Quantitative Volumetric Analysis of Brain MR: Normative Database Spanning 5 Decades of Life

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PURPOSE: To present a normative volumetric database, spanning 5 decades of life, of cerebrospinal fluid, subarachnoid cerebrospinal fluid, total brain volume, total ventricular volume (component ventricular volumes of lateral, temporal horn, and third and fourth ventricles) and estimates of white and gray matter, based on a multispectral segmentation of brain MR. This database is presented as a reference for future studies comparing pathologic states. **METHOD:** One hundred ninety-four healthy subjects, ranging in age from 16 to 65 years, received standard axial intermediate- and T2-weighted spin-echo MR images. Multispectral segmentation and volume analysis were performed using ANALYZE. **RESULTS:** Normative volumetric estimates, both uncorrected and corrected for differences in total intracranial volume, were obtained for all subjects and presented by decade and sex. Age-related cerebrospinal fluid changes were evident for both male and female subjects. Most gender differences were eliminated by correction for differences in total intracranial volume. Standard and fast spin-echo acquisition methods gave comparable volume estimates. Total brain volume measurements from MR compare favorably with data from large autopsy series. **CONCLUSION:** Although there may be limitations to generalizations, these normative data tables can provide a comparison index for contrasting pathologic groups with a normative sample.

Index terms: Brain, magnetic resonance; Brain, volume

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Modern imaging techniques, including computed tomography (1–6) and more recently magnetic resonance (MR) imaging (7–20) have provided the opportunity for noninvasive antemortem volumetric quantification of intracranial structures. Methods for volumetric quantification based on MR have typically used segmentation based on either single-dimensional thresholding, typically from highly T1-weighted images (7–9), or multispectral segmentation based on two or more spatially registered images (10).

We report herein the results of a volumetric analysis of 194 healthy volunteers including both female and male subjects and spanning 5 decades of adult life, from 16 to 65 years. Using a multispectral segmentation algorithm, measurements of ventricular (including lateral, third, and fourth, as well as temporal horns), subarachnoid space, and total brain volumes are reported. We include an analysis of intrarater and interrater reliability and a comparison of our observations with previous large autopsy series (21, 22).

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Methods

Subjects

One hundred ninety-four healthy volunteers (105 female and 89 male) from age 16 to 65 years were examined. Table 3 provides the sample size and age breakdown for the 5 decades studied. Volunteers were recruited by advertising in the hospital and included both employees and their families and friends. We attempted to recruit equal numbers of male and female

subjects in each decade from 16 through 65 years of age. Although the volunteer group included ethnic minorities, the numbers in each group were too small to allow a comparative analysis.

Although there were no formal neurologic or neuropsychiatric examinations, all subjects answered a questionnaire and were excluded if there was a history of any of the following: (*a*) previous head injury causing loss of consciousness; (*b*) any disease affecting the nervous system, including dementia or psychiatric illness; and (*c*) alcohol or drug abuse. Based on an assessment of 12 motor functions, 95% of the volunteers were considered left-hemisphere dominant. The mean educational level of the healthy population was 15.5 years, with a standard deviation of 2.7 years.

The images and subsequent analyses were performed in compliance with an institutional review board–approved protocol. All volunteers gave informed consent.

Imaging

MR images were acquired with a 1.5-T GE Signa MR scanner, operating on the 5.x software platform. The system operates with an actively shielded gradient system with linear rise time of 0.1 mT/cm. A quadriture head coil was used. The main magnetic field (B_0) is shimmed (superconducting and resistive shims) to 0.1 ppm over a 25-cm-diameter sphere. Routine quality control includes monitoring of B_0 homogenicity, gradient linearity, and measurement of signal-to-noise ratio.

The subjects were imaged in the supine position using our routine clinical protocol. Sagittal T1-weighted (500/11/2 [repetition time/echo time/excitations]) images were acquired and used for location. Axial intermediate and T2-weighted (3000/31, 90/1) spin-echo images were then acquired with a section thickness of 5 mm and an interspace gap of 2 mm from foramen magnum to vertex. A 22-cm field of view was used with a 256 $\times$ 192 acquisition matrix. Flow compensation, an inferior saturation pulse, and variable bandwidth were used.

Fast spin-echo sequences became widely used after beginning this study. In order to evaluate for possible differences in volume estimates obtained with standard versus fast spin-echo acquisition sequences, 15 volunteers underwent imaging with both sequences. The axial fast spin-echo images (4000/17, 104/1) were acquired during the same imaging session with identical section thickness, intersection gap, section positioning, and field of view as the standard spin-echo sequence. The echo train length was 8. A 256 $\times$ 256 acquisition matrix was used. Flow compensation was not an available option. Inferior saturation and variable bandwidth were used.

