One-year Age Changes in MRI Brain Volumes in Older Adults

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Longitudinal studies indicate that declines in cognition and memory accelerate after age 70 years. The neuroanatomic and neurophysiologic underpinnings of cognitive change are unclear, as there is little information on longitudinal brain changes. We are conducting a longitudinal neuroimaging study of nondemented older participants in the Baltimore Longitudinal Study of Aging. This report focuses on age and sex differences in brain structure measured by magnetic resonance imaging during the first two annual evaluations. Cross-sectional results from 116 participants aged 59–85 years reveal significantly larger ventricular volumes and smaller gray and white matter volumes in older compared with younger participants and in men compared with women. Regional brain volumes show that the effects of age and sex are not uniform across brain regions. Age differences are greatest for the parietal region. Sex differences tend to be larger for frontal and temporal than parietal and occipital regions. Longitudinal analysis demonstrates an increase of 1526 mm^3 in ventricular volume over 1 year, but no detectable change in total or regional brain volumes. Definition of the pattern and rate of longitudinal brain changes will facilitate the detection of pathological brain changes, which may be predictors of dementia.

Introduction

Cross-sectional and longitudinal investigations reveal age-associated declines in some aspects of cognition and memory, with accelerating decline after age 70 years (Arenberg, 1978; Resnick *et al.*, 1995). However, the neuroanatomic underpinnings of age-associated cognitive and memory change remain unclear, as there is little information on longitudinal brain changes in nondemented individuals.

Substantial age differences in global measures of atrophy, such as greater ventricular or sulcal cerebrospinal fluid (CSF) in older compared with younger individuals, are suggested by cross-sectional investigations (Takeda and Matsuzawa, 1985; Grant *et al.*, 1987; Gur *et al.*, 1991; Coffey *et al.*, 1992; Pfefferbaum *et al.*, 1994; Murphy *et al.*, 1996). Volumetric estimates of brain tissue typically indicate smaller volumes in older compared with younger individuals, although age effects on gray versus white matter volumes are not consistent (Guttmann *et al.*, 1998; Pfefferbaum *et al.*, 1994; Raz *et al.*, 1997). Effects of age on specific brain regions have been examined volumetrically for the hippocampus (Jack *et al.*, 1992; Sullivan *et al.*, 1995; Raz *et al.*, 1997), frontal and temporal lobes (Coffey *et al.*, 1992; Cowell *et al.*, 1994; Murphy *et al.*, 1996; Raz *et al.*, 1997), and using planimetric measures of medial temporal lobe width (Jobst *et al.*, 1994). Furthermore, several cross-sectional studies have suggested that brain aging may be different in men and women, with greater age-related atrophy in men compared with women (Gur *et al.*, 1991; Kaye *et al.*, 1992; Cowell *et al.*, 1994; Coffey *et al.*, 1998).

While many investigators examine the effects of age with cross-sectional studies, such studies yield data only about age differences and are informative only when there are no cohort or time of measurement effects (Diggle *et al.*, 1996). The hallmark of a longitudinal study is that each subject serves as his or her own control, and change is assessed directly over repeated evaluations. A recent longitudinal study of 46 very healthy adults yielded puzzling findings of longitudinal increases in some brain volume measures and decreases in subarachnoid CSF over a 3–6 year interval (Mueller *et al.*, 1998). These findings were based on 4 mm thick double echo images and an image processing technique which yielded inter-rater agreement of only 0.71 for subarachnoid CSF, although intraclass correlations were high for the other brain measures. No information on longitudinal stability was presented. The remaining longitudinal studies of brain aging have been limited primarily to computer tomography (CT) investigations of normal controls studied as reference groups for Alzheimer's disease (AD) patients. Changes in ventricular volume were greater in AD patients than controls and were associated with clinical decline in patients (DeLeon *et al.*, 1989; Wippold *et al.*, 1991; DeCarli *et al.*, 1992; Shear *et al.*, 1995). Cross-sectional hippocampal size on MRI (Golomb *et al.*, 1996; Convit *et al.*, 1997; DeLeon *et al.*, 1997; Kaye *et al.*, 1997) and longitudinal changes in mesial temporal width on CT (Jobst *et al.*, 1994) were associated with memory decline and AD. These studies suggest that brain changes may be predictors or correlates of AD and memory impairment. The potential use of volumetric brain changes as predictors of memory impairment and dementing illnesses highlights the need for longitudinal investigations of older individuals, during the period of accelerating cognitive and memory change.

For these reasons, we are performing a longitudinal investigation of brain changes and their associations with cognitive and memory decline in older participants in the Baltimore Longitudinal Study of Aging (BLSA). Participants undergo annual magnetic resonance imaging (MRI) and neuropsychological assessments, as well as positron emission tomography (PET) to measure regional cerebral blood flow at rest and during the performance of memory tasks. This paper describes the initial data on MRI volumes from this ongoing study. We report cross-sectional age differences and 1 year longitudinal changes in brain volumes in older adults.

Materials and Methods

Subjects

The present sample includes 116 participants (68 men, 48 women, age 59–85 years) in the neuroimaging study of the BLSA (Shock *et al.*, 1984). BLSA participants were prioritized for admission to the neuroimaging study based on health considerations and the amount of prior cognitive data available for each individual. Individuals with central nervous system disease [epilepsy, stroke, bipolar illness, prior diagnosis of dementia according to Diagnostic and Statistical Manual (DSM)-III-R criteria (Spitzer and Williams, 1987)], severe cardiac disease (myocardial infarction, coronary artery disease requiring angioplasty or bypass surgery),

Table 1
Sample characteristics

	Men	Women	Total
n	68	48	116
Age (years)	70.7 ± 7.5	70.1 ± 7.5	70.4 ± 7.5
Education (years)	16.5 ± 2.8	16.2 ± 2.3	16.4 ± 2.6
Race (no. white: nonwhite)	64:4	40:8	104:12
Handedness (no. right:nonright)	64:4	44:4	108:8
Health status:			
No disease	21	20	41
Mild disease[a]:	9	13	22
Untreated hypertension[b]	3	6	9
Hypothyroid on replacement	1	2	3
History of cancer (non-skin)	2	3	5
Other	3	3	6
Moderate disease[a]:	38	15	53
Treated hypertension and/or coronary artery disease	30	8	38
Diabetes	3	1	4
Depression	3	4	7
Other	5	2	7

[a]Participants can have multiple diagnoses.

