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Functional density and edge maps: Characterizing functional architecture in individuals and improving cross-subject registration

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ABSTRACT

Population-level inferences and individual-level analyses are two important aspects in functional magnetic resonance imaging (fMRI) studies. Extracting reliable and informative features from fMRI data that capture biologically meaningful inter-subject variation is critical for aligning and comparing functional networks across subjects, and connecting the properties of functional brain organization with variations in behavior, cognition and genetics. In this study, we derive two new measures, which we term *functional density map* and *edge map*, and demonstrate their usefulness in characterizing the function of individual brains. Specifically, using data from the Human Connectome Project (HCP), we show that (1) both functional maps capture intrinsic properties of the functional connectivity pattern in individuals while exhibiting large variation across subjects; (2) functional maps derived from either resting-state or task-evoked fMRI can be used to accurately identify subjects from a population; and (3) cross-subject alignment using these functional maps considerably reduces functional variation and improves functional correspondence across subjects over state-of-the-art multimodal registration algorithms. Our results suggest that the proposed functional density and edge maps are promising features in characterizing the functional architecture in individuals and provide an alternative way to explore the functional variation across subjects.

1. Introduction

A substantial degree of anatomical and functional variability in the human brain has been observed across individuals (Mueller et al., 2013; Laumann et al., 2015), which has a strong link with differences in behavioral performance (Stephen, 2016). Morphological measurements such as cortical thickness, sulcal depth and curvature can be computed from structural magnetic resonance imaging (MRI) scans and have been widely used to explore individual anatomical variability on the cortex (Fischl and Dale, 2000; Im et al., 2008). Functional variability in individuals can be captured by functional MRI (fMRI) in either task or resting conditions. Recently, functional connectivity derived from fMRI data has been utilized to investigate individual functional variability (Mueller et al., 2013). Individual differences in functional connectivity have been demonstrated to be heterogeneous across the cortex in Mueller et al. (2013). Significantly higher variability has been shown in heteromodal association cortex while lower variability was found in unimodal cortices. However, the entire functional connectome is noisy, sensitive to local perturbations (Jiang et al., 2013), and difficult to visualize due to its high dimensional nature. Independent Component Analysis (ICA) is often employed to reduce the spatial dimension of fMRI data (Smith et al., 2013) but may fail to localize individual components. Low-dimensional functional measurements that can characterize functional connectivity profiles while preserving their spatial localization may provide a better way to compare and visualize functional differences at the individual level.

In contrast to individual-level analysis, group-level fMRI features obtained by averaging data across subjects have been more extensively investigated since the early 1990s. Group-level analysis often benefits from improved signal-to-noise ratio (SNR) but is hampered by substantial anatomical and functional variability across subjects. To enable a reliable group-level analysis, anatomical and functional correspondence need to be established among subjects before calculating the group average for subsequent analysis. Although anatomical variability can be largely removed through an alignment of morphological features (Liu et al., 2004; Gholipour et al., 2007; Fischl et al., 2008; Conroy et al., 2013),

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substantial functional variability often remains after structure-based cross-subject registration. Recent studies (Sabuncu et al., 2010; Conroy et al., 2013; Robinson et al., 2014) have attempted to remove functional variability by using fMRI-derived features in the registration, thus improving the power of analysis at the group level (Glasser et al., 2016).

In this work, we address two fundamental problems in the analysis of functional neuroimaging data. First, state-of-the-art fMRI studies utilize high-dimensional functional connectivity profiles (Yeo et al., 2011) or ICA-based fMRI features (Smith et al., 2013; Glasser et al., 2016). However, these measurements may not well characterize the unique functional architecture of an individual brain. Second, group analysis is complicated by the large cross-subject variability of structure-function relationship, which reduces the power to detect group effects in functional studies. To address these issues, here we derive a functional density map and an edge map from fMRI data to characterize the functional connectivity pattern in individuals, and use these maps to establish functional correspondence across subjects for group analysis. The functional density map quantifies and summarizes functional connectivity strength at each location on the cortex. A cortical location will have a large density value if it is strongly connected to a large number of other locations. The functional edge map derived from the functional density maps was inspired by the work of Gordon et al. (2014). It models the transitions in functional connectivity patterns and corresponds to functional boundaries. Large values in an edge map indicate sharp change of functional connectivity patterns. Using data from 100 unrelated subjects distributed by the Human Connectome Project (HCP) WU-UMinn Consortium (Van Essen et al., 2013), we demonstrate that:

1. The functional density and edge maps are unique at the individual level and capture functional variation across subjects, and thus can serve as functional fingerprints to identify subjects from a large population;
2. Individual functional density and edge maps can be used to establish functional correspondence across subjects and produce sharp group averages. The group-average functional density and edge maps are highly reproducible across independent samples;
3. Cross-subject alignment using functional maps derived from resting-state fMRI improves the alignment of task activations across subjects. These functional maps can be used as promising measures for driving the functional alignment in order to remove inter-subject functional variations and to establish functional correspondence across subjects for group analysis.

