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Voxel-based morphometry of human brain with age and cerebrovascular risk factors

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Abstract

The objectives of this study were to evaluate the correlations of the volumes of the gray matter and white matter with age, and the correlations of the tissue probabilities of the gray matter and white matter with age and several cerebrovascular risk factors. We obtained magnetic resonance (MR) images of the brain and clinical information from 769 normal Japanese subjects. We processed the MR images automatically by correcting for inter-individual differences in brain size and shape, and by segmenting the MR images into the gray matter and white matter. Volumetry of the brain revealed a significant negative correlation between the gray matter volume and age, which was not observed between white matter volume and age. Voxel-based morphometry showed that age, systolic blood pressure, and alcohol drinking correlated with the regional tissue probabilities of the gray matter and white matter.

Keywords: Voxel-based morphometry; Gray matter; White matter; Age; Cerebrovasucular risk factors; MRI

1. Introduction

Several factors are associated with volume or structural change of the human brain. Studies using magnetic resonance (MR) imaging or computed tomography have revealed a decrease in brain volume and an increase in cerebrospinal fluid (CSF) space with age [7,11,17,18,30,34,38,39,48]. These changes are also observed to a significantly greater extent in individuals with elevated blood pressure [13,40,42,43,51] or who are heavy alcohol drinkers [22,33,35,36].

On the other hand, the volume change of the white matter with age is still controversial. Several recent studies indicated that a significant total white matter volume loss is not observed with age [17,37,38], while other studies indicated otherwise [19,39]. Regarding cerebrovascular risk factors, MR imaging studies have found a significant reduction white matter volume in alcoholics [24,33].

However, most of the above studies focused on specific factors or specific regions of the brain, or were based on a small number of subjects, or were carried out with limited age windows.

In recent years, the techniques for correction for inter-individual differences in overall brain size and shape [8], and fully automated classification of MR images into gray matter, white matter, and CSF space [15] have been developed. Automated classification is not operator-dependent, so it is possible to analyze a number of MR images objectively. These methods enable us to perform a voxel-based morphometry [3].

To our knowledge, there are no published in vivo MR imaging studies on the local changes of the gray matter or white matter with age and in relation to several cerebrovascular risk factors. The objectives of this study were to evaluate the global volume change of the gray matter and white matter with age and to evaluate the correlations of the tissue probabilities of the gray matter and white matter with age and several cerebrovascular risk factors by a voxel-based morphometry of structural MR images and clinical data.

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2. Methods

2.1. Subjects

The subjects were Japanese volunteers recruited by the Aoba Brain Imaging Research Center, Sendai, Japan. All of them were normal, and were right-handed. Prior to the acquisition of MR images, the subjects were interviewed by medical doctors of the Institute of Development, Aging and Cancer (IDAC), Tohoku University, to obtain the following clinical data: history of cigarette smoking and alcohol drinking, and present or past history of arrhythmia, diabetes mellitus, hypertension, hypercholesterolemia, and ischemic heart disease. Information in their educational attainment was not collected because educational levels in Japan are quite homogenous in the same generation regardless of economic status. The subjects who had past history or symptoms of a central nervous system disease of any kind or brain injury were excluded from this study by the interview. After the interview, brain MR images were obtained from each subject. The MR images were inspected by radiologists and the images with the following findings were excluded from this study: head injuries, brain tumors, infarctions, hemorrhage, multiple and extensive ischemic changes, severe atrophies, and normal variants such as mega cisterna magna, and arachnoid cyst (57 subjects). MR images containing substantial noise were also excluded (143 subjects) (duplications were included). As for ischemic change, MR images showing only the absence or punctate (diameter < 2 mm) ischemic change were used for further analysis. Finally, 356 men (mean $\pm$ S.D.; age, 45.4 $\pm$ 15.7 years; range: 16–79 years) and 413 women (mean $\pm$ S.D.; age, 47.4 $\pm$ 13.5 years; range: 18–79 years) were selected for the present study. The history of disease and medication, and smoking and alcohol-drinking habits of the subjects are shown in Table 1. The smoking index was equal to the Brinkmann index and was expressed as follows: (number of cigarettes smoked per day) $\times$ (years of smoking). The subjects who consume alcohol more than once a week were designated as alcohol drinkers. Drinking index was defined as follows: (amount of alcohol consumed per day (we assume 33.6 ml ethanol to be equal to 1, i.e. the volume of ethanol that is approximately equal to one glass of wine)) $\times$ (number of drinking times per week) $\times$ (years of drinking history). The smoking indices of men and women were 292.2 $\pm$ 392.7 (mean $\pm$ S.D.) and 37.23 $\pm$ 130.8, respectively. The drinking indices of men and women were 162.4 $\pm$ 333.9 (mean $\pm$ S.D.) and 18.78 $\pm$ 77.60, respectively. Blood pressure in the right brachial artery was measured with the subjects in a sitting position after a 10-min rest. Written informed consent was obtained from each subject after a full explanation of the purpose and procedures of the study, according to the declaration of Helsinki (1991), prior to MR image scanning. Approval for these experiments was obtained from the institutional review board of IDAC, Tohoku University.

