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Age-related changes in intracranial compartment volumes in normal adults assessed by magnetic resonance imaging

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✔ Magnetic resonance (MR) image–based computerized segmentation was used to measure various intracranial compartments in 49 normal volunteers ranging in age from 24 to 80 years to determine age-related changes in brain, ventricular, and extraventricular cerebrospinal fluid (CSF) volumes. The total intracranial volume (sum of brain, ventricular, and extraventricular CSF) averaged 1469 ± 102 cm^3 in men and 1289 ± 111 cm^3 in women. The difference was attributable primarily to brain volume, which accounted for 88.6% of the respective intracranial volumes in both sexes, but was significantly larger in men (1302 ± 112 cm^3) than in women (1143 ± 105 cm^3). In both, the cranial CSF volume averaged 11.4%. Total intracranial volume did not change with age, although the normalized brain volume of both men and women began to decrease after the age of 40 years. This decrease was best reflected by expansion of the extraventricular CSF volume which, after the age of 50 years, was more marked in men than in women.

The volume of the cranial CSF, as determined by MR image-based computerized segmentation, is considerably larger than traditionally accepted and resides mostly extraventricularly. Expansion of CSF volume with age provides a good index of brain shrinkage although evolving changes and growth of the head with age tend to confound the results.

KEY WORDS • cerebrospinal fluid • brain • cerebral ventricles • magnetic resonance imaging • volumetric study

MANY attempts have been made to measure the volume of the various intracranial compartments in humans. Most investigators have used traditional volumetric methods (casts) to make such measurements, which generally have been limited to measurement of the brain and/or ventricular size.[5,27,37] The use of fresh or fixed autopsy material has led to the introduction of various artifacts attributable to post mortem swelling and/or shrinkage due to fixation. Extraventricular cerebrospinal fluid (CSF) volume has been difficult to assess by these methods, including computerized tomography (CT), because of the unavoidable introduction of artifacts, insufficient resolution to depict the entire sulcus system, and the inadequate contrast between the brain and CSF. Many of these artifacts are avoided or minimized with the use of magnetic resonance (MR) imaging, which provides enhanced contrast discrimination and resolution of the various cranial compartments.[8,9,24,36] In the present study we have used MR image–based segmentation[35,39] to measure the brain, ventricular, and extraventricular CSF volumes of normal volunteers.

Clinical Material and Methods

Population Studied

This study was reviewed and approved by the institutional human research committee and all individuals studied provided informed consent prior to participation. A total of 26 male (54 ± 16 years of age, range 24–80) and 23 female (58 ± 16 years of age, range 29–79) volunteers underwent MR imaging of the head between March 1988 and November 1991. Twenty-three men 38 to 80 years old were selected from the database of the Normative Aging Study at the Boston Veterans Administration Outpatient Clinic, details of which have been provided previously.[1] The other 26 participants were selected from our own database, and although they did not undergo laboratory or neuropsychological testing as did those from the normative aging study, they were deemed to be free of any severe cardiovascular, neurological, or psychiatric disorder, including drug abuse and alcoholism.

