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Investigating the Effects of Streamline-based Fiber Tractography on Matrix Scaling in Brain Connective Network

Hengtai Jan, Yi-Ping Chao, Kuan-Hung Cho and Li-Wei Kuo

Abstract— **Investigating the brain connective network using the modern graph theory has been widely applied in cognitive and clinical neuroscience research. In this study, we aimed to investigate the effects of streamline-based fiber tractography on the change of network properties and established a systematic framework to understand how an adequate network matrix scaling can be determined. The network properties, including degree, efficiency and betweenness centrality, show similar tendency in both left and right hemispheres. By employing the curve-fitting process with exponential law and measuring the residuals, the association between changes of network properties and threshold of track numbers is found and an adequate range of investigating the lateralization of brain network is suggested. The proposed approach can be further applied in clinical applications to improve the diagnostic sensitivity using network analysis with graph theory.**

I. INTRODUCTION

Mapping the intrinsic cerebral anatomical circuitry is critical to understand the neural basis of brain functions in healthy and diseased status. With diffusion magnetic resonance imaging (MRI), a non-invasive neuroimaging technique, cerebral white matter bundles can be depicted by detection of the most coherent directions of water molecular diffusion. By employing streamline-based fiber tracking on reconstructed fiber orientations, the structural connectivity between various regions-of-interest (ROIs) defined by appropriate selection of anatomical landmarks can be quantified in terms of anisotropy or track density indices. These quantitative metrics could potentially help us understand the inter-regional fiber integrity and connectivity strength. Previous studies have demonstrated the alteration of structural connectivity may be associated with the change of functional connectivity or behavior measures in diseased patients [1].

To investigate how brain's sub-regions are structurally connected with each other, global network analyses using modern graph theory provide an accessible route to map the whole-brain anatomical network and its properties [2]. Each brain network consists of nodes and edges, which are defined by anatomical sub-regions and their inter-regional connective strength, respectively. Conventional approach to construct the brain network from streamline-based tractography consists of the following procedures: defining nodes, constructing network matrix and deriving network properties. Although the methodological framework has been established, the effects of analysis parameters to the change of network properties not have been fully understood [3].

One of the critical processes in network analysis, which may affect the calculation of network properties, is how to scale the network matrix. In previous studies, applying a threshold for the normalized sparse density of a network matrix has been typically performed to obtain the binarized network matrix [4]. However, another analysis parameter, referred to as track number, has been considered as a critical factor, which has to be taken into concern in the binarization procedure [5].

Therefore, in this study, we aimed to investigate the effects of setting the threshold of track number on the change of network properties in mapping the brain lateralization [6]. A framework to obtain an adequate threshold to binarize the network matrix was proposed and lateralization indices of network properties were calculated among healthy right-handed subjects [7]. Future works may include investigation of inter-hemispheric and intra-hemispheric properties using network analysis, as well as lateralization of brain network on specific cognitive processes or in diseased status.

II. METHOD

A. MRI experiments

A total of ten healthy volunteers (*5* males and *5* females, *18-22* yrs, right-handed) were studied in this study. All subjects provided informed consent, and the experimental procedures were approved by the Institutional Review Board. In this study, handedness was tested by documenting the dominant hand of participants. MR experiments were performed on a 3T MRI system (Tim Trio, Siemens, Erlangen, Germany) with a 32-channel head coil. To reduce the eddy current effect, twice-refocused balanced echo diffusion echo-planar imaging (EPI) sequence was used to acquire MR diffusion images. A total of *162* diffusion-weighted images with a maximum b-value of *3000* s/mm^2 were acquired on a shell in q-space. An additional un-weighted diffusion image was also acquired. Isotropic voxels were obtained with an in-plane resolution and slice thickness of *2* mm. A total of *60* slices with TR of *11.7* seconds were acquired, and the total scan time was approximately *30* minutes. Anatomical T1-weighted image was also acquired for template registration and node definition.

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B. *Streamline-based fiber tractography reconstruction*

Q-ball imaging (QBI) reconstruction was performed on acquired diffusion MR data to obtain the orientational density function (ODF) within each voxel, which can infer to the fiber orientations [8]. The ODF was directly calculated from the attenuated echo signal on a shell in the q-space with a fixed b-value based on the Funk-Radon transform approach. The detailed procedures of QBI reconstruction can be found in Tuch's papers, and were described very briefly here. It bypasses the computation of PDF and estimates ODF and local fiber orientations directly. ODF within each voxel was reconstructed to 362 radial directions pointing at the vertices of regular triangular mesh on the unit sphere surface.

