ORIGINAL CONTRIBUTION

Sex Differences in Brain Aging

A Quantitative Magnetic Resonance Imaging Study

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Background: Little is known about the effect of sex on age-related changes in brain structure.

Methods: Quantitative magnetic resonance imaging of the brain was performed in 330 elderly (age range, 66-96 years) volunteers living independently in the community, all of whom were participants in the Cardiovascular Health Study. Blinded measurements of global and regional brain size were made from T_1-weighted axial images by means of computer-assisted edge detection and trace methods. High measurement reliabilities were obtained.

Results: Age-specific changes in brain size were significantly greater in men than women for the peripheral (sulcal) cerebrospinal fluid volume, the lateral (sylvian) fissure cerebrospinal fluid volume, and the parieto-occipital region area. Main effects of age were observed for all the remaining brain regions examined (cerebral hemisphere volume, frontal region area, temporoparietal region area, lateral ventricular volume, and third ventricle volume), but these effects were similar in men and women. Asymmetries in brain structures were not affected by aging in either sex.

Conclusions: Our results are generally consistent with the few published studies on sex differences in brain aging and suggest that, for at least some structures, aging effects may be more apparent in men than women. The neurobiological bases and functional correlates of these sex differences require further investigation.

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BOTH POSTMORTEM (reviewed by Powers[1]) and in vivo imaging (reviewed by Coffey[2]) studies have demonstrated that advancing age in humans is generally associated with decreased brain tissue size and increased brain cerebrospinal fluid (CSF) volume. Although sex differences have been described in the size, symmetry, and function of several brain structures,[3-8] only a small number of imaging studies have examined the effects of sex on brain aging in nonpatient samples of living humans (**Table 1**).[9-27] While the findings have been inconsistent, a few investigators have reported sex differences in the effects of age on some brain structures, and in most cases males showed greater aging changes than females.[14,17,18,22,25,26] These studies are somewhat difficult to compare, however, given differences in subject samples (eg, sample size, age range, exclusion criteria), imaging and data acquisition protocols (eg, computed tomography vs magnetic resonance [MR] imaging), measurement technique, and statistical analyses (Table 1).

The present study used quantitative MR imaging morphometry to examine the effects of sex on age-related changes in the size of regional brain matter and CSF spaces in a large sample of elderly volunteers living independently in the community. We tested the hypothesis that such changes would be more dramatic in men than in women.

RESULTS

The regional cerebral measures are shown in Table 2. Results are discussed first for measures that showed an effect of sex on age-related changes in volume (ie, an age×sex interaction), and then for measures that showed only a main effect of age without an interaction.

AGE × SEX INTERACTION

Significant age×sex interactions were found for the peripheral CSF volume, the

SUBJECTS AND METHODS

SUBJECTS

Subjects were selected from among participants in the Cardiovascular Health Study (CHS), an ongoing multicenter, population-based observational study of 5888 volunteers 65 years and older, including 2495 men and 3393 women.[28,29] The major goal of the CHS is to identify risk factors related to the development and course of coronary heart disease and stroke in individuals living independently in the community. After providing informed consent, subjects undergo extensive clinical evaluation (home interview and physical examination) and laboratory testing (including brain MR imaging [see below]) at baseline, and annual follow-up assessment. Additional details of the CHS have been published.[28]

A detailed description of subject recruitment for the CHS has been published.[29,30] For the present study, we identified from the CHS cohort a sample of 500 subjects recruited from 2 CHS sites (Pittsburgh, Pa, and Hagerstown, Md) who gave written consent to participate in an ancillary investigation of cognitive functioning and aging (these data will be the subject of a future report). All available subjects from these 2 sites in whom brain MR imaging was performed within 1 year of this cognitive testing were screened for inclusion in this study. We subsequently excluded from this cohort a total of 170 subjects for 1 or more of the following reasons: not right-handed (subjects were determined to be right-handed if they used their right hand to write, throw a ball, and brush their teeth[31]); lifetime history of any psychiatric illness or of any illness or injury referable to the brain (per the CHS clinical evaluation described earlier); incomplete cognitive test data; incomplete MR imaging data (eg, scan artifact, missing slices); or MR images with structural abnormalities (cortical infarct, n=5; hydrocephalus, n=1; tumor, n=1; and markedly thickened calvarium, n=1).[32,33]

The final sample consisted of 330 subjects, 129 men and 201 women, ranging in age from 66 to 96 years (**Table 2**). Our subjects were similar to the CHS population as a whole with regard to age (CHS mean ± SD, 72.77 ± 5.61 years), sex distribution (CHS, 59% female), and education level (CHS mean ± SD, 12.35 ± 3.10 years). Of the subjects, 244 (74%) were taking medications for 1 or more of the following medical conditions: hypertension or ischemic heart disease (74 men [57.4%]; 111 women [55.2%]), peptic ulcer disease (18 men [13.9%]; 21 women [10.4%]), osteoarthritis (14 men [10.9%]; 35 women [17.4%]), hypercholesterolemia (9 men [6.9%]; 30 women [14.9%]), hypothyroidism (4 men [3.1%]; 20 women [10%]), infection (9 men [7.0%]; 14 women [7.0%]), diabetes mellitus (oral agent: 6 men [4.7%]; 4 women [2.0%]; insulin: 8 men [6.2%]; 3 women [1.5%]), postmenopausal hormone replacement (16 women [8.0%]), gout (8 men [6.2%]; 1 woman [0.5%]), chronic obstructive pulmonary disease (2 men [1.6%]; 8 women [4.0%]), benign prostatic hypertrophy (5 men [3.9%]), breast cancer in remission (3 women [1.5%]), and hyperthyroidism (1 man [0.8%]). No subject was taking medication known to affect brain size (eg, corticosteroids). Additional subject characteristics are given in Table 2.

BRAIN MR IMAGING TECHNIQUE

As noted earlier, brain MR imaging was performed in all subjects as a result of their participation in the CHS. The standardized CHS brain MR imaging acquisition protocol has been previously described.[34] Magnetic resonance imaging was performed on either a 1.5-T scanner (General Electric, Milwaukee, Wis) (n=248) or a 0.35-T scanner (Toshiba) (n=82) at 1 of 2 CHS field centers (Pittsburgh and Hagerstown, respectively). Head position was oriented in the scanner and was stabilized during the scanning procedure by the use of Velcro straps and foam head supports. To establish slice orientation, the first scanning sequence consisted of a T_1-weighted sagittal series (repetition time [TR], 500 milliseconds; echo time [TE], 20 milliseconds; thickness, 5 mm; gap, 0 mm; and matrix, 128×256) centered at the midline to define the anterior commissure–posterior commissure (AC/PC) line. Then a second series of proton-density (TR, 3000 milliseconds; TE, 30 milliseconds; flow compensated) and T_2-weighted (TR, 3000 milliseconds; TE, 100 milliseconds; flow compensated) images was obtained (thickness, 5 mm; gap, 0 mm; matrix, 256×192; number of excitations, one-half [1 on the 0.35-T scanner]), oriented parallel to the AC/PC line, and extending from the vertex to the skull base. A third series consisting of T_1-weighted (TR, 500 milliseconds; TE, 20 milliseconds) axial images was then obtained (thickness, 5 mm; gap, 0 mm; matrix, 256×192; number of excitations, 1), oriented parallel to the AC/PC line, and extending from vertex to skull base. Images were stored on 9-track magnetic tape.

