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Structure out of chaos: Functional brain network analysis with EEG, MEG, and functional MRI

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Abstract
The brain is the characteristic of a complex structure. By representing brain function, measured with EEG, MEG, and fMRI, as an abstract network, methods for the study of complex systems can be applied. These network studies have revealed insights in the complex, yet organized, architecture that is evidently present in brain function. We will discuss some technical aspects of formation and assessment of the functional brain networks. Moreover, the results that have been reported in this respect in the last years, in healthy brains as well as in functional brain networks of subjects with a neurological or psychiatrical disease, will be reviewed.

1. Introduction

The understanding of the physiological substrate of complex brain function, such as cognition, has been one of the major challenges in neuroscience. It is thought that higher order actions derive from interactions between specialized areas (Posner et al., 1988; Friston, 2002). Cognition can be assessed with a wide variety of tests and brain activity can also be measured with an increasing variety of imaging techniques, but the true relationship between the two is hard to establish. One of the reasons is that the brain is a very complex system, making it difficult to study with conventional methods (Bullmore and Sporns, 2009; Bassett and Gazzaniga, 2011). The output from modalities that assess brain function (functional MRI (fMRI), electroencephalography (EEG), or magnetoencephalography (MEG) studies) can provide useful information that cannot otherwise be gathered, but usually contains such a large amount of data that constitutes a challenge for analysis and interpretation.

One way to organize and scale down the amount of data is to represent the output as a network (Sporns et al., 2004; Bullmore and Sporns, 2009). A branch of mathematics, called graph theory, describes and quantifies networks by reducing them to an abstract sets of nodes and connections. It provides a context to study aspects of brain function that otherwise remain hidden.

Modern network theory is increasingly used in neuroscience to study the brains of healthy as well as diseased subjects. It is an umbrella theory, based on graph theory for the mathematical description of networks, and uses probability theory and statistical mechanics to deal with stochastic aspects of large networks. Additionally, aspects of dynamical systems theory are involved. For reviews see Bassett and Bullmore (2009), Bullmore and Sporns (2009), Kaiser (2011), Bassett and Gazzaniga (2011) and Stam and van Straaten (2012).

Here, we will describe how brain activity can be transformed to a functional network. Second, methodological

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issues that can influence results are outlined. Finally, an overview of the results of research of complex brain networks in healthy as well as in neurological disease will be given.

2. Graphs

2.1. Network building blocks and forms

A graph (G) is a mathematical representation of a network and consists of a set of vertices or nodes (V) that are connected by a set of so-called edges (E) (Figure 1a). The edges can represent any structural or functional relationship between the nodes. They can have a value (for instance: strength, length or importance of the connection) and these values can be presented in an adjacency matrix A (Figure 1b). This matrix therefore contains all information of the network (see Van Steen (2011) for extensive information on graphs, digitally available through ⟨www.distributed-systems.net/gtcn⟩). The edges can have a direction in which the activity of one node depends on the other and not vice versa, or can be undirected in which the direction of the dependency is both ways or cannot be established. If the network takes into account the value of the edges, it is called weighted. On the other hand, in an unweighted network, the edges either exist or not. The connections have the same value and the adjacency matrix becomes binary.

Individual networks can vary greatly with respect to mean connectivity, and as a result the size (total number of vertices and edges). This variation influences network measures and hampers optimal comparison between (groups of) subjects. The process of normalization enables comparison of network metrics between subjects while leaving the network sizes unchanged. This is done by creating a ratio of the observed network measure and that of a set of random networks of the same size and mean connectivity.

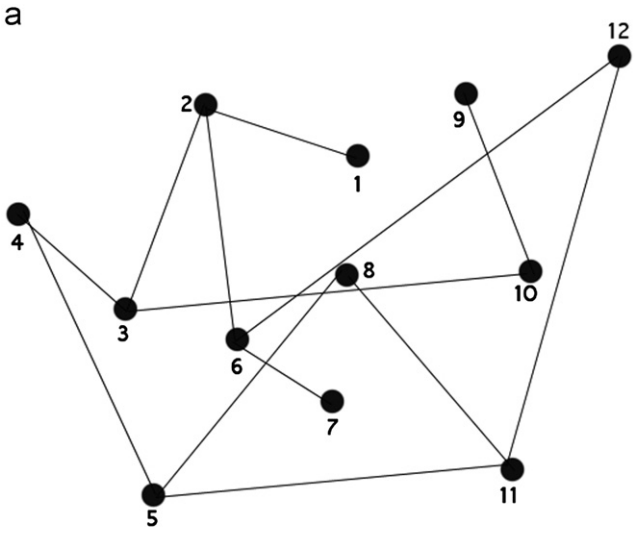

Figure 1 (a) Example of a graph with points as the vertices (V, numbered), and the lines connecting them as the edges (E). From this figure it can be seen which vertices are connected to which others. The connections are undirected (information can go either way) and unweighted (strength of all connections is equal). (b) Example of the adjacency matrix (A) corresponding to the presented network. Cells in gray represent a connection between the vertices.

