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Normal neuroanatomical variation due to age: The major lobes and a parcellation of the temporal region

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Abstract

We used high-resolution MRI to investigate gray and white matter aging in the major lobes of the cerebrum (frontal, parietal, temporal, occipital) and the major sectors of the temporal lobe (temporal pole, superior temporal gyrus, infero-temporal region, parahippocampal gyrus, amygdala, hippocampus). Subjects included 87 adults between the ages of 22 and 88 years. Regions of interest were hand-traced on contiguous 1.5 mm coronal slices. For the cerebrum in general, gray matter decreased linearly with age, resulting in a decline of about 9.1–9.8% between the ages of 30 and 70 years, and a decline of 11.3–12.3% by the age of 80. In contrast, white matter volume increased until the mid-50s, after which it declined at an accelerated rate. At 70 years, white matter volume was only 5.6–6.4% less than at 30 years, but by age 80, a cubic regression model predicted that the decrease would be 21.6–25.0%. Multivariate analyses indicate that the frontal gray matter was most strongly associated with age, while occipital gray and white matter were least associated. Reduction in volume in the hippocampus was best modeled by a cubic regression model rather than a linear model. No sex differences in aging were found for any regions of interest.

Keywords: White matter; Gray matter; MRI; Hippocampus; Amygdala; Frontal lobe; Parietal lobe; Temporal lobe; Occipital lobe; Volumetrics

1. Introduction

Over the years, the relationship between age and brain volume has been explored using a variety of different methods. Almost all studies, no matter what the method, confirm the basic observation that as adults get older, their brains become smaller and the sulci visibly increase in size and depth [41]. Autopsy studies indicate that brain weight in both men and women declines by at least 10% between the ages of 25 and 75+ years [10,22,34,47]. Miller et al. [28], in another post-mortem study (in which gray and white matter volumes were determined from fixed sagittal slices taken at 2–3 mm intervals), found that volume decreases at the rate of about 2% per decade following the age of 50. This same study also found that the gray/white ratio declined up to the age of 50, after which it increased, indicating that although overall brain volume remains steady between 20 and 50 years, gray matter volume may be decreasing while white matter volume may be increasing.

Over the past decade, volumetric MRI analyses have added much to our understanding of many aspects of brain aging [6,8,9,43,48,50]. Although different studies have produced some conflicting results, MRI based studies indicate that age-associated brain atrophy does not occur in a uniform manner. For example, age-associated volume reductions have been reported by some to be more pronounced in the frontal lobe compared to other brain regions [9,24], while others have found that the frontal and temporal lobes age at similar rates [3]. The hippocampus may be more sensitive to age effects than the amygdala, cortical gray matter, or basal gray structures [24,39].

Several aging studies have shown that gray and white matter volumes do not change over the life span at the same rate [3,21,24]. Gray matter volume declines throughout adulthood

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and into old age at a more or less linear rate. In contrast, other studies have shown that white matter volumes actually may increase slowly through adulthood, peaking in volume in the 40–50 year range [3,48]. After 60 years of age, there is a precipitous decline in white matter volume according to Guttman et al. [21]. Although some MRI based studies show that the gray matter decline in women may be slower than in men [6,9,17,31,53], others have not shown significant sex differences in brain aging [5,24,48].

In this report, we present the results of an MRI study of the effects of age on gray and white matter volumes of the major cerebral lobes (frontal, temporal, parietal, and occipital) and of the major sectors of the temporal lobe (temporal pole, superior temporal gyrus, infero-temporal region, parahippocampal gyrus, amygdala, and hippocampus). A total of 87 subjects (43 men, 44 women), between the ages of 22 and 88 years, were included in this cross-sectional analysis. This study constitutes a novel contribution to the MRI brain aging literature in that it provides a high-resolution and comprehensive (manual tracing of regions of interest on contiguous 1.5 mm slices of non-resized brains) assessment of regional volumetric changes in a relatively large subject group.

2. Methods

2.1. Subjects

Subjects were 43 men (mean age = 49.4 years, S.D. = 20.8, range 22–88) and 44 women (mean age = 47.0 years, S.D. = 16.7, range 23–74) (see Table 1 for age distributions). All were right-handed (assessed by the Oldfield–Geschwind handedness inventory; mean score = 95, S.D. = 11) with no left-handedness in first degree relatives, healthy, and with no history of neurological or psychiatric illness. Older subjects (greater than 60 years) were assessed by interview on a case-by-case basis for general health status and medication usage. None had a clinical history of heart disease, hypertension, diabetes, or any other common age-associated disease. All brain MRIs were screened for the presence of visible pathology. All subjects gave informed consent in accordance with institutional and federal rules.

Table 1
Age distribution of subjects

Age (years)	No. of men	No. of women
20–29	12	11
30–39	5	6
40–49	6	6
50–59	3	8
60–69	9	11
70–79	5	2
80–89	3	0
Total	43	44

2.2. Image acquisition

Thin cut T1-weighted MR images were obtained in a GE Signa scanner operating at 1.5 T, using the following protocol: SPGR/50, TR 24, TE 7, NEX1, matrix 256×192, FOV 24 cm. We obtained 124 contiguous coronal slices, 1.5 or 1.6 mm thick and interpixel distance 0.94 mm. The slice thickness was adjusted to the size of the brain so as to sample the entire brain, while avoiding wrap artifacts. Three individual datasets were obtained for each brain during each imaging session. These were coregistered and averaged post hoc using automated image registration (AIR 3.03, UCLA [52]), to produce a single data set, of enhanced quality with pixel dimensions of 0.7 mm in plane and interslice spacing of 1.5 mm between planes [23].

All brains were reconstructed in three dimensions using Brainvox [16], an interactive family of programs designed to reconstruct, segment, and measure brains from MR acquired images. An automated program, extensively validated against human experts [18], was used to segment the images into the three primary tissue types (white, gray, CSF). Before tracing regions of interest (ROIs), brains were realigned, but *not resized*, along a plane running through the anterior and posterior commissures (i.e., the AC-PC line). This realignment limited right–left rotation, and ensured that coronal slices used in the tracing of ROIs were perpendicular to a uniformly and anatomically defined axis of the brain in all subjects.

2.3. Regions of interest

Regions of interest were traced by hand on contiguous coronal slices of the realigned brain. Anatomical landmarks were identified and marked on the surface of 3D reconstructions. The parcellation of the major lobes (frontal, temporal, parietal, and occipital) was based on a scheme modified from [40]; see [1,2] for a very detailed description of the parcellation method and tracing conventions (Fig. 1). Gray and white matter volumes of the insula and cingulate gyrus are excluded from the volumes of the major lobes; gray matter volumes of the basal ganglia, claustrum, and thalamus are also excluded. The cerebellum and brain stem were excluded from all tracings. Although the ROIs were traced separately in the two hemispheres, the volumes of the two hemispheres are combined in this analysis.

The parcellation of the temporal lobe and its subregions was as follows (Fig. 1). Parcellation of the *temporal lobe* itself is described in detail in [1,2]. In brief, the superior boundary of the temporal lobe is formed by the Sylvian fissure (SF), which is followed to its most posterior extension. In cases where the SF splits into two branches, the branch that extends most posteriorly is followed (this is almost always the superior branch). The superoposterior boundary of the temporal lobe is defined by a line drawn on the lateral surface of the hemisphere, which connects the end of the SF to a plane that separates the occipital lobe from the rest of the cerebrum; the inferoposterior boundary is defined by this

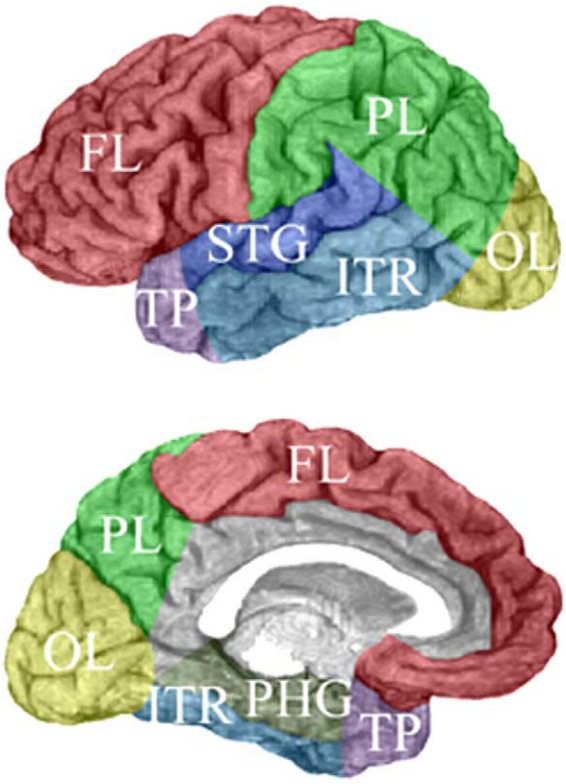

Fig. 1. Parcellation of the cerebrum. FL: frontal lobe; PL: parietal lobe; OL: occipital lobe; TP: temporal pole; STG: superior temporal gyrus; ITR: infero-temporal region; PHG: parahippocampal gyrus.

