



# Characterization of anatomical and functional connectivity in the brain: A complex networks perspective

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## ARTICLE INFO

Available online 23 June 2010

### Keywords:

Graph theory  
'Small-world' networks  
'Scale-free' networks  
Resting-state  
Complexity  
Synchronization

## ABSTRACT

A central question in modern neuroscience is how anatomical and functional connections between brain areas are organized to allow optimal information processing. In particular, both segregation and integration of information have to be dealt with in a single architecture of brain networks. There is strong evidence that synchronization of neural activity, both locally and between distant regions is a crucial code for functional interactions. However, a powerful theoretical framework to describe the structural and functional topology of system-wide brain networks has only become available with the discovery of 'small-world' and 'scale-free' networks in 1998 and 1999. There is now strong evidence that brain networks, ranging from simple nets of interconnected neurons up to macroscopic networks of brain areas display the typical features of complex systems: high clustering, short path lengths (both typical of 'small-world' networks), skewed degree distributions, presence of hubs, assortative mixing and the presence of modules. This has been demonstrated for anatomical and functional networks using neuroanatomical techniques, EEG, MEG and structural and functional MRI, in organisms ranging from *C. elegans* to man. In addition, network topology has been shown to be highly heritable, and very predictive of cognitive functioning. A short path length, which implies that from any area in the brain any other area can be reached in a small number of steps, is strongly correlated with IQ. Computational models are now beginning to reveal how the complex structure of adult brain networks could arise during development.

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## 1. Introduction

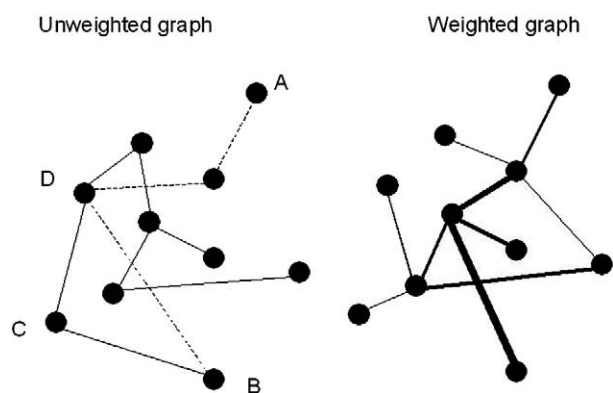
Cognitive functions require the delicate cooperation of multiple specialized areas in the brain. One of the challenges of cognitive neuroscience is to determine how these areas exchange information and succeed in establishing functional neuronal ensembles, not unlike those anticipated by Hebb (1949). Communication between neurons and neuronal ensembles is probably established to a large extent through a synchronization of their activity (Varela et al., 2001). Interregional synchronization can be determined in a relatively straightforward way from signals of the electrical (EEG) or magnetic (MEG) activity of the brain using one of the many currently available techniques (Pereda et al., 2005). Synchronization in different frequency bands may correspond here to different networks and different cognitive functions (Basar et al., 2001). In a slightly more general sense, any statistical interdependence between neurophysiological signals recorded between different brain areas could be considered to reflect some form of communication between them. This model-free concept is called functional connectivity, and has become the topic of many fMRI studies as well (Lee et al., 2003; Stephan et al., 2008). In addition to the shift in attention from local activation to

interregional communication studies, there has been an increasing awareness that recordings during a so-called resting-state may reveal valuable information about the underlying brain networks.

Studies of functional connectivity based upon large numbers of EEG channels, MEG sensors or MRI regions of interest (ROIs) present major challenges in terms of statistical analysis and neurophysiological interpretation. Levels of interregional synchronization may increase or decrease, in different frequency bands and between different electrodes or sensors in ways that are difficult to track. Until recently, synchronization has been studied in neurophysiology mainly as a phenomenon occurring between two neurons or two brain areas. What has been lacking until recently was a theoretically supported perspective of synchronization in large-scale complex brain networks (McIntosh and Korostil, 2008). A few years ago a number of major breakthroughs occurred in the mathematical theory of complex networks (Barabasi and Albert, 1999; Watts and Strogatz, 1998). As a result, several powerful new models, concepts and analytical approaches became available for systems with a network like structure. The modern theory of complex networks now has a major impact on such various field of science as genomics and proteomics, engineering of communication and transport networks and sociology.

In just a few years, network theory has been applied to neuroscience and interest in this approach is increasing rapidly (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009; Reijneveld et al., 2007; Sporns et al., 2005; Stam and Reijneveld, 2007). In this

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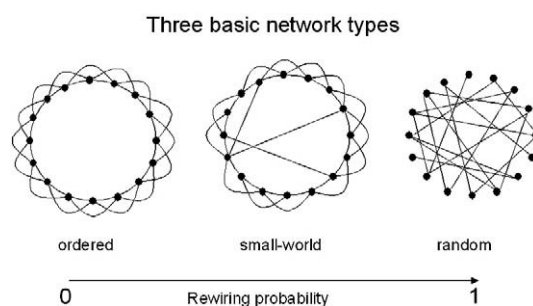
**Fig. 1.** Representation of a network as a graph. In the case of an unweighted graph (left panel) black dots represent the nodes or vertices, and the lines connecting the dots the connections or edges. The shortest path between vertices A and B consists of three edges, indicated by the striped lines. The clustering coefficient of a vertex is the likelihood that its neighbours are connected. For vertex C, with neighbours B and D, the clustering coefficient is 1. When weights are assigned to the edges, the graph is weighted (right panel). Here the weights of the edges are indicated by the thickness of the lines. (From: Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomedical Physics* 2007; 1: 3.)

review we want to introduce the reader to the main concepts, models and tools of modern network theory and their applications on neuroscience. We will review the rapidly expanding literature on graph theoretical analysis of both structural and functional brain networks in healthy subjects using the major imaging techniques such as EEG, MEG and structural and functional MRI. Finally we will discuss how the image of the brain as a complex structural and functional network emerges from these studies.

