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Gender differences in age effect on brain atrophy measured by magnetic resonance imaging

(brain volume/cerebrospinal fluid volume/neuroimaging/hemispheric specialization)

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ABSTRACT **A prospective sample of 69 healthy adults, age range 18–80 years, was studied with magnetic resonance imaging scans (T_2 weighted, 5 mm thick) of the entire cranium. Volumes were obtained by a segmentation algorithm that uses proton density and T_2 pixel values to correct field inhomogeneities ("shading"). Average (±SD) brain volume, excluding cerebellum, was 1090.91 ml (±114.30; range, 822.19–1363.66), and cerebrospinal fluid (CSF) volume was 127.91 ml (±57.62; range, 34.00–297.02). Brain volume was higher (by 5 ml) in the right hemisphere ($P < 0.0001$). Men ($n = 34$) had 91 ml higher brain and 20 ml higher CSF volume than women ($n = 35$). Age was negatively correlated with brain volume [$r(67) = -0.32$, $P < 0.01$] and positively correlated with CSF volume ($r = 0.74$, $P < 0.0001$). The slope of the regression line with age for CSF was steeper for men than women ($P = 0.03$). This difference in slopes was significant for sulcal ($P < 0.0001$), but not ventricular, CSF. The greatest amount of atrophy in elderly men was in the left hemisphere, whereas in women age effects were symmetric. The findings may point to neuroanatomic substrates of hemispheric specialization and gender differences in age-related changes in brain function. They suggest that women are less vulnerable to age-related changes in mental abilities, whereas men are particularly susceptible to aging effects on left hemispheric functions.**

The study of brain regulation of human behavior requires measurement of structural variables, and this has been done primarily by postmortem studies (e.g., refs. 1–6). Atrophy was inferred from reduced brain weight or volume or increased differences between brain volume and cranial capacity—i.e., cerebrospinal fluid (CSF) volume. Several studies found aging associated with atrophy (7–9). Others did not find age effects until senescence (usually defined as age >55 or 60; refs. 4, 10, and 11). Women have lower brain volume, related to body and cranial size (e.g., refs. 4, 6, and 9).

In vivo measurement of brain volume became feasible with computed tomography, and more recently with magnetic resonance imaging (MRI), which is more sensitive than computed tomography for determining sulcal changes and has better tissue contrast, multiplanar imaging capabilities, absence of bone artifact, and no ionizing radiation. In addition to elucidating structural substrates of brain function, anatomic volume measures are important for interpreting metabolic data (12). Thus, decline in cerebral blood flow and metabolism with age (e.g., refs. 13–15), and higher cerebral blood flow in women (16), could be explained by structural effects (17).

Several computed tomography studies investigated age-associated changes. Takeda and Matsuzawa (18) measured supertentorial CSF volume in 176 men and 205 women, aged 21–79, "without neurologic disturbances." Both CSF and a "brain atrophy index" (percent CSF volume relative to the cranial cavity volume) increased with age (see also ref. 19). Steiner *et al.* (20) examined parameters of brain volume in 148 neurologically intact subjects, aged 28–84 years. They reported that aging was associated with loss of brain substance, both cortical and central.

Using MRI, Grant *et al.* (21) examined 64 normal volunteers (25 men and 39 women, aged 18–64 years), with a 0.15-T magnet and a sequence yielding maximal separation of CSF from brain tissue. They reported increased CSF volume with age in both genders. The increase for ventricular CSF was significant for men but not for women. Condon *et al.* (22) measured brain volumes in 40 normal volunteers (20 men and 20 women) and reported a decrease between the ages of 20 and 60 years. The negative correlation between brain volume and age increased when brain volume was normalized to cranial volume to control for cohort effects. The decline was significant in men but not in women. If it is upheld that women show less effects of aging on brain atrophy, this may suggest a protective influence for female sex hormones.

Yoshii *et al.* (17) reported no decline in a sample of 58 subjects aged 21–81 studied with a 2-T magnet and a spin-lattice relaxation time (T_1)-weighted sequence. However, in contrast to the other studies, which yielded brain volume estimates averaging 1100–1200 ml, their estimates were >2000 ml for men and >1800 ml for women. Jernigan *et al.* (23) found a linear reduction in brain volume and an increase in CSF with age, but gender differences were not examined.

