Analysis of the Difference Between Alzheimer's Disease, Mild Cognitive Impairment and Normal People by Using Fractal Dimensions and Small-World Network

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Abstract -*This study analyzed the differences of brain network between Alzheimer's disease (AD),mild cognitive impairment (MCI), and control groups, in which magnetic resonance images (MRIs) and mini-mental state examination(MMSE) data were downloaded from ANDI(N=40, each group). The correlation maps for analyzing brain network were created by fractal dimension (FD) analysis that can quantify the morphological change of cortical and cerebral regions. In the present study, we applied the graph theory, in which a node represents each parcellated region and an edge between two nodes, to calculate the small-world network properties of each group.*

In comparison with the control group, AD group presents significantly lower FD values ($p<0.05$) in temporal lobe, motor cortex, part of occipital and parietal, hippocampus, amygdala, and entorhinal, accompanied by the atrophy of these regions. The regions highly related to memory were also found to manifest significantly lower FD values in MCI, including hippocampus, parahippocampus, amygdala, and entorhinal cortex. Moreover, less connectivity and decreased efficient network were found in AD and MCI.

In conclusion, FD can be used to demonstrate the progress of declination from MCI to AD. In the future, more clinical assessments are needed to substantiate the findings in the present study.

Keywords:*Alzheimer's Disease, Alzheimer's Disease Neuroimaging Initiative, Fractal Dimension, Mild Cognitive Impairment, Small-World Network.*

1 Introduction

Alzheimer's Disease is a chronic neurodegenerative disease, and it is the most common form of the dementia. It was discovered and named by Dr. Alois Alzheimer in1906. Early symptom includes difficulty in memorizing the recent events and short-term memory dysfunction. With the advance of disease, more abnormalities such asthe problem of language, orientation, and independent living skill would occur.So far, the tools used to assist in diagnosing AD includes imaging,for examples MRI, PET; biochemistry, neuropsychological test,such as mini-mental state examination (MMSE), Clinical Dementia Rating (CDR), Global Deterioration Scale (GDS)[18]. In terms of anatomy and physiology, it was discovered the accumulation of β-amyloid plaque and neurofibrillary tangle, that will cause seriously loss of neurons and synapse, and make the neuron connection loss and the volume atrophy occur on many region of brain cortex [8,13,14]. The typical symptoms of AD, including the disorders of memory, language, disorientation, motion, are derived from these impairments in brain. Also, Ronald C. Petersen [17] indicated that amnesic mild cognitive impairment might be the early stage of the AD.

The progress of dementia is a slow process and the stage is referred to as mild cognitive impairment (MCI), indicating the intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia. It can involve abnormalities in memory, language, thinking and judgment[17].Recently, studies showed that about 10% to 15% of patients with amnesic MCI eventually deteriorate in AD[17]. Previous studies reported that MR images of MCI presents the atrophy in the hippocampus and temporal lobe, and also demonstrated amyloid accumulation in PET[17].

In addition, fractal dimensions (FD), which can quantify the brain cortex complexity, has been applied on the normal and several diseases [1,4,5,8]. Previous studies demonstrated that the patients with AD showed significantly decreased in several cortical regions and hippocampus [14]. Moreover, Stam et al. [3] also demonstrated that the patients with AD showed impaired small-world network, which has short distance of the connection between brain regions and high cluster level of nearby regions [4]. Therefore, in the present study, we aimed to investigate the differences of FD and the properties of small-world network created by FD between AD, MCI, and normal control. We hypothesized that the complexity of cortical surface would decrease in the atrophic brain regions, which would be the memory-related regions, such as hippocampus.