Volumetric Image Analysis

The axial intermediate and T2-weighted spin-echo images were processed using ANALYZE (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) (23) running on SPARC 10 workstations (SUN Microsystems, Mountain View, Calif). Because ANALYZE can perform the multispectral segmentation only with 8-bit images, the original 16-bit images were converted by linear interpolation to 8-bit images using the load command. The images were then archived permanently onto an optical disk using a lossless compression algorithm. A multistep volume analysis was then performed using several image processing tools available in ANALYZE, including multispectral tissue segmentation, interactive image editing, and region-of-interest pixel counting. The multispectral tissue segmentation was performed in a manner similar to that described in a previous report (11). Regions of cerebrospinal fluid (CSF), white matter, and gray matter were defined by the user and plotted in a two-dimensional feature space in which the pixel signal intensity in the T2-weighted sequence is represented on the x-axis, and the pixel signal intensity in the intermediate-weighted image is represented on the y-axis (Fig 1). A k-nearest-neighbor multispectral algorithm (24, 25) was then applied to the pixels of the entire section. Because of inhomogeneity in the sensitivity of the radio frequency coil, the same feature-space map could not be successfully applied to all the images of the study, particularly the more inferior sections, in which the sensitivity of the radio frequency coil was slightly decreased. For these sections, separate feature-space maps were generated.

The classified images were edited using a manual trace tool to remove pixels representing the calvarium and extracranial soft tissues. The inner table of the skull was used as the landmark for separation of intracranial versus extracranial compartments. All the pixels assigned to each segmented category (gray matter, white matter, CSF) were then summed over all of the classified, edited images from foramen magnum to vertex. In a second editing step, subregions that included the lateral ventricles, the temporal horns of the lateral ventricles, the third ventricle, and the fourth ventricle were traced manually. Because the segmentation step of the process had already identified the interface between CSF and brain, precise tracing was not necessary as long as all of the desired CSF-containing structure was included with some surrounding brain parenchyma. The pixels assigned to CSF in these subregions were summed again.

The total brain volume was determined by summing the white and gray matter pixels and then multiplying by the voxel dimension (4.801×10^{-3} cm^3). Total ventricular volume was obtained by summing the measurements of the lateral ventricles and the third and fourth ventricles. The subarachnoid CSF volume was obtained by taking the difference of total CSF and total ventricle. The total intracranial volume (TICV) was obtained by summing the total brain and total CSF volumes. The ventricle-to-brain ratio was calculated by dividing the total ventricle volume by total brain volume and multiplying by 100.

Reliability

Following the methods described above, an initial rater (S.D.G., a PhD graduate student) was trained as an "expert" under the direction of a neuroradiologist (D.D.B).

Fig 1. Multispectral segmentation of MR images. *A*, Intermediate- and *B*, T2-weighted spin-echo images at the level of the body of the lateral ventricles. Operator-identified regions of interest are indicated: CSF, in the left atrium (*blue*); right perisylvian gray matter (*yellow*); and left frontal white matter (*khaki*).

C, Plot of two-dimensional feature space in which each pixel is plotted with the signal intensity on the T2-weighted image as the x-axis and the signal intensity on the intermediate-weighted image as the y-axis. The location in feature space of the pixels obtained in the user-identified regions are shown in their respective colors.

D, Two-dimensional feature space after application of the k-nearest-neighbor segmentation algorithm demonstrates the regions assigned to each segmented tissue type.

E, Application of the segmentation to the original image.

The images of five healthy volunteers were selected randomly to serve as training cases. Volumetric analysis using these cases was performed repetitively until interrater reliability between the neuroradiologist and expert rater could be established to exceed 0.9 for all measures, except for gray and white matter volumes. When this level of proficiency was reached, a separate randomly selected group of 15 scans was used to determine intrarater and interrater variability. These were analyzed at two separate times by the expert in order to determine the intrarater reliability. Four additional raters were then trained by the expert using the initial five training studies. Each additional rater then analyzed the subsequent 15 scans in order to determine the interrater reliability. To assess test-retest reliability, eight subjects were imaged a second time on a different day.

Statistical Analysis

Descriptive statistics, including mean and standard deviations, were calculated for each age and sex group. Age- and sex-related effects were evaluated with Pearson correlations, paired *t* tests, and analysis of variance.

Results

Reliability

The results of the analysis of intrarater and interrater reliability are given in Table 1. Comparing the first and second analyses performed by the expert rater, there were no statistically significant differences in any of the volume measurements based on paired *t* tests. With the exception of gray matter, white matter, and fourth ventricle, all correlation coefficients, as shown in Table 1, were greater than .94. Reliable separation of gray and white matter compartments of the total brain measurement was more difficult than any of the other measure-

TABLE 1: Intrarater and interrater correlations of volumetric analyses in 15 randomly selected studies

	CSF	SubCSF	Vents	Lat	L Horn	R Horn	GM	WM	Brain	VBR	IV	III
Intrarater												
Expert	.959	.955	.994	.994	.975	.975	.763	.842	.974	.992	.859	.940
Interrater reliability with Expert												
Rater 2	.963	.959	.994	.997	.974	.963	.621	.682	.976	.992	.932	.934
Rater 3	.935	.934	.985	.990	.917	.957	.545	.594	.967	.979	.849	.772
Rater 4	.938	.933	.986	.990	.959	.918	.480	.552	.946	.978	.881	.833
Rater 5	.969	.973	.990	.992	.974	.962	.715	.567	.901	.984	.950	.880
Mean rater correlations	.951	.950	.989	.992	.956	.950	.590	.599	.948	.983	.903	.855

Note.—CSF indicates cerebrospinal fluid; SubCSF, subarachnoid CSF; Vents, total ventricle; Lat, lateral ventricle; VBR, ventricle-to-brain ratio; III, third ventricle; IV, fourth ventricle; GM, gray matter; WM, white matter; L Horn, left temporal horn; and R Horn, right temporal horn.

ments. The intrarater correlation coefficients for these measures were .763 and .842, respectively.

