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Selective Atrophy of Left Hemisphere and Frontal Lobe of the Brain in Old Men

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In this study, volumes of the whole brain, hemispheres, and frontal lobes of young and elderly adults were quantified by an automated method. Effects of age, sex, and side on absolute and relative volumes of the brain structures were evaluated. Compared with the young group, elderly participants showed a 15% volume loss in the whole brain and hemispheres, and a 22% volume loss in the frontal lobes. The relative volume of the left hemisphere in the elderly group decreased more than that of the right hemisphere. Elderly men showed significantly greater left hemisphere and left frontal lobe volume losses than did elderly women, indicating that the larger left hemisphere relative volume reduction is largely contributed to by selective atrophy of the left frontal lobe volume in elderly men. These results may reflect age- and sex-related functional deterioration in the left brain.

OBTAINING quantitative data on the aging human brain is important in understanding human brain function, improving clinical diagnosis, and distinguishing between normal aging and dementia. Therefore, the study of age-related brain-volume changes is an area of increasing interest. Previous studies (1–15) have reported the following findings: a) there is a global volume loss with age; and b) cortical volumes decrease linearly with age as cerebrospinal fluid (CSF) volumes increase. Yet, very little is known about interactions between sex (male vs female) and side (left brain vs right brain) effects on regional age-related brain-volume losses.

Recent functional neuroimaging studies have found that brain-activation patterns change asymmetrically in elderly participants (see Discussion for more information). However, only few studies (3–5,13,16) have addressed asymmetrical brain structural changes in elderly people, and no studies have reported age–sex–side interactions on hemisphere or frontal lobe volume changes. Besides the unsolved regional sex–side issue in brain tissue loss in aging, a number of other important issues need to be addressed. First, Coffey and colleagues (3) described that effects of aging on regional brain volumes are more apparent in men than in women. However, Good and colleagues (7) reported no such regional or sex effects. Both studies (3,7) were based on a large sample size, 460 and 465 people, respectively. The possible reasons for this inconsistency may have arisen from variations in human races and body sizes of the participants in the two samples. Other factors such as rater bias when segmentation was manually performed might also have played a role in this inconsistency. Second, it has been shown that age-related volume changes in temporal, parietal, and frontal lobes depend on side (left–right) (5). However, other studies have reported no such side effect (3,4,13,16).

In this study, we carefully matched the participants, young and elderly healthy adults, from the same race with similar height and weight. The automated methods used for the analysis have high reproducibility and accuracy for volume measurement of the whole brain and brain structures (17,18). The purposes of this study were to examine age-related volume changes in the whole brain, hemispheres, and frontal lobes and to determine whether the changes were dependent on sex, side, or both. Our study also adds information to the repository for determination of normative values.

Method

Participants

Twenty-six healthy white male and female participants participated in the study. Average age of the men ($n = 5$) and women ($n = 8$) in the young group was 28.2 ± 2.3 and 26.9 ± 6.0 years, respectively. Average age of the men ($n = 5$) and women ($n = 8$) in the elderly group was 70.4 ± 1.5 and 69.4 ± 2.1 years, respectively. All the elderly participants were healthy without known neurological or psychological disorders at the time of the study. Thus, they were considered cognitively intact in their age group. Additional participant information is provided in Table 1. There were no significant height or weight differences between young and elderly men, or young and elderly women. The experimental procedures were approved by the Institutional Review Board at the Cleveland Clinic Foundation. All participants gave informed consent prior to their participation.

Magnetic Resonance Imaging Data

All the images of the participants were collected by a Siemens Vision 1.5 Tesla MR scanner (Siemens Medical Systems, Iselin, NJ) using a Turbo FLASH (Fast Low Angled Shot) pulse sequence, which is a premagnetization T1-weighted three-dimensional imaging sequence. The imaging parameters were as follows: repetition time = 11.4 ms, echo time = 4.4 ms, flip angle = 10°, field of

Table 1. Height and Weight of Old and Young Participants

Participants	Age (y)	Height (cm)	Weight (kg)
Men ($n = 5$)			
Young	28.2 ± 2.3	182.6 ± 6.7	80.83 ± 2.54
Old	70.4 ± 1.5	178.2 ± 6.8	87.54 ± 4.72
Women ($n = 8$)			
Young	26.9 ± 6.0	166.0 ± 2.3	74.98 ± 3.40
Old	69.4 ± 2.1	166.0 ± 2.7	75.66 ± 9.07

Note: Values represent means ± standard deviation. There were no significant differences of height and weight between young and old men, or young and old women. There was no significant difference of age between young men and women, or old men and women.

view = 256 mm × 256 mm, number of slices (contiguous) = 128, slice thickness = 2 mm, and in-plane resolution = 1 mm × 1 mm. Images were collected in the coronal direction. The scanning time for collecting the entire three-dimensional image set using the Turbo FLASH sequence was about 5 minutes.

Image Processing

All the images were processed using the totally automated methods recently developed by our group (17,18). Briefly, a histogram-based brain segmentation (HBRS) method was used to separate brain images from head images and to render the whole-brain volume. The HBRS algorithm, to the best of our knowledge, is among the most accurate automated brain segmentation methods. The algorithm consists of three steps: excluding background noise voxels; disconnecting the brain images from the skull images; and removing the residual fragments of CSF, dura, and fat from the images. Details of the HBRS method are described elsewhere (17).

After the brain images were separated from the head images, we used an automated brain structure identification algorithm to label the left and right hemispheres and frontal lobes. Because the identification algorithm does not need human intervention, potential errors such as rater bias are avoided. Furthermore, this algorithm does not resort to image registration or warping procedures; instead, the landmarks of a number of brain structures (longitudinal fissure, central and lateral sulci) were first extracted from the images. Then the sulci were identified automatically by an artificial intelligence algorithm. On the basis of the identified landmarks, the method defined the left and right hemispheres and frontal lobes according to the widely accepted protocols used in other studies (19–22). Left and right hemisphere division was based on the medial surface of the longitudinal fissure, which was extended perpendicularly through tissues in which the actual fissure was not present. On the surface, the lateral, anterior, and superior boundaries of the frontal lobes were defined by its natural limits. The posterior boundary of the frontal lobe was the central sulcus and the inferior boundary was the lateral sulcus. On the medial wall (to which the sulci do not extend), an imaginary vertical line, beginning from the point where the central sulcus intersects with the midsagittal plane to the lateral sulcus, was defined as the posterior boundary. An imaginary plane starting from the lateral sulcus and extending to intersect with the midsagittal plane was defined as the inferior boundary. The longitudinal fissure defined the boundary of the left and right frontal lobes. Details of delineation of the left and right hemispheres and frontal lobes are described elsewhere (18).

The volumes of the whole brain, hemispheres, and frontal lobes were determined by voxel counting and by multiplying the number of voxels in each region by unit volume of the voxel.

