Normal Brain Aging and its Risk Factors-Analyses of Brain MRI Database of Healthy Japanese

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Abstract

We analyzed structural change of the human brain with aging using MRI of the 2,000 healthy Japanese subjects. Volumetric analysis in each brain tissue segment revealed that gray matter volume linearly decreased with age, while white matter volume remained unchanged during aging. On the other hand, longitudinal study in the same subjects with 8 year-interval revealed that there were sex differences in speed and pattern of gray matter loss, the loss being slower in women that that in men. Correlation analyses revealed that there were negative correlations between gray matter volume and cerebrovascular risk factors, such as hypertension, amount of alcohol intake and obesity. Correlation analysis between fractional anisotropy (FA) measured with MRI and regional glucose metabolism measured with ^{18}F-fluorodeoxyglucose PET revealed that glucose metabolism in the bilateral frontal lobe showed a statistically significant positive correlation with the FA of the genu of the corpus callosum. The anatomical network analysis using regional gray matter volume exhibited "small-world" attributes. Importantly, the results demonstrated that significant statistical differences exist in the small-world properties between different sex and among decades from 20 to 70.

1. Introduction

Recently, projects to construct a large scale database for human brain image have been vigorously performed by major neuroscience center in Europe and USA. The scientific and social significance and needs for database are electric data sharing in neuroscience community as well as the construction of more sophisticated and complete model of brain structure and function. This model of normal brain structure and function can be used as the references not only for neuroimaging research but also for computer based objective diagnosis of the brain diseasesThere are many groups aiming neuroimage database development. Among them, International Consortium for Brain Mapping (ICBM), is a well known and one of the powerful multi-centered groups. This consortium is governed by professor Mazziotta (UCLA), and composed of four core research sites, UCLA, Montreal Neurological Institute (MNI), University of Texas at San Antonio, and the Institute of Medicine, Juelich/Heinrich Heine University - Germany. In addition, data acquisition sites in Asia (Sendai, Japan) and Europe (France, Finland, Netherlands) contribute to this international consortium. We are one of the members of ICBM and only one group in Asia involving the human brain database project.

1.1. Construction of brain MRI database

In 1998, we founded "Aoba Brain Imaging Center (ABIC)" supported by a grant from Telecommunications Advancement Organization (TAO) of Japan (project leader: Hiroshi Fukuda, the author). The purpose of this center was to construct a virtual brain laboratory where several brain institutes were connected with high-speed information network, to collect and accumulate brain images into the ABIC, and to promote brain research under collaboration and sharing with brain images and software. By the end of this project, we collected brain MRI of 1,700 healthy Japanese (Aoba-1). We registered a brain image together with subject's age, sex, length, weight, blood pressure, medical history, social history, etc, and constructed a database [1]. Second source of brain images were from the Tsurugaya Project study, which was a comprehensive geriatric assessment (CGA) of the elderly population aged 70 years or older living in the Tsurugaya district, Sendai, Japan (performed from 2002 to2004, project leader: professor Tsuji, Tohoku University). In this project, we randomly selected subjects from the 1200 participants and collected 400 brain MRIs (Tsurugaya-1 and 2). Furthermore, in 2007, we performed longitudinal MRI study for the Aoba-1 subjects who agreed with the second MRI 8 years after the first measurement. The final number of subjects was 388 (Aoba-2). Total number of subjects in our database reached 2,502 and this is only one in Japan and one of the largest database in the world. The age of the subjects ranged from 20 to 70 for both gender and therefore, our

database is a very good tool for the analysis of brain aging. Table 1 shows the number of subjects in each subdatabase. We have analyzed structural change of the brain with aging and published remarkable results [2-5]. In this report, the following analyses were performed and outcome in early 2008 and on going preliminary results were described.