A streamline-based fiber tracking algorithm was applied on the reconstructed ODF to obtain the whole brain white matter tractography. At each seeding point, tracking process was started in the direction of the most prominent fiber. The parameters for tractography proceeded step-size of 0.5 voxel length, turning angle threshold of 60° and total reconstructed track number of Nt. The propagation direction was calculated by applying tri-linear interpolation on the fiber orientations provided from eight nearby voxels of the current point. For each nearby voxel, only the fiber orientation that had the smallest turning angle was considered for interpolation. Voxels with generalized fractional anisotropy less than 0.02 were excluded for interpolation. The analysis of QBI reconstruction and fiber tracking was performed using an academically available tractography software package, DSI Studio (http://dsi-studio.labsolver.org).

C. *Network analysis using graph theory*

To construct the adjacency matrix from a network, anatomical automatic labeling (AAL) approach was firstly applied on each subject's T1-weighted data and a total of 116 ROIs normalized to MNI template were obtained to be the un-directed network nodes. In this study, the dependency between the track threshold (D_{th}) of normalized track number and network properties was investigated, where the normalized track number between ROI i and ROI j was defined as the ratio of track number between ROI i and ROI j (n_{ij}) and the total track number (N_t) within whole brain. Here, the track threshold was used to binarize the adjacency matrix of the network. Three metrics to describe the network properties were derived from the resulting adjacency matrix, including the degree, betweenness centrality and efficiency. Here, we summarize these metrics and their corresponding physical property briefly:

(a) Degree:

The degree of a node is the number of connections that link it to the rest of the network. The stable mean degree ($<N_{deg}>$) denoted a network has stable structure so that we can confirm its property in steady. Besides, the mean degree is proportional to the sparse density of the matrix by the factor of inverse node number.

(b) Betweenness centrality:

Betweenness centrality is a widely used measure to identify the most central nodes in a graph, which are associated to those nodes that act as bridges connecting any other two nodes. It is defined as the fraction of shortest paths between pairs of nodes that passes through a given node. Mathematically, σ_{kj} is the number of paths from node k to node j, and $\sigma_{kj}(i)$ is the number of these paths passing through node i, the betweenness centrality of i is

$$b_i = \sum_{\substack{k,j \in G \\ k \neq i \neq j}} \frac{\sigma_{kj}(i)}{\sigma_{kj}}.$$

(c) Efficiency:

The efficiency (E_g) of a network G reflects how efficiently information can be exchanged over G, considering a parallel system in which each node sends information concurrently along the network. It is defined as

$$E_g = \frac{1}{n(n-1)} \sum_{\substack{i,j \in G \\ i \neq j}} \frac{1}{d_{ij}},$$

where n is the number of nodes, and d_{ij} is the shortest path length over all pairs of nodes. The local efficiency of G (i.e. of hemi-sphere brain) is defined as the average efficiency of the local sub-network:

$$E_{lo} = \frac{1}{n} \sum_{i \in G} E_g(G_i),$$

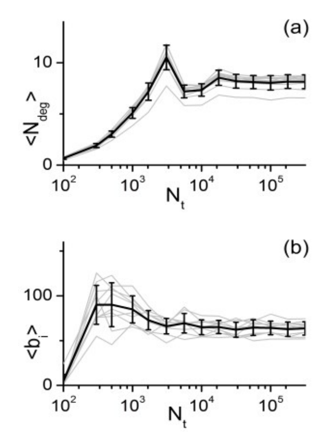
where G_i is the sub-network of the first neighbors of node i. The efficiency of a brain structural network reflects the potential parallel exchange of neural information between the involved anatomical regions. The efficiency of a hemi-spherical brain network can be estimated by average of local efficiency after individual efficiency has been estimated in a whole brain respect.

D. *lateralization index calculation*

To characterize asymmetry for a given network measure X (degree, betweenness centrality or efficiency), a lateralization index (L_i) was calculated by

$$L_i(X) = 100\% \times \frac{X_{Left} - X_{Right}}{X_{Left} + X_{Right}},$$

where X_{Left} indicates the network measure in left hemi-sphere and X_{Right} indicates that in right hemi-sphere. This measure allows us to investigate the asymmetry of the brain structural network and quantify the degree of lateralization, which is positive when X is much leftward, and vice versa.