2.2. Network metrics

2.2.1. Clustering coefficient, path length, degree and degree distribution

The most basic and frequently used measures are the clustering coefficient C, path length L, degree k, and degree distribution $P(k)$.

The clustering coefficient C is a measure of local connectivity and defined as to what extent the neighboring nodes to which a node is connected are connected with each other (Figure 2). So, if a node A is connected to nodes B, C and D (its neighbors), the clustering coefficient of A is the probability that the nodes B, C and D will be connected to each other. For the whole graph, a mean C can be computed.

Shortest path length is the smallest number of edges between two nodes, so it is the minimum number of steps to travel through the network from node A to B (Figure 3).

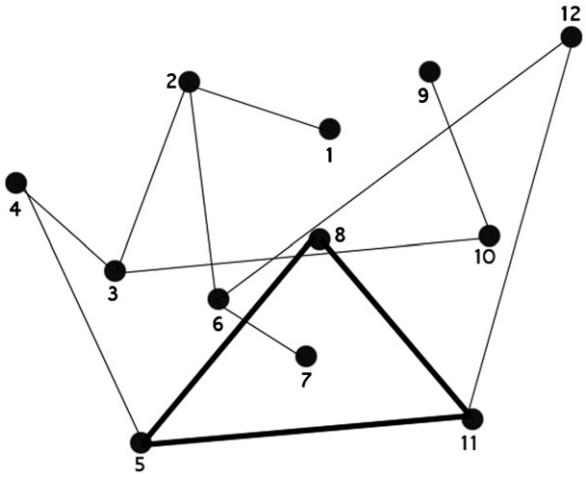

Figure 2 Example of a clustering coefficient. Vertex 8 has two neighbors that are themselves also connected. The clustering coefficient is defined by the number of edges between neighboring vertices divided by the total number of possible connections. In this case: $C = 1/1 = 1$.

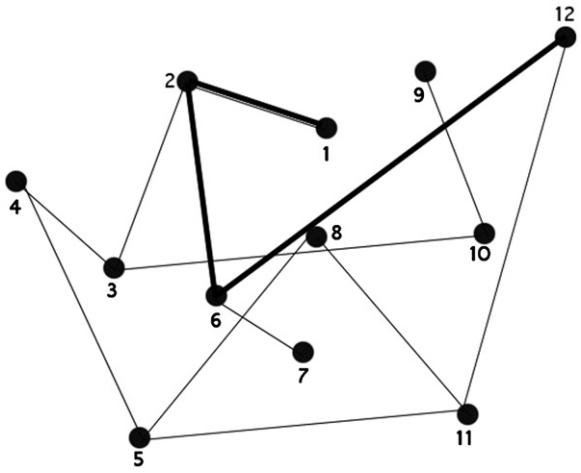

Figure 3 Example of a shortest path length. The minimum number of vertices that is involved to travel from vertex 1 to vertex 12 through connecting edges is 4 (including the start- and end-vertex).

The average shortest path length L is thought of as a measure of global efficiency. It is defined as the mean number of steps along the shortest paths between all possible pairs of network nodes. Intuitively, when the average path length is short, it is easy to travel fast from one point in the network to a random other point.

The degree k of a node is the number of edges connecting this node to others. The degree can give a 'meaning' to or indicate the relative importance of the node: nodes with a high degree can be regarded as important points in the network (so-called hubs). A mean degree can be computed for the whole network.

In addition, the degree distribution $P(k)$ reflects the probability that a randomly chosen node will have degree k. A power-law degree-distribution, in which some vertices have an exceptionally high degree, and most others a low degree, indicates the presence of hubs.

2.2.2. Other measures: Degree correlation, modularity/motifs, centrality, and graph spectral analysis

With the above mentioned basic network measures, some network models can be described. However, for further characterization, other measures might be informative as well. The goal is to have a set of measures that would allow a description of that part of the network that is informative, more specifically the part that deviates from a completely random network. Here we mention some measures that have an application in neuroscience.