These results suggest that the proposed functional density and edge maps capture intrinsic properties of subject-specific functional connectivity patterns, and have the potential to characterize functional variation in the population, improve function-based cross-subject alignment and increase the power of group-level inferences.

2. Materials and methods

2.1. Data

A data set of 100 unrelated young and healthy subjects was downloaded from the HCP WU-Minn Consortium (Van Essen et al., 2013). Multimodal MR images, including T1-weighted and T2-weighted imaging, fMRI and diffusion-weighted imaging were collected from all subjects on a customized Siemens 3T Connectome Skyra scanner using HCP's acquisition protocol (Van Essen et al., 2012). Structural images were acquired using a 3D MPRAGE T1-weighted sequence with 0.7 mm isotropic resolution. Other parameter settings included: TR = 2400 ms; TE = 2.14 ms; TI = 1000 ms; flip angle = 8°. Two resting-state and seven task fMRI sessions were collected for each subject. The tasks included working memory (WM), gambling, motor, language, social cognition, relational processing and emotional processing. In each session, two runs were acquired using single-shot EPI with alternating (left-to-right, LR and right-to-left, RL) phase encoding directions. The two resting sessions were acquired on separate days with the following scanning parameters: TR = 720 ms; TE = 33.1 ms; flip angle = 52°; slice thickness = 2.0 mm; 72 slices; 2 mm isotropic voxels; multiband factor = 8; matrix size = 104 × 90; partial Fourier = 6/8; echo spacing = 0.58 ms; bandwidth (BW) = 2290 Hz/px; time points = 1200. The acquisition protocol of the task sessions was identical to that of the resting sessions to achieve maximal compatibility between task and resting data. Full details about subject recruitment and MRI data acquisition can be found in (Smith et al., 2013; Barch et al., 2013).

2.2. Preprocessing

The HCP minimal preprocessing pipeline (Glasser et al., 2013) was utilized to process the data set, which included artifact removal, motion correction and alignment to standard space using cortical folding features. Software used by this pipeline included FSL (FMRIB's Software Library) (Jenkinson et al., 2012), FreeSurfer (Fischl, 2012), and the Connectome Workbench (Marcus et al., 2013). Specifically, the processing of structural MRI comprised the PreFreeSurfer (Jovicich et al., 2006; van der Kouwe et al., 2008), FreeSurfer recon-all (Dale et al., 1999; Fischl et al., 1999a, b, 2001; 2002; Ségonne et al., 2007) and Post-FreeSurfer steps (Glasser et al., 2014), and the cortical and subcortical fMRI signals were processed separately in fMRISurface (Glasser et al., 2013) and fMRIVolume (Andersson et al., 2003; Greve and Fischl, 2009) pipelines. fMRI data were resampled onto a standard "grayordinate" space, which used a surface representation with 32,492 vertices on each hemisphere. The fMRI time series were then temporally demeaned and linearly detrended within each run, followed by a bandpass filtering (0.01–0.08 Hz). Next, the whole-brain signal was regressed out and surface-based smoothing using a Gaussian kernel with 6 mm full-width at half-maximum (FWHM) was applied. Finally, two runs within each resting-state or task session were concatenated.

2.3. Calculation of functional density and edge maps

Given a cortical mesh P with N vertices, in order to calculate a density value for each vertex, we first constructed a weighted graph by connecting all neighboring vertices of the mesh and computing the Pearson distance between each pair of neighboring vertices i and j:

$$d_{ij} = 1 - \langle y_i, y_j \rangle \tag{1}$$

where y_i and y_j are the normalized fMRI time series and $\langle \cdot, \cdot \rangle$ denotes the standard inner product. The shortest path between each pair of vertices through the weighted graph was then computed and defined as their geodesic distance (Honnorat et al., 2015). The geodesic distance between two vertices reflects the dissimilarity of their time series through the surface. However, it should be mentioned that the geodesic distance is also affected by the spatial distance since it is the accumulated sum along the shortest path. Tow vertices with a long spatial distance are more likely to have a large geodesic distance. The density value at vertex i can then be computed using a Gaussian kernel (Rodriguez and Laio, 2014):

$$\rho_i = \sum_{k=1, k\neq i}^{N} a \exp\left(- \frac{\left(\overline{d}_{ik} - b\right)^2}{d_c^2} \right) \tag{2}$$

where $\overline{d}_{ik}$ is the geodesic distance between vertex i and vertex k, N is the total number of vertices, and d_c is a free parameter. The parameter a was set to 1 and the parameter b was set to zero as suggested in Rodriguez and Laio (2014). It can be seen that a vertex which is functionally similar to other vertices (i.e., has short geodesic distances to other vertices) tends to have a larger density value. In the present study, for each subject, the parameter d_c was set to the top 0.1% smallest geodesic distance for each subject since we found that with this parameter setting the functional