Table 1
History of disease and medication of each gender

Factor	Medication	Male ($n = 356$)	Female ($n = 413$)
Hypertension		48 (13%)	43 (10%)
	Medication	45	37
	None	3	6
Diabetes mellitus		17 (5%)	8 (2%)
	Medication	15	7
	None	2	1
Hypercholesterolemia		26 (7%)	37 (9%)
	Medication	17	28
	None	9	9
Ischemic heart disease		3 (1%)	5 (1%)
	Medication	3	2
	None	0	3
Arrhythmia		5 (1%)	5 (1%)
	Medication	2	2
	None	3	3

2.2. Image collection

Brain images were obtained from each subject using the same 0.5 T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with three 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 (FA), 90°; voxel size, 1.02 mm $\times$ 1.02 mm $\times$ 1.5 mm); (2) 63 contiguous, 3-mm thick axial planes of proton probability images (spin echo (SE): TR, 2860 ms; TE, 15 ms; voxel size, 1.02 mm $\times$ 1.02 mm $\times$ 3 mm); and (3) 63 contiguous, 3-mm thick axial planes of T2-weighted images (SE: TR, 2860 ms; TE, 120 ms; voxel size, 1.02 mm $\times$ 1.02 mm $\times$ 3 mm). Prior to further computational procedures, all MR images were filmed in a conventional format and inspected by experienced radiologists.

2.3. Image analysis

After acquisition, all MR images were transferred to the Montreal Neurological Institute and were processed automatically in Silicon Graphics workstations as follows. First, intensity non-uniformity in MR data was corrected by the non-parametric non-uniform intensity normalization method [41]. Next, MR images were transformed into the Talairach stereotaxic space [45] using nine rigid linear parameters, namely three scalings, three rotations, and three translations [8]. As a reference, brain of this transformation, we used an average brain made up of 305 normal brains for the standardization procedure [8]. Then, tissue classification was performed with an artificial neural network classifier [15]. This method involves classifying each pixel according to its combination of intensities from each image type. The nature and the precision of this method were described in detail by Zijdenbos et al. [52]. As described in Section 2.1, using the MR images showing absence or a slight ischemic change,

little misclassifications were found by visual inspection. In this study, the cerebellum and the brain stem were automatically excluded from MR images using the same masks [9]. Those processes were performed on the brain MR images of each subject independently. After the image processing, the MR images resulted in the binary images of the gray matter, white matter and CSF.

2.4. Volumetric analysis

The stereotactically normalized gray matter and white matter binary images were restored to native space using the scaling factors of the transformation into the Talairach stereotaxic space, and the actual volumes of gray matter and white matter were measured by summing the voxels automatically. Then, we calculated "gray matter ratio," which is defined as the percentage of the gray matter volume divided by the intracranial volume. Then, the correlations of gray and white matter volumes, intracranial volume and gray matter ratio with age was determined by simple regression analysis.