The measure 'degree correlation' indicates to what extent nodes with the same or different degree are connected to each other. When nodes show a tendency to be connected to nodes with the same degree, the network is said to be assortative. When the nodes tend to be connected to nodes with a different degree, the network is called disassortative. Interestingly, most social networks are assortative and most biological and technological networks are disassortative (Newman, 2003). The brain, as measured macroscopically with EEG, MEG and fMRI, seems to have an assortative degree organization (Deuker et al., 2009; Hagmann et al., 2008; Braun et al., 2012) while it is disassortative at the neuronal level (Bettencourt et al., 2007). The assortative tendency of high degree (macroscopically, fMRI) nodes to connect to each other was referred to as rich-club organization (van den Heuvel and Sporns, 2011). However, this assortativity is not always confirmed and decisions on the parcellation and centrality measures might contribute to varying results (Zuo et al., 2012). With high parcellation schemes, where local connections are abundantly represented and the probability of high degree hubs is less, assortativity might be easier to detect than with low parcellation schemes (Fornito et al., 2010). On the other hand, even with a low parcellation scheme, such as the Automated Anatomical Labelling (AAL), assortativity could be found (Braun et al., 2012). Apparently, at least in the brain, degree correlation is a measure with different values when looking at complex networks at different levels. The explanation for this phenomenon is not known. Newman proposed that in networks with a modular structure such as the brain, the degree correlation points toward assortativity (Newman, 2006). High degree nodes might serve as the connector hubs, a part of the communication line between the modules, for the integration of locally processed information. The assortativity at the macroscopic scale might arise from the way the network is formed: by modulation based on synchronization rather than growth (Stam, 2010).

Nodes can be grouped in such a way that a simple subgraph, called motif, can be recognized (Milo et al., 2002). Triangles of three interconnected nodes are examples of such motifs. The simple motif of a triangle underlies the important property of clustering. When larger groups of nodes tend to be more connected within groups than between groups, this group is called a module (Figure 4) (Newman, 2006). Algorithms exist to detect and quantify modular structure (Newman, 2006), where the number of edges within groups minus the expected number of edges from an equivalent random network play a role. Modules can be connected to other modules in a hierarchical

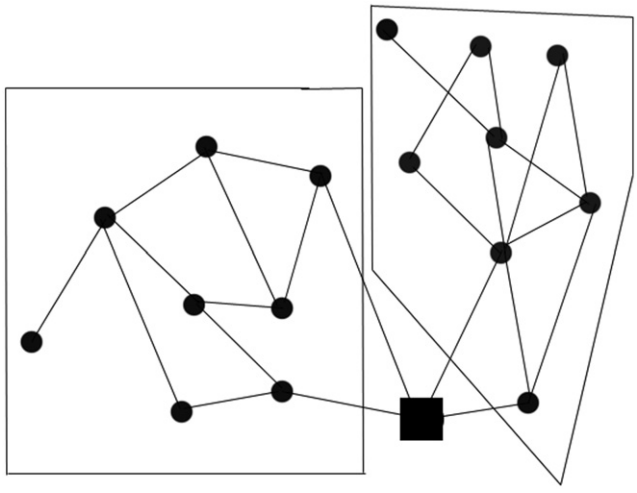

Figure 4 Example of a graph with modules. The network can be divided into two subgraphs (clusters of vertices within the lines) that have a higher connectivity within the subgraph than going outside. The vertex that is indicated with the black square is the connection between the modules (connector-hub).

fashion, resulting in subsystems within systems, sometimes several levels deep (Simon, 1965). This enables a phenomenon that is typical of hierarchical systems: influencing the neighboring modules or subsystems, without affecting directly their intrinsic function (Simon, 1965). We can therefore distinguish interactions within subsystems and between subsystems, and characterize specific nodes and their function in the network: for example connector hubs for connections going out of the module (Guimera and Nunes Amaral, 2005), and regional hubs for important connections within the modules.

The importance of a node can be quantified by means of centrality measures, of which degree is a simple example. Another measure is the betweenness centrality. It is defined as the number of shortest paths going through a node or edge. The betweenness centrality is high when the node or edge is used for many shortest paths. This measure can be normalized by dividing it by its maximum value (the total amount of shortest paths in the network). A relative drawback of this method is that, especially in networks with many nodes, computation time can be long. A different measure of node centrality is the eigenvector centrality. Eigenvector centrality allocates a value to each node in the network in such a way that the node receives a large value if it has strong connections with many other nodes that have themselves a central position within the network (Lohmann et al., 2010). In other words, the connections to important nodes count more, making the nodes with relatively few edges to very important nodes also important (maybe more important than nodes with many edges to less important nodes). The advantages of the eigenvector centrality are therefore the fact that the quality of the connections is taken into account, and the relatively short computation time. In the brain, the centrality measures are not interchangeable and can provide additional information about the network (Zuo et al., 2012).