2 Material and Method

2.1 Image acquisition and Subjects

MRI images and data used in this work were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

database. It is an open dataset, belonging to Laboratory of Neuro Imaging (LONI), University of Southern California (USC). We only used the baseline data including a total of 120 subjects (40 NC, 40 MCI and 40 AD). The general inclusion/exclusion criteria used by ADNI are summarized as follow: 1) Normal subjects: Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) of 0, non-depressed, non-demented and non-MCI; 2) MCI subjects: MMSE scores between 24 and 30 (inclusive), a memory complaint, have objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II; 3) AD subjects: MMSE scores between 20 and 26 (inclusive), CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria. No significant group differences were noted in age or sex ratio (Age P-value: Normal-MCI: 0.15, Normal-AD: 0.74, MCI-AD: 0.34; Sex P-value: Normal-MCI: 0.22, Normal-AD: 0.34, MCI-AD: 0.06). Details of the demographics and clinical characteristics of the sample used in this paper are presented in Table1

The acquisition consisted of T1- weighted MRI scans, using a sagittal gradient-echo sequence(MP-RAGE), with repetition time (TR) of 9 msec, echo time (TE) of 4 msec, flip angle of 8, and acquisition matrix size of 256 · 256 · 166 with a voxel size of 0.94 · 0.94 · 1.2 mm. the raw T1- weighted MRI applied N3 algorithm for intensity inhomogeneity correction.

Table1. ADNI Data

Group	MMSE	Genders	Age
Normal (N=40)	29.33±0.92	M:22,F:18	77.40±5.03
MCI (N=40)	27.78±1.64	M:25,F:15	78.85±3.77
AD (N=40)	22.95±2.12	M19:,F:21	77.80±5.80

2.2 Imageprocessing

We used SPM12(Statistic Parametric Mapping, University College of London) for transformation of the original data into the ACPC coordinate. Using volumetric segmentation and cortical surface reconstruction methods based on the publicly available FreeSurfer software package (Laboratory for Computational Neuroimaging), volumetric measures were created for hippocampus, amygdala, caudate, putamen, nucleus accumbens and thalamus. The surface was then parcellated into cortical ROIs (Desikan-Killiany Atlas) in subject-specific native space.

2.3 Fractal Dimensions: Box-counting method

FD could be used to quantify the complexity of object's surface. We use Box-counting method to calculate and quantify each ROI on cortical surface. First, we cover the image with a grid, and then count how many boxes of the grid are covering part of the image. Then we repeat the same procedure but using a finer grid with smaller boxes. By shrinking the size of the grid repeatedly, we end up more accurately capturing the structure of the pattern. Using the box counting method, fractal dimension is again the slope of the line when we plot the value of log(count) on the Y-axis against the value of log(1/b) on the X-axis. N is the number of boxes that cover the pattern, and b is the box size. (Figure1)

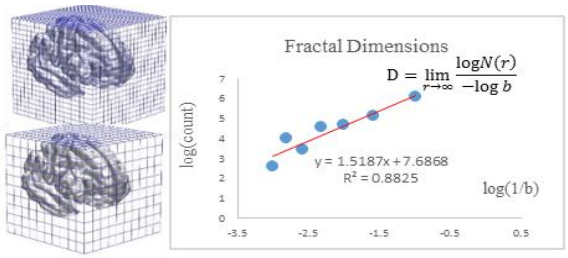

Figure1. FD: Box-counting method

2.4 Small-World Network

2.4.1 Structural Correlation Matrix

Structural correlation networks (SCN) was constructed at the group level. An 86 × 86 association matrix was generated for each group where the entry of each matrix was calculated by performing Pearson correlation coefficient between the FD values of any paired regions across subjects within this group. These morphometric correlations might reflect anatomical connectivity, as axonal connected regions are believed to be influenced by common developmental, trophic or maturational effects[15,16].

2.4.2 Small-World Network Indicators

We computed five different Small-World Network Indicator, namely, Degrees, Strengths, Clustering coefficient, Efficiency and Distances. In the network, every node has its connection with other nodes ($K_{i,i=1,2,\dots N}$), and "Degrees" is the numbers of connection connected to the node. Then, we calculated the average to be the Global Degrees of this network. "Strengths" refers to how strong the connection is (denoted by $Z(i,j)$), which is represented by correlation coefficient. The nodal Strengths calculate from the summation all of the node's correlation coefficients and divide by every node's Degrees. Global Strengths of network is the average of Strengths of every node."Clustering coefficient" is calculated as the ratio which is the number of real connections among the nodes that connect to a specific node divided by the number all possible connections among these nodes."Efficiency" is the reciprocal of Distance. The shorter the Distance from one node to another node is, the higher the transfer efficiency. Global Efficiency (E_{Global}) is the average of nodal Efficiencies. "Distance" is the average of path length from a node to another node (denoted by $L_{i,j}$), and the average of nodal Distances is the Global Distance (denoted by L_G) (Table2).