Intratechnique (test-retest) reliability was assessed by repeating MR examinations on eight subjects on different days. No statistically significant differences in any of the volume measurements were observed between the first and second studies.

In the determination of interrater reliability, there were no statistically significant differences, based on paired *t* tests, between any volume measurements obtained by any of the raters and those obtained by the expert. Correlation coefficients obtained by each of the raters compared with those obtained by expert are shown in Table 1. Again, with the exception of separation between gray and white matter compartments of the brain, a high degree of correlation was observed consistently for all of the volumetric measurements.

A comparison of the results of standard spin-echo with fast spin-echo sequences is shown in Table 2. There were no statistically significant differences between the measurements of total brain volume or any CSF structures obtained with the two techniques. The volume of gray matter was significantly higher (717 cm^3 versus 756 cm^3; $P = .04$) with the fast spin-echo images. All of the intertechnique correlation coefficients were highly significant.

TABLE 2: Comparison of standard and fast spin-echo images: descriptive and correlative statistics

	Spin-Echo Images		Correlation	Significance (paired *t* test)
	Standard	Fast		
CSF				
Mean	137.92	149.07	0.88	NS
SD	45.29	49.94	. . .	. . .
SubCSF				
Mean	116.79	128.31	0.88	NS
SD	42.41	46.65	. . .	. . .
Vents				
Mean	21.12	20.76	0.97	NS
SD	8.86	8.99	. . .	. . .
Lat				
Mean	17.82	17.59	0.98	NS
SD	8.25	8.29	. . .	. . .
L Horn				
Mean	0.22	0.18	0.95	NS
SD	0.22	0.18	. . .	. . .
R Horn				
Mean	0.31	0.32	0.92	NS
SD	0.22	0.21	. . .	. . .
GM				
Mean	716.55	756.22	0.56	0.04
SD	81.65	70.60	. . .	. . .
WM				
Mean	556.71	529.17	0.72	NS
SD	88.07	112.76	. . .	. . .
Brain				
Mean	1273.26	1285.40	0.99	NS
SD	155.62	147.78	. . .	. . .
VBR				
Mean	1.69	1.64	0.79	NS
SD	0.77	0.72	. . .	. . .
IV				
Mean	1.88	1.92	0.87	NS
SD	0.51	0.64	. . .	. . .
III				
Mean	0.88	0.87	0.98	NS
SD	0.38	0.44	. . .	. . .

Notes.—Mean values are volumes given in cubic centimeters. NS indicates nonsignificant at the $P < .05$ level; SubCSF, subarachnoid CSF; Vents, total ventricle; Lat, lateral ventricle; L Horn, left temporal horn; R Horn, right temporal horn; GM, gray matter; WM, white matter; VBR, ventricle-to-brain ratio; IV, fourth ventricle; and III, third ventricle.

Volume Measurements

Descriptive statistics for volume measurements of the selected intracranial structures are given in Table 3 by age and sex, along with an analysis of variance for each volume measure by age. In Table 4, Pearson correlations are given for each volume measure with age.

For the female subjects, the TICV was not correlated with age ($r = -.147$, $P = .135$). Similarly, an analysis of variance was nonsignificant ($F(4, 105) = 1.24$, $P = .29$). For male subjects, there was a trend toward lower TICV with increasing age; however, the correlation did not achieve statistical significance ($r = -.190$, $P = .074$). The analysis of variance was also nonsignificant ($F(4, 89) = 1.22$, $P = .309$).

A significant difference in the TICV was observed between male ($1558 \text{ cm}^3 \pm 97 \text{ cm}^3$) and female ($1352 \text{ cm}^3 \pm 115 \text{ cm}^3$) ($t$ (192) = 11.86, $P < .001$) subjects. For both male and female subjects there was a statistically significant correlation between TICV and each of the other volume measures, except the volume of the temporal horns.

To correct for population variation and sex differences in head size, a correction was made based on the TICV for each of the other volumes except the temporal horns. This correction was performed by multiplying each measured volume by a ratio of the mean TICV for the entire sample population (1446 cm^3) divided by the observed TICV for each individual subject. Table 3 gives values for both the corrected and uncorrected volumes by decade and sex.

In Figure 2, bar graphs illustrate age and sex differences in uncorrected and corrected measurements by decade. Uncorrected measurements for total brain volumes for male subjects were larger than for female subjects in all age groups. After correction for TICV, there were no differences in this measure. No sex differences in either temporal horn or fourth ventricle volumes were observed for any of the decades studied. In the later decades studied, the uncorrected measures showed significantly larger total CSF, subarachnoid CSF, and total, lateral, and third ventricle volumes for male subjects than for females. After correction, the trend for larger CSF spaces in male than female subjects was still present; however, statistically significant differences were present only for the third ventricle and total ventricular volume in the age 46 to 55 decade.

