Modelling hierarchical structure in functional brain networks

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In this work, we focus on a complex-network approach for the study of the brain. In particular, we consider functional brain networks, where the vertices represent different anatomical regions and the links their functional connectivity. First, we build these networks using data obtained with functional magnetic resonance imaging. Then, we analyse the main characteristics of these complex networks, including degree distribution, the presence of modules and hierarchical structure. Finally, we present a network model with dynamical nodes and adaptive links. We show that the model allows for the emergence of complex networks with characteristics similar to those observed in functional brain networks.

Keywords: complex networks; functional brain networks; synchronization

1. Introduction

The human brain is perhaps the most complex system in nature. Despite increasing efforts to understand its organization and function, a vast number of issues remain as open problems. Recently, a complex-network approach, in which the brain is considered to be a complex network, has received considerable attention and allowed for new insights (Sporns et al. 2004; Reijneveld et al. 2007; Stam et al. 2007; Arenas et al. 2008). Data on anatomical connectivity has revealed that a small-world structure, characterized by the presence of highly clustered modules and a short mean distance between nodes, seems to be present at many different levels (Hagmann et al. 2008). This complex-network structure is hypothesized to be an optimal configuration that satisfies opposing requirements of functional connectivity (Sporns et al. 2000). On the one hand, functional segregation calls for the localization of specific functions to well-defined brain areas. On the other hand, functional integration requires that the activity of these localized regions be highly coherent. Recent works have tackled this issue and precisely shown that a small-world network structure provides an optimal topological substrate that allows for efficient communication between modules, both from local and global points of view (Latora & Marchiori 2001; van Leeuwen 2007).

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The small-world structure of the brain seems to be robust at different scales, and also when different measuring techniques are applied. An interesting open problem that has been a subject of debate recently is whether other complex-network characteristics, such as the degree distribution or the organization of modules in hierarchical structures, are also robust (Eguíluz et al. 2005; Achard et al. 2006; Park et al. 2008).

In §2, we will analyse a functional brain network, built from functional magnetic resonance imaging (fMRI) data. Then, we will show a model that allows for the emergence of complex-network structures with the characteristics observed in functional brain networks. In particular, we will discuss a novel approach where the nodes of the network are considered as dynamical systems, and the evolution of the interactions in the network is an adaptive process coupled to the dynamical state of the nodes. Finally, we will analyse hierarchical structures in a large-scale functional brain network, and discuss the results in the light of the adaptive model.

2. Human-brain functional networks from functional magnetic resonance imaging analysis

We used fMRI to obtain information on the brain activity in 90 cortical and sub-cortical regions. In figure 1, we present the different steps used to extract a complex network from the fMRI analysis. The technical aspects are described in detail in Spoormaker et al. (2010). The activity of region \( x \) at time \( t \) is denoted by \( V(x, t) \). As in Eguíluz et al. (2005), we calculated the linear correlation coefficient between any pair of regions \( x_1 \) and \( x_2 \) as

\[
r(x_1, x_2) = \frac{\langle V(x_1, t) V(x_2, t) \rangle - \langle V(x_1, t) \rangle \langle V(x_2, t) \rangle}{\sigma(V(x_1)) \sigma(V(x_2))},
\]

where

\[
\sigma^2(V(x)) = \langle V(x, t)^2 \rangle - \langle V(x, t) \rangle^2
\]

and \( \langle \cdots \rangle \) indicates temporal average.

In figure 1, we present the correlation matrix for the 90 cortical and sub-cortical regions obtained using equation (2.1). The diagonal line that crosses the matrix corresponds to self interactions, which are not taken into account. Figure 1 shows well-defined regions that present a high correlation, revealing the presence of functional modules.

In order to characterize the structure and interactions between functional modules, a threshold value, \( R \), can be set to the correlation matrix to build a binary adjacency matrix, \( A_{ij} \) (Eguíluz et al. 2005; Achard et al. 2006). If the correlation between sites \( i \) and \( j \) is larger than the threshold \( R \), then \( A_{ij} = 1 \). If \( r(x_1, x_2) < R \), then \( A_{ij} = 0 \). In this way, it is possible to obtain a representation of the correlations in the brain as a complex network, where only regions with correlations above the threshold are connected. For very low threshold values, the networks obtained are densely connected, on the contrary, for very large threshold values, few connections remain, and the networks are almost completely disconnected. In the intermediate regime, rich information can be extracted.

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Figure 1. Analysis pipeline of graph theoretical analysis of fMRI time series. Time-course extraction is performed on the recorded time series with a specific anatomic parcellation (in our case, based upon the automated anatomical labelling atlas by Tzourio-Mazoyer et al. (2002)). Linear correlations are calculated and thresholded in order to obtain a binary adjacency matrix and graph. (Online version in colour.)