2.3. Network models

A number of typical network models have been described that are useful in understanding optimal and suboptimal networks. They have helped putting network metrics into perspective. Here we will discuss some of the models that are frequently used in functional brain network research. With C, L and $P(k)$, four types of networks can be characterized: the random graph, the regular graph, the small-world network, and the scale-free network. Historically, the concepts of the graphs have grown and the descriptions of the network models were published in the course of several years.

The first network model was the *random graph*, described by Erdös and Rényi (1959). This model consists of a set of nodes and connections between them that are totally random. There is a probability p that a connection exists between two nodes, and this p is equal for every combination of two nodes. This model is characterized by a low clustering coefficient, because there is no preference for extra local connections, other than based on chance. In other words, the fact that a node A is connected to nodes B and C does not influence the probability that node B is connected to node C. The average shortest path length L is also low in the random graph: it takes few steps to travel from one point in the network to a randomly chosen other point.

Watts and Strogatz (1998) published a paper in which they described a new network model: the *small-world network* (Figure 5). Starting with a set of nodes represented on a ring, each node is only connected to its nearest neighbors (the number of nearest neighbors can vary with k, and is symmetrical so $k/2$ connections on each side of the node on the ring). This was called a *regular or lattice network*. In this model, C is high (only connections to neighbors exist) and L is high as well: it takes a large number of steps to travel through the network to a distant node, via small steps only. Then, with a probability p, a few connections in the lattice network are randomly rewired. This results in a fast decrease in L because of the newly formed 'short-cuts', whereas C initially remains high. This network was called 'small-world' and the authors showed that the values for C and L of this new network matched real networks (for example the anatomical network of neurons in the worm *Caenorhabditis elegans* and social networks) better than the values of C and L of random

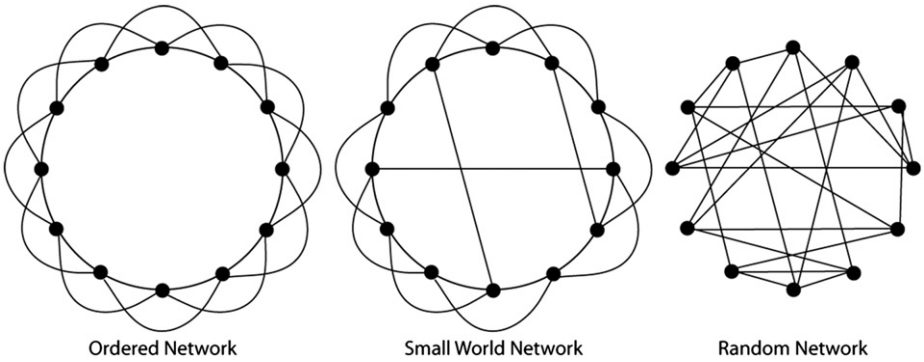

Figure 5 Representation of the construction and principle of three networks. On the left the regular network, with each node connected to its neighbors in a repetitive way, and without long distance connections. On the right the random network where the connections between the vertices are totally random (some local and some long distance connections). In the middle the small-world network, as a transition situation between the regular and random networks. Taking the regular network, and rewiring only few local connections to become long distance connections, C stays high (as in regular networks) and L drops (as in random networks).

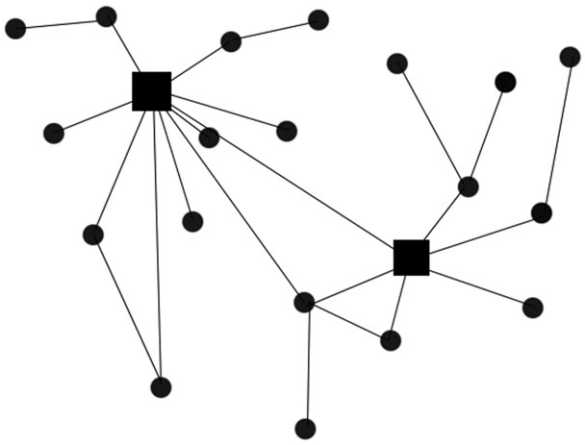

Figure 6 Example of a scale-free network. Characteristic are few vertices with a high degree (black squares) and many more vertices with a low degree (dots). From van Dellen et al. PLoS One 2009.