[b]Blood pressure elevated at imaging visit (systolic > 160 or diastolic > 95) and intermittent elevation during prior BLSA visits.

pulmonary disease or metastatic cancer were excluded from participation. Individuals showing signs of cognitive decline which did not meet criteria for dementia and those with past or current depression were included, as these factors may be risk factors for dementing illness. Exclusions were minimized to allow a representative sample of aging BLSA subjects. Demographic and medical data for the 116 participants are presented in Table 1. The research protocol is approved by the local Institutional Review Board, and informed consent is obtained annually from all participants.

Image Acquisition

MRI scans were acquired on a GE Signa 1.5 Tesla scanner. A thermoplastic mask, constructed for each subject, was used in conjunction with a custom head-holder to reduce motion and to aid in repositioning for repeated longitudinal assessments. A brief sagittal localizer was first acquired with repetition time (TR) = 500; echo time (TE) = 15; field of view (FOV) = 28 cm; matrix = 256 × 128; number of excitations (NEX) = 1; slice thickness = 5 mm. Following the localizing scan, a volumetric 'spoiled grass' (SPGR) scan was acquired axially with TR = 35, TE = 5, flip angle = 45, FOV = 24, matrix = 256 × 256, NEX = 1, voxel dimensions of 0.94 × 0.94 × 1.5 mm slice thickness. Additional image series, including a double echo protocol for quantitation of sulcal CSF, were also acquired but were not utilized for the present report.

Image Analysis

Our initial approach to volumetric quantitation of MRIs focuses on ventricular CSF, gray matter, white matter and brain (gray + white) volumes. In addition to the total volumes, gray, white and brain volume measurements were defined for frontal, parietal, temporal and occipital regions. The approach and validation are detailed elsewhere (Goldszal *et al.*, 1998).

Briefly, images are first corrected for head tilt and rotation, and reformatted parallel to the plane containing the anterior and posterior commissures (AC–PC; Fig. 1*a* – original image). Tissue outside the brain is removed using a semi-automated procedure (Fig. 1*b*), followed by manual editing (Fig. 1*c*) to remove any remaining extracranial tissue, the cerebellum, and brainstem structures inferior to the level of the mamillary bodies. As this approach also removes a varying amount of sulcal CSF, a limitation of this technique is the inability to quantify extraventricular CSF. In our experience, the interface between CSF and the cranium is difficult to reliably determine on SPGR images. Images are next segmented into gray, white and CSF compartments (Fig. 1*d*) (Yan and Karp, 1995), with an accuracy of <2–3% error when tested against our realistic digital brain phantom (Goldszal *et al.*, 1998). Ventricular CSF is

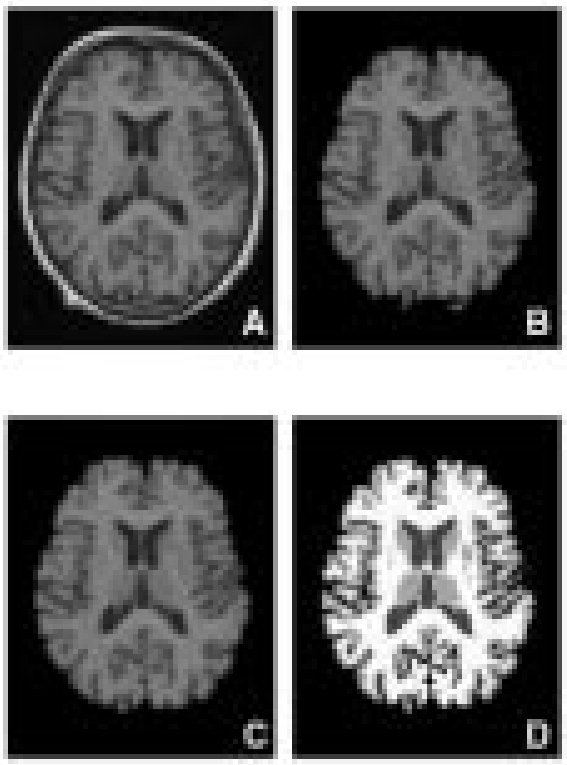

Figure 1. Sequence of image processing steps. Original image (*a*); image after automated (*b*) and manual (*c*) removal of cranial and extracranial tissues; segmented image after reclassification of ventricles (*d*).

reclassified by drawing a crude region of interest (ROI) to eliminate any CSF falling outside the ventricular system, and this ROI is used as a mask to define ventricular CSF voxels.

The final steps involve stereotaxic normalization and tissue quantitation within Talairach coordinate space (Talairach and Tournoux, 1988). Normalization is performed using the elastic deformation approach developed by Davatzikos (Davatzikos, 1996). This approach to normalization has several advantages, including the preservation of true tissue units, allowing quantitation of absolute volumes within the standard reference space, and the application of a boundary constraint for the ventricles, which minimizes distortions caused by variability in ventricular size. Additional constraints to the interhemispheric and Sylvian fissures are also applied. In the final step, the number of voxels classified as gray matter, white matter and ventricular CSF are quantified for each of the 1056 Talairach boxes or 'boxels' and are extracted for statistical analysis.

Total gray, white, brain and ventricular volumes are calculated by summing the number of voxels across all 'boxels'. Ventricle-to-brain ratios (VBR) are also calculated to control for individual differences in overall brain size. Volumes of frontal, parietal, temporal and occipital brain regions, including gray and white matter, are determined automatically using the groupings of Talairach 'boxels' described and validated by Andreasen and colleagues (Andreasen *et al.*, 1996).

Statistical Analysis

Statistical analysis was performed using SAS Version 6.12 on an Alpha/VMS and SPSS Version 4.1 on a VAX/VMS computer.

