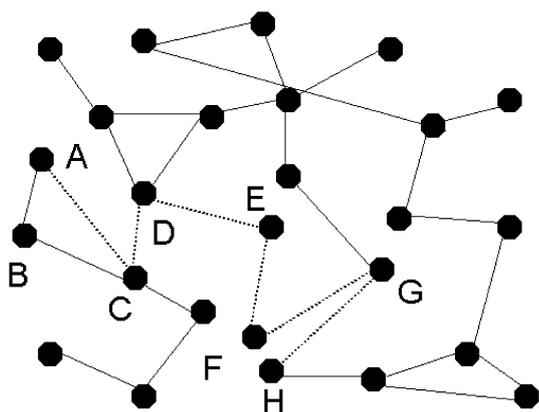


Fig. 3. Schematic representation of a network in the form of a graph. A graph is a basic representation of a network and consists of vertices (black dots). If two vertices are connected, an edge is drawn between them (black lines). In a graph, all vertices need to be connected. The characteristic path length L of a graph is the mean of all shortest paths connecting all pairs of vertices. The shortest path from vertex A to vertex H has a length of 6 edges (dotted line). To compute the clustering coefficient for vertex A, we first determine the other vertices to which it is directly (with $L = 1$) connected, in this case vertices B and C. Then we determine how many edges exist between the set of neighbors. In this case, B and C, and C and D are connected. Next we determine how many edges could have existed between the neighbors. In this case this is 3 (B-C, C-D, and B-D). The cluster coefficient of A is the ratio of these two numbers: $2/3$. In a similar way, the cluster coefficient can be determined for all vertices. This results in an average clustering coefficient C for the whole graph.

degree correlation a graph is called disassortative. Interestingly, most social networks tend to be assortative, while most technological and biological networks tend to be disassortative (Freeman, 1979a,b; Newman, 2003). An index of the relative importance of a vertex or edge is the 'betweenness'. Betweenness is the number of shortest paths that run through an edge or vertex. This measure also reflects the consequences of the loss of a particular edge or vertex. Another recently described measure is the traversal time for random walks on small world networks (Parris and Kenkre, 2005). They showed that the mean traversal time for random walks on a small world network decreases as the number of small world connections in the network increases. In the absence of any small world shortcuts, the mean traversal time became equal to the mean time that it takes to diffuse through the network. Furthermore, the authors demonstrated that both the 'jump rate' (i.e. how fast is the small world connection compared with other connections) and the number of small world connections influence the traversal time.

3.2.2. Weighted graphs

Graphs in which edges either exist or do not exist, and in which all edges have the same significance, are called 'unweighted' graphs. When weights are assigned to each of the edges the corresponding graph is called a 'weighted' graph (Fig. 4).

Weights can be used to indicate the strength or effectiveness of connections, or the distance between vertices;

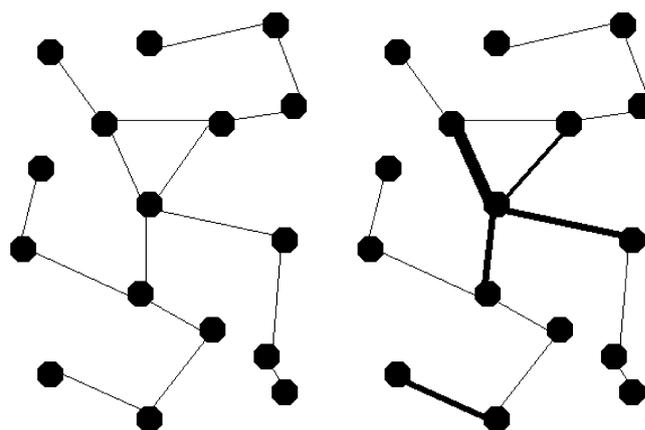


Fig. 4. Unweighted and weighted graphs In an unweighted graph (left) all edges have the same strength. In a weighted graph (right) the thickness of the edge correlates with the strength (or effectiveness) of the edge.

negative weights can also be used. Most graph measures have only been defined for the simplest case of unweighted graph, but in many cases weighted graphs are more accurate models of real networks (Latora and Marchiori, 2001, 2003; Newman, 2004; Barrat et al., 2004; Park et al., 2004; Barthelemy et al., 2005; Onnela et al., 2005). In order to characterize such networks, one could simply convert them to unweighted graphs, for instance by setting all edges with a weight above a certain threshold to 1, and the others to 0. Although this approach works and has been used in EEG and MEG studies (Bartolomei et al., 2006b), it has several disadvantages: (i) much of the information available in the weights is not used; (ii) when the threshold is too high some vertices may become disconnected from the graph which poses problems in the computation of C and L ; (iii) the choice of the threshold remains arbitrary. Latora and Marchiori have proposed a framework to address some of these problems through defining the efficiency of the path between two vertices as the inverse of the shortest distance between the vertices (note that in weighted graphs the shortest path is not necessarily the path with the smallest number of edges) (Latora and Marchiori, 2001, 2003; Vragovic et al., 2005). In the case where a path does not exist, the length is considered to be infinite, and thus the efficiency is zero. The average over-all pair-wise efficiency is the global efficiency of the graph. The local efficiency is the mean of the efficiencies of all sub-graphs of neighbors of each of the vertices of the graph. The approach based upon efficiencies is attractive since it takes into account the full information contained in the graph weights, and provides an elegant solution to handle disconnected vertices. Efficiency has been used to show that scale free networks are very resistant to random errors, but quite sensitive to targeted attacks on specific vertices (e.g. 'hubs') (Crucitti et al., 2003). By taking the harmonic mean of the inverse of the efficiencies a weighted path length can be defined, which is a bit closer to the original path length (Newman, 2003). Apart from the local efficiency, other

definitions of C have been proposed for weighted networks (Barrat et al., 2004; Onnela et al., 2005).

