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Changes in structural and functional connectivity among resting-state networks across the human lifespan

Richard F. Betzel [a], Lisa Byrge [a], Ye He [b], Joaquín Goñi [a], Xi-Nian Zuo [b], Olaf Sporns [a,*]

[a] Psychological and Brain Sciences, Indiana University, Bloomington, USA
[b] Key Laboratory of Behavioral Science and Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

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ABSTRACT

At rest, the brain's sensorimotor and higher cognitive systems engage in organized patterns of correlated activity forming resting-state networks. An important empirical question is how functional connectivity and structural connectivity within and between resting-state networks change with age. In this study we use network modeling techniques to identify significant changes in network organization across the human lifespan. The results of this study demonstrate that whole-brain functional and structural connectivity both exhibit reorganization with age. On average, functional connections within resting-state networks weaken in magnitude while connections between resting-state networks tend to increase. These changes can be localized to a small subset of functional connections that exhibit systematic changes across the lifespan. Collectively, changes in functional connectivity are also manifest at a system-wide level, as components of the control, default mode, saliency/ventral attention, dorsal attention, and visual networks become less functionally cohesive, as evidenced by decreased component modularity. Paralleling this functional reorganization is a decrease in the density and weight of anatomical white-matter connections. Hub regions are particularly affected by these changes, and the capacity of those regions to communicate with other regions exhibits a lifelong pattern of decline. Finally, the relationship between functional connectivity and structural connectivity also appears to change with age; functional connectivity along multi-step structural paths tends to be stronger in older subjects than in younger subjects. Overall, our analysis points to age-related changes in inter-regional communication unfolding within and between resting-state networks.

Introduction

The brain is a complex system that can be conceptualized as a network of anatomically linked regions and thereby made amenable to analysis using tools from graph theory (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Sporns, 2014). The brain's structural connectivity (SC), together with other factors, contributes to shape neurophysiological activity, and thereby influences functional connectivity (FC) among neuronal populations (Wang et al., 2013) and brain regions (Deco et al., 2010; Honey et al., 2009). Whereas SC refers to physical connections between two brain regions, FC is defined as the statistical dependency – e.g. correlation, coherence, mutual information, etc. – between those regions' activity time courses. Graph theoretical analyses of SC/FC networks have revealed a host of non-random attributes, including small-worldness (Achard and Bullmore, 2006; Gong et al., 2009), hubs and cores (Achard et al., 2006; Hagmann et al., 2008; Zuo et al., 2012), a structural rich club (van den Heuvel and Sporns, 2011), modular architecture (Meunier et al., 2009, 2010), and economic wiring (Bassett et al., 2010; Bullmore and Sporns, 2012), among others.

Resting brain FC can be decomposed into resting-state networks (RSNs) composed of brain regions that exhibit coherent activity in a task-free state (Buckner et al., 2013), exhibit consistent spatial topographic patterns across the cerebral cortex (Power et al., 2011; Yeo et al., 2011), and strongly resemble collections of brain regions corresponding to task-evoked sensory, motor and higher-order cognitive systems (Crossley et al., 2013; Smith et al., 2009). RSNs can be extracted using different methodologies, including independent component analysis (ICA; Beckmann et al., 2005) and clustering approaches applied to whole-brain FC networks (e.g., Bellec et al., 2010; Power et al., 2011; Yeo et al., 2011). A number of recent studies have focused on changes in connectivity within and between RSNs, both on fast time scales in the course of spontaneous brain dynamics (Allen et al., 2014; see Hutchinson et al., 2013 for a systematic review), as well as in the course of visual perceptual learning (Lewis et al., 2009), acquisition of motor skills (Ma et al., 2011) and cognitive practice (Jolles et al., 2013).

This report aims to characterize changes in the pattern of SC/FC over the course of the human lifespan, with a focus on connectivity changes within and between RSNs. A number of previous studies have shown that patterns of SC/FC undergo characteristic changes over developmental stages and aging (Cao et al., 2014; Wang et al., 2012; Yang et al., 2014; Zuo et al., 2010). In childhood, FC is dominated by short-range

* Corresponding author.
E-mail address: osporns@indiana.edu (O. Sporns).

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local links, which are gradually replaced by long-distance functional connections in adulthood, forming mature RSNs (Fair et al., 2009; Kelly et al., 2009; Power et al., 2011; Supekar et al., 2010). In contrast, aging studies have demonstrated the opposite effect, with RSNs exhibiting decreased FC (Andrews-Hanna et al., 2007; Ferreira and Busatto, 2013; Geerlings et al., 2014). Studies of SC across the lifespan have demonstrated that hub regions and modules are present by early childhood, though changes of cortical white-matter connectivity continues across the lifespan (Gong et al., 2009; Hagmann et al., 2008; Lim et al., 2013).

While these studies and others have provided insight into the development and maturation of specific RSNs (e.g. Fair et al. (2007, 2008, 2009) for control networks and Andrews-Hanna et al. (2007) for the default mode and dorsal attention networks), few reports have examined age-related changes in connectivity at the whole-brain level across the entire lifespan. Moreover, studies that focus on the intrinsic connectivity of a specific RSN necessarily overlook any connections that that RSN makes to the rest of the brain and how these connections change as a function of age. Here, we aim to bridge this particular gap in knowledge by tracking the age-related change in all functional and structural connections in the human brain over the course of the lifespan. Because RSNs are thought to correspond to the brain's functional systems, it was of particular interest to observe how these changes were related to the boundaries of RSNs and their distributed subcomponents. An additional aim was to gain insight into how changes in SC and FC might be interrelated, and what these changes might reveal about age-related changes in interregional communication.

