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Estimates of segregation and overlap of functional connectivity networks in the human cerebral cortex

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ABSTRACT

The organization of the human cerebral cortex has recently been explored using techniques for parcellating the cortex into distinct functionally coupled networks. The divergent and convergent nature of cortico-cortical anatomic connections suggests the need to consider the possibility of regions belonging to multiple networks and hierarchies among networks. Here we applied the Latent Dirichlet Allocation (LDA) model and spatial independent component analysis (ICA) to solve for functionally coupled cerebral networks without assuming that cortical regions belong to a single network. Data analyzed included 1000 subjects from the Brain Genomics Superstruct Project (GSP) and 12 high quality individual subjects from the Human Connectome Project (HCP). The organization of the cerebral cortex was similar regardless of whether a winner-take-all approach or the more relaxed constraints of LDA (or ICA) were imposed. This suggests that large-scale networks may function as partially isolated modules. Several notable interactions among networks were uncovered by the LDA analysis. Many association regions belong to at least two networks, while somatomotor and early visual cortices are especially isolated. As examples of interaction, the precuneus, lateral temporal cortex, medial prefrontal cortex and posterior parietal cortex participate in multiple paralimbic networks that together comprise subsystems of the default network. In addition, regions at or near the frontal eye field and human lateral intraparietal area homologue participate in multiple hierarchically organized networks. These observations were replicated in both datasets and could be detected (and replicated) in individual subjects from the HCP.

Introduction

Distributed neocortical brain areas form large-scale networks that exhibit complex patterns of divergent and convergent connectivity (e.g., Felleman and Van Essen, 1991; Goldman-Rakic, 1988; Jones and Powell, 1970; Mesulam, 1981; Pandya and Kuypers, 1969; Ungerleider and Desimone, 1986). A major challenge in systems neuroscience is to make sense of these connectivity patterns to infer functional organization. In the visual system, connectivity patterns suggest a separation of processing into largely parallel, but interacting, hierarchical pathways (Felleman and Van Essen, 1991; Ungerleider and Desimone, 1986). In contrast, the association cortex comprises networks of widely distributed and densely interconnected areas without rigid hierarchical organization (Goldman-Rakic, 1988; Selemon and Goldman-Rakic, 1988; but see Badre and D'Esposito, 2009).

Resting-state functional connectivity MRI (rs-fcMRI) provides a powerful, albeit indirect, approach to make inferences about human cortical organization (Biswal et al., 1995). Despite its limitations (Buckner et al., 2013), we and others have used functional connectivity to estimate cortical network patterns (e.g., Bellec et al., 2010; Damoiseaux et al., 2006; He et al., 2009; Margulies et al., 2007; Power et al., 2011; Smith et al., 2009; van den Heuvel et al., 2009; Yeo et al., 2011).

The majority of functional connectivity studies have focused on dissociating functionally distinct networks or modules (Beckmann et al., 2005; Calhoun et al., 2008; Craddock et al., 2012; Damoiseaux et al., 2006; De Luca et al., 2006; Dosenbach et al., 2007; Doucet et al., 2011; Fox et al., 2006; Greicius et al., 2003; Margulies et al., 2007; Rubinov and Sporns, 2011; Salvador et al., 2005; Seeley et al., 2007; Smith et al., 2009; van den Heuvel et al., 2009; Varoquaux et al., 2011). Fewer studies have examined the relationships among different functional networks (Sepulcre et al., 2012a; Sporns, 2013). For example, Fox et al. (2005) and Fransson (2005) have investigated the antagonistic relationship between the default and task-positive networks. Others (Doucet et al., 2011; Lee et al., 2012; Meunier et al., 2009) have investigated the (spatial) hierarchical relationship across functional networks.

We previously employed a mixture model that relied on a winner-takes-all assumption to map network topography in the human cerebral cortex (Yeo et al., 2011). Each brain region was assigned to a single, best-fit network allowing us to derive connectivity maps that emphasize the

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interdigitation of parallel, distributed association networks. The key features of this parallel organization are that (1) each association network consists of strongly coupled brain regions spanning frontal, parietal, temporal, and cingulate cortices, and (2) the components of multiple networks are spatially adjacent (Yeo et al., 2011; also see Vincent et al., 2008; Power et al., 2011).

However, it is unlikely that the brain is simply parcellated into a discrete number of nonoverlapping networks (Mesulam, 1998). Interactions across networks, as well as the existence of 'convergence zones' of regions that participate in multiple networks, are likely important features of brain organization (Beckmann et al., 2005; Bullmore and Sporns, 2009; Fornito et al., 2012; Jones and Powell, 1970; Mesulam, 1998; Pandya and Kuypers, 1969; Power et al., 2013; Sepulcre et al., 2012b; Spreng et al., 2010). Relevant to this point, we have observed variability in the goodness of fit of certain regions to their winner-takes-all network (Figs. 8 and 10 of Yeo et al., 2011), consistent with the notion that certain brain regions might participate in multiple networks (Andrews-Hanna et al., 2010; Beckmann et al., 2005; Leech et al., 2011; Rubinov and Sporns, 2011; Sporns et al., 2007).

Here, we address the possibility of multiple network membership by applying latent Dirichlet allocation (LDA; Blei et al., 2003) and spatial Independent Component Analysis (ICA; Calhoun et al., 2001; Beckmann and Smith, 2004) to examine the topography of overlapping networks. This is an important consideration because network topography may change substantially from our original estimates (Yeo et al., 2011) if constraints are relaxed to permit overlapping networks. Conversely, unbiased estimation of network topography may broadly confirm previous estimates and allow us to investigate the interactions and overlaps among networks.

