



The connectivity of functional cores reveals different degrees of segregation and integration in the brain at rest

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ABSTRACT

The principles of functional specialization and integration in the resting brain are implemented in a complex system of specialized networks that share some degree of interaction. Recent studies have identified wider functional modules compared to previously defined networks and reported a small-world architecture of brain activity in which central nodes balance the pressure to evolve segregated pathways with the integration of local systems. The accurate identification of such central nodes is crucial but might be challenging for several reasons, e.g. inter-subject variability and physiological/pathological network plasticity, and recent works reported partially inconsistent results concerning the properties of these cortical hubs. Here, we applied a whole-brain data-driven approach to extract cortical functional cores and examined their connectivity from a resting state fMRI experiment on healthy subjects. Two main statistically significant cores, centered on the posterior cingulate cortex and the supplementary motor area, were extracted and their functional connectivity maps, thresholded at three statistical levels, revealed the presence of two complex systems. One system is consistent with the default mode network (DMN) and gradually connects to visual regions, the other centered on motor regions and gradually connects to more sensory-specific portions of cortex. These two large scale networks eventually converged to regions belonging to the medial aspect of the DMN, potentially allowing inter-network interactions.

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Introduction

The existence of a structured pattern of neuronal activity generated in the brain in the absence of an explicit task (i.e. in the resting state) is now a well reported phenomenon. Multiple techniques (e.g. fMRI, MEG) showed that spontaneous, slow (<0.1 Hz) fluctuations of cerebral activity are temporally coherent within widely distributed functional networks that closely resemble those evoked by sensory, motor, and cognitive paradigms (Biswal et al., 1997; de Pasquale et al., 2010, 2012; Fox et al., 2007; He et al., 2008; Nir et al., 2008). Therefore, the two fundamental properties of functional segregation and dynamic integration (Friston, 2002), which have characterized previous models of brain activity focusing at the local scale, i.e. related to specific regions of interest, need now to be integrated in a network model.

Initially, resting state networks (RSN) emerged as segregated functional systems of highly coupled nodes (Biswal et al., 1997; Fox

et al., 2005). The existence of an internal network architecture was later hypothesized in which distinct nodes played different functional roles, a view that has received experimental support by structural and functional connectivity studies (Andrews-Hanna et al., 2007; de Pasquale et al., 2010; He et al., 2007; Iturria-Medina et al., 2008; Tomasi and Volkow, 2010). Finally, recent studies have provided evidence of a consistent interaction across networks over time (de Pasquale et al., 2012; Deshpande et al., 2009, 2011). Therefore, the two original principles of functional specialization and integration seem to be implemented in a complex system of internally structured, and functionally specialized, networks that share some degree of interaction. Consequently, the original distinction in separate resting state networks does not appear to be such a clear cut. As a matter of fact, recent studies based on graph theory have shown the emergence of wider functional modules compared to the originally identified networks, in which components from different networks are grouped together (e.g. motor and auditory areas; see (He et al., 2009; Meunier et al., 2009a, 2009b)). In this context, data from different imaging modalities suggested the small-world architecture (Achard et al., 2006; Bullmore and Sporns, 2009; Stam, 2004) as an efficient model of

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segregation and integration in the brain. According to this model, central nodes, characterized by many local connections and a few distant ones, serve to balance the pressure to evolve segregated pathways with the integration of local networks by minimizing the cost of wiring and metabolism (Bassett et al., 2006).

The accurate localization of such nodes is crucial to understanding the brain functional architecture in healthy aging (Alalade et al., 2011; Galvin et al., 2011; Oghabian et al., 2010; Westlye et al., 2011) as well as in disease (Buckner et al., 2009; Greicius, 2008; Li et al., 2011; Wu et al., 2009). In this work we adopted the term 'core' to identify a node characterized by a high number of connections in the whole brain, while we used the term 'hub' when referring to specific graph theory results (Guimerà and Amaral, 2005; Meunier et al., 2010). The identification of functional cores may be challenging for several reasons. For example, the use of nodes obtained from independent studies may not be the optimal choice, due to both inter-subject variability and to the eventual presence of physiological (e.g. healthy aging) or pathological (e.g. recovery from a brain injury) network plasticity (Castellanos et al., 2011). Furthermore, recent studies based on graph theory analyses have reported interesting, but partially inconsistent, results concerning hub location. The observed discrepancies could be ascribed either to methodological differences (see for example (Buckner et al., 2009; Tomasi and Volkow, 2011a, 2011b)) or to the fact that, due to the computational complexity, these studies are typically based on a limited set of regions of interest within the brain. To overcome these limitations, we have investigated here the architecture of connections involving functional brain cores by using a whole-brain data-driven approach. First, we identified cores based on their statistically significant connections within the brain and their reproducibility across subjects. Then, we proposed a multi-level organization of these cores based on a statistical criterion. Finally, we examined the spatial topography of connections involving the identified cores.

