Mapping Putative Centrality Hubs in Rhesus Macaques and Humans Using Diffusion Tractography and Graph Theory

Longchuan Li[1], Xiaoping Hu[2], Todd Preuss[3,4], Matthew F. Glasser[5], Frederick W. Damen[2], Yuxuan Qiu[6], and James Rilling[4,7]

[1]Biomedical Imaging Technology Center, Emory University/Georiga Tech, Atlanta, GA, United States, [2]Department of Biomedical Engineering, Emory University/Georgia Tech, Atlanta, GA, United States, [3]Division of Neuropharmacology and Neurologic Diseases, Yerkes National Primate Research Center, Emory University, Atlanta, GA, United States, [4]Center for Translational and Social Neuroscience, Emory University, Atlanta, GA, United States, [5]Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, United States, [6]School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, United States, [7]Department of Anthropology, Emory University, Atlanta, GA, United States

Introduction: Recently, there has been significant interest in mapping the brain's anatomical networks using diffusion tractography and in analyzing the derived complex networks via graph theory, as the approach may provide critical clues as to how the brain works as networks(*1*). However, one urgent question that remains to be answered is the accuracy of the tractography-derived brain networks, as currently there is no gold standard to validate such networks in human brains. Here we reconstructed anatomical brain networks from 10 monkeys and 10 humans via probabilistic tractography(*2*) and derived putative hubs across their cerebral cortices based on graph-theoretic metrics. We then (i) compared our tractography-derived hubs with those from a recent study in which tracer-derived connection information collated over 400 studies was utilized to identify similar hubs in macaque monkeys(*3*) and (ii) compared the tractography-derived brain networks across the two species for insight into putative hubs that have been preserved and modified in human evolution.

Methods: Ten female rhesus monkeys (14±6.7 yrs) and ten female human volunteers (42.5±9.8 yrs) were included in the study. MRI data were obtained using two 3T Trio Tim scanners (Siemens Trio, Pennsylvania, US). The imaging parameters are as follows: for macaques, three averages of T1-weighted images with isotropic resolution of 0.5mm^3 were acquired. Ten averages of diffusion MR data with isotropic resolution of 1.1mm^3, 60 directions, b of 0 and 1000 and opposite phase encoding directions were obtained. For humans, one average of T1-weighted image with isotropic resolution of 1mm^3 was acquired. The human diffusion MR data were obtained with isotropic resolution of 2mm^3 and two averages, 60 diffusion directions, b of 0 and 1000 and opposite phase encoding directions. Post-processing of diffusion MRI data included definition of nodes and edges of brain networks. To define the nodes of the brain networks, we parcellated the entire cerebral cortex (two hemispheres) using a random parcellation approach with two network resolutions (N=300 and 600) for a balance of robustness and sensitivity. To define the edges of the brain networks, we utilized the local probabilistic tractography algorithm in FSL to derive interparcel connections, and then thresholded the derived connectivity matrices at five thresholds (network density: 10, 15, 20, 25, 30%). Lastly, we identified putative hubs (*3*)(defined as the brain areas with at least two out of four centrality measures, i.e., closeness centrality, betweenness centrality, vulnerability and dynamic importance, being among the top 10% of the respective measure across all brain areas) under the 2 network resolutions and 5 thresholds. The individually derived putative hubs were then averaged for a probability map.

Results: When comparing the identified putative hubs in our tractography-derived macaque brain networks with those from tracer-derived brain networks, we found a relatively good correspondence of the identified hubs in the ventrolateral, polar and medial prefrontal cortex, the medial parietal cortex and inferior parietal cortex. On the other hand, major discrepancies were observed in the inferior temporal cortex, the mid-cingulate cortex, the insular cortex, and the retrosplenial/prostriate cortex. In both macaques and humans, putative hubs were identified in the insular cortex, the medial parietal cortex and the retrosplenial cortex, suggesting largely evolutionarily conserved hubs in these areas. Differences between the two species were found in the polar and medial prefrontal cortex, with both tracer- and tractography-derived results in macaques demonstrating structural hubs in these areas, in contrast to the absence of such hubs in the tractography-derived human brain networks.

Discussion: Although invasive tracers are probably the most reliable ways to study inter-areal connections in real brain tissues, they are not without problems. Both tracer and tractography methods have limitations (i.e., lack of directionality, sensitivity to weak connections, and geometric biases on the gyral connectivity in tractography methods; lack of inter-subject and inter-hemispheric variability, commissural connections in tracer methods). Therefore, the graph-theoretic characteristics of the two types of networks are not expected to be identical. When comparing with the hubs in the prefrontal cortex between macaques and humans, we found interesting differences in this region between the two species, largely in line with the significant interspecies morphological and functional differences in the prefrontal cortex in literature (*4*, *5*). However, caution is warranted, as reconstructing brain networks with tractography is a complex and not yet fully validated procedure. Future studies in a larger sample size and utilizing multiple tractography strategies are needed to confirm these preliminary findings.

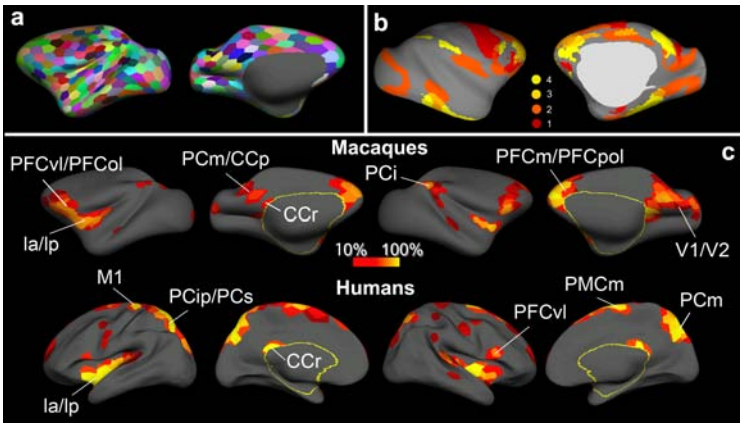

Fig.1. The putative structural hubs in macaques and humans. Fig.1a shows an example of macaque random parcellation scheme with 600 parcels in two hemispheres. Fig.1b shows the putative centrality hubs modified adapted from Haggier et al.(3) Fig.1c shows the probability map of identified centrality hubs under 2 network resolutions (N=300,600) and 5 thresholds for each resolution. 10% in the map indicates that hub is identified at least once under the 2 network resolutions and 5 thresholds, whereas 100% indicates they were identified in all these conditions.

Acknowledgement: This work was kindly supported by NIH 5P01 AG026423-03. We must thank Govind Nair and Xiaodong Zhang for assisting in acquiring the data. **References:** 1.P. Hagmann *et al.*, *PLoS Biol* **6**, e159 (Jul 1, 2008); 2. M. Jenkinson, C. F. Beckmann, T. E. Behrens, M. W. Woolrich, S. M. Smith, *NeuroImage* **62**, 782 (Aug 15, 2012); 3. L. Harriger, M. P. van den Heuvel, O. Sporns, *PLoS One* **7**, e46497 (2012); 4. D. C. Van Essen, D. L. Dierker, *Neuron* **56**, 209 (Oct 25, 2007); 5. K. Denys *et al.*, *Journal of cognitive neuroscience* **16**, 1505 (Nov, 2004).