3.2.3. Directed graphs

Graphs can be undirected, when information can flow in both directions along edges connecting vertices, or directed, when information can only flow in one direction. Many networks, e.g. the World Wide Web and metabolic networks, have directed edges. It is important to realize that in directed networks, not all nodes can be reached from a given node (Albert and Barabási, 2002). In directed graphs each vertex may have different numbers of ingoing and outgoing edges; correspondingly there are separate in degree and out degree distributions for such graphs. A study of the cluster structure of the World Wide Web demonstrated that 28% of the nodes, which was denominated the 'strongly connected component', was connected by paths in either direction, whereas a quarter of the nodes could be reached from that component but could not connect to it in the other direction, and another quarter vice versa (Broder et al., 2000). This structure was also reported in other types of directed networks (Newman et al., 2001; Dorogovtsev et al., 2001). Up to now, however, most network models ignore the network's directedness.

3.3. Dynamic processes in networks

One of the most interesting and active research areas in modern network theory is the study of correlations between structural network characteristics and synchronization dynamics in these networks (Motter et al., 2006). This also is a research area that is particularly important when applying network theories to functional brain dynamics in clinical neurophysiology. It is thought that the synchronization, or 'functional connectivity', of distant brain areas plays an important role particularly in higher brain functioning (Aertsen et al., 1989). The basic assumption of this concept is that statistical interdependencies between time series of neuronal activity or related metabolic measures at separate areas in a neural network reflect functional interactions between these neurons and brain regions. Before we move on to functional connectivity in neural networks, we will first review the existing knowledge on the influence of network topology on synchronizability in general.

3.3.1. Influence of network topology on synchronizability

Initially, the general assumption was that synchronizability was directly related to the average path length of a network, and in particular that small world networks displayed a high level of synchronizability as demonstrated already in the Watts and Strogatz paper (Watts and Strogatz, 1998). Several research groups, however, have demonstrated that other factors such as for instance the degree distribution also influence synchronizability, and that in some instances networks with a higher average path length even synchronize more easily (Barahona and Pec-

ora, 2002; Hong et al., 2002; Nishikawa et al., 2003). In order to better quantify the term synchronizability, it was tried in several ways to define a measure of synchronizability. In particular, the eigenvalue ratio $R = \lambda_N / \lambda_2$, which is the ratio of the largest and second smallest eigenvalue of a graph, may be a useful indicator of synchronizability (Nishikawa et al., 2003; Boccaletti et al., 2006). Briefly, for this purpose the spectrum of eigenvalues from the graph Laplacian L is determined, which is the difference between the diagonal matrix of node degrees and the adjacency matrix A . The adjacency matrix A contains the information about the connectivity structure of a graph; when an edge exists between two vertices, the corresponding entry of the adjacency matrix is 1, otherwise 0. Subsequently, the eigenvalues are ordered from the largest to the smallest, where $\lambda_1 = 0$. The application of the ratio R as a measure of synchronizability has demonstrated that factors such as heterogeneity of the degree distribution and average degree have different effects on synchronizability of weighted and unweighted networks (Nishikawa et al., 2003; Donetti et al., 2005; Motter et al., 2005; Zhou and Lipowsky, 2005; Zhou et al., 2006a). Currently, based on the evidence available in the literature, it is thought that in the case of weighted networks, scale free networks have the highest synchronizability, followed (in order of decreasing synchronizability) by random, small world, and regular networks (Chavez et al., 2005, 2006).

3.3.2. Influence of other factors on synchronizability

Several other factors influence the synchronizability of networks. Surprisingly, networks with scale free or random topology sometimes synchronize more easily when delays between the coupled dynamical units are introduced, whereas regular and small world networks usually demonstrate decreased synchronizability after the addition of delays (Atay et al., 2004). Adding links between two networks generally increases the synchronizability of the individual networks, but decreases the synchronizability of the combined network (Atay and Biyikoglu, 2005). Critical coupling strength for synchronizability of scale free networks was found to be smaller than for small world or random networks, depending on the scaling exponent value (large differences between $k = 2-3$ and $k \geq 3$) (Lee, 2005; Zhou and Lipowsky, 2005). Several studies have shown that the synchronizability of a weighted random network is mainly determined by the average degree and the heterogeneity of the node's intensity, which is the sum of the strengths of all inputs of a node, and reflects the heterogeneity of the degree as well as the links; the smaller the heterogeneity and the lower the degree, the more synchronizability was enhanced (van den Berg and Van Leeuwen, 2004; Zhou and Kurths, 2006; Zhou et al., 2006a).

All these studies underscore the importance of structure–function relationships in complex networks. The general image that arises is that spatial features of networks determine to what extent networks facilitate synchronization. In general, the threshold for synchronization seems

to decrease going from regular to small world, random, and finally scale free networks. However, factors such as the weighted or unweighted nature of the network, the presence of delays, and the degree distribution may complicate this picture. It is important to keep these principles in mind for the next section.