Highly significant age-related changes are observed (Tables 3 and 4) for both male and female subjects. A decreasing total brain volume and increasing subarachnoid CSF volume were the changes most highly correlated with advancing age. These changes were greater and more highly correlated with age for male than female subjects. Increases in the third and lateral ventricle volumes were seen for both male and female subjects; again, the differences were greater and seen at an earlier age for the male subjects. The volume of the third ventricle in male subjects showed the highest correlation with age of any ventricular volume.

To assess the accuracy of the database, we compared the total brain volume obtained by analysis of the MR with autopsy reports (21, 22). The comparison is somewhat limited because autopsy data report only total brain weight, and conversion to units of volumes is necessary. Despite this limitation, the comparison can provide a good indication of the overall accuracy of the technique.

In Table 5, the average brain weight, given by decade from the report of Ho et al (21), is compared with the volume measurements from the current data (average total brain volumes, combined for male and female subjects) (see Table 3). The weights reported in the autopsy data have been converted to volume by subtracting the reported average weight for the dura and then multiplying by 1.019, an estimate of the gravimetric density of brain based on computed tomography data (26). Excellent agreement between the autopsy and the MR volume measurement is shown. Two sample t tests performed for each decade show no significant differences between the autopsy and MR volume estimates.

Discussion

A variety of techniques have been reported for quantitative volumetric analysis based on brain MR. These reports have focused on a description of methods and have included small numbers of healthy control subjects (7–9, 11–14). Subsequent studies, which have successfully applied these techniques to the study of various pathologic states, have typically compared the results obtained in patients with those of age-matched healthy control subjects (15–20).

Pfefferbaum et al recently reported a normative database derived from a volumetric analysis of MR images of 161 subjects (27). Analysis of the images was limited to an analysis of only seven sections of the cerebrum. Volumes were statistically adjusted, through a regression procedure, for normal variation in head size. Volumes of total brain were not reported. The subjects included 88 medical controls ranging from

TABLE 3: Normative volumetric measures of intracranial structures for MR imaging, given by age and gender

Age Decade, y	n	Age, y		Total CSF				Subarachnoid CSF				Total Ventricle			
		Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD
Female subjects															
16–25	20	21.30	2.47	89.35	36.65	91.39	33.97	71.99	30.86	73.64	28.84	17.36	7.15	17.75	6.60
26–35	24	30.71	3.07	95.88	32.73	103.70	32.94	79.02	29.61	85.48	30.28	16.86	7.16	18.22	7.28
36–45	22	40.68	2.98	111.24	31.70	118.82	31.23	95.83	29.86	102.42	30.08	15.40	5.00	16.39	4.82
46–55	24	50.38	2.73	116.30	30.31	125.18	29.23	100.79	28.88	108.45	28.31	15.52	3.76	16.72	3.57
56–65	15	59.80	2.18	147.35	34.93	160.53	40.77	123.12	30.91	134.03	35.28	24.23	12.15	26.50	13.63
	N = 105														
F score				8.04		10.75		8.02		10.37		4.34		5.28	
P				<.0001		<.0001		<.0001		<.0001		.0028		.0007	
Male subjects															
16–25	24	23.17	1.90	85.81	29.82	78.23	28.11	67.70	29.19	61.89	27.67	18.12	6.58	16.35	5.67
26–35	19	30.89	3.33	112.77	37.79	105.02	33.53	94.52	35.72	88.01	31.90	18.25	4.49	17.01	3.96
36–45	16	41.13	2.70	138.60	37.95	129.58	33.61	118.92	35.02	111.18	31.20	19.67	6.47	18.39	5.75
46–55	15	51.07	2.66	136.38	38.75	129.67	39.19	115.45	36.54	109.81	36.43	20.93	5.13	19.86	5.34
56–65	15	60.60	3.04	191.07	65.49	177.67	56.07	162.98	62.34	151.56	54.35	28.08	12.29	26.11	10.50
	N = 89														
F score				15.46		17.15		14.16		15.38		5.21		6.17	
P				<.0001		<.0001		<.0001		<.0001		.0009		.0002	

Age Decade, y	n	Age, y		Lateral Ventricle				L Temporal Horn		R Temporal Horn		Third Ventricle			
		Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Uncorrected Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD
Female subjects															
16–25	20	21.30	2.47	14.73	6.79	15.05	6.36	0.25	0.15	0.20	0.12	0.69	0.18	0.71	0.17
26–35	24	30.71	3.07	14.25	6.89	15.37	7.02	0.19	0.16	0.27	0.33	0.65	0.24	0.71	0.27
36–45	22	40.68	2.98	12.79	4.74	13.60	4.63	0.21	0.23	0.17	0.14	0.71	0.31	0.76	0.31
46–55	24	50.38	2.73	13.16	3.66	14.20	3.61	0.15	0.11	0.18	0.11	0.75	0.24	0.81	0.24
56–65	15	59.80	2.18	21.11	11.31	23.10	12.60	0.25	0.25	0.25	0.21	1.19	0.60	1.30	0.66
	N = 105														
F score				4.17		5.03		1.1		1.13		7.88		8.63	
P				.0036		.001		.3603		.345		<.0001		<.0001	
Male subjects															
16–25	24	23.17	1.90	15.32	6.22	13.82	5.38	0.18	0.12	0.22	0.25	0.69	0.22	0.63	0.20
26–35	19	30.89	3.33	15.17	4.46	14.12	3.96	0.18	0.15	0.27	0.16	0.73	0.21	0.68	0.19
36–45	16	41.13	2.70	16.11	6.27	15.04	5.57	0.24	0.17	0.23	0.19	1.01	0.39	0.95	0.36
46–55	15	51.07	2.66	17.89	4.81	16.98	4.94	0.16	0.13	0.20	0.09	1.13	0.40	1.07	0.39
56–65	15	60.60	3.04	24.78	12.05	22.98	10.27	0.20	0.17	0.27	0.21	1.30	0.42	1.22	0.39
	N = 89														
F score				5.22		6.1		0.75		0.42		11.77		12.74	
P				.0008		.0002		.558		.795		<.0001		<.0001	

