AJNR

Gender Effects on Age-Related Changes in Brain Structure

Jiang Xu, Shotai Kobayashi, Shuhei Yamaguchi, Ken-ichi Iijima, Kazunori Okada and Kazuya Yamashita

AJNR Am J Neuroradiol 2000, 21 (1) 112-118
http://www.ajnr.org/content/21/1/112

AJNR Am J Neuroradiol 21:112–118, January 2000

Gender Effects on Age-Related Changes in Brain Structure

Jiang Xu, Shotai Kobayashi, Shuhei Yamaguchi, Ken-ichi Iijima, Kazunori Okada, and Kazuya Yamashita

BACKGROUND AND PURPOSE: **Previous reports have suggested that brain atrophy is associated with aging and that there are gender differences in brain atrophy with aging. These reports, however, neither exclude silent brain lesions in "healthy subjects" nor divide the brain into subregions. The aim of this study is to clarify the effect of gender on age-related changes in brain subregions by MR imaging.**

METHODS: **A computer-assisted system was used to calculate the brain matter area index (BMAI) of various regions of the brain from MR imaging of 331 subjects without brain lesions.**

RESULTS: **There was significantly more brain atrophy with aging in the posterior parts of the right frontal lobe in male subjects than there was in female subjects. Age-related atrophy in the middle part of the right temporal lobe, the left basal ganglia, the parietal lobe, and the cerebellum also was found in male subjects, but not in female subjects. In the temporal lobe, thalamus, parieto-occipital lobe, and cerebellum, brain volume in the left hemisphere is significantly smaller than in the right hemisphere; sex and age did not affect the hemisphere differences of brain volume in these regions.**

CONCLUSION: **The effect of gender on brain atrophy with aging varied in different subregions of the brain. There was more brain atrophy with aging in male subjects than in female subjects.**

CT and MR imaging have provided revolutionary means for morphologic study of the brain in vivo. MR imaging obtains much more precise data than CT because of better tissue contrast and the absence of bone artifact. The majority of previous reports indicate that brain volume is reduced and the volume of the ventricles is enlarged with physiologic aging, which suggests that brain atrophy in humans is associated with aging (1–23). Some authors found gender differences in brain atrophy with aging and showed that the degree of change was milder in women than in men (2, 6–8, 11, 14, 17–21, 23). Other reports present the opposite results (3–5, 13, 16, 22, 24). Therefore, it still is controversial whether there are gender differences in brain atrophy with aging.

Many problems still face the study of gender differences in brain atrophy with aging. In previous reports, silent brain lesions were not clearly excluded from healthy subjects. The so-called silent brain lesions included subcortical silent brain infarction, focal white matter T2 hyperintensity lesions (similar to subcortical silent brain infarction but without correlative T1 hypointensity), and periventricular hyperintensity (25). Incidence of silent brain lesions increases with aging and hypertension (25, 26). Recently, silent brain lesions also were reported to have a close association with brain atrophy (27). Results may be affected if this factor is not excluded from the analysis. Therefore, healthy subjects should have no brain disease confirmed by history or MR imaging, no risk factors for stroke, and no white matter signal abnormality.

Brain atrophy with aging occurs heterogeneously, and differences in the location and degree of brain atrophy with aging vary with gender. This makes it difficult to assess exactly gender differences in brain atrophy with aging, unless regional differences in the brain are examined in detail as a crucial part of any study. There also are individual differences in brain volume. If the measured brain volume is not adjusted for head size, height, or weight, the reliability of results may diminish. In previous reports on gender differences in brain atrophy with aging, adequate statistical comparisons were not made (7, 8, 17). Because of individual differences in brain atrophy with aging, it is difficult to have confidence in the results of previous

Received February 23, 1999; accepted after revision July 12, 1999.

From the Department of Internal Medicine III (J.X., S.K., S.Y., K-I.I., K.O., K.Y.), Shimane Medical University, Izumo, Japan; and the Shimane Institute of Health Science (S.K.), Izumo, Japan.

Address reprint requests to Jiang Xu, MD, Department of Internal Medicine III, Shimane Medical University, 89-1, Enya-cho, Izumo, Shimane, 693-8501, Japan.

TABLE 1: Age distributions of the subjects

Age	Men	Women	Total
30–39	17	9	26
40–49	29	27	56
50–59	88	70	158
60–69	31	37	68
70–79	11	12	23
Total	176	155	331

reports based on a small number of subjects. The number of subjects is a crucial factor for any study of brain atrophy with aging.

Most previous studies analyzed only the frontal and temporal lobes as a whole, but not their subregions. Only a few reports on parietal lobe (15, 20) and cerebellar (28–30) atrophy with aging have been published. The aim of this study was to overcome the flaws of previous reports and use MR imaging to clarify the effects of gender differences with aging on subregions of the brain.