4. Do biological neural networks display small world and scale free properties?

An important question is to what extent the abovementioned features are relevant for networks of neuron-like elements. It is thought that generally speaking the brain is faced with two opposing requirements: (i) segregation, which means local specialization for specific tasks and (ii) integration, combining all the information at a global level (Sporns et al., 2000a,b; McIntosh, 2000). The first key question is which kind of anatomical and functional architecture allows both functions to be combined in an optimal way. The second key question is what the optimal architecture of neural networks is in terms of ‘wiring costs’ and optimal component placement, as well as resilience to errors (Karbowski, 2001). In the next section, we will demonstrate to what extent the application of network theories can provide answers to these key questions. We will first focus on computational models and *in vitro* and *in vivo* studies. Most of these studies have used neuro-anatomical data, sometimes by creating a network of cultured neurons, whether or not with additional computational models, in other instances through the analysis of previously mapped neural networks of organisms such as *C. elegans*, vertebrates, and primates. We will then move on to research on healthy subjects, most of the time using neurophysiological data, collected through fMRI, EEG, or MEG.

4.1. Simulated neural network models

Sporns et al. studied computational neural network models that were allowed to develop to maximize certain properties. Networks which developed while optimizing for ‘complexity’ showed increasing small world characteristics and low wiring costs (Sporns et al., 2000a). The authors defined complexity as a measure of the extent to which patterns of functional connectivity produced by units or areas within a neural system combined the dual requirements of functional segregation and integration (Sporns and Tononi, 2002). The authors speculate that this type of network architecture emerges as an adaptation to rich environments and promotes the development of a ‘dynamic core’ (Sporns et al., 2000b; Sporns and Tononi, 2002; Sporns and Zwi, 2004). This dynamic core could be a potential substrate of higher cognition and consciousness. Gong and van Leeuwen demonstrated that small world networks can arise from initially randomly coupled networks, given a simple synchronization-dependent rewiring rule (Gong and Van Leeuwen, 2004). Karbowski studied the trade off between minimizing energetic (axonal length or wiring costs) and

biochemical (number of synapses or axons) costs in cerebral cortex architecture through a computational model (Karbowski, 2001). The model showed some similarity with small world networks, but in contrast to these had a distance-dependent probability of connectivity.

Several computational studies suggest that a small world type of architecture is optimal for information processing in neural networks. Small world topology facilitated both coherent oscillations of network neurons coupled by excitatory synapses as well as fast system responses. In these studies, neural network dynamics suddenly changed over a small range of p values, suggesting a phase transition; increasing p replaced precise local with rough global synchrony. It was also demonstrated that network dynamics were influenced by the degree distribution; with so-called ‘balanced rewiring’ (same degree for all vertices) the optimal p vanished (Lago-Fernandez et al., 2000; Roxin et al., 2004; Masuda and Aihara, 2004). Other studies on properties of two-dimensional excitatory neural networks mainly demonstrated a correlation between shorter path lengths and better performance. Local properties such as the clustering coefficient turned out to be less important (French and Gruenstein, 2006; Vragovic et al., 2006). Studies on networks with both inhibitory and excitatory synapses showed the same picture; the transition between non-periodic and periodic dynamics as a function of p was again suggestive of a phase transition. The optimal balance between excitation and inhibition proved to be crucial (Shin and Kim, 2006; van Vreeswijk and Sompolinsky, 1996; de Arcangelis et al., 2006; Paula et al., 2006; Zemanova et al., 2006; Zhou et al., 2006b).

It remains to be determined, however, if the situation in ‘real life’ is in agreement with these theoretical considerations.

4.2. *In vitro* and *in vivo* experimental studies

In fact, the paper of Watts and Strogatz also was the first example of an application of graph theory to a neuroscientific question, as they found that the C and L of the nervous system of *C. elegans* were in agreement with the definition of a small world configuration connectivity (Watts and Strogatz, 1998). Similar conclusions could be drawn for cortico-cortical connection data from macaque and cat (Hilgetag et al., 2000). Although optimal component placement could substantially reduce wiring length in networks of macaque cortex and *C. elegans*, this resulted in an increase of the number of processing steps along the shortest paths (Kaiser and Hilgetag, 2006). These findings implied that neural networks are more similar to network layouts that minimize length of processing paths, rather than minimize wiring length. When searching for the optimal layout in terms of wiring costs in the neural network of *C. elegans*, most neurons ended up close to their actual position (Chen et al., 2006). Some neurons, however, got a new position that strongly deviated from the original one, suggesting the involvement of other biological factors.

One might speculate that at least one of these other biological factors could be an optimal architecture in terms of processing steps (Kaiser and Hilgetag, 2006).

This raises the question whether the pattern of anatomical connectivity determines the patterns of functional connectivity (Felleman and Van Essen, 1991). Stephan et al. were the first to demonstrate a small world pattern in functional connectivity data of papers on the spread of (epileptic) activity after strychnine-induced disinhibition in macaque cortex *in vivo*, suggesting a correlation between anatomical and functional connectivity patterns (Stephan et al., 2000). While the study of Stephan et al. was based upon data from the literature, Kotter and Sommer modeled the propagation of epileptic activity in a large-scale model of cat cortex. They concluded that association fibers and their connection strengths were useful predictors of global topographic activation patterns in the cerebral cortex and that a global structure–function relationship could be demonstrated (Kotter and Sommer, 2000). Other studies on macaque visual and whole cortex, cat cortex as well as the human brainstem reticular formation confirmed small world features of functional neural networks, and demonstrated little or no evidence for scale free degree distributions (Sporns and Zwi, 2004; Humphries et al., 2006).

Taken together, these studies suggest a strong global structure–function correlation, with small world features of the network being pivotal for optimal functional connectivity.

