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Measures of brain morphology and infarction in the framingham heart study: establishing what is normal

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Abstract

Numerous anatomical and brain imaging studies find substantial differences in brain structure between men and women across the span of human aging. The ability to extend the results of many of these studies to the general population is limited, however, due to the generally small sample size and restrictive health criteria of these studies. Moreover, little attention has been paid to the possible impact of brain infarction on age-related differences in regional brain volumes. Given the current lack of normative data on gender and aging related differences in regional brain morphology, particularly with regard to the impact of brain infarctions, we chose to quantify brain MRIs from more than 2200 male and female participants of the Framingham Heart Study who ranged in age from 34 to 97 years. We believe that MRI analysis of the Framingham Heart Study more closely represents the general population enabling more accurate estimates of regional brain changes that occur as the consequence of normal aging.

As predicted, men had significantly larger brain volumes than women, but these differences were generally not significant after correcting for gender related differences in head size. Age explained approximately 50% of total cerebral brain volume differences, but age-related differences were generally small prior to age 50, declining substantially thereafter. Frontal lobe volumes showed the greatest decline with age (approximately 12%), whereas smaller differences were found for the temporal lobes (approximately 9%). Age-related differences in occipital and parietal lobe were modest. Age-related gender differences were generally small, except for the frontal lobe where men had significantly smaller lobar brain volumes throughout the age range studied.

The prevalence of MRI infarction was common after age 50, increased linearly with age and was associated with significantly larger white matter hyperintensity (WMH) volumes beyond that associated with age-related differences in these measures. Amongst men, the presence of MRI infarction was associated with significant age-related reductions in total brain volume. Finally, statistically significant associations were found between the volume of MRI infarcts in cubic centimeters and all brain measures with the exception of parietal lobe volume for individuals where the volume of MRI infarctions was measured.

These data serve to define age and gender differences in brain morphology for the Framingham Heart Study. To the degree participants of the Framingham Heart Study are representative the general population, these data can serve as norms for comparison with morphological brain changes associated with aging and disease. In this regard, these cross-sectional quantitative estimates suggest that age-related tissue loss differs quantitatively and qualitatively across brain regions with only minor differences between men and women. In addition, MRI evidence of cerebrovascular disease is common to the aging process and associated with smaller regional brain volumes for a given age, particularly for men. We believe quantitative MRI studies of the Framingham community enables exploration of numerous issues ranging from understanding normal neurobiology of brain aging to assessing the impact of various health factors, particularly those related to cerebrovascular disease, that appear important to maintaining brain health for the general population.

Keywords: Aging; Gender; MRI; Brain morphology; Cerebral infarction

1. Introduction

Interest in healthy aging, particularly with regard to maintaining cognitive ability, has grown as the proportion of

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older individuals within our society steadily increases [38]. A variety of health risk factors, including some that can be influenced through medications or behavior, are associated with accelerated brain aging and diminished cognitive performance [20,25–27,50,65,93,94] suggesting the possibility for improving brain health through primary prevention strategies should these processes be fully understood.

Numerous anatomical and quantitative brain imaging studies confirm that aging is associated with differences in brain structure that may be regionally specific [20,25–27,50,65,93,94]. Many of these studies, however, were based on either small samples of individuals or used stringent health criteria [21,69] limiting our understanding of brain aging in the presence of common medical illnesses that may be modified through more rigorous preventive health care. Some studies, however, have examined the associations between abnormal white matter signals that are increased in prevalence and severity in association with cerebrovascular risk factors and aging [12,23,41,42,66], but, to our knowledge, none have examined the impact that the presence and volume of cerebral infarction detected by MRI might have on regional brain and cerebral spinal fluid (CSF) volumes with aging.

Beginning in 1999, participants of the Framingham Heart Study were approached to participate in an MRI study of brain aging. Quantification of regional brain, CSF, white matter hyperintensity (WMH) and MRI infarctions from 2266 individuals from within this population imaged between March 1999 and December 2001 form the basis of this report.

2. Methods

2.1. Subjects

The general design and demographics of the Framingham Heart Study have been previously described [16]. In brief, the Framingham Heart Study is a community-based population sample of individuals living in Framingham, MA. Currently, the Framingham Heart Study consists of two cohorts, the original participants of the study and their offspring as well as the spouses of their offspring.

The original cohort of the Framingham Heart Study consisted of 5209 participants from Framingham MA who were enrolled into the study in 1948. At enrollment, the mean age was 44 years (range 28–62 years), 55% were female, the majority were white and of middle socioeconomic class. In November 2001, the 26th biennial examination of the original cohort was completed on 558 participants (73% of the surviving cohort). The average age of participants undergoing this examination was 86 years (range 79–103-year-old); 55% were female.

The offspring cohort includes 5124 offspring of the original cohort and their spouses who were enrolled into the study in 1971. At enrollment, the mean age was 36 years (range 5–70 years), 52% were female. In October 2001, the seventh examination of the offspring cohort was completed on 3539 participants (82% of surviving cohort). The average age of participants undergoing this examination was 62 years (range 33–90-year-old); 53% were female.

Between March 1999 and December 2001, 2266 individuals from both the original cohort and the offspring cohort received an MRI of the brain. Virtually all offspring cohort attending examination 7 and all of the original cohort who underwent examination 26 were given the opportunity to undergo brain imaging. Each subject agreeing to participate gave informed consent prior to the imaging. We anticipate that through the end of 2003 approximately +2800 of the approximately 4100 original and offspring cohort who attended examinations 7 and 26, respectively, will receive a brain MRI. Reasons for not being imaged included participant refusal due to reasons not specified (20%), medical contraindications for MRI (2.5%), and claustrophobia (5%). As expected, offspring participants who refused or were unable to receive a MRI were older and generally less healthy than those with an MRI (Table 1).

Review of medical history and physical examination findings was used to exclude individuals with symptomatic neurological disease resulting in further exclusion of 185 individuals, most from the original cohort, leaving a final study group of 2081 (109 from the original cohort and 1972 from the offspring cohort) individuals free of stroke, dementia, multiple sclerosis or other clinically evident neurological conditions. Prevalent disease and differences between the two cohorts are summarized in Table 2.

3. MRI

3.1. Acquisition parameters

The majority of subjects were imaged on a Siemens Magnetom 1 T field strength magnetic resonance machine using a T2-weighted double spin-echo coronal imaging sequence of 4 mm contiguous slices from nasion to occiput with a repetition time (TR) of 2420 ms, echo time (TE) of TE1 20/TE2 90 ms; echo train length 8 ms; field of view (FOV) 22 cm and an acquisition matrix of 182 × 256 interpolated to a 256 × 256 with one excitation. A total of 146 individuals had moved from Framingham, MA. Brain MRI for 48 of these individuals was obtained at one of 16 centers in FL, CA and AZ, USA. Comparable imaging protocols were established for all MR vendors used and each site was required to submit a test image to verify adequate implementation of the protocol before subject data was acquired. Analyses of MRI measures across sites showed no substantial differences amongst the offsite images and those acquired at Framingham, MA (data available upon request). MRI vendors consisted primarily of Siemens and General Electric, but also included a small number of Philips machines. For the Siemens offsite MRI machines, every attempt was made

Table 1
Demographic characteristics at time of examination 7 for offspring participants with and without an MRI

Parameter	No MRI	MRI	*P*-value
Female (%)	54.4	53.1	0.473
Mean age at examination 7 (years)	61.9 ± 9.6	60.6 ± 9.4	<0.001
Mean SBP (mmHg)	129.3 ± 19.4	125.9 ± 18.5	<0.001
Mean DBP (mmHg)	74.5 ± 10.1	73.8 ± 9.6	0.030
Percentage hypertensive	51.6	42.3	<0.001
Percentage treated with anti-hypertensives	39.6	30.9	<0.001
Mean total cholesterol (mg/dL)	199.0 ± 37.2	201.0 ± 36.7	0.137
Mean HDL cholesterol (mg/dL)	53.9 ± 17.4	53.4 ± 16.9	0.389
Mean body mass index (BMI)	28.6 ± 5.1	28.0 ± 5.2	0.003
Percentage obese (BMI > 30)	32.8	28.6	0.011
% Diabetic	12.9	9.5	0.002
Glucose (mg/dL)	106.3 ± 28.7	103.4 ± 26.4	0.004
% Current smoker	14.4	12.5	0.110
Mean cigarettes smoked per day	2.6 ± 7.6	2.2 ± 7.0	0.096
Pack years smoked[a]			
0	86	88	0.091
≤1	11	10	
>1–≤2	3	2	
>2–≤3	<1	<1	
Alcohol consumption (oz/day)	0.37 ± 0.55	0.35 ± 0.54	0.983
Percentage LVH on ECG	1.2	0.6	0.089
Percentage atrial fibrillation	5.4	3.0	<0.001
Percentage history of CVD	16.6	11.5	<0.001
Percentage history of PVD	4.3	2.5	0.004
Percentage history of stroke/TIA	3.8	2.4	0.019
Percentage history of MI	6.3	4.0	0.002
Percentage history of CHD	11.3	8.0	0.002

SBP: systolic blood pressure; DBP: diastolic blood pressure; LVH: left ventricular hypertrophy; ECG: electrocardiogram; CVD: cardiovascular disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; MI: myocardial infarction; CHD: coronary heart disease. Numbers are percentages or mean ± standard deviation. *P*-value assesses significance of the difference between the two groups using one-way analysis of variance or Wilcoxon rank sum test for continuous parameters and the chi-square test or Fisher's Exact test for dichotomous parameters.

[a] Values for with and without MRI are given as percentages.

to match the Framingham scanner type; for all other machines, 1.5 T field strength was chosen.

3.2. Image analysis

After acquisition of the MR scans, the digital information was transferred to a central laboratory directed by one of the authors (C.D.) for processing and analysis. All analyses were performed blind to any subject personal identifying information. MRI quantification was performed with a custom-written computer program operating on a Unix, Solaris platform. Image evaluation was based on a semiautomatic segmentation analysis that involves operator-guided removal of non-brain elements as previously described [18]. In brief, non-brain elements were manually removed from the image by operator guided tracing of the dura matter within the cranial vault including the middle cranial fossa, but above the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the total cranial volume (TCV) and served as an estimate of head size to correct for recognized gender differences (please see Section 5 for complete description).