Materials and methods

Overview

We applied the LDA model to resting-state data from 1000 healthy young adults from the Brain Genomics Superstruct Project (GSP), as well as to 12 high quality, high-resolution individual subject datasets from the Human Connectome Project (HCP; Van Essen et al., 2013). The large sample size in GSP and the multiple sessions of individual HCP subjects permitted us to quantify patterns of cortico-cortical coupling that reveal insights into interactions within and across functional networks. Analyses proceeded in four stages. First, we applied the mixture model (Yeo et al., 2011) and LDA model (Blei et al., 2003) to both the GSP and HCP group datasets, in order to examine how cortical network organization changes as regions are permitted to participate in multiple networks (Fig. 1). For this analysis, the GSP and HCP datasets were used to provide independent replication samples. Next, we further analyzed several cortical regions participating in multiple sub-networks (Figs. 2 to 4). We then exploited the high quality, multi-session HCP data to determine if network organization can be estimated and replicated in individual subjects (Figs. 5 and 6). This increased the confidence that the discovered network organization was not merely a consequence of averaging across subjects. Additional control analyses confirmed similar network organization regardless of whether global signal regression was performed during preprocessing (Supplemental Fig. 7) and across degenerate (i.e., not highest likelihood) network estimates (Figs. 7 and 8).

Datasets

The GSP subjects were between ages 18–35 (mean age = 21.3; 42.7% male). Participants underwent one or two runs of eyes open rest (EOR). Analyses of the GSP data have been published previously (e.g., Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011). The HCP subjects were between ages 26–35 (mean age estimate = 30.9; 16.7% male). HCP provides aggregated data concerning age, hence mean age can only be estimated. HCP participants underwent two runs of passive fixation (FIX) in each of two separate sessions, for a total of four runs (~24 h interval between sessions).

GSP MRI data acquisition and preprocessing

Data were acquired on 3 T Tim Trio scanners (Siemens, Erlangen, Germany) using a 12-channel phased-array head coil. Functional data consisted of gradient-echo echo-planar images (EPI) sensitive to blood oxygenation level-dependent (BOLD) contrast. Parameters for the resting data were: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle (FA) = 85°, 3 × 3 × 3 mm voxels, field of view (FOV) = 216, and 47 axial slices collected with interleaved acquisition. Slices were oriented along the anterior commissure–posterior commissure plane. Functional runs lasted 6.2 min (124 time points). Structural data included a multiecho T1-weighted magnetization-prepared gradient-echo (MP-RAGE) image (van der Kouwe et al., 2008).

fMRI processing steps included 1) discarding the first four frames of each run, 2) correcting for slice acquisition-dependent time shifts in each volume with SPM2 (Wellcome Department of Cognitive Neurology, London, UK), and 3) correcting for head motion using rigid body translation and rotation parameters (FSL; Jenkinson et al., 2002; Smith et al., 2004). This was followed by standard functional connectivity preprocessing (Fox et al., 2005; Van Dijk et al., 2010; Vincent et al., 2006). Linear trends over each run were removed and a low-pass temporal filter retained frequencies below 0.08 Hz. Spurious variance was removed using linear regression with terms for head motion, whole brain signal, ventricle signal, white matter signal and their derivatives.

Individual participants' T1 scans were reconstructed into surface representations using FreeSurfer (http://surfer.nmr.mgh.harvard.edu; Fischl, 2012). Functional data were registered to structural images using FreeSurfer's FsFast package (Greve and Fischl, 2009; http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). The structural preprocessing and structural–functional data alignment steps were described in Yeo et al. (2011). Functional data were projected onto the FreeSurfer surface space (2 mm mesh), smoothed on the surface using a 6 mm full-width half-maximum kernel, and were then downsampled to a 4 mm mesh.

HCP MRI data acquisition and preprocessing

HCP data were part of the HCP initial October 2012 public data release (http://www.humanconnectome.org/data). Data were acquired on a 3 T Skyra scanner (Siemens, Erlangen, Germany) using a standard 32-channel head coil. The scanner has a customized SC72 gradient insert and a customized body transmitter coil with 56 cm bore size. The HCP Skyra has the standard set of Siemens shim coils (up to 2nd order). Functional data consisted of gradient-echo EPI sensitive to BOLD contrast. Parameters for the resting data were: TR = 720 ms, TE = 33.1 ms, FA = 52°, 2 × 2 × 2 mm voxels, FOV = 208 × 180 mm, and 72 oblique axial slices alternated between phase encoding in a right to left direction in one run and phase encoding in a left to right direction in the other run (Feinberg et al., 2010; Moeller et al., 2010; Setsompop et al., 2012; Xu et al., 2012). Each functional run lasted 14.55 min (1200 time points). Structural data included a T1-weighted MP-RAGE image. Parameters for the structural scan were as follows: TR = 2400 ms, TI = 1000 ms, TE = 2.14 ms, FA = 8°, 0.7 × 0.7 × 0.7 mm voxels and FOV = 224 × 224 mm. More details of the acquisition strategy can be found in Van Essen et al. (2012).

We utilized the fMRI preprocessed data released by the HCP (Glasser et al., 2013). fMRI processing steps included 1) gradient distortion correction (Jovicich et al., 2006, 2) motion correction, 3) distortion correction, 4) registration to the T1 scan (Greve and Fischl, 2009), 5) spline resampling to FSL MNI152 2 mm space using FSL FNIRT (Jenkinson et al., 2002; Smith et al., 2004), and 6) intensity normalization to mean of 10,000 and bias field correction. This was followed by standard functional connectivity preprocessing as in the GSP dataset. The preprocessed