IMAGE ANALYSIS AND BRAIN MORPHOMETRY

For the present study, the brain images were transferred from magnetic tape to read/write magneto-optical disks. Data were analyzed on a workstation (Power Mac 8100, Apple, Cupertino, Calif) with high-resolution color graphic monitor. The measurements of regional brain size were made on the recalled T_1-weighted axial images by 1 of 2 trained technicians blinded to all subject characteristics. Window center settings were first standardized to ensure precision in boundary detection.[35] Structures were identified with the help of brain and MR imaging atlases[36,37] and then measured with a combination of computer-assisted edge detection and manual tracing, using graphic analysis software (MedVision, Imnet/Evergreen Technologies, Castine, Me). The area (in square centimeters) within the outline was calculated automatically; volume (in milliliters) was determined by multiplying the area by the slice thickness and summing over the multiple slices in which the structure appeared (described later).

The following regions were defined for volume measurement.

Intracranial volume (IV) was defined by the internal surface of the diploe[16] and measured in every slice between the vertex and the superior border of the midbrain (approximately 12-15 slices per subject were measured). Intracranial size could not be reliably measured inferior to this level because of the presence of structures such as the globes and sinuses. As such, this measure is an underestimate of the true total intracranial volume. There was no

significant correlation between age and intracranial volume.

Cerebral hemisphere volume was measured in every slice between the vertex and the skull base (approximately 18-20 slices per subject). Ventricular volumes were excluded from this measurement.

Lateral ventricle volume was measured in each slice on which lateral ventricles were present. We also measured the various subregions of the lateral ventricles, including the body, the frontal horns, the posterior horns, and the temporal horns.

Third ventricle volume was measured in each slice beginning at the level of the foramen of Monro and extending inferiorly to the superior border of the midbrain (approximately 3-4 slices per subject).

Peripheral (sulcal) CSF volume was a calculated value derived by subtracting the cerebral hemisphere and ventricular volumes from the intracranial volume, for each slice on which intracranial volume was measured. As such, this measure is an underestimate of the true total peripheral CSF volume.

Lateral (sylvian) fissure CSF volume provided an indirect estimate of atrophy of the temporal lobe, as well as of the frontal and parietal lobes. The lateral fissures were measured in each slice on which they were present, beginning at the level of the foramen of Monro. When the lateral fissure communicated freely with the peripheral CSF, the anterior boundary of the fissure was defined by a horizontal line connecting the anterior tip of the temporal lobe to the medial temporal region.

It was not possible to reliably subdivide the cerebral hemisphere into its various lobes (ie, frontal, temporal, parieto-occipital) because of difficulties in establishing boundaries for such subregions in the axial plane of orientation.[2] Nevertheless, a regional brain morphometric analysis was possible on 1 of our axial slices. For this analysis, we followed the method of Pearlson et al[38] and chose a T_1-weighted axial slice that passed through both the pineal gland and foramen of Monro (hereafter designated the "region-of-interest [ROI] slice"). This slice is approximately 1 slice above the AC/PC line and is especially suited to subregional analysis because it contains both gray and white matter, it is not dominated by CSF spaces, and it contains anatomical regions believed to be associated with performance on a number of neuropsychological tests.[38] Using the boundary definitions of Pearlson et al,[38] the following 4 subregions were defined for area measurement on the ROI slice (ventricular areas were excluded from all regions) (**Figure**).

Frontal region area: The posterior border of this region was defined by a horizontal line intersecting the anteriormost aspect of the lateral ventricles.

Temporoparietal region area: This region was the area situated between the frontal lobes anteriorly and the parieto-occipital lobes posteriorly, and was bordered medially by the internal capsule.

Parieto-occipital region area: The anterior border of this region was defined by a horizontal line intersecting the anterior atria of the ventricles.

Intracranial area (IA): This area was defined by the inner surface of the diploe (per above).

Extensive reliability studies of our measurement techniques have indicated that area/volume measurements of these regions are highly reliable.[16] On the basis of a randomly selected sample of 10 brains from the current study, intraclass correlation coefficients for interrater reliability of the 2 raters ranged from 0.85 (for small regions such as the third ventricle) to 0.99 (for large regions such as the cerebral hemisphere). Intraclass correlation coefficients for intrarater reliability ranged from 0.84 to 0.99.

STATISTICAL ANALYSIS

Preliminary Analysis

By exploratory methods, the data were examined for outliers and extreme values by means of box plots and normal quantile-quantile plots. Transformations of the outcome variables—in particular, cube root transformations for the volume data, square root transformations for the ROI data, and logarithmic transformations for both—were reviewed. These analyses demonstrated no need for transformation.

Regressions, using the full model given below, were conducted on untransformed and logarithmically transformed outcome variables. The residuals from these regressions were examined by means of deviation plots and normal quantile-quantile plots, again to assess whether the outcome variables needed transformation. The results of these analyses also indicated that the untransformed data best fit the assumptions of normal-theory linear regression.

Our analysis treated intracranial size as a covariate. An alternative approach is to use percentage size based on the ratio of brain structure size to intracranial size. We rejected this approach for 2 reasons. First, the ratio approach implicitly assumes that brain size is perfectly correlated with intracranial size. Although the 2 are highly correlated, we found the assumption of perfect correlation untenable. Second, the ratio approach creates outcome variables that are necessarily bounded between 0 and 1. Such variables may have distributions poorly suited for linear regression analysis.

Regression Analyses

The outcome variables consisted of the cerebral volumes, the left−right differences for the relevant cerebral volumes, the cerebral areas from the ROI slice, and the left-right differences for these cerebral areas. There were 4 predictor variables. The first predictor in the regression equation was either IV (for the 2 sets of volume data) or IA (for the 2 sets of area data), as appropriate. The second predictor was sex, with the effect coded as 1 for men and −1 for women. The third was age, centered at 75 years (roughly the mean age of the sample) to eliminate colinearity with the age×sex interaction. The fourth predictor was the age×sex interaction, created by multiplying the (centered) age variable by the sex variable.