Table2. Small-World Network Indicator and Formulas

Indicators	Formula
Degrees	$K_{Global} = \frac{1}{N}\sum_{i\in N} K_i$ .....(2)
Strengths	$E_{Global} = \frac{1}{N}\sum_{i\in N}(\frac{1}{K_i}\sum_{j\in N} Z(i,j))$ .....(3)
Clustering coefficient	$C_G = \frac{1}{N}\sum_{i\in N}\frac{(Numberofrealconnect)}{K_i(K_i-1)/2}$ .....(4)
Efficiency	$E_{Global} = \frac{1}{N(N-1)}\sum_{i\neq j\in N}\frac{1}{L_{i,j}}$ .....(5)
Distances	$L_G = \frac{1}{N}\sum_{i\in N}\frac{1}{N-1}\sum_{j\neq i\in N} L_{i,j}$ .....(6)

3 Results

3.1 Fractal Dimensions

We performed Two-Sample T-test at same region between two groups, which are NC vs. MCI, MCI vs. AD and NC vs. AD) and colored the significant difference (P-value<0.05) areas on brain model as displayed in Figure 2. MCI and AD group have the significantly (P-value<0.05) lower FD value at entorhinal cortex(black arrow)compared with Normal group. Also, the temporal lobe shows the significantly (P-value<0.05) lower FD value, which is one of the target areas that appear atrophy in AD patients. In comparison with the MCI group, AD group have lower FD not only in temporal lobe but also at occipital lobe, part of parietal lobe, hippocampus(blue arrow) and amygdala. These areas that have significant lower FD demonstrate the gradual atrophy when people progress from Normal to AD.

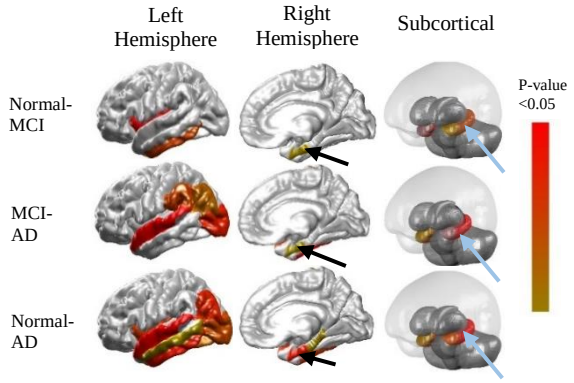

Figure2. Fractal Dimensions significant lower area

3.2 Small-World Network

The Normal group has the larger Degrees, stronger Strengths, higher Efficiency, and shorter Distances then the MCI and AD groups. These results manifest the trend that Normal group has the superior network performance than the MCI and AD groups.

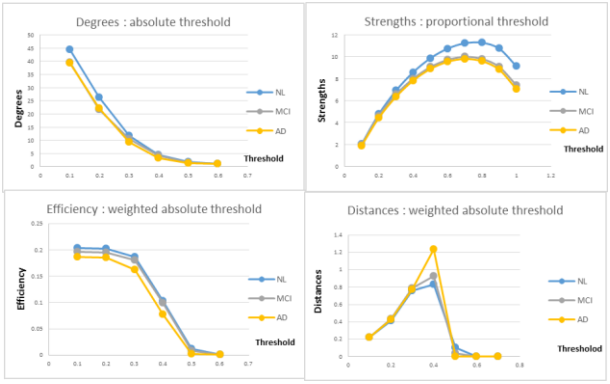

Figure3. Small-World Network

Furthermore, we calculated network strength on six regions, namely, the frontal lobe, farietal lobe, temporal lobe, occipital lobe, cingulate cortex and the subcortical region and cerebellum. Figure 4 displays two different patterns of network strengths in the left and right panels, respectively. In the left panel, the strength in the frontal lobe, parietal lobe and temporal lobe are significant higher than the MCI and AD groups. In contrast, there are no significant network strength differences between MCI, AD and control groups in the occipital lobe, cingulate cortex, subcortical region and cerebellum.

