



Functional connectivity dynamics: Modeling the switching behavior of the resting state



Enrique C.A. Hansen^{a,1}, Demian Battaglia^{a,b,*}, Andreas Spiegler^a, Gustavo Deco^c, Viktor K. Jirsa^{a,*}

^a Université Aix-Marseille, INSERM UMR 1106, Institut de Neurosciences des Systèmes, 27 Bd Jean Moulin, 13005 Marseille, France

^b Bernstein Center for Computational Neuroscience, Am Faßberg 17, 37077 Göttingen, Germany

^c Center for Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain

ARTICLE INFO

Article history:

Accepted 3 November 2014

Available online 10 November 2014

Keywords:

Functional connectivity

Functional connectivity dynamics

Structural connectivity

Resting state

Brain dynamics

Whole brain computational model

ABSTRACT

Functional connectivity (FC) sheds light on the interactions between different brain regions. Besides basic research, it is clinically relevant for applications in Alzheimer's disease, schizophrenia, presurgical planning, epilepsy, and traumatic brain injury. Simulations of whole-brain mean-field computational models with realistic connectivity determined by tractography studies enable us to reproduce with accuracy aspects of average FC in the resting state. Most computational studies, however, did not address the prominent non-stationarity in resting state FC, which may result in large intra- and inter-subject variability and thus preclude an accurate individual predictability. Here we show that this non-stationarity reveals a rich structure, characterized by rapid transitions switching between a few discrete FC states. We also show that computational models optimized to fit time-averaged FC do not reproduce these spontaneous state transitions and, thus, are not qualitatively superior to simplified linear stochastic models, which account for the effects of structure alone. We then demonstrate that a slight enhancement of the non-linearity of the network nodes is sufficient to broaden the repertoire of possible network behaviors, leading to modes of fluctuations, reminiscent of some of the most frequently observed Resting State Networks. Because of the noise-driven exploration of this repertoire, the dynamics of FC qualitatively change now and display non-stationary switching similar to empirical resting state recordings (Functional Connectivity Dynamics (FCD)). Thus FCD bear promise to serve as a better biomarker of resting state neural activity and of its pathologic alterations.

© 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-SA license (<http://creativecommons.org/licenses/by-nc-sa/3.0/>).

Introduction

The complexity of human cognition is echoed in the dynamic organization of its accompanying brain signals. Even at rest, the brain does not remain in a state of equilibrium, but reveals complex spontaneous dynamics with intermittent spatiotemporal fluctuation patterns. In fact, functional magnetic resonance imaging (fMRI) studies have demonstrated that in the absence of an overt task, fluctuations in the blood oxygenation-level dependent (BOLD) fMRI signals correlate across

functionally related brain regions in task conditions (Gusnard and Raichle, 2001; Laird et al., 2011; Raichle and Mintun, 2006). Further studies identified several intrinsic *resting state networks* (RSNs), which are found across subjects (Damoiseaux and Greicius, 2009), correlate with neuroelectric activity (Britz et al., 2010; Mantini et al., 2007) and are shaped, though not fully determined, by structural connectivity (SC) (Damoiseaux and Greicius, 2009).

Modeling studies (Deco et al., 2009; Deco et al. 2011; Ghosh et al., 2008; Honey et al., 2007) have demonstrated the importance of the interplay between anatomical structure, local neural dynamics and noise in the emergence of resting-state inter-regional correlations described by functional connectivity (FC) (Friston, 2011). Many of these models (Deco and Jirsa, 2012; Deco et al., 2013a; Ghosh et al., 2008) operate at a working point close to the critical edge of instability (Deco et al., 2013b). They are easily implemented within dedicated simulation environments such as The Virtual Brain (Sanz Leon et al., 2013) and are capable of reproducing time-averaged resting state FC. It has been pointed out, however, that purely statistical models, which predict FC on the basis of local and global descriptors of SC-weighted networks alone, are able to achieve a comparable or even closer fit (Goñi et al., 2014; Messé et al., 2014). This means that previous dynamic models went

Abbreviations: SC, structural connectivity; FC, functional connectivity; FCD, functional connectivity dynamics; MFM, mean-field model; LSM, linear stochastic model; eMFM, enhanced non-linearity mean-field model; RSN, resting state network; DSI, diffusion spectrum imaging; fMRI, functional magnetic resonance imaging; BOLD, blood oxygenation-level dependent.