In order to present a quantitative analysis of the modular structure, we present, in figure 2, the fraction of sites in the largest connected component as a function of the threshold $R$. For low threshold values, the network is composed of a single connected component. Then, as the abrupt drop at $R \approx 0.78$ shows, the network fragments. This jump reveals the presence of a small module with no overlap with the rest of the network above this threshold value. As $R$ is increased further, the largest component does not present more jumps, and a more or less smooth monotonous decay to zero is observed.

In order to advance further in the characterization of the modular structure, we show, in the inset of figure 2, the fraction of links in the largest connected component as a function of threshold $R$. Note that there are no abrupt changes in the whole range, and a linear decay is observed for thresholds above $R = 0.7$. The dashed line shows the best linear fit, and is presented as a guide to the eye.

These results present evidence of a hierarchical structure with overlapping modules. The strongest links form the backbone structure of the modules and the connections between them. As the threshold is lowered, less correlated connections link nodes inside the same module and also allow for larger overlaps between modules.

In figure 3, we show the clustering $C$ as a function of degree $k$ for three different threshold values, $R = 0.6$, 0.7 and 0.8. As the threshold is lowered, the network becomes more clustered. Note that this effect is distributed along the whole range of the degrees. This effect is owing to the hierarchical structure of the network.

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Figure 2. Fraction of sites and fraction of links (inset) in the largest component as a function of threshold \( R \). The dashed line in the inset is the best linear fit, presented as a guide to the eye.

Figure 3. Clustering \( C \) as a function of degree \( k \), for three different thresholds. The inset presents a comparison between the network with \( R = 0.8 \) and a randomized version with the same number of nodes and the same degree distribution (squares, \( R = 0.8 \); triangles, \( R = 0.7 \); black diamonds, \( R = 0.6 \); black circles, \( R = 0.8 \); circles, randomized work). (Online version in colour.)

In fact, as the threshold is lowered, the small modules become more clustered, and also more connections between these clusters are established, thus allowing for an increase in the clustering for the hubs. The inset shows a comparison of the network for \( R = 0.8 \) and a random network with the same number of nodes and
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Figure 4. Degree distribution for five different thresholds. The same qualitative behaviour is observed in all cases (open black circles, $R = 0.700$; open squares, $R = 0.725$; open diamonds, $R = 0.750$; open triangles, $R = 0.775$; open inverted triangles, $R = 0.800$). (Online version in colour.)

the same degree distribution. The plot shows that almost in all the range of $k$, the network presents larger clustering values than a random system, and thus to the well-established small-world structure of the brain (Bassett & Bullmore 2006).

As discussed in §1, the degree distribution of functional brain networks is currently a subject of particular interest. Functional brain networks present broad degree distributions. The role of hubs for different functional forms has particular consequences in the resilience and synchronization properties of the system (Arenas et al. 2008), thus leading to an interest to find whether the degree distribution is robust in functional brain networks.

In figure 4, we present the degree distribution of the largest connected component for five different threshold values. For degrees up to $k \approx 30$, the distribution presents a very slow decay, and then, for larger degrees, a crossover to a faster exponential-like decay. The same qualitative behaviour is observed for a wide range of threshold values, showing that this is a robust characteristic of the network. We point out that this qualitative behaviour resembles the results obtained by Achard et al. (2006) and Park et al. (2008), where a slow decay for small degrees presents a crossover to an exponential-like decay for larger degrees. These results are in accordance with the extended analysis presented recently by Hayasaka & Laurienti (2010), who compared characteristics between region- and voxel-based networks in resting-state fMRI data, and also Zalesky et al. (2009), who analysed brain networks at different ranges of scales, grey-matter parcellations and acquisition protocols. Their results show that comparison of networks across different studies must be made with reference to the spatial scale of parcellation.

In the following section, we will present a growing network model that allows for the emergence of complex networks with broad degree distributions. In particular, Gomez Portillo & Gleiser (2009) obtained degree distributions that present a slow decay followed by a crossover to an exponential decay.
For increasing system sizes, the crossover moves to larger degree values, thus presenting a finite size effect similar to the one observed in functional brain networks (Gomez Portillo & Gleiser 2009).