The difficulty in volumetric analysis of magnetic resonance images is that there are region-dependent intensity distortions related to interactions of the magnetic field surrounding the image space ("shading"). In brain image segmentation, this precludes conventional pixel value thresholding, which is the basis of most three-dimensional analysis algorithms (24). Slice thickness also introduces error in the interpolation process, which is compounded when dealing with complex geometric structures such as sulcal CSF spaces.

We assessed age-associated changes in a prospective normative sample across the age range of 18–80 years. Improvements were (*i*) a higher field magnetic resonance imager producing smaller pixels and better resolution for a given time, (*ii*) standard image acquisition protocols for proton density scans and spin-spin relaxation time (T_2)-weighted images, and (*iii*) a computerized volumetric image analysis method with established reliability and validity. Results are

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Abbreviations: MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; VCR, ventricular CSF-to-cranial volume ratio; SCR, sulcal CSF-to-cranial volume ratio; MANOVA, multivariate analysis of variance.

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reported for the whole brain, and ventricular (central) and sulcal (cortical surface) CSF are compared for slices containing ventricles. We tested the hypothesis that aging is associated with brain atrophic changes (i.e., reduced brain volume and increased CSF volume). Gender differences and hemispheric asymmetry are also evaluated.

SUBJECTS AND METHODS

Subjects. The sample of 69 volunteers included 34 men aged 18–80 years (mean ± SD = 41.35 ± 20.66) and 35 women aged 18–77 years (44.49 ± 20.15). The mean difference is not significant [$t(67) < 1$], and the genders did not differ in years of formal education (men, 15.12 ± 2.04; women, 14.54 ± 2.05; range, 12–18 for both genders; $t = 1.17$, P not significant) or on a 9-point scale assessing sociodemographic background (men, 5.22 ± 2.14; women, 5.67 ± 2.33; range, 1–9 for both genders; $t < 1$).

Subjects underwent medical, neurological, and structured psychiatric evaluations (25), including laboratory tests. They also received neuropsychological testing, including sections of the Wechsler Adult Intelligence Scale (revised) and mental status evaluation. Subjects were screened for history of disorders that can affect brain function (e.g., central nervous system infection, seizure, head trauma with loss of consciousness, cerebrovascular disease, cognitive decline, alcohol or other substance abuse) and psychiatric disorders in first-degree relatives. Two men and one woman were left-handed.

MRI Measurement. *Scanning.* MRIs were acquired on a GE Signa 1.5-T scanner. Sagittal imaging used a repetition time of 600 and an echo time of 20 msec. Axial images for quantitative analyses were in contiguous 5-mm interleaved slices parallel to the canthomeatal axis, a repetition time of 3000 and an echo time of 30 and 80 msec.

Neuroradiologic evaluation of MRI. Because of variability in the size of cisterna magna and basilar cisterns, anatomic demarcation of the infra- from supratentorial compartment on axial planes requires precise neuroanatomic knowledge. The following problems were encountered. (*i*) Often the occipital lobes projected onto the same section as the cerebellar hemispheres and brain stem. Because the tentorium slopes superiorly centrally, the margins have to be reconciled, and CSF in the superior cerebellar and quadrigeminal plates cisterns has to be subtracted. (*ii*) The sella turcica and pituitary was excluded since this is outside the dural covering of the brain, and enlargements of CSF space in and around the pituitary gland depend upon the intactness of the diaphragma sella. However, CSF in the chiasmatic cistern was included. (*iii*) For the uppermost portion of the midbrain and the cisterns anterior to it, a line was drawn connecting the two cerebral peduncles with the basilar artery, and the brain stem posterior to this was excluded. The most superior portion of the midbrain and the CSF in the chiasmatic cistern anterior to it, along with the hypothalamus and mammillary bodies, tuber cinereum and infundibular stalk, and optic chiasm, were included. (*iv*) A difficult area is the posterior third ventricle and velum interpositum, the cleft of CSF superior to the posterior third ventricle. This is a difficulty when volumes of CSF within the third ventricle need to be calculated separately from the remaining ventricular volume. In the axial plane it was frequently impossible to separate CSF in the velum interpositum from that within the third ventricle. Therefore, third ventricle volumes were not analyzed.