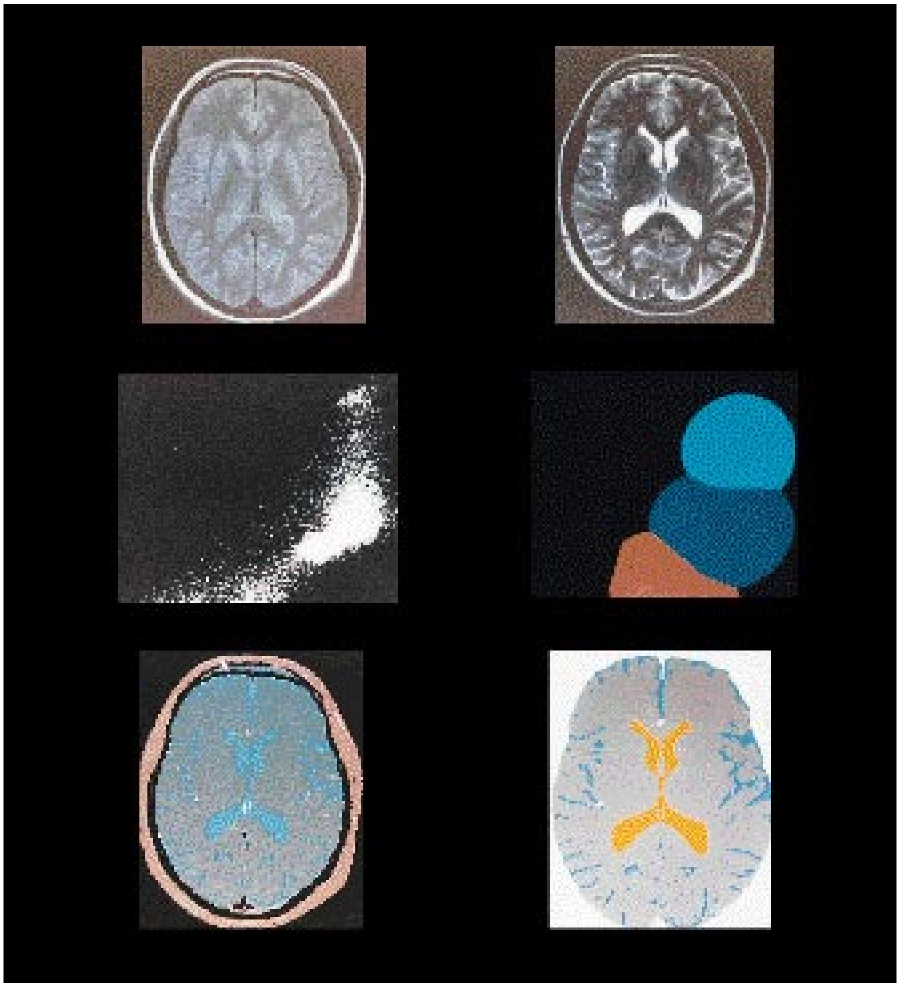

FIG. 1. a: Proton density magnetic resonance (MR) image of the brain in a normal subject. b: A T_2-weighted MR brain image in a normal subject. c: Scatterplot derived from a proton density (y-axis) and a T_2-weighted (x-axis) image. d: Calculated feature map derived from the scatterplot. Background is depicted as black, extracranial tissue as orange, brain as gray, and cerebrospinal fluid (CSF) as blue. e: Segmented image derived from the calculated feature map. f: Final segmented image in which background is depicted in black, brain in gray, ventricle CSF in yellow, and extraventricular CSF in blue.

Magnetic Resonance Imaging Procedures

Magnetic resonance images of the brain were obtained on a 1.5-tesla imaging system (Signa; General Electric Corp., Milwaukee, WI) using double-echo (echo times 30 and 80 msec), long-repetition time ((TR) 2000–4000 msec), multislice (interleaved 3- or 5-mm slice thickness), spin-echo data and 256 × 192 matrix, with a half Fourier technique. The images covered the entire brain from the vertex to the foramen magnum. The data were processed on a Sun Microsystem (Mountain View, CA). Initially, the double-echo long TR images were filtered[20] to improve the signal/noise ratio. Figure 1a and b shows paired proton density and T_2-weighted images that were obtained from one of our volunteers. A scatterplot (Fig. 1c) was derived by plotting the pixel signal intensities from the proton and T_2-weighted images in which the operator identified standard sampling points for each tissue category. Proton density images were used to identify air and bone for background and extracranial tissue. Because the CSF appears isointense on the proton density image and bright on the T_2-weighted image, the latter images were used to identify brain and CSF. The selected loci for brain were the frontal cortex, cerebellar cortex, dentate nucleus, head of the caudate nucleus, red nucleus, globus pallidus, internal capsule, cerebral penduncle, splenium, and genu of the corpus callosum, and for CSF the cerebellopontine and prepontine cisterns, and both of the anterior horns and trigone of the lateral ventricles. Each selected locus appears on the scatterplot, and computer interpolation was used to calculate the nearest neighbor and to create a feature map (Fig. 1d). The latter was then used to derive the segmented images (Fig. 1e) from which the computer automatically extracted the signal for extracranial tissues. Correction for ventricular CSF was made semiautomatically with a connectivity program[6] that generated the final segmented image (Fig. 1f). The areas in square centimeters were then calculated from the final segmented image

TABLE 1

Mean age and number of individuals in the three groups of normal adults studied for age-related changes in brain volume

Sex, Age (yrs)	Age Group	Mean Age ± SD*	No. of Cases
both sexes		56 ± 16	49
24–40	I	35 ± 6	12
41–60	II	50 ± 6	15
61–80	III	72 ± 5	22
all women		58 ± 16	23
29–40	I	36 ± 5	6
41–60	II	52 ± 7	5
61–79	III	71 ± 5	12
all men		54 ± 16	26
24–40	I	34 ± 7	6
41–60	II	48 ± 6	10
61–80	III	72 ± 5	10

* Abbreviation: SD = standard deviation.

by counting pixels, and the volume in cubic centimeters was generated by multiplying by the slice thickness. All image processing was done on an MR console with programs developed by General Electric and the Surgical Planning Laboratory of this institution. Segmentation and volumetric analysis were performed using methods that have been previously tested for accuracy and reliability.[7] Intracranial, brain, ventricular, and extraventricular CSF volumes were examined separately. Intracranial volume in cubic centimeters was calculated as the sum of the brain, ventricular, and extraventricular CSF volumes.

Values for the absolute or relative volume of the various intracranial compartments in men and women are reported either as sample means ± sample standard deviations (SDs) or as percentages of the intracranial volumes, respectively. The latter, referred to as regular volumes, do not require correction for the long-term increase in brain weight postulated to affect the population as a whole during the last century[43,50] because it can be assumed that such increases, which generally are attributed to such factors as improved nutrition and increased body stature, would affect brain and intracranial volume similarly. To determine the influence of age on these parameters, values for both women and men were sorted according to age into three 20-year age-span groups or plotted as a function of age in scatterplots. Table 1 shows the average age and SD and the number of people for each group.

Two different values for the TR and for the slice thickness were used. No significant difference was observed in the absolute and relative values for brain volume, extraventricular CSF, and ventricular volumes, when these two parameters were interchanged in controls.

Assessment of Error

To assess the error (SD/mean) of these measurements, segmentation and volumetric determinations were repeated three times on each of four men and four women ranging in age from 37 to 77 years who were selected randomly. To reduce bias, repeat measurements on each participant were separated by more than 1-month intervals. The repeat segmentation and volumetric determination of the eight selected cases indicated the errors to be 1.0%, 1.9%, 4.6%, and 7.7% for the respective intracranial, brain, ventricular, and extraventricular CSF volumes.