3. An adaptive complex-network model for the emergence of hierarchical networks

Understanding the origin of the different complex-network structures observed in functional brain networks presents a great challenge. We stress that, even at this abstract level where the brain is considered as a set of dynamical nodes and their links, the mechanisms that allow for the emergence of different complex-network structures remain an open problem (Boccaletti et al. 2006). Also, a strong effort is being devoted to the study of processes that take place on these structures, such as the synchronization of dynamical nodes (Acebrón et al. 2005; Arenas et al. 2008). In this section, we review models that tackle these issues, and analyse which are the main mechanisms that allow for the emergence of complex networks with characteristics similar to those observed in functional brain networks. These models consider a novel approach, where the evolution of the network structure is considered as an adaptive process, which is coupled to the dynamical state of the nodes (Gong & van Leeuwen 2003, 2004; van den Berg & van Leeuwen 2004; Gleiser & Zanette 2006). Following this approach, Gomez Portillo & Gleiser (2009) recently presented a growing adaptive network as a model for functional brain networks. The dynamics of the microscopic units is given by nonlinear phase oscillators

\[
\frac{d\phi_i}{dt} = \omega_i + \frac{r}{M_i} \sum_{j=1}^{N} W_{ij} \sin(\phi_j - \phi_i),
\]

where \(\omega_i\) is the natural frequency of oscillator \(i\) and \(r\) is the coupling strength (Acebrón et al. 2005). The natural frequencies \(\omega_i\) are chosen at random from a Gaussian distribution \(g(\omega) = \exp(-\omega^2/2)/\sqrt{2\pi}\). The weights \(W_{ij}\) define the adjacency matrix of the interaction network: \(W_{ij} = 1\) if oscillator \(i\) interacts with oscillator \(j\), and 0 otherwise. The number of neighbours of oscillator \(i\) is \(M_i = \sum_j W_{ij}\). Interactions are symmetric, so that \(W_{ij} = W_{ji}\) and the network is a non-directed graph. For a detailed analysis of this model, see Gomez Portillo & Gleiser (2009).

The new nodes that enter the system first connect their links at random, and then are allowed to rewire their connections. Two different rewiring rules were considered. The global rewiring allows information on the state of all the nodes in the system to be available to the new nodes. In figure 5, we show the average frequency \(\Omega\) of all the oscillators versus their natural frequency \(\omega\) for global rewiring dynamics and system sizes \(N = 200\) (inset) and 1600. Figure 5 shows that already for small system sizes, synchronized clusters are present. They can be clearly distinguished as horizontal arrays of dots, which show nodes with different natural frequencies that now have the same average frequency. The global rewiring dynamics of the algorithm is, in some sense, optimal, since it allows each new node that enters the system to rewire its links with those nodes in the system with
which it can synchronize more easily. As a consequence, when the system size
grows, the new nodes synchronize with an existing cluster, and the number of
modules remains constant. Also, since the number of new connections that each
new node has is fixed, the modules become sparser and sparser as the system
grows. In fact, a quantitative analysis reveals that the clustering coefficient decays as $C \sim N^{-0.45}$, thus revealing the absence of a hierarchical network structure (Gomez Portillo & Gleiser 2009).

In figure 5, we also show the adjacency matrices obtained using the global
rewiring algorithm for system sizes $N = 100$ and 200. These matrices have
been reordered according to the mean frequency $\Omega$ of the oscillators in order
to show the relation of the synchronized clusters with the underlying network
structure. The matrices reveal the presence of well-defined modules directly
associated with the synchronized clusters.

Since the global rewiring dynamics does not allow for hierarchical networks to
emerge, Gomez Portillo & Gleiser (2009) proposed a simple modification to the
algorithm that changes the global point of view of the new nodes to a restricted
local environment. This simple modification has dramatic consequences in the
complex-network structures that emerge. In figure 5, we show the behaviour
of $\Omega$ versus $\omega$ for the local rewiring dynamics and system sizes $N = 200$ and
1600. The figure shows that, as for global rewiring, the presence of synchronized
clusters can already be distinguished for $N = 200$. However, for $N = 1600$, a
large number of small clusters for intermediate frequencies can also be observed.

Figure 5. Average frequency $\Omega$ versus natural frequency $\omega$ for global rewiring dynamics and system
sizes $N = 200$ (inset) and $N = 1600$. Synchronized clusters can be clearly distinguished as horizontal
arrays of dots. Note that the number of clusters remains constant, while the size of the clusters
grows with increasing system size. The corresponding adjacency matrices reordered according to the
average frequency are shown below. Note how the topological modules can be directly associated
with the synchronized clusters.
As the system size grows, these clusters grow and also new small clusters appear at intermediate frequencies. For the local rewiring dynamics, the new nodes that enter the system cannot always find the best nodes to rewire in order to synchronize their states. As a consequence, the emergence of new small clusters of synchronization at different average frequencies is observed. As the system size grows, the number of new clusters also grows. A quantitative analysis reveals that for local rewiring, the algorithm allows for the emergence of hierarchical networks (Gomez Portillo & Gleiser 2009).

In figure 5, we show the adjacency matrices obtained using the local rewiring algorithm for system sizes $N = 100$ and 200. These matrices have also been reordered according to the average frequency $\Omega$ of the oscillators in order to show the presence of overlapping functional modules. It is worth stressing that these matrices strongly resemble the functional modules observed in the synchronization dynamics in the cortical brain network of the cat (Zhou et al. 2006).