Volumetric analysis technique. Our approach (26) uses two independent properties of the object that influence the image: proton density and T_2. With a multiecho acquisition protocol, these properties can be isolated as multiple, spatially registered, independent features of brain. Distributions of pixel values in the image are generated for each feature, and discrete clusters are identified representing tissue classes. Classes that can be visualized can be resolved mathematically in a "feature space" plot. Shading artifact distorts the shape of the cluster, but even in severe shading the ability to segment CSF and brain is preserved.

The segmentation program was written in C and implemented on a Unix-based Sun workstation. It retrieves MRI data and headers from tape, using Sunview programming tools to design the window and icon-based interface. Operator interaction is minimized by automatic cluster separation and volume calculations. It is required for guiding the boundary separating brain and CSF from skull and for drawing the regions of interest and midline by line tracing with the mouse. These definitions are saved with the volume and segmentation data. For cluster separation, the user identifies the general location of clusters to be segmented. The program performs a regions-growing operation, gathering local statistics of each cluster, until it can reliably separate them. Volume calculation is based on the segmented slice data.

Validation. The program was tested in phantom studies with agarose gel and graphite powder. The details are in Kohn *et al.* (26). Briefly, 12 phantoms were constructed, 8 simple cylindrical and 4 complex phantoms. In the first set, phantoms of 1% (wt/vol) liquid agarose of volumes ranging from 5 to 35 ml were poured into cylindrical molds. Once hardened, the agarose was removed, and the volumes were measured by oil displacement in a graduated cylinder (±0.5 ml). The volumes ranged from 4.5 to 32.5 ml. Subsequently, each cylindrical chunk was embedded in a larger container of 1% (wt/vol) agarose, which also contained 0.5% (wt/vol) graphite. To assure uniform distribution of graphite particles, these larger containers were gently rotated while the surrounding agarose gelled. To construct the more geometrically and morphologically complex phantoms, 1% agarose evenly mixed with 0.5% graphite powder was allowed to gel in four cylindrical molds. The volume of each gelled mass, measured by oil displacement, was dissected into small fragments ranging from coarse to fine and nonuniform in size and shape. The fragments from each gelled mass were then embedded into a larger container of 1% agarose, which did not contain graphite, and evenly dispersed by mixing. After gelling of the surrounding graphite-free agarose, the embedded graphite-containing pieces attained random orientations and positions and mimicked the natural boundary of CSF and brain. The complex phantoms ranged from 16.5 to 20.5 ml. Two phantoms were constructed to contain 12 small irregular fragments, the third contained four medium-sized crossed hemicylinders, and the fourth had two large crossed hemicylinders.

The algorithm achieved a correlation of $r = 0.998$ for volume estimates by using the same scanning sequence under three different slice orientations (axial, sagittal, and coronal), slice thicknesses, and times. It was applied independently by two operators, and the intraclass correlation was 0.998. Its volume estimates were within 1.6 ml of the actual volume (measured by liquid displacement), yielding a root-mean-square error of 0.91 ml (25). This compares favorably with published standards (27, 28).

The interoperator reliability of the program was examined in a sample of 10 randomly selected brain scans analyzed by three operators (M.K., S.M.R., and P.D.M.). The pairwise correlations for brain and ventricular and sulcal CSF volumes ranged from 0.96 to 0.99, and the intraclass correlations were all >0.94. For the present study, a fourth operator (D.B.) was trained on these 10 scans to an intraclass correlation of 0.95 with the other three raters before analyzing a subsample of the scans.

MRI data processing. Each scan was analyzed by two of the operators independently. The correlations were 0.977 for