## 2. Graph theory: a short history

Technically, modern network theory is a branch of graph theory, the mathematical theory that studies graphs, simplified representations of networks as ensembles of nodes (vertices) and connections (edges) (Fig. 1). Graph theory is a relatively old branch of mathematics that started in 1737 when Leonhard Euler (1707–1783) solved the problem of the seven bridges of Königsberg by realizing it could be cast in the form of a network. An important step forward was taken when the model of a random graph was introduced (Solomonoff and Rapoport, 1951; Erdős and Rényi, 1959). In this model, also referred to as the ER random graph, edges exist between any pair of vertices with probability  $p$ . The ER model has many interesting mathematical properties such as the occurrence of a phase transition between a disconnected and a connected state as a function of increasing  $p$ . However, despite its mathematical elegance, the ER model is not yet a satisfactory description of many real world systems such as social networks. The Hungarian writer Frigyes Karinthy was one of the first to point out, in a short story in 1929, the curious idea that in social networks no one is separated from any other person by more than six handshakes. This idea was confirmed experimentally by Stanley Milgram (1967). He referred to the short distances in social networks as the ‘small-world’ phenomenon. Now the problem had a name, but not yet a solution.

This changed overnight, when Watts and Strogatz published their model of ‘small-world’ networks in a small Letter in Nature (Watts and Strogatz, 1998). The Watts and Strogatz model (WS model) starts with a network on a ring, where each vertex is connected to a fixed number of neighbours (Fig. 2). Such a regular or lattice like network has a high clustering coefficient (probability that the neighbours of a vertex will also be connected to each other) but a long path length (average number of edges that have to be traveled to get from one vertex to another). Next, edges from this initial ordered network are picked with a rewiring probability  $p$ , and randomly attached to another vertex. When  $p = 1$ , all edges are rewired, and a fully random



**Fig. 2.** Three basic network types in the model of Watts and Strogatz. The leftmost graph is a ring of 16 vertices ( $N = 16$ ), where each vertex is connected to four neighbours ( $k = 4$ ). This is an ordered graph which has a high clustering coefficient  $C$  and a long path length  $L$ . By choosing an edge at random, and reconnecting it to a randomly chosen vertex, graphs with increasingly random structure can be generated for increasing rewiring probability  $p$ . In the case of  $p = 1$ , the graph becomes completely random, and has a low clustering coefficient and a short path length. For small values of  $p$  so-called small-world networks arise, which combine the high clustering coefficient of ordered networks with the short path length of random networks. (From: Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomedical Physics* 2007; 1: 3.)

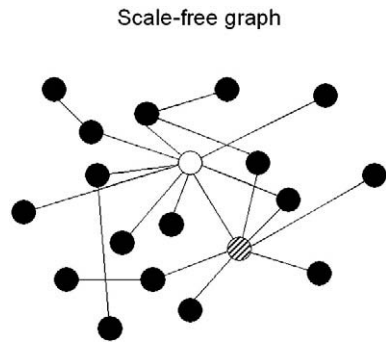
ER like network results. This fully random network has low clustering, but short path length. The really interesting observation is what happens for intermediate values of  $p$ . Even for small, non-zero values of  $p$ , when only a few edges are randomly rewired, the path length drops strongly, while the clustering is hardly affected. This intermediate type of network, called ‘small-world’ networks, has both high clustering and short path lengths, exactly the combination of properties observed in many real networks.

Within a year, another significant new model of complex networks was introduced by Barabasi and Albert (1999). They proposed a model of a growing network, where the edges of newly added vertices attach preferentially to existing vertices with a high degree (degree = number of edges connecting to a vertex). Networks that evolve according to this scenario turn out to have a degree distribution that can be described by a power law with exponent  $-3$ . Since such networks do not have a characteristic scale, they are also referred to as scale-free networks. The introduction of the ‘small-world’ and scale-free models, both very effective descriptions of real world complex networks, marked the start of modern network theory.

## 3. Modern network theory

Some of the important concepts were already briefly mentioned in the historical overview. Here we give a more comprehensive overview of the mathematics of complex networks. Detailed information can be found in several excellent reviews and textbooks (Barrat et al., 2005; Boccaletti et al., 2006; Rubinov and Sporns, 2009). Networks can be represented mathematically by a graph  $G(V, E)$  where  $V$  is a set of nodes (vertices) and  $E$  is a set of connections (edges). The connection structure of a graph is given by the adjacency matrix  $A$ , where each entry  $A_{ij} = 1$  if an edge exists between vertices  $i$  and  $j$ , and  $A_{ij} = 0$  otherwise. Vertices connected by edges are called neighbours. In undirected, symmetric graphs  $A_{ij} = A_{ji}$ ; in directed networks this requirement does not hold. In weighted networks, a weight  $W_{ij}$  can be assigned to each edge; such weights may represent, for instance, the strength or the length of the edges (Fig. 3). The number of edges connected to (incident upon) a vertex is called its degree  $k$ . The degree distribution  $P(k)$  gives the probability that a randomly chosen vertex will have degree  $k$ . In the case of scale-free networks the degree distribution follows a power law:  $P(k) \propto k^{-\gamma}$ . Graphs with power law degree distributions are also characterized by the presence of hubs, vertices with exceptionally high degree.

The shortest path length  $d_{ij}$  between vertices  $i$  and  $j$  in an unweighted graph is the number of edges that have to be traveled to get from  $i$  to  $j$ . The average shortest path length  $L$  of a graph is



**Fig. 3.** Scale-free graphs are characterized by a scale-free degree distribution  $P(k)$ . In scale-free graphs, different vertices have very different degrees, and typically a few vertices with extremely high degrees (so-called 'hubs') are present. In the schematic example shown here the white ( $k=9$ ) and the striped ( $k=7$ ) vertices are examples of hubs. (From: Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomedical Physics* 2007; 1: 3.)

obtained by averaging over all pairs  $i$  and  $j$  in the graph. In weighted graphs, the distance  $d_{ij}$  is defined as the sum of the edge weights of this path. Distances in graphs can also be approached in terms of efficiency measures (Latora and Marchiori, 2001, 2003). The global efficiency of a graph is defined as the average of the inverse of all shortest paths. In the case of vertex pairs that are not connected, the path length is assumed to be infinite, and the efficiency is zero. The local efficiency is the efficiency of a subgraph consisting of all neighbours of a vertex of interest. The betweenness of a vertex or an edge is the fraction of all shortest paths that cross the vertex or edge. Hubs are often characterized by high betweenness as well as high degree.