(*Table continues*)

TABLE 3: continued

Age Decade, y	n	Age, y		Fourth Ventricle				Gray Matter				White Matter			
		Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD
Female subjects															
16–25	20	21.30	2.47	1.48	0.56	1.53	0.57	694.78	112.71	716.54	99.84	616.21	109.00	638.38	116.15
26–35	24	30.71	3.07	1.49	0.39	1.63	0.45	647.54	98.61	702.58	75.57	586.26	79.34	640.02	90.83
36–45	22	40.68	2.98	1.52	0.38	1.63	0.41	611.71	105.79	654.49	102.68	628.68	108.83	672.99	105.49
46–55	24	50.38	2.73	1.27	0.49	1.36	0.50	580.94	81.68	626.62	69.21	645.95	103.27	694.50	75.87
56–65	15	59.80	2.18	1.42	0.49	1.56	0.61	597.59	60.71	648.10	64.19	590.55	106.22	637.67	95.02
	N = 105														
F score				1.04		1.12		4.72		4.45		1.37		1.56	
P				.388		.351		.0016		.0024		.2506		.191	
Male subjects															
16–25	24	23.17	1.90	1.70	0.58	1.54	0.52	761.84	106.99	689.96	75.31	746.45	89.25	678.11	78.01
26–35	19	30.89	3.33	1.90	0.68	1.78	0.66	749.09	83.62	700.15	78.98	687.56	106.49	641.13	88.93
36–45	16	41.13	2.70	2.08	0.57	1.96	0.57	740.70	112.63	693.26	94.83	666.61	120.34	623.46	101.10
46–55	15	51.07	2.66	1.54	0.54	1.47	0.53	712.74	73.27	672.88	62.42	683.77	108.43	643.75	83.00
56–65	15	60.60	3.04	1.54	0.42	1.46	0.50	691.47	130.51	644.62	102.43	666.37	137.92	624.02	124.45
	N = 89														
F score				2.7		2.53		1.35		1.16		1.86		1.14	
P				.036		.047		.258		.334		.125		.344	

Age Decade, y	n	Age, y		Total Brain				TICV		VBR	
		Mean	SD	Uncorrected Mean	SD	Corrected Mean	SD	Uncorrected Mean	SD	Uncorrected Mean	SD
Female subjects											
16–25	20	21.30	2.47	1310.99	79.74	1354.91	33.97	1400.33	93.09	1.32	0.53
26–35	24	30.71	3.07	1233.79	102.43	1342.60	32.94	1329.67	112.37	1.36	0.56
36–45	22	40.68	2.98	1240.39	102.96	1327.48	31.23	1351.62	110.79	1.24	0.37
46–55	24	50.38	2.73	1226.89	138.06	1321.12	29.23	1343.19	146.41	1.27	0.28
56–65	15	59.80	2.18	1188.14	95.75	1285.77	40.77	1335.49	82.98	2.08	1.11
	N = 105										
F score				3.17		10.75		1.24		5.82	
P				.017		<.0001		.298		.0003	
Male subjects											
16–25	24	23.17	1.90	1508.29	106.90	1368.07	28.11	1594.10	101.39	1.20	0.42
26–35	19	30.89	3.33	1436.66	79.85	1341.28	33.53	1549.43	81.91	1.27	0.31
36–45	16	41.13	2.70	1407.31	99.34	1316.73	33.61	1545.91	103.94	1.40	0.45
46–55	15	51.07	2.66	1396.51	108.58	1316.63	39.19	1532.89	89.29	1.52	0.43
56–65	15	60.60	3.04	1357.84	100.59	1268.63	56.07	1548.91	106.09	2.07	0.88
	N = 89										
F score				6.33		17.15		1.22		7.56	
P				.0002		<.0001		.309		<.0001	

Note.—VBR indicates ventricle-to-brain ratio.