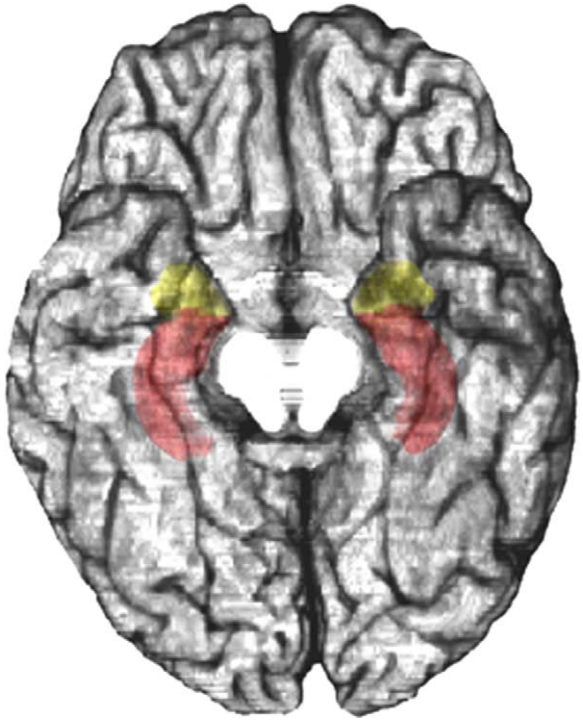

Fig. 2. Parcellation of the amygdala (yellow) and hippocampus (red), as seen in an inferior perspective of a semi-transparent 3D volume reconstruction of the cerebral hemispheres.

occipital plane (see [1] for a definition of this plane). The *temporal pole* is limited posteriorly by a plane that includes the following three points (see [14] for more detail): on the lateral side of the hemisphere, point 1 is defined as the intersection between the SF and the horizontal and vertical branches of the SF, and point 2 is the most inferior point of the temporal lobe on its lateral surface. Point 3 is defined on the first coronal slice (going from anterior to posterior) in which a white matter connection is visible in the fronto-temporal stem. On this slice, point 3 is placed on the mesial surface of the hemisphere at the level of the most inferior extension of the circular sulcus. The *superior temporal gyrus* is limited superiorly by the SF, and inferiorly by the superior temporal sulcus. Its anterior boundary is the temporal pole cut, and its posterior boundary is the posterior edge of the temporal lobe. If the superior temporal sulcus splits posteriorly into inferior and superior branches, the superior branch is followed (i.e., the branch that extends into the parietal lobe as the angular sulcus [33]). The *infero-temporal region* is bounded superolaterally by the superior temporal sulcus, and infero-mesially by the collateral sulcus. Its anterior boundary is the temporal pole, and its posterior boundary is the posterior end of the temporal lobe. The *parahippocampal gyrus* is bounded inferiorly by the collateral sulcus and superiorly by the hippocampal fissure. Its anterior boundary is the temporal pole. Its posterior boundary is formed by an arbitrary line drawn on the mesial surface that runs from the intersection of the collateral sulcus and the occipital cut to the most inferior point of the splenium of the corpus callosum. The hippocampus and amygdala were included in the parahippocampal gyrus ROI, and the parahippocampal gray matter volumes reported include those structures. The cortical volume of the parahippocampal gyrus was calculated by subtracting the volumes of the hippocampus and amygdala.

Criteria for the boundaries of both the *amygdala* and *hippocampus* were derived from the atlas of Duvernoy [12] (Fig. 2). Although the amygdala and hippocampus are clearly visible in coronal slices, separating the posterior amygdala from the anterior end of the hippocampus is not straightforward. Using a method similar to that of Convit et al. [7; see also 49], pointsets tracing the boundaries of the amygdala and hippocampus were first made in parasagittal and axial planes; these pointsets were then projected to the coronal slices to guide tracing of the ROIs. In addition, while tracing in the coronal orientation, regions or voxels that could not be unambiguously assigned to the amygdala or hippocampus were checked in parasagittal and axial planes. We refer readers to Convit et al. [7] for a detailed description of the amygdala, hippocampus, and their relation to other anatomical structures as visualized in MR images.

The hippocampus appears as a discrete structure throughout its rostro-caudal course when viewed in most coronal slices. It can be readily identified from the surrounding parahippocampal gyrus, lateral ventricle, and other basal-medial structures. Anteriorly, it is separated from the amygdala by the inferior horn of the lateral ventricle (although the

inferior horn can be difficult to see in some subjects, hence the need for pointsets made in other orientations), emerging initially as a structure inferior to the amygdala. Posteriorly, care must be taken to separate the tail of the hippocampus from the fasciolar gyrus, which is a small gyrus that originates on the medial surface near the end of the hippocampus (see [13, p. 160]). Again, simultaneously viewing the tail of the hippocampus in multiple orientations allowed accurate tracing of the ROI. The fimbria, which runs along much of the superior surface of the hippocampus, was included in the hippocampus ROI; however, since white matter volumes were excluded from the volume measurement of the hippocampus, it probably made a minimal contribution, if any, to the reported hippocampal volume.

The amygdala is bounded postero-inferiorly by the hippocampus. In coronal MR images, there are no definitive landmarks to signal the anterior origin of the amygdala. Other researchers [7,49] have used the optic chiasm as a landmark to initiate tracing the amygdala. Since the temporal lobes are rarely bilaterally symmetric, we elected to use a landmark that could be identified independently in each hemisphere, namely the first coronal slice in which there is a definitive connection between the temporal and frontal lobes at the anterior end of the temporal stem. This slice was designated as slice 1, and moving posteriorly through the brain (through the coronal slices 1.5–1.6 mm thick), the most anterior amygdala slice was traced on slice 4 (see [13, pp.108–115]). The rationale behind this decision was as follows: In the region of the temporal stem, the uncus forms a cortical "cap" over the anterior amygdala. By starting the amygdala three slices posterior to the fronto-temporal junction, we can be certain that we are posterior to the anterior cortex of the gyrus ambiens of the uncus (on the assumption that the cortex is approximately 4 mm thick). Given variation in the relationship between the slice orientation and the fronto-temporal junction, on some occasions the anteriormost slice of the amygdala was traced on slices 3 or 5 beyond the junction, rather than slice 4. Although our method still uses an arbitrary process to identify the anterior limit of the amygdala, it has the advantage of making use of local anatomical details in the same hemisphere, and close to the amygdala to be traced. The amygdala was traced as the entire ovoid gray mass in the medial temporal lobe, bounded by the white matter of the parahippocampal gyrus and the mesial surface of the temporal lobe. Cortex of the uncus (including the gyrus ambiens and the semilunar gyrus) was undoubtedly included in the amygdala ROIs on some slices, since it is impossible to distinguish it from the gray mass of the amygdala.

2.4. Reliability

All regions were consensually traced by two of the authors (JSA and JB), in consultation with a third author (HD). In a reliability study (two raters, 36 normal subjects) conducted in our laboratory using these criteria for tracing the amygdala and hippocampus, intraclass correlation coefficients for two fixed raters were 0.792 for the left amygdala, 0.921 for the right amygdala, 0.918 for the left hippocampus, and 0.942 for the right hippocampus.

Interrater reliability for tracing the major lobes is also high, and has been reported previously [1].

2.5. Statistical analysis

The gray and white matter volumes of specified brain ROIs were examined using multiple regressions. The data from each ROI measurement were fit to a set of seven multiple regression models (Table 2). Each model included a subject gender term and either linear, quadratic, or cubic polynomial regression term(s). These seven models were compared to determine the model that best fit the ROI data by evaluating the statistical significance of the gender by age interaction terms and by evaluating the statistical significance of the higher order polynomial regression terms. Predicted mean values were obtained from the models established as best fitting at ages 30, 70, and 80 for both female and male subjects. Rate of volume change over the age range was examined graphically by plotting the results of differentiating the multiple regression equations of the best-fitting models.

A multivariate multiple regression analysis was undertaken in order to evaluate the relative contributions to overall rates of change with age in the gray and white matter volumes of the major lobes (frontal, parietal, temporal, and occipital). Based on the best-fitting univariate multiple regression results, multivariate Cubic 3 and Cubic 0 models were examined for white matter volume. For the gray matter volume, not only Cubic 3 and Cubic 0 models were examined, but also Linear 1 and Linear 0 models. The canonical structures

Table 2
Multiple regression models used to examine association among brain volume, age and gender

Model	Effects						
	Gender	Age	Age^2	Age^3	Gender × age	Gender × age^2	Gender × age^3
Linear 0	Yes	Yes	No	No	No	No	No
Linear 1	Yes	Yes	No	No	Yes	No	No
Quad 0	Yes	Yes	Yes	No	No	No	No
Quad 1	Yes	Yes	Yes	No	Yes	No	No
Quad 2	Yes	Yes	Yes	No	Yes	Yes	No
Cubic 0	Yes	Yes	Yes	Yes	No	No	No
Cubic 3	Yes	Yes	Yes	Yes	Yes	Yes	Yes

obtained from each of these multivariate analyses were used to compare the strength of association of each of the contributing major lobes to the overall gender and age effects. The multivariate test statistics are derived from weighted sums (principal eigenvectors) of the ROIs being analyzed multivariately, obtained from a test matrix analogous to the *F*-ratio of an univariate analysis. The canonical structure presented here for an effect is the set of correlations of the weighted sum with each ROI volume showing the relative strength of association of each volume with the multivariate effect, after adjustment for the residual associations among the ROI volumes.