The clustering coefficient  $C_i \in [0-1]$  of vertex  $i$  is the fraction of possible edges between its neighbours that are actually present. By averaging over all vertices the clustering coefficient  $C$  of the whole graph can be computed. Minor modifications of the clustering coefficient have been described (Newman, 2003b). There are also several proposals to compute clustering coefficients from weighted graphs (Barrat et al., 2005; Onnela et al., 2005; Stam et al., 2009). Often  $C$  and  $L$  are compared to their average values in a large ensemble of random networks with the same number of vertices  $N$  and degree  $k$ :  $\gamma = C / \langle C \text{-random} \rangle$  and  $\lambda = L / \langle L \text{-random} \rangle$ , where  $\langle \rangle$  denotes an ensemble average. In generating these random networks, the degree distribution has to be preserved as well (Maslov and Sneppen, 2004). The defining feature of 'small-world' networks is the combination of a large clustering coefficient and a short path length. This can be quantified with the 'small-world' index (Humphries et al., 2006; Humphries and Gurney, 2008). The 'small-world' index is defined as:  $\sigma = \gamma / \lambda$ .

Motifs are small subgraphs that occur more frequently than in a reference random graph. Motifs have also been defined for weighted networks (Onnela et al., 2005). Modules are large subgraphs with vertices that are more connected to each other than to the rest of the network (Fig. 5). In the case of hierarchical modularity, modules can be further subdivided into submodules, and sub-sub modules. A subdivision of the network into modules allows a further characterization of various roles of vertices (Guimerà and Nunes Amaral, 2005). The most important of these are the provincial hubs, that connect mainly to other vertices within the same module, and the connector hubs, that connect mainly to vertices outside its own module. Vertices may preferentially connect to other vertices that either have the same (assortative mixing) or opposite properties (disassortative mixing). The type of mixing may be determined with assortativity coefficients that have been defined for unweighted and weighted networks (Leung and Chau, 2007; Newman, 2002, 2003a).

The spatial distribution of edges on a graph, its topology, can determine the dynamical processes taking place on this graph. In particular, topological characteristics can predict whether dynamical

processes on the graph can synchronize. This is studied most often with graph spectral analysis. The Laplacian of a graph is a matrix obtained from its adjacency matrix, by setting all  $A_{ij}$  to  $-A_{ij}$ , and all  $A_{ii}$  equal to the degree of vertex  $i$ . The ratio of the largest eigenvalue  $\lambda_N$  and the smallest non-zero eigenvalue  $\lambda_2$  then determine the synchronizability of the graph:  $\lambda_N / \lambda_2$  (Barahona and Pecora, 2002; Nishikawa et al., 2003). The synchronizability mainly indicates whether the synchronized state of the dynamics on a graph will be stable for a sufficiently large range of the parameters of the dynamics. Alternatively, the threshold of the transition between the desynchronized and synchronized state can be related to graph topology. This threshold is inversely related to both the average degree and its first moment as indicated by a measure  $\kappa = \langle k^2 \rangle / \langle k \rangle$  (Barrat et al., 2008). The synchronization threshold also depends upon the largest eigenvalue of the adjacency matrix (Van Mieghem, 2010).

#### 4. Smart wiring in the brain

Complex network analysis is equally relevant for anatomical as well as functional brain networks. In fact, one of the attractive features of this approach is that it allows us to deal with these disparate domains with the same concepts and tools. Moreover, it allows us to understand how structural networks may constrain dynamical processes such as synchronization that takes place on them. In agreement with this, we will first address anatomical networks in a variety of organisms, and then turn our attention to functional networks.

The first and the simplest organism studied is the nematode *C. elegans*. This organism consists of 959 cells, 302 of which are neurons. These neurons are connected by 6393 synapses and 890 electrical junctions, all of which are known. The fact that *C. elegans* have a nervous system with a wiring diagram that is completely known, prompted Watts and Strogatz to test their new ideas concerning 'small-world' networks on it (Watts and Strogatz, 1998). For their analysis they considered a subgraph consisting of 282 neurons with an average degree of 14. The central nervous system of *C. elegans* turned out to have a clustering coefficient of 0.28 (equivalent random network: 0.05) and a path length of 2.65 (equivalent random network: 2.25). With this relatively high clustering and short path length, the central nervous system of *C. elegans* could be considered a typical example of a 'small-world' network. This was the first time a 'small-world' architecture was demonstrated in a brain in any organism. Subsequent studies have refined our knowledge of the topology of the *C. elegans* brain. According to Sporns et al. (2007) a scale-free degree distribution or the presence of hubs cannot be demonstrated in *C. elegans*. They suggested that this could be a fundamental limitation of networks of neurons, since any neuron can tolerate only a limited number of connections. This statement has been challenged recently with the demonstration of hub neurons in developing hippocampal neural networks (Bonifazi et al., 2009). The presence of motifs was demonstrated by Sporns and Kotter (2004). Itzhack and Louzou (2010) showed that the configuration of the *C. elegans* central nervous system (CNS) could be explained by a random distance dependent attachment model. It has been shown that the modular structure of the CNS cannot be explained solely in terms of wiring cost and minimizing path length, but also depends upon the functional requirements of the system (Pan et al., 2010).