The regression models were the same for all outcome variables. Each outcome variable was first regressed against the full model consisting of IV (or IA, as appropriate), sex, age, and age×sex, using the hierarchical method in the order given. In this approach, the significance of a

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predictor is adjusted for all predictors preceding it in the list, but not adjusted for any predictors following it. In all tests, the significance level was set at .05. If age × sex was found significant, the full model was accepted, regardless of the significance values of any of the preceding predictors, and testing was stopped. If age × sex was not significant, then it was eliminated from the equation and the regression was run again. If age was significant, then this model was accepted and testing stopped. Otherwise, age was eliminated and the regression was run again. These iterations were repeated until a significant effect was found or no predictors were left. The regression coefficients from the final accepted model were then used to interpret the results.

lateral fissure CSF volume, and the parieto-occipital region area. For each of these regions, men showed greater age-related changes than did women. **Table 3** illustrates these interactions for persons with an average intracranial size, from ages 65 to 95 years. For the peripheral CSF volume, the regression coefficient was 2.11 for men but only 0.06 for women ($P<.03$). At age 65 years, men had a mean peripheral CSF volume about 5.70 mL smaller than that of women, but at age 95 years, men had a mean peripheral CSF volume about 55.67 mL larger than that of women (Table 3). For the lateral fissure CSF volume, the regression coefficient was 0.23 for men but only 0.10 for women ($P<.04$). At age 65 years, men had a mean lateral fissure volume about 0.80 mL larger than that of women, but at age 95 years, this difference increased to 4.86 mL (Table 3). For the parieto-occipital region area, the regression coefficient was –0.31 for men but only –0.09 for women ($P<.03$). At age 65 years, men had a mean parieto-occipital region area about 2.15 cm^2 larger than that of women, but at age 95 years, men had a mean parieto-occipital region area about 4.54 cm^2 smaller than that of women (Table 3).

AGE MAIN EFFECTS

Age was significantly related to each of the remaining brain matter and CSF regions measured. Increased age was associated with decreased cerebral hemisphere volume (coefficient = –2.79, $P<.001$), frontal region area (coefficient = –0.13, $P<.001$), and temporoparietal region area (coefficient = –0.13, $P<.001$). Increased age was also associated with increased volumes of the lateral ventricles (coefficient = 0.95, $P<.001$) and the third ventricle (coefficient = 0.05, $P<.001$).

REGIONAL CEREBRAL ASYMMETRIES

To examine potential laterality differences in the effects of sex on age-related changes in regional cerebral size, left – right differences were analyzed by means of the same hierarchical regression model described above. There were no age × sex interactions and no main effects of age or sex for any of the regions. A main effect was found for intracranial area, but for the frontal region only. Increasing intracranial area was associated with an increased left – right difference in frontal region area (coefficient = –0.01, $P<.01$), a result of greater increases of the right side than of the left.

COMMENT

We found that age-specific changes in brain size were significantly greater in men than women for the peripheral (sulcal) CSF volume, the lateral (sylvian) fissure CSF volume, and the parieto-occipital region area. Main effects of age were observed for all the remaining brain regions examined, but these effects were similar in men and women. Asymmetries in brain structures were not affected by aging in either sex. Our blinded measures of these brain regions were highly reliable, and our estimates of their age-specific sizes agree closely with previous reports, including those that used more sophisticated voxel-by-voxel techniques.[2] Our results shed light on some of the conflicting findings in the literature (discussed later) and extend these observations to a large sample of elderly persons living independently in the community.

METHODOLOGICAL LIMITATIONS

Our findings are subject to certain potential limitations. Although cross-sectional studies of age effects allow for relatively efficient and rapid acquisition of large amounts of data, they are subject to secular effects, such as birth cohort. This effect refers to the possibility that brain size, like cranial size, may exhibit systematic changes over successive birth cohorts in the general population. If such trends actually exist in the population at large and if they are not secondary to secular trends associated with correlates such as cranial size (in the present study, cranial size was not correlated with age), then an assessment of the true effects of aging per se on brain volume will require longitudinal investigation.

A second issue relates to the health status of our subjects. First, our sample represents a group that may be somewhat healthier than the entire population because of selection criteria for the CHS and the current study.[30] As such, our findings may not be applicable to the entire population of seniors. Second, there is heterogeneity of health status within our subjects, in that 26% were also free of major systemic illness while 74% had at least some mild physical disease, corresponding to the distinction between successful and usual aging.[39] Such differences in health status could account for differences in brain aging, and indeed systemic disease such as hypertension has been found to be associated with changes in brain structure.[40,41] The prevalence of this condition was generally similar among the men and women in our study, however. Furthermore, studies in subjects free of major medical illness have reported sex differences in age-related changes in brain structure similar to our present findings.[22,25] Still, it is possible that sex differences in the prevalence of systemic diseases may account for some of the sex differences observed in structural brain aging.

The measurements of regional brain size in our study are subject to certain limitations. First, because of

Table 1. Imaging Studies of Sex Differences in Human Brain Aging*

Source, y	Subjects	Imaging and Measurement Technique	Findings
Grant et al,[9] 1987	64 healthy volunteers 18-64 y old 25 M; 39 F No history of neurologic disease; psychiatric history not reported Handedness not specified	MR imaging (0.15 T) Mathematically derived estimate of ventricular volume from signal intensity measurements made on single sagittal slice (No. of raters not specified)	Age associated with increased lateral ventricular volume in M but not F; however, apparent gender difference not tested statistically Effects on asymmetries not reported No control for size of brain or head
Condon et al,[10] 1988	40 volunteers 20-60 y old 20 M; 20 F No additional details provided	MR imaging (0.15 T) Volume measurement (2 raters) derived from computer-assisted pixel segmentation of contiguous sagittal slices (variable slice thickness and number)	Age negatively correlated with ratio of total brain volume to IV in M but not F; however, correlations not statistically compared
Yoshi et al,[11] 1988	58 healthy volunteers 21-81 y old 29 M; 29 F Neurologic and psychiatric histories not reported Handedness not specified	MR imaging (1.0 T) Blinded global ratings (4-point scales) of cortical atrophy and lateral ventricular enlargement from inversion recovery films (axial slices [No. unspecified], 10 mm thick, 3-mm interscan gap) Mathematically derived estimate of brain volume from inversion recovery films, based on planimetric area measurement made on single slice (10 mm thick) at level of foramen of Monro No. of raters and rater reliabilities not specified	Age correlated with ratings of cortical atrophy and lateral ventricular enlargement (M and F) Laterality effects not reported No correlation between age and brain volume, in either M or F
Krishnan et al,[12] 1990	39 healthy volunteers 24-79 y old 17 M; 22 F No evidence of major medical, neurologic, or psychiatric illness	MR imaging (1.5 T) Blinded stereological measurement (1 of 2 raters) of axial slices (variable number, 5 mm thick, 2.5-mm interscan gap) from intermediate and T_2-weighted films	Age negatively correlated with total caudate volume (M and F) Caudate volume was less in subjects older than 50 y (n=22) No adjustments for cranial size Effects on asymmetries not reported
Doraiswamy et al,[13] 1991	36 healthy volunteers (overlap with subjects in Krishnan et al[12] and McDonald et al[15]) 26-79 y old 16 M; 20 F No evidence of major medical, neurologic, or psychiatric illness	MR imaging (1.5 T) Area measurement of T_2-weighted midsagittal image (5 mm thick) using computer-assisted trace method Rater reliabilities not reported	Age negatively correlated with corpus callosum area in M but not F No adjustments for cranial size
Gur et al,[14] 1991	69 healthy volunteers 18-80 y old 34 M; 35 F No neurologic or psychiatric illness 66 dextrals; 3 sinistrals	MR imaging (1.5 T) Volume measurements (any 2 of 4 raters) derived from segmentation technique based on 2-feature pixel classification of multiple spin-echo axial images (5 mm thick, contiguous)	Older (≥55 y) subjects had smaller whole brain volumes (M=F), larger total CSF volume (M>F), larger ratio of ventricular CSF volume to IV (M=F), and larger ratio of sulcal CSF volume to IV (M>F) Effects of age on ratio of ventricular CSF volume to IV were asymmetric (L>R) in M but not in F
McDonald et al,[15] 1991	36 healthy volunteers (subjects also included in Krishnan et al[12]) 24-79 y old 13 M; 23 F No evidence of major medical, neurologic, or psychiatric illness	MR imaging (1.5 T) Same as Krishnan et al[12]	Age negatively correlated with total putamen volume (M=F; left=right), but no adjustments for cranial size