Table 1. Number of subjects in Japanese brain MRI database

Name of subdatabase	Number of subjects		
	male	female	Total
Aoba-1	860	840	1700
Aoba-2	159	224	383
Tsurugaya-1	92	104	196
Tsurugaya-2	118	105	223
Total	1229	1273	2502

1.2. Structural change of the human brain

Most remarkable recently developed method for brain image analysis is a voxel-based morphometry (VBM). It includes anatomical standardization of the brain to a standard brain, brain tissue classification, and finally voxel-based statistical analysis based on general linear model. This technique enables us to extract brain regions which show correlations between tissue volume and variables, such as age, sex and subject's characteristics. We can analyze not only age-related normal changes but also diseased brain, such as dementia and schizophrenia. It has been believed that functional imaging precede structural imaging to detect early pathological findings of the diseases. However, recent development of high resolution structural imaging and sophisticated analytical technique enable us to detect the brain disease at very early stage.

Furthermore, there are more sophisticated methods such as deformation based morphometry (DBM) [7], which calculate deformation parameter(vector) and use it as a parameter of structural changes or brain network analyses based on the graph theory [8].

1.3. Age-related volume change in the gray matter-a longitudinal analysis

In the previous report, we clarified that gray matter volume negatively correlated with age. However, the results from the cross sectional analysis do not provide grade of brain volume loss but only provide cross generational differences. Only longitudinal study can provide these parameters. However, this kind of study with sufficient number of subjects is very difficult to perform. In order to obtain speed of brain volume loss with age, we designed longitudinal study.

1.4. Cross generational differences of brain shape

The shape of skull is different among races. It is well known that cephalic index, which is the ratio of length and width of the head, is different among the races. Generally, European head is longer and narrower than that of Mongolian skull. Furthermore, even in a race, the index also changes depending on the era in which the people lived.

Japanese archeologist, Kochi reported the ratio of Japanese brain gradually increased during recent 100 years and this process is called as brachycephalization. However the index remained constant during 1960 to 1980 and she concluded that the brachycephalization ceased around year of 1960. In the report, they measured the length and breadth of the head at outer surface of the skull or scalp of the living human. In this study we measured the ratio of length and width of the brain itself using our brain database.

1.5. Correlation between white matter fiber connection and regional glucose metabolism

Activity in neural cells is coupled with glucose metabolism. Neural function of signaling are carried out by the interconnection of neurons via neuronal fibers. Diffusion-tensor imaging (DTI) has recently become an established technique that allows in vivo visualization of white matter fiber tracts by measuring the anisotropy of water molecular diffusion. Several studies focusing on normal aging have reported significant reduction in fractional anisotropy (FA) in the corpus callosum. The purpose of this study was to examine whether degradation of microstructure of fiber tracts in the elderly was associated with change in the glucose metabolism in the cerebral cortex measured with ^{18}F-FDG-PET.

1.6. Anatomical network analyses using regional gray matter volume based on graph theory

Generally, brain network analysis is performed using functional imaging data such as PET or fMRI. MNI group developed a method of network analysis using regional cortical thickness based on graph theory [8]. Using this methods and calculation results, they examined whether the network property shows small-worldness or not. In this study, we made network analysis using regional gray matter volume (RGMV).

2. Methods

2.1. Subjects

Subjects of Aoba-1 consisted of 1637 healthy Japanese male and female living in and around Sendai, Japan. Before the MRI measurement, subjects with past and present history of malignancies, head trauma,

cerebrovascular diseases, epilepsy, neurological and psychological disorders were excluded by interview.

A longitudinal study of brain MRI measurement was proposed to 930 out of 1637 Aoba-1 subjects. Five hundred and thirteen subjects responded to the proposal and 469 subjects agreed with the proposal. Actually, 442 subjects successfully took MRI measurement. Among them, 54 subjects who did not coincide with inclusion criteria were excluded. Finally, 388 subjects were analyzed in this study (Aoba-2).

The Tsurugaya Project study, which was a comprehensive geriatric assessment (CGA) of the elderly population aged 70 years or older living in the Tsurugaya district, Sendai, Japan (performed in 2002). In this project, we randomly selected subjects from the 1200 participants and collected 200 brain MRIs (Tsurugaya-1). Two years later (2004), we took brain MRI for 223 subjects from Tsturugaya-1 who participated in a program of cognitive intervention (Tsurugaya-2).