Statistical Methods

Analysis of variance was used for determination of statistical significance between the absolute intracranial compartment volumes and the relative values of the two sexes and the three age groups. Computer programs were used for statistical analysis and to derive best fitting curves (Figure-P; Biosoft, Ferguson, MO).

Results

Total Intracranial Volume

All subjects were sorted into three age groups, each covering two decades (Table 1). The absolute and relative mean values for the intracranial and brain volumes and the various CSF volumes for men and women are shown in Table 2, whereas the p values for comparisons between volumes are listed in Table 3. The average total intracranial volume was significantly greater ($p < 0.0001$) in men (1469 ± 102 cm^3) than in women (1289 ± 111 cm^3) and reached 1384 ± 139 cm^3 in all 49 subjects. With increasing age the total intracranial volumes of both men and women remained fairly constant, even though there was a tendency for the women's intracranial volume to increase when plotted against age (not shown). However, in all three age groups the men's intracranial volume remained significantly higher than that of the women.

Brain Volume

The mean brain volume in all participants was 1227 ± 135 cm^3 and was significantly larger ($p < 0.0001$) in men (1302 ± 112 cm^3) than in women (1143 ± 106 cm^3), as shown in Table 2. This difference between sexes decreased with age when the absolute brain volumes were compared, because the values for men decreased significantly faster (-4.7 cm^3/year; $p < 0.05$) than those for women (-0.6 cm^3/year), which remained almost stable. From the middle to the oldest age group the absolute brain volume declined significantly ($p < 0.001$) in the men, by 12% and was not significantly different from the value for women in the oldest age group. Interestingly, and in contrast to the absolute values, the relative brain volumes for both sexes were 89% overall. Likewise, when the individuals were divided by age, there was no difference between the sexes in relative brain volume (Table 2). When the relative brain volumes were plotted as a function of age (Fig. 2), the values for both sexes decreased with age, although less distinctly for women.

Cranial CSF Volume

The total cranial CSF volume averaged 157 ± 59 cm^3 in all subjects, 167 ± 67 cm^3 in men, and 146 ± 47 cm^3 in women and accounted for 11.4% of the intracranial volume in each case (Table 2). In both men and women the cranial CSF volume expanded with age, more markedly between the middle and old age group (men 63%, $p < 0.01$; women 53%, $p < 0.001$) than between the young and middle age group (men 28%, $p < 0.05$; women 26%, not significant). In each of the three respective age groups

TABLE 2

*Average values of absolute and relative brain compartment volumes in normal adults assessed by magnetic resonance imaging**

	Volume (cm^3)								
Sex & Age Group	Intracranial Absolute	Brain Absolute	Brain Relative	CSF Absolute	CSF Relative	Ventricular Absolute	Ventricular Relative	Extra-ventricular Absolute	Extra-ventricular Relative
both sexes	1384 ± 139	1227 ± 135	89 ± 4	157 ± 59	11 ± 4	25 ± 11	1.8 ± 0.8	133 ± 52	10 ± 3
I	1357 ± 133	1255 ± 126	93 ± 1	102 ± 21	8 ± 1	17 ± 5	1.3 ± 0.3	85 ± 21	6 ± 1
II	1427 ± 151	1293 ± 145	91 ± 2	134 ± 25	9 ± 2	19 ± 6	1.3 ± 0.5	115 ± 24	8 ± 2
III	1370 ± 133	1167 ± 108	85 ± 3	204 ± 54	15 ± 3	33 ± 10	2.4 ± 0.6	171 ± 49	12 ± 3
all women	1289 ± 111	1143 ± 106	89 ± 4	146 ± 47	11 ± 4	25 ± 11	1.9 ± 0.8	121 ± 40	9 ± 3
I	1257 ± 88	1162 ± 78	93 ± 1	95 ± 21	8 ± 1	15 ± 3	1.2 ± 0.2	80 ± 21	6 ± 1
II	1254 ± 98	1134 ± 110	90 ± 2	120 ± 15	10 ± 2	20 ± 6	1.6 ± 0.5	100 ± 17	8 ± 2
III	1320 ± 125	1137 ± 122	86 ± 2	183 ± 31	14 ± 2	32 ± 10	2.4 ± 0.7	151 ± 27	12 ± 2
all men	1469 ± 102	1302 ± 112	89 ± 4	167 ± 67	11 ± 4	25 ± 11	1.7 ± 0.7	142 ± 59	10 ± 4
I	1458 ± 82	1349 ± 89	93 ± 2	109 ± 21	8 ± 2	20 ± 4	1.4 ± 0.4	90 ± 22	6 ± 2
II	1513 ± 81	1373 ± 80	91 ± 2	140 ± 27	9 ± 2	18 ± 6	1.2 ± 0.4	123 ± 24	8 ± 2
III	1431 ± 122	1203 ± 80	84 ± 4	228 ± 66	16 ± 4	35 ± 10	2.4 ± 0.6	194 ± 60	13 ± 3

* Relative volumes are calculated as compartment volume/intracranial volume × 100% ± standard deviation. CSF = cerebrospinal fluid.

and in the groups as a whole the cranial CSF volume was consistently larger in men and in women, but the difference was statistically significant only for the oldest age group ($p < 0.05$). A continuous increase over the entire adult age span was observed when the relative cranial CSF volume was plotted as a function of age (Fig. 3), in which the rate tended to be greater in men (0.24%/year) than in women (0.18%/year).