3. Results

3.1. Regression models

The results of the regression analyses are presented in Figs. 3–7 and Tables 3 and 4. Several general patterns of age-associated changes in brain volume are apparent in these results. First, for the whole cerebrum and most of the major lobes, gray matter volumes decrease linearly across the lifespan. In contrast, a cubic regression model best-fits the white matter volume data. White matter volume increases up to 50–60 years of age. Thereafter it begins to decline, at first gradually and then around the age of 70 years, more precipitously. The adjusted R^2 values (all values reported are statistically significant at $p < 0.05$) for the best-fit models indicate that age accounts for a substantial proportion of the variance in brain volume. Adjusted R^2 values range from 0.37 to 0.08, with most of them greater than 0.25.

There are regional exceptions to some of the general pattern outlined above. The occipital lobe white matter is best-fit by a quadratic regression model rather than a cubic regression (Fig. 4). It shows a volume peak at around 40 years of age, which is somewhat earlier than for the other major lobes. For the occipital gray matter volume, although as for other regions, a linear model best-fits the data, the adjusted R^2 value is relatively low (0.08) but still significant. This value is significantly lower than the adjusted R^2 values for both the

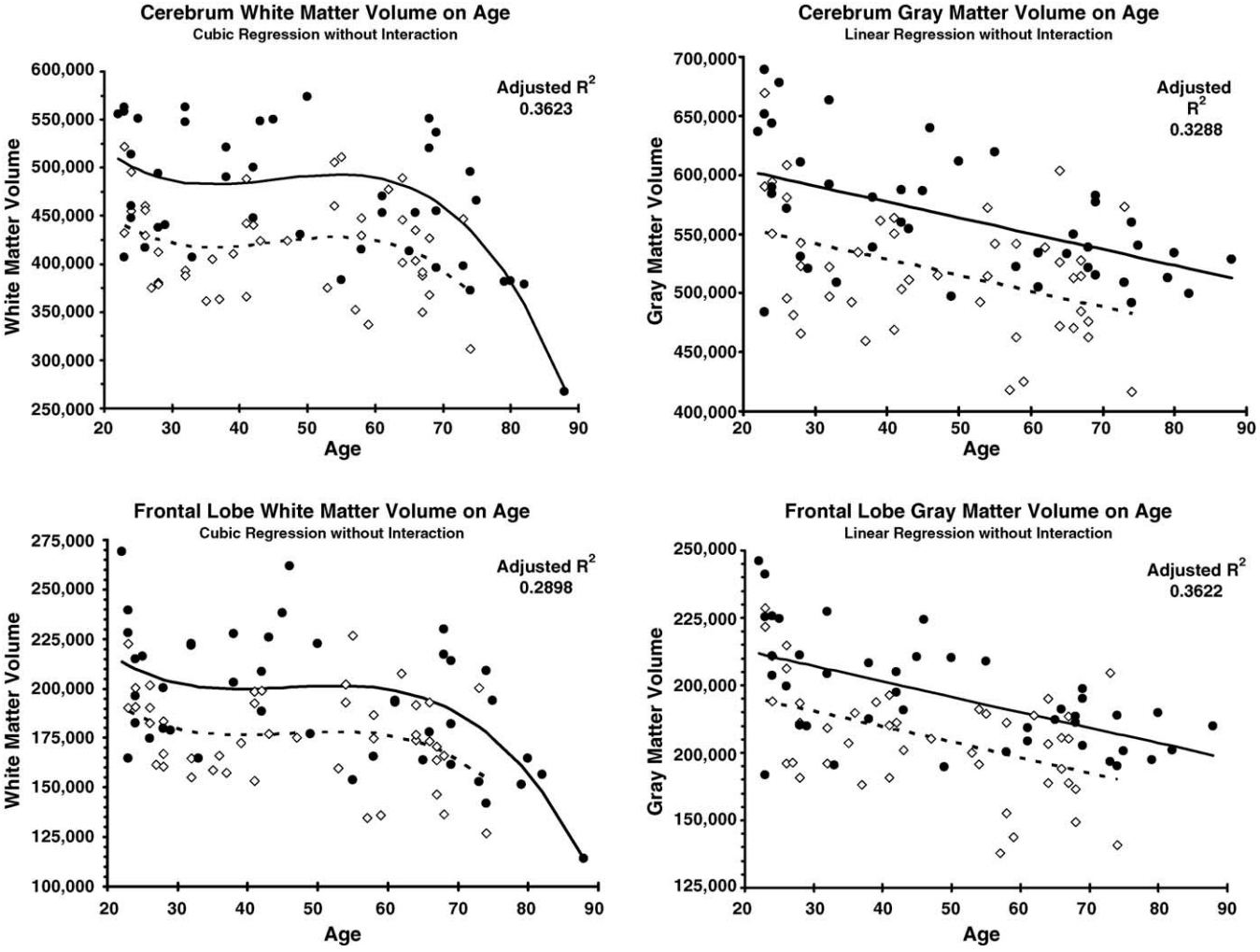

Fig. 3. Plots of gray and white matter volumes vs. age (including best-fit regression lines) for the cerebrum and frontal lobes. Solid lines, males; dashed lines, females.

Table 3
Best-fitting gray matter polynomial regression equations by region of interest (volume in mm^3)

Region of interest	Best-fitting model	Adjusted R^2	Equation[a]
Cerebrum[b]	Linear 0	0.3288	582 034 + 49 060 + [(age)(−1345)]
Frontal lobe	Linear 0	0.3622	207 413 + 16 891 + [(age)(−571.0)]
Parietal lobe	Linear 0	0.2185	123 196 + 10 356 + [(age)(−268)]
Occipital lobe	Linear 0	0.0834	57 751 + 3523 + [(age)(−105)]
Temporal lobe	Cubic 0	0.3245	213 967 + 16 202 + [(age)(−4971) + $(age)^2$(97.54) + $(age)^3$(−0.6226)]
Temporal pole	Cubic 0	0.1371	28 052 + 2098 + [(age)(−761.8) + $(age)^2$(18.33) + $(age)^3$(−0.1335)]
Superior temporal gyrus	Cubic 0	0.1939	52 653 + 2962 + [(age)(−1535) + $(age)^2$(27.94) + $(age)^3$(−0.1647)]
Infero-temporal region	Cubic 0	0.3324	103 332 + 7723 + [(age)(−2423) + $(age)^2$(46.50) + $(age)^3$(−0.2936)]
Parahippocampal gyrus	Linear 0	0.2775	23 466 + 2087 + [(age)(−43.44)]
Amygdala	Linear 0	0.1787	3494 + 442 + [(age)(−7.195)]
Hippocampus	Cubic 0	0.1421	10 406 + 415 + [(age)(−252.5) + $(age)^2$(5.411) + $(age)^3$(−0.03721)]

[a] Second term in the equation is scaling term for male gender; to calculate predicted female means, exclude this term.
[b] Does not include subcortical gray structures.

cerebral (cortical) gray matter ($p < 0.05$) and the frontal lobe gray matter ($p < 0.01$).

The temporal lobe also showed some differences in relation to the other major lobes (Fig. 5). The temporal lobe gray matter was best-fit by a cubic model rather than linear model, showing an aging pattern more typical of the cerebral white matter. Compared to the other regions, the temporal lobe white matter appears to have a slightly later peak in volume (greater than 60 years). The temporal pole, superior temporal gyrus, and infero-temporal region all show the same aging patterns as that seen for the temporal lobe as a whole.

The parahippocampal gray matter volume includes both the amygdala and the hippocampus. It showed a linear decline with age (Fig. 7), as did the volume of the amygdala. In contrast, changes in hippocampal volume with age were best-fit by a cubic regression model, indicating a stable volume until about age 60 followed by an accelerating rate of volume decrease. The volume of the parahippocampal cortical gray matter (including entorhinal and perirhinal cortexes) can be calculated by subtracting the volumes of the amygdala and hippocampus from the total volume of the gray matter of the parahippocampla gyrus. The parahippocampal cortex showed a linear decline with age, with an adjusted R^2 value of 0.2038. These results indicate that the aging pattern observed for the hippocampus is different from that observed in the rest of the gray matter of the parahippocampal gyrus (i.e., the cortical gray plus the amygdala).

Rates of volume change with age for the whole cerebrum are shown in Fig. 8. These were obtained by differentiating the best-fit lines for gray and white matter volumes. Rates of change for the gray matter volume remain steady across the lifespan, with an average gray matter loss of a little more than 1000 mm^3 per year. Rates of white matter change vary across the lifespan. White matter atrophy begins at about age 50, and by age 60, gray and white matter volumes are declining at about the same rate. After this point, white matter atrophy continues to accelerate with each passing year. The rate of change of gray/white ratio reaches a (negative) minimum at about age 50, but increases steadily after this point. This indicates that after about age 50, the rate of white matter loss begins to exceeds the rate of gray matter loss.

