Prefrontal Gray and White Matter Volumes in Healthy Aging and Alzheimer Disease

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Objectives: To quantify the contribution of gray and white matter volumes to total prefrontal volume in healthy aging. To determine if prefrontal tissue volumes distinguish healthy aging from Alzheimer disease (AD).

Design: Volumes of total prefrontal cortex, prefrontal gray matter, and prefrontal white matter were compared among young healthy elderly (YHE) (n = 14; mean age, 70 years), old healthy elderly (OHE) (n = 14; mean age, 90 years), and subjects with AD (n = 14; mean age, 70 years) by analysis of variance. Additionally, Pearson correlations were performed between volumes and age.

Results: Old healthy elderly and subjects with AD had significantly less total prefrontal volume (approximately 15% less in both groups) and prefrontal white matter volume (approximately 30% less and 20% less in the OHE and AD groups, respectively) than YHE, but there were no differences between the OHE and AD groups. There was a significant difference in gray-white matter volume ratio with OHE having a higher ratio than YHE. Subjects with AD did not differ from YHE or OHE in this ratio. There were significant negative correlations between age and total prefrontal volume and age and prefrontal white matter volume in the healthy subjects.

Conclusions: In the very old, the decline of white matter volume is disproportionately greater than the decline of gray matter volume. In subjects with AD both gray and white matter loss contribute to the decline of prefrontal volume. This is demonstrated by the gray-white matter ratio that does not differ between YHE and subjects with AD. Thus, it is likely that AD is different from accelerated aging.

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Studies of frontal lobe cognition and morphology suggest that the frontal lobe, and specifically the prefrontal cortex, may be disproportionately sensitive to changes with aging compared with other areas of brain. The prefrontal cortex is involved in mediating certain cognitive processes, including metamemory, source memory, working memory, behavioral inhibition, and the nonconscious biases that guide decision making. These and other frontal lobe cognitive functions are often the first to decline in early senescence.

Cognitive changes with aging may be related to age-related decreases in volume of the frontal lobe demonstrated in studies measuring volume in vivo through magnetic resonance imaging (MRI). Age-related decline in regional brain volume is an indirect measure of atrophic degeneration. Many areas of the brain, such as the hippocampus, temporal lobe, and corpus callosum show age-related declines in volume. The frontal lobe shows a greater age-related degeneration than the temporal lobe in MRI studies of both structures. Thus, disproportionate degeneration of the frontal lobe could be responsible for the cognitive changes observed with aging.

Within the prefrontal cortex white matter as compared with cortical gray matter may be particularly susceptible to age-related degeneration and contribute to cognitive decline. In humans, myelin lipid concentrations in the brain begin to decrease from as early as 20 years of age and show a progressive decrease to 100 years of age examined post mortem. Similarly, the aged rhesus monkey exhibits a breakdown in the integrity of myelin around axons that correlates with cognitive decline. Various mechanisms of white matter damage, including strokes and oxidative stress, could cumulatively contribute to the atrophic loss of white matter volume with healthy aging. Thus, age-related prefrontal white matter degeneration may make a significant contribution to the cognitive changes observed with aging.
SUBJECTS AND METHODS

SUBJECTS

Three groups of subjects were studied, YHE (aged, 65-76 years), OHE (aged, ≥85 years), and subjects with AD (aged, 61-75 years; see Table 1 for subject characteristics). The MRIs from OHE and YHE subjects (n = 14 in each group) were examined as part of a longitudinal study of brain aging and cognition (Oregon Brain Aging Study) at the Oregon Health Sciences University and Veterans Affairs Medical Center in Portland. The OHE subjects were 85 years of age or older. Subjects with AD (n = 14) were studied as part of a National Institute on Aging Alzheimer’s Disease Center clinical protocol at the Oregon Health Sciences University. Subjects with AD were age matched to the YHE group. All groups were matched for education and there was an equal number of men and women within and among groups (7 men and 7 women). Detailed descriptions of the recruitment procedures and inclusionary and exclusionary criteria on the Oregon Brain Aging Study and Alzheimer’s Disease Center subjects, as well as extensive medical and cognitive data on all subjects have been published elsewhere. Briefly, the OHE and YHE subjects were functionally independent, had English as their principal language, had not sought evaluation for cognitive impairment, scored well on a variety of clinical tests including the Instrumental Activities of Daily Living, the Mini-Mental State Examination, the Cornell Depression Scale, and the Geriatric Depression Scale. They did not have significant medical disorders and did not use medicines that affect cognitive function. No subjects had cerebral infarctions. Only minor degrees of periventricular white matter hyperintensity were present in these subjects’ images. These subjects were examined biannually for signs of dementia or changes in their medical status and had annual neurologic, neuropsychological (Weschler Adult Intelligence Scale—Revised, Weschler Memory Scale, and Verbal Fluency) and MRI examinations. Subjects with AD met the same health and screening criteria except they met the National Institute of Neurological Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria for probable AD. Thus, these are medically healthy subjects so that cognitive or neural changes are not due to medical comorbidities. The magnetic resonance scans on both healthy elderly and subjects with AD obtained as part of the annual examinations were those used for this study. Scans chosen for analysis were randomly picked from those who met 2 criteria: (1) the scan was taken at a time during which the subject was within the age range of the subject group and (2) the scan was free from movement artifact that would disrupt the analysis. All subjects or subjects’ caregivers gave informed consent to participate in this project.