2.2. MRI data acquisition

Brain MR images were taken from each subject using 0.5 T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with two different pulse sequences: (1) 124 contiguous, 1.5-mm thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in steady state: repetition time (TR), 40 ms; echo time (TE), 7 ms; flip angle, 30.; voxel size, 1.02 mm × 1.02 mm × 1.5 mm); (2) 63 contiguous, 3-mm thick axial planes of gapless (using interleave) proton probability weighted images / T2-weighted images (dual echo fast spin echo: TR, 2860 ms; TE, 15 / 120 ms; voxel size, 1.02 mm × 1.02 mm × 3 mm). Number of examination (NEX) was 2.

2.3. Image processing and statistical analyses

All the brains with different size and shape were transferred into a standard stereo-tactic space (Talairach space) and their size and shape were transformed into a standard template brain using liner and non-linear parameters (anatomical standardization). Next step is brain tissue segmentation. A brain images were segmented into gray matter, white matter, cerebrospinal fluid space (CSF) and outer brain space depending on the differences of signal intensities on T1 weighted MRI of each tissue (Fig. 2). The volumes of each tissue segment were calculated by summing up the value of all the voxels which belong to each tissue segment.

The standardized and segmented gray matter images were smoothed by convoluting a 12-mm-FWHM isotropic Gaussian kernel. Then, the smoothed gray matter images were statistically analyzed by voxel based morphometry (VBM) technique using SPM2 package (Fig. 2). VBM was performed to investigate correlation between regional gray matter volume and attributes to the subject, such as age, cerebro-vascular risk factors, and scores of cognitive functions. This approach is not biased toward any one brain region and permits the identification of unsuspected potential brain structural abnormalities. Simple or multiple regression analysis was performed using SPM2. These attributes were used as dependent variables, and regional gray matter volume as an independent variable. We set the significance level at $P<0.05$ for multiple comparison. The method is a voxel based t-statistics extended to the three dimensional space based on the general linear model. Simple or multiple regression analysis and group comparison using t-test were performed.

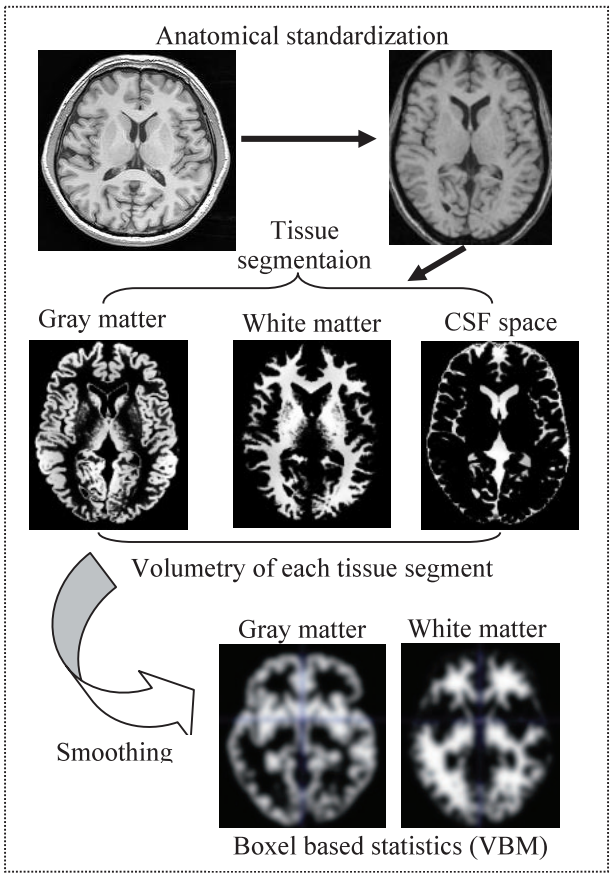

Fig. 1. Anatomical standardization, tissue segmentation of the brain MRI and statistical analyses.

2.4. Measurement of brain shape index on brain MRI

We randomly selected 270 male brains from the database with birth year from 1920 to 1980 (age range from 19 to 79). After removing extra brain tissues automatically, antero-postal and left-to-right diameters of the brain were measured automatically and ratio of them (brain shape index) (a/b) was calculated (Fig. 2). Cephalic index is determined as A/B, which is measured on the surface of the skull or scalp.