Methods

Subjects

One thousand one hundred and fifty-five subjects (685 men, 470 women; age range 27 to 87 years) were selected from persons undergoing health screening of the brain at the Shimane Institute of Health Science between September 30, 1992 and July 9, 1997. None had neurologic complaints. Only subjects who met all of the following conditions were used in this study: 1) subjects had no previous brain disease; 2) no white matter signal abnormality and cerebral tumors, infarction, or hemorrhage were found on MR imaging; 3) subjects had no risk factors for stroke, such as hypertension, diabetes, cardiovascular diseases, or hyperlipidemia; 4) subjects took neuropsychological tests, including the Okabe mental scale (a shortened version of the Wechsler Memory scale) (31) and the Kohs' block design test—neither test showed intellectual impairment (higher than 40 points on Okabe's scale and higher than 80 IQ on Kohs' test); 5) subjects were right-handed; 6) MR images of the head in all subjects were consistent with the measuring criteria set before the MR imaging examination. Of the 331 individuals who met all these conditions, 176 were men and 155 were women. Their age distribution is summarized in Table 1.

To study changes in brain volume with aging, all qualified subjects were divided into two groups. The young group included subjects younger than 50 years (46 men, 36 women) and the old group included those older than or equal to 50 years (130 men, 119 women). The mean duration of their formal education was 13.3 $\pm$ 2.8 (mean $\pm$ SD) years for male subjects and 12.7 $\pm$ 2.7 years for female subjects. The Okabe mental scale was 49.4 $\pm$ 4.5 in male subjects and 49.3 $\pm$ 5.3 in female subjects. Kohs' IQ was 110.2 $\pm$ 14.2 in male subjects and 108.5 $\pm$ 15.4 in female subjects. No gender differences were seen in age, years of education, Okabe mental score, or Kohs' IQ. A marginal interaction of age $\times$ sex ($P = .089$) was in the analysis of variance (ANOVA) for Kohs' block design test. A post hoc analysis showed that Kohs' IQ in the old group decreased by 11.9 points in male subjects ($P < .001$) and by 5.6 points in female subjects ($P = .06$), compared with the younger group. On the other hand, the mean consumption of alcohol was 25 grams per day in male subjects and 7 grams per day in female subjects ($P < .0001$); 43.2% of male subjects smoked compared with 4.3% of female subjects ($P < .0001$).

MR Imaging

Brain MR imaging was performed with a 0.2-T scanner (Siemens, Erlangen, Germany). Pictures of horizontal, sagittal, and coronal sections were taken in all subjects. The analyzed images were sagittal and coronal sections. Eleven coronal slices from the frontal to the occipital lobe were obtained using T1-weighted images (350/15 [TR/TE]). The sixth slice passed through the interthalamic adhesion. The slice thickness was 7 mm and the gap was 1.75 mm. Nine sagittal slices also were obtained using T1-weighted images (350/15 TR/TE). The fifth slice passed through the interhemispheric tissue. The slice thickness was 7 mm and the gap was 1.75 mm.

Slice Selection

The midline T1-weighted image of the sagittal sections and five coronal slices were selected for this study. The coronal slices were defined as follows: slice-a, passing through the anterior branch of the lateral sulcus; slice-b, passing through the ascending branch of the lateral sulcus; slice-c, the fifth coronal section that was selected according to the direction from the frontal to the occipital lobe; slice-d, the seventh coronal section; and slice-e, passing through the tonsil of the cerebellum (Fig 1). Although slice-c and slice-d were not anatomically defined, they were located 8.75 mm, respectively, in front of and behind the sixth slice corresponding to the interthalamic adhesion. Our method can eliminate the differences in slice level according to brain size.

Methods of Measurement

Each selected image was scanned into a computer (Macintosh Quadra 700) using a high-resolution CCD camera (Fujix FV-6000). The areas of the brain structures (a total of 26 regions for each subject, including the frontal, parietal, and temporal lobes, basal ganglia, thalamus, and cerebellum) were measured on a 17-inch CRT monitor using National Institutes of Health image software (version 1.59b4) and a mouse. The data were obtained for both hemispheres. The following subregions were defined (Fig 1). In the coronal sections, the upper (F2) and lower frontal lobes (F1) were separated by the anterior branch of the lateral sulcus in slice-a. The upper (F4) and lower frontal lobes (F3) were separated by the ascending branch of the lateral sulcus in slice-b. This slice also was used for measuring the temporal pole (T1). In slice-c, the posterior parts of the frontal lobe (F5) and basal ganglia were separated by a line from the top of the circular sulcus of the insula to the top of the lateral ventricle. This slice also was used for measuring the middle part of the temporal lobe (T2). In slice-d, a line between the sylvian fissure and the top of the lateral ventricle separated the parietal lobe from the thalamus. This slice also was used for measuring the temporal lobe in part (T3). Slice-e was used to measure the parieto-occipital lobe and cerebellum. Finally, we measured the cross-sectional area of the cranial cavity on the midline sagittal section of the skull by drawing a line on the CRT monitor to set the measurement boundary along the skull. The lower boundary of the area was a line between the basion and opisthion.