Materials and methods

Experimental setup

Twenty healthy subjects (9 women and 11 men; mean age \pm standard deviation: 30 ± 10 years) provided informed written consent and participated in this study, which was approved by the local ethics committee. The study comprised four consecutive resting state sessions. Subjects were told to stay still and relaxed and no particular instructions were given to attend or fixate a particular stimulus. This strategy was adopted to simulate the acquisition of data from patients whose clinical conditions may not allow them to perform even basic attentional task. More details on this are provided in the Discussion section. The fMRI data were acquired on a 3 T Allegra scanner (Siemens Medical Solutions, Erlangen, Germany) with a maximum gradient strength of 40 mT/m, using a standard quadrature birdcage head coil for both RF transmission and RF reception. The adopted sequence was a gradient echo-EPI, with 38 axial slices with a voxel size of $3 \times 3 \times 3.75$ mm³ (matrix size 64×64 ; FOV 192×192 mm²; TR = 2470 ms) in ascending order. Each resting state session consisted of 100 volumes. Anatomical data consisted of T₁-weighted images obtained in the sagittal plane using a modified driven equilibrium Fourier transform (MDEFT) (16) sequence (TE/TR = 2.4 ms/7.92 ms, flip angle = 15°, voxel size = 1 mm³).

fMRI pre-processing

Our pre-processing pipeline consists of several steps performed using a combination of tools from the FMRIB's Software Library (FSL – <http://www.fmrib.ox.ac.uk/fsl>) and the Physiologic Estimation by Temporal Independent Component Analysis (PESTICA) software (Beall, 2010).

The data are initially motion corrected using the FSL MCFLIRT tool (Jenkinson et al., 2002). Then, physiological respiration and cardiac artifacts were removed by means of PESTICA. This is a data-driven estimator of cardiac and respiratory effects that uses the Infomax algorithm with enforced temporal independence (software available at (www.nitrc.org/plugins/mwiki/index.php/pestica:MainPage)). This approach identifies 4 cardiac and 2 respiratory time-series regressors, based on spatial weighting maps of cardiac and respiratory effects and manual selection of the artifact temporal power-spectrum band. For each individual dataset, we manually estimated the spectral peak range nearest to the suggested maxima of 17 bpm and 60 bpm (respiratory and cardiac peaks, respectively). In the first phase PESTICA estimators are obtained by means of a temporal slice-wise ICA decomposition of the EPI data after the co-registration to the cardiac and respiration templates (see Fig. S1). Then, a fifth order regression is performed on the BOLD data based on the obtained estimators (RETROICOR step). In a final refinement step (IRF-RETROICOR) a principal component analysis (PCA) is applied to extract those regression coefficients explaining most of the variance. The details of this approach can be found in (Beall, 2010). Once the data have been cleaned from the physiological artifacts, the FSL-BET tool was used to estimate a gray matter (GM) mask (Smith, 2002). Eventually, a mean-based intensity normalization of all volumes was performed; high-pass temporal filtering; Gaussian low-pass temporal filtering (FWHM sigma = 2.8); coregistration to the MNI152 standard space (FSL FNIRT tool).

Identification of connectivity cores

The procedure used to identify connectivity cores is schematized in Fig. 1. First, the adopted measure of functional connectivity was based on the Pearson correlation coefficient computed between BOLD time series and a cross-correlation matrix was obtained for each subject and session including all the voxels in the estimated gray matter mask ($N_{\text{voxel}} = 36571$ within the brain 54% of which within the gray matter), see Fig. 1A in which the first session of a representative subject is reported). After the PESTICA step no further regression to remove a global mean signal was performed (as in (Fox et al., 2005)). Typically, global signal regression is performed to remove common fluctuations associated with nuisance variables, e.g. respiration. However, here such fluctuations have already been removed by PESTICA, in which the regression steps are carefully implemented in order to maintain the signal variance as high possible (Beall, 2010). In addition, it has been argued that the global signal regression could have controversial effects on the correlation values ((Cordes et al., 2001; Guo et al., 2012; Murphy et al., 2009), see 'Methodological concerns' of the Discussion section).

Second, the cross-correlation matrix was Fisher transformed to obtain normally distributed values. From these values, z-scores from a $N(0,1)$ distribution were computed by normalizing the variance and subtracting a baseline value corresponding to the average connectivity among all the possible pairs of voxels within the gray matter.

Third, since we assume that a candidate core shows connections statistically stronger than the baseline value, core identification was performed through a hypothesis test with $H_0: z = 0$. The test was corrected for multiple comparisons using the false discovery rate (Benjamini and Hochberg, 1995) and performed at three different significance levels, namely $\alpha = [0.01, 0.02, 0.05]$. In this way, the obtained cores could be ranked based on the strength of their connections at each level of significance. This step was repeated for each session and subject. In Fig. 1B we show the distribution of z and the threshold obtained for a representative session of one subject (inset panel-shaded red area).

Fourth, for each subject, a binary mask was generated for those voxels passing the test at each statistical level in each session. The resulting four masks were multiplied together (logical AND) across

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