Results in primates confirm and extend those in *C. elegans*. Optimal set analysis of anatomical brain networks of the macaque, consisting of 73 brain areas and 834 connections, demonstrated the existence of five large modules (Hilgetag et al., 2000). A similar analysis in the cat brain revealed five to nine modules. These anatomical brain modules could be tentatively related to major categories of brain function such as vision, sensation and motor behavior. The brain network of the macaque has a path length of 2.18 (random: 1.95) and a clustering coefficient of 0.49 (random: 0.159). Thus, the brain network of the macaque could also be considered a typical 'small-world' network. The same conclusion was reached in the analysis of the cat brain. In both primate brains hub-like



nodes with a high degree, short distance to other nodes and a high betweenness centrality could be demonstrated (Sporns et al., 2007). Hubs were mainly found in association areas. They could be classified as provincial, mainly connecting to other vertices in the same modules, or connector, mainly connecting to vertices outside their own module. Hubs were also preferentially connected to each other, consistent with an assortative type of network mixing. Despite the presence of Hub like elements, the network was too small to directly demonstrate a power law of the degree distribution. Kaiser et al. (2007) used an indirect approach to explore the possible scale-free nature of the primate brain. In simulation studies they demonstrated a high robustness of the networks against random error, but a high sensitivity to targeted attacks directed at the hubs. This pattern of sensitivity to damage would classify the primate brain as belonging to the scale-free category.

It took some time before all these results could be confirmed in humans. He et al. (2007) used an ingenious approach whereby they computed correlation matrices of the thickness of 54 cortical gray matter areas in a large sample of 124 healthy subjects. The assumption behind this method was that covariation in cortical thickness across subjects would reflect the presence of anatomical connections between brain regions. The authors found that 104 pairs of thickness correlations were significant; half of these concerned interhemispherical connections. The clustering coefficient of this network (actually a compound network of 124 brains) was 0.30 (random control: 0.13) and the path length 3.05 (random control: 2.36). This was the first demonstration of a 'small-world' architecture in human anatomical brain networks. The degree distribution of this network followed a power law only over a small range; it was described as an exponentially truncated power law. Overall, 12 hub regions were identified, mostly in association areas. Simulations showed that the network was resilient to random damage, but sensitive to hub removal, in line with earlier findings of Kaiser et al. (2007). In a subsequent study the same group demonstrated the presence of six modules, each consisting of 4–10 cortical regions, in human anatomical brain networks (Chen et al., 2008). These modules could be linked to basic categories of brain function. Based upon the division into modules, hubs could be classified as provincial or connector like.

The method of cortical thickness correlations was an important first step, but it had two significant shortcomings: (i) any conclusions on anatomical connections between brain areas could only be tentative, since no direct demonstration of fiber tracts was involved; (ii) it took a large group of subjects to construct a single network, and nothing could be said about brain networks in individual subjects. These limitations were overcome when Hagmann et al. (2007) showed how MRI DTI (diffusion tensor imaging) could be used to reconstruct whole brain anatomical networks in individual subjects. In the first study, involving 2 subjects, networks with 1000 vertices and 50,000 edges were constructed (Hagmann et al., 2007). This study demonstrated high clustering and short path lengths, consistent with a 'small-world' network, but failed to show a power law degree distribution or hubs. In a subsequent study involving five subjects' networks with either 1000 regions or with 66 large ROIs were investigated (Hagmann et al., 2008). This study showed that the global network could be subdivided into six major modules. The degree distribution still was not scale-free, but now hubs could be demonstrated. Connector hubs of the network were preferentially connected to each other, constituting a 'connectivity backbone', and classifying the network as assortative. Major components of the 'connectivity backbone' were the cingulate gyrus, cuneus and precuneus and the parietal lobe, all components of the resting-state default mode network.

Since the work of Hagmann et al. MRI DTI has become the most dominant approach in characterizing anatomical complex brain networks. In addition to confirming the 'small-world' character of anatomical brain networks Iturria-Median et al. (2008) demonstrated the presence of motifs and used simulations to point out the special vulnerability of nodes in the parietal lobe and the precuneus. In this study, the degree distribution was of the truncated power law type. In a

large study of 80 healthy subjects most of the, by now, familiar observations of 'small-world' patterns, exponentially truncated power laws, and the presence of hubs in association areas were confirmed (Gong et al., 2009a). In another large study of the same group ageing was shown to be associated with loss of connectivity strength (Gong et al., 2009b). Local, but not global efficiency was lost in the posterior cingulate gyrus and the precuneus. Females had higher connectivity strength and higher local and global efficiency. The gender effects were most clearly visible in left hemisphere association areas. The significance of brain network topology for cognitive functioning was demonstrated in a very elegant study by Li et al. (2009). Anatomical brain networks derived from MRI DTI in 79 healthy subjects displayed the, by now, expected high clustering and short path length typical of 'small-world' networks. After correction for the effects of age and gender they found that a higher IQ was strongly correlated with a larger number of connections, a shorter path length and a higher efficiency. The direct demonstration of a strong link between topological features of complex brain networks, and a general measure of cognitive performance, underscored the great potential of a complex networks approach to the brain. Almost at the same time, a study based on functional networks showed essentially the same findings; this will be discussed in the next section on functional brain networks.