Using the midline sagittal image of 30 randomly selected subjects, we twice measured the areas of the right parietal lobe, left cerebellum in the coronal sections, and the cranial cavity, comparing the areas to determine the reliability of measurement. Furthermore, an independent observer who was blinded to the aim of this study measured the same regions. To verify the reliability of the data, correlation analysis was used to compare the observer's results with those of the authors. There were strong correlations between the authors' and the observer's results ($r = 0.958$–0.979, $P < .0001$), as well as between the

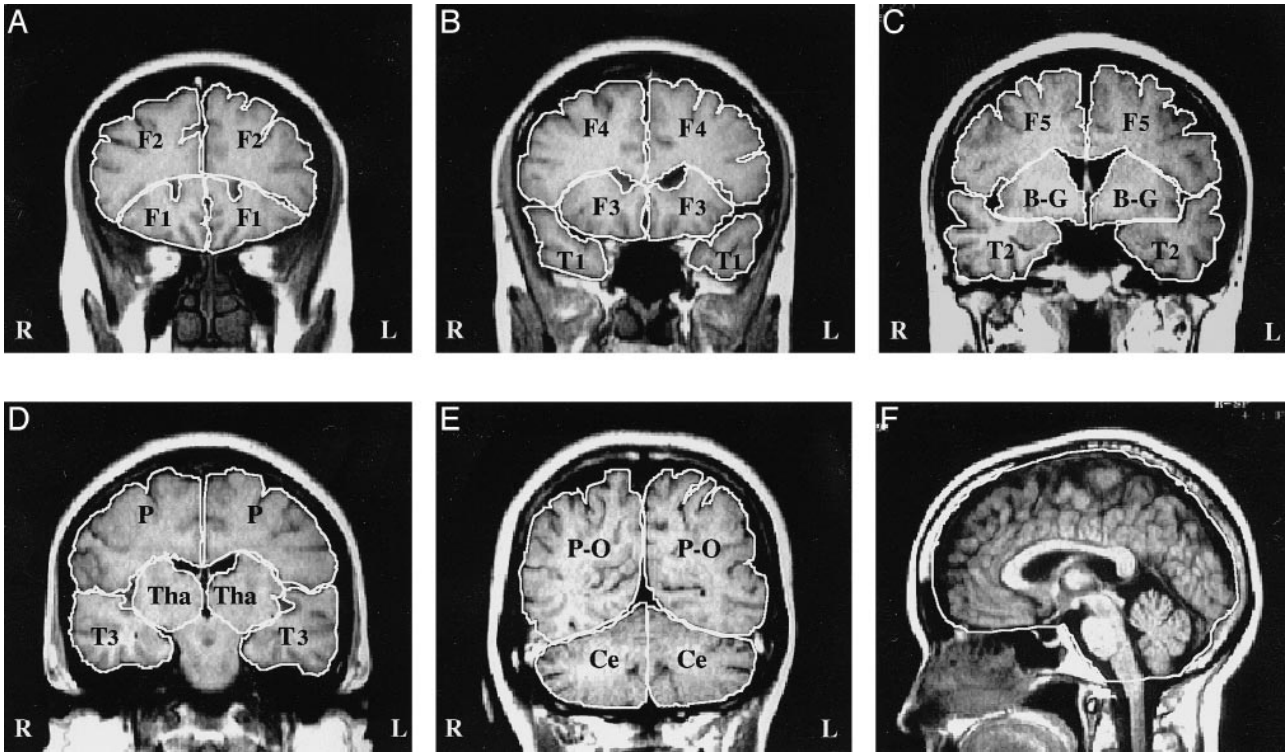

FIG 1. T1-weighted MR slices (350/15/7 [TR/TE/excitations]) used for definition of regions of interest.
A, F2, upper frontal lobes; F1, lower frontal lobes.
B, F4, upper frontal lobes; F3, lower frontal lobes; T1, temporal lobe.
C, F5, posterior parts of frontal lobe; B-G, basal ganglia; T2, middle part of temporal lobe.
D, P, parietal lobe; Tha, thalamus; T3, posterior part of temporal lobe.
E, P-O, parieto-occipital lobe; Ce, cerebellum.
F, Midline sagittal cross-sectional area of cranial cavity.

authors' two results ($r = 0.976$–0.993, $P < .0001$), which suggest that the method of measurement in this study was reliable.