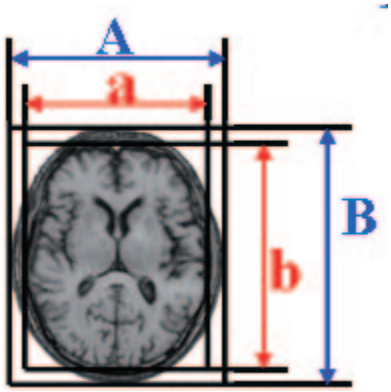

Fig. 2. Measurement of brain shape index a/b: brain shape index, A/B: cephalic index.

2.5. Correlation between fiber connection and cerebral glucose metabolism

Fifteen healthy volunteers (male 8, female 7, age 73.0±2.2 yr) participated. A 10 min emission scan was performed with a PET scanner from 45 min after the injection of 217±32 MBq of ^{18}F-FDG. MRI measurement was performed using a 1.5T system. A volumetric T1-weighted image (T1WI) was acquired using a MPRAGE sequence. DTI was acquired using a single-shot diffusion-weighted echo planar imaging with six sets involving diffusion gradients placed along non-collinear directions (b = 1000 seconds/mm^2) and another set without diffusion weighting (b = 0).

2.6. Anatomical network analysis using regional gray matter volume

To study on the properties of anatomical network among decades from 20-70 between different gender, we examined the correlation matrix using graph-theoretical analysis

To analyze the anatomical network, we made an anatomical connection matrix by using the regional gray matter volume (RGMV) of 56 regions. We computed the Pearson correlation coefficient (PRC) between RGMV across subjects in each group to construct the interregional correlation matrix (N × N, where N is the number of gray matter regions, here N=56). Each connection matrix (12 in total) can be converted to a binarised and undirected graph G by considering a threshold T (range from 0 to 1). For increasing values of the threshold, more and more edges will be lost and the resulting graphs will become sparse, leading to a decrease of the mean degree. As the correlation threshold reaches the maximum Tmax, the mean degree of the resulting network will be less than the log of the number of nodes (here K_{min}<log(N)=4.025) and the properties of small-world will become inestimable. Since the structure of the graph is generally biased by the number of existing edges, statistical measures should be calculated on graphs of equal degree K. Therefore, threshold T was chosen such for each connection matrix (12 in total) that all the produced graphs had a fixed mean degree ($T_{K=i}$, i=5, 6, 7; K=5, 6, 7> K_{min}). Thresholding each connection matrix with $T_{K=i}$, we obtained the anatomical connection matrix described as the binarized and undirected graph G.

We calculated the 3 important metrics of the graph G, namely, the mean degree K, the clustering coefficient C and the characteristic path length L [2]. Network topology was said to correspond to a ‘‘small world’’ if the network’s clustering coefficient is much greater than that of equivalent random controls C>C_{rand} or γ= C/C_{rand}>1, while their path lengths are comparable L≈ L_{rand} or λ=L/L_{rand}≈1. The small-worldness σ_{sw} is defined as σ_{sw} =γ/ λ >1. Comparisons are carried out against populations of n =1000 degree-matched random networks [2, 3].

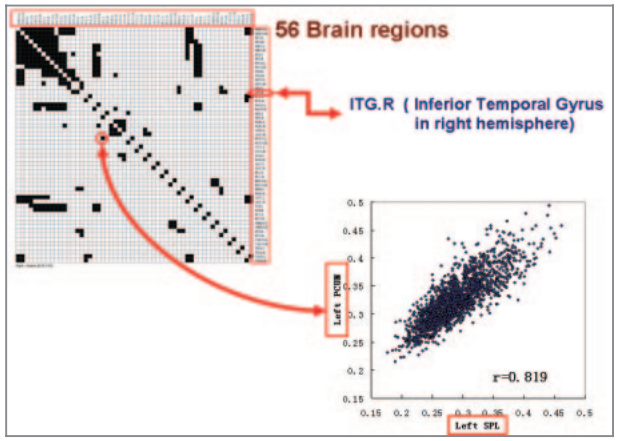

Fig. 3. Correlation matrix using regional gray matter volume across subjects.