2.5. Voxel-based morphometry

Statistical analysis of the local volume change of the gray matter and white matter was carried out by statistical parametric mapping (SPM) (SPM99, Wellcome Department of Cognitive Neurology, London, UK) [16] in Matlab (Math Works, Natick, MA). The stereotactically normalized gray matter and white matter binary images were smoothed using a 20 mm full width at half-maximum isotropic Gaussian kernel. The smoothing made the data more normally distributed [3]. The voxel values in the resulting smoothed gray or white matter images were referred to as gray or white matter probability. Gray or white matter probability means the probability of a voxel being gray and white matters, respectively. To investigate the regionally specific effects of each factor on the imaging data, multiple regression analysis was performed. The voxel values, which represent tissue probability, were used as a dependent variable and each factor was used as an independent variable. Age, and systolic and diastolic blood pressures were used as continuous variables. Since the distributions of both smoking and drinking indices were highly deviated from the normal distribution (smoking index: one peak existed at 0 in each gender; drinking index: two peaks existed at 0 and about at 300 in men, the peak existed at 0 in women), these factors were used as discrete variables, as follows: If the subject had no history of smoking, or no alcohol-drinking habit or drinks less than once a week, "0" was used, and if they did, "1" was used.

For the correction of multiple comparisons, height threshold was corrected and $P < 0.05$ was chosen.

The results of SPM image analysis were superimposed on structural MR images on horizontal slices, which were the average images of all subjects' normalized T1-weighted images, to facilitate correlation with anatomy.

3. Results

3.1. Volumetric analysis of correlation of gray and white matter volume with age

The cross-sectional analysis showed a significant negative correlation between gray matter volume and age in both men ($R^2 = 0.58$, $P < 0.001$) (Fig. 1A) and women ($R^2 = 0.39$, $P < 0.001$) (Fig. 1B). On the other hand, the white matter volume did not show a significant correlation with age in men ($R^2 = 0.02$, $P = 0.75$) and women ($R^2 = 0.02$, $P = 0.70$) (Fig. 2A and B). In addition, men had a significantly steeper decline in the regression line of the gray matter volume and age than women ($P < 0.05$). The mean gray matter volume was significantly greater in men (599,493 mm^3) than in women (518,307 mm^3), Mann–Whitney U test, $P < 0.001$. In this study, we determined the intracranial volume by summing the gray matter volume, white matter volume, and volume of CSF space. There was no significant correlation between intracranial volume and age in both men and women (data not shown). Gray matter ratio and age showed a significant negative correlation in both men ($R^2 = 0.70$,

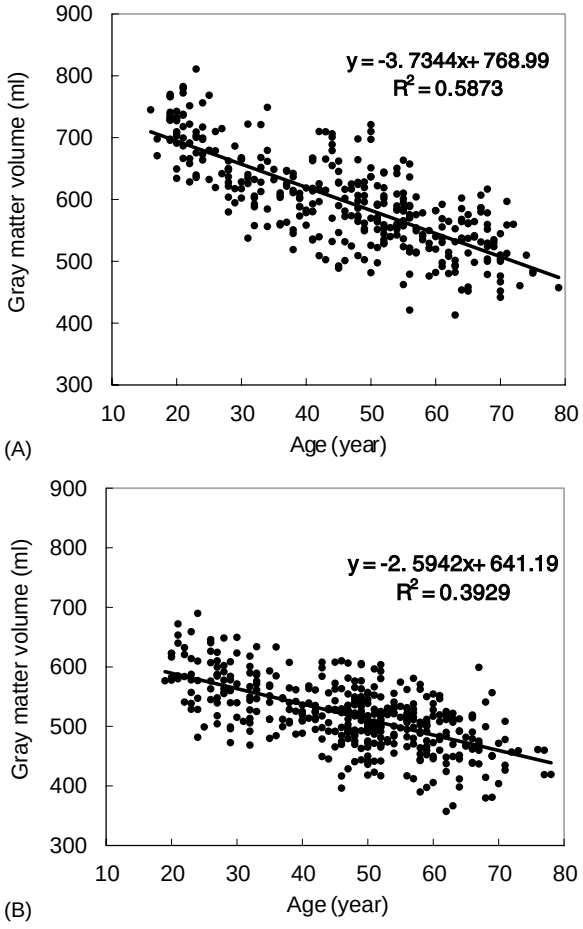

Fig. 1. (A) Correlation between gray matter volume and age in men. (B) Correlation between gray matter volume and age in women.