Cross-sectional Analysis of Age and Sex Effects

To examine the associations between age and MRI volumes, Pearson product–moment correlations were computed for the total sample, and for men and women separately. Next, a series of mixed-effects regressions was performed to investigate the effects of age and sex on different brain

regions, including hemisphere, simultaneously. Separate analyses were conducted for total brain volumes, ventricular size, VBR to control for variability in brain volume, and regional brain volumes. In these analyses, sex, hemisphere, tissue type (gray versus white) and region (frontal, parietal, temporal, occipital) were treated as class variables, and age and height were treated as continuous covariates. In addition, all two-way interactions, excluding those with height, and three-way interactions of interest were included in the initial model. A backward elimination procedure was employed, whereby all lower order terms remained in the final model but non-significant interactions ($P > 0.05$) were eliminated at each step until a final solution was reached (Morrell *et al.*, 1997). Cross-sectional analysis was performed separately for year 1 and year 2 data.

The mixed-effects regression approach allows examination of multiple regions simultaneously and yields information on the unique effects of each predictor, adjusting for all other terms in the analysis. The effects of age and sex for each individual MRI volume were examined through a series of simple regressions. The incremental change in variance associated with each predictor was estimated using hierarchical regressions with age, age-squared, height, sex, age by sex interaction and education entered in a fixed order. Height was omitted for analysis of VBR. Age was always entered first, and the remaining significant terms were retained in the final model. Annualized age differences adjusting for sex and height were also estimated. Note that while these estimates are often described as yearly rates of change, true age changes can only be estimated from longitudinal data. Secular changes and subsequent cohort effects confound estimates of age effects based on cross-sectional studies. This limitation is especially critical in the investigation of age effects on brain volume, as secular drifts in body and brain weight (Miller and Corsellis, 1977) have been documented, likely influenced by nutritional and medical care factors.

Longitudinal Analysis of Age Changes

Pearson correlations were calculated to estimate the stability of the brain measurements from year 1 to year 2. The effects of time (1 year change) on brain volumes, ventricular volumes and VBR were examined using the mixed-effects regression procedure adding time as an additional class variable.

Effects of Health Status

All cross-sectional and longitudinal analyses were repeated restricting the sample to the 41 individuals (21 men, 20 women) free of any medical problems, because our sample includes individuals with some common medical conditions in the elderly. Treated hypertension (38 men, 15 women) and elevated blood pressure during the neuroimaging visit (3 men, 7 women) accounted for most of the observed medical conditions.

Results

Cross-sectional Analysis of Age and Sex Effects on MRI Volumes

Means and standard deviations for MRI volumes at year 1 evaluation are shown by age group and sex in Table 2.

Correlations between Age and MRI Volumes

Pearson correlations between age and MRI volumes for the total sample and for men and women separately are presented in Table 3. Note that correlations for the total sample can be misleading in the presence of significant sex differences. Age was significantly associated with all brain measures, except total gray and occipital volumes in women. Positive correlations between age and ventricular size were substantial, with age accounting for ~24–35% of the variance in ventricular volume and VBR (Fig. 2*a*). Negative correlations between age and total brain, gray and white brain volumes (Fig. 2*b–d*) were more modest, although significant.

Table 2
Year 1 MRI volumes (in cm^3) by age group and sex

	Age		Sex	
	59–69	70–85	Men	Women
n	63	53	68	48
Age (years)	64.6 ± 3.2	77.3 ± 4.7	70.7 ± 7.5	70.1 ± 7.5
VBR	0.025 ± 0.010	0.043 ± 0.023	0.039 ± 0.021	0.026 ± 0.014
Right	0.012 ± 0.005	0.021 ± 0.011	0.019 ± 0.010	0.013 ± 0.007
Left	0.013 ± 0.006	0.022 ± 0.012	0.020 ± 0.011	0.013 ± 0.007
Ventricular volume	25.2 ± 10.8	41.1 ± 23.0	39.0 ± 20.5	23.2 ± 12.0
Right	12.3 ± 5.3	20.4 ± 11.2	19.1 ± 9.9	11.5 ± 6.4
Left	12.9 ± 5.9	20.7 ± 12.0	19.9 ± 11.0	11.7 ± 5.8
Brain	999.7 ± 99.1	946.8 ± 81.8	1017.6 ± 80.3	915.9 ± 81.7
Right	502.2 ± 50.2	475.2 ± 40.8	511.2 ± 40.9	459.7 ± 40.5
Left	497.5 ± 49.2	471.7 ± 41.3	506.4 ± 39.8	456.3 ± 41.5
Gray	538.6 ± 51.0	516.0 ± 47.8	550.4 ± 40.9	497.0 ± 46.6
Right	272.0 ± 26.4	259.9 ± 24.1	277.7 ± 21.5	250.5 ± 23.3
Left	266.6 ± 25.1	256.1 ± 24.0	272.7 ± 20.0	246.4 ± 23.6
White	461.0 ± 53.2	430.8 ± 45.4	467.2 ± 48.0	419.0 ± 43.5
Right	230.2 ± 27.0	215.3 ± 22.7	233.4 ± 24.3	209.1 ± 21.7
Left	230.9 ± 26.6	215.5 ± 23.6	233.8 ± 24.5	209.8 ± 22.1
Frontal	370.1 ± 37.2	353.0 ± 33.0	377.4 ± 31.0	340.8 ± 32.2
Right	187.4 ± 19.1	178.6 ± 17.4	191.3 ± 16.1	172.3 ± 16.6
Left	182.6 ± 18.6	174.3 ± 16.3	186.1 ± 15.7	168.5 ± 16.1
Parietal	211.8 ± 20.8	196.4 ± 17.1	212.3 ± 18.5	194.2 ± 18.9
Right	105.9 ± 11.0	98.3 ± 8.5	106.3 ± 9.7	97.0 ± 9.4
Left	106.0 ± 10.0	98.1 ± 9.0	106.0 ± 9.1	97.2 ± 9.8
Temporal	201.4 ± 21.8	189.6 ± 17.7	205.1 ± 18.2	183.1 ± 17.2
Right	99.8 ± 10.8	93.1 ± 8.6	101.2 ± 9.3	90.4 ± 8.3
Left	101.7 ± 11.2	96.4 ± 9.4	103.9 ± 9.2	92.7 ± 9.1
Occipital	115.4 ± 12.4	109.1 ± 10.3	117.1 ± 11.2	106.1 ± 9.8
Right	58.3 ± 6.9	55.2 ± 5.2	59.2 ± 6.1	53.7 ± 5.4
Left	57.1 ± 6.0	53.9 ± 5.6	57.9 ± 5.8	52.4 ± 4.9

