Diffusion Tensor Tractography Reveals Disrupted Structural Connectivity during Brain Aging

Lan Lin, Miao Tian, Qi Wang and Shuicai Wu

Biomedical Engineering Department, Beijing University of Technology, Beijing, China,
Email: lanlin@bjut.edu.cn, tianm@email.bjut.edu.cn, qiwang@bjut.edu.cn, shuicaiwu@bjut.edu.cn

Abstract. Brain aging is one of the most crucial biological processes that entail many physical, biological, chemical, and psychological changes, and also a major risk factor for most common neurodegenerative diseases. To improve the quality of life for the elderly, it is important to understand how the brain is changed during the normal aging process. We compared diffusion tensor imaging (DTI)-based brain networks in a cohort of 75 healthy old subjects by using graph theory metrics to describe the anatomical networks and connectivity patterns, and network-based statistic (NBS) analysis was used to identify pairs of regions with altered structural connectivity. The NBS analysis revealed a significant network comprising nine distinct fiber bundles linking 10 different brain regions showed altered white matter structures in young-old group compare with middle-aged group ($p < .05$, family-wise error-corrected). Our results might guide future studies and help to gain a better understanding of brain aging.

1. Introduction

With the rapid growth of people aged 60 or older in China, it has been increasingly important to understand the characteristics of age-related brain and cognitive changes. Brain aging is a complicated biological process and changes in a myriad of ways, often related to the brain shrinkage, replicating cells' damage, and decline in cognitive functions. Much of the cognitive changes were the result of aging: poorer vision and hearing, increased forgetfulness, slower information processing, etc. Brain aging itself does not constitute a disease, but those aged related changes are amplified in most common neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, stroke, etc [1-3].

Human brain, as the center of the nervous system, is one of the most remarkable aspects of the adult nervous system. The average human brain is estimated to contain approximately 100 billion neurons [4], each connected by synapses to several thousand other neurons. An increasing number of theoretical and empirical studies study the organization of the human brain as a synthesis of the sciences of complex networks. By mapping brain, as a set of nodes and edges, connectome analysis [5] could help us to understand the brain from the perspective of the network. The application of graph theoretical analysis to human neuroimaging data has uncovered topological features of the connectome [6, 7]. Tractography based on diffusion tensor imaging (DTI) [8], has been widely adopted as a tool by researchers to investigate structural connectome, due to its advantage of in-vivo white matter (WM) mapping. Although some research has examined the organization of the brain network during brain aging at the nodal-level [9, 10], relatively few studies have specifically performed for network level.

In the graph theoretical analysis of structural brain network, a large number of univariate statistical tests are undertaken to test the local level hypothesis related to network nodes or edges. The more inferences are made, the more likely erroneous inferences are to occur. There is no universally accepted
approach for the problem of multiple comparisons; most approaches require a stricter significance threshold for individual comparison, which may not offer sufficient statistical power. The aims of this study were to explore the DTI to investigate the topological WM changes during the normal aging by using network-based statistic (NBS) approach, to translate conventional cluster statistics to a graph during brain aging.

2. Subjects and Method

2.1 Subjects and Data Acquisitions
The study included seventy-five right-handed healthy elderly subjects (age range, 50-70 years; 39 females, 36 males). Subject inclusion criteria: No history of psychiatric disorders and other diseases which can affect the central nervous system; the Mini-Mental State Examination (MMSE) scores ≥ 26; Hamilton Depression Rating Scale ≤ 10. The subjects were divided into two groups: middle-aged group (MAG) (aged 50 to 60) and young-old group (YOG) (aged 60 to 70). Subject characteristics are shown in Table 1.

| Group    | Age (years) ± SD | Gender (Male/Female) | Education ± SD |
|----------|------------------|----------------------|----------------|
| MAG: (50-60) | 56.1 ± 2.7       | 17/20                | 16.0 ± 4.0     |
| YOG: (60-70) | 65.0 ± 2.7       | 21/18                | 18.0 ± 1.6     |