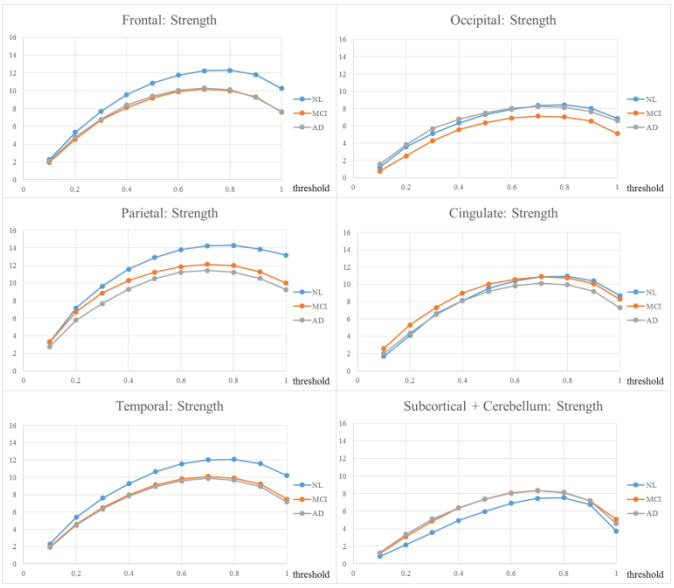

Figure4. Regional network Strength on six regions, including frontal lobe, parietal lobe, temporal lobe, occipital lobe, Cingulate cortex and the remaining area (Subcortical region and Cerebellum)

4 Discussion and Conclusions

In the present study, both MCI and AD had significantly diminished FD in the memory-related regions. Moreover, the progress of the deterioration was demonstrated;

that is, the FD values of subcortical regions, such as hippocampus, entorhinal cortex, and amygdala, had decreased in MCI, and of further regions, including temporal lobe and part of parietal lobe, were found in AD (Fig. 2). Also, compared to normal control, both AD and MCI had decreased connectivity and less efficient network, which were shown by the lower strengths, efficiency and longer distance in these patient groups (Fig. 3).

It is known that cerebral cortex, especially temporal, parietal and pre-frontal lobes are related to our memory, orientation, calculation and abstract thinking. So, the weaker network connectivity in the frontal, parietal, and temporal lobes in the AD and MCI groups compared to the normal subjects may reflect on their memory impairment and mentality decline. (left panel of Fig.4) However, it is interesting that the occipital lobe, cingulate cortex, basal ganglia and the cerebellum of the AD and MCI patients are relatively spared from the disease process in our study. (right panel of Fig.4).

Being consistent with previous studies, temporal region was regarded as the target region of atrophy in the patients with AD[14].Temporal lobe is the main region for language, learning, semantic and recognition memory, and the impairments of AD in memory and language are highly correlated with this region. In addition, impaired small-network was also found in previous studies [3]. Stam et al. demonstrated that AD was characterized by a longer characteristic path length with relative sparing of the local clustering. The significant correlation between path length and cognitive assessment provided further evidence for the concept of AD as a disconnection syndrome.

Consequently, since that FD represented different declination from MCI to AD, FD analysis may be used to evaluate the progress of cognitive degeneration. The properties of network created by FD can indicate the abnormality at the prodromal stage of dementia, i.e. MCI. In the future, FD may develop to be a tool for assist in diagnosis. To provide stronger evidence, the relationship between the decreased FD and cognitive declination, collected by clinical assessments, are needed to examine in the future.

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6 References

[1] Bullmore, E., M. Brammer, I. Harvey, R. Persaud, R. Murray, and M. Ron. "Fractal analysis of the boundary between white matter and cerebral cortex in magnetic resonance images: A controlled study of schizophrenic and manic-depressive patients". Psychol. Med. 1994, 24:771–781.

[2] Claus C. Hilgetag, Alexandros Goulas. " Is the brain really a small-world network?". 15 July 2014.

