A Study of Effect of Compiling Method on Interregional Connectivity Maps of Brain Networks via Diffusion Tractography

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Introduction: Compiling anatomical interregional connections of large-scale brain networks via diffusion magnetic resonance imaging (MRI) and tractography has recently gained significant interest because of its fundamental role in understanding brain functions [1]. However, reconstructing such a brain network is a complex process [2] and many parameters selected during the procedure can affect the outcomes of the mapping. For example, deriving connectivity strength between brain areas via probabilistic tractography might generate different connectivity fingerprints when the white matter, rather than the cortical grey matter, is used as the seed masks for tracking, as the two approaches have different distance-related effect in Monte Carlo random walk-based probabilistic tractography. The aim of the current study is to investigate the influence of different compiling methods used for reconstructing anatomical brain networks on the resultant interregional connectivity maps.

Methods: ***Subject:*** Ninety-four healthy right-handed human subjects (age: 24.2±0.84 yrs, 48 females) were recruited in this study after informed written consent. ***Image acquisition***: MRI images were obtained using a 3T Trio scanner (Siemens Trio, Pennsylvania, US). T1-weighted images were acquired with 3D MPRAGE sequence with the following parameters: FOV=240×256×176 mm^2, matrix size: 240×256×176, 1 mm isotropic voxel. Diffusion MR data were acquired with the following parameters: dual spin-echo diffusion echo-planar imaging sequence with GRAPPA (factor of 2), FOV=230×230 mm, matrix size: 108×128, 64 slices covering the whole brain, 2 mm isotropic voxels, two averages with opposite phase encoding directions to remove the susceptibility distortion [3]. ***Network Reconstruction:*** All preprocessing steps of the data were carried out using FSL. FreeSurfer was used to parcellate the brain into 82 cortical and subcortical regions, which serve as nodes and one white matter mask, which serves as the white-matter seed mask used in the first compiling method. Then probabilistic tractography toolbox Fdt implemented in FSL was employed to derive the inter-node connectivity information. In the first method (M1), 2000 streams were sent from each voxel in the white-matter seed mask. Any "probabilistic streamline" where two ends reached two different grey matter targets was counted, contributing one unit to the connectivity strength between the two given nodes. In contrast to M1, the second method (M2) started tracking from the gray matter/white matter (GM/WM) interface of each of 82 brain regions defined in partitioning process. The third method (M3) initiated tracking the same way as in M2, but used the thresholded tract volume instead of the number of connected "probabilistic streamlines" as the connectivity index. Simulated diffusion MR data of white-matter fiber bundles with different coherence (FA=0.7, 0.2), length (0-160mm) but identical diameters were generated. Then the three methods were applied on the simulated data to study the influence of fiber length on connectivity index.

Results & Discussion: Figure 1 shows the distance effect of the simulated fibers with various lengths on the connectivity index in the simulations. The results demonstrated that when the fiber coherence was high (FA=0.7), the connectivity index in both M1 and M2 showed a clear distance-related effect (Fig1A, M1: R^2=0.99; M2: $y=0.42x^{-0.43} + 0.04$, R^2=0.95), indicating a possible bias in the normalized connectivity density (NCD), favoring longer white matter tracts in M1 and vice versa in M2. In contrast, no significant distance effect was seen in M3 (Fig1A, $y=-1.5^{-5}x + 0.12$, R^2=0.02). This could be partially explained by the fact that in M3, even though the two brain regions linked by longer tracts have reduced connectivity due to the dispersion of the local probability density functions (*pdfs*), the increased tract volume (normalized tract volume, NVD) could partially compensate for that. When fiber coherence was low (FA=0.2), the connectivity indices in all three methods decreased significantly as the increase of the fiber length (Fig.1B). The betweenness centrality (BC) derived from the interregional connectivity maps are listed in Figure 2. The four graph theoretic measures, i.e., the local efficiency, degree, strength and BC, were demonstrated to be cross-correlated with each other within as well as between each method (mean R_{all_within}=0.76, mean $R_{all\_between}$=0.67), with BC showing the lowest correlation coefficients among the four graph measures (mean R_{BC_within}=0.63, mean $R_{BC\_between}$= 0.58). Among the sixteen nodes with the highest BC (top 20% of 82 nodes), the bilateral putamen, bilateral superior frontal cortex and left precuneus were unanimously identified as hubs in all three methods, consisting of approximately 31% of the selected nodes. Interestingly, the precuneus is the only brain region that has been identified as the hub in all the brain connectivity studies, including ours, based on a meta-analysis (results not shown here).

Conclusions: we demonstrated in the simulated and *in vivo* diffusion MR data that although the graph theoretic measures across different compiling methods are moderately to highly correlated, significant between-method differences exist, resulting in discrepancies in hub identification and hemispheric asymmetry in connectivity patterns. Therefore, the compiling method employed for reconstructing connectivity information via probabilistic tractography must be considered as a confounding factor when comparing interregional connectivity information across studies.

References: [1]. O., Sporns., et al., PLoS Comput Biol, 1(4),2005,e42;[2]. P., Hagmann, et al., PLoS Biol, 6(7),2008,e159; [3]. J., Andersson, et al., Neuroimage, 2003,20(2), 870.

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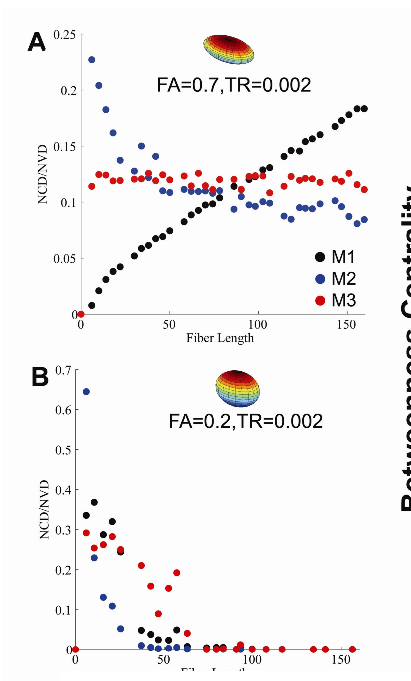

Figure 1. The effect of the fiber length on the derived connection information in the cases when fiber bundles are coherent (A) and incoherent (B).

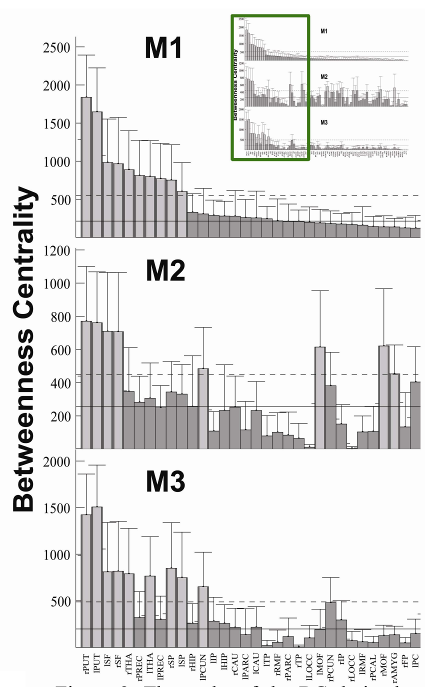

Figure 2. The ranks of the BC derived using the three methods. The main figure is part of the magnified figure shown in the upper right corner.