4.3. Studies in humans

4.3.1. Functional magnetic resonance imaging

The first more or less direct demonstration of small world like anatomical connectivity in human was reported recently (He et al., 2007). The authors studied MRI scans of 124 healthy subjects, and assumed that two regions (vertices) were connected (i.e.: an edge is present) if they displayed statistically significant correlations in cortical thickness. With this approach, the authors could show that the human brain network had small world characteristics, that is a combination of a high C and a low L . Furthermore, the degree distribution corresponded to an exponentially truncated power law, as described previously (Achard et al., 2006).

Several years earlier, the first attempt was made to apply graph theoretical concepts to functional MRI. Starting from BOLD (blood oxygen level dependent) time series of brain activity, a matrix of correlations between the time series was computed. This matrix was converted to a (undirected, unweighted) graph by assigning edges to all supra-threshold correlations between activated brain areas (vertices). The authors demonstrated various functional clusters in the form of sub-graphs during a finger-tapping task (Dodel et al., 2002). The authors acknowledged the fact that the threshold had a significant influence on the results, and that criteria for choosing an optimal threshold should be considered. Eguiluz et al. were the first to study cluster-

ing coefficients, path lengths, and degree distributions in relation to fMRI data (unweighted, undirected). They defined that any two fMRI voxels (vertices) were functionally connected (i.e. edge is present) when their temporal correlation exceeded a predefined threshold. They concluded that the functional brain networks displayed both scale free as well as small world features (Eguiluz et al., 2005). Since these properties did not depend upon the task, they assumed that graph analysis mainly reveals invariant properties of the underlying networks, which might be in a ‘critical’ state (Chialvo, 2004).

A different approach was taken by the Cambridge group who reported several studies regarding fMRI BOLD time series during a ‘resting state’ with eyes-closed and no task (Achard et al., 2006; Achard and Bullmore, 2007; Salvador et al., 2005a,b). In the first study, BOLD time series were taken from 45 regions of interest of both hemispheres of 12 healthy subjects (Salvador et al., 2005a). From these 90 time series (vertices), a matrix of partial correlations was obtained and thresholded. It was defined that an edge was present when the time correlation exceeded the threshold. Graph analysis applied to these unweighted graphs suggested small world characteristics of the resting state functional network. The authors noted that the anatomy did not always precisely predict functional relationships (Salvador et al., 2005b). An extensive graph analysis of this data set displayed a single giant cluster of highly connected brain regions (79 out of 90) (Achard et al., 2006), which might reflect the previously described dynamic core (Sporns et al., 2000b; Sporns and Tononi, 2002; Sporns and Zwi, 2004). The strongest hubs corresponded to the most recently developed parts of heteromodal association cortex.

The most clear-cut small world pattern was found in the frequency range of 0.03–0.06 Hz. Furthermore, the authors found that the real brain networks were as resistant to random attacks (i.e. removal of a randomly chosen vertex) as either random or scale free networks. In contrast, the real brain networks were more resistant to targeted attacks (i.e. removal of the largest hubs) than scale free networks. This finding, as well as the absence of power law scaling, and arguments from brain development (where hubs develop late rather than early), suggested to the authors that brain networks are not scale free, in contrast with Eguiluz et al. (Eguiluz et al., 2005).

4.3.2. Electroencephalography (EEG) and magnetoencephalography (MEG)

The first application of graph analysis to MEG was published in 2004 (Stam, 2004). We studied correlations between the time series of the 126 MEG channels in five healthy subjects with the synchronization likelihood (SL), a non-linear measure of statistical interdependencies (Stam and van Dijk, 2002; Montez et al., 2006). The matrices of pair-wise SL values were converted to unweighted graphs by assuming an edge between pairs of channels (vertices) with an SL above a threshold, and no edge in the case of

a sub-threshold SL (see Fig. 5). In all cases the threshold was chosen such that the mean degree was 15. This analysis was performed for MEG data filtered in different frequency bands. For intermediate frequencies ($8 \text{ Hz} < F < 13 \text{ Hz}$), the corresponding graphs were close to regular networks (high C , high L). For low ($< 8 \text{ Hz}$) and high ($> 30 \text{ Hz}$) frequencies the graphs showed small world features (high C , low L). These results were fairly consistent when the degree k was varied between 10 and 20, although both C and L increased as a function of k .

Graph theoretical properties of MEG recordings in healthy subjects were studied more extensively in a recent paper (Bassett et al., 2006; Sporns and Honey, 2006). The authors applied graph analysis to MEG recordings in 22 healthy subjects during a no-task, eyes-open state and a simple motor task (finger tapping). To quantify the strength of the correlation between MEG signals at specific frequencies in different brain regions (vertices), they calculated the absolute value of the correlation between wavelet coefficients for each pair of sensors. They converted these continuous wavelet correlations to an undirected graph by setting any correlation lower than a predefined threshold to zero, and correlations above the threshold to one (i.e. edge is present). These undirected graphs were characterized in terms of an impressive range of graph theoretical measures. They found small world architectural features in the six major frequency bands, which were remarkably stable over different frequency bands as well as experimen-

tal conditions. During the motor task, relatively small changes in network topology were observed, mainly consisting of the emergence of long distance interactions between frontal and parietal areas in the beta, and gamma bands. Analysis of the synchronizability showed that the networks were in a critical dynamical state close to transition between the non-synchronized and synchronized state.

Micheloyannis et al. applied graph analysis to 28-channel EEG recorded during a working memory test. Twenty healthy subjects with a few years of formal education and low IQ were compared to the same number of healthy subjects with university degrees and high IQ. Mean SL and graph analysis of the unweighted, undirected graphs during no-task condition were determined in the same way as described by Stam (Stam, 2004), and did not show differences between the groups. However, during the working memory task, the networks of the group of lower educated subjects were closer to small world in the theta, lower and higher alpha, beta, and gamma bands (Micheloyannis et al., 2006b). One might speculate that the controls with low education display a compensatory mechanism during the task, which is not needed by the highly educated controls.