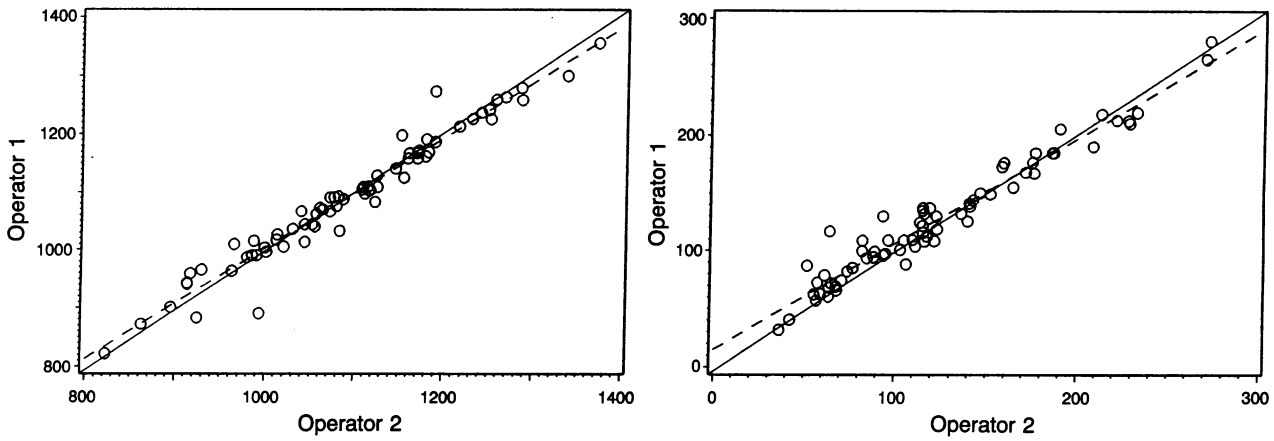

FIG. 1. Scatter plots and identity (solid line) and regression (dashed line) lines showing interoperator reliability of segmentation for brain volume (*Left*) and CSF volume (*Right*).

brain and 0.977 for CSF and, within CSF, 0.995 for ventricular and 0.973 for sulcal CSF volume (Fig. 1).

Statistical Analyses. The average of the two operators was used for analyses. To test the main hypothesis, brain and CSF volume, summed across all slices, was correlated (product-moment) with age. Secular effects were examined by correlating age with cranial volume (brain plus CSF). Partial correlations were also calculated, removing age correlations, with cranial volume.

A limited regional analysis examined age group, gender, and laterality effects. Age groups were obtained by dividing subjects into young (age <55, $n = 34$; 23 men and 20 women) and elderly ($n = 25$; 11 men and 15 women).§ The analyses were as follows: (*i*) Whole-brain volumes of brain and CSF were the dependent measures in a multivariate analysis of variance (MANOVA) (SAS general linear model procedure; ref. 26), with age group and gender as grouping factors and laterality (left and right) as a within-group (repeated-measures) factor. (*ii*) CSF was further subdivided into ventricular and sulcal, and a brain atrophy index (18) was calculated as ventricular CSF-to-cranial and sulcal CSF-to-cranial volume ratios (VCR and SCR, respectively). Only slices that contain both ventricular and sulcal CSF were included in this analysis to assure an equivalent cranial segment. These were dependent measures in a MANOVA, with age group and gender as grouping factors and hemisphere and ventricles vs. sulci as within-group factors. Interactions were decomposed with bonferroni-corrected univariate contrasts, and the percent VCR and the percent SCR were plotted by using SASGRAPH. The analyses were repeated with height and weight as covariates.

§Age was entered as a grouping factor for the specific purpose of examining the laterality effect, since the two hemispheres yield highly correlated data and we are interested in contrasting them. The age × gender groups did not differ in education or in age within gender P values > 0.2).

RESULTS

Average (±SD) brain volume was 1090.91 ml (±114.30; range, 822.19–1363.66), and CSF volume was 127.91 ml (±57.62; range, 34.00–297.02). For men, brain volume was 1137.36 (±100.51; range, 937.58–1363.66), 91 ml higher than that for women (1045.79 ± 109.86; range, 822.19–1272.68) [$t(67) = 3.22$, $P = 0.002$]. CSF volume was also higher in men (137.90 ± 62.80; range, 58.89–297.0) than in women (118.21 ± 51.13; range, 34.00–267.35) ($t = 3.69$, $P < 0.0005$).

Correlation of Volumes with Age. Age was negatively correlated with brain volume [$r(67) = -0.32$, $P < 0.01$] and positively correlated with CSF volume ($r = 0.74$, $P < 0.0001$) (Fig. 2). Partialling out cranial volume, these correlations increased to −0.56 and 0.76 (both $P < 0.001$). The slope of the regression with age did not differ for genders on brain volume but was steeper for men on CSF [$F(1, 65) = 4.93$, $P = 0.029$]. There was no correlation between age and cranial volume [$r(67) = 0.05$, P not significant], hence no secular effect was evident.