* Corresponding authors at: Université Aix-Marseille, INSERM UMR 1106, Institut de Neurosciences des Systèmes, 27 Bd Jean Moulin, 13005 Marseille, France.

E-mail addresses: enrique-carlos.hansen@etu.univ-amu.fr (E.C.A. Hansen), demian.battaglia@univ-amu.fr (D. Battaglia), andreas.spiegler@univ-amu.fr (A. Spiegler), gustavo.deco@upf.edu (G. Deco), viktor.jirsa@univ-amu.fr (V.K. Jirsa).

¹ These authors contributed equally to this work.

scarcely beyond the exploration of how the SC skeleton expresses itself in spontaneous neural activity.

One drawback of all of these studies is that they assume –often implicitly– that FC is spatiotemporally stationary. In doing so, they ignore the profound non-stationarity of resting state activity (Hutchison et al., 2013). This activity possibly mirrors free thought modalities (Doucet et al., 2012) associated to neural activity events localized in space and time or to faster electrophysiological processes (Liu and Duyn, 2013), which are necessarily overlooked when averaging correlations throughout long recording periods. Thus models able to go beyond the mere replication of the constraints exerted by SC on FC are required to account for the time-dependence of FC.

Through simulations of computational models in a subcritical regime of activity, we show how the noise-driven exploration of a broad landscape of possible dynamical behaviors results in rapid switching between a discrete number of multistable FC states. This switching in turn gives rise to spatial correlation patterns reminiscent of known RSNs. Hence our approach offers a plausible interpretational framework for the non-stationarity of FC. In short, we propose that resting state Functional Connectivity Dynamics (FCD) are a manifestation of the self-organized activity of cortical networks, in which noise-driven fluctuations far from equilibrium lead to the stochastic sampling of a rich repertoire of characteristic system's trajectories.

Materials and methods

All empirical data used herein stem from a well-investigated data set as presented in Hagmann et al. (2008), comprising structural data from five healthy subjects and its associated time-series of resting state BOLD signals. In the following we organized the Materials and Methods into three subsections: on Connectivity, Mathematical Models, and Analyses.

Connectivity

Structural connectivity

Structural Connectivity is the set of anatomical connections between brain regions. Here we used the SC matrix of 66 regions derived from Diffusion Spectrum Imaging (DSI) as previously published and detailed in Hagmann et al. (2008) with the modifications introduced by Cabral et al. (2011), which made this matrix slightly asymmetrical. Connections in this SC matrix were defined within a standard parcellation scheme (Desikan et al., 2006) and averaged over five healthy subjects. Table S1 provides the names and abbreviations of these Regions Of Interest (ROIs). We analyzed the SC matrix using graph theoretical measures (Rubinov and Sporns, 2010), to assess correspondences with neural activity patterns. In particular, we calculated the *in-strength* of each network node, that is the sum of the weights of the incoming connections (the sum of all the entries in each row of the SC matrix) to determine the local topology of individual brain regions. A second approach called *s-core decomposition* (described in Hagmann et al. (2008)) provided insight into more global correlations between the in-strength of different nodes in the network. The *s-core* is a connected subnetwork in which nodes have an in-strength greater than or equal to *s*. We varied the value of *s* in the range $[0, \hat{s}]$, where \hat{s} is the maximum value of all entries of the SC.