Table 3
Year 1 assessment: correlations between age and MRI volumes

Region	Male	Female	Total
VBR	0.59**	0.54**	0.55**
Ventricular volume	0.56**	0.50**	0.49**
Brain volume	–0.38**	–0.32*	–0.28**
Gray volume	–0.32**	–0.26	–0.23*
White volume	–0.36**	–0.32*	–0.29**
Frontal	–0.32**	–0.33*	–0.26**
Parietal	–0.49**	–0.40**	–0.39**
Temporal	–0.42**	–0.29*	–0.29**
Occipital	–0.37**	–0.26	–0.27**

*$P < 0.05$; **$P < 0.01$; two-tailed.

Mixed-effects Regression Examining Effects of Age and Sex

Total Brain, Gray and White Matter Volumes. The analysis included age, sex, hemisphere, tissue type and height as predictor variables and brain volumes (right gray, left gray, right white and left white) as dependent measures. There were highly significant effects of age [$F(1, 345) = 11.5$, $P = 0.0001$] and sex [$F(1,345) = 11.8$, $P < 0.001$]. These findings reflect larger overall brain volumes in younger compared with older individuals and larger brain volumes in men than women. While height and hemisphere did not reach significance, there was a highly significant effect of tissue type [$F(1,345) = 1361.2$, $P = 0.0001$], with larger gray than white matter volumes (gray to white ratio = 1.19), and a significant tissue type by hemisphere interaction [$F(1,345) = 5.48$, $P < 0.05$]. The tissue by hemisphere interaction reflected greater volumes for gray matter on the right compared

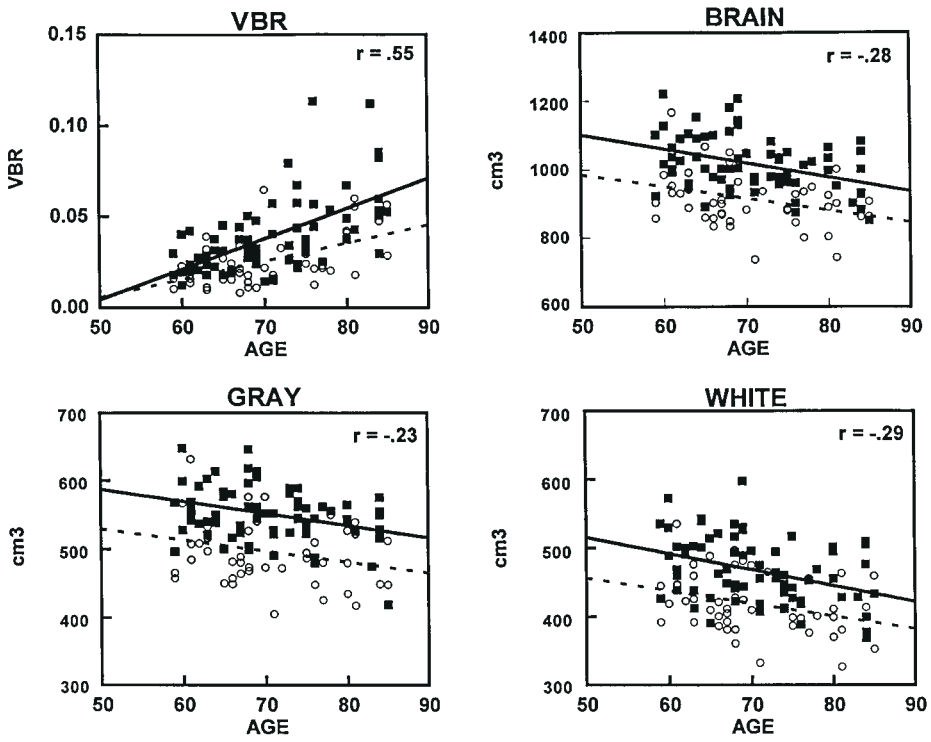

Figure 2. Correlations between age and brain measurements. (*a*) VBR; (*b*) brain volume; (*c*) gray volume; (*d*) white volume. Values and regression lines for men and women are depicted by filled squares–solid lines and open circles–dashed lines, respectively.

with left and greater left than right asymmetries for white matter. While significant in this large sample, these asymmetries accounted for only modest amounts of brain tissue and could be due to variability associated with placement of voxels along the midline. There were no other significant interactions, indicating similar effects of age and sex for gray and white matter volumes and for both hemispheres. All findings remained significant in analysis of the year 2 cross-sectional data.

To visualize the age differences in gray matter volumes, we dichotomized subjects into two age groups based on age at initial evaluation: 59–69 years (n = 63; mean = 64.6 ± 3.2 years) and 70–85 years (n = 53; mean = 77.3 ± 4.7 years). Average gray matter maps in stereotaxic space were computed for all 116 subjects, and for each age group separately. The gray matter for all 116 subjects is depicted as an average intensity map in the top row of Figure 3. The average intensities depict the amount of gray matter present in each location. Average gray matter intensity maps for the two age groups are subtracted to show local age differences in gray matter volumes. Age differences in local gray matter volumes are shown for the 59–69 versus 70–85 year olds in the bottom row of Figure 3, with the yellow and bright green regions indicating larger differences. Greater gray matter volumes in younger compared with older subjects are apparent in the hippocampus (H), inferior (IT) and mesial temporal lobes, orbital frontal cortex (OFC) and insula (I).