Quantification of regional brain, WMH and stroke volumes required a multi-step process that began with image segmentation to define brain matter from cerebral spinal fluid (CSF) (for detailed example see [20]). For segmentation of brain from CSF, a difference image was created by the subtraction of the second echo image from the first echo image. Image intensity non-uniformities were then removed from the difference image [22], and the resulting corrected image was modeled as a mixture of two Gaussian probability functions with the segmentation threshold determined at the minimum probability between these two distributions [18,64].

After image segmentation into brain matter and CSF, the operator returned to the image for measurement of lobar brain volumes. To increase the reliability of the lobar analyses, the images were rigidly rotated into anatomic standard space, using common cerebral landmarks. This was done by identification of the interhemispheric fissure in the axial and coronal planes and a by drawing a line joining the anterior and posterior commissures in the sagittal plane. Segmented brain-CSF images were rotated separately from the original image to preserve measurement precision.

Table 2
Prevalent medical conditions for offspring and original cohorts

Variable	Offspring cohort		Original cohort	
	Male $N = 916$	Female $N = 1056$	Male $N = 32$	Female $N = 77$
Mean age at MRI (years)	61.4 + 9.4[a]	61.0 + 9.3	84.2 + 3.8	83.6 + 2.6
Mean SBP (mmHg)	127 + 17.1	125 + 19.3	139 + 18.8	141 + 20.8
Mean DBP (mmHg)	75.3 + 9.5	72.3 + 9.3	68.2 + 11.9	67.5 + 10.8
Percentage hypertensive	45	39	87	82
Percentage treated with anti-hypertensives	35	28	72	69
Mean total cholesterol (mg/dl)	193 + 34.5	208 + 36.8	169 + 35.8	195 + 34.9
Mean HDL cholesterol (mg/dl)	45 + 12.5	61 + 16.7	46 + 11.9	60 + 17.7
Mean body mass index (BMI)	28.5 + 4.3	27.4 + 5.8	26.2 + 3.2	26.1 + 4.2
Percentage obesity (BMI>30)	30	26	11	18
Percentage diabetic	12	7	25	22
Glucose (mg/dl)	108 + 29.8	99 + 22.2	130 + 54.8	113 + 45.3
Percentage current Smokers	12	12	0	3
Mean cigarettes smoked per day	2.3 + 7.4	2.1 + 6.6	0.0 + 0.0	0.9 + 5.2
Pack years smoked[b]				
0	88	88	100	97
≤1	9	11	0	0
>1–≤2	3	1	0	3
>2–≤3	<1	<1	0	0
Mean alcohol consumption (oz/day)	0.5 + 0.6	0.2 + 0.4	0.4 + 0.6	0.2 + 0.4
Percentage LVH on ECG	1	<1	0	3
Percentage atrial fibrillation	5	2	22	12
Percentage history of CVD	15	7	44	34
Percentage history of PVD	3	2	13	10
Percentage history of TIA	1	1	16	8
Percentage history of MI	7	1	13	4
Percentage fistory of CHD	12	4	38	22

SBP: systolic blood pressure; DBP: diastolic blood pressure; LVH: left ventricular hypertrophy; ECG: electrocardiogram; CVD: cardiovascular disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; MI: myocardial infarction; CHD: coronary heart disease.

[a] Mean ± standard deviation for continuous variables.

[b] Values for both offspring and original cohort are given in percentages.

After the image was transformed into anatomic standard space, the operator returned to the image and identified brain lobar and regional CSF measures according to previously published methods and summarized in Fig. 1 [6,18,63,64]. In brief, frontal lobar regions were defined as all supratemporal structures anterior to the aqueduct of Sylvius. Temporal lobe volume was traced from the anterior pole of the temporal lobe to the aqueduct of Sylvius. The superior-medial temporal lobe boundary was defined as a straight line drawn from the angle of the medial temporal lobe, where it attaches to the temporal stem, to the midpoint of the operculum (for example see [6,21]). The dura of the middle cranial fossa was then traced around each temporal lobe to complete the temporal lobe region. The parietal lobes were defined as the brain matter posterior to the aqueduct of Sylvius, extending to the medial transverse fissure of the striate cortex. The remaining caudal portions of the cerebral hemispheres were defined as occipital.

Central CSF spaces were also analyzed from these rotated images. Analysis of central CSF spaces was divided into the lateral ventricles excluding the temporal horns of the lateral ventricles that were analyzed separately as an estimate of hippocampal size [15]. For convenience, the term temporal horn of the lateral ventricle is shortened to temporal horn for the purpose of this report.

For segmentation of WMH from brain matter, the first and second echo images were summed after removal of CSF and correction of image intensity non-uniformities [22]. A repeat gaussian distribution was fitted to the summed image data and a segmentation threshold for WMH was a priori determined as 3.5 S.D. in pixel intensity above the mean of the fitted distribution of brain parenchyma (for detailed example see [20]). Morphometric erosion of two exterior image pixels was applied to the image before modeling to remove the effects of partial volume CSF pixels on WMH determination.

The presence or absence of cerebral infarction, including volume of infarcted tissue if present, on MRI was determined for a subset of the first 1282 consecutive subjects imaged according to previously published protocols [20]. The presence of MRI infarction was determined from the size, location and imaging characteristics of the lesion. The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2 weighted image at three times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on

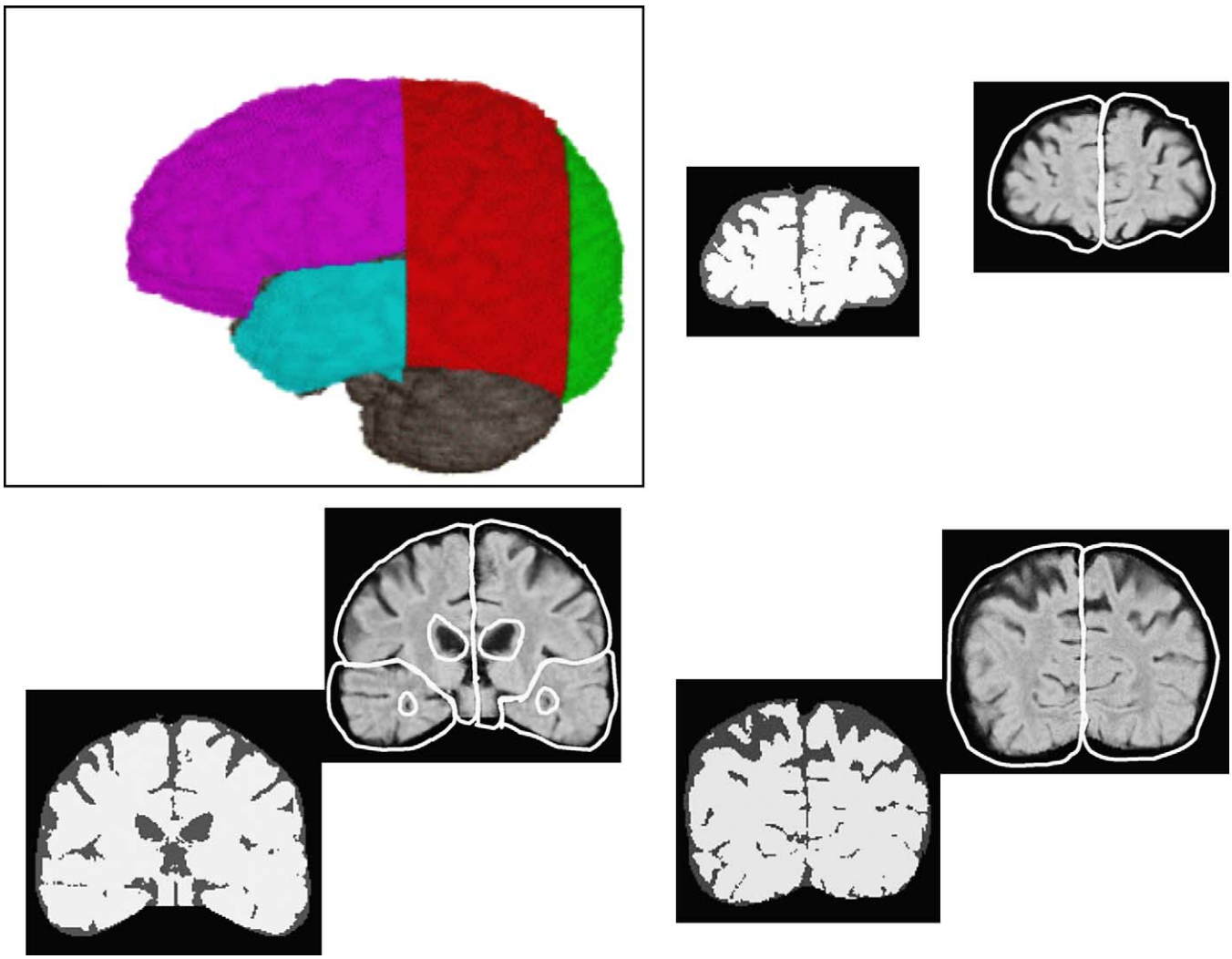

Fig. 1. Graphic illustration of regional boundaries for lobar determination. Color coded three-dimensional view of lobar regions is shown in the top left panel. The remaining three panels show regional boundaries for lobar and CSF volumes and the accompanying segmented brain-CSF images. The aqueduct of Sylvius (shown in the bottom left panel) and the striate cortex (shown in the bottom right panel) form the transition boundaries for frontal-parietal and parietal-occipital boundaries respectively. See text for details.

the T2 weighted image was interpreted to indicate a vessel. Only lesions 3 mm or larger qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included (1) CSF density on the subtraction image and (2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels. Three raters determined the presence of cerebral infarction on MRI (CD, JH and MT). Kappa values for agreement amongst the three raters were generally good and ranged from 0.73 to 0.90.

All volumes were calculated as the sum of the pixels within the identified region of interest multiplied by the pixel volume in milliliters. Inter-rater reliabilities for these methods have been previously published [18,21,63]. Repeat analysis of intra- and inter-rater reliabilities for the purpose of this study were consistently above 0.90.

