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Modeling the outcome of structural disconnection on resting-state functional connectivity

Joana Cabral [a,b,*], Etienne Hugues [a], Morten L. Kringelbach [b,c], Gustavo Deco [a,d]

[a] Center of Brain and Cognition, Theoretical and Computational Neuroscience Group, Universitat Pompeu Fabra, Barcelona, Spain
[b] Department of Psychiatry, University of Oxford, Oxford, UK
[c] Center of Functionally Integrative Neuroscience (CFIN), Aarhus University, Denmark
[d] Institut Català de Recerca i Estudis Avançats, Barcelona, Spain

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ABSTRACT

A growing body of experimental evidence suggests that functional connectivity at rest is shaped by the underlying anatomical structure. Furthermore, the organizational properties of resting-state functional networks are thought to serve as the basis for an optimal cognitive integration. A disconnection at the structural level, as occurring in some brain diseases, would then lead to functional and presumably cognitive impairments.

In this work, we propose a computational model to investigate the role of a structural disconnection (encompassing putative local/global and axonal/synaptic mechanisms) on the organizational properties of emergent functional networks. The brain's spontaneous neural activity and the corresponding hemodynamic response were simulated using a large-scale network model, consisting of local neural populations coupled through white matter fibers. For a certain coupling strength, simulations reproduced healthy resting-state functional connectivity with graph properties in the range of the ones reported experimentally. When the structural connectivity is decreased, either globally or locally, the resultant simulated functional connectivity exhibited a network reorganization characterized by an increase in hierarchy, efficiency and robustness, a decrease in small-worldness and clustering and a narrower degree distribution, in the same way as recently reported for schizophrenia patients. Theoretical results indicate that most disconnection-related neuropathologies should induce the same qualitative changes in resting-state brain activity.

Introduction

The spatial patterns observed in brain activity during rest are thought to be shaped by the underlying anatomical structure (Bullmore and Sporns, 2009; Jirsa et al., 2010; Skudlarski et al., 2008). The availability of whole-brain maps of anatomical connections (Hagmann et al., 2008; Kötter, 2004; Sporns et al., 2005) together with computational models of the brain's large-scale neural dynamics have shed light on the relationship between anatomical and functional connectivity (Cabral et al., 2011; Deco et al., 2009; Ghosh et al., 2008; Honey et al., 2007, 2009). Importantly, models can be used to predict the effects of structural alterations on brain dynamics (Alstott et al., 2009; Honey and Sporns, 2008), which is beyond reach on the experimental side, making models a unique tool for the comprehension of brain diseases.

Brain networks have been widely studied by means of graph theory (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010), whether derived from white-matter connections (anatomical networks) or from temporal correlations (functional networks) between brain areas. The application of graph theoretical measures to functional networks derived from blood oxygenation level-dependent (BOLD) signals measured using functional magnetic resonance imaging (fMRI) during rest has shown clinical relevance. Indeed, this procedure has revealed significant alterations in the resting-state patterns of patients with neuropathologies such as schizophrenia (Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010) and Alzheimer's disease (Supekar et al., 2008), among others.

In this study, we focus on the effects of a structural disconnection on resting-state functional networks. Resting-state functional connectivity is investigated using a model of large-scale ongoing brain neural activity. The model consists of local neural populations dynamically coupled via white-matter anatomical pathways. The coupling weights between neural populations scale the long-distance excitatory strength between brain regions considering simultaneously two factors: 1) the number of white matter fiber tracts detected between those regions using DTI/DSI tractography and 2) the excitatory synaptic weights. From the simulated ongoing brain activity, we estimated the hemodynamic response and computed functional

* Corresponding author at: Universitat Pompeu Fabra, Roc Boronat, 138, 08018 Barcelona, Spain. Fax: +34 93 542 2451.
E-mail address: juanitacabral@hotmail.com (J. Cabral).

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connectivity matrices. Subsequently, simulated functional networks were characterized using graph theory following the methodology from Lynall et al. (2010) for a reliable comparison. In a first step, using a healthy anatomical connectome, we study how the topological organization of simulated functional networks depends on the global structural coupling strength. For a range of coupling strengths, the simulated functional networks were found to have graph properties similar to the ones reported for healthy controls in the work of Lynall et al. (2010). Subsequently, the effects of a pathological disconnection were simulated in two different ways: either by globally decreasing the coupling strength, or by randomly pruning anatomical connections. Theoretical results indicate that, in the model, all disconnections should induce the same qualitative changes.

Schizophrenia is a disorder which has been hypothesized to be related with disconnection effects, and so we have compared our results with experimental measures from schizophrenia patients (Lynall et al., 2010). We found that the reorganization of resting-state functional networks observed between healthy volunteers and people with schizophrenia can be explained by a structural disconnection, both schemes leading to similar results. Overall, these results support the hypothesis that the functional network alterations underlying schizophrenia are caused by a disconnection (encompassing putative local/global axonal/synaptic mechanisms), in agreement with current theories of schizophrenia (Bullmore et al., 1997; Friston and Frith, 1995; Skudlarski et al., 2010; Stephan et al., 2006; Wernicke, 1906; Winterer and Weinberger, 2004; Zalesky et al., 2011). Taken beyond the schizophrenia disorder, our results could provide a new light towards the understanding of altered resting-state functional connectivity occurring in other mental illnesses characterized by disconnection.