Ventricular Volume and VBR. For examination of ventricular volume and VBR, age, sex, hemisphere, height and the appropriate interactions were predictors. Separate analyses were performed for each set of dependent measures (right and left ventricular volumes; right and left VBR). For ventricular volumes, there were highly significant effects of age [$F(1,114) = 40.8$, $P = 0.0001$] and sex [$F(1,114) = 9.2$, $P < 0.01$], but no significant effect of hemisphere. Similar effects of age and sex were obtained for VBR [age, $F(1,114) = 49.2$, $P = 0.0001$; sex, $F(1,114) = 6.7$, $P = 0.01$], although there was also a modest main effect of hemisphere [$F(1,114) = 4.1$, $P < 0.05$], with left VBR greater than right. Results for ventricular volume and VBR indicated larger ventricular size in older compared with younger individuals and in men compared with women. However, there were no significant interactions between age and sex within the restricted age range of our sample. An identical pattern of results was obtained when analyses were repeated for year 2 cross-sectional data.

Regional Brain Volumes. This analysis included age, sex, brain region (frontal, parietal, temporal, occipital), hemisphere and height as predictors and the eight volume measures (brain region × hemisphere) as dependent measures. The first set of analyses examined the effects of age and sex on regional volumes, combining both gray and white matter. Consistent with the results for the global gray and white matter volumes, the analysis of regional brain volumes yielded significant main effects of age and sex, as described above. There were significant effects of hemisphere [$F(1,798) = 5.0$, $P < 0.05$] and the expected effects of brain region, as brain volumes differ across lobes. There was also a significant region by hemisphere interaction [$F(3,798) = 14.9$, $P = 0.0001$]. This interaction reflected greater right than left frontal and left compared with right temporal volumes (Table 2). In addition, there were significant interactions between age and region [$F(3,798) = 13.7$, $P = 0.0001$], and between sex and region [$F(3,798) = 49.6$, $P = 0.0001$]. These interactions indicate that age and sex differences vary systematically across brain regions.

To illustrate the interactions adjusting for overall volume differences between regions, brain volumes for each region were

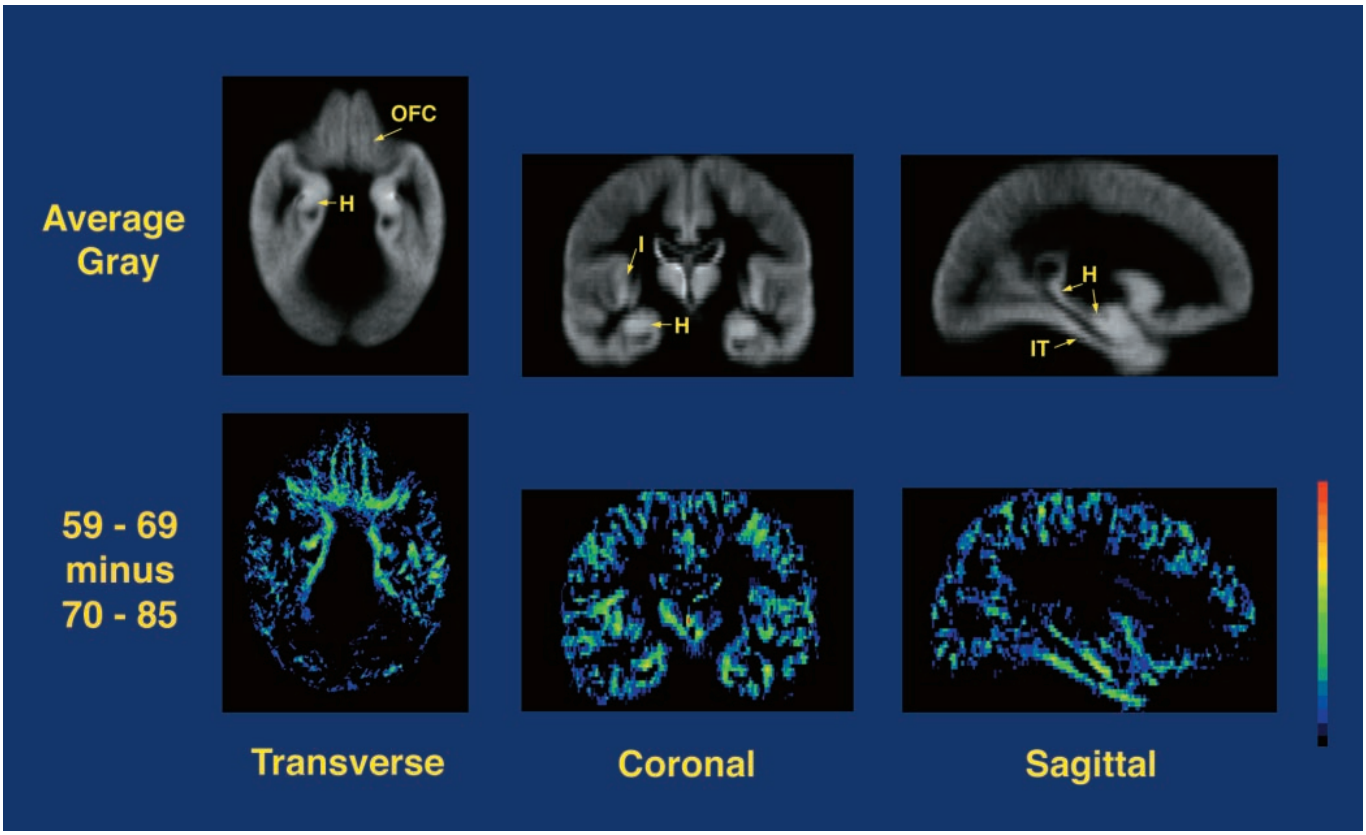

Figure 3. Triplanar views of gray matter maps through the hippocampus and adjacent structures. The average gray matter map (top row) shows the distribution of gray matter, with brighter regions indicating greater gray matter volumes. Age differences in the gray matter distributions are shown at bottom as the difference between the average maps for age 59–69 (64.6 ± 3.2) and age 70–85 years (77.3 ± 4.7). Greater gray matter volumes in younger compared with older subjects are apparent in the hippocampus (H), inferior (IT) and mesial temporal lobes, orbital frontal cortex (OFC) and insula (I).

standardized to *z*-scores, using the mean and standard deviation for each brain region. Year 1 and year 2 data were standardized separately, with age group defined by age at initial evaluation (59–69 versus 70–85 years). As shown in Figure 4, differences between groups in profiles depict the nature of the interactions, while differences in overall levels show main effects of age group and sex. Age differences were greatest for the parietal region. In contrast, sex differences in regional brain volume were greater for frontal and temporal compared with parietal and occipital regions. Results were nearly identical for year 1 and year 2 data.