4. Statistical methodology

For clarity, descriptive statistics of regional brain volumes are presented by gender and age quartile. Gender differences in age and other demographic variables were examined with two-sample *t*-test analysis for continuous variables and chi-square analysis for categorical variables. Gender differences in total cranial volume (TCV) and regional brain volumes (total brain, temporal lobe, frontal lobe, parietal lobe, occipital lobe, WMH, total lateral ventricle and temporal horn, expressed as a ratio of TCV) were examined with analysis of covariance adjusting for age. The relationship of TCV and regional volumes with age was assessed using linear regression adjusting for gender. Assessment of age-by-gender interactions was also performed. For WMH,

total lateral ventricle and temporal horn, analysis was performed on the natural logarithm of the volume ratios to TCV due to the skewness of the untransformed volumes and the more symmetrical distribution of values after logarithmic transformation. *T*-test statistics, linear regression analysis and Pearson correlations were used to explore the impact of MRI infarctions on regional brain and CSF volumes.

We were keenly aware of the limitations of biological inference based on cross-sectional analysis of two cohorts independently recruited and longitudinally evaluated. We also note that the original cohort is significantly older than the offspring cohort with virtually no age overlap (i.e. 99% of the offspring were at or below the minimum age of the original cohort). Thus, one limitation of our analysis will be the inability to discern the effect of advanced age on regional brain volumes from the effect of having recruited two separate cohorts. In order to mitigate potential cohort differences, we limited all analyses to those individuals from both cohorts who were free of neurological conditions such as dementia and stroke in order to make the cohorts more similar, although, as expected, the prevalence of cerebrovascular risk factors was substantially greater amongst the original cohort (Table 2). In addition, we examined graphical displays of the data to assess possible discontinuities of age-related trends that may be related to cohort effects. As will be discussed below, trends between age and all measured brain volumes were reasonably constant, suggesting that the effect of aging on the brain overwhelmed other, less apparent, differences between the cohorts. In recognition of these facts, we describe each cohort separately, but the impact of age, gender and MRI infarction on brain structure are examined for the two cohorts combined.

All statistical analyses were performed using SAS (version 8.1 for Windows, Cary, NC).

5. Results

Unless otherwise specified, results are presented for the 2081 participants free of dementia, stroke, multiple sclerosis and other neurological conditions.

5.1. Demographic variables

Group means and gender differences in age and as well as other demographic and prevalence of medical illness variables are summarized in Table 2. The average age of the participants was 62.4 ± 10.4 years (range, 34–96). Age ranged from 79 to 96 years for the original cohort, whereas the age range of the offspring cohort was 34–88 years. Approximately 45% of the cohort was male. The average age did not differ significantly by gender (62.2 ± 10.1 years for men and 62.5 ± 10.7 for women, $P = 0.478$). As noted previously, despite health screening for symptomatic neurological disorders, many subjects of the original cohort suffered from various diseases of the vascular system.

5.2. Cohort differences

Given that this is a cross-sectional study involving two separate cohorts, we are sensitive to potential cohort specific confounders. Since we use head size as the denominator for brain and CSF calculations, cohort differences in head size would confound comparison across cohorts. Analysis of cohort differences in head size found that the original cohort head size (1218 ± 122 cm^3, range: 986–1569; $N = 109$) was significantly smaller than the mean offspring cohort mean (1258 ± 134 cm^3, range: 538–1777; $N = 1972$), $P = 0.002$. On further analysis, however, we noted a disproportionate distribution of females in the original (71%) as compared to the offspring (53%) cohort. Since that average head size of women are approximately 150 cm^3 smaller than men (see below), we repeated the analyses according to gender. The average head size for the men of the original cohort ($N = 32$) was 1330 ± 105 cm^3 with a range of 1176–1569 cm^3. This was not significantly different from the average head size of the offspring cohort (1344 ± 109 cm^3, range: 1004–1777; $N = 916$, $P = 0.478$). Similarly, the average head size for the women of the Original cohort ($N = 77$) was 1171 ± 97 cm^3 with a range of 986–1497 cm^3 and not significantly different from the women of the offspring cohort (1183 ± 105 cm^3, range: 538–1529; $N = 1056$, $P = 0.323$). Therefore, while there is a trend toward smaller head size amongst the subjects of the original cohort, the mean differences according to gender were relatively small.

5.3. Gender differences in regional brain, WMH and CSF volumes

Gender differences in total cranial volume (TCV) are shown in Fig. 2. On average, the age-adjusted mean TCV for women was 160.1 cm^3 smaller than that for men (1343.2 ± 109.2 cm^3 for men versus 1182.5 ± 104.4 cm^3 for women; $P < 0.001$). While significant decreases in cranial volume were found in association with advancing age after adjusting for gender, they were subtle, decreasing at only 1.7 cm^3/year of age ($P < 0.001$). Further, this relationship between age and TCV was not significantly different for men and women (age by gender interaction $P = 0.419$). Thus, when comparing gender differences on total and regional brain volumes in subsequent analyses, we first divided each volume by TCV as a reasonable method for correcting for gender differences in head size between men and women across the age range in the study.

Mean gender differences for total brain and lobar volumes collapsed across age are summarized in Table 3 and Fig. 3. Statistically significant gender differences existed for all regional brain and CSF volumes ($P < 0.05$) with the exception of temporal lobe ($P = 0.638$) as shown in Table 3. In particular, women had significantly larger total brain and frontal lobe volumes. The magnitude of these gender differences, however, was rel-

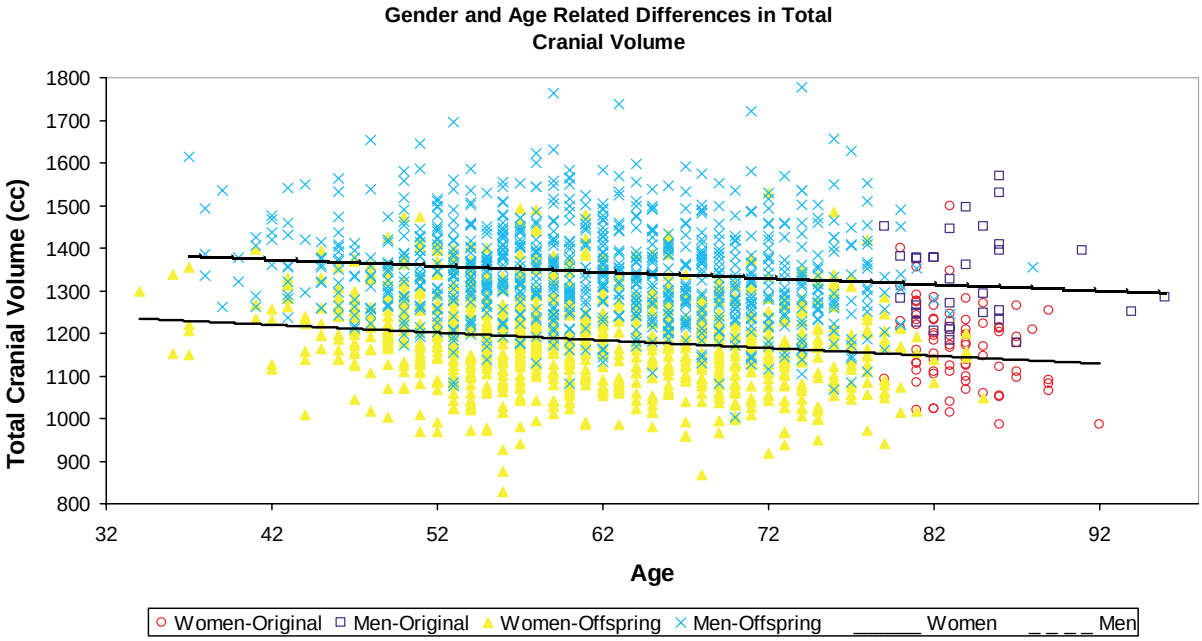

Fig. 2. Age-related differences in total cranial volume (TCV) for the men and woman of the study. Women show consistently smaller TCV volumes than men throughout the age-range.

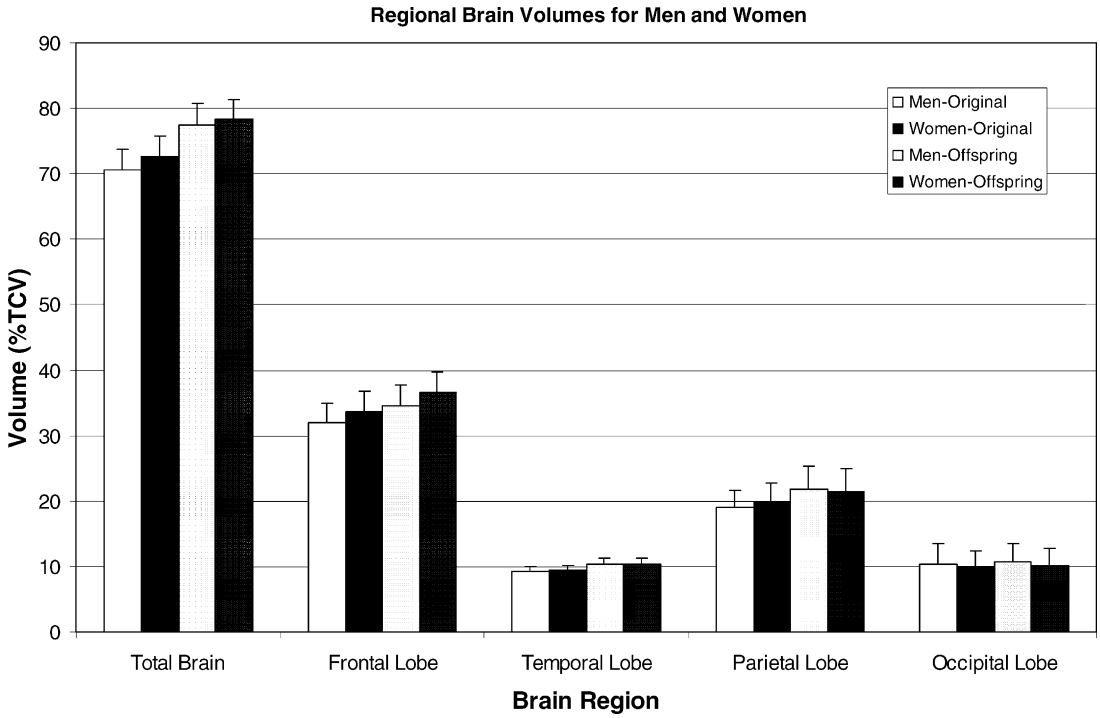

Fig. 3. Mean lobar brain volumes according to study cohort for men and women of the study. Consistent, but modest differences are seen in total brain and frontal lobe volumes between men and women.

atively small (generally <1%; Table 3, Figs. 3, 4 and 6). Conversely, men had consistently larger CSF volumes. On average, WMH volumes were significantly larger in women, but this difference was only marginally significant.