(continued)

Table 1. Imaging Studies of Sex Differences in Human Brain Aging* (cont)

Source, y	Subjects	Imaging and Measurement Technique	Findings
Coffey et al,[16] 1992	76 healthy volunteers 36-91 y old 25 M; 51 F No lifetime evidence of neurologic or psychiatric illness All right-handed	MR imaging (1.5 T) Volume measurements (1 of 3 raters with established reliabilities) using computer-assisted trace method of T_1-weighted coronal images (n=30-35, 5 mm thick, contiguous) Blinded clinical ratings (5-point scale) of cortical atrophy and of lateral ventricular enlargement from films (average score of 2 experienced raters)	Adjusting for IV, age associated with decreasing total volumes of cerebral hemispheres (0.23%/y), frontal lobes (0.55%/y), temporal lobes (0.28%/y), and amygdala-hippocampal complex (0.30%/y) (M=F for all regions) Adjusting for IV, age associated with increased volumes of third (2.8%/y) and lateral (3.2%/y) ventricles Increasing age associated with increasing odds (8.9%/y) of "cortical atrophy," from 0.08 at age 40 y to 2.82 at age 80 y (M=F) Age associated with increased odds (7.7%/y) of at least mild lateral ventricular enlargement, from 0.10 at age 40 y to 2.22 at age 80 y (M=F) No lateralized effects
Kaye et al,[17] 1992	107 healthy volunteers 64 M (21-90 y old) 43 F (23-88 y old) No major medical, neurologic, or psychiatric illness Handedness not specified	CT Volume measurement derived from computer-assisted segmentation technique (ASI-II program) Axial slices, 10 mm thick, 7-mm interscan gap	Age associated with increased ratio of ventricular volume to IV (about 20%/decade) (M=F); precipitous increases observed beginning in fifth decade in M and in sixth decade in F Effects on asymmetries not reported
Golomb et al,[18] 1993	154 healthy elderly volunteers 55-88 y old 73 M; 81 F No evidence of active medical, neurologic, or psychiatric illness Handedness not specified	CT (n=51); MR imaging (1.5 T) (n=81); both CT and MR imaging (n=22) Blinded ratings (4-point scale) of hippocampal atrophy as defined by dilation of transverse choroidal fissure on films Interrater reliabilites established, but No. of raters not reported	Subjects with hippocampal atrophy (rating of 2 or greater in either hemisphere; n=50) were significantly older than those without atrophy More M (41%) than F (25%) had hippocampal atrophy Effects on asymmetries not reported
Raz et al,[19] 1993	29 healthy volunteers 18-78 y old 17 M; 12 F No major medical, neurologic, or psychiatric illness Handedness not specified	MR imaging (0.30 T) Blinded volume measurements (digital planimetry) from films of T_1-weighted and proton density images in sagittal and coronal planes Good rater reliabilities, but No. of raters not specified	After controlling for head size, age associated with increased lateral ventricular volume (M=F) and decreased visual cortex volume (F>M); age not associated with volumes of dorsolateral prefrontal cortex, anterior cingulate gyrus, prefrontal white matter, hippocampal formation, postcentral gyrus, inferior parietal lobule, or parietal white matter
Sullivan et al,[20] 1993	114 healthy volunteers 21-82 y old (mean±SD, 51.2±17.7 y) 84 M; 30 F No history of major medical, neurologic, or psychiatric illness 90% right-handed	CT Volume measurements derived from computer-assisted segmentation technique Axial slices (n=10), 10 mm thick	Adjusting for head size, age correlated with total ventricular volume, third ventricular volume, and CSF volume in sylvian fissure and in vertex, frontal, and parieto-occipital sulci (M=F for all regions) Effects on asymmetries not reported
Christiansen et al,[21] 1994	142 healthy volunteers 21-80 y old 78 M; 64 F No major medical neurologic illness Psychiatric history and handedness not specified	MR imaging (1.5 T) Volume measurements using manual tracing of T_2-weighted axial images (4 mm thick, 4-mm interscan gap) No additional details provided	Age associated with increased lateral ventricle volume in M (134%) and F (66%), but these apparent gender differences were not statistically compared
Cowell et al,[22] 1994	130 healthy volunteers 18-80 y old 70 M; 60 F No major medical, neurologic, or psychiatric illness All right-handed	MR imaging (1.5 T) Volume measurements using combination of computer-assisted trace method and pixel segmentation of 3-dimensional images reconstructed from T_2-weighted axial images (5 mm thick, no gap) Good rater reliabilities, but "blindness" not specified	Ratio of frontal lobe to IV smaller in M >40 y of age than in younger M; no such group difference seen in F; R>L asymmetry of frontal lobe to IV larger in older F than younger F; no such group difference observed in M Ratio of temporal lobe to IV also smaller in M >40 y old than in younger M; no such group difference seen in F; no lateralized effects

(continued)

Table 1. Imaging Studies of Sex Differences in Human Brain Aging* (cont)