TABLE 4: Correlations between brain structures and age: uncorrected and corrected for total intracranial volume

	Male subjects (n = 89)				Female subjects (n = 105)				All Subjects (n = 194)	
	Uncorrected		Corrected		Uncorrected		Corrected		Corrected	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
CSF	.650	.000	.675	.000	.477	.000	.539	.000	.608	.000
Subarachnoid CSF	.633	.000	.653	.000	.490	.000	.545	.000	.599	.000
Total ventricles	.412	.000	.458	.000	.171	.081	.220	.024	.324	.000
Lateral ventricles	.401	.000	.444	.000	.172	.080	.218	.026	.318	.000
L temporal horn	.030	.777	. . .	. . .	−.043	.667	. . .	. . .	. . .	. . .
R temporal horn	.040	.701	. . .	. . .	−.004	.970	. . .	. . .	. . .	. . .
Third ventricle	.617	.000	.634	.000	.376	.000	.406	.000	.508	.000
Fourth ventricle	−.126	.239	−.076	.476	−.125	.204	−.081	.413	−.080	.265
Gray matter	−.257	.015	−.200	.059	−.391	.000	−.372	.000	−.294	.000
White matter	−.239	.024	−.179	.092	.050	.611	.126	.199	−.014	.850
Total brain	−.485	.000	−.675	.000	−.310	.001	−.539	.000	−.608	.000
TICV	−.190	.074	. . .	. . .	−.147	.135	. . .	. . .	. . .	. . .
Ventricle-to-brain ratio	.498	.000	. . .	. . .	.248	.011	. . .	. . .	. . .	. . .

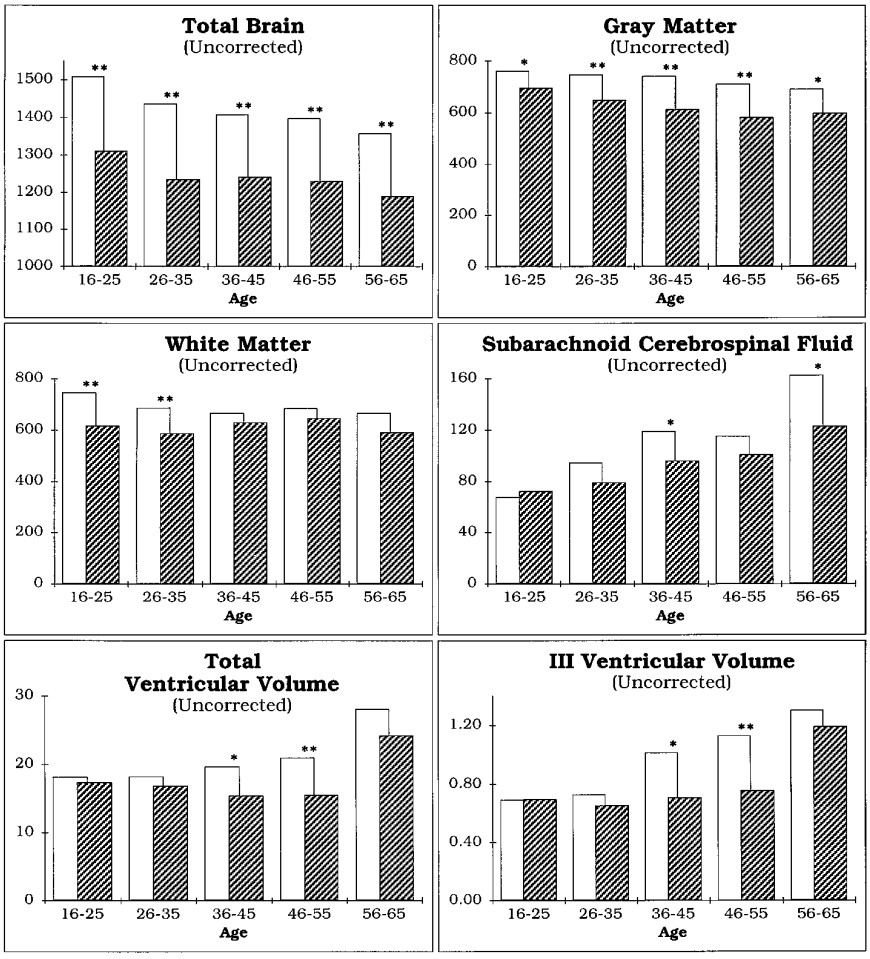

Fig 2A. Comparison of selected intracranial volume estimates by age and sex. Graphs for volume data both before (*A*) and after (*B*) correction (see next page) for differences in TICV. Each *bar* indicates the mean volume for the decade shown below. *Crosshatched bars* are female values; *noncrosshatched bars* are male values. *Asterisk* indicates a significant ($P < .05$) difference between male and female subjects.