MRI PROCEDURES

Scan Protocol

The MRIs were performed as previously described using a 1.5-T magnet (GE Medical Systems, Waukesha, Wis). The imaging protocol used to image the entire brain consisted of continuous slice, multiecho, multiplanar image acquisition, with 4-mm-thick coronal slices, a 24-cm field of view using a 256 × 256 matrix, with 2 as the number of excitations. The brain was visualized using the following sequence: multiecho coronal sequence, repetition time (3000 milliseconds), and echo time (30 and 80 milliseconds). T1-weighted images centered in the midsagittal plane were used to orient the coronal plane. The coronal plane was determined as the plane oriented perpendicularly to a line drawn from the lowest point of the splenium to the lowest point of the genu of the corpus callosum on the midsagittal image. Analysis of MRIs was performed with computer-assisted techniques using a program called REGION, developed for use with any Macintosh series computing equipment (Apple Computer Inc, Cupertino, Calif).

Region of Interest Analysis

Coronal slices used in these analyses were those in which the superior frontal gyrus could first be visualized (the tip of the frontal pole) and continued posteriorly until the anterior tip of the corpus callosum was visualized. This contribution to cognitive and behavioral changes in healthy aging.

In contrast to healthy aging, a combination of both white and gray matter degeneration may contribute significantly to Alzheimer disease (AD). Studies of brain degeneration in subjects with AD have demonstrated pathologic features in cortical gray matter. Other studies have additionally demonstrated a relationship between white matter degeneration and clinical measures in subjects with AD. For example, abnormal white matter volume is related to poor cognitive performance independent of cortical gray matter volume in AD. Thus, alteration of both gray and white matter in subjects with AD may lead to cognitive dysfunction.

Using quantitative MRI, we examined gray and white matter volume differences in young healthy elderly (YHE) (mean age, 70 years), old healthy elderly (OHE) (mean age, 90 years), and a group of subjects with AD (mean age, 70 years) age matched to YHE. This study is in contrast to most MRI studies of frontal lobe volume that have looked only at the total brain volume of the region or MRI white matter hyperintensities (a measure of putative white matter lesions most commonly attributed to ischemia). Instead, we measured separately total gray and white matter volume in the prefrontal cortex in addition to total prefrontal volume. Finally, previous studies of frontal lobe volume have not examined significant numbers of healthy subjects in the oldest old age range (subjects, ≥85 years of age). Thus, this study provides new information on changes in prefrontal tissue volume in healthy oldest old and in subjects with AD.

RESULTS

SUBJECT CHARACTERISTICS

Clinical and demographic characteristics of the subjects are described in Table 1. The Wechsler Adult Intelli-
process uses approximately 8 slices per subject and the slices used encompass approximately 90% of the total prefrontal cortex. For the purpose of discussion this area is referred to as prefrontal.

Data were collected from 3 regions of interest (ROI): total prefrontal volume, prefrontal white matter volume, and prefrontal gray matter volume. Total prefrontal volume and prefrontal white matter volume for all subjects were determined, by the same analyst, by outlining the structures with a cursor directly on a computer display. Total prefrontal volume was defined by tracing all gyri and sulci around the cortical ribbon of each hemisphere in the T1-weighted image (Figure 1, A). Prefrontal white matter volume was traced in the proton density–weighted image. This was performed by first enhancing the windows and levels of the image so that ambiguous pixels were reduced without changing relative pixel intensities. This procedure was used to augment differences between gray and white matter boundaries (Figure 1, B). Prefrontal gray matter volume was calculated by subtracting prefrontal white matter volume from total prefrontal volume.