The MRI data were collected with GE Signa II 3.0T. DTI scans were collected by using a single-shot spin echo diffusion sensitized echo-planar imaging (EPI) sequence. Scanning parameters: eight directions without proliferation-sensitive gradient, b=0 s/mm²; 51 directions are applied to the proliferation of sensitive gradient, b=1000 s/mm²; TR=12500ms, TE=71ms, matrix=128 × 128, FOV = 250 × 250 mm², slice thickness= 2.6 mm. The T1-weighted data were acquired using 3D Spoiled Gradient-echo(3DSPGR) sequence (TR = 5.3 ms, TE = 2.0 ms;TI = 500; flip angle = 15°; matrix = 256 × 256; FOV = 256 × 256 mm²) with 204 contiguous1.0 mm thick coronal slices.

2.2 Image Processing
DTI images were processed by using PANDA (a Pipeline for Analysing braiN Diffusion images, http://www.nitrc.org/projects/panda/) [11] (Figure 1). DICOM images were first converted to NIFTI format. In order to eliminate motion artifact and image distortions, all images have been processed by eddy correction and head movement correction. Voxel-wise diffusion tensor matrix was calculated by weighted linear least squares fitting to the log-transformed diffusion data and registering images to a standardized template in the MNI space.

The procedure used for getting connectivity matrices was similar to described in previous studies [12]. A graph of a network is determined by a set of nodes, and a collection of edges describing the interactions between the nodes. The standard Automated Anatomical Label (AAL) [13] atlas, which is the most commonly used in structural network investigations, was used to divide the brain into 90 cortical and sub-cortical parcellations regions. The inverse of the estimated deformation field is applied to the AAL labels, producing masks for 90 regions in DTI native space. Reconstruction of white matter tracts was conducted by continuous tracking (FACT) [14] algorithm to generate network edges. If the FA value was lower than 0.2 or the angle between the current and the previous path segment was higher than 45 degrees, the tracking would be stopped. Based on the nodes and edges, we got the fiber number between two regions (which is called FN). A symmetric 90×90 FN connectivity matrix was generated. If at least three fibers are located between two regions, the weight of the edge would be kept; otherwise, the weight would be placed at zero. Weighted adjacency matrices were used to express the FN for each pair of nodes in the whole-brain tractography.
2.3 NBS Analysis

NBS introduced by Zalesky et al. [15, 16], is a nonparametric statistical test to avoid the multiple comparison problems encountered when used to isolate regional brain networks that differ significantly between two distinct groups. It identifies differences between groups, isolates sets of highly interconnected regions, thus giving information on the structural organization of the whole-brain. The framework of NBS (Melbourne Neuropsychiatry Center, the University of Melbourne and Melbourne Health, Australia, http://www.nitrc.org/projects/nbs/) was used in this study. General linear models (GLM) were formulated to quantify the inter-group differences in connectivity measures.

A 90×90 connectivity matrix stores a total of 90(89−1)/2=4005 unique edges. For individual edge of these associations, a two sample t-test contrasting the MAG and YOG is calculated independently for each pair of regions in the AAL template, to test the null hypothesis of equality based on the differences in structural connectivity values (i.e., FN) between MAG and YOG groups. Pairs of regions with a t-statistic exceeding a predefined t threshold of 2.2 were identified. The basis of the network-based statistic is to correct for multiple comparisons by testing for evidence against the null at the level of graph components, rather than at the level of individual connections. All subthreshold edges are assessed for mutual connections to form clusters in a topological space. Permutation testing is then applied to compute p-values for every component previously identified. Finally, previous steps are repeated for each of the 5000 random permutations where participants are randomly assigned to one of the two groups with the same size as the origin groups of MAG and YOG, with noting the maximum component size resulting in a null distribution for the largest component size. The final hypothesis test is then performed for the empirically determined components by comparing their sizes with the proportion of permutations yielding a component with equal or greater size. The final result controls a family-wise error (FWE) rate at cluster level with p<0.05. Two hypotheses (MAG > YOG and MAG <
YOG) were evaluated independently. This method effectively controls for false-positives due to multiple comparisons