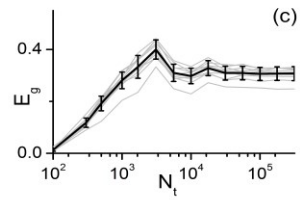


Figure 1. Network indices vs. number of tracks (whole-brain). (a) Degree, (b) Betweenness centrality and (c) Efficiency. The results of individual subjects are plotted in gray and the averaged values are in black.

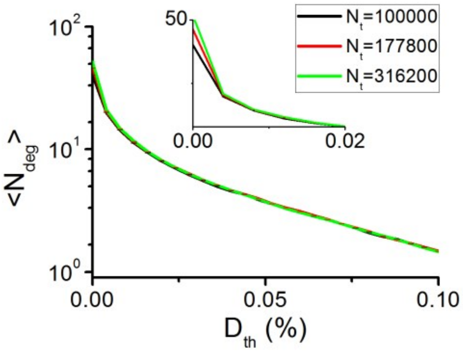
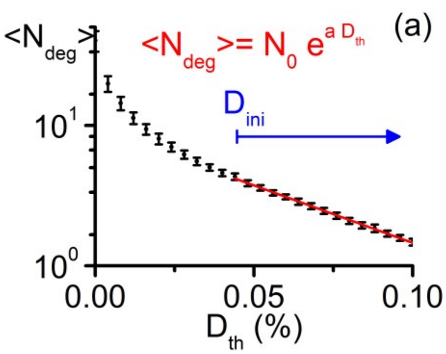


Figure 2. Degree vs. track threshold among different numbers of tracks.

III. Result and discussion

Figure 1 shows the averaged whole-brain network indices against the number of whole-brain tracks among ten subjects. A similar tendency between the degree and efficiency was observed and a cut-point of track number can be found at approximately *50000*. However, the betweenness centrality shows a slightly different pattern, suggesting that it doesn't alter too much among different numbers of whole-brain tracks. As shown in figure 2, the results of degree among different numbers of tracks were plotted against the track threshold. Three different numbers of tracks were used here, that is *100000*, *177800* and *316200*. Above a certain threshold of approximately *0.05%*, no significant difference of the results of degree was found among these three numbers of tracks, suggesting that the N_t of *100000* could be used for following analysis. The zoom-in figure in the upper-right corner shows that a slight difference was found in the range of track threshold below *0.05%*.



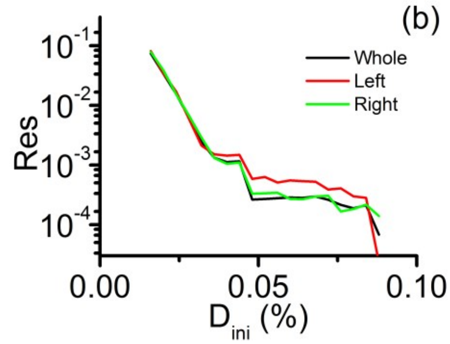


Figure 3. Determination of the fitting range on track threshold in network matrix binarization. (a) Exponential law fitting on the range from Dini and (b) The fitting residure v.s. Dini (Whole-brain: black; left: red; right: green)

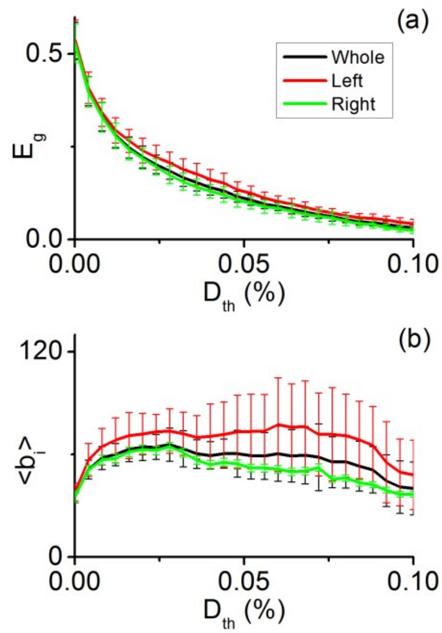


Figure 4. *The results of efficiency and betweenness centrality against the track threshold. (a) Efficiency and (b) Betweenness centrality. (Whole-brain: black; left: red; right: green)*

Figure 3 shows how the association between the track threshold D_{ini} and the residuals of network properties is. Sub-figure (a) shows the fitting curves with exponential law and (b) shows the residuals for different threshold D_{ini}, respectively. The black, red and green plots indicate the residual results in the networks of whole brain, left hemisphere and right hemisphere, suggesting that one can obtain stable results of network properties in the threshold range above 0.05%.