Accuracy of Methods Used for Volume Measurements

A major concern of brain-volume measurements is the accuracy of the methods. HBRS, the automated method we developed to estimate human whole-brain volume, is one of the most accurate methods for this purpose. The accuracy rate of the HBRS method, evaluated by simulated brain images obtained from McGill University in Canada (http://www.bic.mni.mcgill.ca/brainweb), was 98.6%. The accuracy of the HBRS method was also evaluated by manual segmentation provided by the Center for Morphometric Analysis (CMA) at Massachusetts General Hospital and Harvard University (http://www.cma.mgh.harvard.edu/ibsr/). The average similarity index (Kappa index) of images between the HBRS method rendered and manually traced was 0.963. The tested reproducibility of the HBRS method was 99.5% (17).

The accuracy of the automated methods that we developed to segment the hemispheres and frontal lobes and measure their volumes has recently been evaluated by comparing the automated results with manual segmentation performed by an experienced investigator. The similarity indices of images of the hemispheres and frontal lobes between the automated and manual segmentations were 0.979 and 0.948, respectively (18).

Statistical Analysis

Age-related volume changes in the whole brain were evaluated in absolute values. Those in the hemispheres and the frontal lobes were evaluated in both absolute and relative values. Relative volumes of the hemispheres were calculated as a percentage of each hemisphere's volume in relation to the whole-brain volume. Similarly, relative volumes of the frontal lobes were determined as a percentage of each frontal lobe volume to the volume of the two frontal lobes combined. Data on whole-brain volume were evaluated by a two-way analysis of variance (ANOVA); the two factors were age (young vs old) and sex (female vs male). Absolute and relative volume data of the hemispheres and frontal lobes were analyzed by separate three-way ANOVA (absolute and relative volume data were analyzed separately); the three factors were age (young vs old), sex (female vs male), and side of brain (left vs right). The coefficient of variation (CV) for the volume of the whole brain, left or right hemisphere, or left or right frontal lobes in the young or elderly group was calculated as the standard deviation of the volume divided by the mean volume. For all the analyses, the level of significance was determined as $p \leq .05$.

Results

Whole-Brain Volume

The two-way ANOVA showed that there was no significant age–sex effect on whole-brain volume, which means

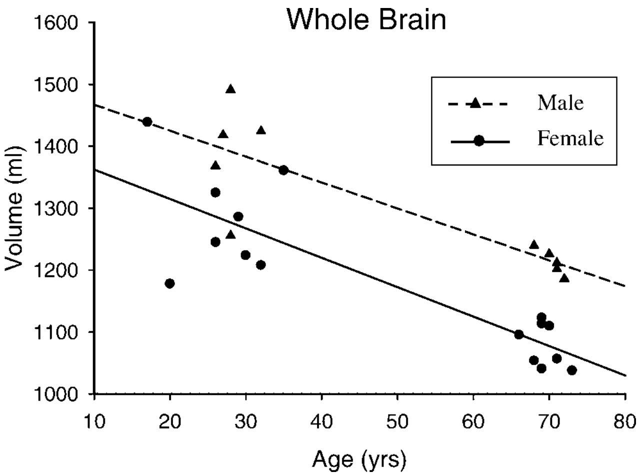

Figure 1. Scatterplots of absolute whole-brain volumes as a function of age in 26 healthy human participants. The best-fitting linear regression curves for women and men are superimposed.

that age-related whole-brain volume changes were not sex dependent. There was, on average, a 16% volume loss ($p < .001$) from young to old participants (Figure 1). For elderly men, volume loss was 14% ($p < .005$), and for elderly women 17% ($p < .001$). Figure 2 shows two brain images, one from a young male and the other from an elderly male; these images demonstrate substantial brain atrophy in the elderly participant compared with the young one. Male participants showed greater brain volume compared with female participants ($p < .001$), regardless of whether the data from young and old participants were analyzed together or separately. Exact whole-brain volume values for all participants are listed in Table 2.

Hemisphere Volume

Absolute volume.—No significant ($p > .1$) age–sex, age–side, sex–side, or age–sex–side interactions on absolute hemispheric volume measurements were found (Table 3). Figure 3 shows changes of absolute volume in the left and right hemispheres from young to old male and female participants. When we combined the data from male and female participants, elderly participants had 18% volume loss in the left hemisphere ($p < .001$) and 13% volume loss in the right ($p < .001$). Compared with those in the young men, the volumes of the left and right hemispheres in the elderly men declined 16% ($p < .001$) and 11% ($p < .001$), respectively. Compared with those in the young women, the volumes of the left and right hemispheres in the elderly women decreased 18% ($p < .001$) and 16% ($p < .001$), respectively. In addition, male participants showed greater left or right hemisphere volume compared with the female participants ($p < .001$), regardless of whether the data from young and elderly participants were analyzed together or separately. Left hemisphere volume was similar to right hemisphere volume in young and old participants, regardless of whether male or female participants' data were analyzed together or separately. Detailed hemisphere volume values are provided in Table 2.

Relative volume.—For the relative hemispheric volume measurements, significant interactions of age–side ($p < .001$) (Figure 4a), sex–side ($p < .02$) (Figure 4b), and age–sex–side ($p < .01$) (Figure 5) were detected (Table 3). These interactions indicate that age-related relative hemispheric volume changes depended both on side (left and right hemispheres had asymmetrical changes) and sex (male and female groups had asymmetrical volume changes). Figure 5 shows the relative volume values of left and right hemispheres. It is quite clear from each plot that the left hemisphere volume reduction in elderly men was greater than that in elderly women.

Frontal Lobe Volume

Absolute volume.—No significant ($p > .1$) age–sex, age–side, sex–side, or age–sex–side interactions on absolute frontal lobe volume measurements were observed (Table 3). Figure 6 shows changes of absolute volume in the left and right frontal lobes from young to old male and female participants. When we combined the data from male and female participants, elderly participants had a 24% volume loss in the left frontal lobe ($p < .001$) and a 25% volume loss in the right frontal lobe ($p < .001$). Compared with those in the young men, the volumes of the left and right frontal lobes in the elderly men declined 26% ($p < .001$) and 21% ($p < .001$), respectively. Compared with those in the young women, the volumes of the left and right frontal lobes in the elderly female participants decreased 22% ($p < .001$) and 28% ($p < .001$), respectively. In addition, male participants showed greater left or right frontal lobe volume compared with the female participants ($p < .002$), regardless of whether the data from young and old participants were analyzed together or separately. Left frontal lobe volume was similar to right frontal lobe volume in young and old participants, regardless of whether male and female participants' data were analyzed together or separately. Detailed frontal lobe volume values are provided in Table 2.

Relative volume.—For the relative frontal lobe volume measurements, significant interactions of sex–side ($p < .001$) (Figure 7a) and age–sex–side ($p = .01$) (Figure 8) were observed (Table 3). The sex–side interaction indicates that, in the male and female participants, the relative volumes of the left and right frontal lobes were asymmetrically distributed. In men, the left frontal lobe relative volume was smaller than the right frontal lobe volume; in women, this asymmetry is reversed. The age–sex–side interaction suggested that age-related relative frontal lobe volume changes depend both on side (asymmetry changes in left and right frontal lobes) and sex (male and female participants had asymmetrical changes). The age–side interaction was not significant. However, if the two outlying data points representing two young women were removed (see Figure 8a), the age–side interaction became significant ($p = .01$, Figure 7b), indicating that, in young and old participants, the relative volume of the left and right frontal lobes are asymmetrically distributed; in elderly participants, the left frontal lobe volume was smaller than that of the right frontal lobe, but in young participants, the opposite was true.