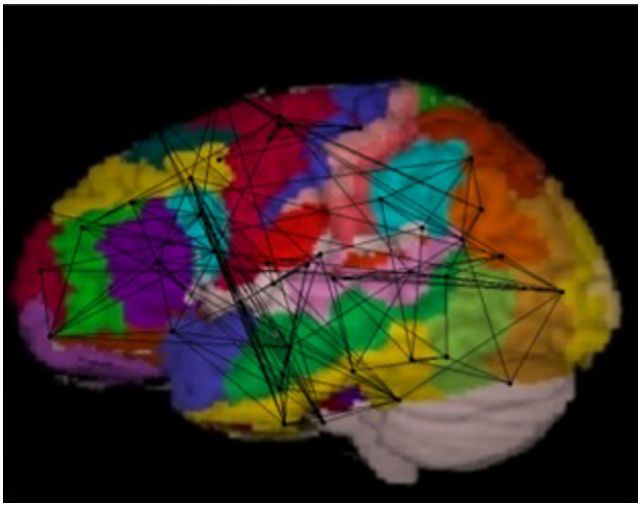

Figure 7 Result of a three dimensional brain network based on coupling of MEG signals.

and regular networks. When p is increased further, C eventually drops and the network becomes an Erdős–Rényi random network with low C and low L. The small-world network model can thus be placed in between the Erdős-Rényi and lattice network models.

Barabasi and Albert (1999) proposed a model for network growth. They took into account the degree of the network: the probability of a new connection depends on the number of edges a node already has: nodes with a high degree have a higher probability of getting a new connection. The result of this preferential attachment is a so-called *scale-free network* with a power law degree distribution: few nodes have a very large k and a large number of nodes have a small k (Figure 6).

3. The brain as a functional network

3.1. The complex brain

How can the principles of network analyses be applied to the human brain? It has been shown that the brain has the characteristics of a complex structure. The definition of complex in this context describes a network that is large, sparsely connected, and has an organization between order and randomness (Sporns, 2011).

The brain network can be studied on various scales. At the cellular level, the network is made up of neurons as the vertices and the synapses as the connecting edges. At this level, connectivity between a limited number of neurons can be studied at the same time, providing information on the details of information exchange but limited information on large scale information integration. We are maximally zoomed in. It was shown that at this level, brain networks show a scale-free topology with short path lengths, and high synchronizability (Bonifazi et al., 2009).

On a higher level, neurons sharing a particular function are grouped into so-called modules, and are organized to communicate with other sets of neurons with a different function (Tononi et al., 1994). This modular hierarchy seems essential for the presence of sustained spontaneous brain activity (S.J. Wang et al., 2011).

At an even larger scale, larger brain regions can be regarded as the vertices, with the long distance white matter tracts as the edges. These regions can comprise one to several cubic millimeters (fMRI, voxel level) or larger (several square centimetres in EEG).

At this level, brain activity can be measured macroscopically, even outside the skull. With these functionalities, global brain network topology can be studied in analogy with other existing networks (Figure 7). Order can be seen in the way the network is functioning, with high clustering and hierarchical levels (Meunier et al., 2010; Kaiser, 2011).

How the network at the macroscopic level is organized, is a result of how it grows and evolves at the cellular level. The human adult brain contains on average 2×10^{10} neurons and 15×10^{13} synapses, resulting in a mean number of connections of 7000 for each neuron (Pakkenberg and Gundersen, 1997; Pakkenberg et al., 2003). With a limited amount of cost (in terms of material and metabolism) the network has to be highly efficient and robust. The network organization is the result of a multiconstraint optimization process where limiting the number of long distance connections reduces wiring cost (Bullmore and Sporns, 2012). The continuing trade-off between wiring cost and optimal information processing results in the network characteristics that can be found in neuronal systems. The question is how this trade-off can be modeled to replicate these networks. Kaiser et al. (2009) showed that a model for random growth of axons, with the rule that the axons establish a new connection to the first neurons they hit, resulted in a pattern of decreasing connectivity with increasing distance, as found in neural networks. The resulting network was highly connected locally, but allowed for some long distance connections. In a study on the development of the neuronal network of *C. elegans*, it was found that the long distance connections start out as short distant connections when the worm is young and small and grow along as the animal grows (Varier and Kaiser, 2011). This indicates that the long distance connections are in fact the oldest ones. Vertes et al. (2012) proposed a

model for the emergence of brain networks based upon rules for a price for long distance connections and a higher likelihood of connections between regions receiving the same input. With this model, many of the qualities of real networks could be explained. Taken together, this research opens the road to the search for universal rules of the organization of brain function.