Figure 4 shows the results of efficiency and betweenness centrality against the track threshold. As shown in sub-figure (a), the tendency of efficiency in both left and right hemispheres is consistent with the whole-brain efficiency. As shown in sub-figure (b), a slightly larger difference between left and right hemispheres was found in the range of higher track threshold between *0.06%* and *0.10%*, which may suggest that the nodes in left and right hemispheres may have different centralized patterns because they control different specific cognitive functions.

Figure 5 shows the averaged lateralization indices of efficiency (sub-figure a) and betweenness centrality (sub-figure b) among ten healthy subjects. Positive values of lateralization indicate the leftward lateralization. In results, leftward lateralization is shown in both efficiency and betweenness centrality, especially in the regions of higher track threshold.

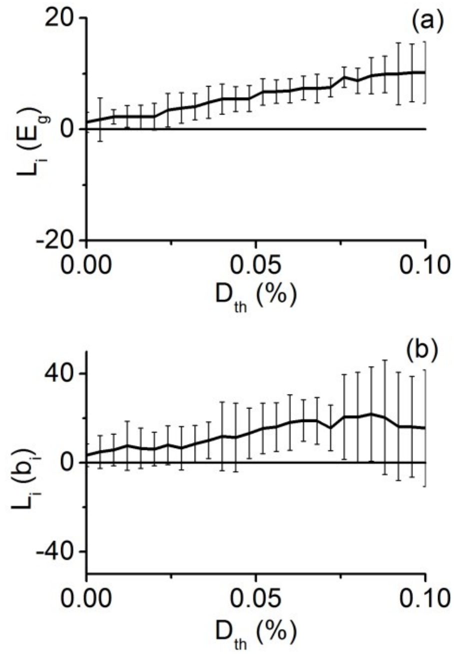


Figure 5. *Lateralization indices of (a) efficiency and (b) betweenness centrality against the track threshold. The results are averaged from ten subjects and error bars represent the standard deviations.*

IV. CONCLUSION

In this study, we proposed a systematic framework using a fitting approach with exponential laws to investigate an adequate range of threshold of track numbers. The results of network properties, including degree, efficiency and betweenness centrality, show consistent tendency in both of left and right hemispheres. The lateralization patterns of brain connective networks were investigated by varying different thresholds. This proposed framework could potentially help us to improve the robustness of structural network analysis with streamline-based tractography. Future works may include a systematic optimization framework of general tracking parameters using machine learning or neural network methods.

REFERENCES

[1] E. Bullmore and O. Sporns, "Complex brain networks: graph theoretical analysis of structural and functional systems," Nature Reviews Neuroscience, 10, 186–198, 2009..

[2] O. Sporns, "The human connectome: a complex network," Ann. N.Y. Acad. Sci., 1224 109–125, 2011.

[3] D.S. Bassett and E. Bullmore, "Small-World Brain Networks," The Neuroscientist, 12, 512-523, 2006.

[4] Alex Fornito, Andrew Zalesky, and Edward T. Bullmore, "Network scaling effects in graph analytic studies of human resting-state fMRI data," Frontiers in Systems Neuroscience, 22, 1-16, 2010

[5] A. Zalesky, L. Cocchi, A. Fornito, M.M. Murray, E. Bullmore, "Connectivity differences in brain networks," NeuroImage, 60, 1055–1062, 2012.

[6] A. W. Toga and P. M. Thompson, "Mapping brain asymmetry," Nature Reviews Neuroscience, 4, 37-48, 2003.

[7] Y. Iturria-Medina et al., "Brain Hemispheric Structural Efficiency and Interconnectivity Rightward Asymmetry in Human and Nonhuman Primates," Cerebral Cortex January; 21, 56-67, 2011.

[8] D.S Tuch, "Q-Ball Imaging," Magn. Reson. Med., 52, 1358-72, 2004.