Ventricular Volume

As shown in Table 2, the respective overall mean ventricular volumes for men and women were similar (25 cm^3). There was a significant difference between the sexes in the mean ventricular volumes for the youngest age group only ($p < 0.05$). On comparing ventricular volumes between the youngest and middle age groups, little or no change was found for either sex. However, a marked and significant increase in ventricular volume of men (94%, $p < 0.001$) and women (60%, $p < 0.05$) was noted between the middle and oldest age groups. When the relative ventricular volumes were plotted as a function of age (Fig. 4 *left*), it was apparent that the ventricular volume of men and women increased continuously, and at the same rate, with age. However, this was no longer evident when the

TABLE 3

*Comparison of brain compartment volumes in different age groups and between the sexes in normal adult volunteers**

	p Value								
Sex & Age Group	Intracranial Absolute	Brain Absolute	Brain Relative	CSF Absolute	CSF Relative	Ventricular Absolute	Ventricular Relative	Extra-ventricular Absolute	Extra-ventricular Relative
all									
I vs. II	—	—	<0.01	<0.01	<0.01	—	—	<0.01	<0.01
II vs. III	—	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
I vs. III	—	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
female									
I vs. II	—	—	—	—	—	—	<0.01	—	—
II vs. III	—	—	<0.01	<0.001	<0.01	<0.05	<0.05	<0.01	<0.05
I vs. III	—	—	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
male									
I vs. II	—	—	—	<0.05	—	—	—	<0.05	<0.05
II vs. III	—	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.01	<0.001
I vs. III	—	<0.01	<0.001	<0.001	<0.001	<0.01	<0.01	<0.01	<0.001
female vs. male									
I	<0.05	<0.01	—	—	—	<0.05	—	—	—
II	<0.001	<0.001	—	—	—	—	—	—	—
III	<0.05	—	—	<0.05	—	—	—	<0.05	—
all	<0.001	<0.001	—	—	—	—	—	—	—

* Statistical significances of differences were calculated by analysis of variance. Age groups are defined in Table 1. CSF = cerebrospinal fluid; — = no significant difference detected.

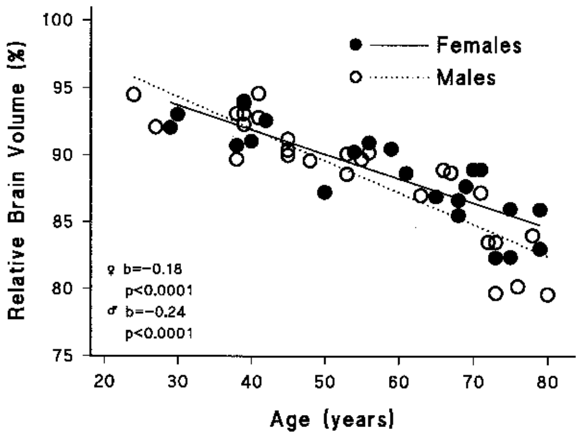

FIG. 2. Scatterplot showing relative brain volume as a percentage of intracranial volume plotted against age. All relative values are calculated as compartment volume/intracranial volume × 100%.

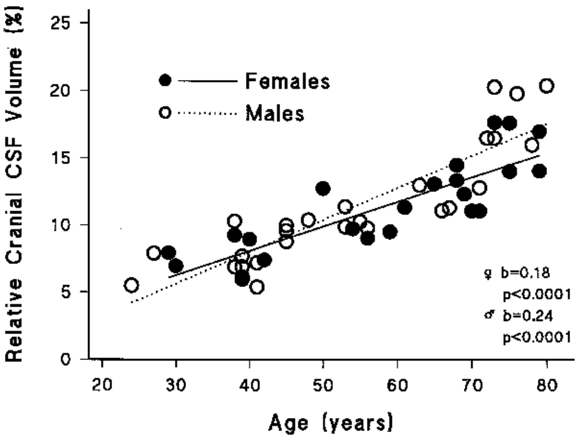

FIG. 3. Scatterplot showing the relative cranial cerebrospinal fluid volume plotted as a function of age.

relative ventricular volumes were plotted as a function of brain volume (Fig. 4 *right*). The relative ventricular volume of the men was significantly and inversely correlated with total brain volume (brain volume = -0.004, $p < 0.001$), whereas for women no such correlation was observed. This may be partially explained by the fact that the relative ventricular volume of the women may have been underestimated because of skull volume, which tended to increase with age. Additionally no age correlation was observed for brain volume in the women, so that one would not expect a correlation between the clearly age dependent relative ventricular volume and the brain volume.

Extraventricular CSF Volume

The overall average extraventricular CSF volume tended to be larger in men (149 ± 59 cm^3) than in women (121 ± 40 cm^3) (Table 2). Similarly, the mean extraventricular CSF values for each respective age group tended to be higher in men than in women, but were significantly different only for the oldest age group ($p < 0.05$). However, the extraventricular CSF volume of men as well as women increased with age, almost doubling over the 56-year age span of the participants; the most striking increase in extraventricular CSF volume was observed in both sexes between the middle and the oldest age group (male, 58%, female, 51%; $p < 0.01$ for both). Comparing the relative extraventricular volumes of the various age groups, no statistically significant differences were detected between the two sexes. But when the relative extraventricular CSF volumes were plotted as a function of age and as a function of brain volume, both men ($p < 0.01$) and women ($p < 0.05$) showed a significantly inverse correlation (Fig. 5 *left* and *right*).