An interesting question that arises is to what extent these results depend on the particular choice of the dynamics of the nodes. Recently, Gomez Portillo & Gleiser (2010) analysed the effects of the local rewiring dynamics when the microscopic units of the system are logistic maps, extending the model originally presented by Gong & van Leeuwen (2003). Gomez Portillo & Gleiser (2010) noted a similar qualitative behaviour as observed with phase oscillators. Their results show that the algorithm is robust, and the qualitative properties of the networks that emerge do not seem to depend on the details of the dynamics of the nodes. The fundamental ingredient necessary for the emergence, or absence, of a hierarchical structure seems to reside on the rewiring rules. In the following section, we will compare the results of these theoretical models with empirical evidence from fMRI studies.

4. Hierarchical clustering of a globally rewired, locally rewired and large-scale functional brain network

In the previous section, we showed that when there are no constraints, and the nodes have a global view on the state of the system, then the rewiring of the links results in a preferential connection of that node to a synchronized cluster with an average frequency closest to its natural frequency. As a result, adding nodes to such a network will cause existing synchronized clusters to grow in size and result in a system in which several subsystems are functioning in parallel with minimal overlap. In contrast, rewiring with local constraints may prevent new nodes with a particular natural frequency to connect to the preferred nodes/clusters, and these may end up in a different (local) cluster with a different frequency. As a consequence, clusters with new average frequencies emerge, and such new communities cluster together into larger subsystems, which finally results in a network organization with a hierarchical structure. In figure 6a,b, we display the differences in hierarchical structure between a globally and locally rewired network with 90 nodes. These dendograms were generated by a hierarchical clustering analysis employing Ward’s (1963) method, which uses an analysis of variance approach to determine which observations belong to a particular cluster by minimizing the cluster
error sum of squares. Figure 6 demonstrates that the hierarchical clustering is more pronounced in the locally rewired network (b) than in the globally rewired network (a).

To compare these dendograms with a dendogram from an actual functional brain network, we used fMRI data acquired during quiet wakefulness (resting state) from 25 subjects (see Spoormaker et al. (2010) for a description of the data and preprocessing steps). We generated one average correlation matrix of 90 cortical and subcortical regions defined according to the automated anatomical labelling (AAL) (Tzourio-Mazoyer et al. 2002). The hierarchical clustering analysis was performed on the correlation matrix with the same method, see figure 6c. The results of the hierarchical clustering analysis of the functional brain network appear more similar to a locally (b) than a globally (a) rewired network.

It is interesting to note that the hierarchical clustering analysis of the functional brain network demonstrates a hierarchical organization of a large-scale human functional brain network that consists of two main branches: the upper branch contains the subcortical, limbic and paralimbic regions and the lower branch
contains the neocortical association and primary sensory cortices. The lower branch further splits into a cluster consisting of visual cortices and into a cluster that contains other primary sensory, such as the auditory and (pre)motor clusters. The lowest two clusters are a temporal-precuneus and a frontoparietal cluster. In line with Salvador et al. (2005) and Ferrarini et al. (2009), we observe several clusters that are grouped according to anatomy, with the subcortical, limbic and occipital clusters as examples. Yet at the same time, in line with studies on resting-state networks as derived from resting-state fMRI (Damoiseaux et al. 2006; Fox & Raichle 2007), we also observe long-distance connectivity between other regions, which is manifested in, for instance, the frontoparietal cluster. A model in which rewiring takes place with local restraints provides a greater understanding of such results, and can explain both the observed hierarchical structure and the branching of the clusters into a tree with high face validity and a remarkable overlap with the functional anatomy of resting-state networks.

5. Discussion

In this work, we presented an analysis of the brain from a complex-network point of view. We replicated previously reported findings on the functional modules in a low-frequency functional brain network derived from 90 predefined cortical and subcortical nodes. We further presented a complex-network model with dynamical nodes and adaptive links that allows for the emergence of complex-network structures; the dynamical rules of the model show a robust behaviour that does not seem to depend on the particular dynamics of the nodes. For a global rewiring dynamics, where each new node uses information on the state of all the other nodes in the system, non-hierarchical networks emerge. On the other hand, for a restricted local dynamics, where each new node can only access information through its neighbours, hierarchical structures are observed to emerge. When we compared the results of this model with the hierarchical structure observed in a group analysis of a large-scale functional brain network, we noted the presence of several clusters with long-distance and local connectivity. These clusters show an overlap with so-called resting-state networks, and the hierarchical structure suggests a network organization in which nodes are rewired with local constraints. In this manner, the proposed algorithm may provide insight into which mechanisms dominate in the presence (or absence) of a hierarchical structure observed in functional brain networks, and could be relevant for understanding the development of the brain.

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References


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