5.4. The effect of age on WMH, regional brain and CSF volumes

Regional brain and CSF volume measurements as well as WMH volume are graphically displayed according to age,

Table 3
Age and gender related differences in regional brain volumes

MRI measure	Mean value	Ages				*P*-value					
		34–54 (948, 233)[a]	55–61 (229, 288)[a]	62–70 (271, 275)[a]	71–96 (215, 272)[a]	Δ/year	R^2	Age	Age^2	Gender	Age*gender
TCV (cm^3)											
Male	1343.2 ± 109.2	1356.3 ± 103.2	1357.1 ± 105.8	1337.2 ± 106.6	1321.7 ± 118.6	−1.45	0.02	<0.001	0.791	<0.001	0.419
Female	1182.5 ± 104.4	1209.0 ± 110.7	1189.1 ± 103.3	1167.9 ± 95.2	1161.4 ± 100.6	−1.82	0.03	<0.001	0.035		
Total brain[b]											
Male	77.18 ± 3.61	79.84 ± 2.31	78.53 ± 2.49	76.55 ± 2.82	73.63 ± 3.50	−0.24	0.45	<0.001	<0.001	<0.001	<0.001
Female	77.96 ± 3.27	79.82 ± 2.37	78.96 ± 2.56	77.85 ± 2.57	74.98 ± 3.34	−0.18	0.35	<0.001	<0.001		
Temporal lobe[b]											
Male	10.39 ± 0.92	10.85 ± 0.82	10.65 ± 0.77	10.31 ± 0.80	9.71 ± 0.92	−0.04	0.22	<0.001	<0.001	0.638	<0.001
Female	10.35 ± 0.87	10.57 ± 0.88	10.59 ± 0.80	10.39 ± 0.73	9.81 ± 0.85	−0.03	0.12	<0.001	<0.001		
Frontal lobe[b]											
Male	34.54 ± 3.11	36.55 ± 2.48	35.44 ± 2.85	33.70 ± 2.73	32.45 ± 2.74	−0.16	0.26	<0.001	0.103	<0.001	0.410
Female	36.32 ± 3.29	38.11 ± 2.66	36.97 ± 3.05	36.03 ± 2.81	33.96 ± 3.15	−0.15	0.23	<0.001	0.817		
Parietal lobe[b]											
Male	21.64 ± 3.52	21.70 ± 3.36	21.82 ± 3.64	21.67 ± 3.38	21.35 ± 3.72	−0.02	0.03	0.079	<0.001	0.049	0.030
Female	21.31 ± 3.45	20.91 ± 3.20	21.15 ± 3.56	21.75 ± 3.31	21.46 ± 3.67	0.01	0.01	0.229	<0.001		
Occipital lobe[b]											
Male	10.70 ± 2.88	10.84 ± 2.85	10.73 ± 2.96	10.97 ± 2.93	10.17 ± 2.69	−0.02	0.05	0.026	0.666	<0.001	0.859
Female	10.10 ± 2.58	10.35 ± 2.47	10.38 ± 2.71	9.80 ± 2.42	9.84 ± 2.68	−0.02	0.05	0.013	0.816		
WMH[b,c]											
Male	−3.10 ± 1.03	−3.69 ± 0.80	−3.42 ± 0.81	−2.96 ± 0.93	−2.32 ± 1.04	0.05	0.27	<0.001	0.015	0.030	0.298
Female	−2.99 ± 1.10	−3.61 ± 0.90	−3.40 ± 0.88	−2.83 ± 0.91	−2.05 ± 1.02	0.06	0.34	<0.001	0.017		
TLV[b,c]											
Male	0.70 ± 0.51	0.36 ± 0.42	0.52 ± 0.43	0.80 ± 0.41	1.12 ± 0.43	0.03	0.32	<0.001	0.194	<0.001	0.192
Female	0.57 ± 0.55	0.27 ± 0.46	0.38 ± 0.45	0.63 ± 0.48	1.04 ± 0.46	0.03	0.31	<0.001	<0.001		
Temporal horn[b,c]											
Male	−2.78 ± 0.66	−3.02 ± 0.51	−3.07 ± 0.60	−2.75 ± 0.55	−2.25 ± 0.67	0.03	0.23	<0.001	<0.001	<0.001	0.093
Female	−3.01 ± 0.73	−3.24 ± 0.59	−3.25 ± 0.66	−3.01 ± 0.69	−2.49 ± 0.70	0.03	0.18	<0.001	<0.001		

TCV: total cranial volume; WMH: white matter hyperintensities; TLV: total lateral ventricular volume; temporal horn: volume of temporal horn of the lateral ventricles. *P*-values for age and age^2 are listed separately for each gender. R^2: percentage of variance in MRI measure explained by linear estimate of age; Δ/year: difference in volume of MRI measure per year of age based on linear estimate.

[a] The first value in parentheses is number of males and the second value is number of females.

[b] Expressed as percentage of TCV.

[c] Natural log transformed; negative values result from the estimate as a fractional percentage of TCV.

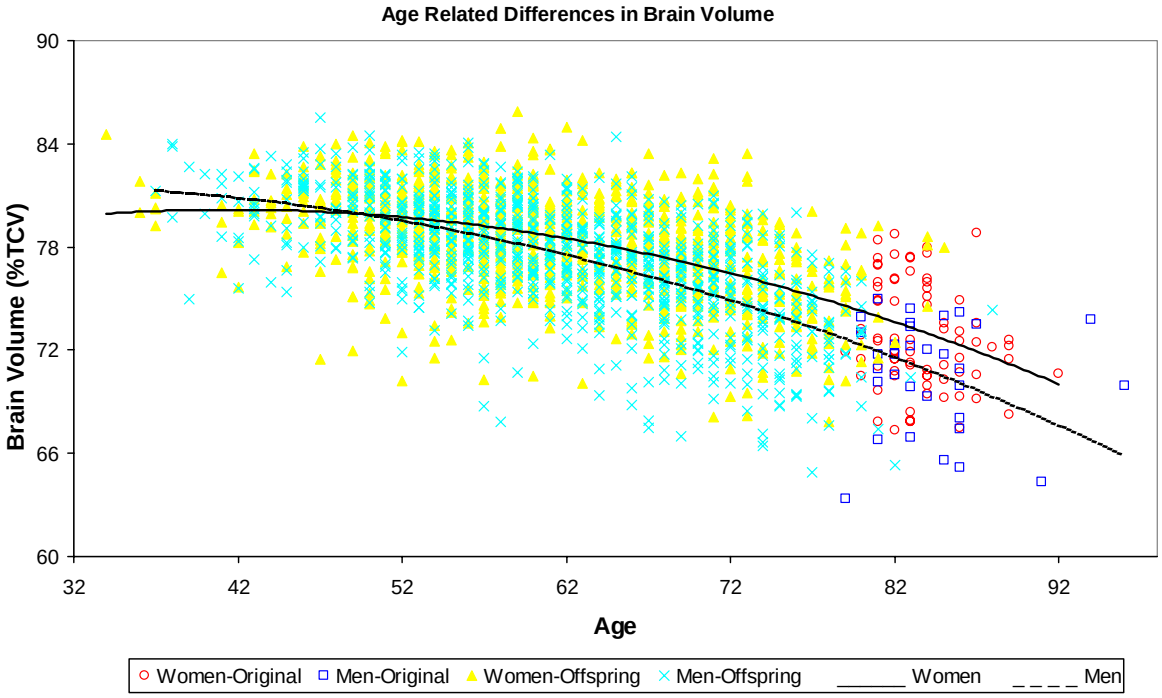

Fig. 4. Age-related differences for total brain volumes according to study cohort for men and women. Relatively little difference is seen in total brain volumes prior to age 55 years after which age-related differences are much more pronounced and the best fit regression model is quadratic.

gender and cohort membership in Figs. 4–11. Visual inspection of the data suggested non-linear differences with age for some of the MRI measures and therefore each region was analyzed as a mixture of linear and non-linear components. The significance of each component is listed in Table 3 and the best fitting regression model is plotted on the graphs of respective MRI measures. The magnitude of linear difference with age is also summarized.

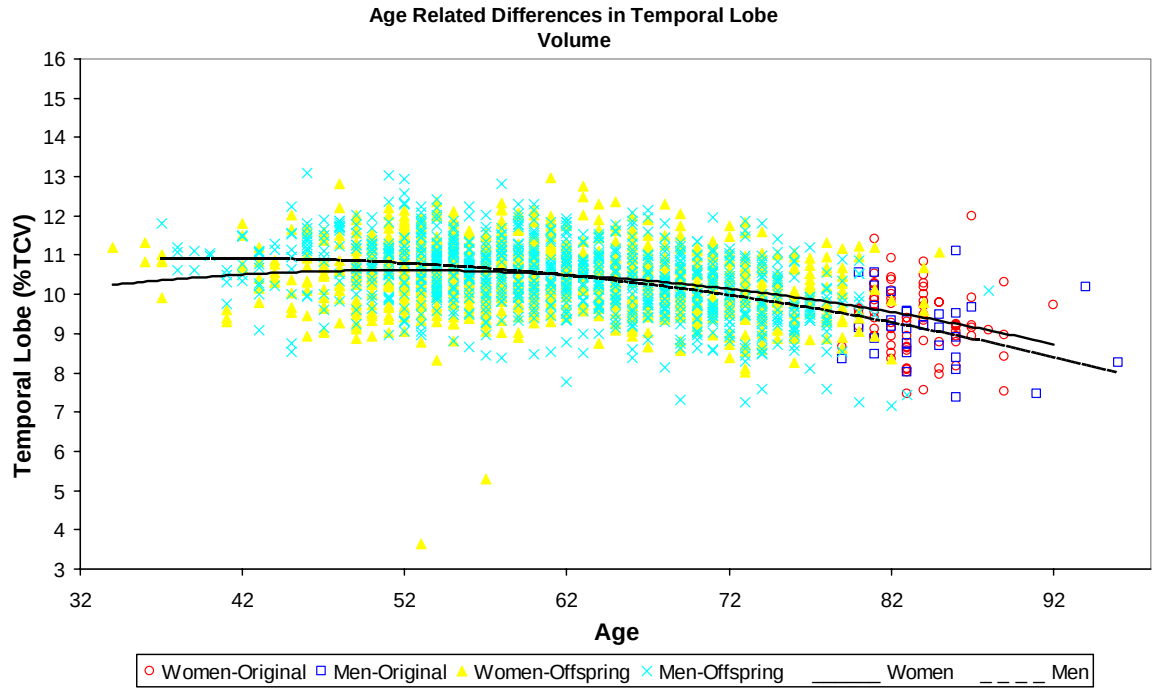

Fig. 5. Age-related differences for temporal lobe volumes according to study cohort for men and women. Relatively little difference is seen in total brain volumes prior to age 62 years after which age-related differences are much more pronounced and the best fit regression model is quadratic.

