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Individual differences and time-varying features of modular brain architecture

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ABSTRACT

Recent studies have suggested that human brain functional networks are topologically organized into functionally specialized but inter-connected modules to facilitate efficient information processing and highly flexible cognitive function. However, these studies have mainly focused on group-level network modularity analyses using "static" functional connectivity approaches. How these extraordinary modular brain structures vary across individuals and spontaneously reconfigure over time remain largely unknown. Here, we employed multiband resting-state functional MRI data (N=105) from the Human Connectome Project and a graph-based modularity analysis to systematically investigate individual variability and dynamic properties in modular brain networks. We showed that the modular structures of brain networks dramatically vary across individuals, with higher modular variability primarily in the association cortex (e.g., fronto-parietal and attention systems) and lower variability in the primary systems. Moreover, brain regions spontaneously changed their module affiliations on a temporal scale of seconds, which cannot be simply attributable to head motion and sampling error. Interestingly, the spatial pattern of intra-subject dynamic modular variability largely overlapped with that of inter-subject modular variability, both of which were highly reproducible across repeated scanning sessions. Finally, the regions with remarkable individual/temporal modular variability were closely associated with network connectors and the number of cognitive components, suggesting a potential contribution to information integration and flexible cognitive function. Collectively, our findings highlight individual modular variability and the notable dynamic characteristics in large-scale brain networks, which enhance our understanding of the neural substrates underlying individual differences in a variety of cognition and behaviors.

Introduction

Modularity (i.e., the decomposability of a system into small modules) is a ubiquitous organization principle in most complex systems, including social, economic and biological networks (Hartwell et al., 1999). Using human resting-state functional MRI (R-fMRI) that can capture the brain's intrinsic or spontaneous activity (Biswal et al., 1995), recent studies have demonstrated that the human brain functional network during rest is organized into several functionally specialized but interconnected modules, such as the sensorimotor, visual, default-mode, fronto-parietal and attention modules (He et al., 2009; Meunier et al., 2009; Power et al., 2011). This intrinsically cohesive modular structure, which is presumably shaped by evolutionary constraints, allows the brain to enable efficient information communication with low wiring costs (Bullmore and Sporns, 2012) and fast adaption to changeable task demands (Bassett et al., 2011; Braun et al., 2015; Liang et al., 2016), and serves as a fundamental network basis for cognitive flexibility (Bertolero et al., 2015). Recent studies found that these brain modules exhibit distinct cerebral blood flow rates (Liang et al., 2013) and are closely associated with the correlated gene expression (Richiardi et al., 2015), further suggesting underlying physiological and molecular mechanisms. Notably, two important questions remain to be further elucidated, despite greatly growing interests in investigating the intrinsic network modules in the resting human brain.

The first question concerns individual differences in the functional modular brain architecture during rest. Human brain structure and function greatly vary across individuals. For example, structural brain imaging and histology studies show remarkable structural variability in language areas in either the regional cytoarchitecture (Amunts et al.,

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1999;Amunts et al., 2004;Eickhoff et al., 2005) or cortical morphology (Hill et al., 2010a). Functional brain imaging studies based on task- and R-fMRI reveal substantial functional variability in the association cortex (e.g., lateral frontal areas) in either task-evoked activations (Frost and Goebel, 2012;Pinel et al., 2007), intrinsic functional connectivity (Finn et al., 2015;Mueller et al., 2013), cortical parcellations (Langs et al., 2016;Wang et al., 2015a) or functional systems (Gordon et al., 2015). These structural and functional variations may origin from the joint effects of genetic and environmental factors (Brun et al., 2009;Chen et al., 2012;Gao et al., 2014;Hill et al., 2010b;Johnson et al., 2009;Petanjek et al., 2011) and have greatly advanced our understanding of the neural substrates of individual differences in cognition and behavior. Quantifying the inter-subject variability in the intrinsic modular organization would provide system-level insights. Until recently, only two R-fMRI studies directly examined individual differences in the functional modular architecture, with a primary focus on the consistent network modules across individuals (Moussa et al., 2012) or the deviation of individual modular structures from the group-level organization (Laumann et al., 2015). However, how the intrinsic modular brain architecture, especially the constitution of functional modules, varies across individuals remains largely unknown.

The second question concerns the time-varying dynamics of modular architecture in the brain functional networks. Recent task-related fMRI studies demonstrated that the dynamic reconfiguration of the functional modular structure in response to task demands are associated with individual performances in motor skill learning (Bassett et al., 2011) and working memory tasks (Braun et al., 2015). Existing literature has suggested that both the dynamic functional architecture during tasks and the individual behavioral performances can be shaped by the intrinsic brain networks during rest (Cole et al., 2014;Sadaghiani et al., 2015;Schultz and Cole, 2016;Wang et al., 2016). Hence, exploring the time-varying characteristics of intrinsic modular organization may provide fundamental insights into flexible cognitive functions (Anderson, 2014;Pessoa, 2014). Several R-fMRI studies demonstrated that during the resting state, the functional modular architecture, such as network modularity and the connectivity strength associated with the modules, temporally changes on a short time scale (e.g., seconds) (Allen et al., 2014;Betzel et al., 2016;Di and Biswal, 2015;Jones et al., 2012;Schaefer et al., 2014). However, how the brain regions dynamically switch their module affiliations over time and the functional implications remain to be elucidated.