3. Results and Discussion

3.1. Age related brain volume change (longitudinal study)

Results of volumetry by cross sectional analysis in 860 men were shown in Fig. 4. In this graph, volume of each brain tissue was expressed as the volume ratio to whole brain volume in order to normalize the differences in skull size. Gray matter ratio linearly decreased with age (a negative correlation between gray matter volume and age). While white matter ratio remained unchanged during aging (no significant correlation between white matter ratio and age), although data variation was very large. CSF space ratio increased with age (positive correlation with age). Brain volume in female showed almost the same tendency to those in male.

Results of longitudinal study were shown in Fig. 5. In this study, we took MRI in the same subjects between 8 years interval. Two data of the same subject were connected by a line. Gray matter ratio linearly decreased with age in almost all men as was in the cross sectional analysis. From this curve, we calculate annual decrease of gray matter ratio. On the other hand, gray matter ratio for women decreased slowly than that for men until the age of 50 and then went down as the similar slope for men. White matter volume increased until age of 40 and went down thereafter in either men or women, although variation of the data was large (Fig. 6).

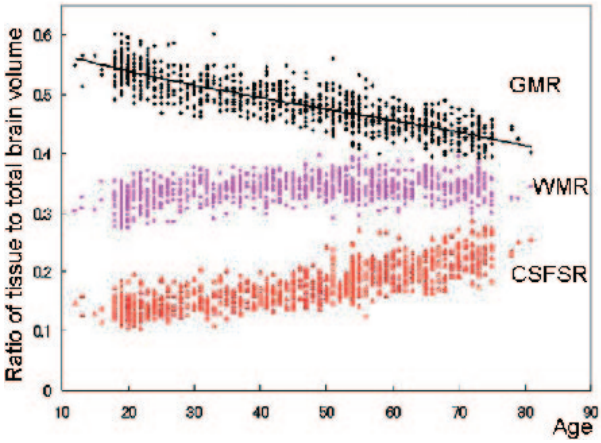

Fig. 4. Age-related volume change of the human brain (cross sectional study). GMR: gray matter ratio, WMR: white matter ratio, CSFSR: cerebrospinal fluid space ratio.

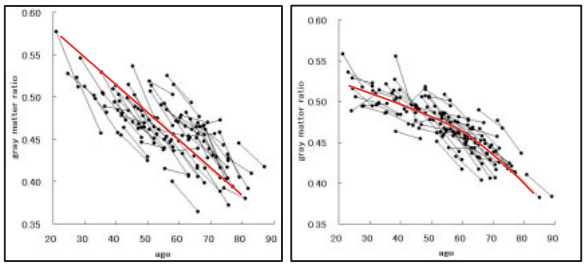

Fig. 5. Age-related change in gray matter ratio (GMR) for men (left) and women (right) by longitudinal study.

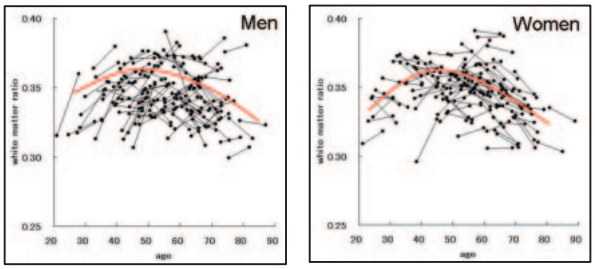

Fig. 6. Age-related change in white matter ratio for men (left) and women (right) by longitudinal study.

3.2. Cross generational differences in brain shape index

Figure 7 shows mean values of brain shape index against birth year of the subjects. The value of brain shape index was small in older generation, increased in younger generation and reached plateau in around 1960-1970. The similar trend was observed for the change of cephalic index, which is a ratio of length and breadth of the head. Kochi [7] reported the cephalic index in Japanese gradually increased during recent 100 years. However the index remained constant during 1960 to 1980 and she concluded that the increase ceased around year of 1960. This suggests that the shape of head synchronizes with the shape of brain. Biological meaning of the temporal change of brain shape in the secular time scale is not unclear. Further investigation is required.