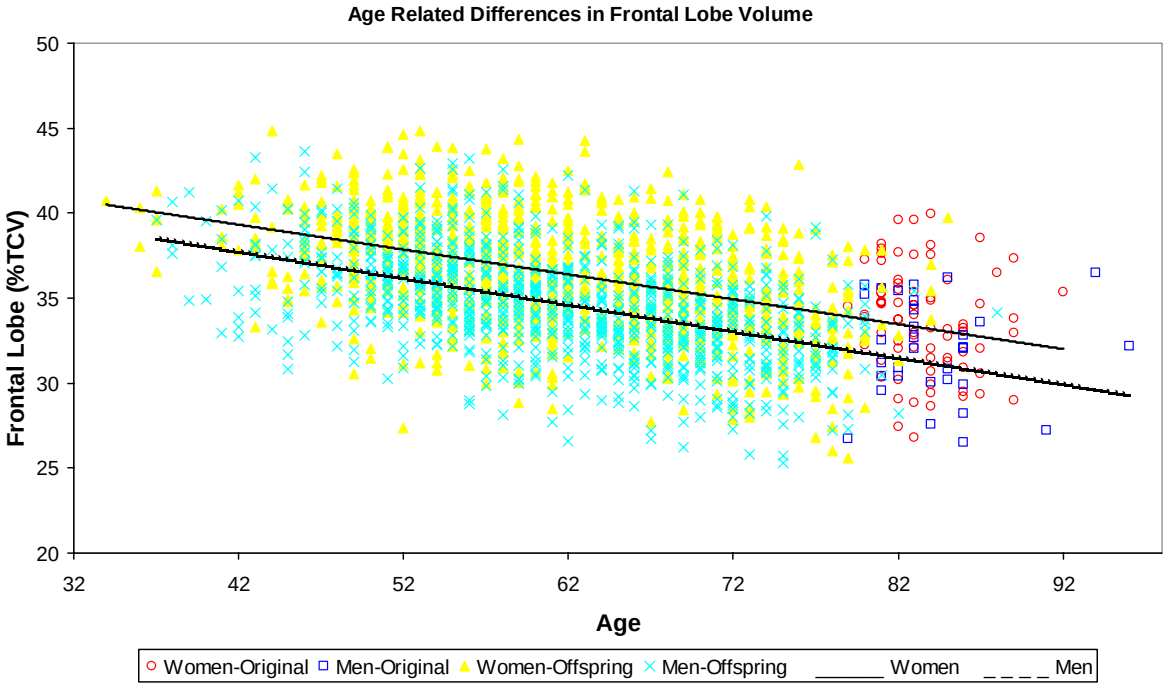

Fig. 6. Age-related differences for frontal lobe volumes according to study cohort for men and women. Age-related differences are clearly linear with men having consistently smaller volumes for each year age as compared to women.

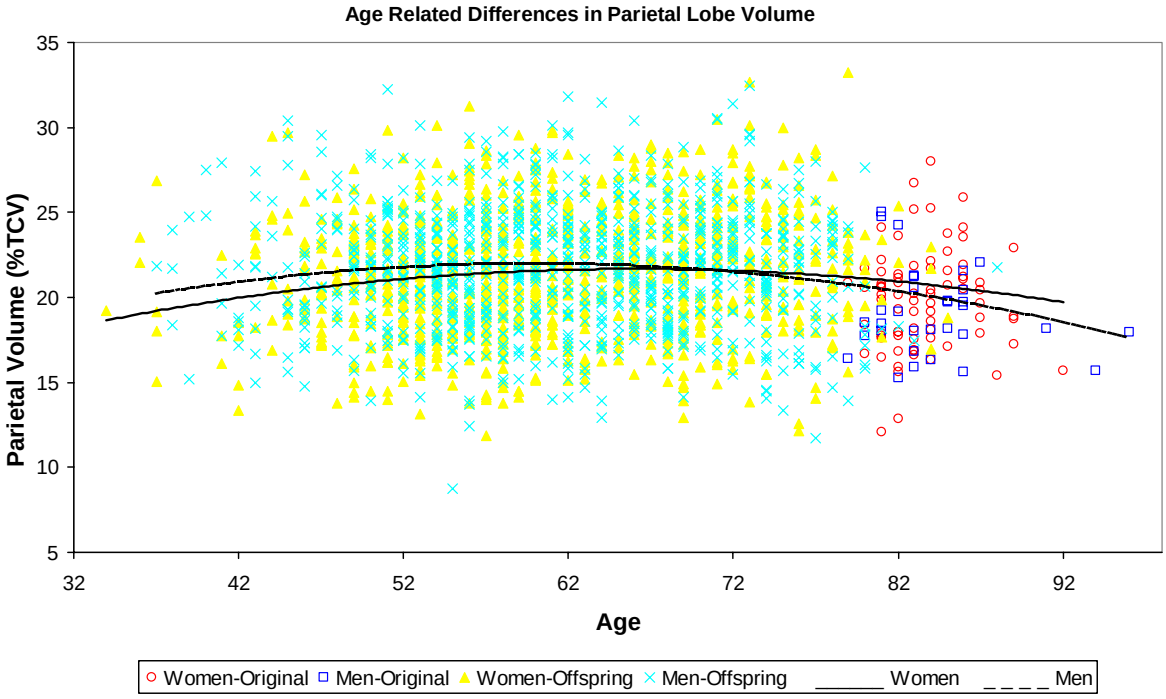

Fig. 7. Age-related differences for parietal lobe volumes according to study cohort for men and women. Although the best fit regression model is quadratic, very little difference in volume is seen across the age-range studied.

Age-related differences were found for most MRI measures, with the exception of parietal lobe volumes that did not differ significantly with age and occipital lobe volumes that were of borderline significance. Total brain volumes declined approximately 0.2 per year as percentage of TCV over the age-range studied. Most of these differences were explained by age-related reductions in frontal lobe volumes (approximately 0.15 per year as percent-

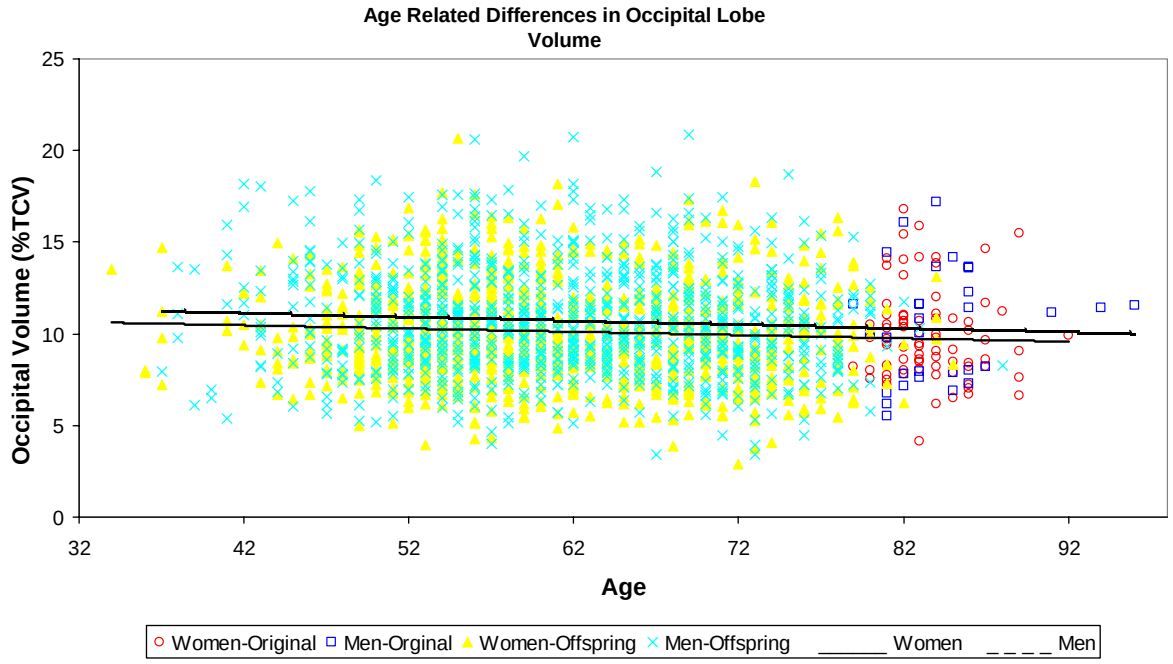

Fig. 8. Age-related differences for occipital lobe volumes according to study cohort for men and women. Although age-related differences are significant, the magnitude of these differences are small in comparison to other brain regions studied.