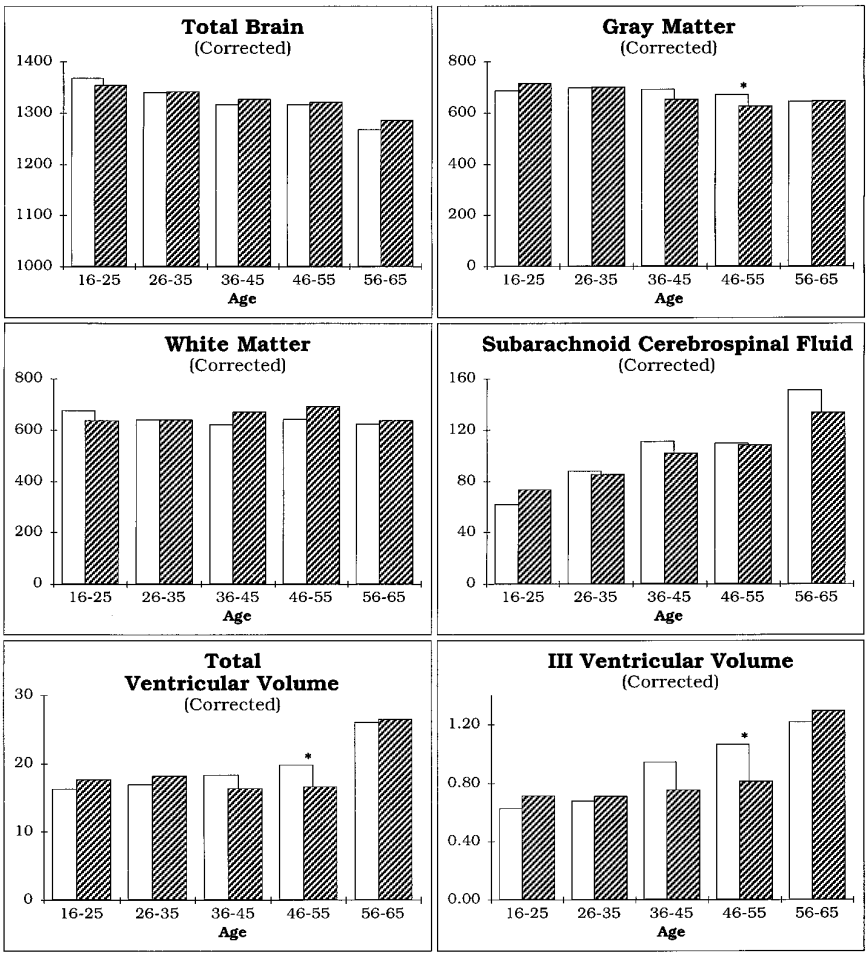

Fig 2B. Comparison of selected intracranial volume estimates by age and sex. Graphs for volume data both before (*A*) (see previous page) and after (*B*) correction for differences in TICV. Each *bar* indicates the mean volume for the decade shown below. *Crosshatched bars* are female values; *noncrosshatched bars* are male values. *Asterisk* indicates a significant ($P < .05$) difference between male and female subjects.

3 months through 30 years of age, providing data on the developing brain that is not included in the present study. Seventy-three healthy male volunteers, ages 21 to 70 years, formed the second study group. No female subjects were included in the older group.

To be broadly applicable, we have attempted to use methods that are both widely available and accepted as state-of-the-art. The method is readily reproducible and has a well-defined interrater reliability. Nevertheless, there are significant factors that may limit the ability to generalize this data. First, we did not compare images obtained from a number of different scanners, particularly scanners of different manufacture and field strengths. Sophisticated brain phantoms, if developed, could be helpful in assessing the magnitude of possible differ-

TABLE 5: Comparison of brain weight by autopsy and brain volume by MR imaging

Autopsy*			Calculated Volume, cc†	MR		
Age, y		Average Brain Weight ± SD, gm		Age, y		Measured Volume ± SD, cc‡
Average	Range			Average	Range	
30	25–34	1349 ± 131	1342	31	26–35	1323 ± 137
40	35–44	1313 ± 151	1305	41	36–45	1311 ± 130
50	45–64	1290 ± 154	1281	51	46–55	1292 ± 151
60	55–64	1307 ± 159	1299	60	56–65	1273 ± 129

* See reference 21.

† Based on gravimetric value of 1.019 g/cm^3 and subtracting the reported weight of the dura matter.

‡ One-sample *t* tests indicate no significant difference from corresponding autopsy volume estimates.

ences in measurements made using different scanners. Such phantoms could be used for both calibration of different instruments and routine quality control.

In addition, potential biases may exist in our population of healthy volunteers. The average educational level of the volunteers was 15.5 years, with a standard deviation of 2.7 years, compared to a 13.5-year average reported for the state of Utah based on the national census data (28). Although a correlation of brain size with educational level has not been reported, brain size and IQ have been shown to be correlated (29, 30). Although the differences are small, this may introduce a bias in these data toward larger brain size. Other potentially significant factors were not evaluated, such as previous nonneurologic medical history (hypertension, cardiac disease, etc). Ethnic differences were neither controlled nor analyzed in this study. These and other as yet unrecognized potential sources of population bias should be considered before generalizing these results to any patient population. Despite these potential sources of bias, the results obtained do correlate well with previously reported total brain volumes from large autopsy studies (21, 22).

Although not a specific study of aging effects or sex-based differences, changes with age and sex differences observed in these data are consistent with what has been known previously. Brain weight and volume decrease with age, a trend that begins earlier and results in a larger total brain loss in men than in women. For both male and female subjects, the subarachnoid CSF volume was a strong indicator of brain loss and correlated more highly with age than any other measure. In male subjects, brain loss with aging was also reflected by ventricular expansion, with third ventricular volume correlating most highly. In comparison, for female subjects, increases in the volume of the lateral ventricles and third ventricle were delayed, reaching statistical significance only in the age 56 to 65 decade.