3.2. Network construction

To investigate the highly complex neuronal network in vivo, a representation of the network at the macroscopic scale can serve as a biomarker of the cellular network. Neuronal populations generate oscillations which can be measured (Buzsaki, 2006). For functional brain networks, activity as measured with EEG (electrical activity), MEG (magnetic activity) and fMRI (changes in cerebral blood flow as a measure of neural activity) forms the building block of the network (Stephan et al., 2000). The nodes are therefore EEG electrodes, MEG sensors and fMRI voxels or regions of interest (ROIs), consisting of a compound signal of the activity of many neurons, with a spatial distribution. The connecting edges are formed by establishing some sort of functional connection between the nodes. This functional connection builds on the general rule that interconnected oscillating systems will synchronize their activity (Strogatz, 2003).

The proportion or likelihood of similarity in two or more time series can be addressed in various ways. Once the coupling between the time series is quantified, an adjacency matrix can be formed, composed of cells with a value that describes the probability or strength of the connection. With this adjacency matrix, network metrics are computed.

3.3. Establishing connections

Statistical interdependencies between two or more neurophysiological time series can be characterized in various ways (Pereda et al., 2005). A straightforward approach is by applying a linear method, such as coherence: how similar are the waveforms of each frequency when a time-lag is applied to one of them, quantified by a cross-correlation function. Since non-linear components of coupling are abundantly present in neuronal activity, non-linear connectivity measures are also available (Stam and van Dijk, 2002). In resting-state EEG and MEG studies, the problem of volume conduction interferes with analysis (Nunez et al., 1997, 1999). When different electrodes or sensors pick up activity of the same generating cortical source, the functional coupling is spurious. Measures like the imaginary part of the coherence (Nolte et al., 2004) and the Phase Lag Index (PLI) (Stam et al., 2007b) partly correct for this problem by discarding zero lag connections, since these cannot reliably be distinguished from volume conduction or common reference effects. Many possible solutions for the volume conduction problem have been proposed, but none provide a complete solution. This hampers the conversion from signal space (the EEG or MEG recording points) to source space and with that anatomically localizing the activity.

Resting-state fMRI has the advantage of lacking the common source problem. The resulting time series have a high spatial resolution, but a lower temporal resolution. The relationship with neuronal activity is indirect, and influences of other physiological oscillations have to be taken into account. Functional coupling between fMRI regions can be established with seed-based techniques, which require the identification of a region of interest before analysis (Fransson, 2005; Andrews-Hanna et al., 2007). Alternatively, methods exist that can assess whole brain activity, such as independent component analysis (ICA) (Calhoun et al., 2001; Beckmann and Smith, 2004). In addition, parcellation scales (the size of the nodes) influence properties of the networks (Zalesky et al., 2010; Joudaki et al., 2012).

It is important to be aware that the characteristics of a functional brain network depend on recording technique, and the way the parameters and thresholds are chosen (Dodel et al., 2002; van Wijk et al., 2010). Reassuringly, there is similarity in results between the methods.

4. Healthy and developing functional brain networks

It has been shown that the brain displays an architecture that optimizes information processing combining specialization and integration (Tononi et al., 1994; Sporns et al., 2000). The hierarchical modular structure, with regions that have more connections within than between themselves, and the scale-free degree distribution are optimal configurations for efficient information processing (Latora and Marchiori, 2001; Sporns, 2006; Achard and Bullmore, 2007). In healthy subjects, several brain areas are consistently found to be interconnected under certain circumstances. For example, when a subject is processing a visual stimulus, brain areas that are functionally coupled during that task can be regarded as belonging to the same functional network. Several networks have been identified in healthy subjects. When the subject is awake, but not active and with eyes closed, resting state networks can be identified. One of them is the default mode network (Raichle et al., 2001; Greicius et al., 2003). Structures involved in this network are the precuneus, posterior and anterior cingulate cortex, lateral parietal, and medial prefrontal cortex. It is robust, easy to register and is therefore frequently used in studies (Raichle et al., 2001; Greicius et al., 2003; Damoiseaux et al., 2006; Laufs, 2008; de Pasquale et al., 2010).

After the paper of Erdős and Rényi on random networks, it was noted that real neural networks do not behave exactly like random networks. Especially, a larger local clustering was found (Muller et al., 1996). With the description of small-world networks, part of this problem was accounted for: functional brain networks have small-world like features combining high local clustering and short path length (Stam, 2004; Bassett et al., 2006; Achard et al., 2006; Micheloyannis et al., 2006b). In children, this structure seems to develop with age: the networks of children were found to be more regular at age seven, as reflected by higher clustering and longer path lengths, than at five years of age (Boersma et al., 2011). In a longitudinal EEG study on twins and siblings, the functional networks showed an inverse U-shaped change in path length over the years,

with the resulting networks being most small-world-like in middle age and more random in adolescence and later life (Smit et al., 2010). Also, network measures *C* and *L*, as well as the connectivity measure SL, were found to be inheritable to a great extent (Smit et al., 2008). Scale-free and modular characteristics could also be demonstrated in functional brain networks (Eguiluz et al., 2005; Salvador et al., 2005; Bassett et al., 2006; van den Heuvel et al., 2008; He et al., 2009; Meunier et al., 2009; Ferrarini et al., 2009; Van de Ville et al., 2010), although a scale-free topology was disputed in other studies (Achard et al., 2006; Gong and Zhang, 2009).