Pixel area data were collected separately from each ROI for each coronal slice of the prefrontal cortex. Volumetric data for each ROI was calculated by summing the pixel area of each ROI to get a total pixel volume for each region. All regions were normalized by dividing volumes by the subjects’ total intracranial volume. Total intracranial (supratentorial cavity) volume was defined as all nonbone pixels beginning with the first slice in which the frontal poles were present and ending at the occipital pole. This was determined with an automated technique called recursive segmentation built into the REGION analysis program. Within each image, tissue types are coincidentally sampled on the spatially registered multiecho images by selecting a predetermined number of sample points comprised of a $3 \times 3$ pixel sample within 3 tissue types: bone, brain (gray and white matter combined), and cerebrospinal fluid. The recursive segmentation is completed automatically by successively applying a discriminant function to the established tissue type sample intensities and “peeling” away bone from the image leaving total intracranial contents for analysis. At the base of the brain, brainstem structures were excluded from supratentorial structures by manually tracing those pixels to be excluded according to atlas-based rules. Left and right sides for each ROI were analyzed together as the total volume. The examiner was blinded to all subject demographics, including group status, sex, and age. All scans were analyzed by the same examiner and both intrarater and interrater reliability (intraclass and interclass correlation coefficients) with this method for all regions was greater than 0.80.

Previous studies have reported systematic alterations in signal intensity with aging. This type of age-related change could affect data acquisition. We have examined this issue and it is not likely that age-related changes in signal intensity affect the current study. For example, we compared mean pixel intensities in multiple areas of both white and gray matter in a subset of 6 YHE and 6 OHE subjects (3 men and 3 women in each group) using NIH Image, which is an image analysis software package developed at the National Institutes of Health. No significant differences in mean pixel intensities of white or gray matter were found between YHE and OHE subjects in any area. In addition, images opened in REGION were autoadjusted by the program to attain similar mean pixel intensities for all subjects. Thus, systematic alterations in signal intensity with aging are not likely to affect data acquisition in this study.

**STATISTICAL ANALYSIS**

Group demographic characteristics at entry were compared by 1-way analysis of variance. Separate analyses for total prefrontal volume, prefrontal white matter volume, prefrontal gray matter volume, and prefrontal gray-white matter volume ratio (calculated by dividing total prefrontal gray matter volume by total prefrontal white matter volume) were performed to determine differences in ROI volumes among OHE, YHE, and subjects with AD. Differences were considered significant when $P < .05$. When significant differences were found, post hoc Fisher-protected least significant difference tests were used to determine which groups differ. Age-related volume decreases were also examined by calculating Pearson correlations between each region and age with both factors as continuous variables in the combined YHE and OHE groups.

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**Table 1. Subject Clinical and Demographic Characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, y</th>
<th>Sex</th>
<th>No. of Years of Education</th>
<th>SES</th>
<th>MMSE</th>
<th>WAIS-R Vocabulary</th>
</tr>
</thead>
<tbody>
<tr>
<td>YHE</td>
<td>70.9 (64.6-75.8)</td>
<td>7M/7F</td>
<td>14.6 (9-19)</td>
<td>48.4 (25-66)</td>
<td>29.0 (28-30)</td>
<td>53.7 (32-63)</td>
</tr>
<tr>
<td>OHE</td>
<td>90.01 (84.3-95.4)</td>
<td>7M/7F</td>
<td>13.6 (7-18)</td>
<td>47.6 (22-66)</td>
<td>28.3 (25-30)</td>
<td>48.2 (26-61)</td>
</tr>
<tr>
<td>AD</td>
<td>69.9 (60.8-75.4)</td>
<td>7M/7F</td>
<td>13.8 (8-18)</td>
<td>52.1 (26-66)</td>
<td>17.2§ (2-28)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Values are mean (range). Age represents age at magnetic resonance imaging scan. Education presented in years of schooling. SES indicates socioeconomic status; MMSE, Mini-Mental State Examination; YHE, young healthy elderly; OHE, old healthy elderly; AD, Alzheimer disease; and ellipses, Wechsler Adult Intelligence Scale–Revised vocabulary data were unavailable for subjects with (AD).

†Wechsler Adult Intelligence Scale–Revised (WAIS-R). Vocabulary data were not available for subjects with (AD).

‡Significantly differs from YHE and AD.

§Significantly differs from YHE and OHE.
tion scores between the groups \(F[2, 39] = 23.2; P < .001\) with this difference due solely to the subjects with AD. The YHE and OHE groups did not differ in Mini-Mental State Examination score.

MRI ROI ANALYSIS

A summary of all group mean ROI volumes is presented in Table 2. Total prefrontal volume differed among groups \(F[2, 39] = 5.9; P = .006\). Post hoc testing showed that YHE had significantly greater total prefrontal volume than OHE and AD groups (\(P < .004\) and \(P < .007\), respectively; Figure 2, A). The OHE and AD groups did not differ in total prefrontal volume. To further examine the age-related nature of these differences, analysis of covariance was performed with age as the covariate. The main effect of total prefrontal volume was no longer present in this analysis, suggesting that age is the factor responsible for these differences.