The general picture that emerges from these, rather limited data is that functional neural networks approach optimal small world characteristics, and that it is still a matter of debate whether such networks also exhibit scale free properties. Other factors (e.g. anatomical structures,

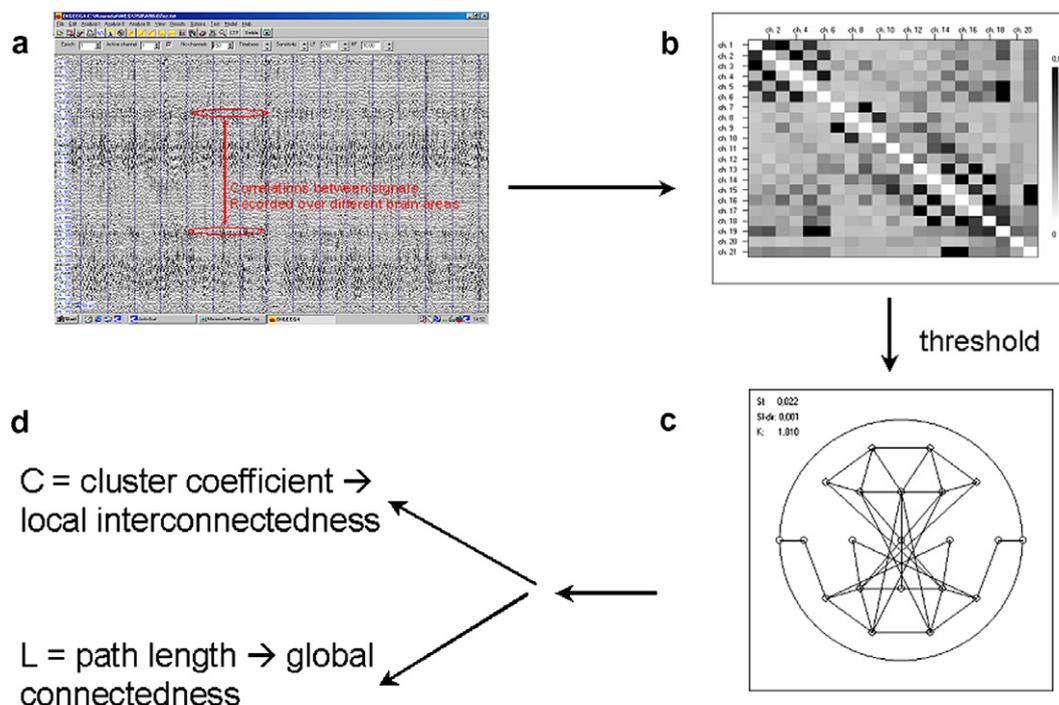


Fig. 5. Schematic illustration of graph analysis applied to multichannel MEG recording of brain activity. The first step consists of computing a measure of correlation between all possible pairs of channels of recorded brain activity (a). Subsequently, these correlations can be represented in a correlation diagram (b) (strength of correlation indicated with black white scale). Next a threshold is applied, and all correlations above the threshold are considered to be edges connecting vertices (channels). Thus, the correlation matrix is converted to an unweighted graph (c). From this graph various measures such as the clustering coefficient C and the path length L can be computed (d).

processing efficiency in terms of wiring costs), however, may be responsible for deviations of neural networks from the optimal small world configuration. Furthermore, network properties do not seem to change extensively during the performance of simple cognitive tasks, although, again, only limited evidence is available. The relative impact of, for example, genetic factors on network properties might be more substantial (Posthuma et al., 2005; Smit et al., in press).

5. What is the effect of damage on network properties?

Considering functional connectivity and network properties to be a physiological substrate for segregated and distributed information processing (Salvador et al., 2005a,b; Achard et al., 2006; Achard and Bullmore, 2007), intervention, whether on purpose (e.g. medication) or accidentally (e.g. brain disease), would lead to changes in these parameters. In the next section, we will summarize existing evidence on the effect of intentional manipulation or disease-related neuronal dysfunction on experimental neural networks and their dynamics. Subsequently, we will apply this knowledge in the light of functional brain dynamics of patients with several brain disorders.

5.1. Experimental studies

There is hardly any information on the effect of purposeful intervention on neural network topology and their dynamics. The only study on this subject applied the global and local efficiency measures as introduced by Latora and Marchiori (Latora and Marchiori, 2001) to fMRI data in 15 healthy young and 11 healthy old subjects (Achard and Bullmore, 2007). The subjects were studied during a resting state no-task paradigm, either with placebo treatment or with sulpiride, which is an antagonist of the dopamine D2 receptor in the brain. The analysis was based upon wavelet correlation analysis of low frequency correlations between BOLD time series of 90 regions of interest followed by thresholding, as described previously (Bassett et al., 2006). The efficiency measures were related to a ‘cost’ factor, defined as the actual number of edges divided by the maximum number of edges possible in the graph. Local and global efficiency, normalized for cost, were shown to be decreased both in the old compared to the young group, and in the sulpiride condition compared with the placebo condition. The effect of age on efficiency was stronger and involved more brain regions than the sulpiride effect. These results were similar irrespective whether the analysis was done on unweighted or weighted graphs reconstructed from the correlation matrix.