Methods

Anatomical connectivity

The brain's anatomical connectivity (AC)—or connectome—is defined as the map of neural connections in the brain. In low-resolution maps such as the ones used here, nodes correspond to segregated brain regions and links are derived from the white matter anatomical pathways interconnecting them. These networks have shown to be a key ingredient to models of resting-state functional connectivity (Cabral et al., 2011; Honey et al., 2009). Given that results can be influenced by the parcellation scheme (Bassett et al., 2011; Zalesky et al., 2010), we used two distinct structural networks (see Fig. 1) in order to be able to generalize: one with $N=90$ brain regions defined using the Automated Anatomical Labelling (AAL) template from Tzourio-Mazoyer et al. (2002), and another with $N=66$ brain regions derived by Hagmann et al. (2008). In both networks, the connectivity strength C_{np} from region p to region n was assumed to be proportional to the number of fibers incoming to region n and inversely proportional to the size of that region (as in Cabral et al. (2011)).

The anatomical brain network with 90 regions was constructed using diffusion tensor imaging (DTI) from the brains of 21 healthy participants following the methodology from Gong et al. (2009). For each subject, a 90×90 weighted network was constructed. Networks were then averaged across subjects resulting in a reliable representation of the anatomical organization of cerebral cortex (see *Supplementary Information (SI)-Methods* for details). For this network, the distance D_{np} between a pair of regions was taken as the Euclidean distance between the corresponding centers of gravity in the AAL template.

The network with 66 regions, previously used in resting-state computational models in Honey et al. (2009) and Cabral et al. (2011), was derived from diffusion spectrum imaging (DSI) by Hagmann et al. (2007) according to the Freesurfer parcellation scheme (surfer.nmr.mgh.harvard.edu (Desikan et al., 2006)) and averaged over 5 healthy subjects. In this case, the distance D_{np} between two regions was given as the average length of the fibers detected connecting these two regions.

The AC in both parcellation schemes, AC_{66} and AC_{90}, is given by the matrices C and D (see Figs. 1B–C).

Simulating disconnection

In the model, local neural networks are connected with each other according to the weight matrix K with $K_{np}=\frac{k}{c_1}C_{np}$. In general, disconnection implies that some or all of these weights decrease, meaning that the disconnected weight matrix K^d has coefficients $K^d_{np}\leq K_{np}$. As there is an infinite number of ways to implement disconnection, we chose two representative examples of it. Note that the specific type of disconnection occurring in a particular disease or in particular patients is out of the scope of the present paper, in which we are interested in the general effects of disconnection on the graph properties of functional networks.

As a first implementation of disconnection, all weights decrease in equal proportion, which is done by decreasing the global coupling strength k ($K^g=(\frac{K_g}{C_1})\ C$, where $k^g<k$). In a second implementation, we have chosen to remove links randomly from the original structural matrix $C_{90\times90}$, a method called random pruning. To simulate the progression of a disconnection disease, we generated a sequence of pruned matrices $C^p_1, \ldots, C^p_m, \ldots, C^p_M$ from the original one, where at each sequence step, a fixed number of links was removed randomly. The corresponding weight matrices write $K^p_m=(\frac{k}{C_1})\ C^p_m$, where the original prefactor k is kept unchanged. Choosing to remove 1% of the total possible links of the binary $C_{90\times90}$ (that is 0.01 $(90)^2=81$ links), which has about 39% of the possible links, a sequence of $M=39$ pruned matrices was generated.

Neural dynamics model

To obtain the BOLD signal during rest, we first simulated the brain's spontaneous neural activity. The model simulates the activity of a network of N brain regions—or nodes—each representing a local network of excitatory and inhibitory neurons. The main assumption of the model is that functional connectivity at the brain-scale level emerges mainly through the interplay between the long-distance brain connectivity and the local node dynamics. For simplicity, the neural networks within a node were assumed to be homogeneous, that is without a specific structure. The nodes are connected via the known AC, given by the $N\times N$ matrices of connection strengths C and inter-regional distances D. We calculate the conduction delay matrix τ dividing the distances by a chosen conduction velocity V ($V=10$ m/s here).

The model is further defined by specifying the dynamics at the node level and how these nodes interact. According to many studies, local neural networks are considered to be in a stable asynchronous state, meaning that neurons tend to fire irregularly and out of synchrony and, in response to a constant input, the network firing rate always decays towards a constant value. Assuming that during rest the mean level of external stimulations remains constant, we hypothesize that the perturbations of neural activity around the constant asynchronous state are small. Therefore, dynamical equations for the evolution of the neural network's firing rate can be written by considering only their linearized version. These equations describe the dynamics of firing rate deviations of local neural networks around their asynchronous state.

To derive the local node dynamical equations, we use a theoretical framework introduced in Mattia and Del Giudice (2002) which describes the dynamics of a neural network. Considering a homogeneous network of neurons, the Fokker–Planck equation (Risken, 1989) describes the temporal evolution of the probability distribution of the neuronal variables over the neural network population. An associated equation gives the neural population firing rate. In this