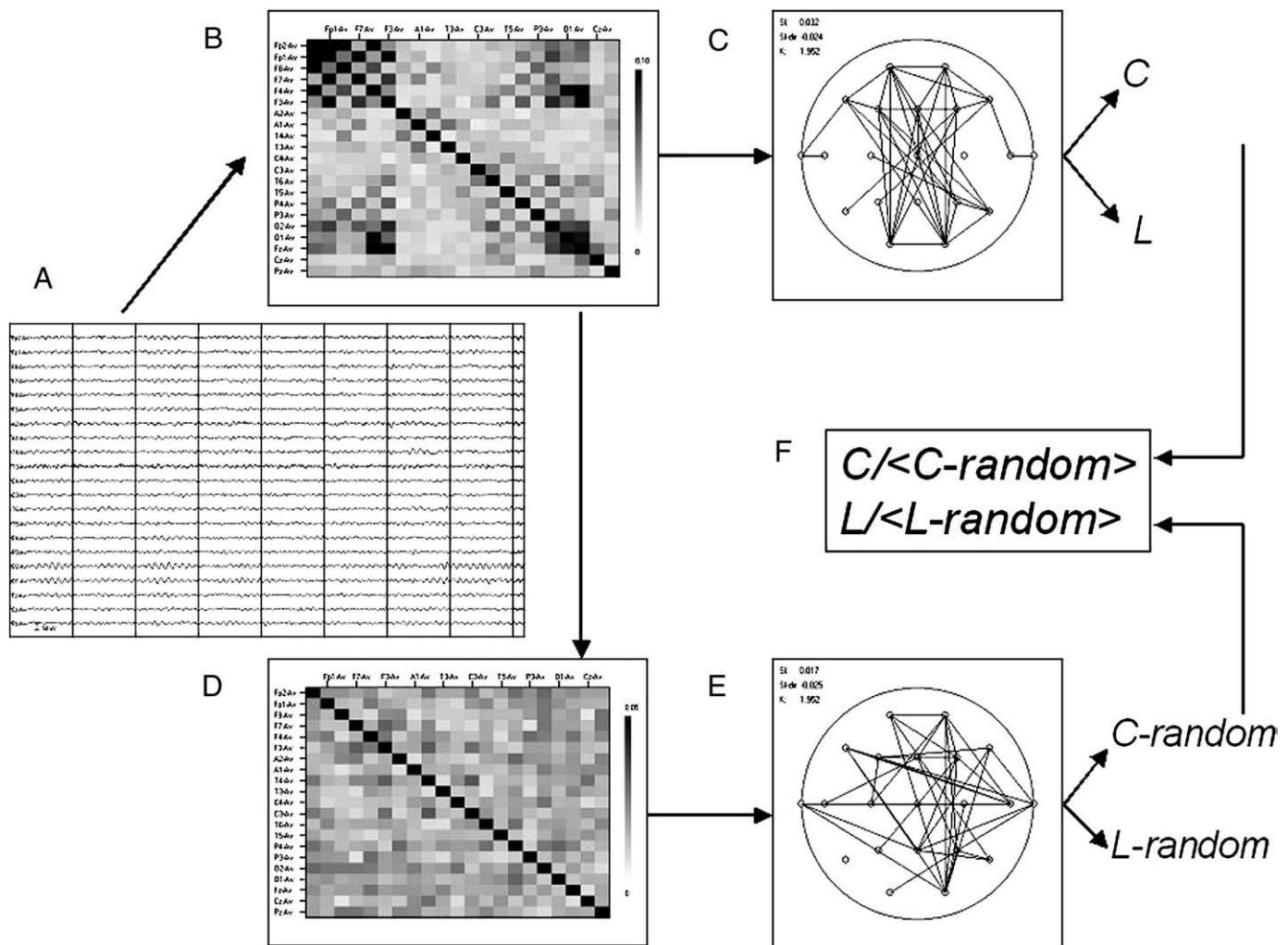
## 5. The emergence of complex functional brain networks

### 5.1. In vivo and in vitro model studies

As indicated above, graph theoretical analysis can be applied easily to all types of network-like structures, including anatomical and functional brain networks. In this section we will focus on functional networks as they have been studied in cell cultures, animals and humans, using a variety of techniques such as EEG, MEG and fMRI. The reconstruction and analysis of graphs from functional data is illustrated schematically in Fig. 4.

Attempts to track the functional connectivity of the brain have a long history. The Dutch neuroscientist JG Dussier de Barenne, working in Amsterdam, in the UK with Sherrington, and finally in Yale, used strychnine-induced disinhibition to track functional interactions in the macaque cerebral cortex. Many years later Stephan et al. (2000) collected this type of data from the literature to reconstruct functional as opposed to anatomical networks of primate cortex. These functional networks had the same characteristic combination of high clustering and short path lengths as found in anatomical primate cortex. However, it should be stressed that this study was based on purely historical data, and that the concept of functional connectivity here was rather indirect since it was not based upon the direct observation of correlated or synchronized electrical activity in distance neuronal populations.

A more direct observation was made by Bettencourt et al. (2007) who looked at the spiking activity of cultured neuronal cell assemblies. Assessment of functional connectivity was based upon mutual information analysis of neuronal spike trains. The functional networks derived from the mutual information analysis were of the 'small-world' type. In contrast to previous anatomical studies the network was weakly disassortative. Small networks of neurons have also been studied in vivo by Yu et al. (2008). Here, recordings were made in the visual cortex of anesthetized cats from up to 24 neurons. Again, functional networks based upon patterns of correlated firing had a typical 'small-world' character. Although the networks were too small to detect a scale-free degree distribution, neurons did show a remarkable heterogeneity in their degree, suggesting the possibility of hub neurons. The existence of clear hub neurons was shown convincingly in a recent study in rats and mice (Bonifazi et al., 2009). Here, the authors determined functional brain networks from calcium activity analysis in developing hippocampal networks. Networks with up to 806 neurons could be studied. The degree distribution was scale-free, with an exponent of 1.3. Hub neurons



**Fig. 4.** Schematic illustration of graph analysis applied to multi channel recordings of brain activity (fMRI, EEG or MEG). The first step (panel A) consists of computing a measure of correlation between all possible pairs of channels of recorded brain activity. The correlations can be represented in a correlation diagram (panel 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 (panel C). From this graph various measures such as the clustering coefficient  $C$  and the path length  $L$  can be computed. For comparisons, random networks can be generated by shuffling the cells of the original correlation matrix of panel B. This shuffling preserves the symmetry of the matrix, and the mean strength of the correlations (panel D). From the random matrices graphs are constructed, and graph measures are computed as before. The mean values of the graph measures for the ensemble of random networks are determined. Finally, the ratio of the graph measures of the original network and the mean values of the graph measures of the random networks can be determined (panel F). (From: Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomedical Physics* 2007; 1: 3.)

were shown to be GABAergic, and had long axonal arborization. Experimental manipulation demonstrated that these hub neurons could exert significant influence on large-scale network dynamics, in particular patterns of synchronization.