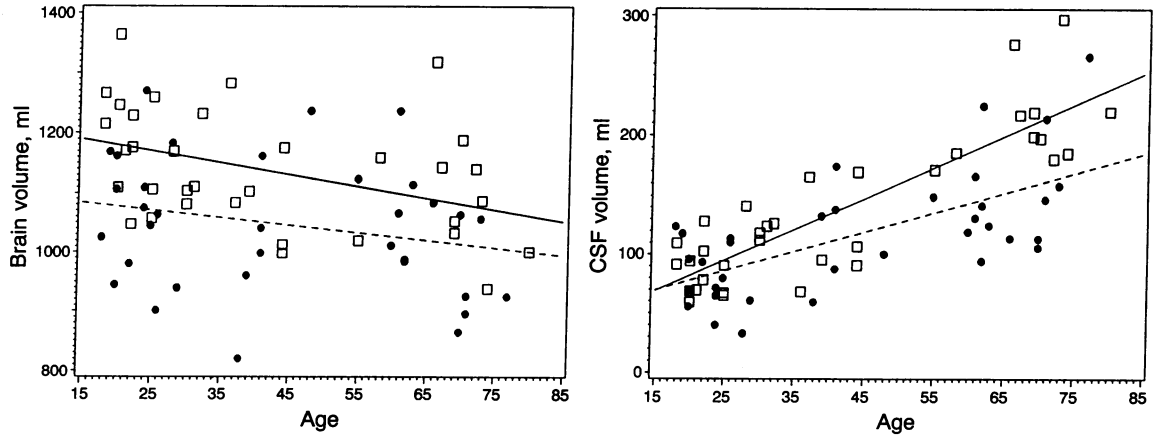

FIG. 2. Scatter plots and regression lines showing the relationship between age and brain volume (*Left*) and age and CSF volume (*Right*). The values for the men are represented by squares and a solid regression line, and the values for women are represented by circles and a dashed regression line.

Table 1. Means ± SD by age and gender groups for age and for left (L) and right (R) hemispheric volumes of brain (BR) and cerebrospinal fluid (CSF) and, within CSF, for ventricular (VEN) and sulcal (SUL) volumes

	Young		Elderly	
	Men (n = 23)	Women (n = 20)	Men (n = 11)	Women (n = 15)
Age	28.4 ± 8.6	28.7 ± 9.2	68.5 ± 7.1	65.6 ± 6.1
BR				
R	580.7 ± 47.0	532.8 ± 59.4	551.3 ± 53.2	514.5 ± 48.1
L	575.5 ± 47.7	529.3 ± 57.9	546.7 ± 53.2	509.5 ± 51.3
CSF				
R	50.4 ± 14.8	45.8 ± 19.3	103.8 ± 21.4	76.7 ± 23.2
L	51.3 ± 16.8	46.6 ± 17.2	109.8 ± 19.5	75.8 ± 25.8
VEN				
R	8.4 ± 3.9	6.3 ± 2.7	16.6 ± 6.8	13.5 ± 12.0
L	7.7 ± 3.3	7.6 ± 2.9	19.9 ± 7.3	14.0 ± 13.0
SUL				
R	42.0 ± 14.7	39.4 ± 19.5	87.2 ± 19.1	63.2 ± 19.0
L	43.6 ± 15.9	39.0 ± 17.7	89.9 ± 18.2	61.9 ± 21.3

(i) Regional analysis of whole-brain volumes. Means for the age and gender groups by hemisphere are given in Table 1. The MANOVA on brain volume showed a main effect for gender, men having higher volumes [$F(1, 65) = 10.35$, $P = 0.002$], and a marginal effect for the age group, young subjects having higher volumes ($F = 3.39$, $P = 0.07$). There was a main effect for hemisphere ($F = 19.06$, $P < 0.0001$), with the right hemisphere having a slightly (about 5 ml) higher brain volume. This small effect is significant because of its consistency; only 19 subjects had a higher left hemispheric brain volume. There were no interactions. For CSF, there were main effects for gender, (higher for men; $F = 13.64$, $P < 0.0005$) and age group (lower for the young age group; $F = 81.58$, $P < 0.0001$). There was a gender × age group interaction ($F = 7.36$, $P = 0.008$), reflecting a more pronounced elevation in CSF for older men than for women.