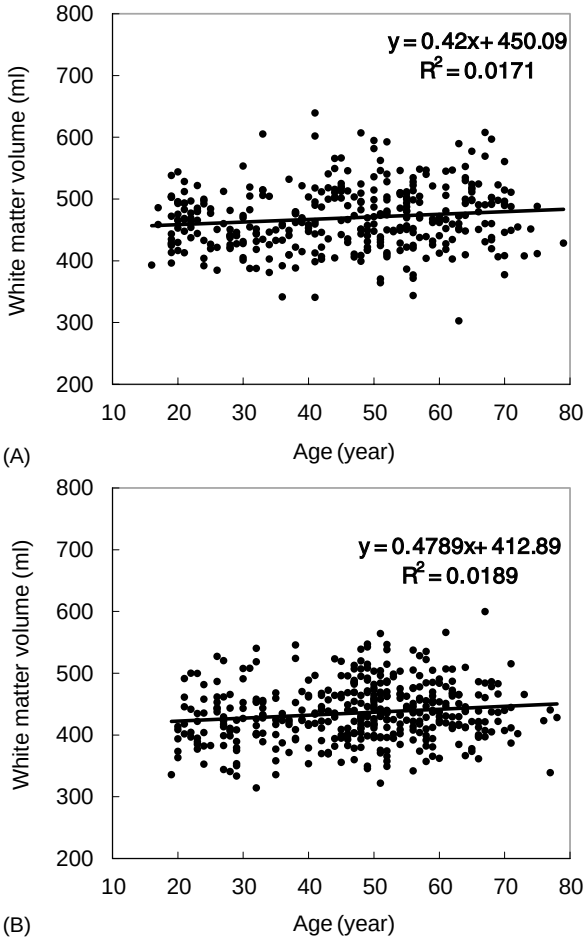

Fig. 2. (A) Correlation between white matter volume and age in men. (B) Correlation between white matter volume and age in women.

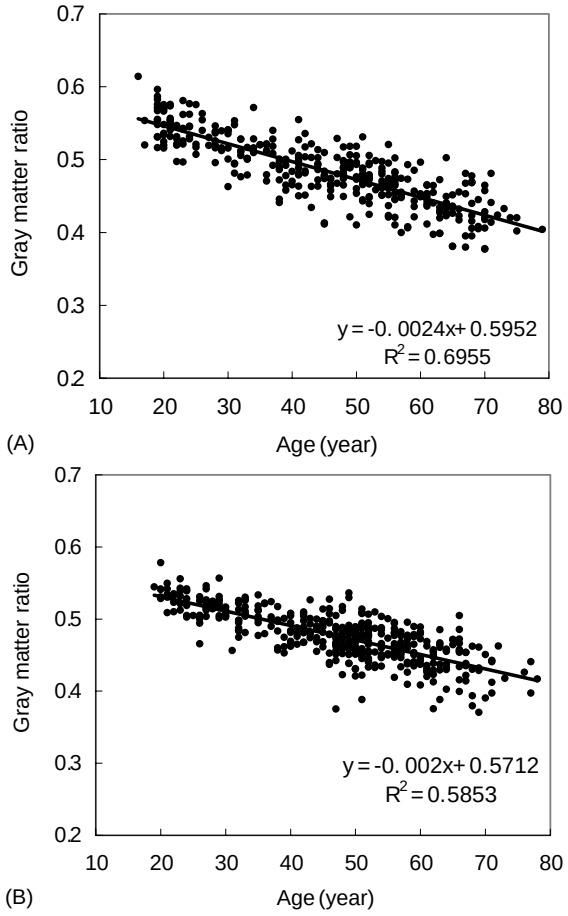

Fig. 3. (A) Correlation between gray matter ratio and age in men. (B) Correlation between gray matter ratio and age in women.

$P < 0.001$) (Fig. 3A) and women ($R^2 = 0.59$, $P < 0.001$) (Fig. 3B). There was not significant difference in the decline with age in each gender.

3.2. Voxel-based morphometry of gray matter

Fig. 4A and B shows the regions of the gray matter in which gray matter probability significantly and negatively correlated with age in men and women, respectively. The probability in almost all cerebral cortices and the basal ganglia showed a significant negative correlation with age. In particular, strong correlations were found in the bilateral superior temporal gyri in men, and in the left superior temporal gyrus and the left precentral gyrus in women.

Fig. 5A-1 and A-2 shows the regions in which gray matter probability showed a negative correlation with systolic blood pressure in men and women, respectively. The correlations were found in the left cuneus and right inferior temporal gyrus in men, and in the right cuneus and left medial frontal gyrus in women.