Index

The formula for the brain matter area index (BMAI) reflects the relative brain volume adjusted to the individual cranial size. BMAI = regional brain area / intracranial area × 100.

Statistics

Two-factor ANOVA with age and sex for the different regions was used to analyze the gender difference in the changes of brain structure with aging. Three-factor ANOVA (age, sex, and left-right) was used to study hemispheric asymmetry. A post hoc analysis was performed using the Newman-Keuls test. Significant differences were accepted at a probability value of less than .05.

Results

Gender Effect on Regional Brain Structure Changes with Aging

Gender Effect.—The BMAI was significantly larger in female subjects than in male subjects in the thalamus and right basal ganglia. In contrast, BMAI was significantly smaller in female subjects than in male subjects in the parieto-occipital lobe and cerebellum (Table 2).

Age Effect.—The BMAI was markedly smaller in the older group than in the younger group in all the regions measured except for the basal part of the frontal lobe (F1) and the left cerebellum, showing that brain atrophy progresses with aging (Table 2).

Age by Gender.—Two-factor ANOVA of age × sex showed a significant gender difference in BMAI with aging in the posterior part of the right frontal lobe (F5), the middle part of the right temporal lobe (T2), the left basal ganglia, parietal lobe, and cerebellum (Table 2).

In the posterior parts of the right frontal lobe, post hoc analysis showed that brain atrophy with aging was larger in male subjects compared with female subjects. Furthermore, the rate of reduction of the BMAI ([BMAI of younger group − BMAI of old group]/BMAI of younger group × 100%) was used to assess the degree of brain atrophy with aging. For this region, the reduction rate was markedly higher in male subjects at 7.22% ($P < .0001$) than in female subjects at 3.03% ($P < .05$) (Fig 2), which suggests that brain atrophy in this region was milder in female subjects than in male subjects. Moreover, in the middle part of the right temporal lobe (right T2), left basal ganglia, parietal lobe, and cerebellum, post hoc analysis demonstrated that differences in the BMAI between the old and

TABLE 2: Effects of gender on aging in BMAI[a]

Region		Men		Women		*P* value		
		Young (n = 46)	Old (n = 130)	Young (n = 36)	Old (n = 119)	Age Effect	Sex Effect	Age × Sex
Frontal lobe								
f1	right	7.95 ± 1.03	7.49 ± 1.00	7.48 ± 0.81	7.52 ± 1.15	.11	.056	.062
	left	7.81 ± 1.05	7.68 ± 0.96	7.60 ± 0.80	7.50 ± 1.06	.37	.076	.88
f2	right	14.26 ± 1.64	13.33 ± 1.36	14.15 ± 1.53	13.61 ± 1.30	<.0001	.57	.27
	left	14.40 ± 1.29	13.32 ± 1.29	14.14 ± 1.35	13.73 ± 1.40	<.0001	.602	.052
f3	right	7.53 ± 0.75	6.98 ± 0.79	7.39 ± 0.76	7.23 ± 0.87	.0007	.5	.055
	left	7.57 ± 0.79	7.14 ± 0.73	7.46 ± 0.70	7.27 ± 0.79	.0012	.93	.2
f4	right	15.48 ± 1.58	14.23 ± 1.23	15.50 ± 1.39	14.72 ± 1.37	<.0001	.091	.18
	left	15.60 ± 1.35	14.35 ± 1.21	15.67 ± 1.52	14.71 ± 1.34	<.0001	.14	.39
f5	right	16.76 ± 1.36	15.55 ± 1.30	16.50 ± 1.25	16.00 ± 1.32	<.0001	.51	.035
	left	16.74 ± 1.36	15.64 ± 1.26	16.57 ± 1.23	16.01 ± 1.35	<.0001	.47	.11
Temporal lobe								
t1	right	4.92 ± 1.06	4.36 ± 1.10	4.56 ± 0.93	4.31 ± 0.90	.0016	.066	.23
	left	4.73 ± 1.28	4.00 ± 1.02	4.44 ± 1.09	4.06 ± 0.97	<.0001	.34	.20
t2	right	10.84 ± 1.27	9.86 ± 1.20	10.40 ± 1.12	10.04 ± 1.20	<.0016	.33	.041
	left	10.32 ± 1.17	9.31 ± 1.05	10.05 ± 1.14	9.46 ± 1.21	<.0001	.63	.16
t3	right	11.08 ± 1.28	10.45 ± 1.01	10.70 ± 1.00	10.56 ± 1.12	.005	.24	.078
	left	10.61 ± 0.99	9.83 ± 0.95	10.18 ± 0.88	9.85 ± 1.02	<.0001	.058	.07
Basal ganglia	right	7.15 ± 0.81	6.77 ± 0.63	7.17 ± 0.67	7.09 ± 0.74	.011	.025	.094
	left	7.22 ± 0.63	6.79 ± 0.63	7.11 ± 0.78	7.14 ± 0.75	.023	.12	.012
Thalamus	right	4.83 ± 0.64	4.61 ± 0.58	5.25 ± 0.80	4.76 ± 0.63	<.0001	<.0001	.105
	left	4.82 ± 0.63	4.48 ± 0.54	5.17 ± 0.80	4.56 ± 0.62	<.0001	.0016	.09
Parietal lobe	right	18.13 ± 1.52	16.94 ± 1.28	17.65 ± 1.47	17.56 ± 1.54	.0005	.66	.003
	left	18.25 ± 1.20	17.08 ± 1.42	17.78 ± 1.50	17.59 ± 1.54	.0002	.7	.0085
Parieto-occipital lobe	right	29.63 ± 2.71	28.56 ± 2.06	28.16 ± 2.67	27.65 ± 2.31	.007	<.0001	.34
	left	29.28 ± 2.87	28.18 ± 2.03	27.61 ± 2.22	27.30 ± 2.25	.015	<.0001	.17
Cerebellum	right	13.02 ± 1.19	12.20 ± 1.07	11.66 ± 1.19	11.87 ± 1.19	.037	<.0001	.0005
	left	12.73 ± 1.26	12.06 ± 1.05	11.63 ± 0.94	11.81 ± 1.10	.079	<.0001	.0026