5.2. Spinal cord injury

De Vico Fallani et al. compared cortical connectivity of five patients with cervical spinal cord injury (SCI) and five healthy volunteers through analysis of high-resolution

EEG recordings of twelve regions of interests (ROI; vertices) coincident with Brodmann areas. They constructed a connection matrix containing directed transfer function (DTF) values for each pair of ROIs and subsequently put a threshold in order to define whether a connection (edge) was present or not. They not only found significant differences compared with computed random networks of the same size in both groups, but also a higher local (but not global) efficiency (Latora and Marchiori, 2001) in the SCI group, suggesting a compensatory higher level of internal organization and fault tolerance in these patients, as was expected (De Vico Fallani et al., 2007).

5.3. Disturbed cognition

5.3.1. Physiology

It is tempting to hypothesize that topological changes leading to suboptimal network dynamics are correlated with suboptimal higher brain functioning, which already was suggested by Bressler in 1995 (Bressler, 1995). In the 1990s, several research groups demonstrated that cognitive tasks induce changes in brain complexity, sometimes even related to the difficulty of the task or the type of thinking involved (Stam et al., 1996; Micheloyannis et al., 1998, 2003; Bizas et al., 1999; Tomberg, 1999; Muller et al., 2003). At the same time, however, other studies reported decreases in complexity during cognitive tasks (Molnar et al., 1995; Sammer, 1996). Based on these conflicting results, it was suggested that complexity of brain dynamics in itself might not be the most relevant parameter to understand cognitive processing (Houlihan et al., 1996; Stam, 2000, 2005). Activities such as listening to music, watching paintings, and mental rotation were shown to be associated with changes in functional coupling between brain regions as measured by EEG. These changes were more pronounced in experts than in non-experts in the particular field (Bhattacharya et al., 2001a,b,c; Bhattacharya and Petsche, 2002; Bhattacharya and Petsche, 2001). Based on these results, it was suggested that measures of coupling between different brain regions might be a better measure than complexity. Since then, evidence has accumulated that higher cognitive functions require functional interactions, or connectivity, between multiple distinct neural networks (Lowe et al., 1998; Meyer-Lindenberg et al., 1998; Quigley et al., 2001; Stam et al., 2002a,b; Micheloyannis et al., 2003; Salvador et al., 2005a). Neurophysiological techniques such as fMRI, MEG, and EEG are eminently suitable to determine functional connectivity in the brain (Stam, 2005). Functional networks revealed by graph analysis of fMRI, EEG or MEG data might represent a ‘physiological substrate for segregated and distributed information processing’ (Salvador et al., 2005a,b; Achard et al., 2006; Achard and Bullmore, 2007).

It has been demonstrated that in a resting state, the ‘basic’ brain network gives rise to constantly changing, weakly synchronized networks (Stam et al., 2002b; Langheim et al., 2006). This process of constantly creating and

dissolving functional networks is called ‘fragile binding’, and is thought to underlie spontaneous information processing. The optimal normal brain dynamics are thought to be near the phase transition between low and high levels of synchronization (Stam, 2005). The two previously mentioned studies by Micheloyannis et al. and the study by Bassett et al. showed the influence of a cognitive or motor task on network topology (Bassett et al., 2006; Micheloyannis et al., 2006a,b). Another study, using a method to extract cerebral networks from these EEG data described previously by Stam (Stam, 2004), showed that (unweighted, undirected) networks demonstrated more small world characteristics during all sleep stages compared to the awake state, and that these features were even more pronounced during cyclic alternating pattern sleep phases A1 than B (Ferri et al., 2007). Thus network features can change during a cognitive task as well as under the influence of sleep.

5.3.2. Disturbances

The first application of (unweighted, undirected) graph analysis to patients with cognitive disturbances was published in 2006 (Stam et al., 2006). Here a group of 15 patients suffering from Alzheimer’s disease (AD) was compared to a non-demented control group of 13 subjects. EEG recorded during an eyes-closed, no-task state and filtered in the beta band (13–30 Hz) was analyzed with the SL, and these data were converted to graphs (see Stam, 2004). When C and L were computed as a function of threshold (same threshold for controls and patients), the path length was significantly higher in the AD group. For very high thresholds it was noted that the graphs became disconnected, and the path length became smaller in the AD group. When C and L were studied as a function of degree k (same k for both groups), the path length was higher in the AD group, but only for a small range of k (around 3). For both controls and patients, the graphs showed small world features when C and L were compared to those of random control networks (with preserved degree distribution). A higher mini mental state examination score correlated with a higher C and smaller L . One might hypothesize that the type of damage in AD, which is best described as ‘random error’ resulting in diffuse cortical damage in extensive brain areas, leads to a less optimal, i.e. less small world like network organization.

It is thought that brain tumors, that are also frequently accompanied by cognitive disturbances, are an example of more ‘targeted attack’, concentrated in a specific brain area. Bartolomei et al. applied graph analysis to MEG resting state recordings in a group of 17 patients with brain tumors and 15 healthy controls (Bartolomei et al., 2006a). Unweighted, undirected graphs were obtained from SL matrices of MEG filtered in different frequency bands (see Stam, 2004), using an average degree $k = 10$. In patients, the ratio of C and the mean C for random networks (C/C_r) was lower than in controls in the theta and gamma bands (for right sided tumors); the ratio of L and

mean L of random networks (L/L_r) was lower in patients in the theta band, the beta band (for left sided tumors), and the gamma band (for right sided tumors), indicating more random network features compared with healthy controls.

The general pattern that emerges from these studies is that networks of patients with disturbed cognition are further remote from a small world configuration. Further research regarding the exact correlations between cognition and network features in patients with diverse brain diseases, and the influence of different types of damage (e.g. random error in AD patients and targeted attacks in brain tumor patients) is warranted.