Fig. 5B shows the regions in which gray matter probability showed a significant negative correlation with alcohol drinking in men. The correlation was found in the right superior frontal gyrus, left middle occipital gyrus, left precentral gyrus, left middle inferior gyrus, left postcentral gyrus, and left cuneus. In women, no region showed significant correlation between alcohol drinking and local gray matter probability.

No region showed significant correlation between diastolic blood pressure or cigarette smoking and local gray matter probability in each gender.

No factor showed a significant positive correlation with local gray matter probability in each gender.

3.3. Voxel-based morphometry of white matter

Fig. 6A-1 and A-2 shows the regions of the white matter in which white matter probability showed a significant negative correlation with age in men and women, respectively. The probability in almost the entire bilateral periventricular regions of the lateral ventriculus and third ventriculus showed significant negative correlation with age in each gender. In particular, a strong correlation was found in the bilateral lateral periventricular regions and left fasciculus occipitofrontalis in men, and in the bilateral

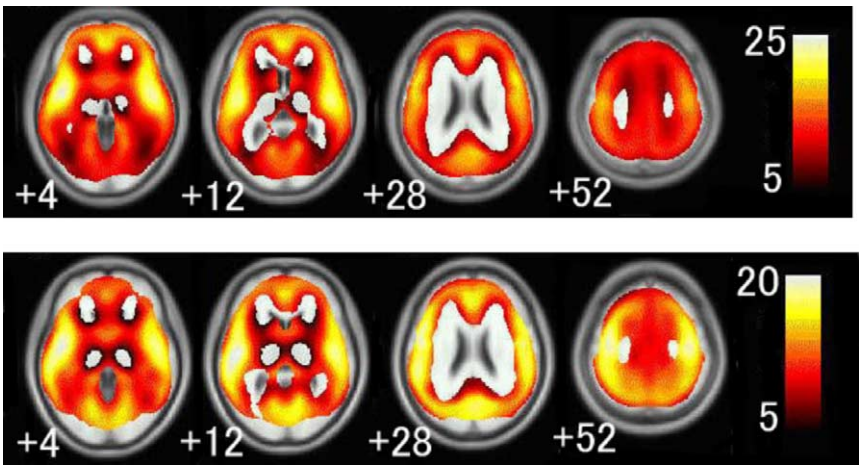

Fig. 4. (A) Regions of the gray matter in which gray matter probability significantly and negatively correlated with age in men. The left side of the image represents the left side of the brain. Color scales indicate *t*-score. The number at the bottom left of each image indicates the value of the *z*-axis in the Talairach stereotaxic space. (B) Regions of the gray matter in which gray matter probability significantly and negatively correlated with age in women. Details are the same as in (A).

lateral periventricular regions and left corpus callosum in women.

Except for age, there were no other factors that showed significant negative correlation with local white matter probability in each gender.

Fig. 6B-1 and B-2 shows the region in which white matter probability showed a significant positive correlation with age in men and women, respectively. Almost entire bilateral white matter of subcortical region showed a significant negative correlation in each gender. In particular, a strong correlation was found in the white matter of the left cuneus and bilateral external capsules in men, and in the right cuneus, right superior temporal gyrus, and left fornix in women.

Fig. 7A shows the regions of the white matter in which white matter probability showed a significant positive