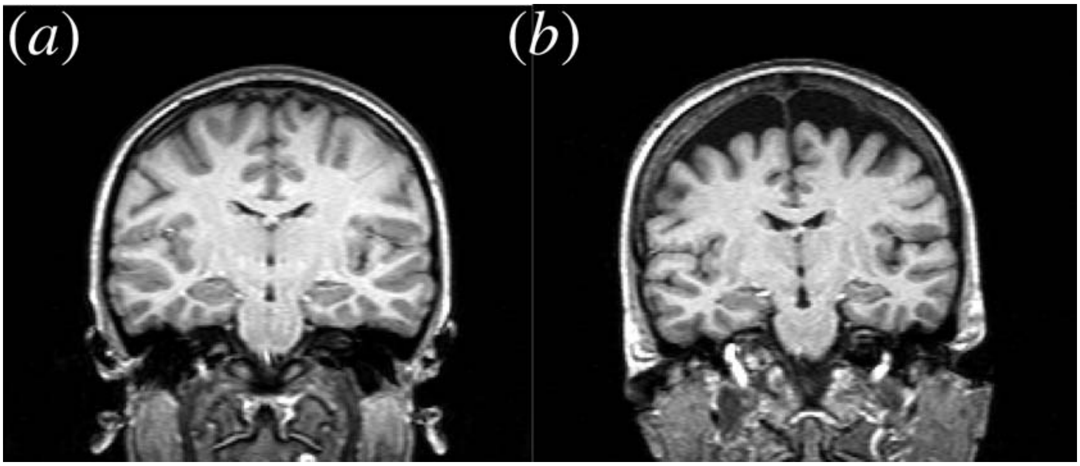

Figure 2. Comparison of brain images from a young and an elderly participant. Brain images were taken in the coronal plane. An image slice of a young man's brain (**a**) and an image of an elderly man's brain (**b**), both acquired near the midline position. Brain atrophy is apparent in the elderly participant.

We also measured relative frontal lobe volumes based on the whole-brain volume. Figure 8c and d illustrates that, similar to Figure 8a and b, in which the relative volume of the individual frontal lobe was calculated as a percentage of the total volume of the two frontal lobes, the left frontal lobe volume loss in elderly men was greater than that in elderly women. In addition, we found that, on average, the left or right frontal lobe volume was about 16% of the whole-brain volume for the young participants and 15% of the whole-brain volume for the elderly participants.

CV of Brain Volume

Figure 9 shows the CV of volumes of the whole brain, left and right hemispheres, and left and right frontal lobes. The CV values of the whole-brain volume in young and old participants were 7% and 2% (average over the male and female participants), respectively. The CV values of the hemisphere volumes in young and old participants were 7% and 3% (average over the male and female participants), respectively. The CV values of frontal lobes in the young and old participants were 13% and 6% (average over the male and female participants), respectively. On average, the CV values of the elderly participants were less than 50% of those of the young persons.

Discussion

In this study, we found, for the first time, that elderly men had more severe left hemisphere and frontal lobe volume losses than did elderly women; this finding may have physiological relevance for the assessment and treatment of neurological disorders. In addition, we observed significant decreases in volumes of the whole brain, hemispheres, and frontal lobes with age. The age-related volume decline was more severe in the frontal lobes than in the hemispheres or

Table 2. Average Volumes of Whole-Brain and Sub-Brain Structures

		Absolute Volume (ml)			
Participant	Whole Brain	Left Hemisphere	Right Hemisphere	Left FL	Right FL
Young					
Male	1391.4 ± 87.4	700.6 ± 47.1	690.6 ± 41.5	219.2 ± 28.7	226.4 ± 23.1
Female	1283.3 ± 87.6	645.8 ± 49.7	637.5 ± 38.6	200.9 ± 22.3	205.4 ± 29.2
Old					
Male	1213.2 ± 20.9	593.2 ± 13.0	620.0 ± 11.5	169.6 ± 7.9	183.4 ± 7.0
Female	1079.1 ± 35.1	536.3 ± 17.1	542.9 ± 19.4	161.8 ± 9.5	156.6 ± 12.0

	Relative Volume (% Whole Brain)		Relative Volume (% FL)	
	Left Hemisphere	Right Hemisphere	Left FL	Right FL
Young				
Male	50.34 ± 0.55	49.64 ± 0.55	49.13 ± 1.00	50.87 ± 1.00
Female	50.30 ± 0.60	49.70 ± 0.60	49.55 ± 3.02	50.45 ± 3.02
Old				
Male	48.89 ± 0.54	51.11 ± 0.54	48.04 ± 0.40	51.96 ± 0.40
Female	49.70 ± 0.47	50.30 ± 0.47	50.83 ± 0.76	49.17 ± 0.76

Notes: Values represent means ± standard deviation.
FL = frontal lobe.

Table 3. Three-Way ANOVA of Sub-Brain Structure Volumes

Factor	Hemispheres (Absolute Volume)	Frontal Lobes (Absolute Volume)	Hemispheres (Relative Volume)	Frontal Lobes (Relative Volume)
	p Values			
Age	1.71e-13***	1.87e-10***	0.99	1.00
Sex	1.07e-07***	1.90e-03**	0.98	1.00
Side	0.77	0.48	0.06	0.06
Age × sex	0.50	0.83	0.98	1.00
Age × side	0.21	0.76	1.72e-07***	0.56 (0.01**)[†]
Sex × side	0.63	0.33	0.02*	1.01e-14***
Age × sex × side	0.57	0.47	8.05e-03**	0.01**

Notes: $^*p \le .05$; $^{**}p \le .01$; $^{***}p \le .001$.
[†]After removing the two extreme data points in Figure 7.
× = interaction; ANOVA = analysis of variance.

the whole brain. These findings are consistent with those of other studies (2,4,13).

Whole-Brain Volume

The average whole-brain volume was 1391 ml for young men, 1283 ml for young women, 1213 ml for elderly men, and 1079 ml for elderly women. These results are consistent with those in textbook reports (20,23), postmortem analysis (24), and in vivo magnetic resonance imaging measurements (7). However, the volume measurements are greater than those reported by Allen and colleagues (1), 1274 ml for young men and 1113 ml for young women. The discrepancy may come from a difference in the definition of the brain in the methods of the two studies. In our study, we included in the volume measurement part of the brain stem superior to the bottom of the cerebellum; the reason for this was discussed elsewhere (17). This portion of the brain stem was not included in the other study (1).

