Revealing the topological architecture of human cortical anatomical network by DTI tractography

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Introduction: An important issue in neuroscience is to reveal the architecture of complex brain network that might underlie fundamental structural and functional organization in the brain. By using postmortem tracing methods, anatomical networks in the mammalian cerebral cortex (primate, cat) and their topological properties were previously established at a macroscale[1]. Recent studies have demonstrated that DTI tractography can obtain numerous brain anatomical connections (i.e. white matter tracts) non-invasively, which are faithful to known white matter anatomy shown in previous postmortem studies[2]. While the effort to establish structural brain networks using diffusion MRI has emerged[3], anatomical connectivity patterns of the entire human cerebral cortex common to a population remains lacking. The objective of this study was to employ a large sample of subjects to (i) construct a macroscale cortical connectivity network in humans by using DTI tractography, and (ii) further analyze its underlying topological properties by using graph theoretical approaches.

Materials and Methods: This study included 80 young adults (m/f=38/42; age, 18-31 years) with no history of neurological disease or injury. All DTI scans were performed on the same 1.5T Siemens Sonata scanner using dual spin echo EPI, 40 3mm slices (no gap), image matrix 96×128 zero-filled to 256×256, TE/TR = 88 ms/6400 ms, b=1000 s/mm^2, 8 averages and 6 directions, 6:06 minutes long. As well, high resolution (1×1×1 mm^3) structural MRI of the whole brain was acquired for each subject by using a magnetization prepared rapid acquisition gradient echo sequence. The distortion of DWI due to eddy current was corrected by using an affine registration. **1) Cortical Network Construction**. Anatomical network of the human cortex was constructed by using DTI tractography as follows. a) Cortical parcellation: The Automated Anatomical Labeling (AAL) template[4] was employed to subdivide the entire cerebral cortex into 78 cortical regions (39 for each hemisphere), each representing a node in the network. For each subject, the cerebral cortex was subdivided in DTI native space by nonlinearly mapping the AAL mask from the MNI space into the native space (implemented in SPM5 package) (Fig a). b) Inter-regional anatomical connection: A continuous streamline tracking algorithm[5] was first used to reconstruct all fibers of the brain by selecting all white matter voxels (obtained by tissue classification of structural MRI) as seed voxels for fiber tracking. Two cortical regions were considered connected if there exist fibers with two end-points located in their masks, respectively. For each subject, the numbers of existing fibers connecting every pair of regions were counted. c) Cortical connectivity network: To identify highly consistent connections across subjects, a non-parametric hypothesis test (i.e. sign test) was applied to every pair of cortical regions with the null hypothesis that there is no existing connection, i.e. "fiber number = 0". A Bonferroni method was further used to correct multiple comparisons at $P < 0.05$. Under this conservative statistical criterion, a symmetric and binarized matrix capturing underlying cortical network topology was yielded, in which 1 represents existence of a connection and 0 otherwise. **2) Cortical Network Analysis.** The resulting cortical network was analyzed by using graph theoretical approaches as follows. a) Small-world analysis: Average clustering coefficient C_p and path length L_p were calculated for this network[6]. The network would be considered small-world if $\gamma = C_p^{cortex} / C_p^{rand} >> 1$ and $\lambda = L_p^{cortex} / L_p^{rand} \approx 1$, where C_p^{rand} and L_p^{rand} are the mean clustering coefficient and characteristic path length of 1000 matched random networks that preserve the same number of nodes, edges and degree distribution as the real network. b) Node and edge betweenness centrality: The betweenness of a node or an edge is defined as the number of shortest paths between pairs of other nodes that pass through the node or the edge[7, 8]. The nodes or edges with high betweenness values can be considered pivotal nodes or connections within the network.