Discussion

Various studies have shown that as the brain ages its weight and volume decrease and conversely the volume of the cranial CSF increases. This relationship of the brain and cranial CSF to aging is based primarily on studies made on autopsy material. Some studies have shown that values derived from such material are prone to errors attributable either to brain swelling after death or to shrinkage during fixation.[2,13,27,30,43,44,46,53] The introduction of pneumoencephalography made possible *in vivo* measurements of these compartments and consequently the circumvention of post mortem and fixation artifacts. However, such studies were mostly limited to measurement of linear dimensions and the calculation of various ratios used as indices of ventricular enlargement or brain atrophy.[14] Moreover, this approach had its own limitations, such as expansion of CSF compartments following introduction of air,[33,45] and because of its invasive nature, its restriction to patients with neurological disorders. Computerized tomography offers a much less invasive *in vivo* procedure to study brain structure and ventricular architecture, and many reports have appeared on the use of CT to measure ventricle volume.[3,4,10,18,19,47,49,60] Unfortunately, because of the difficulty in distinguishing true extraventricular CSF from brain, due to artifacts produced by calvarial bone and to inadequate contrast and poor resolution on CT images, only a few attempts have been made to measure the cranial extraventricular CSF volume.[18,19,47,60] Such image artifacts are minimized with MR imaging, which allows for better contrast and resolution, and thus a more accurate measurement of the extraventricular CSF space.

Intracranial and Brain Volume

Age-related decrease in the weight of adult brains has often been noted in cross-sectional studies. Some investigators have questioned whether such decreases are due to aging, because it is known that the stature of humans, as well as the size of the head and brain, has increased during the last century.[44,50] Thus, it is argued that the decrease in brain weight or volume observed in cross-sectional studies may reflect this trend; those born earlier in the century would have on average smaller heads and brains than those born later. However, in a study of 130 cadavers of normal men and women, Miller and Corsellis[43] found that even after correction for the effects of fixation and long-term increase in brain size, the volume of the cerebellar

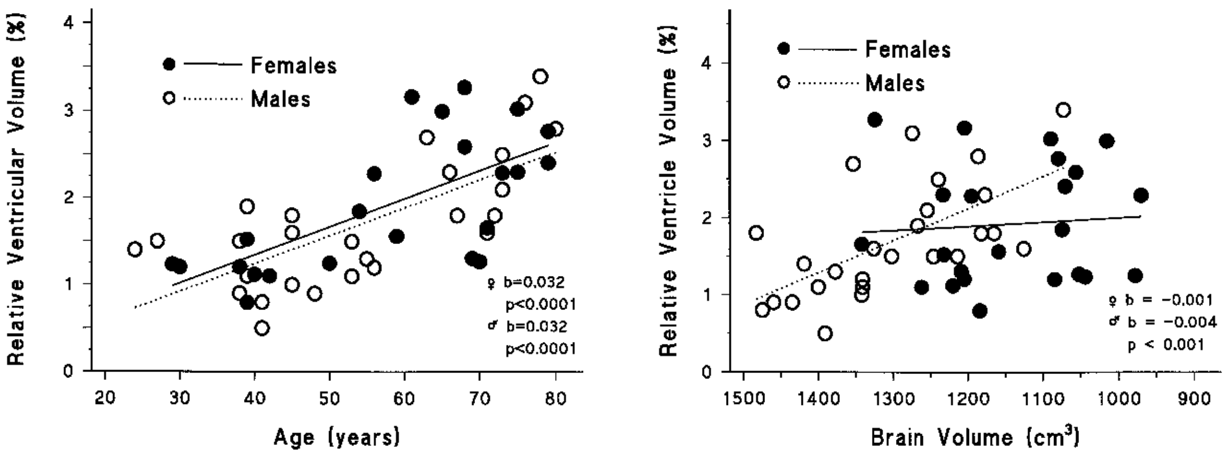

FIG. 4. Scatterplots showing relative ventricular volume plotted against age *(left)* and brain volume *(right)*.

hemispheres of both men and women over the age of 50 declined approximately 2% per decade.

