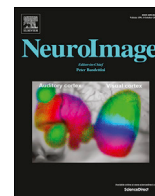


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Resting state networks in empirical and simulated dynamic functional connectivity



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ABSTRACT

It is well-established that patterns of functional connectivity (FC) - measures of correlated activity between pairs of voxels or regions observed in the human brain using neuroimaging - are robustly expressed in spontaneous activity during rest. These patterns are not static, but exhibit complex spatio-temporal dynamics. Over the last years, a multitude of methods have been proposed to reveal these dynamics on the level of the whole brain. One finding is that the brain transitions through different FC configurations over time, and substantial effort has been put into characterizing these configurations. However, the dynamics governing these transitions are more elusive, specifically, the contribution of stationary vs. non-stationary dynamics is an active field of inquiry. In this study, we use a whole-brain approach, considering FC dynamics between 66 ROIs covering the entire cortex. We combine an innovative dimensionality reduction technique, tensor decomposition, with a mean field model which possesses stationary dynamics. It has been shown to explain resting state FC averaged over time and multiple subjects, however, this average FC summarizes the spatial distribution of correlations while hiding their temporal dynamics. First, we apply tensor decomposition to resting state scans from 24 healthy controls in order to characterize spatio-temporal dynamics present in the data. We simultaneously utilize temporal and spatial information by creating tensors that are subsequently decomposed into sets of brain regions (“communities”) that share similar temporal dynamics, and their associated time courses. The tensors contain pairwise FC computed inside of overlapping sliding windows. Communities are discovered by clustering features pooled from all subjects, thereby ensuring that they generalize. We find that, on the group level, the data give rise to four distinct communities that resemble known resting state networks (RSNs): default mode network, visual network, control networks, and somatomotor network. Second, we simulate data with our stationary mean field model whose nodes are connected according to results from DTI and fiber tracking. In this model, all spatio-temporal structure is due to noisy fluctuations around the average FC. We analyze the simulated data in the same way as the empirical data in order to determine whether stationary dynamics can explain the emergence of distinct FC patterns (RSNs) which have their own time courses. We find that this is the case for all four networks using the spatio-temporal information revealed by tensor decomposition if nodes in the simulation are connected according to model-based effective connectivity. Furthermore, we find that these results require only a small part of the FC values, namely the highest values that occur across time and ROI pair. Our findings show that stationary dynamics can account for the emergence of RSNs. We provide an innovative method that does not make strong assumptions about the underlying data and is generally applicable to resting state or task data from different subject populations.

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1. Introduction

The question of how large-scale cortical function arises from underlying anatomical connectivity has been the object of much investigation since the advent of non-invasive imaging techniques (Vincent et al., 2007; Matsui et al., 2011; Wang et al., 2013), in particular since it was discovered that interareal functional relationships found under task conditions are maintained during rest (Biswal et al., 1995; Cordes et al., 2000; Beckmann and Smith, 2004; Fox et al., 2005). With magnetic resonance imaging (MRI) it is possible to obtain both functional and structural connectivities (FC and SC, respectively). Although there is large variability across subjects and sessions, both in SC (Heiervang et al., 2006) and FC measures (Mueller et al., 2013; Finn et al., 2015), studies using group averages have revealed general principles of information processing in the brain (Raichle et al., 2001; Doucet et al., 2011; Van den Heuvel and Sporns, 2011; Deco and Jirsa, 2012; Haimovici et al., 2013).

In order to connect SC and FC, computational models are an important tool for understanding how activity propagates from one node to another to produce the observed data (Honey et al., 2009; Cabral et al., 2012; Deco et al., 2014a,b). Most models optimize their parameters by fitting the average FC. Only recently, the question of whether and how relevant information can be extracted from the spontaneous fluctuations in pairwise FC strength, and how to describe the richness of the temporal dynamics, has received increasing attention in data analysis (Chang and Glover, 2010; Hutchison et al., 2012; Allen et al., 2012; Tagliazucchi et al., 2012a,b; Liu et al., 2013; Leonardi and Van de Ville, 2013a; Zalesky et al., 2014; Yaesoubi et al., 2015) and modelling (Hansen et al., 2014; Ponce-Alvarez et al., 2015). This has led to the notion of dynamic functional connectivity (dFC); dFC has been shown to be relevant for behavior (Kucyi et al., 2013; Kucyi and Davis, 2014; Barttfeld et al., 2015; Chen et al., 2015; Yang et al., 2014), development (Madhyastha and Grabowski, 2014; Hutchison and Morton, 2015; Tagliazucchi et al., 2016; Marusak et al., 2017), and disorders (Damaraju et al., 2014; Wee et al., 2016; Miller et al., 2016; Rashid et al., 2014; Sourty et al., 2016; Demirtaş et al., 2016) and is therefore likely to have a basis in neural activity.

Here, we use a dynamic mean field model (Wong and Wang, 2006) of the human cortex which has been shown to reproduce average resting state (RS) FC (Deco et al., 2014a,b). It is our goal to determine whether simulated data exhibit FC patterns over time that resemble those of empirical data. Specifically, we want to test whether resting state networks (RSNs) can be explained in this way. To this end, we analyze RS data from 24 healthy subjects (Schirner et al., 2015) and compare to simulated data. The cortex is modelled by 66 nodes corresponding to 66 brain areas also used to parcellate the empirical data. The nodes are connected according to empirical SC derived from the same subjects via diffusion weighted MRI and fiber tracking.