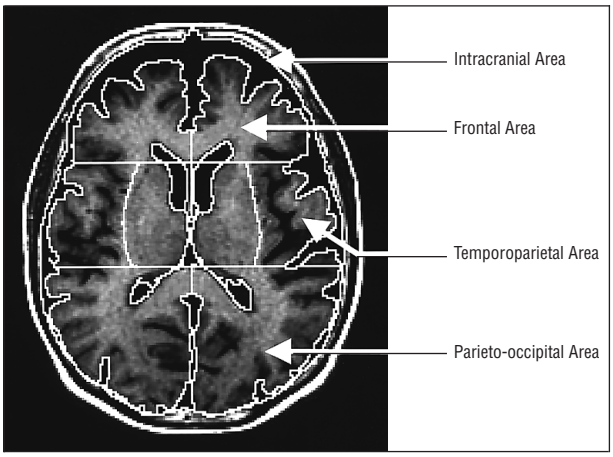
Source, y	Subjects	Imaging and Measurement Technique	Findings
			Ratio of the remaining brain volume to IV smaller in older than younger subjects (M=F); no lateralized effects
Blatter et al,[23] 1995	194 healthy volunteers 16-65 y old 89 M; 105 F No history (by questionnaire) of any neurologic or psychiatric illness 95% right-handed	MR imaging (1.5 T) Volume measurements derived from semiautomated pixel segmentation and trace methods, of intermediate and T_2-weighted axial images (5 mm thick, 2-mm gap) High rater reliabilities (blinded status?)	Adjusting for IV, age associated with decreased total brain matter volume and gray matter volume (F only), but not white matter volume; increased subarachnoid CSF volume; and increased lateral and third ventricular volumes, but not fourth ventricular volume; except for gray matter volume, correlations tended to be higher for M than F, but apparent differences not analyzed Effects on asymmetries not reported
Parashos et al,[24] 1995	80 healthy volunteers (overlap with subjects in Coffey et al[16]) 30-91 y old 28 M; 52 F No lifetime history of neurologic or psychiatric illness All right-handed	MR imaging (1.5 T) Blinded area measurements using computer-assisted trace method of T_1-weighted midsagittal image (5 mm thick), made by single rater with established rater reliabilities	Adjusting for IV, increasing age associated with smaller total and regional callosal areas, especially of anterior regions (M=F)
Murphy et al,[25] 1996	69 healthy volunteers 35 M (mean±SD age, 44±23 y) 34 F (50±21 y) No major medical or psychiatric illness All right-handed	MR imaging (0.5 and 1.5 T) Blinded volume measurements using computer-assisted segmentation and trace method of contiguous coronal images (5-6 mm thick) No. of raters not specified	Relative to "young" subjects (age, 20-35 y), "old" subjects (60-85 y) had smaller brain matter volume ratios of cerebellum to IV (M=F), cerebrum to IV (M>F), frontal lobe to IV (M>F), temporal lobe to IV (M>F), parietal lobe to IV (F>M), parieto-occipital lobe to IV (M=F), parahippocampal gyrus to IV (M=F), amygdala to IV (M=F), hippocampus to IV (F>M), thalamus to IV (M=F), lenticular nucleus to IV (M=F), and caudate to IV (M=F); old subjects also had larger lateral ventricular (M=F), third ventricular (F>M), and peripheral CSF to IV (M=F) ratios For frontal lobe, right side decreased more than left with age in M, but in F left side decreased more than right
Raz et al,[26] 1997	148 healthy volunteers 18-77 y old 66 M (mean±SD age, 47.39±18.07 y) 82 F (45.72±16.48 y) No major medical, neurologic, or psychiatric illness Handedness not specified	MR imaging (1.5 T) Blinded volume measurements (digital planimetry) from films of T_1-weighted reformatted coronal images (1.3 mm thick, contiguous) Good rater reliabilities among 8 raters	Adjusted for height, age significantly related to smaller volumes of whole brain (M=F), prefrontal gray matter (M=F), inferior temporal cortex (M>F), fusiform gyrus (M=F), hippocampal formation (M=F), primary somatosensory cortex (M=F), superior parietal cortex (M=F), prefrontal white matter (M=F), and superior parietal white matter (M=F) No age effects found for anterior cingulate cortex, parahippocampal cortex, primary motor cortex, inferior parietal cortex, visual cortex, and precentral, postcentral, and inferior parietal white matter No lateralized age effects
Yue et al,[27] 1997	1488 healthy elderly volunteers from CHS 65-80+ y old No. M and F not specified Handedness not specified No major medical or neurologic illness (psychiatric illness not reported)	MR imaging (0.35 or 1.5 T) Blinded ratings (10-point scales) of sulcal prominence and ventricular size from T_1-weighted axial images Good to excellent rater reliabilities, but No. of raters not specified	Age associated with sulcal prominence and ventricular enlargement (M=F)

**MR indicates magnetic resonance; IV, intracranial volume; CSF, cerebrospinal fluid; CT, computed tomography; and CHS, Cardiovascular Health Study.*

Table 2. Subject Characteristics and Regional Brain Size as a Function of Sex*

	All Subjects (N=330)	Men (n=129)	Women (n=201)
Subject characteristics			
Age, y†	74.98±5.09	75.38±5.60	74.72±4.72
Education, y	12.88±3.00	13.12±3.25	12.73±2.82
WAIS-R Vocabulary	46.66±14.19	46.33±15.22	46.98±13.60
MR imaging intracranial volume, mL	940.83±99.79	1000.22±96.22	902.72±81.90
Brain matter size			
Cerebral hemispheres, mL			
Total	945.33±99.72	996.60±100.22	912.44±84.55
Left	474.58±50.10	500.81±49.46	457.74±42.83
Right	470.76±50.30	495.79±51.43	454.69±42.48
Left − right	3.82±11.58	5.01±11.86	3.05±11.36
Frontal lobe region, cm^2			
Total	37.68±4.57	38.68±4.84	37.03±4.27
Left	18.57±2.33	19.00±2.45	18.29±2.21
Right	19.11±2.45	19.69±2.63	18.74±2.25
Left − right	−0.54±1.40	−0.69±1.55	−0.44±1.29
Temporoparietal region, cm^2			
Total	26.03±3.57	25.63±3.69	26.13±3.44
Left	12.87±1.86	12.73±2.05	12.97±1.74
Right	13.06±1.97	12.90±1.94	13.16±1.99
Left − right	−0.18±1.48	−0.17±1.52	−0.19±1.45
Parieto-occipital region, cm^2			
Total	59.68±5.86	61.77±6.43	58.33±5.04
Left	30.20±3.14	31.29±3.42	29.49±2.74
Right	29.48±3.05	30.48±3.28	28.84±2.71
Left − right	0.71±2.0	0.81±1.87	0.65±2.08
CSF volume, mL			
Peripheral CSF	211.75±50.90	235.28±49.74	196.64±45.74
Lateral fissures			
Total	9.73±3.30	11.21±3.58	8.78±2.72
Left	4.70±1.64	5.36±1.79	4.28±1.40
Right	5.03±1.92	5.85±2.11	4.50±1.58
Left − right	−0.32±1.37	−0.49±1.57	−0.22±1.22
Lateral ventricles			
Total	29.10±19.32	35.19±20.35	25.19±17.60
Left	15.16±10.45	18.33±11.11	13.13±9.49
Right	13.93±9.18	16.86±9.53	12.06±8.45
Left − right	1.23±3.71	1.47±3.87	1.08±3.61
Third ventricle	2.29±0.90	2.63±0.96	2.04±0.79

*Data are mean±SD. WAIS-R indicates Wechsler Adult Intelligence Scale–Revised; MR, magnetic resonance; and CSF, cerebrospinal fluid.
†There was no significant correlation between age and MR imaging intracranial volume.