Men have a greater whole-brain volume than do age-matched women (4,7,13). Our study reports the same observation (Figure 1). However, the two-way ANOVA did not show an age–sex interaction on the volume change. This finding was similar to that of Good and colleagues (7), which suggests that the rate of whole-brain volume loss in men and women is similar as they grow old. A number of studies, however, have reported sex effects on age-related brain atrophy (5,15,16,25–27). Typically, these studies have shown that whole-brain volume loss was greater in old men than in old women. We think this inconsistency is probably introduced by methodological factors, especially rater bias if manual or semiautomated methods were used for the measurements.

Absolute Volumes of Hemispheres and Frontal Lobes

No side–sex, age–side, or age–sex–side interactions were observed for the absolute volumes of the two hemispheres and frontal lobes. In general, men showed greater absolute volumes of the hemispheres (Figure 3) and frontal lobes (Figure 6) than did women, although this sex effect was less apparent in the frontal lobes than in the hemispheres. Figures 3 and 4 indicate that, as people grow old, their absolute hemisphere and frontal lobe volumes decline. These absolute volume reductions are independent of sex (male vs female) and side (left vs right) influences.

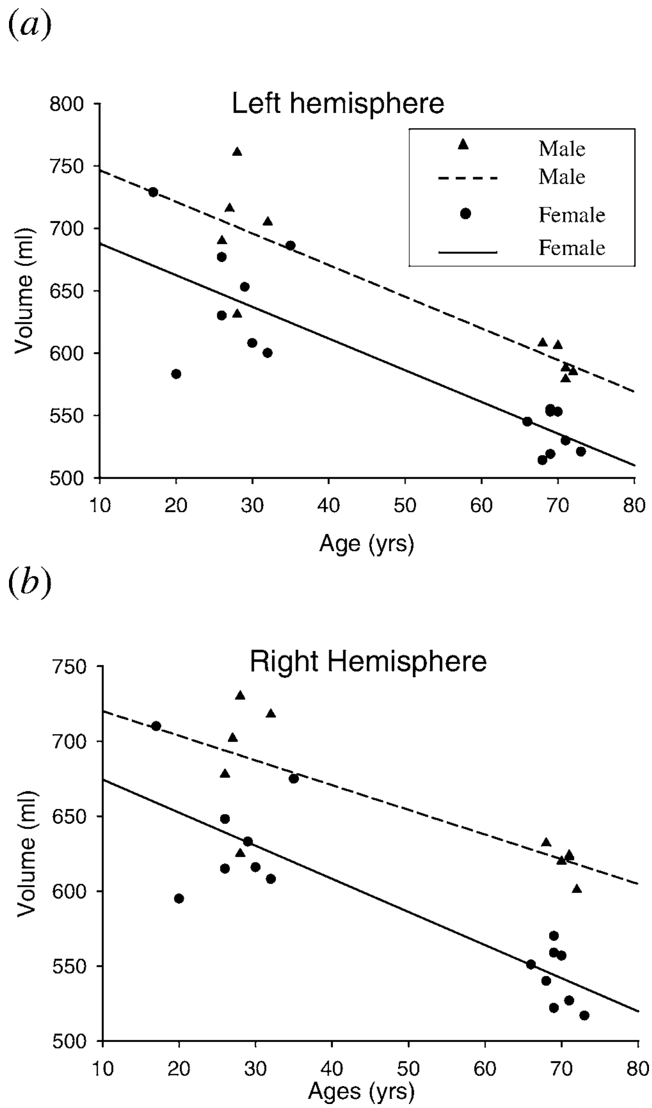

Figure 3. Scatterplots of absolute left (**a**) and right (**b**) hemisphere volumes as a function of age in 26 healthy participants. The best-fitting linear regression curves for women and men are superimposed.

Relative Volumes of Hemispheres and Frontal Lobes

To evaluate the left and right asymmetry of the hemispheres and frontal lobes, we divided the relative unilateral hemisphere and frontal lobe volumes by the total brain and total frontal lobe volumes, respectively. The left and right hemisphere and frontal lobe volumes were not normalized to the intracranial volume, because we thought that the large intracranial volume might obscure the small asymmetry found between the volumes of the left and right hemispheres or frontal lobes.

Relative volumes of the hemispheres.—The relative volume of each hemisphere was measured as a percentage of the whole-brain volume. This normalization allowed us to detect possible age- or sex-related asymmetrical atrophy between the two hemispheres. Significant sex–side, age–side, and age–sex–side interaction on age-related relative

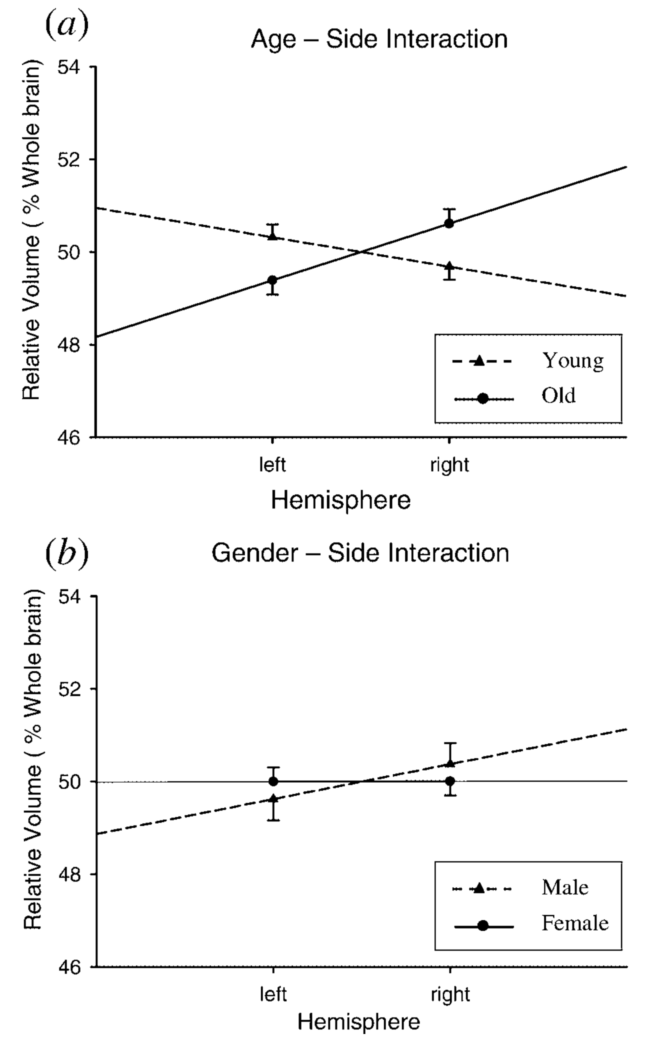

Figure 4. Illustrations of age–side (**a**) and sex–side (**b**) interactions in relative hemispheric volumes. Average relative hemisphere volumes of young participants and those of elderly participants are plotted against hemispheres (a). In (b), average relative hemisphere volumes of men and those of women are plotted against hemispheres.