Results: Fig b illustrates examples of anatomical connections involving three major long-range tracts and one short-range tract. Under our statistical criterion ($P_{corrected} < 0.05$), 329 pairs of cortical regions showed significant anatomical connectivity, resulting in a symmetric and binarized cortical network without isolated nodes (Fig c). The clustering coefficient of the cortical network ($C_p^{cortex} = 0.49$) is approximately four times that of a comparable random network ($C_p^{rand} = 0.12$), whereas the path length ($L_p^{cortex} = 2.32$) is approximately equivalent to the random network ($L_p^{rand} = 2.02$), thus exhibiting a prominent small-world characteristic ($\gamma = 4.07$; $\lambda = 1.15$). Furthermore, pivotal nodes and edges can be identified in this network (Fig d). The nodes with high betweenness centrality (i.e. hubs) are predominantly involved in the regions of the heteromodal or unimodal association cortices (e.g. the precuneus, middle occipital gryus and dorsolateral prefrontal cortex), and the edges with high betweenness centrality (i.e. bridges) are mainly associated with the white matter tracts connecting the two hemispheres (e.g. corpus callosum) or different lobes within one hemisphere (e.g. inferior fronto-occipital fasciculus).

Discussion: In this study, we employed DTI tractography to construct a macroscale anatomical network that captures the underlying common connectivity pattern of cerebral cortex (i.e. backbone) across a population (N=80) of healthy young adults, rather than a very detailed network for an individual brain[3]. This cortical network was found to exhibit small-world topology with the embedded pivotal nodes and connections mainly involving the association cortex regions and long-range white matter tracts, respectively. The results are compatible with previous functional network studies using fMRI data[9] and structural network studies using T1-weighted MRI data[10] in humans, which suggests that DTI tractography is a valid and complementary approach for the construction of anatomical networks. This approach could be applied to explore the changes in the topological properties of the cortical network with normal development, aging and brain disorders.

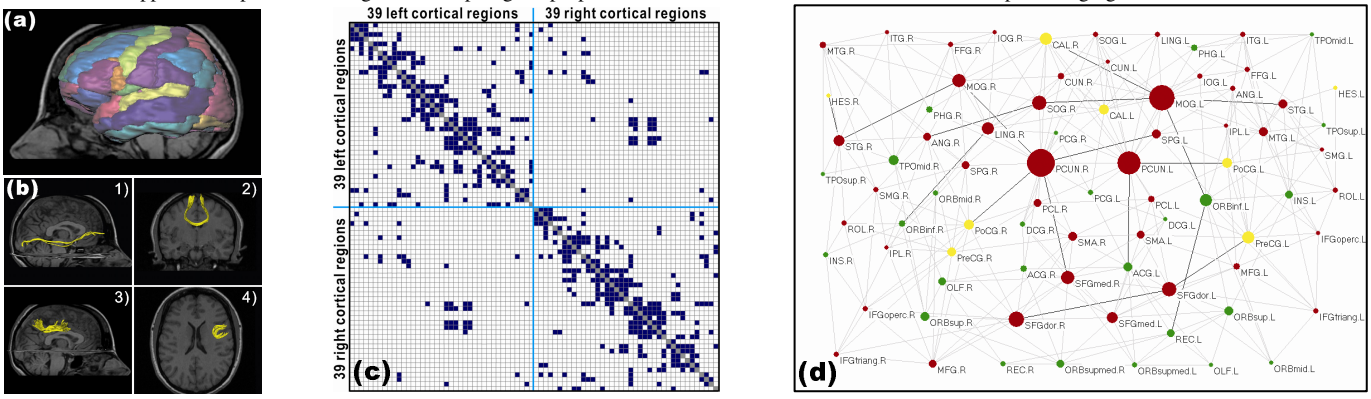

Figure (a) Cortical parcellation of one subject. (b) White matter fibers of connection examples in the same subject: 1) inferior fronto-occipital fasciculus connecting right middle frontal gyrus (orbital part) and right lingual gyrus; 2) the body of corpus callosum connecting the left and right paracentral lobules; 3) superior longitudinal fasciculus connecting right precentral gyrus and right inferior parietal gyrus; 4) a U-shape tract in right frontal lobe connecting right inferior frontal gyrus (opercular part) and right precentral gyrus. (c) Anatomical connection matrix of human cortical network demonstrating both intra- and inter-hemispheric connections (space too limited to label individual cortical regions). (d) The topological map of human cortical network by using the Pajek software with established abbreviations[9]: Circle size represents the magnitude of node betweenness. Association, primary and paralimbic cortex were marked as red, yellow and green, respectively. Dark solid lines represent pivotal connections with high edge betweenness.

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