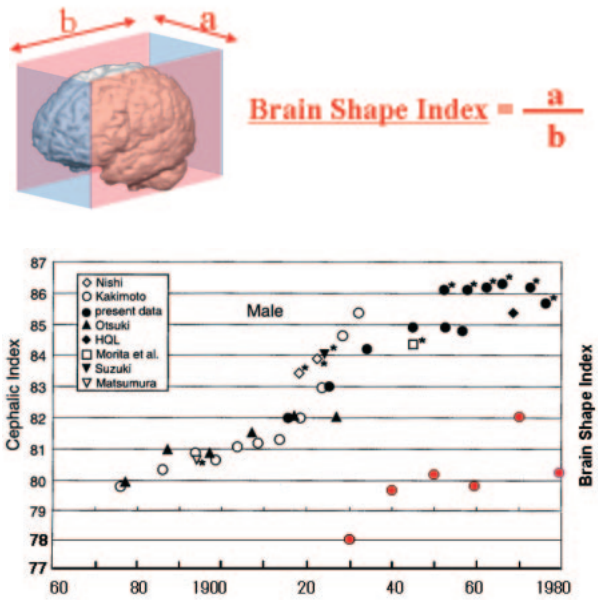

Fig. 7. Change of brain shape index over 50 years
Red circle: brain shape index superimposed on the graph reported by Kouchi M (J Physical Anthropology, 112(3), 2000).

3.3. Correlation between fiber connection and cerebral glucose metabolism

There was no statistically significant correlation of FA with age, FA with GM concentration, or GM concentration with age. On the other hand, we found statistically significant positive correlation of ^{18}F-FDG accumulation in the lateral frontal cortex bilaterally with FA of the genu of the corpus callosum (Figure 8a). Correlation curve between FA of the genu of the corpus callosum and ^{18}F-FDG accumulation in the area indicated by arrow in Figure 8a was shown in Fig. 8b. While no significant correlation was observed between FA of the ampoule of the corpus callosum . There was

no age effect in FDG accumulation. The results suggest that neuronal activity in the frontal cortices may decrease with the disruption of the microstructures of the CC without corresponding gray matter atrophy.

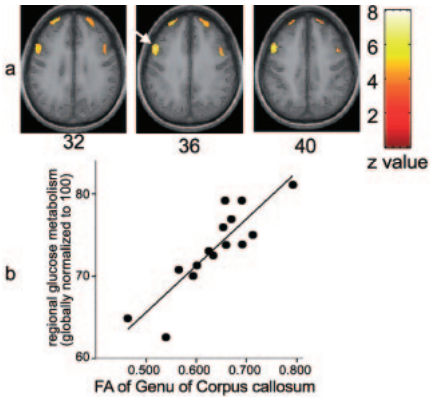

Fig. 8. Areas that showed a significant positive correlation of glucose metabolism with the FA of the genu of the corpus callosum (a). A relationship between glucose metabolism and the FA on the right middle frontal gyrus (arrow) (b) (Inoue K, et al, *Human Brain Mapping*. **29**(4), 2008)

3.4. Anatomical network analysis using regional gray matter volume

There are three types of network pattern, that is regular, random and small world. Figure 9 shows the schematic concept of these networks. In regular network, each node is connect regularly and therefore, density of network is high (high clustering). However, it takes many steps (long path length) to reach a node in opposite site. In random network, there are some direct connection to nodes in opposite or further point (short path length), although network density is low (low clustering). Small-world is a network with high clustering (γ <1.0) and short path length ($\lambda \div$ 1.0).

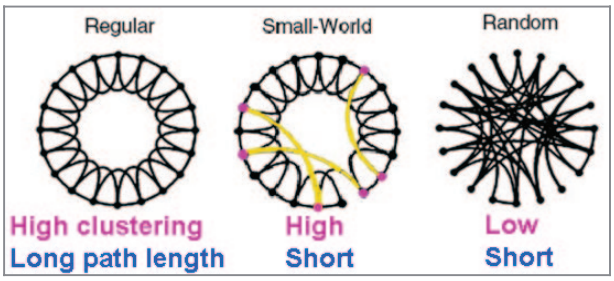

Fig. 9. Anatomical network pattern

There exist significant statistical difference in all the small-world properties by the group of the fixed mean degree (K=5, 6, 7). Gamma and Lambda show the significance at P<0.05. Sigma shows the significance at P<0.01. In addition, we analyzed the small-world properties by gender with different mean degree K (K=5, 6, 7). With the fixed mean degree K=5, only Gamma shows the significance at P<0.01. Gamma and Sigma show the significance at P<0.05 both with K=6 and K=7. Moreover, Lambda from K=6 has higher F-score than that from K=7. In conclusion, the choice for K=6 was identical to this study.