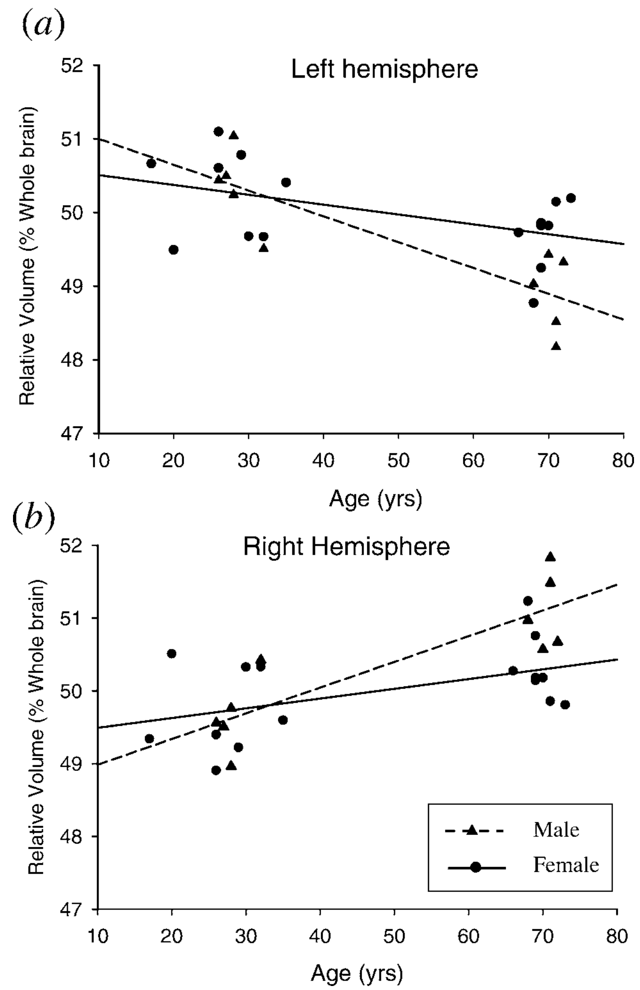

Figure 5. Scatterplots of relative left (**a**) and right (**b**) hemispheric volumes as a function of age in 26 normal participants. The best-fitting linear regression curves for women and men are superimposed. The two plots illustrate significant age–sex–side interaction in relative hemisphere volumes.

hemisphere changes were observed (Table 3). The significant age–side interaction indicated that the relative volume of the left hemisphere was smaller than that of the right hemisphere in elderly participants, whereas the reverse is true for relative volumes in the young (Figure 4a). The significant sex–side interaction in this study showed that the left hemisphere relative volume in the men was smaller than that in the women (Figure 4b). Furthermore, elderly men showed a significantly smaller left hemisphere relative volume than did elderly women (significant age–sex–side interaction). Although a number of previous studies (3–5,13,16) have reported left-right asymmetry on age-related volume changes in some brain regions, ours is the first report to show age-related left–right asymmetrical relative volume changes at the hemispheric level and left–right asymmetrical atrophy in elderly men.

It is well known that the left hemisphere of human brain is especially important for functions such as language and memory (23). These functions deteriorate as people grow old (28,29). The result of selective atrophying of the left hemisphere in old age supports the notion that deterioration of cognitive function in elderly people is associated with asymmetrical volume losses in the left hemispheres. The significant age–sex–side interaction on relative volumes of the hemispheres indicates that the effect of left–right asymmetry of age on the hemispheres was more pronounced in male than in female participants. This result suggests that the functional deterioration described above may be more pronounced in elderly men than in elderly women. Alternatively, preferential enlargement of CSF space in the left hemisphere in elderly men may have contributed to these greater relative hemispheric volume losses. Gur and colleagues (25) found that, in men, the relative CSF volume in the left hemisphere increased more than that in the right hemisphere with age. Coffey and colleagues (3,4) found that the lateral fissure CSF volume was significantly greater in men than in women. Greater volume losses in the left parietal, occipital, temporal, and

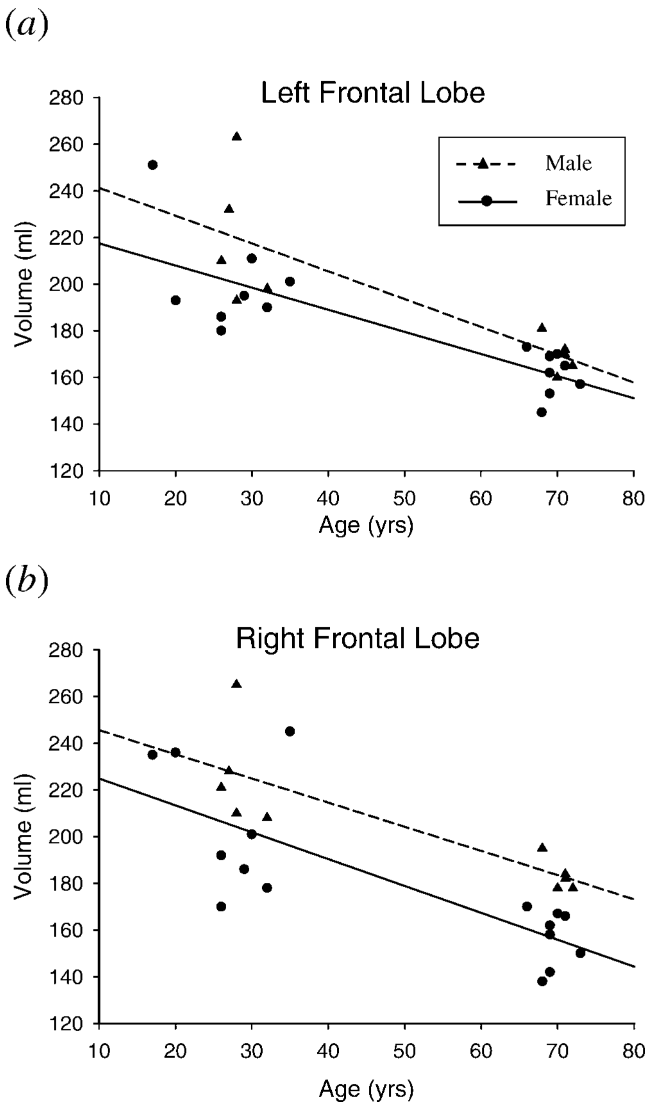

Figure 6. Scatterplot of absolute left (**a**) and right (**b**) frontal lobe volumes as a function of age in 26 normal participants. The best-fitting linear regression curves for women and men are superimposed.