Consistent with previous reports from autopsy data (21, 22), we observed a significantly greater TICV and total brain volume for male than for female subjects in all age groups. The sex difference in total brain volume narrowed with the greater age-related brain loss in male subjects. The TICV was not significantly correlated with age in either male or female subjects, a finding consistent with previous autopsy reports (31).

Population variation in head size has been correlated with a number of factors including body height, weight, and gender. Authors working with both autopsy (32) and MR (8, 14) data have noted that a significant reduction in the population variation of brain structure volumes can be achieved by normalizing for TICV. We observed a statistically significant correlation between TICV and all of the measured structures except the temporal horns. The sex difference in total brain volume was eliminated when the measurements were corrected for intracranial volume. Furthermore, within a given age and sex group, the standard deviation of nearly all of the measurements was reduced by this correction.

In summary, the current results present a normative database spanning 5 decades that provides volumetric estimates of total brain and selected intracranial CSF-containing structures. This investigation demonstrates the usefulness of a rapidly automated method for segmenting images that provides an accurate volume estimate of selected clinically relevant neural structures. The volumetric estimation can be used in a comparative fashion to determine significant deviation from normal structure values in other normative studies or in actual clinical cases.

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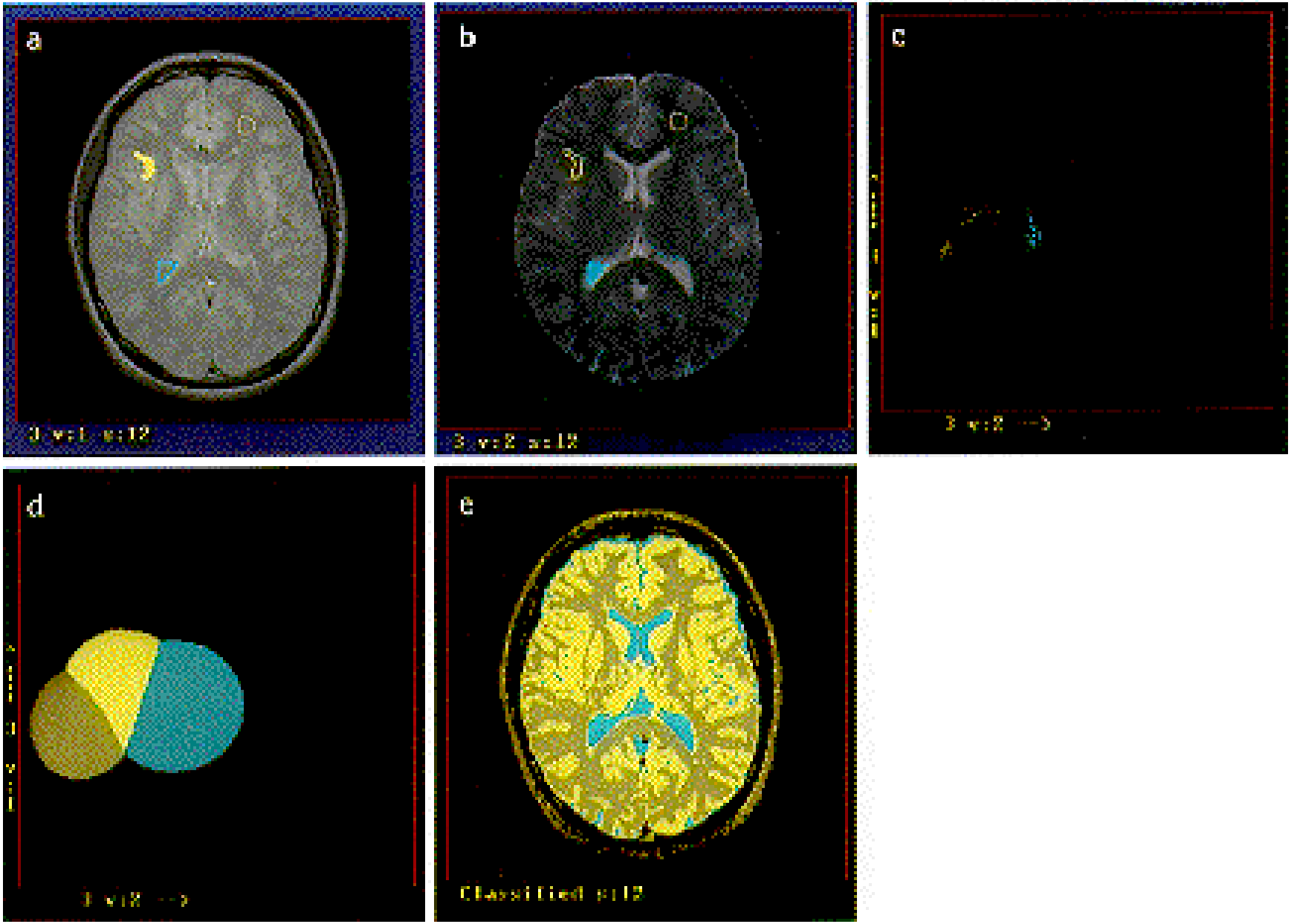
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