[3] C. J. Stam, B. F. Jones, G. Nolte, M. Breakspear, and Ph. Scheltens. "Small-World Networks and Functional Connectivity in Alzheimer's Disease". Cereb Cortex 2007, 17 (1): 92-99.

[4] Free, S. L., S. M. Sisodiya, M. J. Cook, D. R. Fish, and S. D. Shorvon. "Three-dimensional fractal analysis of the white matter surface from magnetic resonance images of the human brain". Cereb Cortex 1996, 6:830–836

[5] Jing Z. Liu, Lu D. Zhang, and Guang H. Yue. "Fractal Dimension in Human Cerebellum Measured by Magnetic Resonance Imaging". Biophys J. 2003, 85(6): 4041–4046.

[6] Mandelbrot, B. B. "The Fractal Geometry of Nature". Freeman, New York. (1982)

[7] Qawi K. Telesford, Karen E. Joyce, 1Satoru Hayasaka, Jonathan H. Burdette, andPaul J. Laurienti. "The Ubiquity of Small-World Networks". Brain Connect 2011, 1(5): 367–375.

[8] Richard D. Kinga, Brandon Browna, Michael Hwangb, Tina Jeonb, Anuh T. Georgeb, the Alzheimer's Disease Neuroimaging Initiative. "Fractal dimension analysis of the cortical ribbon in mild Alzheimer's disease".Neuroimaging, 53(2), November 2010, Page471-479.

[9] Tzu-Yun Wang, Chii-Wen Jao, Bing-Wen Soong , Hsiu-Mei Wu, Kuo-Kai Shyu, Po-Shan Wang, Yu-Te Wu. "Change in the cortical complexity of spinocerebellar ataxia type 3 appears earlier than clinical symptoms". PLoS One 2015;10(4):e0118828. doi.

[10] Yong He, Zhang J. Chen and Alan C. Evans. "Small-World Anatomical Networks in the Human Brain Revealed by Cortical Thickness from MRI". Cereb Cortex 2007, 17(10): 2407-2419.

[11] Yong Liu, Meng Liang, Yuan Zhou,Yong He, Yihui Hao, Ming Song, Chunshui Yu, Haihong Liu, Zhening Liu, and Tianzi Jiang. "Disrupted small-world networks in schizophrenia". Brain 2008, 131, 945-961.

[12] Yu-Te Wu, Kuo-Kai Shyu, Chii-Wen Jao, Zun-Yun Wang, Hsiu-Mei Wu,Bing-Wen Soong,Po-Shan Wang. "Fractal Dimension Analysis for Quantifying Cerebellar Morphological Change of Multiple System Atrophy of the Cerebellar Type (MSA-C)".NeuroImage 2010;49(1):539-551

[13] Yongxia Zhou and Yvonne W. Lui. "Small-World Properties in Mild Cognitive Impairment andEarly Alzheimer's Disease: A Cortical Thickness MRI Study". Hindawi Publishing Corporation,ISRN Geriatrics,Volume 2013, Article ID 542080, 11 pages.

[14] Dennis Chan, MRCP Nick C. Fox MRCP Rachael I. Scahill MA William R. Crum DPhil Jennifer L. Whitwell BA Guy Leschziner MB, BS Alex M. Rossor John M. Stevens FRCR Lisa Cipolotti PhD Martin N. Rossor MD, FRCP. "Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease". Neurology 2001;49(4):433-442.

[15] Zhang K, Sejnowski TJ. "A universal law between gray matter and white matter of cerebral cortex". Proceedings of the National Academy of Sciences of The United States of America 2000;97(10):5621–6.

[16] Wright IC, Sharma T, Ellison ZR, McGuire PK, Friston KJ, Brammer MJ, Murray RM, Bullmore ET. "Supra-regional brain systems and the neuropathology of schizophrenia". Cerebral Cortex 1999;9:366–378.

[17] Ronald C. Petersen. "Mild Cognitive Impairment." Continuum: Lifelong Learning in Neurology 2016; 22(2 Dementia): 404–418.

[18] Osafune M, Deguchi K, Abe K. "Ideal combination of dementia screening tests." Nihon Ronen Igakkai Zasshi 2014;51(2):178-83.