5.4. Epilepsy

Synchronization of neurons in networks is important for normal functioning, in particular information processing, but may also reflect abnormal dynamics related to epilepsy. Several modeling studies have addressed this issue specifically. Netoff et al. started from the observation that in a hippocampal slice model of epilepsy the CA3 regions show short bursts of activity whereas the CA1 region shows seizure like activity lasting for seconds (Netoff et al., 2004). To explain these observations they constructed small world network models of various types of neurons. For increasing p values, the models displayed first normal behavior, then seizure-like transients, and finally continuous bursting. Increasing the strength of the synapses had a similar effect as increasing p . For the CA3 model (higher k) the transition from seizures to bursting occurred for a lower value of p compared to the CA1 model. These findings suggest that the bursting behavior of the CA3 region may represent a dynamical state beyond seizures. This is an important suggestion since similar bursting-like phenomena have also been observed in the scalp recorded EEGs of neurological patients, and their epileptic significance is still poorly understood (Brenner, 2002).

Percha et al. started with the observation that in medial temporal lobe epilepsy, epileptogenesis is characterized by structural network remodeling and aberrant axonal sprouting (Percha et al., 2005). To study the influence of modified network topology on seizure threshold, they considered a two-dimensional model of Hindmarsh-Rose neurons. For increasing p they found a phase transition between a state of local to a state of global coherence; the transition occurred at $p \approx 0.3$. The authors speculated that neural networks might develop towards a critical regime between local and global synchronization; seizures would result if pathology pushes the system beyond this critical state. From that point of view, epilepsy could be regarded as the toll that we pay for our intelligence; we are living on a small edge between optimal intellectual function and epileptic seizures. A similar concept can be found in two other studies (Kozma et al., 2005; Stam, 2005). Dyhrfeld-Johnsen et al. studied the influence of temporal lobe architecture on seizures through a compu-

tational model of rat dentate gyrus with one billion neurons, and no more than three synapses between any two neurons, suggestive of a small world architecture (Dyhrfeld-Johnsen et al., 2006). They showed that loss of long distance hilar cells had only little influence on global network connectivity as long as a few of these long distance connections were preserved. Also, local axonal sprouting of granular cells resulted in increased local connectivity. Simulations of the dynamics of this model showed that network hyperexcitability was preserved despite the loss of hilar cells.

A first preliminary report on network analysis of six channel EEG depth recordings in a single patient during an epileptic seizure was published by Wu and Guan (Wu et al., 2006). The authors constructed graphs with $N = 30$ by using both channels (six) and different frequency bands (five). They used a bispectrum analysis to extract the phase coupling of two EEG signals (vertices), applied a predefined threshold to define the existence of vertices, and subsequently constructed unweighted, undirected networks with degrees varying from 4–7. During the seizure, a change in network configuration was detected in the direction of a small world network: there was an increase in C and a decrease of L . Conversely, one might argue that the preceding interictal network was relatively more random. In a larger study, Ponten et al. investigated seven patients during temporal lobe seizures recorded with intracranial depth electrodes (Ponten et al., 2007). Matrices of pair-wise SL values were converted to unweighted graphs by assuming an edge between pairs of channels (vertices) with an SL above a threshold, and no edge in the case of a sub-threshold SL (see Stam, 2004). In all cases the threshold was chosen such that the mean degree was 15. During seizures the ratio C/C_r in unweighted, undirected graphs increased in delta, theta and alpha bands; L/L_r also increased in the same bands. Thus ictal changes reflected a movement away from a random interictal towards a more ordered ictal network configuration, again suggesting that epilepsy is characterized by interictal networks with a pathological random structure. Such a random structure has an even lower threshold for the spreading of seizures than the normal small world configuration (random networks are more synchronizable than small world networks (Chavez et al., 2006)). The results of Bartolomei et al. seem to be in agreement with this hypothesis and suggest that ‘network randomization’ might be a general result of brain damage and a general route to epileptogenesis (Bartolomei et al., 2006a). Such random networks might not only lead to disturbed higher brain functions, but might also have a lower threshold for seizures. Patients with low-grade brain tumors might represent typical examples as they frequently suffer from both disturbed cognition and epilepsy (Reijneveld et al., 2001; Klein et al., 2003), and demonstrate more random features in their neural networks (Bartolomei et al., 2006a). It is needless to say that this bold hypothesis has to be explored in further studies.

5.5. Schizophrenia

Quite a few EEG and MEG studies have reported lower levels of complexity in neural networks of schizophrenia patients (Rockstroh et al., 1997; Jeong et al., 1998; Kim et al., 2000; Lee et al., 2001; Kotini and Anninos, 2002). Other studies, however, found an increase in complexity (Elbert et al., 1992; Koukkou et al., 1993; Saito et al., 1998). Apart from these conflicting results, the general pattern that emerges is that the abnormalities are the most outspoken in frontal areas, particularly in the left hemisphere (Elbert et al., 1992; Jeong et al., 1998; Kim et al., 2000; Lee et al., 2001; Breakspear et al., 2003). The symptoms of schizophrenia are often explained in terms of disturbed connectivity between different brain regions, the so-called ‘disconnection hypothesis’ (Breakspear et al., 2003). Elaborating on previous work in subjects with low and high education levels, Micheloyannis et al. applied graph analysis to 28 channel EEG (for methodology see Section 4.3.2 and Micheloyannis et al. (2006b)) recorded during a working memory test in 20 healthy control subjects with higher education and 20 patients with schizophrenia (stable disease, under drug treatment) (Micheloyannis et al., 2006a). Task-related networks in the schizophrenia group turned out to be less small world like, and more random in lower and higher alpha, beta and gamma bands compared to controls. Combining these results with those of his previous study in healthy subjects, it might be that low-educated subjects display a compensatory mechanism during the task, which is not needed by higher educated people, and which completely fails in the case of the patients. Of interest, the notion of a more random network in schizophrenia has recently been confirmed in a study in 40 patients and 40 controls (Breakspear et al., 2006). Breakspear et al. determined the presence of segments with non-linear coupling between pairs of EEG channels. Subsequently, a correlation matrix was determined from time series reflecting the absence or presence of non-linear coupling in subsequent segments. Finally, the correlation matrices were thresholded and converted to weighted graphs. It should be noted that the patients in the Micheloyannis et al. and the Breakspear et al. studies were treated with antipsychotic drugs, and that an influence of the drug treatment on the network features was found in the Breakspear et al. study (Breakspear et al., 2006; Micheloyannis et al., 2006a). Thus, the ‘network randomization’ could reflect both disease as well as pharmacological effects.