Cognitive functions are said to be possible because of the combination of specialization and integration (Tononi et al., 1998). It is therefore interesting to know to what extent functional brain network architecture is correlated to cognitive processes. In fMRI and high density EEG studies, a relationship was found between a short path length, consistent with more efficient networks, and higher IQ (van den Heuvel et al., 2009; Langer et al., 2011).

5. Functional networks in neurological and psychiatric disease

An increasing number of studies show disturbances of the optimal organization of brain function in various brain disorders. These results show that even localized processes have an impact on the global topology because of the integrative nature of the system (Sporns, 2011). Some consistent patterns of network changes are being found in several neurological and psychiatrical diseases.

5.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative condition that affects cognitive function, with typically, but not exclusively, memory deficits. Studies showed that functional networks in Alzheimer's disease lose their normal small-world structure, and regress towards a more random architecture (Stam et al., 2006, 2007a; Supekar et al., 2008; de Haan, 2009; Sanz-Arigita et al., 2010).

A hypothesis on the mechanism leading to this pattern was tested using simulations. It was shown that a specific loss of hub areas (simulated lesions of the hubs by so-called targeted attacks) lead to networks with a topology similar to that found in subjects with AD. Loss of less connected areas (the random attack model) did not lead to comparable networks (Stam et al., 2009). By now it has become clear that the hub regions of the default mode network are also the regions that typically show the most amyloid deposition, characteristic for Alzheimer's disease (Buckner et al., 2009). Amyloid deposition and loss of function are therefore anatomically linked to certain regions, in particular the widely connected parts (posterior cingulate, precuneus) of the default mode network. Bero et al. (2011) showed that synaptic activity influences amyloid deposition, linking the patterns found in functional network analysis and pathology. In a simulation study, de Haan et al. (2012) showed that the hub regions of the default mode network (defined by degree centrality) are indeed electrically most active. Additionally, they were also most vulnerable for decompensation and brake-down in case of a general process of decreasing connectivity. Also, a relationship between functional connectivity and APOE genotype, both in healthy subjects as well as Alzheimer patients, was found (Kramer et al., 2008). The APOE 4 allele predisposes for Alzheimer's disease, and it seems that it exerts its action on functional networks before symptoms are manifest, even before amyloid depositions can be visualized with positron emission tomography acquired with Pittsburg compound B (PiB-PET) that specifically binds to these proteins (Sheline et al., 2010). Longitudinal studies are needed to show if network changes are systematically changed before clinical signs and symptoms start, but the findings yield some potential for early diagnostic purposes.

5.2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder with prominent motor signs, but other domains, such as cognition and mood, are increasingly recognized to be involved in the disease as well. Recently, some network analysis studies have become available, showing that in PD network efficiency is reduced (Skidmore et al., 2011). In analogy to AD, it would be interesting to see future studies unraveling the associations of changes in the networks with the pathological process.

5.3. Brain tumors

It is obvious that brain tumors have an impact on anatomical structures. It is also well known that they can lead to loss of function and epilepsy. Interestingly, some cognitive signs of brain tumor patients, such as lack of concentration and slowing of mental speed, are almost invariably encountered and cannot be attributed to the location of the lesion. These symptoms occur in the presence of right as well as left-sided lesions, and regardless of the area within the hemisphere. They seem to represent a non-specific global effect of the focal lesion. Bartolomei et al. (2006a) showed extensive global changes in brain networks of brain tumor patients, especially loss of connectivity independent of the location of the lesion. In a follow-up study, the network analysis revealed a more random topology of brain networks in brain tumor patients (Bartolomei et al., 2006b), and these changes were also related to cognitive disturbances (Bosma et al., 2009), and seizures (Douw et al., 2010). These studies indicate that global cognitive dysfunction is related to disruption of network structure.