3.2. Differences in regression models for the four major lobes

A multivariate multiple regression analysis (see Section 2) was undertaken to see if there were any significant differences among the four major lobes in the relationship between gray/white matter volume and age. The best-fitting univariate regression models suggest that the occipital lobe white matter volume and the temporal lobe gray matter volume have aging patterns that are different from the other major lobes; even among the lobes with the same best-fitting regression

Table 4
Best-fitting white matter polynomial regression equations by region of interest (volume in mm^3)

Region of interest	Best-fitting model	Adjusted R^2	Equation[a]
Cerebrum[b]	Cubic 0	0.3623	688 760 + 65 506 + [(age)(−19 320) + $(age)^2$(444.8) + $(age)^3$(−3.269)]
Frontal lobe	Cubic 0	0.2898	290 934 + 23 330 + [(age)(−7797) + $(age)^2$(173.8) + $(age)^3$(−1.262)]
Parietal lobe	Cubic 0	0.3709	197 790 + 21 597 + [(age)(−5270) + $(age)^2$(122.7) + $(age)^3$(−0.9161)]
Occipital lobe	Quad 0	0.2329	25 155 + 5977 + [(age)(427.7) + $(age)^2$(−5.595)]
Temporal lobe	Cubic 0	0.3009	131 911 + 12 448 + [(age)(−4499) + $(age)^2$(106.8) + $(age)^3$(−0.7751)]
Temporal pole	Cubic 0	0.3363	4666 + 877 + [(age)(−191.4) + $(age)^2$(7.038) + $(age)^3$(−0.0615)]
Superior temporal gyrus	Cubic 0	0.1902	26 460 + 1824 + [(age)(−1053) + $(age)^2$(23.22) + $(age)^3$(−0.1573)]
Infero-temporal region	Cubic 0	0.3474	67 185 + 6377 + [(age)(−2393) + $(age)^2$(54.58) + $(age)^3$(−0.3878)]
Parahippocampal gyrus	Cubic 0	0.2528	12 271 + 1055 + [(age)(−405.0) + $(age)^2$(9.409) + $(age)^3$(−0.06708)]

[a] Second term in the equation is scaling term for male gender; to calculate predicted female means, exclude this term.
[b] Does not include subcortical gray structures.

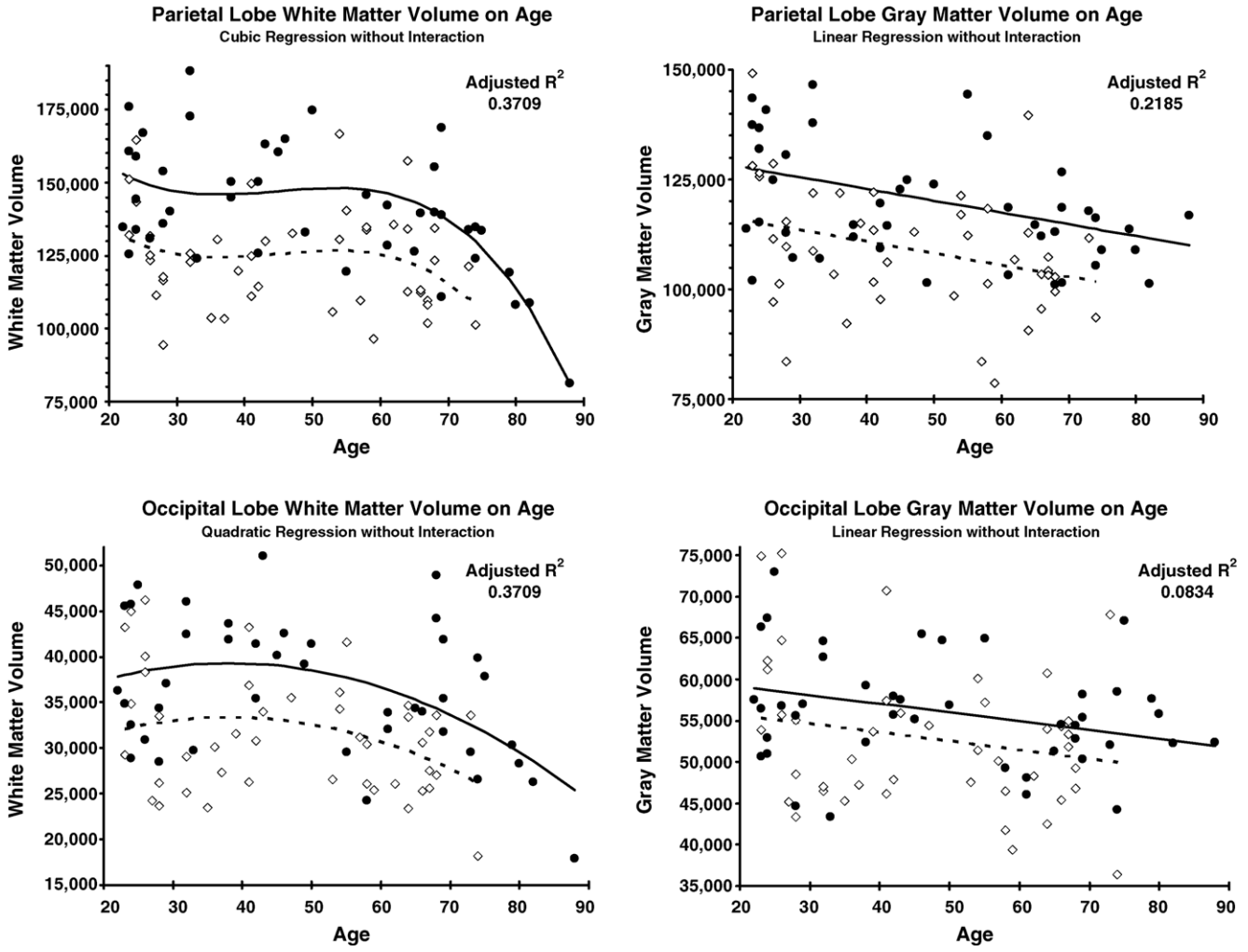

Fig. 4. Plots of gray and white matter volumes vs. age (including best-fit regression lines) for the parietal and occipital lobes. Solid lines, males; dashed lines, females.

models, there could be significant differences among them based on differences in the strength of association between volume and age.

Tables 5a and 5b present the correlations of gray and white matter volume with multivariate age effects for each of the major lobes. The correlations for the gray matter suggest that the strongest association with, or contribution to, the multivariate cubic polynomial regression on age is that of the frontal lobe, followed by the parietal and temporal lobes, and that the weakest is with the occipital lobe. A multivariate test of the null hypothesis, that the age coefficients are equal across the lobe gray matter volumes, was statisti-

Table 5a
Correlations of gray matter volume with multivariate age effects for each of the major lobes (Linear 0 model)

Lobe	r	r^2
Frontal	0.92	0.85
Parietal	0.67	0.45
Temporal	0.61	0.37
Occipital	0.47	0.22

Table 5b
Correlations of white matter volume with multivariate age effects for each of the major lobes (Cubic 0 model)

Lobe	Age r	r^2
Frontal	0.97	0.94
Parietal	0.78	0.61
Temporal	0.75	0.56
Occipital	0.53	0.28
Lobe	Age^2 r	r^2
Frontal	0.96	0.92
Parietal	0.76	0.58
Temporal	0.70	0.49
Occipital	0.52	0.27
Lobe	Age^3 r	r^2
Frontal	0.95	0.90
Parietal	0.77	0.59
Temporal	0.71	0.50
Occipital	0.54	0.29