6. Conclusions and future prospects

In this review, we demonstrate that the modern network theories provide a very useful framework for the study of complex networks in the brain. They offer powerful realistic models and an increasing number of measures to study complex networks in the brain, thereby enabling better understanding of the correlation between network struc-

ture and the processes taking place in these networks, in particular synchronization processes, and providing scenarios how complex networks might respond to different types of damage (random error versus targeted attack). Furthermore, this approach provides a unifying framework for considering modeling, anatomical, fMRI, and neurophysiological studies.

The application of modern network theories has emphasized the importance of structure–function relationships (Honey et al., 2007) and has pointed to the existence of systems with critical dynamics close to onset of synchronization. Anatomical studies strongly suggest that neural networks, from *C. elegans* to primates, are to a large extent organized as small world networks, and that patterns of functional connectivity may follow the same pattern (Hilgetag et al., 2000; Stephan et al., 2000; Kotter and Sommer, 2000). Concomitant neurophysiological studies in humans indeed point in the direction of a small world pattern for functional connectivity (Salvador et al., 2005a,b; Achard et al., 2006), which seem to be a rather constant feature (although scale free networks have also been described (Eguiluz et al., 2005)). Network features seem to be only minimally influenced by tasks, but have been found to reflect genetic factors (Posthuma et al., 2005) and to be related to intellectual capacities (Micheloyannis et al., 2006b). These insights into ‘healthy’ neural networks have led to important new theoretical models regarding neural network function in disease states. Different types of brain disease can disrupt the optimal small world pattern and give rise to a network topology that may be associated with cognitive problems (Bartolomei et al., 2006a) as well as a lower threshold for seizures (Ponten et al., 2007). Of considerable clinical interest is the work suggesting a relationship between network structure and pathological synchronization, providing a possible mechanism for epilepsy (Netoff et al., 2004; Percha et al., 2005; Wu et al., 2006). It remains to be determined if damaging brain processes can really be distinguished in processes resulting in ‘random error’ and processes leading to ‘targeted attacks’.

Important issues to be resolved in future studies are of both methodological and conceptual nature. For one thing it is not yet clear what is the optimal way to convert or combine functional imaging data (derived from fMRI, EEG, or MEG) to graphs for further analysis. A recent paper of Astolfi et al. describes a set of computational methods to integrate fMRI and high-resolution EEG recordings in order to estimate functional connectivity (Astolfi et al., 2007). A related problem is the somewhat arbitrary threshold that is needed to convert a matrix of correlations to an unweighted graph. Studying a whole range of thresholds may raise statistical problems because of the large number of tests that have to be done. At this time, only few measures are available for the analysis of weighted graphs (Latora and Marchiori, 2001; Crucitti et al., 2003; Newman, 2004; Park et al., 2004; Barrat et al., 2004; Barthelemy et al., 2005; Onnela et al., 2005). A further problem that frequently occurs when converting

matrices of correlations to graphs is the fact that some of the nodes may become disconnected from the network; this presents difficulties in the calculation of clustering coefficients and path lengths. Use of global and local ‘efficiency’ measures, and harmonic instead of arithmetic means might provide solutions here (Newman, 2003) (for a practical application see Ponten et al., 2007). Future studies could gain by a careful consideration of all the graph measures that are currently available, and the new measures that are described in physics papers.

A number of conceptual issues for future studies also deserve mentioning. First of all, it is not yet known which network properties are the best predictors of cognitive and psychiatric disturbances, and what the exact correlation is between network properties and susceptibility for seizures. The hypothesis that brain diseases convert a ‘healthy’ small world network to a ‘diseased’ network further remote from the optimal small world configuration, which is less optimal for combining local segregation and global integration for optimal cognition, and also has a lower threshold for pathological synchronization/seizures needs further exploration. Secondly, it is unclear to what extent the brain demonstrates ‘network plasticity’. Several theoretical studies have suggested scenarios that explain how small world or scale free networks emerge by activity-dependent changes in an initially random network, but whether these scenarios are a proper description of human brain development is an open question. An influence of genetic and environmental factors on network properties in young adults has been suggested (Posthuma et al., 2005; Smit et al., *in press*), but the underlying mechanisms are completely unknown. It would be interesting to know if different characteristic scenarios by which brain pathology changes network structure and function could be detected, particularly if different types of brain disease are related to either ‘random error’ or ‘targeted attack’ of brain networks. This would enable us to predict when and how brain disease will give rise to clinical symptoms, and, even more important, to determine which disease-modifying treatment approach is the best option at the network level (Ioannides, 2007).

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