We use tensor decomposition for extracting relevant and general features of the spatio-temporal dynamics. This method has been shown to work well for community detection (Gauvin et al., 2014) and has been applied to brain data (Cichocki, 2013; Leonardi and Van de Ville, 2013a; Ponce-Alvarez et al., 2015; Leonardi and Van De Ville, 2013b). Unlike ICA, which has become the standard method for extracting RSNs (McKeown et al., 1998; Beckmann et al., 2005; Mantini et al., 2007), tensor factorization does not assume spatial independence of the underlying components, which is a strong constraint not directly motivated by the data. Here, such a constraint is not required and the space of possible solutions is not unnecessarily restricted. Furthermore, it has the advantage that it can readily be used at our level of spatial resolution.

The modelling approach aims at linking FC and SC. One conceptual problem of SC is that it provides neither directionality information nor the weights of the connections. These two points are addressed by the concept of effective connectivity (EC). SC can be viewed as an approximation to EC, and it is the latter that is genuinely related to the dynamics in network models (Friston, 1994). Reversely, underlying connectivity (SC or EC) can be inferred from FC, or more generally, from the dynamics

found in the data, through the same kinds of models. Gilson et al. (2016) developed a method to extract EC from RS fMRI data using a noise diffusion model which possesses simpler dynamics than the DMF. They show that the EC that accounts best for empirical FC significantly differs from the SC in a number of points. We use both SC and EC as underlying connectivity in our model and explore how their properties are linked to the spatio-temporal patterns found in empirical and simulated data.

2. Methods

2.1. Empirical data

RS fMRI as well as corresponding diffusion weighted (dw) MRI data were collected from 24 healthy participants (11 female) at the Charité Berlin, Germany, by Petra Ritter and co-workers. The original dataset consisted of 49 subjects, but we chose only those aged 18–35 years (mean 25.7 years) since it is known that FC changes with age (Meunier et al., 2009). Each fMRI dataset amounts to 661 time points recorded at $TR = 2s$, i.e. about 22 min. In the same session, EEG was also recorded, but we do not use the data here. RS BOLD was recorded while subjects were asked to stay awake with their eyes closed, using a 3T Siemens Trim Trio scanner and a 12 channel Siemens head coil (voxel size $3 \times 3 \times 3$ mm). Voxel time courses are averaged inside ROIs defined by the Desikan-Killiany atlas (Desikan et al., 2006) as implemented in FreeSurfer. We removed the areas labeled as corpus callosum on both sides since they only contain white matter, amounting to 33 cortical ROIs for each hemisphere. See Table S1 for details.

The diffusion tensors ($TR = 750$ ms, voxel size $2.3 \times 2.3 \times 2.3$ mm) computed from the dwMRI data recorded with 64 gradient directions were subjected to probabilistic fiber tracking as implemented in MRTrix (Tournier et al., 2004, 2007) in order to obtain structural connectivity (SC) matrices for each subject. Masks derived from high-resolution T1-images were used to determine seed- and stop-locations for fibers in the grey matter/white matter-interface (GWI). SC matrices contain connection strengths which are estimated by combining the number of streamlines obtained from the fiber tracking algorithm with various assumptions based on known limitations imposed by anatomy, notably the size of the GWI of each region. We use the average over all 24 subject in our simulations.

Further details are available in Schirner et al. (2015).

2.2. Model data

A dynamic mean field approximation of a network of populations of

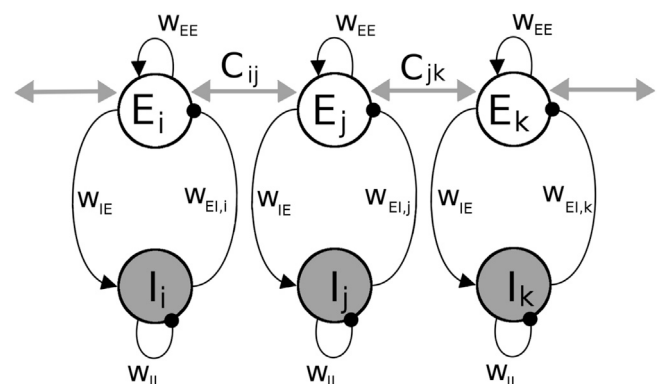


Fig. 1. Schematic view of dynamic mean field (DMF) model used to simulate synaptic activity. Each brain area is modelled by a pair of excitatory (E) and inhibitory (I) pools. The local connectivity is governed by the four weights w_{EE} , $w_{EI,i}$, w_{IE} , and w_{II} , whereby $w_{EI,i}$ is adjusted for each population individually so as to keep the firing rates at a low level (3–10 Hz). Black lines with spheres signify GABA connections, black arrows, NMDA. Grey arrows are long range connections mediated by AMPA synapses and whose weights are set by the entries ij of the SC or EC matrix, C .

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