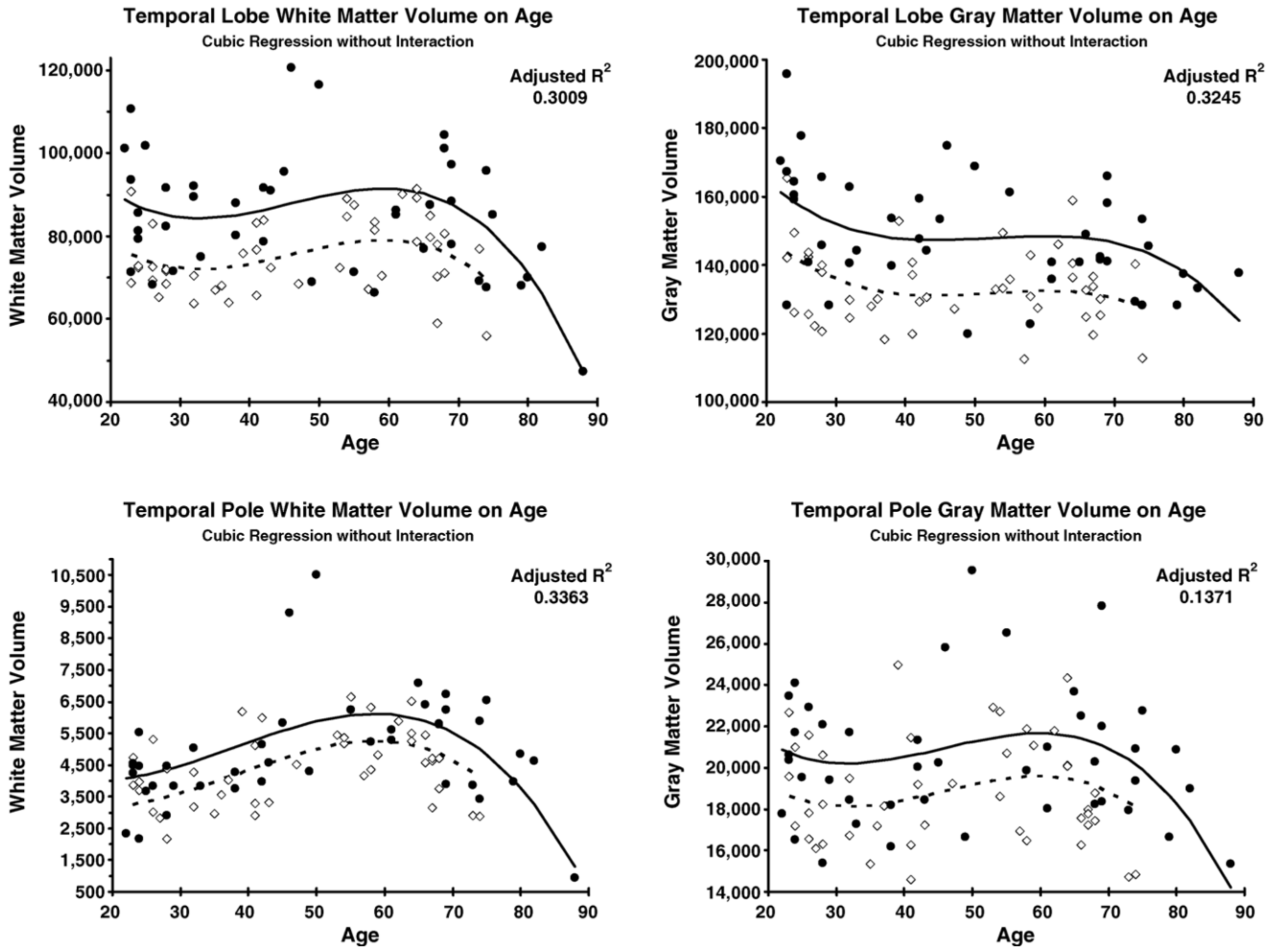

Fig. 5. Plots of gray and white matter volumes vs. age (including best-fit regression lines) for the temporal lobe and temporal pole. Solid lines, males; dashed lines, females.

cally significant (F-ratio = 13.27, 3 and 82 d.f., $p < 0.0001$). Two additional multivariate tests of this null hypothesis were undertaken. In the first, the gray matter volumes of the frontal, parietal, and temporal lobes were included while the occipital lobe was excluded; the result was still statistically significant (F-ratio = 16.63, 2 and 83 d.f., $p < 0.0001$). In the second, the gray matter volumes of the lobes was considered excluding the frontal lobe; again, the result was significant (F-ratio = 3.67, 2 and 83 d.f., $p < 0.05$). These results indicate that the relationship of gray matter volume to age, as modeled by linear regression, differs among the four major lobes, and that relationship may be represented by grouping the lobes into three sets: unique sets of the frontal lobe and occipital lobe and a combined set for the temporal and parietal lobes.

For the white matter volume, the canonical structure again suggests that the lobes can be divided into three sets: the temporal lobe (strongest association with age), the parietal and frontal lobes, and the occipital lobe (weakest association with age). A joint multivariate test of the three cubic polynomial coefficients, with the null hypothesis that they are equal across the white matter volumes of the four lobes, was significant (F-ratio = 6.23, 9 and 194.85 d.f., $p < 0.0001$). Again, two additional multivariate tests of this null hypothesis were undertaken. In the first, the lobe white matter volumes coefficients were considered jointly, excluding the occipital lobe; the result was statistically significant (F-ratio = 6.31, 6 and 162 d.f., $p < 0.0001$). In the second, the temporal lobe white matter volume was excluded, while the coefficients of the other three lobes were considered jointly; again, the result was statistically significant (F-ratio = 4.92, 6 and 162 d.f., $p = 0.0001$). These results indicate that the relationship of white matter volume to age, as modeled by a cubic polynomial, differs among the four major lobes, and that the relationship may be represented by grouping the lobes into three sets: unique sets for the temporal lobe and occipital lobe, and a combined set for the frontal and parietal lobes.

In summary, these multivariate results suggest that while the gray and white matter volumes of the major lobes are all age-associated (as shown by the best-fit univariate regression models), there are some significant differences among the lobes in the strength of association. For both gray and white matter volume, the occipital lobe appears to be the

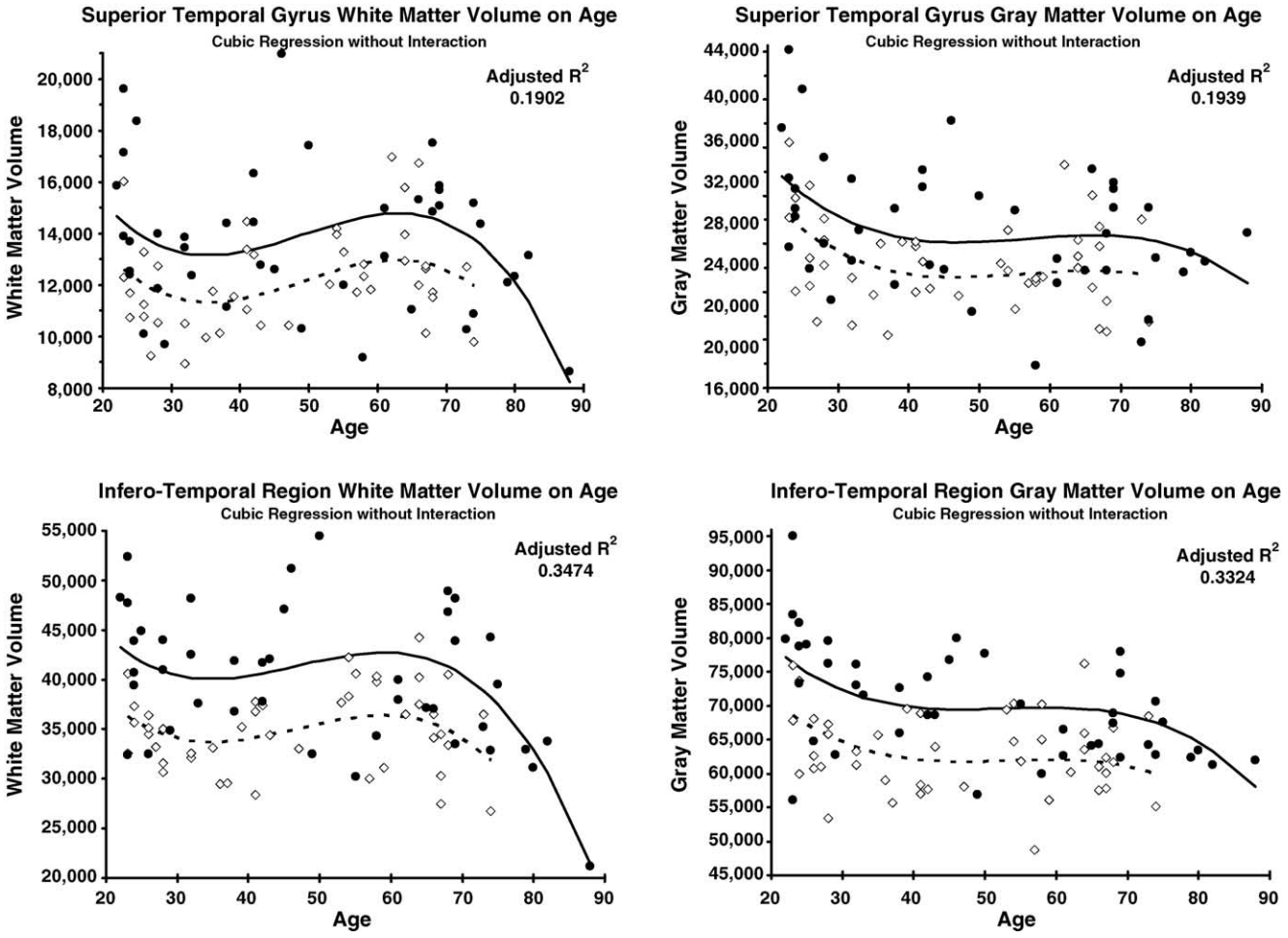

Fig. 6. Plots of gray and white matter volumes vs. age (including best-fit regression lines) for the superior temporal gyrus and infero-temporal region. Solid lines, males; dashed lines, females.

least strongly associated with age. For the gray matter volume, the frontal lobe has the strongest age association, while for the white matter volume, the temporal lobe is the most strongly associated with age.

