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Population-averaged atlas of the macroscale human structural connectome and its network topology

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ABSTRACT

A comprehensive map of the structural connectome in the human brain has been a coveted resource for understanding macroscopic brain networks. Here we report an expert-vetted, population-averaged atlas of the structural connectome derived from diffusion MRI data (N = 842). This was achieved by creating a high-resolution template of diffusion patterns averaged across individual subjects and using tractography to generate 550,000 trajectories of representative white matter fascicles annotated by 80 anatomical labels. The trajectories were subsequently clustered and labeled by a team of experienced neuroanatomists in order to conform to prior neuroanatomical knowledge. A multi-level network topology was then described using whole-brain connectograms, with subdivisions of the association pathways showing small-worldness in intra-hemisphere connections, projection pathways showing hub structures at thalamus, putamen, and brainstem, and commissural pathways showing bridges connecting cerebral hemispheres to provide global efficiency. This atlas of the structural connectome provides representative organization of human brain white matter, complementary to traditional histologically-derived and voxel-based white matter atlases, allowing for better modeling and simulation of brain connectivity for future connectome studies.

Introduction

The organization of the structural connections in the human brain determines how neural networks communicate, thereby serving as a critical constraint on brain functionality and providing potential etiology for clinical pathology (Bota et al., 2015; Sporns, 2014). Characterizing this structural organization has relied on either histological slides or neuroanatomically-validated atlases based on individual subjects (Amunts et al., 2013; Ding et al., 2016); however, a comprehensive population-averaged 3-dimensional (3D) structural connectome at the macroscale level has yet to be constructed. A population-averaged connectome is critical for demonstrating representative topological interconnectivity in the general population, a stated objective of the national investment in the Human Connectome Project (Setsompop et al., 2013; Van Essen et al., 2013). If achieved, such a map of the structural connectome could augment existing histological and single-subject atlases, thus allowing for robust modeling and simulation in both empirical and theoretical studies.

To date, diffusion MRI is the only non-invasive tool for mapping the 3D trajectories of human macroscopic white matter pathways (Fan et al., 2016; McNab et al., 2013), with preliminary success at resolving the normative pattern of several major white matter pathways (Catani et al., 2002; Guevara et al., 2012; Mori et al., 2008, 2009; Peng et al., 2009; Thiebaut de Schotten et al., 2011). This has been realized by resolving local fiber orientations at the voxel level and delineating entire axonal trajectories by implementing a stepwise tracking algorithm (Basser et al.,

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2000; Mori et al., 1999; Wedeen et al., 2012). Nonetheless, there are several caveats to the success of diffusion MRI fiber tracking, including the identification of false tracts and suboptimal coverage of small pathways or those with complex geometry (Reveley et al., 2015; Thomas et al., 2014). Indeed, the percentage of valid connections can range from 3.75% to 92% due to differences in reconstruction methods and tracking algorithms (Maier-Hein et al., 2016). Improving the quality of resolved fiber pathways using diffusion MRI can be achieved by high-angular-resolution modalities (Glasser et al., 2016), a template averaged across a large number of subjects to facilitate fiber tracking (Yeh and Tseng, 2011), and neuroanatomical expertise to resolve errors in the automated fiber tracking process (Meola et al., 2015a). Template-based approaches have been shown to reliably capture the morphological characteristics of several major white matter fascicules when validated against cadaver microdissection approaches (Fernandez-Miranda et al., 2015; Meola et al., 2015a, 2016a, 2016b; Wang et al., 2012, 2016; Yoshino et al., 2016). Yet building a comprehensive tractography atlas of major and minor white matter pathways is still challenged by the problem of false fiber pathways, even when relying on high angular resolution data.

Here we constructed a population-averaged structural connectome, including both major and minor pathways, using an expert-vetted approach. We employed high-angular-resolution diffusion MRI data (n = 842) from healthy subjects in the Human Connectome Project (HCP) database (Van Essen et al., 2012). The data from each subject were spatially registered and simultaneously reconstructed in the standardized ICBM-152 (ICBM: International Consortium for Brain Mapping) template space using q-space diffeomorphic reconstruction (QSDR) (Yeh and Tseng, 2011). QSDR allows for aggregating diffusion data into an averaged template of voxelwise diffusion distributions while preserving fiber continuity after nonlinear deformation to enable template space fiber tracking. The averaged diffusion pattern of the entire sample is thus representative of non-pathological structural characteristics within healthy subjects. Based on this template, a total of 550,000 tracks were generated using a tracking method that was shown to achieve the highest number of valid connections in an open competition (Maier-Hein et al., 2016). Generated tracks were subsequently clustered and then labeled by a team of clinical neuroanatomists, capitalizing on their previous experience in both cadaveric white-matter and comparative tractography techniques (Fernandez-Miranda et al., 2015; Wang et al., 2016). Furthermore, the tracks were categorized into the projection, association, and commissural pathways to generate multi-level connectograms illustrating network topology at the macroscopic level. The strategy of this approach allowed us to compile a comprehensive atlas of the structural connectome in the human brain at the population level, allowing for taxonomical identification of pathways that together comprise the full macroscopic structural connectome.