Functional connectivity

Functional Connectivity (FC) describes the connectedness of two brain regions by means of the covariance between their time series. From the BOLD signals, we extracted a FC matrix by calculating the Pearson (zero-lag) correlation between the BOLD signals of any two brain regions. In a *static* FC matrix, a single correlation value was computed for each pair of regions across the entire time-series of BOLD signals a 20-min session per subject. Furthermore, we estimated the *time-dependent* FC matrices. Each full-length BOLD signal of 20 min is split up into 570 segments of 60 seconds, overlapping by 58 seconds. For each segment, centered at time *t*, we calculated a separate FC matrix,

$FC(t)$, thereby generating a stream of $FC(t)$ matrices from each session. Similarities between different FC or $FC(t)$ matrices were analyzed by plotting scatter plots of the upper triangular parts of two matrices and evaluating the Pearson correlation coefficient of these scatter plots. The static and time-dependent FC analysis was performed for the recordings of each subject as well as for each computational model based on time-series of 20 min of simulated BOLD signals (see below for details). The statistical significance of the differences between inter-FC correlation values (e.g. the correlations between empirical and simulated static FC matrices at the best-fit point of different models, defined below in the Results section) was tested using a resampling approach (1000 bootstrap replicas of each inter-matrix correlation, obtained by direct resampling with replacement of FC matrix entries).

Functional connectivity dynamics

To capture the spatiotemporal organization of functional connectivity, we derived a novel metric by representing the similarities between $FC(t)$ matrices at different times *t* within a single matrix. We refer to this matrix as the *FC Dynamics (FCD) matrix*. The (t_1, t_2) entry of the FCD matrix provided the Pearson correlation between the upper triangular parts of the two matrices $FC(t_1)$ and $FC(t_2)$. Blocks of elevated inter-FC(t) correlations organized around the FCD matrix diagonal denoted epochs of stable FC configurations. The boundaries between such blocks were determined by unsupervised clustering of the $FC(t)$ (with the features for clustering provided by their upper triangular parts), using the K-means method (Hartigan and Wong, 1979). Selecting $K = 4$ was sufficient for capturing all the visible blocks and thus thereby separating prominent epochs of stability. Then we operationally defined a *FC state* as a cluster of similar $FC(t)$ matrices, typified by the cluster-average FC matrix.

Please note that our FCD analysis is similar to the meta-recurrence plots first described in (Manuca and Savit, 1996), constructed by comparing different chunks of the signals themselves, rather than their correlation matrices. We also computed meta-recurrence plots of activity, based on vectors of BOLD signals averaged for the different regions over the same time-windows used for a parallel FCD analysis. Please note that we retained the BOLD baselines in the signals and computed the cross-correlation (not the cross-covariance) between spatial patterns of window-averaged activity.

Mathematical models

Here we present three computational models of resting state network dynamics: a mean field model (MFM), previously introduced in Deco et al. (2013a); a simple linear stochastic model (LSM), already considered in (Galan, 2008; Goñi et al., 2014; Messé et al., 2014); and, finally, a minimally modified variant of the MFM, in which local nonlinearities are enhanced to introduce bi-stability between a high and low firing rate states (eMFM) at the level of each single brain region.

Dynamical mean-field models (MFM and eMFM)

We used a modified version of the mean-field model designed by Wong and Wang (2006), to describe the mean neural activity for each brain region, following the reduction performed in Deco et al. (2013a). The resulting neural mass equations are given by:

$$\frac{dS_i}{dt} = \frac{-S_i}{\tau_S} + (1-S_i)\gamma R_i + \sigma\eta_i(t) \quad (1)$$

$$R_i = \frac{ax_i - b}{1 - \exp[-d(ax_i - b)]} \quad (2)$$

$$x_i = wJ_N S_i + J_N G \sum_j C_{ij} S_j + I_0 \quad (3)$$

Download English Version:

<https://daneshyari.com/en/article/6026727>

Download Persian Version:

<https://daneshyari.com/article/6026727>

[Daneshyari.com](https://daneshyari.com)