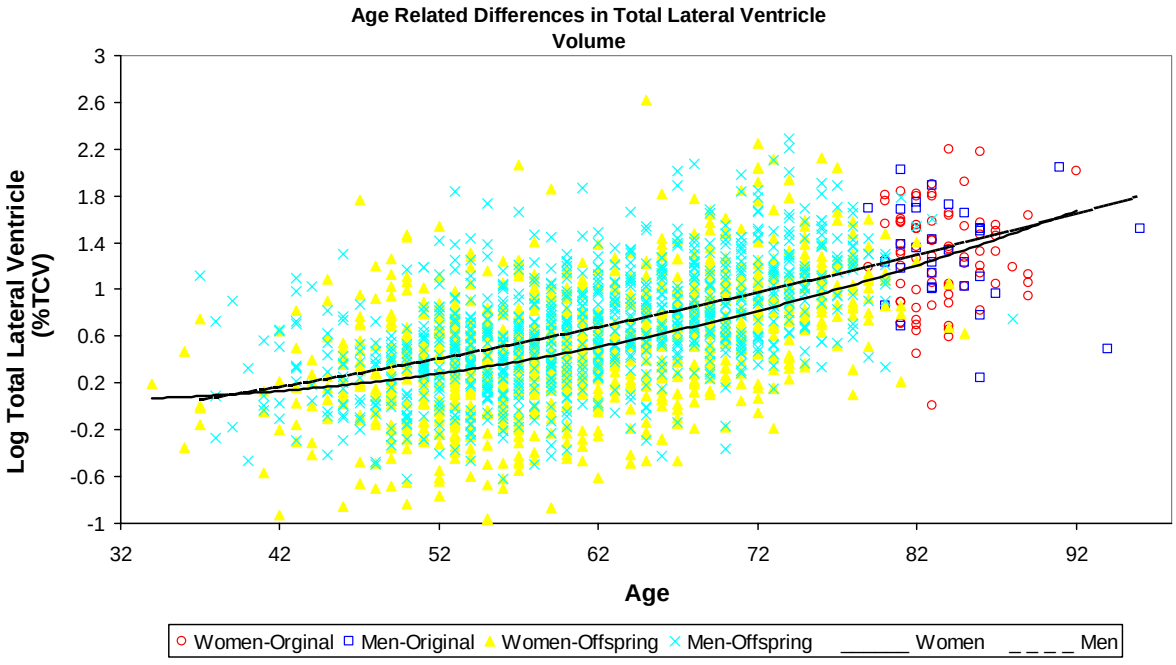

Fig. 9. Age-related differences for temporal lateral ventricle volumes according to study cohort for men and women. Relatively little difference is seen in volumes prior to age 55 years after which age-related differences are much more pronounced and the best fit regression model is quadratic.

age TCV), followed by age-related reductions in temporal lobe volumes (approximately 0.04 per year as percentage TCV).

Visual inspection of age-related differences in total brain and temporal lobe volumes show little change before approximately 60 years of age with substantial reductions in volume thereafter. This pattern of age-related differences is supported by the highly significant quadratic terms in the regression analyses for these two MRI measures. A similar, but inverse, quadratic relation between age and MRI measure was also found for temporal horn volumes. While other regression analyses revealed significant quadratic terms,

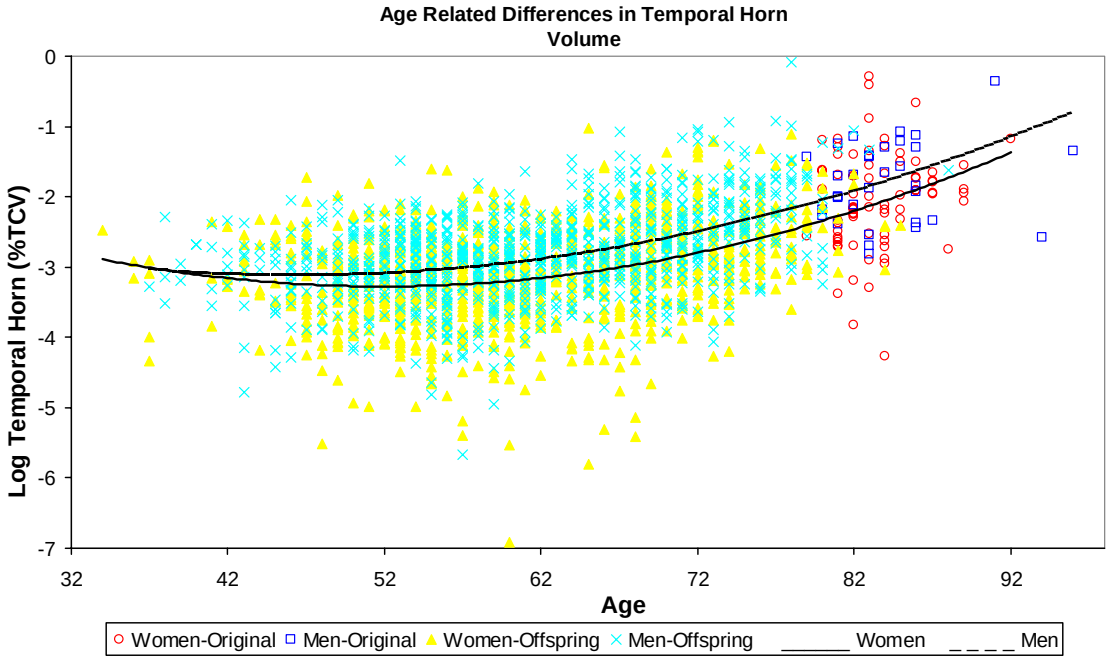

Fig. 10. Age-related differences for temporal horn volumes according to study cohort for men and women. Relatively little difference is seen in volumes prior to age 62 years after which age-related differences are much more pronounced and the best fit regression model is quadratic.

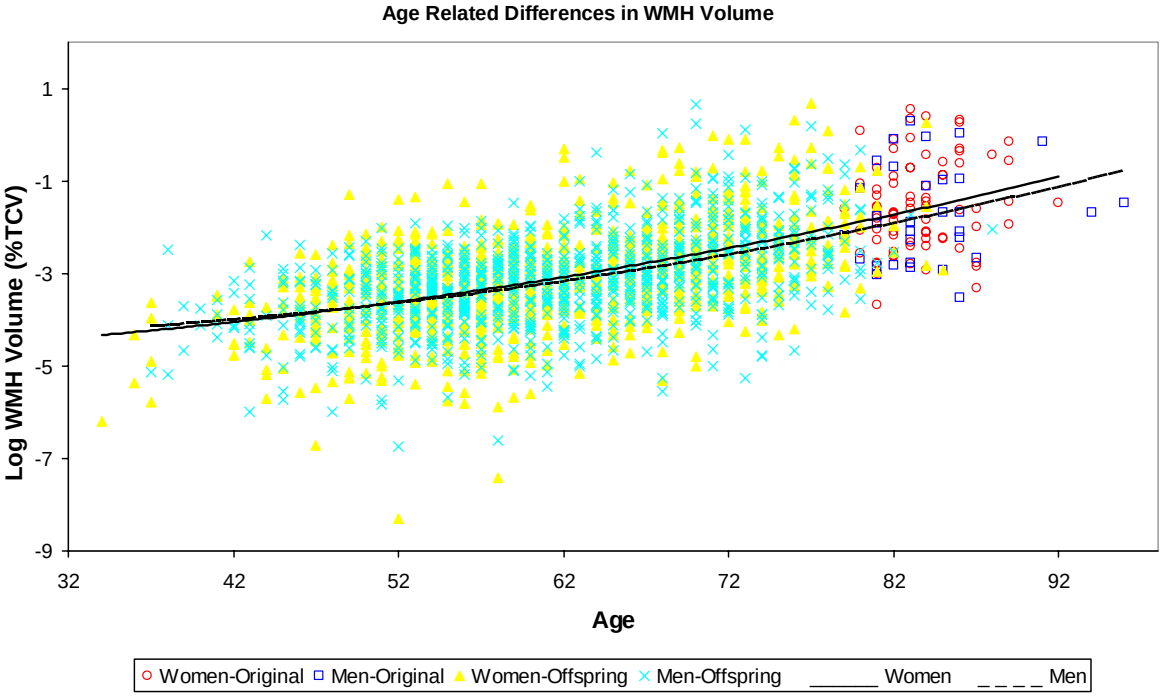

Fig. 11. Age-related differences for WMH volumes according to study cohort for men and women. Although the best fit regression model is quadratic, the quadratic effect is small in comparison to the linear effect. WMH volumes for women are consistently larger than men, although this difference is small.

these were generally small. Importantly, however, the pattern of age-related differences was strikingly different for frontal lobe volumes where there was a robust and strictly linear decline in measured volume beginning at the earliest ages studied.

5.5. Age, gender interactions in total brain, regional brain and CSF volumes

Further evaluation revealed a statistically significant age-by-gender interaction ($P < 0.001$) in total brain and tempo-

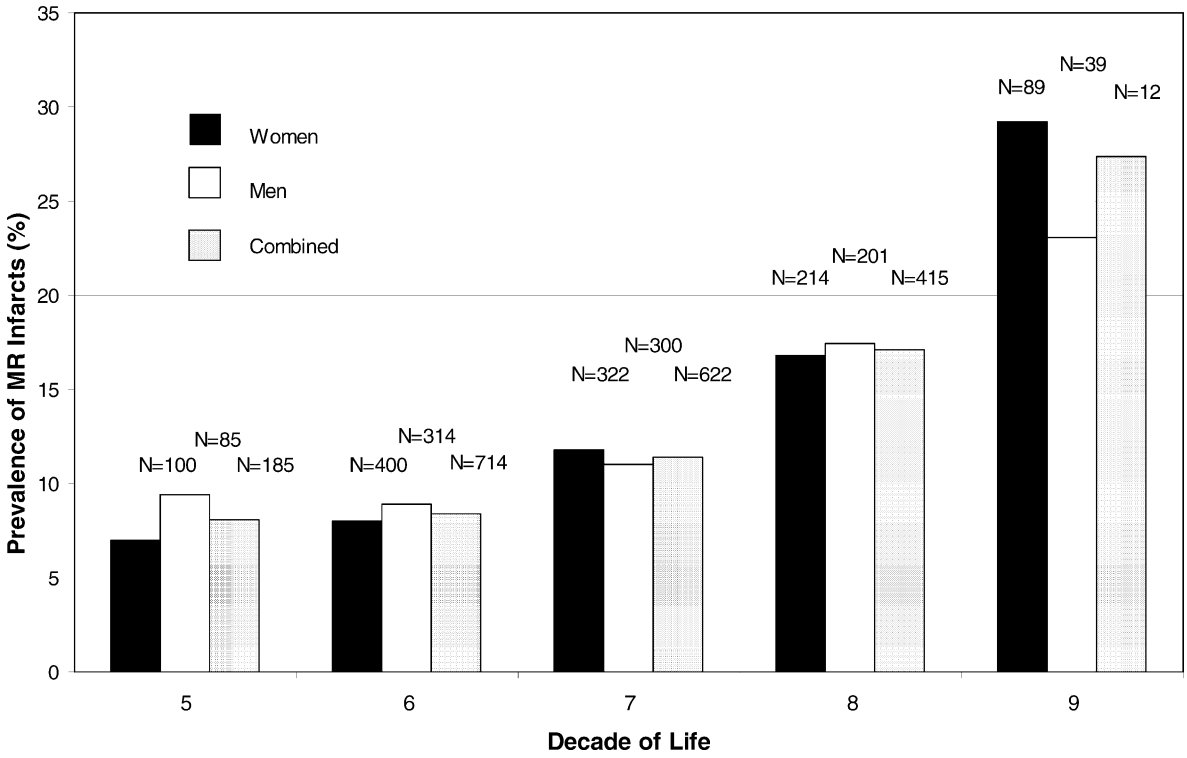

Fig. 12. Age-related prevalence of asymptomatic MRI infarctions. Consistent age-related increases in prevalence is seen for both men and women through the 5th and 9th decades of life where sufficient data are available for interpretation.