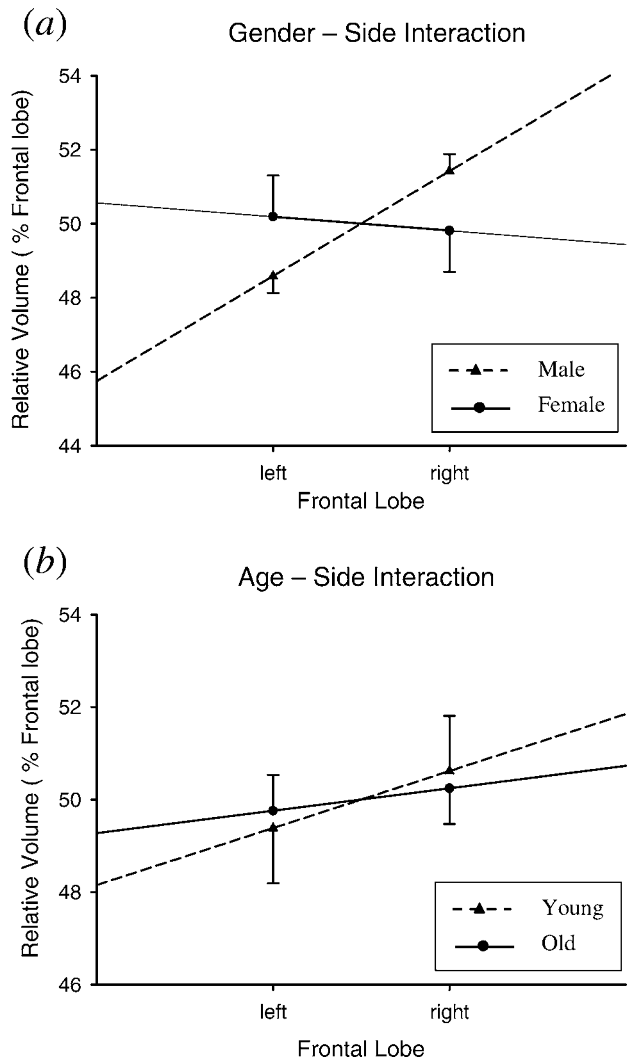

Figure 7. Illustrations of age–side and sex–side interactions in relative frontal lobe volume (% frontal lobe). **a:** Age–side interaction. Two extreme values from two young women (see Figure 8) have been removed. **b:** Sex–side interaction. Men show substantially smaller relative left frontal lobe volume than right frontal lobe volume.

frontal lobes may also contribute to the greater volume loss in the left hemisphere. The selective atrophy of the left hemisphere in old men may also be partly explained by differences in cerebral blood flow between young and elderly men. Recent positron emission tomography (PET) studies have shown that blood flow and metabolic rate tend to be greater in the right hemisphere than in the left after age 60; these observations were not detected in younger men (16,30).

Relative volumes of the frontal lobes.—Normalizing the volume of each frontal lobe to the total size of the two frontal lobes allowed us to determine whether the frontal lobes were asymmetrically affected. The significant sex–side interaction (Table 3) indicates that, in men, the size of the two frontal lobes was not equal; relative volume of the left frontal lobe was smaller than that of the right frontal lobe. The age–side interaction was first found insignificant. However, upon examining Figure 8a and b, the trend of age–side interaction is clear. It appears that two extreme values in the young women might have substantially increased the variation of the data and prevented them from reaching statistical significance. After removal of these two data points, the age–side interaction became significant. Nevertheless, even without removing any data points from the analysis, the trend of smaller relative left frontal lobe volume and larger relative right frontal lobe volume in the elderly participants is relatively clear. Current knowledge regarding human frontal lobe function suggests that major left–right asymmetry of brain function occurs in the frontal lobe, with 90% of language, memory function, and skilled movement control centers being located in the left frontal lobe (23). These functions deteriorate with age, and it is expected that the left frontal lobe would show a more

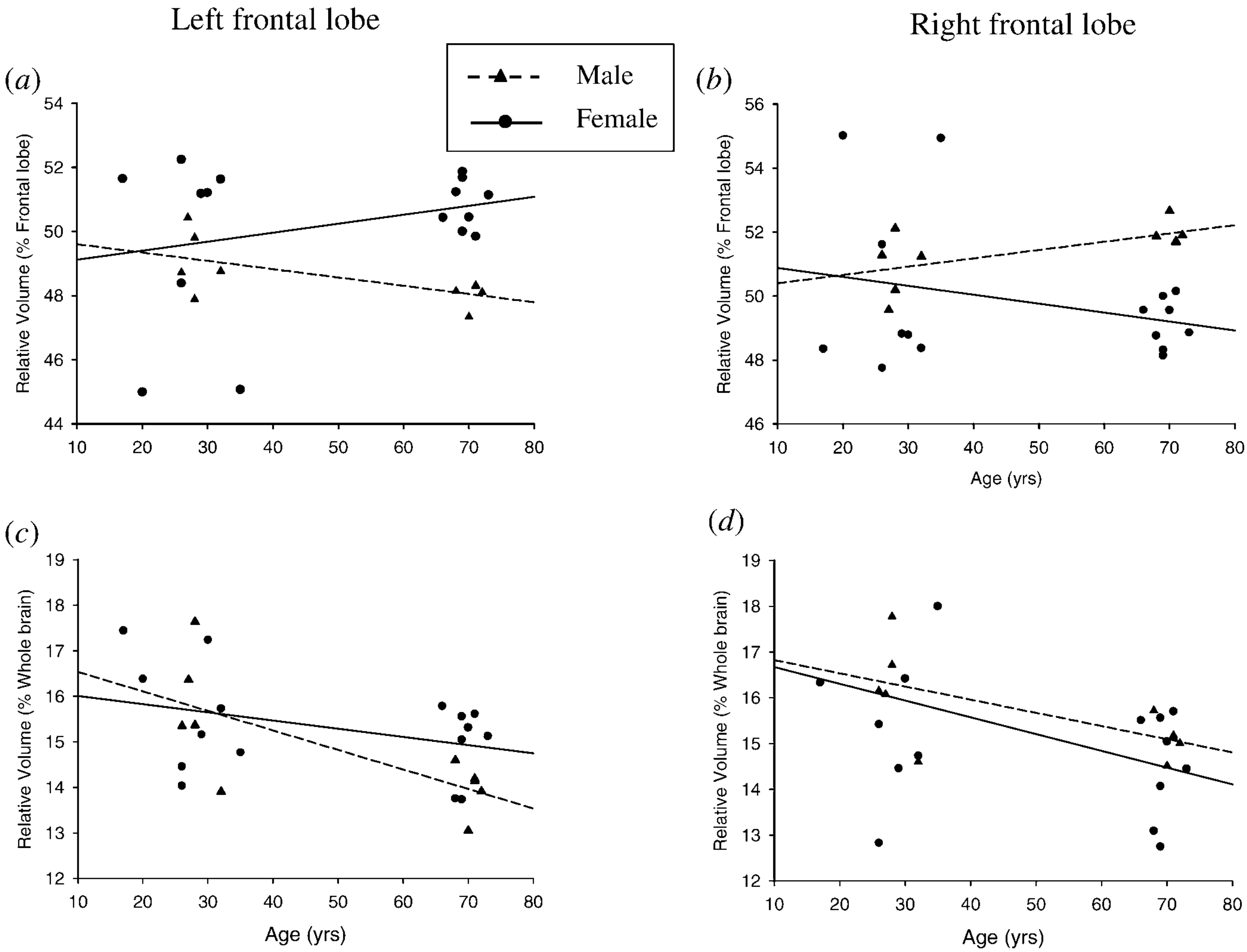

Figure 8. Scatterplots of relative left (**a** and **c**) and right (**b** and **d**) frontal lobe volumes as a function of age in 26 normal participants. The best-fitting linear regression curves for women and men are superimposed. a: Relative left frontal lobe volume (% frontal lobe). b: Relative right frontal lobe volume (% frontal lobe). c: Relative left frontal lobe volume (% whole brain). d: Relative right frontal lobe (% whole brain). Plots (a) and (b) illustrate significant age–sex–side interaction of relative frontal lobe volumes (% frontal lobe).

significant volume reduction than the right frontal lobe. The decreased blood flow in the left frontal regions in old men may contribute to volume losses in the left frontal lobe (31).