There was a main effect of prefrontal white matter volume \(F[2, 39] = 7.9; P = .001\). Post hoc testing showed that YHE had significantly greater prefrontal white matter volume than both OHE and AD (\(P < .001\) and \(P = .01\), respectively; Figure 2, B). The OHE and AD groups did not differ in prefrontal white matter volume. There was a trend toward a main effect of prefrontal gray matter volume \(F[2, 39] = 2.76; P = .07\) with the trend showing the YHE group having a greater prefrontal gray matter volume than the AD group (Figure 2, C). There was no difference in prefrontal gray matter volume between YHE and OHE groups.

There was a main effect of prefrontal gray-white matter ratio \(F[2, 39] = 5.00; P = .01\) with OHE having a greater ratio than YHE (\(P = .003\); Figure 2, D).

There were significant negative correlations between age and total prefrontal volume \((r = -0.467; P = .01\); Figure 3, A) and age and prefrontal white matter volume \((r = -0.541; P = .002\); Figure 3, B) when YHE and OHE groups were combined (subjects with AD were not included in these analyses). Prefrontal gray matter volume did not show a relationship with age when the YHE and OHE groups were combined \((r = -0.26; P = .18\); Figure 3, C). Prefrontal gray-white matter volume ratio showed a significant positive correlation with age in YHE and OHE groups combined \((r = 0.469; P = .01\); Figure 3, D). No significant correlations with age were found for any ROI measure in the AD group or the YHE and OHE examined separately.

There is a decline in volume of the prefrontal cortex in both the very old and in subjects with AD age matched to YHE. In addition, there is an age-related decline in white matter volume that is disproportionately greater than the decline of gray matter volume in the OHE when compared with YHE. In subjects with AD, the decline is more proportional in both tissue types as their gray-white matter ratio does not differ from YHE.

**Table 2. Region of Interest Volumes**

<table>
<thead>
<tr>
<th>Group</th>
<th>Intracranial Volume</th>
<th>Total Prefrontal Volume†</th>
<th>Prefrontal White Matter Volume†</th>
<th>Prefrontal Gray Matter Volume†</th>
<th>Gray-White Matter Ratio†</th>
</tr>
</thead>
<tbody>
<tr>
<td>YHE</td>
<td>1199.2 (24.6)</td>
<td>26.5 (0.83)</td>
<td>10.1† (0.39)</td>
<td>16.5 (0.50)</td>
<td>1.7 (0.05)</td>
</tr>
<tr>
<td>OHE</td>
<td>1151.5 (28.3)</td>
<td>22.3 (0.88)</td>
<td>7.1† (0.51)</td>
<td>15.2 (0.63)</td>
<td>2.3§ (0.17)</td>
</tr>
<tr>
<td>AD</td>
<td>1214.1 (35.5)</td>
<td>22.5 (1.20)</td>
<td>8.1 (0.67)</td>
<td>14.5 (0.69)</td>
<td>1.9 (0.15)</td>
</tr>
</tbody>
</table>

*Values are mean volume (SEM).†Regional volumes are presented as percentage of intracranial volume.‡Young healthy elderly (YHE) significantly differs from both old healthy elderly (OHE) and those with Alzheimer disease (AD).§Old healthy elderly significantly differs from YHE only.
Three findings in this study suggest that the decline in prefrontal volume in the oldest old is due in part to a selective loss of white matter. First, prefrontal volumetric measurements showed significant negative correlations with age. White matter volume was more closely related to age than total prefrontal volume. Prefrontal gray matter did not show a significant relationship with age, suggesting that white matter loss is selective. Second, differences in prefrontal volume between the YHE and OHE groups were removed when data were adjusted for age, suggesting that age is the critical factor that causes the differences in prefrontal volume between groups. Finally, the OHE group had a greater gray-white matter volume ratio compared with the YHE.

Figure 2. Comparison of region of interest volumes among old healthy elderly (OHE), Alzheimer disease (AD), and young healthy elderly (YHE) groups. Circles within each group indicate individual subjects; bars, group means. Volumes presented as percentage of total intracranial volume to correct for head size. A, Total prefrontal volume; B, prefrontal white matter volume; C, prefrontal gray matter volume; and D, prefrontal gray-white matter volume ratio. Fisher least significant differences test was used to determine group differences. Asterisk indicates $P < .05$ compared with OHE and AD; number sign, $P < .05$ compared with YHE.