The mixed-effects regression analyses examining age and sex effects on regional brain volumes were repeated for regional volumes of gray and white matter separately. Results were similar to those described for the combined gray and white matter regions with two exceptions: the interaction between age and region was significant for white but not gray matter volumes, and a significant main effect of hemisphere was apparent only for gray matter volumes.

Regression Analysis: Estimation of the Effects of Age and Sex for each MRI Volume

Results of the simple regression analyses are shown in Table 4. Within this age range, there were no significant quadratic associations with age, age by sex interactions or education effects for any of the brain measurements. The final model included age, height and sex entered hierarchically in a fixed order. Age accounted for 5–30% of the total variance, with the largest effect for VBR. After accounting for the effects of age and height, significant sex effects remained for all brain measurements. Linear estimates of cross-sectional yearly age differences, adjusted for height and sex, are shown in Table 5.

Longitudinal Analysis of Age Changes

One-year Stabilities

One-year stability estimates for the global and regional brain volumes are presented in Table 6. All brain measurements were highly stable over a 1 year interval. One-year stability for ventricular volume and VBR were also high, with correlations between year 1 and year 2 ventricular volume and VBR of 0.997 and 0.996, respectively. Scatterplots and linear regressions for year 1–year 2 stabilities are shown in Figure 5*a–d* for VBR, and total brain, gray and white volumes. Note that the regression line for VBR is slightly higher than the identity line, suggesting an increase over the 1 year interval.

Mixed-effects Regression

Total Brain, Gray and White Matter Volumes. The mixed-effects regressions described above for the cross-sectional analyses were repeated, adding time (year 1, year 2) as an additional predictor variable to investigate 1 year longitudinal changes in gray and white matter, as well as total, brain volumes. Thus, age, sex, tissue type (gray versus white), hemisphere, time and height were the independent variables, and gray and white matter volumes for years 1 and 2 were the dependent measures. Consistent with the findings for the cross-sectional analyses,

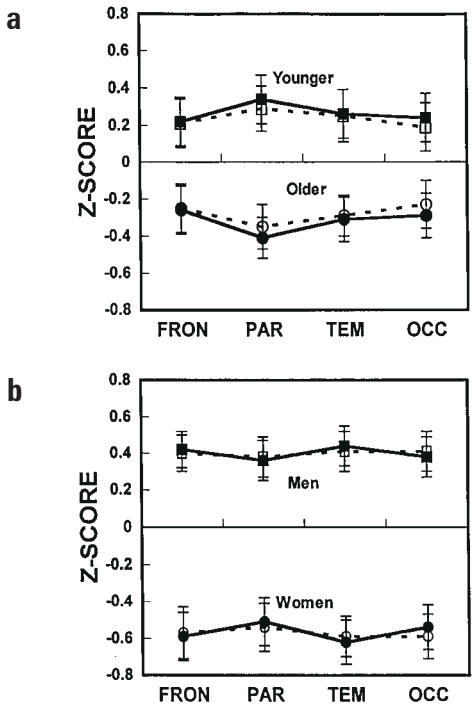

Figure 4. Differential effects of age and sex across brain regions. Age by region and sex by region interactions are depicted in (*a*) and (*b*), respectively. *z*-scores reflect standardized volumes adjusting for overall volume difference between regions separately for year 1 (solid lines, filled symbols) and year 2 (dashed lines, open symbols). In (*a*), squares and circles represent younger and older groups, respectively. In (*b*), squares and circles represent males and females, respectively. Abbreviations: FRON, frontal; PAR, parietal; TEM, temporal; OCC, occipital.

Table 4
Linear regressions: incremental variance (R^2) associated with age, height and sex

Region	Age	Height	Sex	Total
VBR	0.297***	*n*/a	0.099***	0.396
Ventricular volume	0.243***	0.104***	0.051***	0.398
Brain volume	0.080**	0.252***	0.060***	0.392
Gray volume	0.053*	0.248***	0.056**	0.357
White volume	0.085***	0.188***	0.048**	0.321
Frontal	0.068**	0.242***	0.044**	0.354
Parietal	0.152***	0.142***	0.061**	0.355
Temporal	0.086***	0.240***	0.064***	0.390
Occipital	0.075**	0.221***	0.029*	0.325

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

there were significant cross-sectional main effects of age, sex and tissue compartment across year 1 and year 2 data combined. There was also a significant effect of hemisphere [$F(1,806) = 6.3$, $P < 0.05$], right greater than left, and the tissue compartment by hemisphere interaction remained significant. In addition, the age by tissue type interaction reached significance [$F(1,806) = 8.3$, $P < 0.01$]. This interaction indicated greater age effects for white than gray matter. There were, however, no significant longitudinal changes for the global brain volume measures.

Ventricular Volume and VBR. Age, sex, hemisphere, time and height were predictor variables with year 1 and year 2 ventricular volumes and VBR, respectively, as dependent measures in separate analyses. Mixed-effects regression confirmed the highly significant effects of age and sex on ventricular volume and VBR observed for the year 1 cross-sectional data. Furthermore, in contrast to the findings for brain volumes, there were highly significant effects of time for ventricular volume [$F(1,346) = 16.0$, $P = 0.0001$], and for VBR [$F(1,346) = 17.6$, $P = 0.0001$]. One-year longitudinal increases in ventricular volume and VBR, respectively, were 1525.6 mm^3 and 0.0016 (mean ± SD: year 1 ventricular volume 32 464.4 ± 19 105 mm^3; year 2 ventricular volume, 33 990.0 ± 19 958 mm^3; year 1 VBR, 0.0333 ± 0.019; year 2 VBR, 0.0349 ± 0.020).