Methods and materials

NKI-RS lifespan sample and image preprocessing

Lifespan data used in this study are part of the publicly available NKI-Rockland Sample (http://fcon_1000.projects.nitrc.org/indi/pro/nki.html) from the Nathan Kline Institute (NKI, NY, USA) consisting of $N = 126$ subjects (58 female) over the age range 7–85 years (median age = 31.5). The study was approved by the NKI institutional review board and all adult and child subjects provided informed consent (Nooner et al., 2012).

Subjects in this study underwent a scan session using a Siemens TrioTM 3.0 T MRI scanner. Resting fMRI scans were collected using an echo-planar imaging (EPI) sequence with the following parameters: time repetition (TR) / time echo (TE) = 2500 / 30 ms, flip angle (FA) = 80°, field of view (FOV) = 216 × 216 mm^2, voxel size = 3.0 × 3.0 × 3.0 mm^2, distance factor = 10%, number of slices = 38. Each scan session was 650 s long and comprised 260 functional volumes. Inside the scanner, subjects received instructions to keep their eyes closed, relax their minds, and to not move. T1-weighted images were acquired using the following magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR / TE = 2500 / 30 ms, inversion time = 1200 ms, FA = 8°, FOV = 256 × 256 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3, number of slices = 192. T1-weighted images were subsequently used for spatial normalization and group-specific template generation.

This sample has been used in two recent studies on the human brain functional connectivity changes across the lifespan (Cao et al., 2014; Yang et al., 2014). The Connectome Computation System (CCS: http://lfcd.psych.ac.cn/ccs.html) was used to preprocess both R-fMRI and DTI images for subsequent analyses. As in Cao et al. (2014), preprocessing of functional images included discarding the first four EPI volumes to allow for the signal to reach equilibrium, correction for timing offsets, 3D geometrical displacement correction for head motion, and 4D global mean-based intensity correction. Motion correction was performed using the Friston-24 model, which regresses out nuisance parameters including six head motion parameters, those same parameters at the previous time step, and both sets of parameters squared (Friston et al., 1996). Additionally, global mean, white matter, and cerebrospinal fluid signals were also included as nuisance parameters and regressed out. Lastly, the signal was band-pass filtered (0.01–0.1 Hz) and both linear and quadratic trends removed.

The preprocessing steps of DTI images are identical to those used in an earlier study (van den Heuvel and Sporns, 2011). Specifically, DTI images were corrected for eddy-current distortions and realigned to the mean image of the 12 unweighted B0 images (Andersson and Skare, 2002). Using the corrected DTI data, a tensor was fit to the diffusion profile within each voxel and the diffusion direction within each voxel was assigned as the principal eigenvector of the tensor by computing its eigen-system (Chang et al., 2005). To provide information on the diffusion direction within a given voxel, its fractional anisotropy (FA) was computed as the square root of the sum of squares (SRSS) of the diffusivity differences, divided by the SRSS of the diffusivities. Using the information on preferred diffusion direction with each voxel in the whole brain mask, the white matter tracts were reconstructed with FACT (fiber assignment by continuous tracking) algorithm (Mori and van Zilj, 2002; Mori et al., 1999). Specifically, within each voxel, evenly distributed 32 seeds were used as starting points of possible streamlines, which generate the white matter fibers by following the preferred diffusion direction from voxel to voxel. A threshold on FA of 0.1 or a sharp turn of >45° was set to stop tracking a fiber streamline at a voxel.

Construction of FC networks

In order to address questions related to RSNs, we used a previously established functional parcellation of the human cerebral cortex (Yeo et al., 2011). This particular parcellation was derived by clustering the whole-brain functional connectivity networks of 500 subjects (along with a 500 subject replication cohort) according to the similarity of regions' functional connectivity profiles. This procedure resulted in seven clusters, whose boundaries shared a close correspondence to the known topographic boundaries of visual (Vis) and somatomotor (SomMot) networks, limbic regions (Limbic) and distributed association networks for executive control (Cont), attention (DorsAttn, SalVentAttn), and internally-directed cognition (Default). These seven RSNs displayed hierarchical organization such that each of the seven clusters could be subdivided into components with distinct patterns of FC, resulting in a total of 17 RSN components or sub-networks: VisCent, VisPeri, SomMotA, SomMotB, LimbicA, LimbicB, ContA, ContB, ContC, DorsAttnA, DorsAttnB, SalVentAttnA, SalVentAttnB, DefaultA, DefaultB, DefaultC, and DefaultD. Across all the 17 sub-networks, there are in total $n = 114$ separated anatomical regions of interest (ROIs). Specifically, any of the ROIs meets two basic requirements: 1) it is isolated anatomically from other regions within the sub-network it belongs to, and 2) is separated by the network boundaries from regions within other sub-networks. These ROIs were then used to represent nodes in both FC and SC networks. The functional connection between nodes i and j was defined as the Fisher-z transformed Pearson product–moment correlation of the representative BOLD time series recorded at those nodes. In the standard surface space defined by FreeSurfer (i.e., *fsaverage5*), representative time series were computed as the average time series of all voxels within an ROI extracted from the transformed individual preprocessed R-fMRI data on the *fsaverage5* surfaces (Jiang et al., 2014). For each subject, FC between all pairs was organized into an $n \times$ weighted and signed correlation matrix, A^{FC}, whose elements a_{ij}^{FC} denoted the FC between nodes i and j. It is common practice to sparsify A^{FC} by retaining only a fraction of the strongest connections or entries that survive a threshold for statistical significance (Achard and Bullmore, 2006; Cao et al., 2014). In this study FC networks were not sparsified. Eliminating connections impairs our ability to assess how FC changes with age — removing a connection from some subjects but not from others results in fewer observations and a reduction in statistical power. A group-averaged FC matrix (for visualization only) representing all subjects is shown in Fig. 2A. (See Fig. 1.)

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