3.3. Sex differences in rates of brain aging

We found no sex differences in brain aging patterns for any of the regions examined. For each ROI, a general linear model test [32] demonstrated that the addition of gender by age interaction terms did not significantly improve the fit of the regression model over one in which gender by age interaction terms were not included (e.g., the Cubic 0 model versus the Cubic 3 model). There is a significant difference in regional brain volumes between the sexes, and this is accounted for in the regression models by the addition of a scaling factor for males (see Tables 3 and 4). A gender difference was seen in white matter volume aging patterns in some ROIs, but only if a linear model was imposed on the data. In each of those cases, however, the cubic model was the best-fitting regression, and it showed that there was no sex difference.

3.4. Changes in predicted means with aging

In Tables 6 and 7, we present predicted mean gray and white matter volumes for each ROI for men and women at ages 30, 70, and 80 years. These means are based on the best-fit regression equations given in Tables 3 and 4.

The predicted means indicate that whether gray or white matter is considered to be more susceptible to age-related changes depends in part on the comparative context. At 70 years of age compared to 30, gray matter changes will exceed those of the white matter, for all regions. By age 80, however, the accelerating decrease in white matter volume means that white matter decline will substantially exceed the gray matter decline on a percentage basis.

The percent changes from 30 to 70 years indicates the frontal lobe gray matter and the occipital lobe white matter show the greatest age effects. At 80 years, the frontal lobe gray matter still shows the largest percentage decrease in volume, but the occipital lobe white matter no longer shows the greatest relative decline in volume compared to other regions. Compared to the other major lobes, the temporal lobe (gray

Table 6
Predicted volume means at 30, 70, and 80 years for the major lobes

Region	Tissue	Predicted mean at 30 years (cm^3)		Predicted mean at 70 years (cm^3)		Predicted mean at 80 years (cm^3)		% Change 30-year-mean to 70-year-mean		% Change 30-year-mean/80-year-mean	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Cerebrum	Gray[a]	590.7	541.2	536.9	487.9	523.4	474.4	−9.1	−9.8	−11.3	−12.3
	White	486.7	421.2	459.9	394.4	381.4	315.9	−5.6	−6.4	−21.6	−25.0
Frontal lobe	Gray	207.2	190.3	184.3	167.4	178.6	161.7	−11.1	−12.0	−13.9	−15.1
	White	202.7	179.4	187.4	164.1	156.9	133.6	−7.5	−8.5	−22.6	−25.5
Temporal lobe	Gray	152.0	135.8	146.6	130.4	138.0	121.8	−3.6	−4.0	−9.2	−10.3
	White	84.6	72.1	86.8	74.4	71.1	58.6	+2.6	+3.2	−16.0	−18.7
Parietal lobe	Gray	125.5	115.2	114.8	104.4	112.1	101.8	−8.6	−9.4	−10.7	−11.6
	White	146.9	125.3	137.3	115.7	113.7	92.1	−6.5	−7.7	−22.6	−26.5
Occipital lobe	Gray	58.1	54.6	53.9	50.4	52.8	49.3	−7.2	−7.7	−9.1	−9.7
	White	38.9	33.0	33.7	27.7	29.5	23.6	−13.4	−16.1	−24.2	−28.5

[a] Does not include subcortical gray structures.

and white matter) shows the least amount of volume reduction on a percentage basis, at both 70 and 80 years of age.

Within the temporal lobe, all regions show an increase in white matter volume between the ages of 30 and 70 years, with a substantial decrease apparent by the age of 80 (the temporal pole volume changes should be regarded with some caution given the small size of the ROI and its more arbitrary definition). The accelerating rate of tissue loss in the hippocampus past the age of 70 means that compared to the other temporal lobe regions, it shows the smallest percentage loss in volume at age 70, but the greatest loss at age 80.

4. Discussion

Like several other studies of brain aging using MRI data, we find that brain volume is an age-dependent biological variable. We confirm and extend previous results by providing a high-resolution study of regional brain volumes, using a gray–white segmentation algorithm that takes into account partial voxel effects. Before comparing our results to those from previous studies, it is important to mention two issues that should be taken into consideration when reviewing the brain aging literature based on in vivo MRI studies.

First, there is a tremendous amount of methodological variability in the literature that can make comparisons among studies somewhat difficult. For example, the present volumetric study is based on the parcellation of the brain using each of the approximately 100 coronal slices that comprise an MRI brain volume; other "volumetric" MRI studies have estimated regional brain volumes from a half-dozen index or reference slices (e.g. [3,37,53]). Methodological variability is probably a major source of variable results concerning brain aging patterns. On the positive side, results that are robust across varied methods may be accepted with more confidence.

The second issue involves subject selection (see [45]). Virtually all brain aging studies endeavor to include "healthy" older individuals. Of course, given that ill-health is associated with normal aging, the selection of obviously healthy

Table 7
Predicted volume means at 30, 70, and 80 years for temporal lobe regions

Region	Tissue	Predicted mean at 30 years (cm^3)		Predicted mean at 70 years (cm^3)		Predicted mean at 80 years (cm^3)		% Change 30-year-mean to 70-year-mean		% Change 30-year-mean/80-year-mean	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Temporal pole	Gray	20.2	18.1	20.9	18.8	18.3	16.2	+3.4	+3.9	−9.4	−10.5
	White	4.5	3.6	5.5	4.7	3.8	2.9	+22.2	+30.6	−15.6	−19.4
Superior temporal gyrus	Gray	30.3	27.3	28.6	25.7	27.4	24.4	−5.6	−5.9	−9.6	−10.6
	White	13.4	11.5	14.4	12.6	12.1	10.3	+7.5	+9.6	−7.5	−10.4
Infero-temporal region	Gray	72.3	64.6	68.7	61.0	64.6	56.9	−5.0	−5.6	−10.7	−12.0
	White	40.4	34.1	40.5	34.1	32.9	26.5	+0.2	0.0	−18.6	−22.3
Parahippocampal gyrus	Gray	24.3	22.2	22.5	20.4	22.1	20.0	−7.4	−8.1	−9.1	−10.0
	White	7.8	6.8	8.1	7.0	6.8	5.7	+3.8	+2.9	−12.8	−16.2
Amygdala	Gray	3.7	3.3	3.4	3.0	3.4	2.9	−8.1	−9.1	−8.1	−12.1
Hippocampus	Gray	7.1	6.7	6.9	6.5	6.2	5.8	−2.8	−3.0	−12.7	−13.4

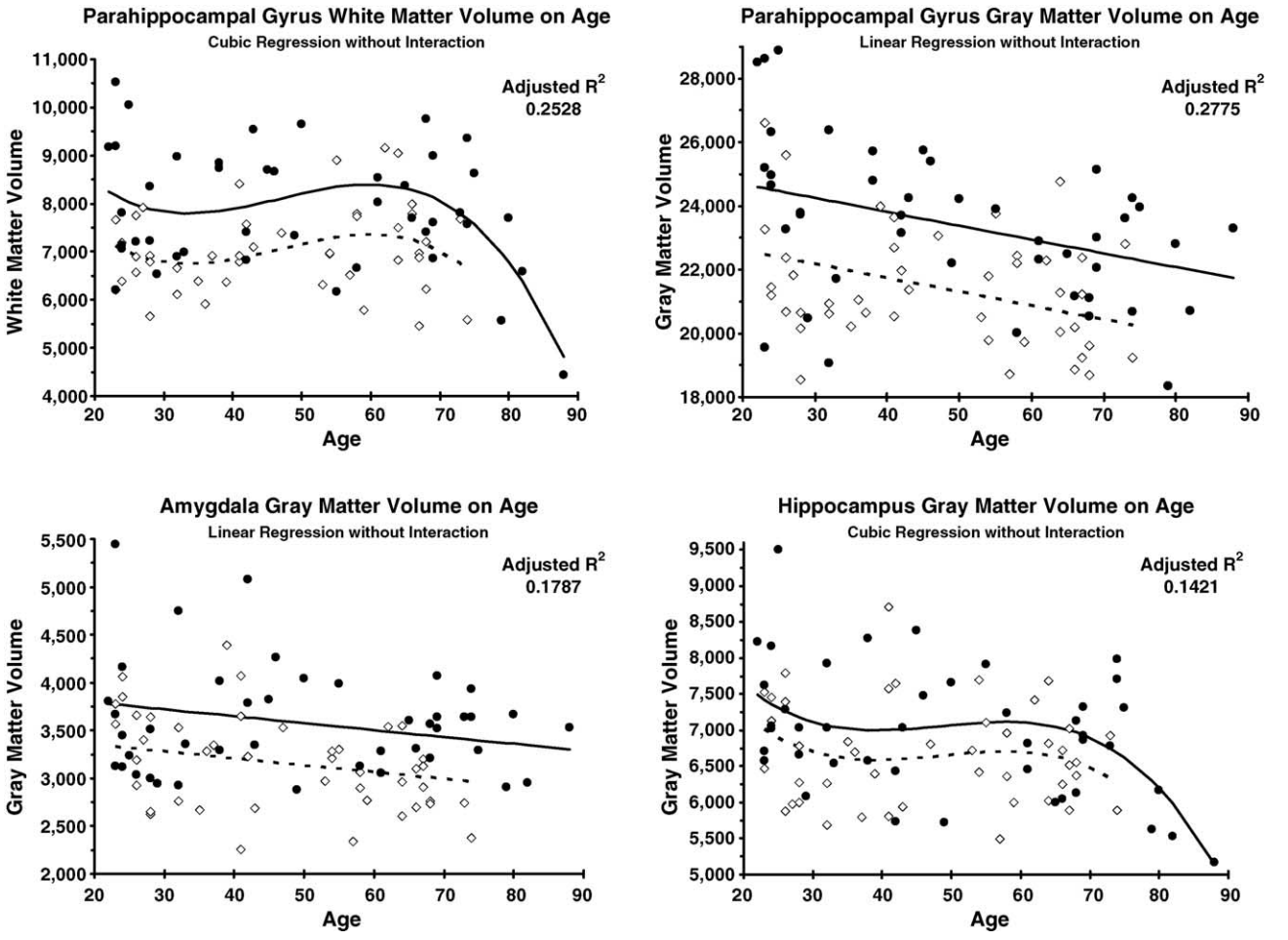

Fig. 7. Plots of gray and white matter volumes vs. age (including best-fit regression lines) for the parahippocampal gyrus, and gray matter volume vs. age plots for the amygdala and hippocampus. Solid lines, males; dashed lines, females.