5.4. Epilepsy

Epilepsy is often referred to as a result of a hyperexcitable state of (parts of) the brain and characterized by an abnormal synchronized firing activity of the neurons involved in the seizure (Lehnertz et al., 2009). The underlying mechanisms are not clear. What happens with functional networks before, during and after a seizure might provide insight into the dynamical processes involved. Netoff et al. (2004) reported in a modeling study of hippocampal neuronal networks that in a small-world configuration increasing connectivity between the neurons was

associated with the tendency of neurons to synchronize their activity into spiking activity seen also in seizures. An fMRI study on the dynamics of the functional networks showed that the networks are near a threshold of order/disorder transition (Bassett et al., 2006). Wu et al. (2006) reported a change from random towards small-world-like during the seizure, as measured with intracerebral EEG depth electrodes. Ponten et al. (2007)confirmed this result in a study with seven patients. They suggested that epilepsy is characterized by an interictal pathologically random functional network that is prone to transitions to a state of hyperconnectivity (due to a pathological process) associated with the start-off and propagation of seizures. The fact that in random networks activity is synchronized more easily than in small-world networks was reported previously (Chavez et al., 2005). Randomness of resting state networks in subjects with epilepsy was also found in an EEG and MEG study (Horstmann et al., 2010). The concept that pathologically active hubs contribute to epilepsy was reported by Ortega et al. (2008). Wilke et al. (2011) studied whether critical nodes could be identified in the networks of patients undergoing epilepsy surgery. With EEG signals from depth electrodes in 25 patients, they found that reduced post-surgery number of seizures was associated with the resection of brain regions that had the highest betweenness centrality, suggesting that critical network points are involved in either beginning or spreading of seizures.

5.5. Schizophrenia

Application of modern network theory to EEG and fMRI data of individuals with schizophrenia revealed loss of overall functional connectivity and small-world properties with increased randomness of the networks (Micheloyannis et al., 2006a; Liu et al., 2008; Rubinov et al., 2009; Yu et al. 2011). In addition, a decrease in efficiency of high degree nodes was noted (Bassett et al., 2008; Lynall et al., 2010; Q. Wang et al., 2011). Decreased functional connectivity and reduced global integration of specific brain areas, especially frontal hubs, were also reported for structural connectivity (van den Heuvel et al., 2010).

On the other hand, other authors found an increase in connectivity of the default mode network, and a decrease in suppression of this network during a task (hyperactivity), and these findings correlated with clinical symptoms (Whitfield-Gabrieli et al., 2009). Changes in functional networks might be detectable many years before the disease is clinically manifest. This could potentially identify subjects at a particular risk of developing the disease and thereby serve as endophenotypes (Bullmore and Sporns, 2009).

5.6. Other psychiatric disease

Changed functional brain networks in patients with attention-deficit/hyperactivity disorder (ADHD) were reported. The topology was changed towards a more regular type of network (Wang et al., 2009).

Functional MRI studies showed disturbed functional networks in subjects with a major depression, more specifically a shift towards a random network type (Zhang et al., 2011) and disturbed modular structure (Lord et al., 2012). In another study, decreased small-world index in depressed individuals was also found (Jin et al., 2011).

In subjects with autism, a decrease in frontal–parietal (Just et al., 2007) and frontal–temporal (Coben et al., 2008) connectivity was found. Additionally, Lai et al. (2010) reported a shift towards randomness. How these network changes relate to the pathological mechanisms involved remains to be studied.

6. Conclusion

It has now become clear that the application of modern network theory to functional brain studies is feasible and provides additional information. It allows the study of the brain as a hierarchical, complex and self-organizing organ and has shown that it has small-world, scale-free and modular characteristics. The description of the default mode network, which is de-activated by activity, has been linked to cognitive function. These findings are in line with the general idea that brain function is a result of a combination of specialization and integration, although additional work is needed to further investigate this relationship. The comparison of the brain networks of healthy subjects to that of individuals with neurological or psychiatrical disease has added to knowledge on the mechanisms involved in disease. Network studies have contributed to progress in understanding the pathophysiological processes and explaining the topology of a variety of neurodegenerative and psychiatric disease. One of the challenges in future studies will be to establish the relationship of network changes to pathological processes for other diseases as well and to relate the functional networks to therapeutic strategies.

Another challenge will be the development of an additional network model that captures the brain even better than the currently available models. The presence of hubs, together with a high local clustering, has to be explained by the model, at the same time taking into account the influence of the factor space, which is an obvious factor inside the skull. Studies of the development of the brain networks might prove of value in this respect.

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Contributors

E.C.W. van Straaten wrote the manuscript. C.J. Stam critically reviewed the manuscript.

Conflict of interest

Elisabeth C.W. is scientifically involved in research of Nutricia Advanced medical nutrition. C.J. Stam reports no conflicts of interest.

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