## 5.2. EEG and MEG in humans

One of the first attempts to detect 'small-world' networks in functional connectivity data of humans was published in 2004 (Stam, 2004). In an eyes-closed resting-state recording in five healthy subjects, levels of synchronization between 126 MEG channels were determined in the usual frequency bands from delta to gamma using the synchronization likelihood (SL). For all frequency bands, matrices of SL values were thresholded to obtain undirected unweighted graphs. In the frequency range of 8–30 Hz, the topology of these functional networks was close to that of ordered networks; however in the delta and theta range, as well as in the gamma range >30 Hz, functional networks displayed the features of 'small-world' networks. The presence of functional 'small-world' networks in healthy humans could also be demonstrated with EEG (Micheloyannis et al., 2006). Somewhat surprisingly, the 'small-world' character of the EEG networks was

negatively correlated with the level of intellectual functioning in this study. The 'small-world' character of EEG networks was also decreased in students (aged 21–26 years) compared to children (8–12 years) in the beta and gamma bands (Micheloyannis et al., 2009).

In a graph theoretical MEG study Bassett et al. (2006) investigated 22 healthy subjects, half of them in a resting-state with eyes-open, half of them during a finger tapping task. Correlations between MEG signals at the 275 sensors were based upon different wavelets. In six different wavelet scales, roughly corresponding to different frequency bands, a clear 'small-world' pattern with high clustering and short path lengths was found. The degree distribution was an exponentially truncated power law. The authors also determined the synchronizability of the MEG networks, and concluded these networks were close to an order / disorder transition. Finally, the finger tapping task in this study was associated with the emergence of long-range functional interactions in the beta and gamma band. When reconstructing graphs from functional connectivity data it is possible to vary the number of supra-threshold edges by varying the threshold; in fact the threshold is a parameter that has to be chosen somehow. The number of suprathreshold edges as a fraction of the total possible number of edges (in a network with  $N$  vertices this is  $N(N-1)/2$ ) is

called the cost of this network. An economic ‘small-world’ network is a network with a high global and local efficiency, and a low cost (Latora and Marchiori, 2003). Bassett et al. (2009) showed that functional MEG networks are also efficient ‘small-world’ networks (Fig. 5).

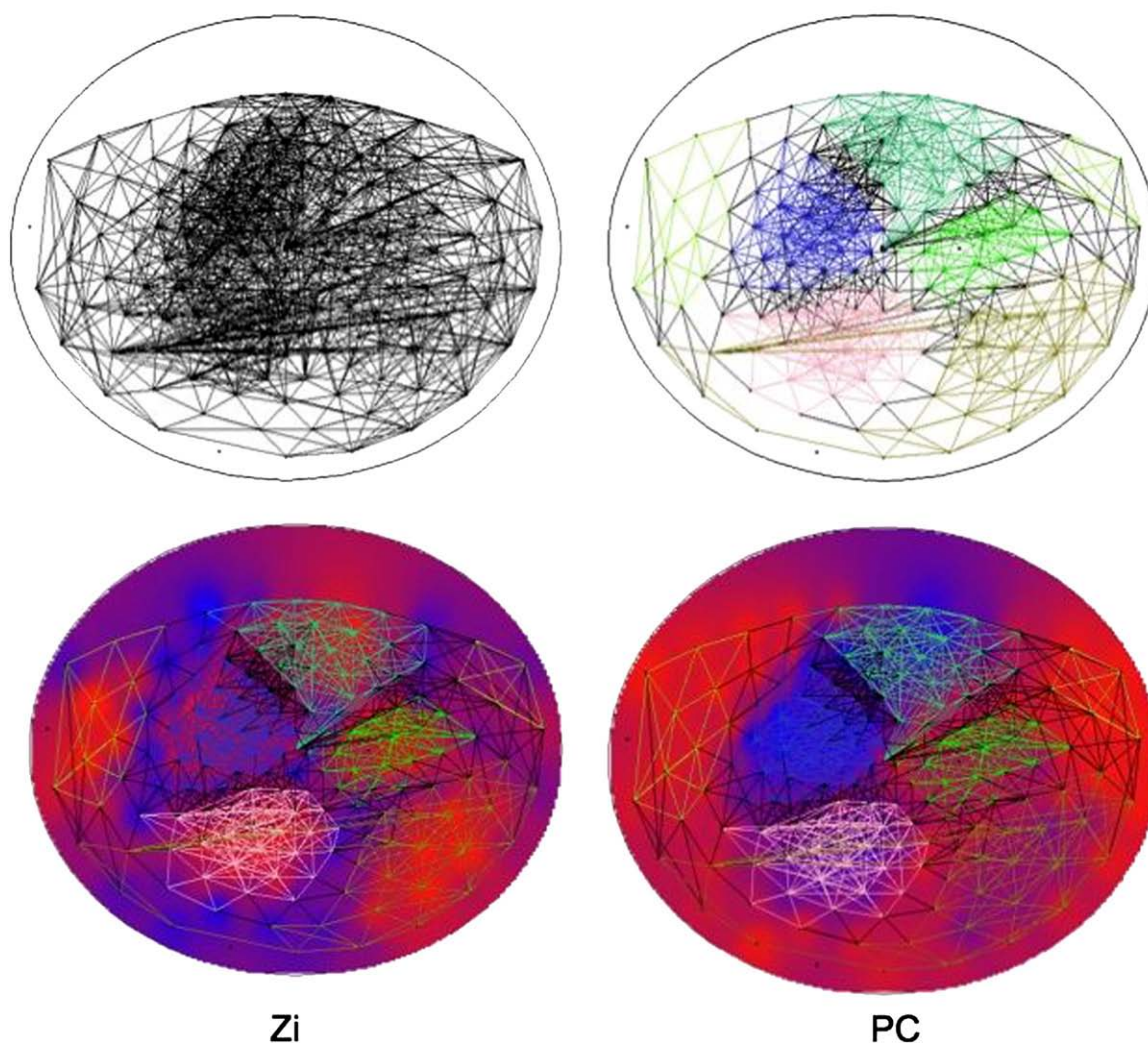
Although the test–retest reproducibility has been shown to be quite good (Deuker et al., 2009), graph theoretical characteristics of functional brain networks may vary from subject to subject. This variability is not only due to noise, but also reflects a significant genetic component. In a study involving 574 twins and their siblings, functional networks were reconstructed in different frequency bands using EEG and synchronization likelihood (Smit et al., 2008). Up to 46–89% of the variance in the clustering coefficient, and 37–62% of the variance in the path length were found to be heritable. In an even larger follow up study with 1438 subjects the heritability of levels of functional connectivity, clustering coefficient and path length were confirmed (Smit et al., 2010). This study also showed an interesting pattern in the evolution of functional network complexity: networks were relatively closer to random in the youngest and the oldest groups, and relatively more ‘small-world’ like in the intermediate age