With the fixed mean degree K=6, the results by the group of gender show that significant difference exist in C, Gamma, Sigma between female and male at level of P<0.05, with the probability of 0.011, 0.012, 0.034 respectively (Table 2). This is a first paper describing the gender differences in small-world properties estimated by anatomical network analysis.

Table 2. Small-Worldness in each gender

	Female		Male			
	mean	S. D.	mean	S. D.	F	Sig.
C	.514	.037	.628	.082	9.74	.011 *
L	2.68	.212	3.06	.453	3.35	.097
Gamma	2.41	.230	3.79	1.072	9.47	.012 *
Lambda	1.09	.088	1.25	.188	3.81	.080
Sigma	2.24	.326	3.04	.739	6.03	.034 *

▲ K=6;
* Correlation is significant at the 0.05 level (2-tailed).

4. Ongoing New Projects and Future Research Plan

4.1. Use of 3T MRI for the estimation of brain development in young children

MRI data of our database are taken mostly by using 0.5 T scanner and small fraction by 1.5T MR scanner. Images taken by 0.5T scanner have low signal to noise ratio, although they have low field in homogeneity and low image distortion. We installed a 3.0T MRI at the end of 2007 fiscal year. By this scanner we can obtain image with high spatial resolution, high tissue density resolution and high signal to noise ratio compared to those by 1.5 T. This enables us to get high accuracy in tissue segmentation resulting in high accuracy analysis.

Figure 10 show brain MRI of 40 years old man and 6 years old children. Gray to white matter contrast of the T1-weighted brain image is higher compared to that taken by 0.5 T or 1.5T MR scanners.

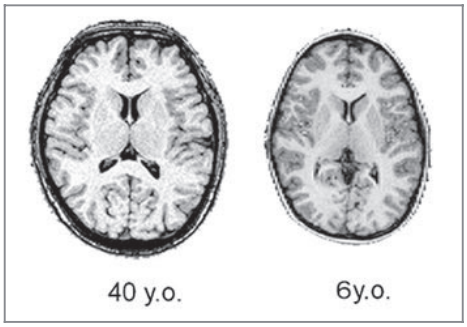

Fig. 10. Brain MRI of subjects with 40 (left) and 6 (right) years old taken by 3T MR scanner.

We started brain development project since this April, 2008. The outline of this project is as follows:

Purpose: To clarify brain development during 6 to 20 years old using brain MRI.
Objects of analyses:

1) Brain volume change (gray matter, white matter, CSF space)
2) Changes in blood flow (gray matter).
3) Changes in fractional anisotropy in the white matter.
4) Correlation between regional brain volume and a specific brain function.
5) Correlation between brain volume and intelligence (IQ/EQ).

In order to analyses articles described above, the following data will be obtained.

1) Structural MRI
2) Diffusion weighted MRI
3) Perfusion MRI
4) Functional MRI
5) Full scale IQ

From this April, we started the project and got 50 brain MRIs of aged 6 to 17 at the end of this October. Preliminary analysis revealed that gray matter volume gradually increased in this age window, while white matter volume largely increased linearly. On the hand, gray matter ratio decreased with increasing of age and white matter ratio slightly increased with age. We will continue to accumulate MRI data and analyze structural development of the children brain.