[a] BMAI, Brain matter area index. (mean ± SD)

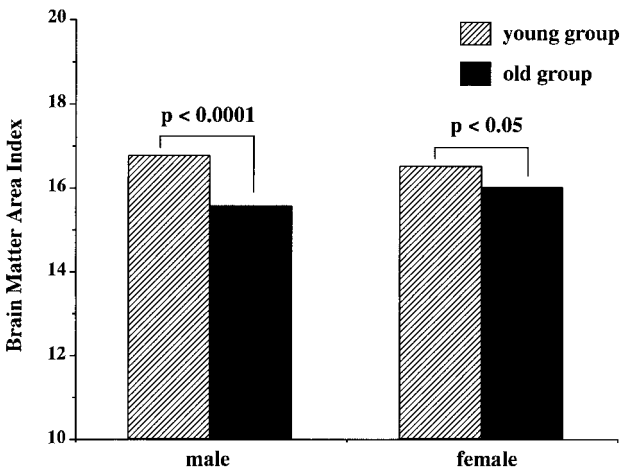

FIG 2. Gender differences in brain atrophy with aging in posterior part of right frontal lobes between young and old groups.

young groups were seen only in male subjects, showing that brain atrophy occurs in fewer regions in women than in men.

Asymmetry of Brain Structure

Significant differences in BMAI were between the hemispheres in all the slices of the temporal lobe (T1, $P = .0002$; T2, $P = .0001$; T3, $P = .0001$), the thalamus ($P = .001$), parieto-occipital lobe ($P = .0001$), and cerebellum ($P = .0023$). All the BMAIs were smaller in the left hemisphere than in the right hemisphere. There were no interactions of hemisphere × age, hemisphere × sex, and hemisphere × age × sex in these regions, which suggests that the left-right differences in BMAI were not affected by sex or age (Table 3).

Discussion

Gender Difference in Brain Structure with Aging

This study showed a gender difference in the changes of brain structures with aging. In the posterior parts of the right frontal lobe, brain atrophy with aging was more significant in male subjects than in female subjects. In the middle part of the right temporal lobe, the left basal ganglia, the parietal lobe, and the cerebellum, brain atrophy with aging was found only in male subjects. These findings indicate that the gender effect on brain atrophy varied among the regions, especially subregions, of the brain.

