Selective Preservation and Degeneration Within the Prefrontal Cortex in Aging and Alzheimer Disease

David H. Salat, PhD; Jeffrey A. Kaye, MD; Jeri S. Janowsky, PhD

Background: The prefrontal cortex (PFC) is a heterogeneous cortical structure that supports higher cognitive functions, including working memory and verbal abilities. The PFC is vulnerable to neurodegeneration with healthy aging and Alzheimer disease (AD).

Objective: We used volumetric magnetic resonance imaging to determine whether any region within the PFC is more vulnerable to deterioration with late aging or AD.

Methods: Volumetric analysis of PFC regions was performed on younger healthy elderly subjects (n=26; 14 men and 12 women [mean age, 71.7 years] for aging analysis; 12 men and 14 women [mean age, 71.4 years] for AD analysis), oldest healthy elderly (OHE) subjects (n=22 [11 men and 11 women]; mean age, 88.9 years), and patients with AD (n=22 [12 men and 10 women]; mean age, 69.8 years).

Results: The OHE subjects had less PFC white matter than did young healthy elderly subjects. The orbital region was selectively preserved relative to other PFC regions in the OHE subjects. Subjects with AD had less total PFC gray matter than did age-matched healthy subjects and significantly less volume in the inferior PFC region only.

Conclusions: Orbital PFC is selectively preserved in OHE subjects. In contrast, degeneration within the PFC with AD is most prominent in the inferior PFC region. Thus, degeneration within the PFC has a regionally distinct pattern in healthy aging and AD.

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SUBJECTS AND METHODS

SUBJECTS

Magnetic resonance imaging scans of older healthy elderly (OHE) subjects (n=22 [11 men and 11 women]; mean age, 88.9 years), subjects with AD (n=22 [12 men and 10 women]; mean age, 69.8 years), and younger healthy elderly (YHE) subjects were examined. The YHE subjects were examined as 2 subgroups for comparisons with the OHE (n=26 [14 men and 12 women]; mean age, 71.7 years) and AD groups (n=26 [12 men and 14 women]; mean age, 71.4 years). These subgroups overlapped by 92% but maximized the number of subjects while keeping YHE and AD subjects matched for age (P=.13). Similar results are found in this study when we analyze the data by matching the YHE and AD groups for age or when we analyze the data using all subjects available for analysis (when the YHE and AD groups are not matched for age).14

Scans for YHE and OHE groups were collected as part of the Oregon Brain Aging Study at Oregon Health Sciences University and the Veterans Affairs Medical Center, Portland. Scans for the AD group were collected as part of the clinical protocol of the Oregon Alzheimer's Disease Center, Portland. All groups were matched for years of education and socioeconomic status.19 The YHE and OHE groups were matched for Mini-Mental State Examination20 (MMSE) score (YHE mean score, 28.7; OHE mean score, 28.2) and general knowledge (Wechsler Adult Intelligence Scale–Revised vocabulary21). The AD patients met criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association22 for probable or possible AD (mean MMSE score, 17.0). All subjects or their responsible caregiver signed informed consent according to the Declaration of Helsinki and the Oregon Health Sciences University Institutional Review Board for Oregon Brain Aging and Oregon Alzheimer’s Disease Center studies.

Recruitment procedures and criteria as well as medical and cognitive data on these subjects have been published.23 Healthy subjects were free from significant medical disorders, eg, diabetes mellitus, hypertension, ischemic heart disease, cardiac arrhythmia, stroke, active cancer, psychiatric disorders, and neurologic disorder; had visual acuity correctable to 20/70 OU or better and hearing that did not interfere with speech perception; and did not take any medications known to affect cognitive function. Healthy subjects performed within age-group norms on a battery of measures of cognitive function and behavior and did not have signs of early dementia.23 Thus, we would not expect the volumetric differences obtained between groups to be due to medical comorbidities.

MR IMAGING PROCEDURE SCAN PROTOCOL

Imaging was performed using a 1.5-T scanner (General Electric Company, Milwaukee, Wis). The brain was visualized using a multiecho coronal sequence (repetition time, 3000 milliseconds; echo time, 30 or 80 milliseconds; 4-mm slices with no skip). The T1-weighted images in the midsagittal plane were used to orient the coronal plane as that perpendicular to a line drawn from the lowest point of the genu to the lowest point of the splenium corpus callosum on the midsagittal image.