3. Result

NBS is used to isolate the components of a 90 × 90 undirected connectivity matrix that differs significantly (p<0.05, corrected) between two groups. A pair of nodes showing a weaker association in the YOG is hereby designated as a disconnection and the set of all such disconnections is referred to as the disconnected subnetwork. The alteration of WM architecture was hallmarked by reduced strengths in nine connections, using the FN model and a statistical threshold of $t = 2.2$ (Figure 2). The NBS identified a single disconnected sub-network that showed significantly ($p = 0.030±0.005$, corrected) decreased inter-regional connectivity in the YOG compared with the MAG. A subnetwork of nine different nodes interconnected by 10 edges linking frontal lobe and central structures was identified as showing decreased connectivity. We did not identify any network with significantly increased connectivity in the YOG compared with the MAG.

![Figure 2](image_url) Significantly decreased white matter connectivity in the YOG compared with the MAG

![Figure 3](image_url) The connection matrix of disconnected subnetwork(From left to right and from top to bottom and regions in AAL atlas)
Table II lists the nodes comprising the disconnected subnetwork as well as their degrees. The connection matrix of disconnected network is given in Figure 3. No individual edge can be declared significant, only the disconnected subnetwork can be declared significant.

Table 2 Node Name and Degree

| Node Name            | degree |
|----------------------|--------|
| Caudate_L            | 2      |
| Frontal_Inf_Oper_L   | 2      |
| Frontal_Mid_Orb_L    | 2      |
| Frontal_Mid_L        | 3      |
| Frontal_Sup_Orb_L    | 2      |
| Olfactory_L          | 1      |
| Precentral_L         | 2      |
| Putamen_L            | 1      |
| Rectus_L             | 2      |
| Rolandic_Oper_R      | 1      |

Table 3 Network-Based Statistics Reveals Group Difference between YOG and MAG

| Region 1  | Region 2        | T value |
|-----------|-----------------|---------|
| Precentral_L | Frontal_Inf_Oper_L | 2.49    |
| Frontal_Mid_L   | Frontal_Inf_Oper_L   | 2.27    |
| Precentral_L    | Rolandic_Oper_R     | 2.26    |
| Olfactory_L     | Frontal_Mid_Orb_L   | 2.48    |
| Frontal_Mid_Orb_L | Rectus_L         | 2.44    |
| Frontal_Sup_Orb_L | Rectus_L      | 2.31    |
| Frontal_Sup_Orb_L | Caudate_L      | 2.43    |
| Frontal_Mid_L   | Caudate_L        | 2.95    |
| Frontal_Mid_L   | Putamen_L        | 2.26    |

Pairwise connectivity that was significantly reduced in YOG is summarized in Table III. The disconnected subnetwork mainly affected the left hemisphere. All connections between nodes were impaired in old subjects, that is, for each edge within the cluster, the FN was consistently reduced in YOG.

4. Discussion
Age-related changes in brain network vary considerably across individuals and across brain regions, with some brain regions appearing more susceptible than others to the effects of aging. Much of the basic research in brain network has focused on nodal level, and indeed analysis of brain network from network level can help the understanding of the brain organization of both normal subjects and neurodegenerative disease subjects. In this study, we found that the impaired structural connectivity affecting subnetworks during brain aging. The disconnected subnetwork identified in this study involved the frontal lobe to central structures disconnectivity of the left hemisphere. This finding is in line with structural imaging study in brain aging [17], which suggests that the most grey-matter changes occur in frontal, temporal, regions. Further studies of subjects through fMRI are needed to evaluate the relationship among affected subnetworks and brain functional network.