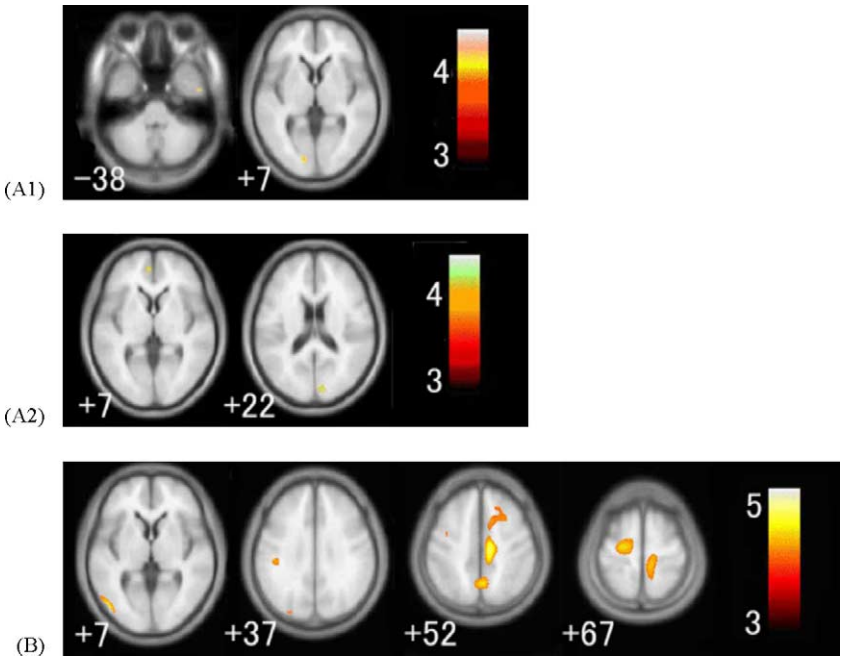

Fig. 5. (A-1) Regions of the gray matter in which gray matter probability significantly and negatively correlated with systolic blood pressure in men. Details are the same as in Fig. 4A. (A-2) Regions of the gray matter in which gray matter probability significantly and negatively correlated with age in women. Details are the same as in Fig. 4A. (B) Regions of the gray matter in which gray matter probability significantly and negatively correlated with alcohol drinking in men. Details are the same as in Fig. 4A.

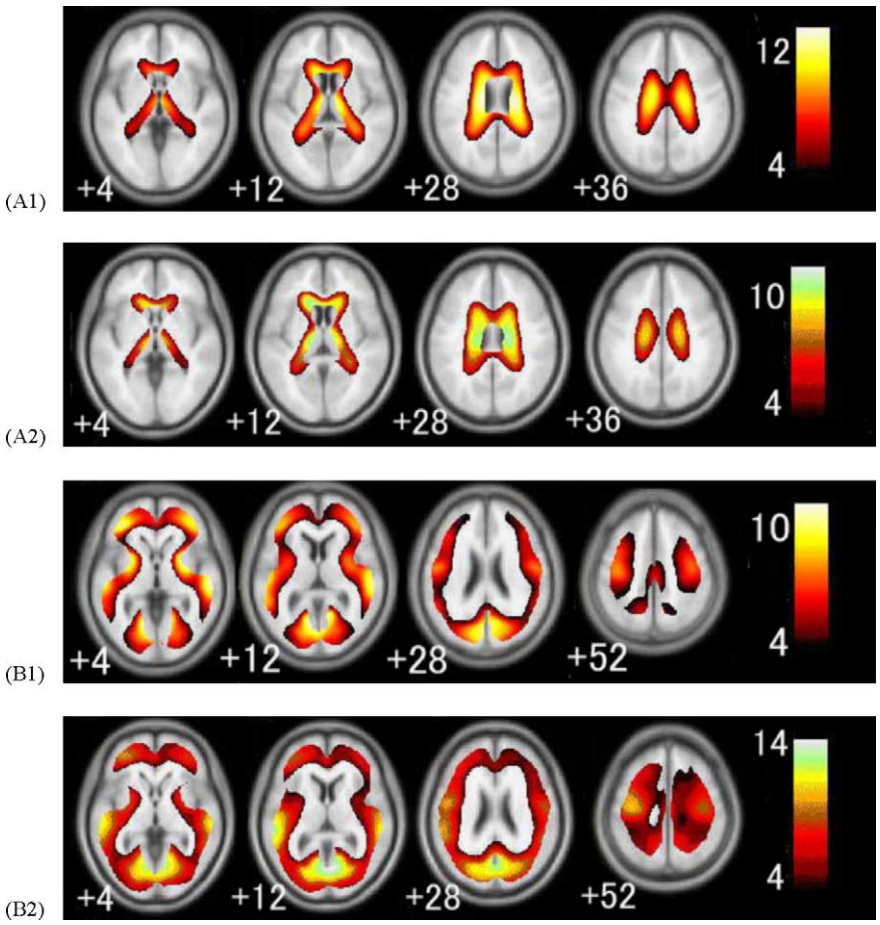

Fig. 6. (A-1) Regions of the white matter in which white matter probability significantly and negatively correlated with age in men. Details are the same as in Fig. 4A. (A-2) Regions of the white matter in which the white matter probability significantly and negatively correlated with age in women. Details are the same as in Fig. 4A. (B-1) Regions of the white matter in which white matter probability significantly and positively correlated with age in men. Details are the same as in Fig. 4A. (B-2) Regions of the white matter in which white matter probability significantly and positively correlated with age in women. Details are the same as in Fig. 4A.