groups. This suggests that network evolution during development may be characterized by the gradual acquisition of order in random networks, converting them to optimal ‘small-world’ networks; this would be somewhat similar to decreasing the rewiring probability in the Watts and Strogatz model. A study in children, who had EEG recorded at age five and age seven, supports this hypothesis on brain network development (Boersma et al., *in press*).

### 5.3. Functional MRI studies

Functional brain networks can also be studied with functional MRI. In general, there is a striking agreement between structural and functional network studies (Honey et al., 2007, 2009; Van den Heuvel et al., 2008b). One of the first studies was performed by Eguíluz et al. (2005) who reconstructed correlation matrices of BOLD signals from all MRI voxels during different finger tapping tasks in seven healthy subjects. The resulting functional networks were ‘small-world’ like with a large clustering coefficient and a short path length, and had a scale-free degree distribution with a scaling exponent close to 2. The probability of a functional connection between any two nodes scaled

## The modular structure of functional brain networks



**Fig. 5.** Illustration of the modular architecture of a complex functional brain network. Eyes-closed resting-state MEG data (151 channel CTF system) filtered in the 8–13 Hz band of a single subject were analyzed. Functional connectivity was determined by phase synchronization. The upper left panel shows the functional connectivity network after applying an arbitrary threshold for optimal visualization. The upper right panel shows the division of the network in modules. Connections with each module are colored, connection between modules are depicted in black. The lower left panel shows the same modules and a color map (blue low values, red high values) of the within module degree  $Z_i$ .  $Z_i$  quantifies how strongly a vertex is connected to other vertices within the same module. The lower right panel shows the models projected on a color map of the participation coefficient  $PC$ .  $PC$  quantifies how strongly a vertex is connected to vertices outside its own module.



as a power law of distance. Salvador et al. (2005b) found a similar distance-dependent pattern of functional connectivity. In a more recent voxel-based study both the 'small-world' configuration as well as the power law degree distribution with a scaling exponent around 2 were confirmed (van den Heuvel et al., 2008a). This study localized the strongest hubs in the anterior and posterior cingulate gyrus, the superior temporal lobe and the thalamus. Other fMRI studies based on network reconstruction from a limited (typically around 90) number of ROIs rather than a high number of voxels did not report a scale-free degree distribution, but rather an exponentially truncated power law (Achard et al., 2006; He et al., 2009). Resolution does seem to be an important factor in determining the true mathematical form of the degree distribution (Hayasaka and Laurienti, 2010). Experimental studies in animals do suggest that scale-free degree distributions may be a fundamental characteristic of brain networks even at the level of neurons (Bonifazi et al., 2009).

In general, fMRI studies have all confirmed the presence of high clustering and short path lengths in functional brain networks (Achard et al., 2006; Salvador et al., 2005a,b). In agreement with MEG findings, fMRI-based functional networks are also economic 'small-world' networks (Achard and Bullmore, 2007). The economic 'small-world' structure is disrupted in ageing, especially in frontal, temporal and subcortical regions (Achard and Bullmore, 2007). There is also considerable support for the presence of five to seven large modules in these brain networks (He et al., 2009; Meunier et al., 2009a,b; Van den Heuvel et al., 2008c; Salvador et al., 2005b). These modules correspond to major categories of brain function. There is a clear similarity between modules detected by graph theoretical analysis, and previously described resting-state networks (Damoiseaux et al., 2006; Van den Heuvel et al., 2008c). Brain modules may be subdivided into other modules in a hierarchical way (Meunier et al., 2009b). One module that stands out in particular is very similar to the default mode networks, a set of brain regions involving medial frontal areas, anterior and posterior cingulate gyrus, precuneus and parietal cortex, that is more activated in rest than during tasks (Damoiseaux et al., 2006). During ageing, the modular structure changes, with a shift from frontal to central and posterior intermodular connectivity.

Hub like nodes are typically found in association areas and may either connect mainly nodes within modules, or may link different modules together. While hubs almost certainly play a key role in information processing, they are also very vulnerable parts of the network as shown in simulations of lesion effects (Achard et al., 2006; He et al., 2009). It has been suggested that connector hubs preferentially connect to each other, constituting a functional connectivity core of the brain (Achard et al., 2006; He et al., 2009). This is remarkably similar to the 'connectivity backbone' described by Hagmann et al. (2008). This type of connectivity, that has also been found in MEG work (Deuker et al., 2009), classifies macroscopic functional brain networks as assortative.

In 2009, within a few weeks time, two studies were published that demonstrated a clear correlation between network structure and intelligence. The anatomical study by Li et al. (2009) was discussed in the previous section on structural connectivity. The functional study was performed by Van den Heuvel et al. (2009). Resting-state fMRI was performed in 19 healthy subjects. Analysis of functional networks was done at the voxel level, resulting in graphs with 9500 vertices. A strong negative correlation ( $r = -0.57$ ) was found between normalized path length and IQ. This correlation was strongest in those voxels that are part of the default mode network. Together, the studies of Li et al. and Van den Heuvel et al. point out that *connectivity is at the core of cognition*.