Previous reports have shown gender differences in brain structure changes with aging in the right frontal lobe. Some authors indicated that the atrophy of the right frontal lobe was found only in men

TABLE 3: Differences of left-right on aging in regional BMAI*

Region	BMAI		*P* value			
	Left	Right	L-R Effect	L-R × Age	L-R × Sex	L-R × Age × Sex
Frontal lobe						
f1	7.63 ± 1.00	7.57 ± 1.05	.49	.38	.83	.034
f2	13.71 ± 1.39	13.65 ± 1.44	.36	.96	.93	.30
f3	7.28 ± 0.77	7.17 ± 0.83	.058	.64	.52	.35
f4	14.80 ± 1.40	14.72 ± 1.43	.079	.44	.74	.45
f5	16.03 ± 1.36	15.99 ± 1.38	.47	.75	.96	.34
Temporal lobe						
t1	4.17 ± 1.08	4.44 ± 1.02	.0002	.21	.43	.88
t2	9.58 ± 1.19	10.12 ± 1.24	.0001	.29	.56	.37
t3	9.98 ± 1.01	10.60 ± 1.10	.0001	.12	.55	.86
Basal ganglia	7.01 ± 0.71	6.98 ± 0.72	.56	.72	.45	.31
Thalamus	4.63 ± 0.65	4.76 ± 0.66	.001	.066	.25	.98
Parietal lobe	17.51 ± 1.49	17.41 ± 1.49	.068	.76	.71	.62
Parieto-occipital lobe	27.96 ± 2.34	28.34 ± 2.40	.0001	.62	.63	.55
Cerebellum	12.02 ± 1.13	12.14 ± 1.21	.0023	.50	.054	.30

*BMAI, Brain matter area index (mean ± SD); l-r, left-right.

whereas others stated that it was found in both men and women, but that the atrophy in this region was more marked in male subjects than in female subjects (18, 20). These studies did not divide the frontal lobe into subregions, however. Other reports found no gender difference in brain structure changes with aging in the dorsolateral prefrontal cortex (15). We divided the frontal lobe into five subregions and found that only the posterior parts of the right frontal lobe showed a gender difference in brain atrophy with aging. Therefore, it seems that the gender differences in right frontal lobe atrophy with aging occur only in the posterior parts of the right frontal lobe. In the temporal lobe, brain atrophy with aging was reported to be more marked in men than in women (18, 20, 21), but these reports also did not divide the temporal lobe into subregions. According to our results, the gender differences in temporal lobe atrophy with aging may exist only in the middle part of the right temporal lobe. These findings suggest that studying subregions of the brain provides a clearer picture of the effect of gender on brain structure changes with aging.

Some reports showed brain atrophy with aging in the caudate and lenticular nuclei (12, 20, 32), but no gender differences. These results may be attributed to too small a sample size. Our study found gender differences in the atrophy of the left basal ganglia with aging. We did not, however, divide the basal ganglia into the caudate and lenticular nuclei, and are therefore unable to distinguish whether this difference occurs in the caudate or lenticular nuclei.

Murthy et al (20) reported that bilateral brain atrophy with aging in the parietal lobe was more marked in women than in men, which is not consistent with our results. This difference may be attributed to the different methods of measurement.

It is reported that the cerebellum is larger in men than in women (28, 29) and that brain atrophy with aging occurs in the cerebellum (30, 20, 33). Our results are consistent with this. To our knowledge, there are few published reports on gender differences in cerebellar atrophy with aging. It is well known that heavy alcohol intake causes cerebellar atrophy. In this study, male subjects drank significantly more alcohol than did female subjects. This might be one of the causes of the gender differences in cerebellar atrophy with aging. When drinkers were compared with non-drinkers, however, there was no significant difference in cerebellar atrophy with aging. Further study of this issue is necessary.

The cause of gender differences in brain atrophy with aging is still unclear and may be attributed to internal and external factors. Sex hormones may be involved in the former, whereas the natural environment, family circumstances, education, and habits (such as smoking and alcohol) may be involved in the latter. Compared with external factors, levels of sex hormones are relatively stable between individuals, so the effect of sex hormones on brain structures may be more important. For example, testosterone level is significantly correlated with the weight of the brain and hippocampus in animal experiments (34). Testosterone administration enhances spatial cognition in older men (35), which suggests a relationship between testosterone, brain volume, and spatial cognition.

Some authors have indicated that there are gender differences in brain metabolism in different regions of the brain (20, 36). These differences are most marked in the same regions as those in which we found gender differences, such as the temporal and parietal lobes and the cerebellum. Because few published studies have investigated changes in brain structure and metabolism with aging in the

same subjects and regions, the mechanism of brain atrophy with aging is not entirely clear.