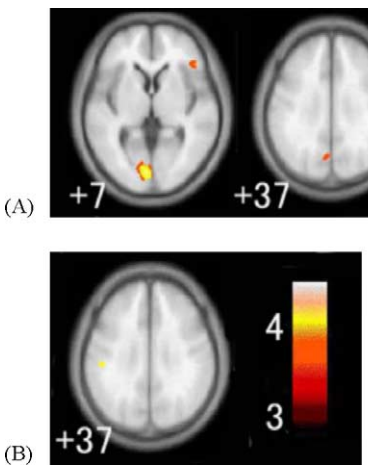

Fig. 7. (A) Regions of the white matter in which white matter probability significantly and positively correlated with systolic blood pressure in men. Details are the same as in Fig. 4A. (B) Regions of the white matter in which white matter probability significantly and positively correlated with alcohol drinking in men. Details are the same as in Fig. 4A.

correlation with systolic blood pressure in men. The regions are the left cuneus and the right inferior frontal gyrus. No area showed significant systolic blood pressure related change in local white matter probability in women.

Fig. 7B shows the regions in which white matter probability showed a significant positive correlation with alcohol drinking in men. The left postcentral gyrus showed a significant negative correlation with alcohol consumption. No area showed a significant alcohol drinking related change in local white matter probability in women.

No other factors showed a significant positive correlation with local white matter probability in each gender.

4. Discussion

To our knowledge, this is the first study that shows the correlations of the tissue probabilities of gray matter and white matter with age and several cerebrovascular risk factors.

4.1. Volumetric analysis of correlation of gray matter and white matter volumes with age

There was a significant negative correlation between gray matter volume and age in each gender, whereas white matter volume did not significantly correlate with age in each gender. The results indicate that the main factor contributing to brain atrophy with age is the volume reduction of the gray matter, and not that of the white matter. We also showed that men had a significantly steeper decline in gray matter volume with age than women. However, there was no significant difference in the decline in the regression line of gray matter ratio, which is the gray matter volume normalized by the intracranial volume with age for each gender.

In most of the previous studies on aging, increased variability with age was found in most aging indicators. However, it was not observed in this study. Generally, the older "normal" group in this kind of studies included subjects with minimum pathological changes but subclinical, that is slight to moderate ischemic changes and very small lacunar infarctions. As described in the methods, we excluded these subjects, and thus older subjects in our study might be supernormal. This might be one of the reasons for the absence of large deviations in older ages. This finding is consistent with the previous study that analyzed the morphometrical changes of 465 normal adult human brains with age [17].

From several previous studies, the normal age-related decrease in the gray matter volume has been attributed to decreased perfusion rate [28,29,44], and neuronal shrinkage and/or loss with decreased cortical synaptic densities [2,26,47], which are probably related to neuronal apoptosis [5,6].

Regarding the factors that influence white matter volume change, the loss of axons is associated with the loss of neurons, loss of myelins, and number of glial cells. Previous studies of autopsied normal human brains showed that approximately 10% of all neocortical neurons are lost over one's life span in each gender [32], and that the total volume of myelinated fibers in elderly subjects is lower than that in young subjects [46]. On the other hand, a parallel process of capillary network and swelling of perivascular spaces may increase the white matter bulk [27]. There was a substantial increase in glial population in the paracortical white matter of the visual cortex of the elderly compared with that of young individuals [14].

4.2. Voxel-based morphometry of correlation of gray matter with age

We showed that the gray matter probability of almost the entire cerebral cortex and basal ganglia showed a significant negative correlation with age. In particular, strong correlations were found in the bilateral superior temporal gyri in men, and in the left superior temporal gyrus and the left precentral gyrus in women. As for precentral gyrus, the results are consistent with a previous study [17]. The other regions, these are new finding of this study.