Davis and Wright[11] used autopsy material obtained from 87 normal brains in persons ranging from 22 to 94 years of age and measured brain and intracranial volume. They noted that the brain/intracranial volume ratio, which remained constant from 22 to 55 years of age, decreased significantly thereafter. The authors reasoned that, because the long-term changes should have affected brain and intracranial volume similarly, the decrease in the ratio must be attributable to brain atrophy. This disparity between the change in cranial capacity and brain volume with age, which was noted by Rudolph[51] as early as 1914, also is apparent in our study, in which the intracranial volume either does not change (men) or has a tendency to increase (women) with age even though in both sexes brain volume decreases significantly. It is not clear from these cross-sectional studies why this discrepancy exists, because the observed increase in stature of humans over the last century has been noted in most populations. The most likely explanation is that the head size of humans, and consequently the intracranial volume, increases with age and that such changes mask the long-term trend that affects the population as a whole. This supposition is supported by the longitudinal studies of Finby and Kraft[16] and of Israel,[31] in which skull radiographs obtained in individuals spanning a 20-year period were compared and significant increases in head size were detected. However, Tallgren,[54] in a study of 32 women aged 20 to 73 years, in which lateral cranial films spanning intervals of 15 years were compared, found no change in the cranial vault or skull thickness with increasing age. In a more comprehensive study of normal aging, Friedlaender, *et al.*,[17] measured the head circumference, length, and breadth of more than 1800 veterans ranging in age from 22 to 80 years and found that in all decades of life the head size of individuals determined at two separate time intervals over a 5-year span increased significantly. Such cyclic and age-related trends act to confound the interpretation of results of cross-sectional studies because, although it is clear that the average brain volume of individuals is larger in the younger than in the older age groups, it is not possible to determine to what extent such changes are due to an aging process.

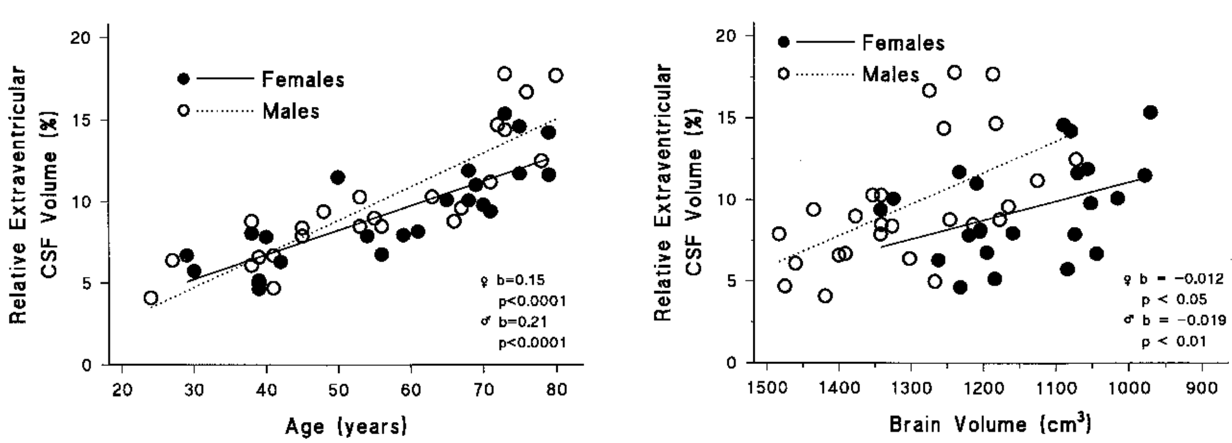

FIG. 5. Scatterplots showing relative extraventricular volume plotted against age *(left)* or as a function of brain volume *(right)*.

There is also some uncertainty as to when adult brain volume or weight begins to decrease. Some have reported that it starts as early as 25 years of age[2,13] but others suggest that its onset is much later in life.[11,30,43,52] In their study of normal adult cerebellar hemispheres Miller, *et al.*,[44] noted that the hemispheres decreased at a linear rate beginning at age 20 and that the rate was significantly greater in men than in women. However, when these values were corrected for the incremental increase reported in their earlier study, an age-related shrinkage of approximately 2% per decade was detected only after the age of 50 years. Moreover, in contrast to the studies of others who had reported brain shrinkage in men to be either faster[53] or slower[30] than in women, the corrected values indicated that the rate of decline was similar for both sexes.[43] Use of autopsy material in some of these studies may have contributed to these disparate results because ionic shifts occurring post mortem are known to alter the volume of the CSF as well as that of the intra- and extracellular compartments of the brain.[2] Furthermore, changes in brain weight, ranging from 1.4% to 8.5%, are known to occur during formalin fixation.[28,30,53] Obviously, these post mortem and fixation artifacts are avoided in *in vivo*, noninvasive techniques such as CT or MR imaging are used.

In our study only the average brain volume of men in the oldest age group is significantly smaller than that of the younger groups. However, when brain volumes of men and women are normalized to the intracranial volume, which in both sexes does not change significantly between the young and middle age groups, it appears that brain volume begins to decline after 60 years, which coincides with the onset of the gradual widening of the third ventricle as reported by LeMay.[38] The decline rate of the relative brain volume in the oldest age group accelerates more in men (0.53%/year) than in women (0.26/year), this compared with the overall decline rate of men (0.24%/year) and women (0.18%/year). This is in line with the divergence and decline rates in total fresh hemispheric volumes noted by Miller, *et al.*,[44] for 47 men (0.28%/year) and 44 women (0.15%/year) ranging from 20 to 98 years of age, and the decline rate of approximately 0.23% per year for the brain/intracranial volume ratio observed after 55 years of age in 87 normal adults.[11] This is also consistent with the observations of Yamaura, *et al.*,[59] who showed that the brain volume index decreased with age, but more dramatically after the age of 50 years. It is tempting to suggest that the long-term trend noted by Miller and Corsellis[43] is the predisposing factor in this divergence but it should be stated that all our volunteers were born after 1900 when, as noted by these investigators, the increase in brain weight for males and females was similar. Menopause may be a factor, as indicated by the studies of Grant, *et al.*,[23] which show that cranial CSF volume in women is significantly altered during the menstrual cycle.