(ii) Ventricular and sulcal ratios. As for whole-brain CSF volumes, there was a main effect of gender [with higher values for men; $F(1, 65) = 13.02$, $P = 0.0006$], age group (with higher values for the elderly; $F = 96.79$, $P < 0.0001$), and a gender × age group interaction ($F = 11.06$, $P = 0.0015$). Elderly men had disproportionately high atrophy indices.

Ratios were higher for sulci than ventricles ($F = 94.25$, $P = 0.0001$), and this difference was larger for men, as indicated by a gender × VCR vs. SCR interaction ($F = 7.88$, $P = 0.0066$). For VCR alone the effect of age is significant ($P = 0.0001$), older subjects having higher values, and there is no gender difference. For SCR both age group and gender differences (higher values for men) are significant (P values = 0.0001). An age group × VCR vs. SCR interaction ($F = 22.62$, $P = 0.0001$) demonstrated a greater increase in sulcal than in ventricular ratios with age (Fig. 3). The three-way interaction of age group × gender × VCR vs. SCR was also significant ($F = 9.10$, $P = 0.0037$). As shown in Fig. 3, this reflects lopsidedly high sulcal ratios for elderly men. Indeed, the age group × gender interaction did not approach significance for VCR ($P = 0.5162$) but was highly significant for SCR ($P = 0.0001$). Whereas for the young group there were no gender differences in either VCR or SCR ($P = 0.5822$ and 0.9356, respectively), older men had equal VCR ($P = 0.4858$) but substantially higher SCR ($P = 0.0001$) than older women.

Hemispheric Asymmetry. There was a main effect of hemisphere, with higher atrophy ratios in the left hemisphere (Fig. 4) ($F = 25.72$, $P = 0.0001$). This asymmetry was more pronounced in men, as indicated by a gender × hemisphere interaction ($F = 4.53$, $P = 0.0371$). However, a stronger gender × age group × hemisphere interaction ($F = 10.69$, $P = 0.0017$) showed that this was primarily attributable to elderly men. Atrophy ratios were higher for the left hemisphere in elderly men compared to all other groups (all P values <0.005). The gender × age group × hemisphere interaction was significant for VCR ($F = 10.97$, $P = 0.0015$) but not for SCR ($F = 2.01$, $P = 0.1608$, P not significant). Thus, elderly men had higher left hemispheric VCR. No higher order interactions approached significance (all P values >0.1).

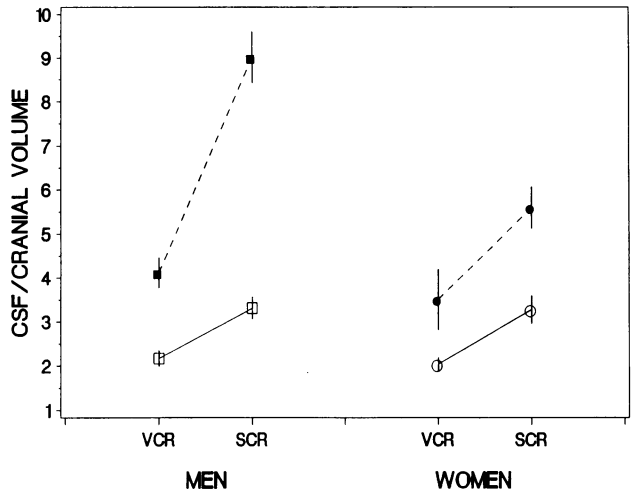

FIG. 3. Means ± SEM of the percent SCR and the percent VCR for young men (□), elderly men (■), young women (○), and elderly women (●).

Age was uncorrelated with education ($r = 0.09$), height ($r = 0.16$), or weight ($r = 0.07$, all P not significant), and the multivariate analysis of covariance partialling out their effects did not alter the findings. Detailed results are available from the authors.

DISCUSSION

Our results support the hypothesis of neural atrophy associated with normal aging, showing increased CSF relative to brain volume. The means and range of values are comparable with earlier reports.¶ (1–6, 9, 18, 21, 22). We also found support for the notion that normalizing brain volume to cranial volume increases

¶Allowing for variability in tissue included and the effects of fixatives in postmortem studies. In the comparable study of Grant *et al.* (21) the mean for CSF volume was 126.80 (range, 57.1–286.5).