4.3. Voxel-based morphometry of correlation of gray matter with systolic blood pressure

We showed that the increase in systolic blood pressure significantly correlated with the decrease in gray matter probability. The correlations were found in the left cuneus and right inferior temporal gyrus in men, and in the right cuneus and left medial frontal gyrus in women, although the mechanism of regional morphometric change is unknown.

We only took one-point data. As shown in Table 1, only about 10% of the subjects had a history of hypertension. In addition, most of those who had a history of hypertension were medicated, and the control of hypertension was good. Nevertheless, the elevation in systolic blood pressure had a significant negative correlation with the morphometrical change of the gray matter or white matter. From this result, it is important to control systolic blood pressure whether or not there is a history of hypertension.

4.4. Voxel-based morphometry of correlation of gray matter with alcohol drinking

From several previous studies of alcoholic patients, it was found that alcohol per se is responsible for structural changes observed in heavy alcohol drinkers [20,23]. Previous studies emphasized mechanisms such as increased production of free radicals and enhanced excitatory neurotransmission, which might be responsible for alcohol-related brain atrophy [4,49]. A previous study of alcoholics revealed a significant volume reduction of the cortical region in the dorsolateral frontal and parietal cortices [22], and several autopsy studies on alcoholics showed a selective neuronal loss in the superior frontal cortex [21,24]. Studies of social drinkers also indicated that alcohol drinking is associated with frontal lobe atrophy [25]. We showed that areas whose gray matter probability shows a significant negative correlation with alcohol drinking are the superior frontal and parietal cortices, in agreement with those reported in previous studies.

As described in methods, the distribution of drinking index among the subjects highly deviated from the normal distribution (two peaks existed at 0 and at about 300 for the male subjects, and one peak existed at 0 for the female subjects), thus we divided the subjects into two groups: non-drinkers or occasional drinkers, and habitual drinkers. In addition, this study is a comparison not between healthy subjects and alcoholics but among healthy subjects only. Nevertheless, the significant differences in morphometric changes of the gray matter and white matter between habitual drinkers and occasional drinkers were observed, and the areas of gray matter probability that showed a significantly negative correlation with alcohol drinking were partially consistent with the results of several previous studies.

4.5. Voxel-based morphometry of white matter

The analysis revealed that the probability of almost the entire periventricular white matter showed a significant negative correlation with age, while that of almost the entire subcortical white matter showed a significant positive correlation with age. Volumetric analysis showed that there was no significant increase or decrease in white matter volume throughout aging. Because the brain is in a closed space with three compartments, a change in one compartment will result in the change in another. There are at least two reasons for these: (1) white matter displacement due to the complementary decrease in gray matter volume. Because the gray matter probability in almost the entire cerebral cortex showed a significant negative correlations with age. (2) The expansion of the ventricles, the expansion of the ventricle may cause white matter displacement.

4.6. Limitation of the study

The limitation of this study as a cross-sectional study is that it cannot assess the impact of each factor on the extent of later-life brain atrophy. Only a longitudinal study can solve these problems. We are currently planning a longitudinal study in order to analyze the correlation of morphometrical change of the gray matter and white matter with age and in relation to several cerebrovascular risk factors.

The identification of risk factors that correlate with the structural change of the gray matter and white matter in the brain is very important because brain shrinkage is considered to be a risk factor for cognitive decline and memory impairment [1,10,12,29,31,50]. Identifying the regions of the gray matter that are affected by each factor will help us understand the functions of the brain that are impaired by each factor, and the mechanism underlying the pathogenesis of brain damage and its pathophysiologic consequences.

In summary, we evaluated the change in gray matter and white matter volumes with age, and identified the regions of the gray matter and white matter that are affected by age and several cerebrovascular risk factors. As a result, we found a significant negative correlation between gray matter volume and age in each gender, while white matter volume did not significantly correlate with age in each gender. Age, systolic blood pressure, and alcohol drinking in men were negatively correlated with local gray matter probability. Age showed a significant negative correlation with white matter probability of almost the entire bilateral periventricular regions of the lateral ventriculus and third ventriculus in each gender, and also a significant positive correlation with local white matter probability of almost the entire bilateral white matter of subcortical regions. Systolic blood pressure and alcohol drinking also showed significant positive correlations with local white matter probability in men. The identification of risk factors that reduce brain volume is very important because brain shrinkage is considered to be a risk factor for cognitive decline.

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