It has long been held that because the brain and cranial CSF are contained within a rigid bony enclosure, changes in brain volume will be reflected by changes in the cranial CSF volume. The results of our study support this supposition although head size and intracranial volume are known to expand with age. For instance, as shown in Fig. 5 *right*, there is a significant correlation between brain volume and relative extraventricular CSF volume, and it becomes apparent that small changes in the volume of the much larger brain compartment will result in marked changes in the volume of the cranial CSF compartment. This indicates that analysis of changes in the relative cranial or ventricular and extraventricular CSF volumes as a function of age may provide good indicators of brain shrinkage.

Cranial CSF Volume

Cranial CSF volume averaged 167 ± 67 cm^3 in men and 146 ± 47 cm^3 in women and in both sexes accounted for 11.4% of the intracranial volume. These values are larger than those reported by Lups and Haan,[41] Weston,[58] Condon, *et al.*,[8] and others (Table 3). Gado, *et al.*,[18] did not provide actual volumes but reported the cranial CSF volume to be 11.4% of the total intracranial volume, a value identical to our relative intracranial CSF volume given above. In our study intracranial CSF volume increased at an average yearly rate of 3.4 cm^3 (2.8%) for men and 2.5 cm^3 (2.5%) for women. These values are slightly greater than those reported by Grant, *et al.*,[22] for a somewhat younger group of normal men (1.9%/year) and women (1.6%/year) whose age ranged from 18 to 64 years.

Ventricular Volume

In the present study the mean ventricular volume (25 ± 11 cm^3) is similar to the average ventricular volume (22.4 cm^3) reported by Last and Tompsett.[37] The later derived their volumetric measurements from ventricular casts made from brains of 24 normal individuals ranging in age from 29 to 73 years. Like us, they observed no difference between the ventricular volumes of men and women. However, in contrast to our results they reported no increase in this volume with age. Participants in our study showed no ventricular expansion between the youngest and middle age group, but between the middle and oldest age group there was a significant enlargement in ventricular volume. Although this observation is consistent with results from others,[28,32,47,49] it is not clear from such comparisons whether expansion of ventricular volume with age differs between men and women. Other groups using casting methods and autopsy material have reported smaller[5] (< 20 cm^3) and larger[26] (30 ± 19 cm^3) mean ventricular volumes than ours. Unfortunately, many of these studies fail to provide the age range of their material and/or the cause of death. The range in ventricular volumes (12–31 cm^3) obtained with CT scanning[4,10,49] is comparable to the range of volumes (7–30 cm^3) reported in MR studies.[9,10,15,34,36,55,56]

Extraventricular CSF Volume

Many investigators have attempted to measure the CSF volume. One of the first was Weston,[48] who aspirated the CSF immediately after death from the cadavers of patients who died from dementia praecox (age range 19–51 years) or paresis (age range 31–54 years) and estimated the cranial CSF volumes to be 110 and 135 cm^3, respectively. Unfortunately, no values for neurologically intact subjects were reported. Davis and Wright[11] used a different method to measure the cranial CSF volume of cadavers. These investigators used a lubricated balloon filled with water to

TABLE 4

*Summary of brain volumes and cranial, ventricular, and extraventricular CSF volumes as determined by various methodologies**

Method	Volume: Brain	Cranial CSF (cm^3)	Ventricular CSF (cm^3)	Extraventricular CSF (cm^3)	Authors, Year
postmortem studies			30		Harvey, 1911
		123			Weston, 1921
	M, 1370 g; F, 1277 g				Shibata, 1936
			M, 23; F, 21		Last & Tompsett, 1953
				7.8%†	Davis & Wright, 1977
	M, 1397 g; F, 1261 g				Dekaban & Sadowsky, 1978
	M, 1354 g; F, 1218 g				Ho, *et al*., 1980
			1.8%‡	10.7%†	Hubbard & Anderson, 1981
	M, 1375 g; F, 1235 g				Hubbard & Anderson, 1983
				8.3%†	Harper & Kril, 1985
	M, 1444 g; F, 1257 g		M, 30; F, 25		Skullerud, 1985
	1371 cm^3		14		Filipek, *et al*., 1989
	M, 1346 g; F, 1181 g		M, 29; F, 25		Regeur & Pakkenberg, 1989
uncertain CT studies		60	35	25	Lups & Haan, 1954
			M, 30; F, 31		Brassow & Baumann, 1978
		11.4%‡	5.3%‡	6.1‡	Gado, *et al*., 1982
			22		Cramer, *et al*., 1990
MR imaging studies		123	25	98	Condon, *et al*., 1986
		M, 146; F, 115			Grant, *et al*., 1988
	1343 cm^3		16		Filipek, *et al*., 1989
			14		Cramer, *et al*., 1990
	1349 cm^3	116	21	116	Kohn, *et al*., 1991
		M, 189 (11.7%‡); F, 146 (10.7%‡)			Malko, *et al*., 1991

* Abbreviations: CSF = cerebrospinal fluid; CT = computerized tomography; MR = magnetic resonance.
† Pericerebral space of the cranial cavity.
‡ Relative value of the cranial cavity.