Table 5
Cross-sectional yearly age differences, adjusted for height and sex[a]

Region	Total sample	Very healthy sample
VBR[b]	0.00138	0.00137
Ventricular volume	1255.0	1283.6
Brain volume	–3280.0	–3021.5
Gray volume	–1388.3	–1842.3
White volume	–1891.8	–1179.1
Frontal	–1115.2	–1199.0
Parietal	–1071.3	–1013.1
Temporal	–760.8	–590.3
Occipital	–378.4	–222.7

[a]Year 1 data: all values are in mm^3 except for VBR.

[b]Linear estimates for VBR are adjusted for sex only.

Table 6
One-year stability estimates

Region	Gray	White	Brain
Total	0.96	0.96	0.99
Frontal	0.94	0.95	0.97
Parietal	0.86	0.94	0.95
Temporal	0.95	0.93	0.96
Occipital	0.89	0.86	0.93

Regional Brain Volumes. Time was added as a predictor in the mixed-effects regression model for regional brain volumes to examine longitudinal change. The main effects of age, sex, brain region and hemisphere, as well as the interactions of age, sex and hemisphere with region, were again consistent with those reported above for the cross-sectional analysis of the year 1 data. There were no significant longitudinal changes for regional brain volumes (gray plus white) or regional gray and white matter volumes.

Effects of Health Status on Overall Findings
Restricting the analyses to the 41 individuals free of any significant medical problems did not change the pattern of findings. Although not all effects reached significance due to a substantial decrease in power, effect sizes were generally in the same range as those reported for the entire sample. One possible exception was the relationship between age and white matter volume. This effect was reduced when individuals with medical problems, the majority of whom were hypertensive, were omitted. The correlation between age and white matter volume in the 41 'super-healthy' subjects was –0.13 (–0.24 for males and –0.17 for females). Note, however, that even in the very healthy sample, both gray and white matter showed cross-sectional decreases with age (Table 5).

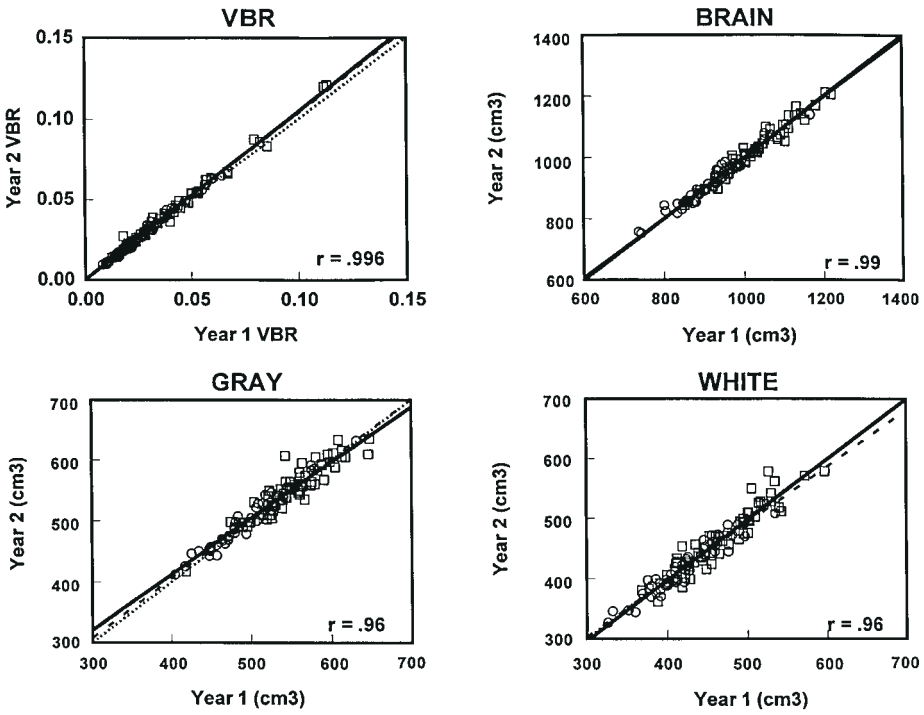

Figure 5. One-year stability of brain measurements, depicted with reference to the identity (dotted) line. (*a*) VBR; (*b*) brain volume; (*c*) gray volume; (*d*) white volume. Values for men and women are depicted by squares and circles, respectively.

Discussion

Our results confirm previous cross-sectional findings of age differences in brain structure and extend them by providing quantitative estimates of 1 year change in brain and ventricular volumes.

Cross-sectional Findings

Consistent with previous cross-sectional studies (Takeda and Matsuzawa, 1985; Grant *et al.*, 1987; Gur *et al.*, 1991; Coffey *et al.*, 1992; Manolio *et al.*, 1994; Pfefferbaum *et al.*, 1994; Yue *et al.*, 1997), we found significant and robust cross-sectional age and sex effects on global measures of brain and ventricular volumes in our sample of older adults aged 59–85 years. Ventricular volume and VBR, thought to index brain atrophy, were significantly greater in the oldest group. Also consistent with previous reports (Gur *et al.*, 1991; Kaye *et al.*, 1992; Manolio *et al.*, 1994; Yue *et al.*, 1997), there were significant sex, as well as age, effects on ventricular volume and VBR. In our sample of older adults, VBR was larger in men than women but the sex by age interaction was not significant within this restricted age range.