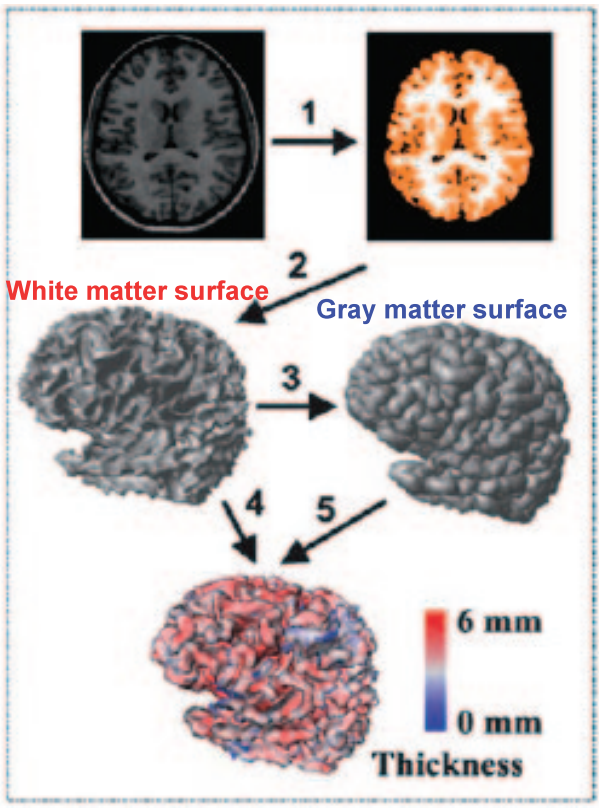

Fig. 11. Calculation of cortical thickness

4.2. Cortical thickness as an indicator of brain aging

We have used global/regional gray matter volume (probability) as an indicator of brain aging. MNI group developed a method to measure cortical thickness of the regional brain and showed that cortical thickness was a better indicator of brain aging than gray matter volume. Figure 11 represents steps of cortical thickness calculation. After brain tissue segmentation into gray matter, white matter and CSF space (step 1), white matter surface (step 2) and gray matter surface (step 3) image were calculated. Then, distances from gray matter surface to white matter surface were calculated in each regional brain (step 4, 5). The calculated values were displayed by triangle mesh (vertex) which was attached to the gray matter surface.

Figure 12 shows age-related change of the regional cortical thickness which was calculated in 450 subjects selected from our data base. Slope of the thickness decrease (slope of the linear regression line) was expressed by color scale. The data showed that medial part of the frontal lobe thinned more rapidly than the other part of the brain did. These results are obtained under collaboration with NMI group. We sent brain MRI data through internet and MNI group calculated cortical thickness using their own software. The results were consistent with those from regional gray matter volume measurement (decrease).

Software for the calculation of cortical thickness is only available in MNI. In February, 2008, we visited MNI for the discussion of further collaboration. NMI computer scientist and we tried to install the software remotely into Sendai site and succeeded in it. By this time we have continuously prepared a platform for image analysis such as pipe line system, and now we can use the cortical thickness software in Sendai. From the next term, we will analyze change of cortical thickness with aging and their risk factors and also anatomical network analysis using regional cortical thickness.

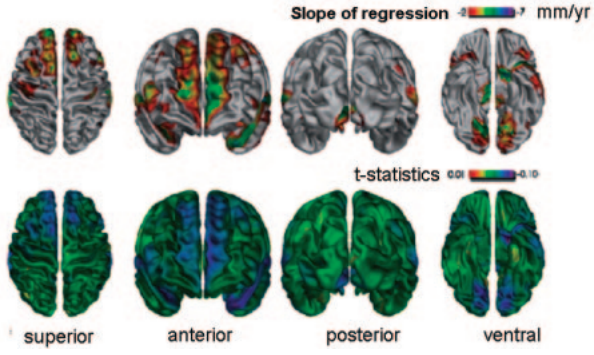

Fig. 12. Age-related change of the cortical thickness in 450 healthy subjects (with the permission of Prof. A. Evans, Montreal Neurological Institute).

5. Conclusion and Prospects in Aging Medicine and Predictive Medicine

We are facing to super aging society in Japan and therefore significance and importance of aging medicine will become higher and higher. In particular, researches on human brain aging become more important because they will contribute to the early diagnosis and prevention of age-related brain diseases such as dementia. In this research, as a part of GCOE project, we try to clarify structural and functional aging of the healthy brain and their risk factor (aging accelerating factors) through innovated methods of image analyses and image statistics. We continue to develop and improve methods for image processing and image statistics and analyze our data base.

We are also trying to develop automated diagnostic software for the discrimination of age-related brain diseases from normal brain utilizing these results. This can be achieved by judging data deviation from normal range. Final goal of this project is to realize these diagnostic methods in clinical setting and contribute to prevention of age-related brain diseases.

Acknowledgements

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