occupy the entire cranial cavity from which the brain, dura, falx, and tentorium had been removed previously. The difference between the volume of the water contained in the balloon and that of the fresh brain, as determined by displacement of water, was referred to as the "pericerebral space volume." This volume, which averaged 7.8% ± 1.6% of the total cranial volume in patients ranging in age from 20 to 100 years, included the volume of CSF and also that occupied by dura mater and major sinuses. Using a similar technique Harper and Kril[25] obtained a comparable value (8.3% ± 3.3%) in patients averaging 58 years of age, and Hubbard and Anderson[29] reported a value of 10.7% in a study of a group of older patients (average age 73 years). Others[47,60] have used CT scanning in attempts to calculate a sulcal ratio, and Gado, *et al.*,[18] calculated a sulcal size ratio of 6.1% ± 2.5% using these techniques. These values are smaller than the extraventricular CSF volumes determined in our study, which averaged 10% ± 3% of the total intracranial volume. As alluded to previously, artifacts associated with brain swelling after death and/or fixation and the poor resolution of the extraventricular CSF space on CT scans are surmised to account for this disparity. Because the direct measurement of extraventricular CSF space has not been possible until recently, the actual volume has remained uncertain. Condon and colleagues,[8] using a different MR imaging sequence from ours, determined the extraventricular CSF volume to be 97.6 ± 36.6 cm^3 in 10 normal subjects averaging 37 years of age. However, others[36] have reported significantly higher values for the extraventricular CSF volume (115.7 cm^3) as well as for the supratentorial extraventricular space (132.6 cm^3).[55] The cranial extraventricular CSF volume for study participants averaged 133 ± 52 cm^3, and although similar to the values reported by Tanna, *et al.*,[55] it too was significantly greater than the 97.6 ± 34.9 cm^3 reported by Condon, *et al.*,[9] in a subsequent study of 12 normal individuals with an average age of 35 years. We suggest that this is due to the fact that on average our participants were older (56 ± 16 years) than those studied by Condon and colleagues.[8,9] Indeed, when the volume determinations are limited to the 19 youngest individuals in our study group (average age 35 ± 6 years) the average extraventricular volume measures 96 ± 25 cm^3, a value almost identical to that of Condon's group. This finding indicates that the average volume of the extraventricular CSF space in studies of normal human adults is dependent on the age distribution of the group. Our results also indicate that the volume of extraventricular CSF increases linearly with age when expressed as a percentage of the intracranial volume; an observation consistent with that of Teasdale, *et al.*,[56] but not of others,[47,60] who have suggested a biexponential increase accelerating with advancing ages.

Although a statistical comparison of the mean extraventricular CSF volumes of men and women in our study did not always prove to be significant, it is apparent that the cranial extraventricular CSF space is consistently larger in men than in women. Others have reported similar findings.[21,23] Moreover, as brain volume decreases with age, the shrinkage is best reflected by measuring increases in the relative extraventricular rather than the relative ventricular CSF volumes. In both sexes the increase of ventricular volume with age represented only a small fraction of the overall increase in cranial CSF volume. Indeed, most of the cranial CSF volume expansion occurring with age was attributable to the increase observed in the extraventricular CSF volume. Teasdale, *et al.*,[56] arrived at the same conclusion, stating that the increase in cortical sulcal volume was predominantly responsible for expansion of the total cranial CSF volume with age.

Finally, as illustrated in Table 4, the extraventricular CSF volumes determined by various MR imaging sequences are considerably larger than those determined by the more traditional methods. Indeed, MR image–generated cranial CSF volumes are on average larger than the combined cranial and spinal CSF volumes (140 cm^3) cited in the literature.[12,41] It may be argued that use of autopsy material in many of the previous studies contributes to this discrepancy, because it is known that brain swelling after death encroaches on the cranial CSF compartments. However, if this were the case it may be anticipated that similar discrepancies exist between the MR image and traditionally generated ventricular and brain volumes as well. This appears not to be the case, because ventricular and brain volumes determined by MR imaging are, in most cases, quite similar to those generated by the more traditional techniques. Multiplying the average brain volumes reported herein by the specific gravity of human brain (1.037)[57] converts these values to brain weights (male, 1350 g; female, 1186 g).

Furthermore, the MR image–generated volumes also are considerably larger than the combined cranial and spinal CSF volumes (127 ± 25 cm^3) determined from ventriculolumbar perfusion studies of three patients (age 63 ± 3 years) with normal or slightly enlarged ventricles.[40] In our studies the volume occupied by arachnoid trabecular and small blood vessels normally found within the cranial subarachnoid space is not discriminated from CSF by MR image segmentation. Consequently, this volume is included in the extraventricular CSF volume determination. The age-dependent expansion of the extraventricular CSF volume could therefore be due to an increase of the cranial subarachnoid space and the extraventricular CSF space. We are not aware of any study in which the volume occupied by these structures has been determined or whether this volume changes with age. If such structures do occupy a significant fraction of this space, the disparity between the MR image and more traditionally generated values may be explained. However, if they do not, MR imaging segmentation may be identifying an extraventricular CSF compartment that heretofore was unrecognized.

Computerized MR image processing segmentation provides a noninvasive *in vivo* technique to measure intracranial, brain, and ventricular and extraventricular CSF volumes that avoids many of the artifacts associated with traditional methods. This technique can be expected to improve our knowledge of physiological and biochemical processes that affect these cranial compartments throughout life. In addition, it should provide a powerful tool to better understand and manage clinical problems associated with the various types of ventricular enlargement.

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