Methods

Diffusion MRI acquisitions

We used the minimally-preprocessed data (Glasser et al., 2013) from Human Connectome Projects (Q1-Q4 release, 2015) acquired by Washington University in Saint Louis and University of Minnesota (Van Essen et al., 2012). A total of 842 subjects (372 males and 470 females, age 22–36, demographics available at https://db.humanconnectome.org/) had diffusion MRI scanned on a Siemens 3T Skyra scanner using a 2D spin-echo single-shot multiband EPI sequence with a multi-band factor of 3 and monopolar gradient pulse. The spatial resolution was 1.25 mm isotropic. TR = 5500 ms, TE = 89.50 ms. The b-values were 1000, 2000, and 3000 s/mm^2. The total number of diffusion sampling directions was 90, 90, and 90 for each of the shells in addition to 6 b0 images. The preprocessed data were corrected for eddy current and susceptibility artifact. The matrices for gradient nonlinearity distortion correction were used in the following diffusion MRI reconstruction.

Q-space diffeomorphic reconstruction

The diffusion data for each subject was registered and reconstructed into the ICBM-152 space simultaneously using the q-space diffeomorphic reconstruction (QSDR) (Yeh and Tseng, 2011). QSDR combines nonlinear spatial registration and high-angular-resolution reconstruction of diffusion data to conserve the diffusible spins and preserve the continuity of fiber geometry for fiber tracking. QSDR used the deformation field to directly calculate the spin distribution function (SDF) in the standard space. SDF, denoted as $\psi(\hat{u})$, is the empirical distribution of the density of spins that have diffusion displacement oriented at direction $\hat{u}$ during the diffusion time. The SDF of each voxel were discretely sampled at 642 directions (8-fold tessellated icosahedron) using the following formula.

$$\psi(\hat{u}) = |J_\varphi| Z_0 \sum_i W_i(\varphi(r)) \mathrm{sinc}\left(\sigma\sqrt{6Db_i} < \hat{g}_i, \frac{J_\varphi \hat{u}}{\|J_\varphi \hat{u}\|} > \right) \quad (1)$$

Where i iterates through each diffusion weighted images W*i*. φ is a diffeomorphic mapping function that maps ICBM-152 space coordinates **r** to the subject's space. J_φ is the Jacobian matrix of the mapping function, whereas $|J_\varphi|$ is the Jacobian determinant. $W_i(\varphi(r))$ are the diffusion signals acquired at φ(r). b_i is the b-value, and $\hat{g}_i$ is the direction of the diffusion sensitization gradient. σ is the diffusion sampling ratio controlling the detection range of the diffusing spins. D is the diffusivity of water, and Z_0 is the constant estimated by the diffusion signals of free water diffusion in the brain ventricle (Yeh and Tseng, 2011). The nonlinearity of diffusion gradients was corrected using the nonlinear terms of the magnetic field obtained from gradient coils. The HCP dataset includes a 3-by-3 gradient deviation matrix for each voxel to estimate the effective gradient direction and strength. This matrix was applied to the diffusion sensitization gradient, $\hat{g}_i$ in Eq. (1) to correct the effect of gradient nonlinearity.

The registration component in QSDR used Fourier basis as the deformation function (Ashburner and Friston, 1999). The original setting used a set of 7-by-9-by-7 Fourier basis at x-y-z directions, and the computation and memory bottleneck was at the inverse of a 1327-by-1327 matrix (not a sparse matrix). We increased the resolution of the Fourier basis by 4-fold (i.e. 28-by-36-by-28 Fourier basis), which required solving an 84676-by-84676 matrix for each optimization iteration. Here instead of solving the large matrix using a standard Gauss-Jordan method (a complexity of O (n^3)), which would increase the computation time by a factor of $(4 \times 4 \times 4)^3 = 262{,}144$, we used the Jacobi method that allowed for parallel processing and could utilize solutions from the previous iteration to speed up the processing. This greatly reduced the computation complexity to O(n) and only increased the computation time by a factor of $4 \times 4 \times 4 = 64$. The parallel processing further reduced the computation time, allowing us to reconstruct the data using multi-thread resources. The FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) fractional anisotropy (FA) template was used as a template for ICBM-152 space, and the subjects' anisotropy maps were used to calculate the deformation parameters. The final SDFs were generated at 1-mm resolution.

The registration accuracy was evaluated by the coefficient of determination (i.e., R^2) value between each subject and template image. The distribution of the R^2 values, as shown in Fig. S1, is skewed with a leftward tail. We therefore looked at subjects with the lowest R^2 values at this tail for identification of outliers. This allowed us to identify two problematic datasets (#173132 and #103515) that were then reported to the HCP Consortium. It is noteworthy that we did not use the existing HCP alignment or other high accuracy diffeomorphic registration methods in our spatial normalization (Archer et al., 2017; Peng et al., 2009; Varentsova et al., 2014; Zhang et al., 2011). The alignment of those methods has good point-to-point matching; however, QSDR requires sufficient a constraint on the Jacobian matrix in the white matter tissue