individuals constitutes a potential source of bias. Furthermore, the assessment of "health" may vary from study to study and may even introduce a bias along gender lines. Still, the reliance on healthy older individuals in brain aging studies is fully justified in that it removes disease-status as a confounding variable. Our subjects were screened based on interview rather than with a clinical examination. Thus our "healthy" older subjects are defined as such based on the absence of a clinical diagnosis, rather than on the results of a clinical examination. This increases the likelihood that our subject population is more heterogeneous (from a health standpoint) than an ideal subject population would be. Such heterogeneity could serve to obscure statistical relationships between regional brain volumes and age.

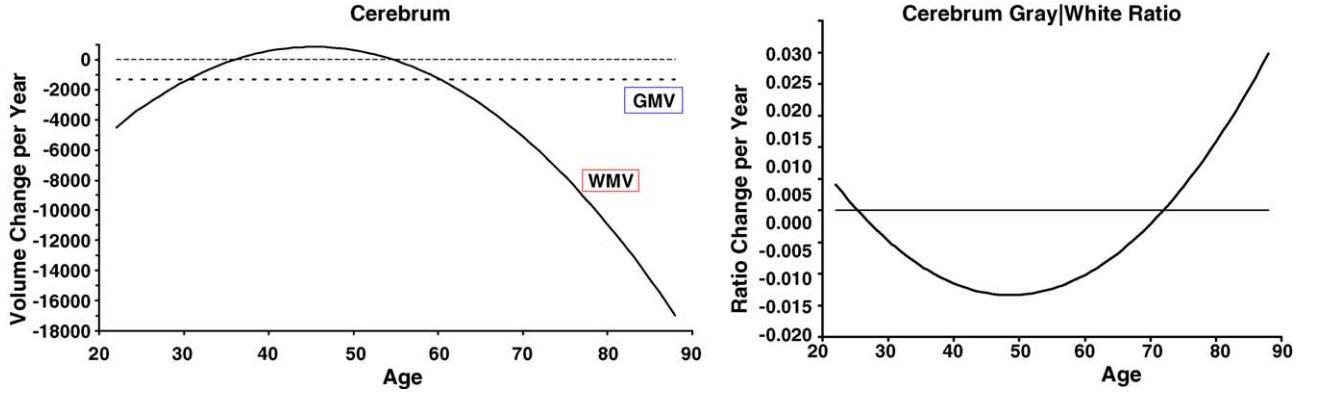

Fig. 8. Plot of volume change per year vs. age for the gray and white matter of the cerebrum, and plot of cerebral gray/white ratio change per year vs. age.

The main limitation of the study is that while a total of 87 subjects is a relatively large number for a high-resolution, MRI-volumetric study using anatomical parcellation, it is not a particularly large number to model the effects of age on brain volumes across the adult human lifespan. As mentioned above, we have more men than women in the latter portion of our age range, which could influence gender comparisons. In addition, given the relatively small sample size, concentrations of subjects in certain parts of the age range, such as in the early 20s, could bias regression models in unpredictable ways.

4.1. Gray and white matter volume changes

For the cerebrum as a whole and for most of the major lobes, we found that gray matter volume declined linearly with age, while white matter volume showed a more age-dependent pattern, whereby it remained steady or increased slightly through adulthood, followed by a precipitous decline starting around the age of 60. These results are consistent with several previous studies [3]. Jernigan et al. [24] found that white matter decline started later but was ultimately more profound than the decrease in gray matter; they reported that between the ages of 30 and 90, there was a 14% loss in cerebral cortex and a 26% loss in cerebral white matter. We estimated that between 30 and 80 years, there is about a 12% loss in cerebral cortex and a 23% loss in white matter. Thus our results are quite comparable despite different methods. Sowell et al. [48] also demonstrated similar patterns of age-associated changes in total brain gray and white matter volumes. Although they have relatively few older subjects, the results of Courchesne et al. [8] and Good et al. [17] are also reasonably consistent with ours (although in Good et al., no significant relationship between age and white matter was found; see also [37]). Mueller et al. [30] found that the regional brain volumes (including gray and white matter) declined at a relatively constant rate across the lifespan, which we also found to be true for the gray matter. In a study of 18–49 years olds, Gur et al. [20] found that whole brain gray matter volume decreased significantly, while white matter volume showed a non-significant increase in volume. These patterns are consistent with the data we present when this same age range is considered.

With regard to white matter volume changes with age, one difference between our study and others (e.g. [4,48]) did emerge: for cerebral white matter as a whole and in most regions, we found that a cubic regression model was a statistically significantly better fit for the data compared to a quadratic regression model (i.e., the coefficient of the volume cubed was significantly different from zero). As discussed above, our cubic regression models showed essentially the same pattern as the quadratic models found by other researchers for ages greater than 40 years. However, below 40 years of age, our cubic models show a white matter peak in the 20-year range, then a slight depression before rising again. This is not the same as seen in the quadratic models, which predict that white matter volume rises and falls over the lifespan following a parabolic curve. Certainly, such a pattern makes broad intuitive sense if white matter volume changes are tracked from birth to old age. However, given the heterogeneous nature of MRI white matter, it would not be surprising if white matter changes in the brain followed a less “ballistic” pattern. In the future, it would be useful if researchers who have large age series of brain volumes were to explore cubic and even higher order polynomial regressions when analyzing their white matter data.

In general, it would appear that the linear decline in gray matter volume over the lifespan and the accelerating decline in white matter volume past the age of 65 is a robust finding. Since white matter increases in volume until about age 50, studies that do not include a sufficient number of older individuals (>70 years) may not detect the accelerating decrease in white matter volume that begins relatively late in life.

It is important to keep in mind that when we say that our findings are “robust”, that is meant to be in the context of studies of brain aging using MRI. A different issue is whether or not these results are consistent with those gained from other approaches to study the aging brain. Post-mortem studies have long established that older brains show loss of volume, with sulcal widening and expansion of the cerebral ventricles. These changes are usually considered to be associated with a more profound loss of white matter than gray matter, which can result from a wide variety of pathological processes [42]; it is possible, however, that these changes could be influenced by the differential effects of fixation on younger and older brains. Pakkenberg and Gundersen [35] have used stereological methods to track the change in neuron number and white matter across the lifespan. They found that neuron number declines in a steady, linear fashion, resulting in about a 10% decline from age 20 to 90; this is in contrast to a 28% decline in white matter. The 10% decline for neuron number is consistent with the slightly higher estimates derived from MRI measures of the cerebral cortex, especially if some of the cortical loss is due to loss of myelinated fibers within the cortex that are classified as gray matter.

The topic of (de)myelination is also important for addressing the cellular basis of white matter loss with aging. Some of the white matter loss is obviously due to Wallerian degeneration, and Pakkenberg and Gundersen [35] speculate that there may be loss of myelin around the fibers without loss of the neuron, a factor which may contribute to cognitive decline in the absence of substantial neuronal loss. Dendritic loss (in the absence of neuronal loss) does not appear to be a general feature of brain aging, although it can be pronounced in some regions [51]. As mentioned above, several factors other than axonal degeneration and demyelination also contribute to white matter loss in aging. Certainly, across the lifespan, the combination of factors that govern white matter composition serve to make it a relatively more “dynamic” tissue, in a volumetric sense, than the gray matter.

Another issue of importance in MRI volumetric studies of gray and white matter involves the fact that the changes in

white matter associated with aging have the collective effect of making the "white matter" less white in T1-weighted MRIs (or cause the presence of hyperintensities in T2-weighted images [54]). For example, localized demyelination, periventricular hypointensities, and the boundaries of minute lesions may all be classified as "gray matter" by automated segmentation programs. Guttman et al. [21] specifically looked at the relationship between lesion-associated hyperintensities (in T2-weighted images) and found that they did not contribute significantly to the pattern of white matter change with age in their study. On the other hand, Jernigan et al. [24] suggest that automated segmentation programs that classify tissues into gray matter, white matter, or CSF, may systematically underestimate gray matter loss with age and over-estimate white matter loss, since signal changes in white matter are typically in a direction that makes some regions of the white matter appear more like "gray matter". Since the segmentation algorithm used in the present study took into account partial–voxel effects (i.e., voxels were not classified on a dichotomous basis into either gray or white matter), we believe that we are less prone to an overestimation of white matter loss; however, our algorithm, like others, is susceptible to underestimating declines in gray matter with age, since some white matter hypointensities will be classified as gray matter.