ral lobe volumes. As shown in Table 3 and Figs. 4 and 6, this effect was due primarily to relatively more rapid age-related differences (as seen by Δ/year in Table 3) for men than women. That is, these volumes were initially larger (as percentage TCV) in men during early life, but were smaller amongst the older men. A similar type relationship existed for parietal lobe volumes, but overall age-differences are quite small, therefore, the magnitude of the age-gender interaction was equally small.

5.6. Prevalence and impact of MRI infarction

MRI infarction was identified as present or absent for all subjects studied. In addition, the actual volume in cubic centimeters of MRI infarction was calculated for a subset of 1302 subjects using the methods described above. The prevalence of at least one MRI infarction was 12.3% (12.1% for men and 12.4% for women; $P > 0.876$). A total of 316 MRI infarctions were detected in the 255 participants with infarctions (145 male, 171 female). Age specific prevalence also was determined for each decade as graphically summarized in Fig. 12. The data displayed included only decades 5 through 9, as there were few participants in their thirties (decade 4) and in their nineties (decade 10) resulting in poor estimates of prevalence. For men and women combined, MRI infarctions increased steadily as age increased to a maximum prevalence of 27.7% at the 9th decade of life (ages 80–89 years). For both genders combined, there was a significant positive linear relationship between rate of infarction and age ($P < 0.0001$; odds of infarction increased by a factor of 1.5 for every 10-year increase in age between 40 and 89 years). Results were similar for men and women separately, as indicated by lack of a significant gender-by-age interaction ($P = 0.308$) on prevalence of MRI infarction.

Mean differences in MRI measures between individuals categorized by the presence or absence of MRI infarctions are summarized in Table 4. While there were many significant differences for unadjusted comparisons, individuals with MR infarcts were older than those without MR infarcts; differences, therefore, were reduced after adjusting for age, particularly for women. WMH volume was consistently larger for participants categorized by the presence of MRI infarction as compared to participants without MRI infarction. Amongst men, the presence of MRI infarction was associated with significantly reduced total brain volume with trends toward significant reductions in frontal and temporal brain volumes even after correcting for age. No significant age corrected differences in total or regional brain volumes after stroke were found with women.

Further analyses of a subset of 1302 individuals for whom the volumes of MRI infarctions were available allowed exploration of the relation between the volume of the infarction and age-related differences in brain measures. Initial univariate analyses for the 202 individuals within this subgroup who had MRI infarction found modest, but significant

Table 4
Regional brain volumes by infarct status

Gender	Volume	Participants with no infarct	Participants with at least one infarct	*P*-value	
				Unadjusted	Age-adjusted
Males	Total brain[a]	77.34 ± 3.51	75.95 ± 4.01	<0.001	0.018
($N = 833$ without infarct; $N = 115$ with infarct)	Temporal	10.42 ± 0.91	10.14 ± 0.98	0.002	0.068
	Frontal	34.66 ± 3.09	33.69 ± 3.17	0.002	0.075
	Parietal	21.60 ± 3.52	21.94 ± 3.51	0.328	0.242
	Occipital	10.76 ± 2.88	10.28 ± 2.83	0.092	0.144
	WMH[b]	−3.17 ± 0.99	−2.61 ± 1.18	<0.001	<0.001
	TLV	0.68 ± 0.51	0.83 ± 0.49	0.002	0.116
	Temporal horn	−2.79 ± 0.66	−2.73 ± 0.68	0.438	0.385
Females	Total brain	78.09 ± 3.20	77.05 ± 3.63	<0.001	0.898
($N = 993$ without infarct; $N = 140$ with infarct)	Temporal	10.37 ± 0.87	10.19 ± 0.87	0.019	0.852
	Frontal	36.43 ± 3.27	35.52 ± 3.34	0.002	0.862
	Parietal	21.23 ± 3.43	21.81 ± 3.52	0.064	0.098
	Occipital	10.17 ± 2.60	9.63 ± 2.41	0.023	0.065
	WMH	−3.08 ± 1.08	−2.42 ± 1.13	<0.001	<0.001
	TLV	0.55 ± 0.54	0.72 ± 0.58	<0.001	0.996
	Temporal horn	−3.03 ± 0.72	−2.81 ± 0.77	<0.001	0.423
Both genders combined	Total brain	77.75 ± 3.37	76.55 ± 3.84	<0.001	0.194
($N = 1826$ without infarct; $N = 255$ with infarct)	Temporal	10.40 ± 0.89	10.16 ± 0.92	<0.001	0.220
	Frontal	35.62 ± 3.31	34.69 ± 3.38	<0.001	0.238
	Parietal	21.40 ± 3.47	21.87 ± 3.51	0.044	0.038
	Occipital	10.44 ± 2.75	9.93 ± 2.62	0.005	0.020
	WMH	−3.12 ± 1.04	−2.51 ± 1.15	<0.001	<0.001
	TLV	0.61 ± 0.53	0.77 ± 0.55	<0.001	0.322
	Temporal horn	−2.92 ± 0.71	−2.78 ± 0.73	0.003	0.973

WMH: white matter hyperintensity; TLV: total lateral ventricle.
[a] All values expressed as percent of total cranial volume.
[b] WMH, TLV and TH were natural log transformed.

correlations between the volume of MRI infarction and total brain ($r = -0.28$, $P < 0.0001$), frontal lobar ($r = -0.14$, $P < 0.05$), temporal lobar ($r = -0.17$, $P < 0.05$), parietal lobar ($r = -0.17$, $P < 0.05$), WMH (r = 0.19, $P < 0.01$) and temporal horn (r = 0.15, $P < 0.05$) volumes. Multiple regression analyses were also preformed in this subgroup and explored the impact of age, volume of MRI infarction and the potential interaction of age and volume of MRI infarction on brain, WMH and CSF volumes. To simplify the analysis, only linear age effects were considered and the genders were combined, but the same variable scaling was used as described in the initial analyses of age-related differences. The results of these analyses are summarized in Table 5 and include re-estimates of age-related differences in MRI measures when the presence of MRI infarction was included in the regression analysis. Significant increases in age-related differences associated with MRI infarction were found for total brain and temporal lobar volumes with the

Table 5
Age-related differences associated with MRI Infarction for subgroup where infarct volume was measured

Structure	Model R^2	Δ/year	*P*-value		
			Age	MRI infarction	MRI infarction*age
Total brain[a]	0.488	−0.26	<0.001	0.282	0.047
Temporal lobe	0.251	−0.05	<0.001	0.121	0.013
Frontal lobe	0.293	−0.16	<0.001	0.816	0.516
Parietal lobe	0.014	−0.03	<0.001	0.951	0.950
Occipital lobe	0.003	−0.02	0.424	0.571	0.228
WMH[b]	0.352	0.06	<0.001	0.679	0.097
TLV	0.374	0.04	<0.001	0.044	0.022
Temporal horn	0.275	0.04	<0.001	0.015	0.012

WMH: white matter hyperintensity; TLV: total lateral ventricle. Δ/year: difference in volume of MRI measure per year of age.
[a] All values expressed as percent of total cranial volume.
[b] WMH, TLV and TH were natural log transformed.

rate of age-related differences increasing from −0.22 to −0.26 for total brain and from −0.03 to −0.05 for temporal lobe volumes. Similar, but inverse associations were seen for total lateral ventricular and temporal horn volumes. The mean volumes of MRI infarction (for the group with MRI infarction) did not differ between men and women (1.81 ± 9.0 cm^3 versus 1.68 ± 6.1 cm^3, $P > 0.9$) and multiple regression analyses that included gender effects found no effect of volume of MRI infarction according to gender (data not shown).

6. Discussion

We believe this to be the first study to examine age and gender related differences in regional brain volumes for a community representative of the general population free of stroke, dementia or other chronic neurological diseases. We purposely limited exclusionary criteria to symptomatic neurological disorders in order to fully capture the spectrum of brain morphology amongst these individuals.

The results of these analyses reveal three important findings. First, chronological age is associated with substantial differences in regional brain volumes that are quantitatively and qualitatively different according to the brain regions examined. While these findings generally confirm previous observations from MRI quantification studies [9–12,21,35,41,42,63,64,66,69–74,89,90], they also lend substantial further support to these findings through the study of a cohort of individuals likely to be representative of the general population. Second, gender differences in brain morphology were generally modest when compared to age-related differences, except for frontal lobe volumes where women had consistently greater volumes than men across the range of ages studied. Age and gender interactions tended to favor initially larger regional brain volumes for men, but the aging processes tended to have greater a greater impact on the brains of men, such that women tended to have less age-related brain differences than men in later life. These findings confirm some previous reports [14,63], but differ from others [69], although the general impression is that gender differences are mild compared to the effects of aging [63,69]. Thirdly, the impact of MRI infarctions, all of which were clinically silent, was substantial. When individuals with MRI infarction were compared to individuals without MRI infarction, significant differences were found for nearly all MRI measures, although the MRI infarction group was significantly older. Correcting for age diminished these differences, but a significant effect was still present for men. Importantly, however, additional analyses, within the subgroup of individuals where the volume of MRI infarctions was quantified, found significant interactions between age and the presence of MRI infarction for total brain, temporal lobe, total lateral ventricle and temporal horn volumes showing evidence of accelerated brain aging (increased age-related differences) in association with the presence of MRI infarctions.