Brain volumes were smaller in the oldest individuals, and men had larger total brain volumes than women, even after adjusting for height. Age differences in brain volume were observed for both gray and white matter. While the possibility of greater age effects on white compared with gray matter was suggested by analysis of the combined year 1 and year 2 data, the age by tissue type interaction did not reach significance for the separate analysis of year 1 and year 2 data. Results of previous cross-sectional investigations of the differential effects of age on gray versus white matter through adulthood have been inconsistent (Jernigan *et al.*, 1991; Raz *et al*, 1993; Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995; Guttmann *et al.*, 1998). Due to difficulties in reliably distinguishing between gray and white matter on T1-weighted SPGR images, most studies have utilized lower resolution double echo MRI scans (spin density/T2-weighted), which are typically 3–5 mm thick. In our study, we applied an image processing approach with demonstrated reliability and validity to a large sample of high resolution volumetric MRI's of older adults. One limitation of our present method is that white matter signal hypointensities on T1-weighted MRI scans are segmented as gray matter, leading to a small overestimation of gray and underestimation of white matter. However, we have estimated by manual tracing that these signal abnormalities account for <1% of the brain volume even in the presence of the most extensive white matter findings in our sample. In a healthy elderly sample (Guttmann *et al.*, 1998), white matter abnormalities averaged only 0.29% of the intracranial volume. Further research including high resolution images and refined classification of white matter signal abnormalities will be necessary to clarify the differential effects of age on gray and white matter volume changes.

Examination of regional brain volumes for the frontal, parietal, temporal and occipital lobes revealed that the cross-sectional effects of age and sex were not uniform across brain regions. Accounting for differences in absolute volumes across regions, age differences were greatest for the parietal region. Yearly age differences in absolute volumes were 1100, 1100, 800 and 400 mm^3 for frontal, parietal, temporal and occipital volumes, respectively. Sex differences were greater for frontal and temporal than parietal and occipital regions. Previous cross-sectional investigations of age and sex effects on regional brain volumes have yielded mixed results. Smaller parietal (Murphy *et al.*, 1996) and temporal (Coffey *et al.*, 1992; Sullivan *et al.*, 1995) lobe volumes in old compared with young subjects have been reported in some studies. Smaller frontal lobe volumes in old compared with young subjects have also been described (Coffey *et al.*, 1992; Cowell *et al.*, 1994; Murphy *et al.*, 1996),

most pronounced for prefrontal gray matter (Raz *et al.*, 1997). In contrast to some reports (Cowell *et al.*, 1994; Murphy *et al.*, 1996), we found no significant age by sex interactions for regional volumes.

To allow comparison between our findings and previous investigations with more stringent health criteria, analyses were repeated restricting the sample to individuals free of any medical problems, i.e. the 'super-healthy' elderly. In general, a similar pattern of findings was observed for this subsample, with age differences for gray as well as white matter. However, the age effects on white matter were somewhat attenuated in the 'super-healthy' sample. The attenuation of the effects of age on white matter may reflect, in part, the impact of vascular disease on white matter, as the majority of subjects excluded from these analyses have hypertension.

Longitudinal Findings

Analysis of intra-individual longitudinal change revealed small but significant increases over 1 year in VBR and ventricular volume. Over this interval, ventricular volumes increased by an average of 1526 mm^3 (which compares with our cross-sectional finding of a yearly age difference of 1255 mm^3). Age did not significantly influence the magnitude of this longitudinal increase in our sample. In contrast to the longitudinal changes in ventricular size, there were no significant 1 year changes for total or regional brain volumes, consistent with the absence of 1 year change in normal subjects studied by Fox and colleagues (Fox *et al.*, 1996). While the increase in ventricular CSF may appear at odds with the absence of significant longitudinal changes in brain volume, a 1526 mm^3 change represents <0.5% of the total brain volume. Such a small or localized change in the large brain volume compartments would not be detectable over 1 year given the limits of our current image processing accuracy. Nevertheless, the excellent 1 year stabilities of our brain measurements combined with our demonstrated ability to detect a 1 year change of 1526 mm^3 in ventricular CSF provide confidence that our approach will allow the detection of brain changes when they occur.

General Discussion

In this initial report, we focused on measures of ventricular volume and large ROIs for automated volumetric analysis with reference to stereotaxic space. Our volumetric analysis is limited to these regions and does not provide distinct measures of primary versus secondary association cortex or specific gyri, which may show differential vulnerability to the effects of age (Raz *et al.*, 1997). While approaches to automated definition of specific regions are under development (Collins *et al.*, 1995; Goldszal *et al.*, 1998), such distinctions currently require operator-based manual definition. Manual definitions of large numbers of ROIs are impractical within a large multi-year longitudinal study. Extensive effort is required to train operators to acceptable reliability, requiring some sacrifice of anatomic accuracy, and operators are likely to change over years, compromising longitudinal integrity. Nevertheless, manual definitions of selected ROIs, such as hippocampus, are underway, and automated definitions of smaller ROIs are being validated using a stereotaxic approach (Goldszal *et al.*, 1998). Ultimately, regional analysis can be viewed as a spatial registration problem; given perfect registration between each individual's MRI and a stereotaxic atlas, ROIs can be defined a single time via the atlas. The present analysis was based on this approach, and we are exploring its accuracy for smaller structures with refinements of the spatial normalization algorithm.

Another important issue is the interpretation of substantial age effects on brain and CSF volumes in view of evidence that neuronal loss in normal aging is less than previously believed (Coleman and Flood, 1987; Morrison and Hof, 1997). This discrepancy may be due in part to the selective nature of neuron loss and the fact that neuropathological investigations do not typically sample regions throughout the brain. Another possible explanation is that age differences in brain volume are due to decreases in dendritic arborization rather than neuron loss (Raz *et al.*, 1997). These and other potential explanations require additional investigation and will be critical in our interpretation of age-associated changes in brain volume.

Summary

To our knowledge, this paper reports the first large-scale longitudinal study of brain changes in older adults, using high resolution MRI and examining changes in both gray and white matter volumes. Employing reliable and valid measures of brain atrophy and tissue volumes, we demonstrated cross-sectional age effects on gray and white matter volumes, as well as ventricular CSF. In addition, changes in ventricular size, but not in global brain volumes, were detectable over a 1 year interval. The definition of the pattern and rate of age-associated brain changes will be critical in the early detection of pathological brain changes, which may help identify individuals likely to benefit from new interventions as they become available.

Notes

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