Typical T_1-weighted axial brain magnetic resonance image at the level of the foramen of Monro, demonstrating the subdivisions of the region of interest slice.

limitations inherent in the CHS MR imaging acquisition protocol, our analyses of brain size were restricted to the axial plane (3-dimensional reconstruction was not possible without dramatic loss of resolution). The axial plane does not permit optimal boundary delineation of many brain regions, and as such our anatomic definitions were arbitrary and frequently underrepresentative of the true size of the structure. In particular, our estimates of regional brain size were based on single-slice area measurements (the ROI slice) rather than multislice volume measures, which are more valid estimates of true brain size.[2] Second, accurate delineation of regional boundaries can be affected by several sources of technical error, including improper window center settings, magnetic field inhomogeneity (resulting in spatial distortion of objects and object pixel nonuniformity), and differences in MR imaging technical variables.[35] The effects of these variables were minimized in this study by use of a set of procedures that has been shown to optimize the accuracy of MR imaging size mea-

Table 3. Effect of Sex on Age-Specific Changes in Regional Brain Size*

	Age, y						
	65	70	75	80	85	90	95
Peripheral CSF volume, mL							
Men	199.36	209.90	220.43	230.97	241.50	252.03	262.57
Women	205.06	205.37	205.68	205.98	206.29	206.59	206.90
Lateral fissure CSF volume, mL							
Men	8.70	9.86	11.02	12.19	13.35	14.51	15.68
Women	7.90	8.38	8.87	9.36	9.85	10.34	10.82
Parieto-occipital region area, cm^2							
Men	62.79	61.23	59.66	58.10	56.54	54.97	53.40
Women	60.64	60.18	59.74	59.29	58.84	58.39	57.94

*Data are for persons with an average intracranial size. CSF indicates cerebrospinal fluid.

surements.[16,35] Third, field strength differences between the 2 scanners could affect estimates of brain size.[2] To test whether such differences could have confounded the relations between brain size and the predictor variables, scanner assignment was entered as a covariate in the regression analyses (entered after sex). Scanner assignment was not confounded with any of the age × sex interactions or the age main effects.

SEX EFFECTS ON AGE-SPECIFIC CEREBRAL ATROPHY

We found that the age-related increase in peripheral CSF volume, a marker of cortical atrophy, was significantly greater in elderly men than women. For example, from ages 65 to 95 years, men (of average IV) had an increase in peripheral CSF volume of approximately 32% compared with less than a 1% increase in women (Table 3). Gur et al[14] also found that the ratio of sulcal CSF volume to IV was greater for elderly (55 years and older) subjects and for men. Similarly, Blatter et al[23] found higher correlations between age and "subarachnoid" CSF volume (adjusted for IV) in men (r=0.653) than in women (r=0.545), although these correlations were not statistically compared. Other studies that examined peripheral CSF volume have found no sex effects on age-related increases.[20,25,26]

We found no sex differences in the age-related decrease in cerebral hemisphere volume (ie, there was no age × sex interaction) and no age effects (neither main nor interaction with sex) on the left – right difference in cerebral hemisphere volume. Similar negative findings have been reported.[11,14,16,19,20,25,26] Although Condon et al[10] found that men, but not women, exhibited a significant correlation between age and the ratio of total brain volume to IV, these correlations were not statistically compared. Similarly, Blatter et al[23] observed higher correlations in men than women between age and the ratio of total brain volume to IV (r=–0.675 vs r=–0.539, respectively), but again these correlations were not statistically compared. Murphy et al[25] reported that men had a significantly greater age-related decrease in the ratio of cerebral hemisphere volume to IV than did women.

Our finding of a significant sex effect on the age-related increase in peripheral CSF volume, in the absence of a sex effect on age-related volume loss of cerebral hemisphere brain matter, is consistent with the observations of Gur et al.[14] Taken together, these reports suggest that while peripheral CSF volume may show a greater age-related increase in men than women (likely as a result of cortical atrophy), such sex differences in cortical atrophy may not be apparent statistically when the cortex is averaged in with a relatively larger structure, such as the cerebral hemisphere. We are not aware of any studies that have examined sex effects on age-related tissue loss in the cortex per se.

SEX EFFECTS ON AGE-SPECIFIC DIFFERENCES IN REGIONAL BRAIN SIZE

We found that the age-associated increase in lateral fissure CSF volume, a marker of frontotemporal (and, to a lesser extent, parietal) atrophy, was significantly greater in men than women. For example, from ages 65 to 95 years, men (of average IV) had an increase in lateral fissure volume of approximately 80%, while women had an increase of only approximately 37% (Table 3). Although Sullivan et al[20] found no sex differences in the age-related increase in sylvian fissure volume, they used computed tomographic scanning and relatively thicker brain slices (10 mm).

In contrast to the results with lateral fissure volume, we found no sex effects on the age-related decrease in temporoparietal region area or frontal region area. Thus, in our study, lateral fissure CSF volume was a more revealing marker of atrophy in these regions than was their direct measurement from the ROI slice. The literature is conflicting with regard to the effects of sex on age-related changes in temporal lobe size (Table 1). Cowell et al[22] and Murphy et al[25] found that men exhibited greater age-related decreases in the ratio of temporal lobe volume to IV than did women. Similarly, Golomb et al[18] found that age-related hippocampal atrophy was more common in men than women, and Raz et al[26] observed greater age-related inferior temporal volume loss in men than women. In contrast, Murphy et al[25] actually observed greater temporal lobe atrophy in women than men. Despite differences in which sex is more affected, the published results suggest that sex may impact the age-related volume loss of the temporal lobe region. These

findings may provide a neuroanatomical substrate for the sex differences noted earlier in age-related verbal memory impairment.[42-44]

The literature is also conflicting with regard to the effects of sex on age-related changes in frontal lobe size (Table 1). Cowell et al[22] and Murphy et al[25] both observed greater age-related frontal lobe volume loss in men than in women. In contrast, others have found no sex effects.[16,19-22,26] These discrepant results may reflect differences between studies in samples and brain measurement techniques (ie, quantitative vs qualitative measures, area measures from a single slice vs volume measures from multiple slices).

Our analysis of left – right difference in temporoparietal and frontal region areas showed no age effect (neither main effect nor interaction with sex). Similar negative results have been reported.[16,20,22,25,26] In contrast, Cowell et al[22] observed that the right greater than left asymmetry of frontal lobe volume to IV was larger in older women than in younger women, whereas in men no such group differences were seen.