Asymmetry of Brain Structure

Concerning the asymmetry of brain structure, particularly in the temporal lobe, anatomic studies indicated that the planum temporale (upper surface of the temporale) was larger on the left than on the right (37, 38). The same results also were obtained by measuring the height of the sylvian point (posterior end of the lateral fissure) and the length of the lateral fissure (39). Because the left hemisphere is considered the dominant hemisphere, the volume of the left hemisphere is larger than that of the right. This view was first attributed to the fact that the speech center is located in the left hemisphere in 97.5% of right-handed people and in 68.2% of left-handed people (40). Not all brain functions, however, are located predominantly in the left hemisphere. We think ''speech dominant hemisphere'' is a more suitable way to describe brain asymmetry than ''dominant hemisphere.'' For example, previous studies showed that the function of spatial attention is found predominantly in the right hemisphere (41). On the other hand, Wernicke's area may be more suitable than the planum temporale for describing the asymmetrical structure of the brain, because Wernicke's area is a large part of the planum temporale. In our study, the temporal lobe was smaller on the left than on the right in three sections. This might reflect the total volume of the temporal lobe. Our results are consistent with those of the in vivo MR imaging study of Jack et al (42).

In general, segmentation and three-dimensional measurement were performed to assess brain volume. Because the brain slices in the present study were obtained from archived data that did not cover the whole cranial cavity, we could not accurately assess the volume of cranial cavity. Thus, we used a two-dimensional method for evaluating the relative size of region of interest.

Conclusion

Brain atrophy may vary with either gender or the brain region. Furthermore, gender effect on brain atrophy with aging varies among different subregions of the brain. There is more brain atrophy with aging in men than in women. The present study only was involved in frontal and temporal lobes of the brain at the level of subregions. Gender differences in brain atrophy with aging in subregions of other parts of the brain, including the parietal lobe, occipital lobe, cerebellum, basal ganglia, and thalamus, are objects of further study.

Acknowledgments

We express our gratitude to Chihiro Ishibashi and Michiko Tamura for collecting the data used in this manuscript.

References

1. Haug G. **Age and sex dependence of the size of normal ventricles on computed tomography.** *Neuroradiology* 1977;14:201–204
2. Gyldensted C. **Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography.** *Neuroradiology* 1977;14:183–192
3. Meese W, Kluge W, Grumme T, Hopfenmüller W. **CT evaluation of the CSF spaces of healthy persons.** *Neuroradiology* 1980;19: 131–136
4. Yamaura H, Ito M, Kubota K, Matsuzawa T. **Brain atrophy during aging: a quantitative study with computed tomography.** *J Gerontol* 1980;35:492–498
5. Zatz LM, Jernigan TL, Ahumada AJ Jr. **Changes on computed cranial tomography with aging: intracranial fluid volume.** *AJNR Am J Neuroradiol* 1982;3:1–11
6. Takeda S, Matsuzawa T. **Measurement of brain atrophy of aging using X-ray computed tomography: sex difference in 1045 normal cases.** *Tohoku J Exp Med* 1984;144:351–359
7. Grant R, Condon B, Lawrence A, et al. **Human cranial CSF volumes measured by MRI: sex and age influence.** *Magn Reson Imaging* 1987;5:465–468
8. Condon B, Grant R, Hadley D, Lawrence A. **Brain and intracranial cavity volumes: in vivo determination by MRI.** *Acta Neurol Scand* 1988;78:387–393
9. Yoshi F, Barker WW, Chang JY, et al. **Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors.** *J Cerebr Blood F Met* 1988;8:654–661
10. Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR. **Cerebral structure on MRI, part I: localization of age-related changes.** *Biol Psychiat* 1991;29:55–67
11. Gur RC, Mozley PD, Resnick SM, et al. **Gender differences in age effect on brain atrophy measured by magnetic resonance imaging.** *Proc Natl Acad Sci USA* 1991;88:2845–2849
12. Murphy DGM, DeCarli C, Schapiro MB, Rapoport SI, Horwitz B. **Age-related differences in volumes of subcortical nuclei, brain matter, and cerebrospinal fluid in healthy men as measured with magnetic resonance imaging.** *Arch Neurol* 1992;49:839–845
13. Coffey CE, Wilkinson WE, Parashos IA, et al. **Quantitative cerebral anatomy of the aging human brain: a cross-sectional study using magnetic resonance imaging.** *Neurology* 1992;42: 527–536
14. Kaye JA, DeCarli C, Luxenberg JS, Rapoport SL. **The significance of age-related enlargement of the cerebral ventricles in healthy men and women measured by quantitative computed X-ray tomography.** *J Am Geriatr Soc* 1992;40:225–231
15. Raz N, Torres IJ, Spencer WD, Acker JD. **Pathoclisis in aging human cerebral cortex: evidence from in vivo MRI morphometry.** *Psychobiology* 1993;21:151–160
16. Sullivan EV, Shear PK, Mathalon DH, et al. **Greater abnormalities of brain cerebrospinal fluid volumes in younger than in older patients with Alzheimer's disease.** *Arch Neurol* 1993;50: 359–373
17. Christiansen P, Larsson HBW, Thomsen C, Wieslander SB, Henriesen O. **Age dependent white matter lesions and brain volume changes in healthy volunteers.** *Acta Radiol* 1994;35:117–122
18. Cowell PE, Turetsky BI, Gur RC, Grossman RI, Shtasel DL, Gur RE. **Sex differences in aging of the human frontal and temporal lobes.** *J Neurosci* 1994;14:4748–4755
19. Blatter DD, Bigler ED, Gale SD, et al. **Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life.** *AJNR Am J Neuroradiol* 1995;16:241–251
20. Murphy DGM, DeCarli C, McIntosh AR, et al. **Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging.** *Arch Gen Psychiat* 1996;53:585–594
21. Raz N, Gunning FM, Head D, et al. **Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter.** *Cereb Cortex* 1997;7:268–282
22. Yue NC, Arnold AM, Longstreth WT, et al. **Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: data from the cardiovascular health study.** *Neuroradiology* 1997;202:33–39
23. Coffey CE, Lucke JF, Saxton JA, et al. **Sex differences in brain aging.** *Arch Neurol* 1998;55:169–179
24. Parashos IA, Wilkinson WE, Coffey CE. **Magnetic resonance imaging of the corpus callosum: predictors of size in normal adults.** *J Neuropsych Clin N* 1995;7:35–41

25. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S. **Subcortical silent brain infarction as a risk factor for clinical stroke.** *Stroke* 1997;28:1932–1939
26. Kobayashi S, Okada K, Yamashita K. **Incidence of silent lacunar lesion in normal adults and its relation to cerebral blood flow and risk factors.** *Stroke* 1991;22:1379–1383
27. Yamano S, Sawai N, Minami S, et al. **The relationship between brain atrophy and asymptomatic cerebral lesions.** *Jpn J Geriat* 1997;34:913–919
28. Escalona PR, McDonald WM, Doraiswamy PM, et al. **In vivo stereological assessment of human cerebellar volume: effects of gender and age.** *AJNR Am J Neuroradiol* 1991;12:927–929
29. Raz N, Dupuis JH, Briggs SD, McGavran C, Acker JD. **Differential effects of age and sex on the cerebellar hemispheres and the vermis: a prospective MR study.** *AJNR Am J Neuroradiol* 1998;19:65–71
30. Koller WC, Glatt SL, Perlik S, Huckman MS, Fox JH. **Cerebellar atrophy demonstrated by computed tomography.** *Neurology* 1981;31:405–412
31. Kobayashi S, Yamaguchi S, Kitani M, Okada K, Shimote K. **Evaluation of practical usefulness of the Okabe's mini-mental scale in normal aged.** *Jap J Neuropsychol* 1987;3:67–72
32. Ranga-Krishnan K, Krishnan K, Husain MM, McDonald WM, et al. **In vivo stereological assessment of caudate volume in man: effect of normal aging.** *Life Sci* 1990;47:1325–1329
33. Raz N, Torres IJ, Spenser WD, White K, Acker JD. **Age-related regional differences in cerebellar vermis observed in vivo.** *Arch Neurol* 1992;49:412–416
34. Perrot-Sinal TS, Kavaliers M, Ossenkopp K-P. **Spatial learning and hippocampal volume in male deer mice: relations to age, testosterone and adrenal gland weight.** *Neuroscience* 1998;86:1089–1099
35. Janowsky JS, Oviatt SK, Orwoll ES. **Testosterone influences spatial cognition in older men.** *Behav Neurosci* 1994;108:325–332
36. Gur RC, Mozley LH, Mozley PD, et al. **Sex differences in regional cerebral glucose metabolism during a resting state.** *Science* 1995;267:528–531
37. Geschwind N, Levitsky W. **Human brain: left-right asymmetries in temporal speech region.** *Science* 1968;161:186–187
38. Witelson SF, Pallie W. **Left hemisphere specialization for language in the newborn neuroanatomical evidence of asymmetry.** *Brain* 1973;96:641–646
39. Rubens AB, Mahowald MW, Hutton JT. **Asymmetry of the lateral (Sylvian) fissures in man.** *Neurology* 1976;26:620–624
40. Zangwill OL. **Speech and the minor hemisphere.** *Acta Neurologica et Psychiatrica Belgica* 1967;67:1013–1020
41. Witelson SF. **Sex and the single hemisphere: specialization of the right hemisphere for spatial processing.** *Science* 1976;193:425–427
42. Jack CR, Gehring DG, Sharbrough FW, et al. **Temporal lobe volume measurement from MR images: accuracy and left-right asymmetry in normal persons.** *J Comput Assist Tomo* 1988;12:21–29