5. Acknowledgment
This work was supported by grants from Natural Science Foundation of Beijing (7143171).

6. References
[1] R. Peters, “Ageing and the brain,” Postgrad Med J, vol. 82, No. 964, pp. 84–88, Feb 2006.
[2] L. Lin, C. Jin, Z. Fu, B. Zhang, G. Bin and S. Wu, “Predicting healthy older adult's brain age based on structural connectivity networks using artificial neural networks,” Comput Methods Programs Biomed, vol. 125, pp. 8–17, Mar 2016.

[3] N. Raz, U. Lindenberger, K. Rodriguez, K. Kennedy, D. Head, A. Williamson, C. Dahle, D. Gerster and J. Acker, “Regional brain changes in aging healthy adults: general trends, individual differences and modifiers,” Cerebral cortex, vol. 15, No. 11, pp. 1676–1689, 2005.

[4] D. Pelvig, H. Pakkenberg, AK. Stark and B. Pakkenberg, “Neocortical glial cell numbers in human brains,” Neurobiology of aging, vol. 29, pp. 1754–1762, 2008.

[5] O. Sporns, G. Tononi and R. Kotter, “The human connectome: a structural description of the human brain,” PLoS computational biology, vol. 1, pp. e42, 2005.

[6] A. Fornito, A. Zalesky and M. Breakspear, “Graph analysis of the human connectome: promise, progress, and pitfalls,” NeuroImage, vol. 80, pp. 426-444, 2013.

[7] A. Fornito, A. Zalesky and M. Breakspear, “Graph analysis of the human connectome: promise, progress, and pitfalls,” NeuroImage, vol. 80, pp. 426-444, 2013.

[8] L. Lin, Z. Fu, B. Zhang, G. Bin and S. Wu, “Recent Advances in DTI Connectomes of Brain Diseases,” China Medical Devices, No. 6, pp. 1–6, 2015.

[9] A. Perry, W. Wen, A. Lord, A. Thalamuthu, G. Roberts, P. Mitchell, P. Sachdev and M. Breakspear, “The organisation of the elderly connectome,” Neuroimage, vol. 114, pp. 414-426, 2015.

[10] L. Lin, C. Jin, X. Xu and S. Wu, “Changes in cortical network topology with brain aging,” Information Technology and Applications: Proceedings of the 2014 International Conference on Information technology and Applications, Xian, China, 8-9 August 2014. CRC Press, vol. 59, pp. 313, 2005.

[11] Z. Cui, S. Zhong, P. Xu, Y. He and G. Gong, “PANDA: a pipeline toolbox for analyzing brain diffusion images,” Frontiers in human neuroscience, July 2013.

[12] C. Jin, Y. Chao, L. Lin, Z. Fu, B. Zhang and S. Wu, “The Study of Graph Measurements for Hub Identification in Multiple Parcellated Brain Networks of Healthy Older Adult,” Journal of Medical and Biological Engineering, pp. 1-13, 2017, In Press.

[13] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer and M. Joliot, “Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain,” Neuroimage, vol. 15, pp. 273-289, 2002.

[14] S. Mori and P. Barker, “Diffusion magnetic resonance imaging: its principle and applications,” The Anatomical Record, vol. 257, pp. 102-109, 1999.

[15] A. Zalesky, A. Fornito and E. Bullmore, “Network-based statistic: identifying differences in brain networks,” Neuroimage, vol. 53, No. 4, pp. 1197-1207, 2010.

[16] A. Zalesky, L. Cocchi, A. Fornito, M. Murray and E. Bullmore, “Connectivity differences in brain networks,” Neuroimage, vol. 60, No. 2, pp. 1055-1062, 2012.

[17] G. Bartzokis, M. Beckson, P. Lu, K. Nuechterlein, N. Edwards and J. Mintz, “Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study,” Archives of general psychiatry, vol. 58, No.5, pp. 461-465, 2001.