4.2. Patterns of aging in the major lobes

Several studies have shown that the frontal lobe appears to show a more a rapid rate of volume decrease with age compared to the other major lobes [9,24,43]. Our results are consistent with this finding, since we found that the percentage decline in gray matter volume in the frontal lobe at 70 and 80 years was somewhat more pronounced than those observed for the other major lobes (Table 6). The multivariate analysis confirms this, showing that the frontal lobe gray matter is more strongly associated with age than the three other major lobes.

Compared to the other major lobes, a different pattern of aging was observed in the temporal lobe gray matter: the temporal lobe pattern was best-fit by a cubic regression model, while linear models were obtained for the other major lobes. At age 70, the gray matter volume of the temporal lobe is relatively well maintained compared to the other lobes (Table 6); a similar result was seen in a study of temporal lobe morphology and aging that used a subject group in which the oldest subjects were just over 70 years of age [4]. However, the temporal lobe shows an increased rate of gray matter decline with increasing age, so that by age 80, the percentage loss of gray matter in the temporal lobe approaches that seen in the other major lobes. Like the other major lobes, the white matter volume of the temporal lobe is best fit by a cubic regression model. However, the white matter decline in the temporal lobe starts somewhat later than in other regions. The multivariate analysis pairs the temporal lobe with the parietal lobe in terms of the strength of association of gray and white matter volume with age.

The occipital lobe gray matter also shows a somewhat different aging pattern from that seen in other regions. Although like the cerebrum as a whole and the frontal and parietal lobes, it shows a linear decline over time, the adjusted R^2 for the occipital gray is substantially lower than for the other regions. This difference reaches statistical significance in comparison to the adjusted R^2 values for the cerebrum and frontal lobe, and is confirmed by the multivariate analysis. This finding indicates that the occipital gray matter is less susceptible to changes with age compared to the frontal and parietal gray matter. Such a result is consistent with other studies that have shown a relatively weak correlation between pericalcarine (visual cortex) gray matter and age [43,44]; in addition, studies of rhesus monkeys show no age-associated loss of neurons or volume in the striate cortex [36].

In summary, the major lobes of the human brain show variable patterns of aging, especially in the gray matter. Indeed, it may be possible that each of the four major regions has a unique aging profile, which is expressed in the context of the general cerebral pattern of a steady, linear decline in gray matter volume and a delayed but accelerated decline in white matter volume.

4.3. Gender and brain aging

We found no gender differences in the patterns of gray or white matter aging in any of the regions of interest examined. Several MRI based studies have shown sex differences in aging patterns for whole brain and for various regions and tissues [6,9,19,31,38,53]. However, there are also numerous reports that failed to show sex differences or observed them in only a few small regions of the brain [17,24,44,48]; Pakkenberg and Gundersen's [35] stereological study of neuron number also did not find any sex differences. In almost every case in which a sex difference is reported, it is in the direction that shows relatively accelerated aging in men compared to women (for an exception see [31]).

There are two methodological reasons that may explain our lack of finding any sex differences. First, for each ROI, we tested several regression models of the association between volume and age. Although some of the linear models for some regions did show a sex difference, in each case a more complex model (which did not show a sex difference) was found to be the best-fitting one. Second, we had several more men in our subject group over the age of 70 than women. Although this could work against finding similar patterns in the sexes, it may be possible that the addition of older women (who maintained brain volume) could have produced an aging pattern different from that which we extrapolated from the younger subjects.

As mentioned above, almost all of the studies that report a sex difference find that brain aging is more pronounced in men (albeit in different regions and somewhat inconsistently expressed); given these moderately consistent results,

it seems that there may be evidence for sex differences in brain aging. However, if there is a "real" sex difference in brain aging patterns, it is probably a relatively subtle one. The argument for sex differences in brain aging would be strengthened if there were a strong theoretical justification for it based on the physiology or evolutionary biology of aging [15,46]. Post hoc explanations (e.g., that sex steroids are somehow responsible) are not very convincing in light of weak or inconsistent empirical evidence.

4.4. Patterns of aging within the temporal lobes

Three sectors of the temporal lobe, the temporal pole, superior temporal gyrus, and the infero-temporal region, all show patterns of gray and white matter aging that are similar to that which is observed for the temporal lobe as a whole. Adjusted R^2 values are substantially (although not significantly) higher for the infero-temporal region (adjusted $R^2 = 0.34$) compared to the superior temporal gyrus (adjusted $R^2 = 0.19$), and therefore more detailed investigations of aging in these two regions may be warranted.

Age-related changes in the hippocampus and entorhinal cortex have received much attention, especially from investigators interested in Alzheimer's disease [11,26,29]. Aging in the amygdala has been less studied. Laakso et al. [27] found that amygdaloid volume was significantly correlated with age ($r = -0.31$ on the right and -0.41 on the left). These results are very similar to ours, in which amygdala volume (left and right combined) was found to decline linearly with age, with an adjusted R^2 of 0.1787 ($r = -0.41$).

A variety of different results have been obtained for aging patterns in the hippocampus: it does not change with age [4,17]; it does change with age [11]; it changes more in women than men [31]; it changes more in men than women [39]. Our results indicate that there is no sex difference in aging of the hippocampus and that hippocampal volume remains steady until about 60 years of age; thereafter its volume begins to decline rapidly. These results are very similar to those obtained by Raz et al. [44] in their large scale MRI study. They modeled hippocampal volume versus age with a quadratic regression equation (based on height-adjusted volumes), but the overall aging pattern, especially in older subjects, is very similar to that obtained in our study. The non-linear pattern of aging in the hippocampus may help explain the diverse results otherwise reported: the results could vary significantly depending on the subject composition of the studies.

Age-related volume change in the hippocampus follows a pattern (best-fit by a cubic regression model) similar to the pattern of gray matter changes in other temporal lobe sectors, with the exception of the parahippocampal gyrus. Gray matter in the parahippocampal gyrus as a whole decreased linearly with age; the same pattern was seen in the amygdala. The same was true for the parahippocampal gyrus when the volumes of the hippocampus and amygdala are excluded. Although the parahippocampal gyrus (minus the amygdala and hippocampus) does not correspond to the entorhinal cortex only, the entorhinal cortex is its major component.

Raz et al. [45] have recently published evidence, based on a longitudinal study, of different patterns of aging in the hippocampus and entorhinal cortex. Our results also provide evidence of differential normal aging in the hippocampus and its surrounding cortex. Studies such as those by Du et al. [11] indicate that entorhinal cortex shows a higher rate of atrophy than the hippocampus in Alzheimer's disease. While this may be true in an absolute sense, if the model of hippocampal atrophy described by us and in Raz et al. [45] is accurate, the entorhinal cortex atrophy rate described in Du et al. may not be more accelerated than the hippocampal atrophy rate. Indeed, according to Du et al.'s results, the atrophy rate in AD shows a 5.1-fold increase in the entorhinal cortex and a 7.4-fold increase in the hippocampus. The baseline aging patterns for the hippocampus and the entorhinal cortex are different before AD pathologies begin to accumulate, thus absolute differences in entorhinal and hippocampal atrophy in AD are not necessarily totally ascribable to pathology. Thus it may be premature to claim that MRI volumetric studies of aging in the hippocampus and entorhinal cortex provide evidence that "AD pathology begins in the entorhinal cortex" [11; see also 25], even if such a conclusion is warranted based on other lines of evidence.

5. Summary and conclusions

Our study provides one of the largest high-resolution, comprehensive volumetric parcellation studies of brain aging using MRI scans so far reported. The results of our study give evidence that aging of the gray and white matter in the human brain takes different courses and that there is considerable variation from region to region in how the effects of age are expressed. As measured by MRI, the cortical gray matter and the amygdala decrease in volume with age in a linear fashion (presumably through the steady loss of neurons over the lifespan). Some regions in the temporal lobe, including the hippocampus, show a non-linear decrease in gray matter. In contrast, white matter volumes increase until relatively late in adulthood, followed by a precipitous decline in volume in older age (probably due to factors such as Wallerian degeneration, demyelination of intact fibers, and other pathological processes [41]). It is important to note that although there is variation, every region of interest examined in this study showed statistically significant age-related changes in volume with age. We found no gender differences in brain aging patterns in the regions we measured.

Although voxel-based morphometry and low-resolution MRI studies can provide important insights into brain aging patterns, high-resolution studies, such as the one described in this report, are necessary to provide a comprehensive understanding of age-related volumetric changes in the brain. As we learn more about normal patterns of brain aging, we will better understand the pathological changes (as seen in MRI)

that occur in connection with neurological diseases associated with increasing age. Ultimately, volumetric research on brain aging should also help us understand normal age-related changes in cognition, as they occur in the wider context of the biology of human aging.

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