We found that age-related decreases in parieto-occipital region area were greater for men than women—for example, from ages 65 to 95 years, men (of average IA) lost approximately 15% of their parieto-occipital lobe area, while women lost only 4% (Table 3). Using a somewhat different definition of this brain region, Cowell et al[22] did not find any sex effect on the age-related decrease in the ratio of the posterior cerebral hemisphere volume to IV. Murphy et al[25] likewise found no sex differences in the age-related decrease in parieto-occipital region volume to IV, although they actually observed worse atrophy in women for the ratio of parietal lobe volume to IV. Similarly, Raz et al[19] reported that women exhibited greater age-related volume loss in the visual cortex than did men. These widely divergent findings indicate a need for additional research. Our analysis of left–right difference in parieto-occipital lobe area disclosed no age effect (neither main effect nor interaction with sex). Similar negative results have been reported.[16,20,22,25]

With regard to ventricular volumes, we found no sex effects on the age-related increase in lateral ventricular CSF volume or third ventricular CSF volume. Similar negative findings have been reported by the majority of studies that have examined the lateral ventricles[11,14,16,17,19,20,25,27] or the third ventricle.[14,16,17,20] Since age-related ventricular enlargement is presumed to occur as a result of shrinkage of periventricular brain matter, our results are also consistent with other studies that found no effect of sex on the age-related volume loss of structures that form the borders of the lateral ventricles (ie, the caudate nuclei)[12,25] or the third ventricle (ie, the thalamus).[25] In contrast, Grant et al[9] reported that men, but not women, exhibited a significant age-related increase in lateral ventricular volume, although this apparent sex difference was not tested. Likewise, Blatter et al[23]observed higher correlations in men than women between age and lateral ventricle volume (adjusted for IV) (r=0.444 vs r=0.218, respectively) and between age and third ventricle volume (adjusted for IV) (r=0.634 vs r=0.406, respectively), but again these correlations were not statistically compared. Kaye et al[17] reported that the precipitous age-related increases in lateral ventricular volume began about a decade earlier in men than women. Finally, Murphy et al[25] found that women actually had a greater age-related increase in the ratio of third ventricle volume to IV than did men.

Our analysis of left – right difference in lateral ventricle volume showed no age effect (neither main effect nor interaction with sex). Similar negative findings were noted by Murphy et al[25] for the ratio of right – left lateral ventricle volume to IV. However, Gur et al[14] found that the ratio of ventricular CSF volume to IV was more pronounced in the left hemisphere than in the right, a difference they attributed primarily to elderly men.

In summary, brain morphologic characteristics in humans appear to be sensitive to the effects of both age and sex, and converging data suggest that these 2 variables may interact over the life span to influence brain size. These data should provide a useful context within which to interpret changes in regional brain structure associated with "abnormal" aging. The neurobiological bases for these sex differences in brain aging are not known. Neuroendocrinological differences between sexes have been proposed as a possible explanation given that gonadal corticosteroids affect brain development and aging, and that age affects both the function and regional distribution of androgen and estrogen systems in the brain.[22] Still, most studies of human brain aging at the cellular level have not examined sex effects.

The behavioral effects in humans of these sex differences in brain aging are likewise unknown. These findings may provide a neuroanatomical substrate for the sexually dimorphic effects of age on cerebral blood flow and metabolism,[3-5,8] and it is possible that sex differences in brain aging could interact with a superimposed pathological process to produce sex differences in brain disorders such as Alzheimer disease.[25] In this regard, sex differences in brain aging are consistent with observed sex differences in some aspects of cognitive aging.[42-44] Correlative neuropsychological investigations are currently under way in our laboratory to determine the potential functional significance of differences between the sexes in brain aging.

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REFERENCES

1. Powers RE. Neurobiology of aging. In: Coffey CE, Cummings JL, eds. *Textbook of Geriatric Neuropsychiatry*. Washington, DC: American Psychiatric Press Inc; 1994:35-69.
2. Coffey CE. Anatomic imaging of the aging human brain: computed tomography and magnetic resonance imaging. In: Coffey CE, Cummings JL, eds. *Textbook*

of Geriatric Neuropsychiatry. Washington, DC: American Psychiatric Press Inc; 1994:159-194.
3. Gur RC, Gur RE, Obrist W, Skolnick B, Reivich M. Age and regional cerebral blood flow at rest and during cognitive activation. *Arch Gen Psychiatry*. 1987;44:617-621.
4. Gur RE, Gur RC. Gender differences in regional cerebral blood flow. *Schizophr Bull*. 1990;16:247-254.
5. Rodriguez G, Warkentin S, Risberg J, Rosadini G. Sex differences in regional blood flow. *J Cereb Blow Flow Metab*. 1988;8:783-789.
6. Schlaepfer TE, Harris GJ, Tien AY, et al. Structural differences in the cerebral cortex of healthy female and male subjects: a magnetic resonance imaging study. *Psychiatry Res*. 1995;61:129-135.
7. Witelson SF. Cognitive neuroanatomy: a new era. *Neurology*. 1992;42:709-713.
8. Shaw T, Moriel K, Meyer J, et al. Cerebral blood flow changes in benign aging and cerebrovascular disease. *Neurology*. 1984;34:855-862.
9. Grant R, Condon B, Lawrence A, et al. Human cranial CSF volumes measured by MRI: sex and age influences. *Magn Reson Imaging*. 1987;5:465-468.
10. 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.
11. 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 Cereb Blood Flow Metab*. 1988;8:654-661.
12. Krishnan KR, McDonald WM, Doraiswamy PM, et al. In vivo stereological assessment of caudate volume in man: effect of normal aging. *Life Sci*. 1990;47:1325-1329.
13. Doraiswamy PM, Figiel GS, Husain MM, et al. Aging of the human corpus callosum: magnetic resonance in normal volunteers. *J Neuropsychiatry Clin Neurosci*. 1991;3:392-397.
14. Gur RC, Mozley PD, Resnick S, 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.
15. McDonald WM, Husain M, Doraiswamy PM, et al. A magnetic resonance image study of age-related changes in human putamen nuclei. *Neuroreport*. 1991;2:41-44.
16. 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.
17. Kaye JA, DeCarli CD, 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.
18. Golomb J, deLeon MJ, Kluger A, et al. Hippocampal atrophy in normal aging: an association with recent memory impairment. *Arch Neurol*. 1993;50:967-973.
19. Raz N, Torres IJ, Spencer WD, Acker JD. Pathoclysis in aging human cerebral cortex: evidence from in vivo MRI morphometry. *Psychobiology*. 1993;21:151-160.
20. 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.
21. Christiansen P, Larsson HBW, Thomsen C, et al. Age dependent white matter lesions and brain volume changes in healthy volunteers. *Acta Radiol*. 1994;35:117-122.
22. Cowell PE, Turetsky BI, Gur RC, et al. Sex differences in aging of the human frontal and temporal lobes. *J Neurosci*. 1994;14:4748-4756.
23. 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.
24. Parashos IA, Wilkinson WE, Coffey CE. Magnetic resonance imaging of the corpus callosum: predictors of size in normal adults. *J Neuropsychiatry Clin Neurosci*. 1995;7:35-41.
25. 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 Psychiatry*. 1996;53:585-594.
26. 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.
27. 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.
28 Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;3:263-276.
29. Longstreth WT, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial mangetic resonance imaging of 3301 elderly people. *Stroke*. 1996;27:1274-1282.
30. Tell GS, Fried LP, Hermanson B, et al. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol*. 1993;3:311-317.
31. Newcombe FG, Ratcliff GG, Carrivick PJ, et al. Hand preference and IQ in a group of Oxfordshire villages. *Ann Hum Biol*. 1975;2:235-242.
32. Yue NC, Longstreth WT Jr, Elster AD, et al. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. *Radiology*. 1997;202:41-46.
33. Bryan RN, Wells SW, Miller TJ, et al. Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly—data from the Cardiovascular Health Study. *Radiology*. 1997;202:47-54.
34. Manolio TA, Kronmal RA, Burke GL, et al. Magnetic resonance abnormalities and cardiovascular disease in older adults: the Cardiovascular Health Study. *Stroke*. 1994;25:318-327.
35. Jack CR, Gehring DC, Sharbrough FW, et al. Temporal lobe measurement from MR images: accuracy and left-right asymmetry in normal persons. *J Comput Assist Tomogr*. 1988;12:21-29.
36. DeArmand SJ, Fusce MM, Dewey MM. *Structure of the Human Brain*. 2nd ed. New York, NY: Oxford University Press; 1976.
37. Daniels DL, Haughton VM, Naidich TP. *Cranial and Spinal MRI: An Atlas and Guide*. New York, NY: Raven Press; 1987.
38. Pearlson GD, Rabins PV, Kim WS, et al. Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia (pseudodementia). *Psychol Bull*. 1989;3:573-584.
39. Rowe JW, Kahn RL. Human aging: usual and successful. *Science*. 1987;237:143-149.
40. Salerno JA, Murphy DGM, Horwitz B, et al. Brain atrophy in hypertension: a volumetric magnetic resonance imaging study. *Hypertension*. 1992;20:340-348.
41. Schmidt R, Fazekas F, Koch M, et al. Magnetic resonance imaging cerebral abnormalities and neuropsychologic test performance in elderly hypertensive subjects. *Arch Neurol*. 1995;52:905-910.
42. Zelinski EM, Gilewski MJ, Schaie KW. Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. *Psychol Aging*. 1993;8:176-186.
43. West RL, Crook TH, Barron KL. Everyday memory performances across the life span: effects of age and noncognitive individual differences. *Psychol Aging*. 1992;7:72-82.
44. Wiederholt WC, Cahn D, Butters N, et al. Effects of age, gender and education on selected neuropsychological tests in an elderly community cohort. *J Am Gerontol Soc*. 1993;41:639-647.