The significant age–sex–side interaction indicated that elderly men had a smaller relative left frontal lobe volume than did elderly women. This preferential relative volume loss in elderly men may largely explain the greater relative volume loss of the left hemisphere found in this group. The consistent new findings of greater asymmetrical volume losses in both the left hemisphere and left frontal lobe in elderly men may provide critical information to address age- and sex-related left frontal lobe and hemisphere functional deterioration and the relationship between structural and functional adaptations in elderly men and women. The findings may also be linked to the effort of sorting out the mysteries of why the health of elderly men deteriorates faster than that of elderly women and why men have a shorter life span than do women (32).

Functional Relevance of Asymmetrical Brain-Volume Losses

Neuropsychological studies (33–36) have consistently found that cognitive performance declines with normal aging; this age-related cognitive deficit is particularly evident in working memory and explicit memory. Recently, investigators using functional neuroimging provided some clues to the observed cognitive deficits. During working memory tasks, young individuals showed activation in the lateral and medial prefrontal, and posterior parietal cortices; and the activation was asymmetrically dependent on the performing task. Verbal tasks were associated with predominantly left-hemisphere activities, whereas spatial tasks mainly activated the right hemisphere (36–38). However, this lateralization in the frontal regions was less prominent, and bilateral activities were seen during both spatial and verbal working memory tasks in elderly participants (38,39). Similar age-related changes were also observed during explicit memory tasks. Young participants generally had acti-

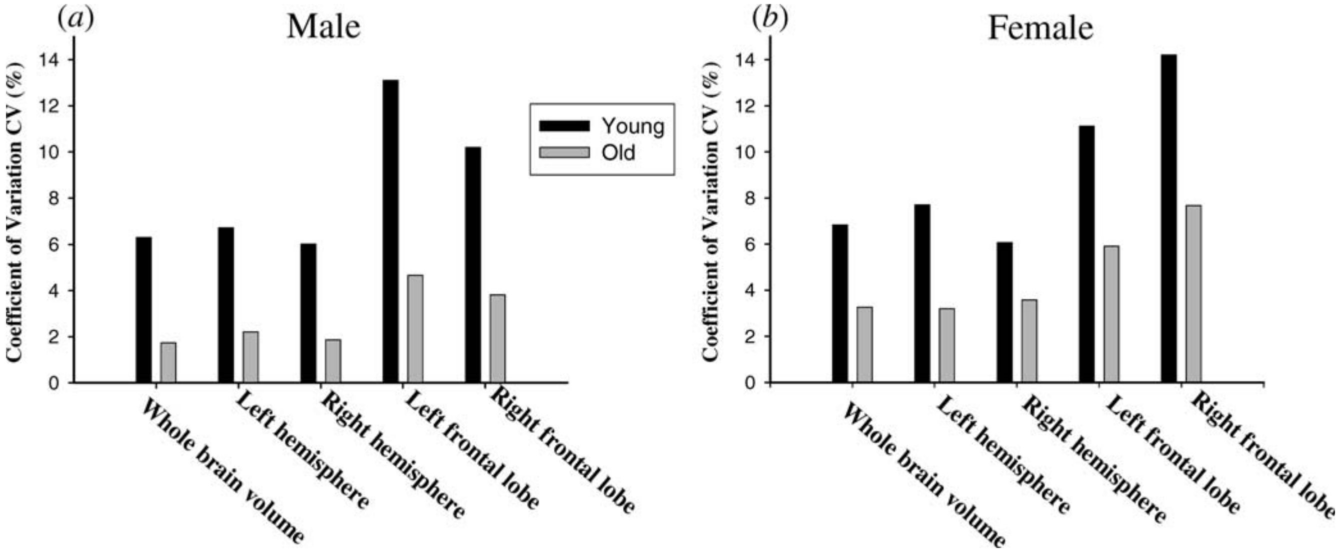

Figure 9. Coefficient of variation (CV) of volumes of the whole brain, hemispheres, and frontal lobes in young and elderly participants. The CV values are lower in the elderly participants than in the young participants.

vation in the frontal, bilateral medial temporal, and fusiform cortices (40,41), whereas elderly participants either failed to activate the left cortical fields (42) or exhibited a reduced activity level during the performance of these tasks (43,44). Unfortunately, these studies did not differentiate functional changes between old men and women, making it difficult to determine whether old men performed differently than old women. Nevertheless, these results and ours are likely to suggest that asymmetrical functional changes, especially in the left hemisphere in elderly participants, are associated with asymmetrical structural adaptations in the left brain.

CV of the Brain Volumes

The CV has been deemed to be inversely related to ontogenetic constraints (32). A previous study reported that, in young adults, the CV value for whole brain was about 8% and that for individual lobes was 14% (45). Comparisons of the CV values for whole brain versus lobes suggest that there are more powerful ontogenetic constraints on the whole-brain volume than on the segmented lobes. We found that the CV of elderly adult volume measurements, regardless of whether they are values for whole brain, hemispheres, or frontal lobes, was substantially smaller than that of young people, suggesting that the volumes of the brain structures in elderly individuals tend to evolve to similar sizes. Furthermore, our results support the theory that the brain is a plastic organ that is adaptable both functionally and structurally.

Limitations

In this preliminary study, we found significantly greater left hemisphere and frontal lobe atrophy in elderly men than in elderly women. To the best of our knowledge, this finding has never been reported before. However, interpretation of these results must include consideration of the inherent limitations of our study. First, the absolute sample size in this study is relatively small despite the fact that the data are relatively consistent and statistical significance has been reached with the given sample size. A large sample size study may be needed to confirm our results. Reports from this research may stimulate the interest of other investigators to launch such larger scale studies. Second, in this study we have investigated regional brain volume, and selective atrophy of the left frontal lobe in elderly men has been found. However, the study did not differentiate the tissue type of the volume losses—whether it was the white matter, gray matter, or both. Our laboratory is developing new algorithms to address this question.

Conclusion

Using recently developed automated brain segmentation methods, this study measured volumes of the whole brain, left and right hemispheres, and frontal lobes in young and elderly adults. Brain volumes decrease with age; the volume loss was more pronounced in the frontal lobes. More importantly, the study shows that the volumes of the left hemisphere and frontal lobe preferentially undergo atrophy in elderly men. The selective volume losses in the left hemisphere and frontal lobe in elderly individuals in general and in elderly men in particular may reflect functional deterioration and adaptation in these brain regions. The CV of the whole brain, hemisphere, and frontal lobe volumes was consistently smaller in elderly than in young individuals. This finding suggests that ontogenetic constraints in people of advanced age are more pronounced than those in young individuals, resulting in more homogeneous brain sizes in elderly adults. The findings also show that, from a volumetric viewpoint, the brain is a dynamic organ.