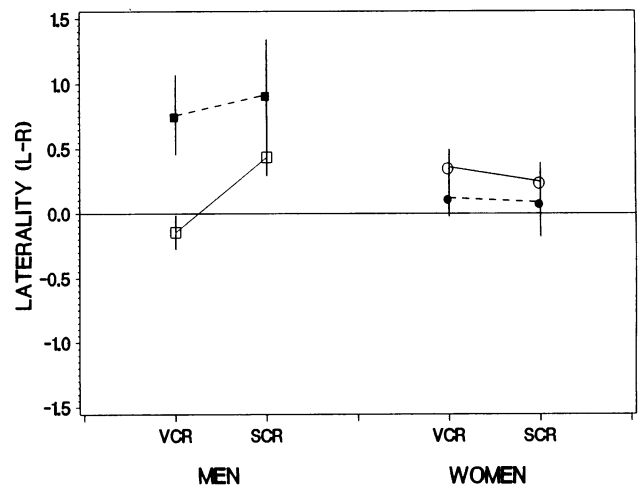

FIG. 4. Means ± SEM of laterality (left-right) for SCR and VCR. Notations are as in Fig. 3.

the correlations with age (22), and all effects sustained controlling for education, height, and weight. Screening criteria make it unlikely that these age-associated findings are a by-product of brain diseases, which may differentially affect the elderly. The lack of correlation between total cranial volume and age and between education and age militate against a secular effect, although caution is appropriate as with any cross-sectional study of aging. Also, the design of the study optimized comparison of young to elderly subjects. We did not evaluate the shape of the curve describing the relationship between brain atrophy and age throughout the age range to determine whether it is linear rather than accelerating at a certain age. This would require a larger sample in the fourth and fifth decade. However, it is noteworthy that Jernigan *et al.* (23) reported linear relationships with age for all measures comparable to the present study.

The additional findings concern gender differences, comparison of sulcal and ventricular CSF, and laterality. The aging effect was greater in men. Condon *et al.* (22) found an age effect in men but not in women, whereas Grant *et al.* (21) did not find a gender difference in slopes. The findings in the present study, where earlier studies reported only suggestive trends, may reflect the larger sample and age range.

Our analyses further showed a differential effect of age on sulcal compared to ventricular CSF. Aging was associated with more pronounced sulcal atrophy. Here too there was a gender difference; this differential effect was stronger in men. These gender differences suggest that female sex hormones may protect the brain from atrophy associated with aging. They also suggest neural substrates to gender differences in aging effects on cognitive performance (29).

Laterality was not examined before, and we report higher right hemispheric brain volume for the whole brain across groups and greater effect of age on atrophy in the left ventricles of men. The first effect is statistically significant but small (5 ml, or about 1% of hemispheric volume), and speculations on its functional significance seem premature. A systematic spatial distortion of the MRI is unlikely to have affected brain and CSF values (particularly sulcal CSF) differentially. Considering the rather prominent functional differences between the two hemispheres in humans, surprisingly few anatomic asymmetries have been reported. These include longer sylvian fissure and larger planum temporale in the left (30), generally deeper fissuration in the left (31), larger frontal regions in the right (32), larger temporal lobe in the right (27), and a higher left hemispheric percentage of gray matter (16, 33, 34).

The pronounced central atrophy in aging men in the left is consistent with evidence from neurophysiologic studies suggesting similarly lateralized age effects on cerebral blood flow (35). Studies of gender differences in the development of hemispheric specialization suggest that the left hemisphere shows latest maturation in boys (reviewed in ref. 36). Perhaps brain regions that have matured last are more susceptible to adverse effects of aging. Direct tests of this hypothesis would require MRI studies of children.

The present study may help us understand neural substrates of behavioral changes associated with aging. A more refined investigation would entail examination of specific brain regions and further segmentation of tissue. For example, other magnetic resonance pulse sequences can be used to optimize separation of gray and white matter. The present scanning orientation is used in many settings, permitting replication. However, other orientations such as coronal slices can help better define certain regions. It would also be important to correlate the anatomic variables to neurophysiologic and behavioral measures. The present methodology is amenable to such a study.

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