To address these issues, in the present study we employed multi-band R-fMRI data and a graph-based modularity analysis to systematically explore the individual variability and the time-varying characteristics of the intrinsic modular architectures in the human brain. Specifically, for each subject, we constructed large-scale static and sliding window-based dynamic functional networks and tracked the modular architectures across subjects or time. Given that higher-order cognitive functions primarily involving association areas (e.g., fronto-parietal areas) (Yeo et al., 2015) exhibit remarkable individual differences, we hypothesized that the association regions would show large inter- and/or intra-subject modular variability. We further investigated whether the subject-specific functional modular architecture and the temporal characteristics were reproducible across repeated scanning sessions. Finally, we examined the associations between inter-/intra-subject modular variability and the functional connectors and cognitive flexibility (Yeo et al., 2015).

Materials and methods

Subjects and data acquisition

Multiband resting-state fMRI (R-fMRI) data were acquired from the publicly available Q2 Data Release of the Human Connectome Project (HCP) (Van Essen et al., 2013). The data set included 142 healthy subjects, of which 132 subjects underwent repeated R-fMRI scanning in two sessions (Table S1). Written informed content was obtained from each subject, and the scanning protocol was approved by the Institutional Review Board of Washington University in St. Louis, MO, USA (IRB #20120436).

All subjects underwent multimodal imaging scans in a customized 32-channel Siemens 3T "Connectome Skyra" scanner at Washington University. For each subject, four R-fMRI runs were collected in two sessions, with two runs separately acquired per session through phase encoding in the left-to-right and right-to-left directions. Specifically, each R-fMRI run was acquired using a multiband gradient-echo-planar imaging sequence as follows: time repetition=720 ms; time echo=33.1 ms; flip angle=52°; field of view=208×180 mm^2; matrix=104×90; 72 slices; voxel size=2×2×2 mm^3; multiband factor=8 and 1200 volumes (i.e., 14.4 min). During the scanning, the subjects maintained a relaxed fixation on a cross. Notably, the R-fMRI data from 27 subjects were excluded from the analysis due to missing time points (N=3) or excessive head motion (N=24) (see "Data preprocessing") (Table S1). The data from the remaining 105 subjects (age 22–35 years, 37 males) were used for the final analysis. In the present study, the R-fMRI data from the first session (i.e., S1) were used for the main analysis and the data from the second session (i.e., S2) were used for the validation and reproducibility analysis unless otherwise indicated. To reduce the potential influence of different phase encoding directions, only the left-to-right encoded runs are included here.

Data preprocessing

We obtained minimally preprocessed R-fMRI data conducted using HCP Functional Pipeline v2.0 (Glasser et al., 2013) involving gradient distortion correction, head motion correction, image distortion correction and spatial transformation to the Montreal Neurological Institute space using one step spline resampling from the original functional images followed by then intensity normalization. Notably, functional data from 24 subjects were discarded due to their large head motions in either run with criteria of a translation/rotation >3 mm/° or a mean framewise head motion >0.14 mm (Finn et al., 2015). The framewise head motion parameters were extracted from 'relativeRMS_mean.txt' in the Q2 release. In this study, these minimally preprocessed images were further analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (Yan and Zang, 2010). Briefly, first the linear trend was removed from these functional images. Then, several nuisance signals were regressed from the time course of each voxel using multiple linear regression, including twenty-four head motion parameters (Friston et al., 1996), cerebrospinal fluid, white matter and global brain signals (Birn et al., 2006;Fox et al., 2009). Finally, temporal band-pass filtering (0.01–0.1 Hz) was performed to reduce the influence of low-frequency drifts and the high-frequency physiological noises (Biswal et al., 1995;Lowe et al., 1998). The resulting time courses were used for the brain network construction and analysis.

Construction of functional brain networks

The brain network construction was implemented with GRETNA (http://www.nitrc.org/projects/gretna/) (Wang et al., 2015b). In this study, we constructed the whole-brain functional networks at the macroscopic level, in which nodes represented regions of interest (ROIs) and edges represented inter-regional functional connectivity. Specifically, we employed a functionally defined atlas (Power et al., 2011) to generate 264 nodal ROIs, each of which denoted 5-mm radius spheres centered on previously reported coordinates. This atlas ensures the functional significance of the brain network nodes and simultaneously reduces the chance of signal blurring from multiple functional areas within a node (Wig et al., 2011). It has been widely used in both resting- and task-state brain network studies (Cole et al., 2014; Cole et al., 2013; Gu et al., 2015; Power et al., 2013; Sadaghiani