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References

1. Allen JS, Damasio H, Grabowski TJ. Normal neuroanatomical variation in the human brain: an MRI-volumetric study. *Am J Phys Anthropol.* 2002;118:341–358.
2. Anderton BH. Ageing of the brain. *Mech Ageing Dev.* 2002;123: 811–817.
3. Coffey CE, Lucke JF, Saxton JA, et al. Sex differences in brain aging: a quantitative magnetic resonance imaging study. *Arch Neurol.* 1998; 55:169–179.
4. 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(3 Pt 1):527–536.
5. Cowell PE, Turetsky BI, Gur RC, Grossman RI, Shtasel DL, Gur RE. Sex difference in aging of the human frontal and temporal lobes. *J Neurosci.* 1994;14:4748–4755.
6. Flood DG, Coleman PD. Neuron numbers and size in aging brain: comparisons of human, monkey and rodent data. *Neurobiol Aging.* 1988;9: 453–463.
7. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage.* 2001;14:21–36.
8. Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR. Cerebral structure on MRI, Part I: Localization of age-related changes. *Biol Psychiatry.* 1991;29:55–67.
9. Lim KO, Zipursky RB, Watts MC, Pfefferbaum A. Decreased gray matter in normal aging: an in vivo magnetic resonance study. *J Gerontol.* 1992;47:B26–B30.
10. Luft AR, Skalej M, Schulz JB, et al. Patterns of age-related shrinkage in cerebellum and brainstem observed in vivo using three-dimensional MRI volumetry. *Cereb Cortex.* 1999;9:712–721.
11. Peters M, Jancke L, Staiger JF, Schlaug G, Huang Y, Steinmetz H. Unsolved problems in comparing brain sizes in Homo sapiens. *Brain Cogn.* 1998;37:254–285.
12. Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol.* 1994;51:874–887.
13. 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.
14. Scheff SW, Price DA, Sparks DL. Quantitative assessment of possible age-related change in synaptic numbers in the human frontal cortex. *Neurobiol Aging.* 2001;22:355–365.
15. Xu J, Kobayashi S, Yamaguchi S, Iijima K, Okada K, Yamashita K. Gender effects on age-related changes in brain structure. *AJNR Am J Neuroradiol.* 2000;21:112–118.
16. Murphy DG, 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 Psychiatry.* 1996;53:585–594.
17. Shan ZY, Yue GH, Liu JZ. Automated histogram-based brain segmentation in T1-weighted three-dimensional magnetic resonance head images. *Neuroimage.* 2002;17:1587–1598.
18. Shan ZY, Liu JZ, Yue GH. Automated human frontal lobe identification in MR images based on fuzzy-logic encoded expert anatomic knowledge. *Magn Reson Imaging.* 2004;22:607–617.
19. Bokde AL, Teipel SJ, Zebuhr Y, et al. A new rapid landmark-based regional MRI segmentation method of the brain. *J Neurol Sci.* 2002;194:35–40.
20. Brodal P. *The Central Nervous System, Structure and Function.* New York: Oxford University Press; 1998
21. Carpenter MB. *Human Neuroanatomy.* Baltimore, MD: Waverly Press; 1976
22. Crespo-Facorro B, Kim JJ, Andreasen NC, et al. Human frontal cortex: an MRI-based parcellation method. *Neuroimage.* 1999;10:500–519.
23. Thibodeau GA, Patton KT. *Anatomy & Pysiology.* St. Louis, MO: Mosby-Year Book, Inc.; 1995
24. Pakkenberg H, Voigt J. Brain weight of the Danes. *Acta Anat (Basel).* 1994;56:297–307.
25. 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 U S A.* 1991;88:2845–2849.
26. Kaye JA, DeCarli C, Luxenberg JS, Rapoport SI. 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.
27. Salat D, Ward A, Kaye JA, Janowsky JS. Sex differences in the corpus callosum with aging. *Neurobiol Aging.* 1997;18:191–197.
28. Cabeza R, McIntosh AR, Tulving E, Nyberg L, Grady CL. Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport.* 1997;8:3479–3483.
29. Krause JB, Taylor JG, Schmidt D, Hautzel H, Mottaghy FM, Muller-Gartner HW. Imaging and neural modelling in episodic and working memory processes. *Neural Netw.* 2000;13:847–859.
30. Kawachi T, Ishii K, Sakamoto S, Matsui M, Mori T, Sasaki M. Gender differences in cerebral glucose metabolism: a PET study. *J Neurol Sci.* 2002;199:79–83.
31. Rodriguez G, Warkentin S, Risberg J, Rosadini G. Sex differences in regional cerebral blood flow. *J Cereb Blood Flow Metab.* 1988;8: 783–789.
32. Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. *Soc Sci Med.* 2000; 50:1385–1401.
33. Parkin AJ, Java RI. Determinants of age-related memory loss. In: Perfect TJ, Maylor EA, eds. *Models of Cognitive Aging.* New York: Oxford University Press; 2000
34. Park DC, Smith AD, Lautenschlager G, Earles JL, Frieske D, Zwahr M, et al. Mediators of long-term memory performance across life span. *Psychol Aging.* 1996;11:621–637.
35. Salthouse TA. The processing-speed theory of adult age difference in cognition. *Psychol Rev.* 1996;103:403–428.
36. Tisserand DJ, Jolles J. On the involvement of prefrontal networks in cognitive ageing. *Cortex.* 2003;39:1107–1128.
37. Smith EE, Jonides J. Working memory: a view from neuroimaging. *Cognit Psychol.* 1997;33:5–42.
38. Reuter-Lorenz PA, Jonides J, Smith EE, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci.* 2000;12:174–187.
39. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging.* 2002;17:85–100.
40. Kapur S, Tulving E, Cabeza R, McIntosh AR, Houle S, Craik FI. The neural correlates of intentional learning of verbal materials: a PET study in humans. *Brain Res Cogn Brain Res.* 1996;4:243–249.
41. Kopelman MD, Stevens TG, Foli S, Grasby P. PET activation of the medial temporal lobe in learning. *Brain.* 1998;121:875–877.
42. Grady CL, McIntosh AR, Horwitz B, et al. Age-related reductions in human recognition memory due to impaired encoding. *Science.* 1995; 269:218–221.
43. Cabeza R, Grady CL, Nyberg L, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci.* 1997;17:391–400.
44. Anderson ND, Iidaka T, Cabeza R, Kapur S, McIntosh AR, Craik FI. The effects of divided attention on encoding- and retrieval-related brain activity: a PET study of younger and older adults. *J Cogn Neurosci.* 2000;12:775–792.
45. Caviness VS Jr, Lange NT, Makris N, Herbert MR, Kennedy DN. MRI-based brain volumetrics: emergence of a developmental brain science. *Brain Dev.* 1999;21:289–295.

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