Evaluating longitudinal reliability and cross-subject sensitivity of structural connectivity networks computed using probabilistic fiber tracking

Alex Smith[1], Madhura Ingalhalikar[1], and Ragini Verma[1]
[1]*Section for Biomedical Image Analysis, University of Pennsylvania, Philadelphia, PA, United States*

Background and Objectives: Characterization of the human brain via whole brain connectivity (functional as well as structural) is an area of increasing interest. Such connectivity networks are generally analyzed at the edge-level [1] or by using global graph-theoretic measures [2]. If these networks and measures are to be used in population studies, it is vital both to investigate their reliability over longitudinal scans of the same subjects, and to show that across-time variation in a single subject is lower than between-subject variability. Reliability studies in this area have typically concentrated on functional connectivity [3] while the limited work that has been done on structural connectivity has focused on networks derived from deterministic fiber tracking [4], or on the effect of tracking algorithms at single time points [5]. In this work, we perform a test-retest analysis across three time points on structural networks constructed via probabilistic tractography. We test for longitudinal and between-subject sensitivity, and assess the reliability of graph metrics in the original networks and at various levels of binary thresholding (which leads to networks at different densities).

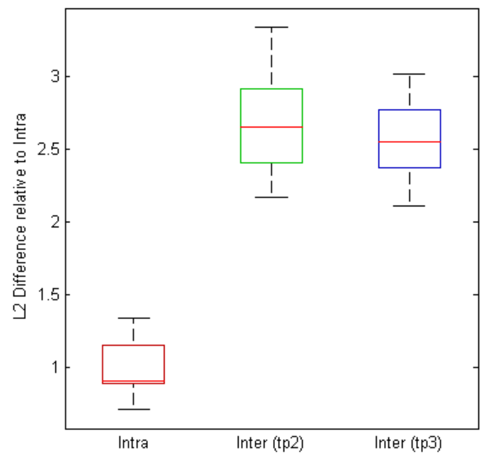

Fig 1. *Box-plot showing intra- and inter- subject L2 differences between weighted connectivity matrices.*

Methods: Our data consisted of 9 subjects (6 male, 3 female). Diffusion Tensor Images were acquired for three time points spaced two weeks apart on a Siemens 3T Verio™ scanner, using a single-shot spin-echo echo-planar sequence with the following parameters: TR/TE=11400/78ms, b-value 1000 s/mm^2, and 64 gradient directions. Cortical parcellation and sub-cortical segmentation were obtained by applying FreeSurfer [6] to structural T1 images and a total of 95 ROIs were extracted to represent the nodes of the structural network, incorporating 68 cortical regions and 27 sub-cortical structures. These node labels were then transferred to the diffusion space via intra-subject affine transformation. Probabilistic tractography [7] was performed on all the subjects with 5000 streamline fibers sampled per voxel. The seed region was limited to the GM-WM boundary of each ROI for reliable tracking. The result was a 95 x 95 matrix **W** of weighted connectivity values, where W_{ij} represents the conditional probability p_{ij} of a pathway between regions i and j, normalized by the active surface area R_i of the ROI i. This matrix was treated as a weighted, undirected network. We first calculated the L2 differences of the weighted matrices both within and across subjects for time points 2 and 3, measuring both the sensitivity of the matrices in differentiating between subjects and the overall consistency of a subject's structural connectivity patterns across time points. The matrices were then thresholded over graph densities ranging from 0.1 to 0.4 to extract four corresponding binary networks in addition to the original weighted network. Then, for each subject, session, and matrix type, we calculated the following graph-theoretic measures: global efficiency, modularity, assortativity, characteristic path length (CPL), and average clustering coefficient (ACC) [2]. The reliability of each of these measures was evaluated using the intra-class correlation coefficient (ICC), to assess whether they were consistent across time points and the sensitivity of that reliability to the different levels of binary thresholding.

Results: Box-plots in Fig 1 show the average inter- and intra-subject L2 differences. The average inter-subject difference is approximately 2.5 times the average intra-subject difference, suggesting that the weighted networks are able to capture individual anatomy and connectivity patterns. Fig 2 displays the results of the reliability analysis for the global graph metrics. The average ICCs across all densities are as follows: global efficiency, ICC=0.830±0.128; modularity, ICC=0.816±0.08; ACC, ICC=0.746±0.155; CPL, ICC=0.772±0.066; assortativity, ICC=0.667±0.067. The ICC for the mean edge weights without thresholding is 0.594.

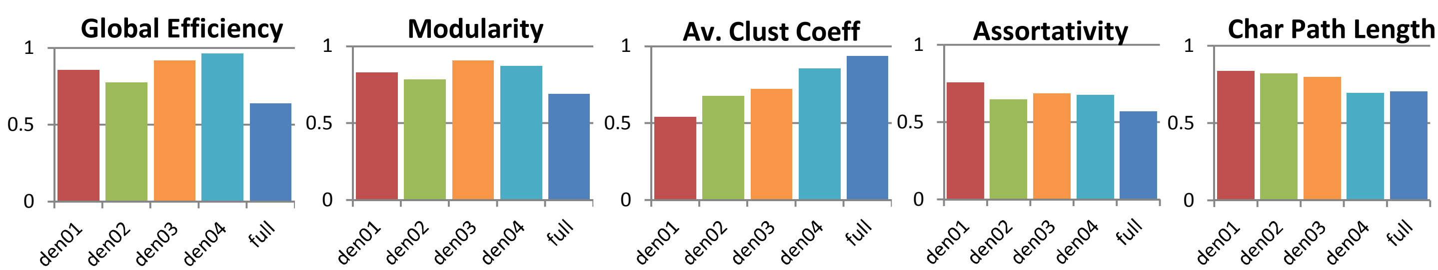

Fig 2. *Plots of the ICCs for the tested metrics. Each metric was assessed using the full weighted connectivity matrix ('full'), and four binary matrices thresholded at densities 0.1, 0.2, 0.3 and 0.4 ('den01', 'den02', 'den03', 'den04' respectively)*

Discussion: In this work, we examined the reliability of graph-theoretic measures extracted from structural connectivity networks, as derived via probabilistic tractography from DTI images, when evaluated on the same subject at different time points. We found that the longitudinal intra-subject variance was lower than the inter-subject variance, indicating that weighted networks can be reliably used in population studies. Furthermore, while the graph-theoretic measures all had moderately high reliability across the three time points (ICCs from 0.667 to 0.830), this reliability varied based on the network density. Overall, while the ACC showed higher repeatability and reduced variance in the weighted network, binary thresholding generally resulted in increased ICCs for global efficiency, CPL, assortativity and modularity. This may reflect the decreased uniformity of the weighted networks versus the binary networks, which may suffer from reduced variability and possibly show less variation across subjects.

References: [1] Zalesky et al., NeuroImage, vol 54, 2010 [2] Rubinov et al., Neuroimage, vol 52, 2010. [3] Braun et al., NeuroImage vol 59, 2012 [4] Bassett et al., NeuroImage vol 54, 2011 [5] Bastiani et al., NeuroImage, vol 62, 2012 [6] Desikan et al., Neuroimage, vol 31, 2006 [7] Behrens et al., Magn Reson Med, vol 50, 2003

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