Before discussing our findings in the context of previous literature, we must note that our analyses were limited to regional brain volume. Due to the vast amounts of data, tissue segmentation into gray matter and white matter was not performed. Therefore, some of our findings differed from previous reports where further tissue segmentation was performed, although, in general, these differences were rather minor as discussed below.

7. Brain aging

Age-related differences in regional brain volumes have been examined in a number of studies [9–12,21,35,41,42,63,64,66,69–74,89,90] with generally comparable results. For example, within a select group of very healthy individuals, Jernigan et al. [41,42] show results similar to those reported here with age related differences being largest for total brain, frontal lobe and temporal brain volumes, whereas age-related differences in parietal and occipital lobe brain volumes were small. Age-related differences similar to those reported here have also been shown for temporal lobe, temporal horn and ventricular CSF [89], supporting the consistency of our findings despite evaluation of a population more representative of general aging with attendant medical illnesses without tissue segmentation into gray matter and white matter. Not only are regional differences apparent, but regional age-related differences are qualitatively different as well. For example, in this study, total brain volume differences were minimal before age 50 although substantial age-related differences were found thereafter, results remarkably similar to those shown previously [66]. Conversely, age-related differences in frontal brain volumes showed a more linear decline. The magnitude of change also differed with more frontal than temporal lobe volume loss on a percent basis, again supporting previous reports [10,12]. Finally, longitudinal studies of brain aging suggest that these regional differences remain ongoing, particularly with regard to loss of frontal lobe volumes [67,75].

Biological studies of human post-mortem tissue support the notion of regional differences in vulnerability to the aging process (for review see [29,44]). For example, estimates of gyral width show 20–30% cell loss in frontal and temporal brain regions, with relative sparing in occipital association regions [44]. Importantly, however, others have shown that neuronal shrinkage may be the prominent component of regional volume loss [29] that disproportionately affects frontal neurons [37]. The exact cause for these regional differences is unknown and multiple hypotheses abound [58–60,77,91,92], although these theories rarely speak to regional variability with age [60,69]. Whatever the cause for regional vulnerability with age, regions with the greatest age-related differences in volume may also be more susceptible to injury by disease such as the impact

of MRI infarctions on temporal lobe volumes seen in our data.

Interestingly, those brain regions showing the largest age-related differences in this study coincide with brain regions found to have high heritability [5,6,68,96] suggesting the possibility that the aging process may be under strong genetic control [39]. Importantly, the frontal and temporal lobe brain regions most influenced by age include large areas of heteromodal cortex most likely influenced by in utero, early developmental or environmental influences, that could impact significantly on how these structures respond to the aging process [6,69]. Whether these genetic factors act during development or later as a response to the aging process [39,69] is not known, but both effects are likely to be present and require further study. The Framingham Heart Study is ideally suited in this regard. DNA samples are available from both the original cohort and their offspring and a third generation cohort is being established to support family linkage studies. Moreover, longitudinal MRI data may also assist with estimating various genetic influences on the trajectories of brain aging, leading to further insights with regard to gene-environmental interactions that might impact on parameters of healthy brain aging.

Finally, the linear age-related differences in size of the frontal lobe volumes are consistent with a number of proposed theories of aging [4,34,78–80] that emphasize progressive loss of cognitive resources beginning in early life and declining nearly linearly with age. Similarly, the relatively stable brain measures for temporal lobe brain volumes until later life also coincide with relatively maintained language abilities [48]. Our findings and those of others [10,42,69] strongly support the importance of further study regarding the role of the frontal lobes in cognitive aging.

8. Gender effects

Estradiol exerts multiple and diverse actions on the brain during development and throughout adulthood [101]. Given the lifetime differences in estradiol concentrations and the trophic effects of this hormone on neurons amongst men and women, gender differences in brain volume would be expected [62]. Estrogen may have additional beneficial effects on cerebrovascular disease [30,57,101] that would be hypothesized to further increase gender differences in regional brain volumes with age [20,63]. More recent evidence, however, actually suggests an increased risk of cerebrovascular disease with estrogen replacement with or without accompanying progesterone [40,76] potentially offsetting any neuronal trophic benefits, drawing into question the beneficial impact of estrogen on brain health beyond brain developmental and pre-menopausal influences.

Our data are consistent with multiple brain imaging studies have found only small gender differences in regional brain volumes throughout the span of normal aging [9,33,36,63,66,69] generally consistent with our own findings. With the exception of frontal lobe volumes, in our data men tended to have larger volumes early in life, but slightly smaller volumes at later life. One study using the same method of quantification [63] found similar gender differences in frontal lobe brain volumes, but this has not been confirmed in other studies [9], particularly where more specific regional comparisons were made [33,69].

Despite these congruent findings, prevalent cerebrovascular risk factors were generally lower in the women of this study, consistent with data from other epidemiological studies of older women [57]. Evidence of cerebrovascular related brain injury (i.e. WMH, prevalent MRI infarctions and volumes of MRI infarctions), however, was nearly identical for both genders. While these findings may explain similarities in regional brain volumes, they raise questions regarding the existence of non-conventional risk factors for cerebral infarctions amongst older women (which may even include hormone replacement therapy) and that warrant further study [40,76,98].

In conclusion, these data in a community-based population with usual age-associated medical illnesses find only modest gender-related differences in regional brain volumes across the span of normal aging. Cross-sectional analysis of a large cohort, however, may obscure more subtle, but important gender differences, particularly amongst the elderly where gender-related differences in neurological diseases, such as Alzheimer's disease is more common [1]. Longitudinal analysis to determine rates of regional brain change with age, particularly amongst the older members of the Framingham Heart Study will help to further elucidate this possibility.

9. Impact of cerebrovascular disease

Cerebrovascular risk factors are associated with a wide spectrum of morphological brain changes in the absence of clinical stroke [7,8,20,23,24,28,51–55,82,94,99,102]. Only limited work, however, has been done to examine the regional impact of these risk factors with mixed results [31,88]. Data from older men suggest preferential frontal atrophy [31], whereas a smaller study of men and women suggest preferential temporal atrophy [88]. Our results are consistent with these second observations [88]. We found significant differences in age-related total brain and temporal lobe atrophy as well as expansion of total and temporal horn CSF in the setting of MRI infarction. As expected, the degree of regional atrophy also was significantly correlated with the volume of the MRI infarction for the subset of individuals with MRI infarctions.

The cause for accelerated brain atrophy and CSF expansion in the setting of MRI infarction is currently unknown. The presence of MRI infarction likely represents end-organ effects of more widespread cerebrovascular disease [97]. While it has been assumed that vascular pathology is the processes by which brain atrophy occurs, only limited work

has been done to explore this possibility [2,3,32,61,95] and further work is necessary to more fully understand how cerebravascular pathology leads to cortical brain injury.

Accelerated brain aging due to cerebrovascular disease as seen in this study may help to explain the increased prevalence of mild cognitive impairment [17,19,45,56] and dementia (including Alzheimer's disease) [46,47,49,84–86] associated with cerebrovacular risk factors and MRI infarctions [100]. Interestingly, hippocampal and generalized cerebral atrophy in the absence of Alzheimer's disease pathology has been observed in the setting of cerebrovascular disease [28] suggesting a potential mechanism by which cerebrovascular disease might lead to dementia, including synergism with the Alzheimer's disease process [81,87]. Longitudinal observation of this younger cohort with MRI infarctions to assess cognitive decline or dementia incidence and associated changes in regional brain morphology will contribute understanding to the process by which cerebrovascular brain injury leads to cognitive impairment.

10. Strengths and limitations

The strengths of this study are the population-based sample and the use of quantitative MRI techniques. This study has several limitations, however. First, age-related differences are based on cross-sectional analyses of two different age cohorts that are genetically related (parents and their offspring). By definition, cross-sectional analyses are limited by potential cohort effects such as nutritional, educational and life-style differences that might adversely effect health and brain aging. While some brain regions are under strong genetic influence [5,6,68,96], the impact of shared genes is likely to be low in this cohort of relatively small family structure. Future longitudinal analyses, however, will explore age-related differences of change in regional brain volumes.

Another limitation of this study is the lack of ethnic diversity amongst the predominantly Caucasian residents of Framingham, Massachusetts. This limits the generalization of these results to other ethnic groups where neurological diseases, such a cerebrovascular disease may be significantly more prevalent [13,43,83]. A second study of regional brain volumes amongst ethnic minorities in Framingham is currently ongoing, allowing for future comparisons of similar measures across different ethnic groups.

The relatively crude regional distinction is another limitation to this study. In order to maintain reliability for this study, lobar boundaries were determined by simple internal landmarks [6,18,63,64] that only approximate true anatomical boundaries. In addition, intra-cranial volumes were determined through operator guided manual outlining. This type of *biased* approach has been recently criticized [33]. Interestingly, the results of this study are remarkably similar to the smaller *unbiased* analysis [33] with regard to regional brain volumes. In contrast, the *unbiased* approach appears to have failed to detect the widespread nature of the anatomical differences with age as well as the inability to detect central CSF space expansion with age. This appears to be a limitation of such methods since regional CSF expansions are clearly the most dynamic brain morphologic changes to occur with age. Finally, such *unbiased* methods have yet to identify WMH and areas of brain infarction, both of which are strongly associated with the aging process.

11. Conclusions

We believe that these data can serve as norms for comparison with morphological brain changes associated with aging and disease. In this regard, these cross-sectional quantitative estimates suggest that age-related tissue loss differs quantitatively and qualitatively across brain regions with only minor differences between men and women. In addition, MRI infarctions are common to the aging process and associated with smaller regional brain volumes for a given age. Further longitudinal analyses of individual differences in regional brain volume and incident cognitive impairment or dementia will help to extend current observations and possibly contribute to our understanding of the neurobiology of brain aging and modifiable risk factors for brain health.

Acknowledgments

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