Figure 3. Regression of subject volume on age in all healthy elderly (old healthy elderly [OHE] and young healthy elderly [YHE] combined). A, Total prefrontal volume; B, prefrontal white matter volume; C, prefrontal gray matter volume; and D, prefrontal gray-white matter volume ratio. There were significant negative correlations between age and total prefrontal volume ($A, r = −0.467, P = .01$) and age and prefrontal white matter volume ($B, r = −0.541, P = .002$). There was no correlation between age and prefrontal gray matter volume ($C, r = −0.26, P > .18$). Prefrontal gray-white matter volume ratio showed a significant positive correlation with age in YHE and OHE groups combined ($D, r = 0.469, P = .01$). No significant correlations with age were found for any region of interest measure in the Alzheimer disease (AD) group or the YHE and OHE examined separately.
group. It is likely that this greater ratio represents the relative loss of white matter rather than an increase in gray matter with aging because neuronal density does not increase with aging.30 These results add to a recent study by Raz et al26 demonstrating selective vulnerability of prefrontal gray matter with early aging (subjects aged 18-77 years; mean age, 43.5 years younger than the OHE of this study).

The finding of disproportional white matter loss in OHE subjects is in contrast to what was observed in subjects with AD. Differences between subjects with AD and YHE in the gray-white matter volume ratio were not found. Although subjects with AD showed an overall loss of total prefrontal volume, this decline seems to be a proportionate loss of white matter and gray matter volume together contributing to the decline of prefrontal volume. These results are similar to previous postmortem findings showing an increase in the gray-white matter volume ratio with aging but not dementia.30 The age matching of subjects with AD to YHE suggests that volume differences between these groups is secondary to disease processes of AD. These findings suggest that tissue loss in the prefrontal cortex with aging is qualitatively different than that of AD.

The decrease of total volume of the prefrontal cortex with increasing age is consistent with previous findings of age-related frontal lobe volumetric differences.1,4,24,41 Additionally, the decline in white matter volume in the oldest old is consistent with previous findings suggesting that white matter degenerates with aging42 and our data extend these findings through to the ninth decade of life.

Another interesting finding in our study is the increasing heterogeneity in regional volumes with increasing age. This increase in intragroup anatomical variability may be related to physiologic changes that occur primarily in late stages of aging. There is a wealth of literature demonstrating a similar increase in variability with age when measuring a variety of parameters including volumetric measures4 and cognition.43 This variability in regional volumes among the OHE subjects may be useful in differentiating between subjects exhibiting successful aging and subjects with incipient dementia.

A multitude of pathologic mechanisms could contribute to the loss of white matter within the prefrontal cortex. It is of interest that free radicals are particularly damaging to myelin owing to its composition of peroxidizable phospholipids.21 Plasma antioxidant levels (ascorbic acid and β-carotene) were significantly correlated with better memory performance in subjects aged 65 to 94 years,20 suggesting that free radical damage may have a negative consequence on cognition. Still, it is unknown if plasma antioxidant levels are directly related to white matter volume in the aged or with central nervous system oxidant stress in general.

Because this was a cross-sectional study of the healthy aged, it is difficult to directly attribute volume differences between the YHE and OHE to atrophic changes with aging. These results may reflect a cohort effect with younger subjects having greater brain volumes to begin with. We did not analyze subjects in the 76- to 84-year age range which contributes to this uncertainty.

It is unclear how our results showing a decline in white matter volume with age relate to other MRI measures of white matter changes such as white matter hyperintensities. Hyperintensities on MRI images are often thought to represent ischemic insult to the tissue and, thus, are an indirect measure of pathologic changes. White matter hyperintensities show significant correlations with electrophysiologic44 and various frontal lobe functional measures.25-35,46 Additionally, hyperintensities have been associated with a variety of cognitive and behavioral disorders including AD,42 depression,46 and psychosis.47 Similar to the decline of white matter volume with age, hyperintensities have been found to increase with age.48-50 Still, preliminary data collected in our laboratory suggest that white matter volume is not correlated with white matter hyperintensities. These results imply that white matter volume loss and white matter hyperintensities occur by different mechanisms in the prefrontal cortex of the aged. Alternatively, these results may be due to the limited range of white matter hyperintensity in the frontal lobe of this sample. Data were available on 19 of the 28 healthy elderly and 7 of the 12 subjects with AD in this study showing that white matter hyperintensities occupied less than 1% of total frontal lobe volume. We are currently looking further into this relationship.

Future longitudinal studies of white matter atrophy and clinical cognitive correlates of white matter volume will be of interest to further understand the neural and behavioral changes that differentiate healthy aging from impending degenerative disease.

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