20. Alpherts WCJ, Aldenkamp AP. Computerized neuropsychological assessment of cognitive functioning in children with epilepsy. *Epilepsia.* 1990;31:S35-S40.
21. Hänninen H, Lindström K. *Behavioral Test Battery for Toxic Psychological Studies.* Helsinki, Finland; Institute of Occupational Health; 1979.
22. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJNR Am J Neuroradiol.* 1987;8:421-426.
23. Könönen M, Partanen JV. Blocking of EEG alpha activity during visual performance in healthy adults: a quantitative study. *Electroencephalogr Clin Neurophysiol.* 1993;84:164-166.
24. Gasser T, Bächer P, Möcks J. Transformations towards the normal distribution of broad band spectral parameters of the EEG. *Electroencephalogr Clin Neurophysiol.* 1981;53:119-124.
25. Norman G, Streiner D. *Biostatistics: The Bare Essentials.* St Louis, Mo: Mosby–Year Book Inc; 1994:66-67.
26. Newman MF, Wolman R, Kanchuger M, et al. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. *Circulation.* 1996;94(suppl 2):II-74–II-80.
27. Savageau JA, Stanton BA, Jenkins CD, Klein MD. Neuropsychological dysfunction following elective cardiac operation. *J Thorac Cardiovasc Surg.* 1982;84:585-594.
28. Moody DM. Is there a role for MR in the development of safer cardiac surgery? *AJNR Am J Neuroradiol.* 1996;17:213-215.
29. Libman RB, Wirkowski E, Neystat M, Barr W, Gelb S, Graver M. Stroke associated with cardiac surgery: determinants, timing, and stroke subtypes. *Arch Neurol.* 1996;54:83-87.
30. Moody DM, Bell MA, Challa VR, Johnston WE, Prough DS. Brain microemboli during cardiac surgery or aortography. *Ann Neurol.* 1990;28:477-486.
31. Gerraty RP, Bowser DN, Infeld B, Mitchell PJ, Davis SM. Microemboli during carotid angiography: association with stroke risk factors or subsequent magnetic resonance imaging changes? *Stroke.* 1996;27:1543-1547.
32. Newman S. The incidence and nature of neuropsychological morbidity following cardiac surgery. *Perfusion.* 1989;4:93-100.
33. Vingerhoets G, Jannes C, De Soete G, Van Nooten G. Prospective evaluation of verbal memory performance after cardiopulmonary bypass surgery. *J Clin Exp Neuropsychol.* 1996;18:187-196.
34. Vingerhoets G, De Soete G, Jannes C. Relationship between emotional variables and cognitive test performance before and after open-heart surgery. *Clin Neuropsychol.* 1995;9:198-202.
35. Schmidt R, Fazekas F, Offenbacher H, et al. Brain magnetic resonance imaging in coronary artery bypass grafts: a pre- and postoperative assessment. *Neurology.* 1993;43:775-778.
36. Toner I, Peden CJ, Hamid SK, Newman S, Taylor KM, Smith PLC. Magnetic resonance imaging and neuropsychological changes after coronary artery bypass graft surgery: preliminary findings. *J Neurosurg Anesthesiol.*1994;6:163-169.
37. Simonson TM, Yuh WTC, Hindman BJ, Embrey RP, Halloran JI, Behrendt DM. Contrast MR of the brain after high-perfusion cardiopulmonary bypass. *AJNR Am J Neuroradiol.* 1994;15:3-7.
38. Moody DM, Brown WR, Challa VR, Stump DA, Reboussin DM, Legault C. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. *Ann Thorac Surg.* 1995;59:1304-1307.
39. Vanninen E, Vanninen R, Äikiä M, Tulla H, Könönen M, Koivisto K, Partanen J, Partanen K, Hippeläinen M, Kuikka J. Frequency of carotid endarterectomy-related subclinical cerebral complications. *Cerebrovasc Dis.* 1996;6:272-280.
40. Gilman S. Cerebral disorders after open-heart operations. *N Engl J Med.* 1965;272:489-498.
41. Mills SA. Cerebral injury and cardiac operations. *Ann Thorac Surg.* 1993;56(suppl):S86-S91.
42. Moody DM. A new role for radiologists in the development of cardiac surgery. *AJNR Am J Neuroradiol.* 1991;12:815-816.

Correction

Error in Text. In the article entitled "Sex Differences in Brain Aging: A Quantitative Magnetic Resonance Imaging Study," published in the February issue of the ARCHIVES (1998;55:169-179), the coefficient for increased age associated with increased volumes of the lateral ventricles was incorrectly stated on page 172 in the paragraph subtitled "Age Main Effects," last sentence. The sentence should have read as follows: "Increased age was also associated with increased volumes of the lateral ventricles (coefficient=0.88, $P<.001$) and the third ventricle (coefficient=0.05, $P<.001$)."