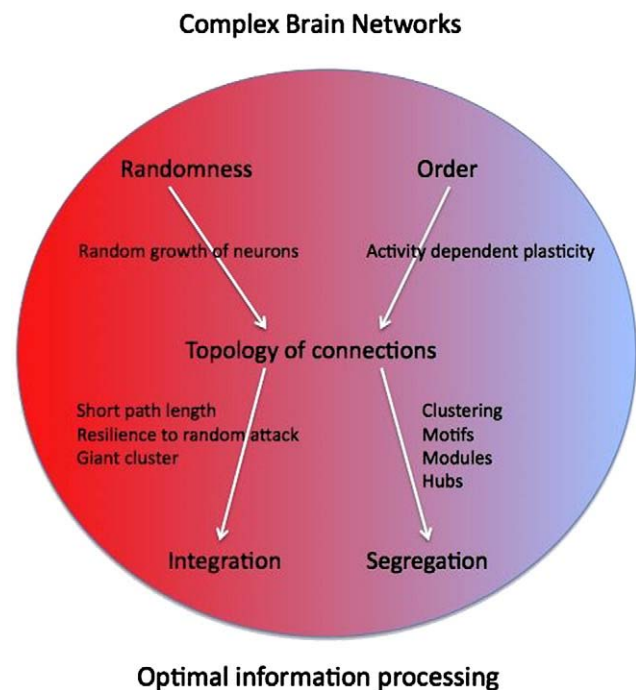
## 6. The brain as a complex network

The central idea behind all the studies discussed in this review is that the brain can be viewed as a complex network. Whereas a network, or

graph, is a set of nodes (vertices) and their connections (edges), a complex network can be defined as a sufficiently large, sparsely connected graph with – most importantly – a topology that is a mixture between randomness and order. The brain fits this description remarkably well across a range of animal species from *C. elegans* to humans, across a range of scales from neurons to macroscopic brain areas, and with respect to anatomical as well as functional networks. Here we summarize the main findings in the literature, and try to determine their biological and cognitive significance, using the definition of complex networks and the scheme in Fig. 6 as a guideline.

Brain networks are large. Human brain are estimated to have about  $10^{10} - 10^{11}$  neurons, an astronomical number, surpassing even such very large complex networks as the Internet and the world wide web. The large size of brain networks has arisen during biological evolution, and most likely confers important advantages for survival. It is seductive to relate numbers of neurons to the capacity of the brain to process and store information. However, more is needed than simple numbers; without connections even the largest brain is useless as an information storing and processing organ. The key question is therefore: how are the  $10^{10}$  neurons connected to enable an optimal organization of behaviour?

Brain networks are sparsely connected. We have  $10^{10}$  neurons, but on average only  $10^4$  connections per neuron. While sparse connectivity is a general characteristic of complex networks, the brain may have one of the lowest connectivity levels of them all. Very likely, the sparse connectivity of brain networks is related to the evolutionary pressure to lower the wiring costs of nervous system. There is a biological 'price' for each connection in terms of biological material and energy; therefore a brain that achieves the same information processing at a lower wiring cost is likely to be at a significant evolutionary advantage. When optimal



**Fig. 6.** Schematic representation of complex brain networks. A complex brain network is a large, sparsely connected network with a topology that is a mixture between random and ordered components. Randomness is symbolized by red, order by blue. The central feature of brain networks is their connection topology. The random component in this topology is due to random neuronal growth processes. Order in the topology is due to activity dependent modification of random connections, in particular synchronization induced increases in connection strength. The randomness in the topology gives rise to short path lengths, resilience to random error, and the emergence of a giant connected component, supporting integration of information processing. The ordered component gives rise to clustering, motifs, modules and hubs. These support segregation of information processing. Integration and segregation together constitute the optimal information processing of complex brain networks.

information exchange has to be preserved with the smallest number of connections, topology – how the connections are placed in the network – becomes crucially important.

Brain network topology is a mixture of order and randomness. Apparently this mixture allows the brain to achieve its goal – optimal and efficient information processing – at the lowest possible wiring cost. There is accumulating evidence that the randomness in brain network topology may be explained by neuronal growth processes, in particular the way dendrites and axons grow and connect (Bettencourt et al., 2007; Kaiser and Hilgetag, 2004, 2007). This growth process has been described as random, and distance dependent (Kaiser et al., 2009). The random component of brain network topology has at least three crucial consequences: (i) it allows the emergence of a single connected giant cluster with a minimal number of connections; (ii) it is responsible for short path lengths, optimal system-wide integration and high synchronizability; (iii) it contributes to the resilience of brain networks to random attacks.

Order is reflected in brain networks on different scales. At the lowest scale, it is manifested by a high clustering, that is high connectivity between the neighbours of each vertex. High clustering further increases the resilience of brain networks to random damage, and may facilitate local information processing. One level up, motifs may reflect structural and functional building blocks of complex brain networks. Finally, hierarchical modularity clearly constitutes a manifestation of self-organized order in brain networks. Modules correspond to specialized categories of high level brain functions. Provincial hubs further optimize the information processing within modules, whereas connector hubs link modules together, constituting a large connectivity backbone. Whereas the random component of network topology probably reflects the random growth process, hierarchical order from clustering to modules most likely derives from activity dependent modification of random connections. In particular, strengthening of connections between highly synchronous elements is an important driving force for the emergence of order in brain networks (Fuchs et al., 2009; Rubinov et al., 2009; Siri et al., 2007).

Together, randomness and order allow integration and segregation of information processing in brain networks. The significant heritability of complex brain network characteristics suggests that the interplay between random neuronal growth and activity dependent plasticity during development and learning is almost certainly under genetic control. Combined, these processes determine how optimal our brain networks will be, and how smart we are.

## Acknowledgements

The author would like to thank Mrs. Els van Deventer for her unrelenting help in retrieving the many papers for this review.

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