REGION OF INTEREST ANALYSIS

Tissue analysis of PFC MR images was assisted using a computer program called REGION as previously described.5,24 Data were first collected from the following 3 tissue regions of interest (ROIs): total prefrontal volume, prefrontal white matter volume, and prefrontal gray matter volume. Structures were outlined using a cursor directly on a computer display. The PFC was defined in the coronal plane beginning with the first slice in which the superior frontal gyrus could be visualized (the tip of the frontal pole), and continued posteriorly until, but not including, the first slice in which the anterior tip of the corpus callosum was visualized. Very posterior PFC areas such as posterior medial and orbital regions were lost because of the use of the genu of the corpus callosum as an absolute posterior boundary. Total prefrontal volume was defined by tracing all gyri and sulci around the cortical ribbon of each hemisphere in the T2-weighted image (Figure 1A). Prefrontal white matter volume was traced in the proton density–weighted image of the same slice after standardized image adjustment to maximize gray to white matter contrast (Figure 1B). Prefrontal gray matter volume was calculated by subtracting prefrontal white matter volume from total prefrontal volume.

RESULTS

SUBJECT CHARACTERISTICS

Per the study design, there was a significant difference in age between YHE and OHE subjects (t46=17.2; P<.01). The YHE and AD groups did not differ in age. Per the
The OHE group had significantly less total absolute and regional absolute volumes. When corrected for ICV, the AD group had significantly less total PFC volume than the YHE group ($t_{46}=2.4; P=.02$). No differences between the YHE and OHE groups were found in the proportions of any other PFC region (Figure 2C-D).

### AD-RELATED ROI ANALYSES

The YHE and AD groups did not differ in total or regional absolute volumes. When corrected for ICV, the AD group had significantly less total PFC volume than the YHE group ($t_{46}=2.2; P=.03$). This difference was primarily due to a difference in gray matter, with the AD group having significantly smaller PFC volumes.
Figure 1. Cartoon representation of volumetric method used to calculate prefrontal region of interest (ROI) volumes. The images are the same as those used in data collection, but regional demarcations have been smoothed for publication purposes. Total prefrontal cortex (PFC) volume, PFC white matter volume, and PFC region volumes for all subjects were determined by edge tracing the cortical ribbon and gray-white matter boundary with a cursor directly on a computer display. A, The most posterior slice of the prefrontal ROI is shown. Total PFC volume was defined by tracing all gyri and sulci around the cortical ribbon of each hemisphere in the T2-weighted image. Pixel areas were transformed to volumes as described in the “Region of Interest Analysis” subsection of the “Materials and Methods” section. B, The PFC white matter volume was traced in the proton density–weighted image of the same slice depicted in A. The PFC gray matter volume was calculated by subtracting PFC white matter volume from total PFC volume. C to F, Regional delineation of 4 posterior coronal PFC slices (C–F represent the most anterior to most posterior) for superior (yellow), middle (pink), inferior (orange), orbital (green), and anterior cingulate (blue) regions. Regions were defined as described in the “Region of Interest Analysis” subsection of the “Materials and Methods” section.

Figure 2. Comparison of younger healthy elderly (YHE) and older healthy elderly (OHE) groups. Regions are described in the “Regions of Interest Analysis (ROI)” subsection of the “Materials and Methods” section. A, Comparison of volumetric measures between YHE and OHE subjects. Volumes are presented as percentage of total intracranial volume (ICV) to correct for head size. The OHE group had less total prefrontal cortex (PFC) and white matter PFC volume than did the YHE group. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates *P<.01. B, Comparison of regional volumes between YHE and OHE groups. Regional volumes did not differ between YHE and OHE groups when corrected for ICV. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. C, Ratio of orbital to all other regions was significantly smaller for the YHE than for the OHE group. Asterisk indicates *P<.05. Data are presented as mean±SEM. D, Scattergram of the ratio of orbital to all other regions. The YHE group had a significantly smaller ratio compared with the OHE group. Circles represent individual subjects. Bars represent group means. Asterisk indicates *P<.05.
AD subjects had significantly less inferior PFC volume and gray matter PFC volume than did YHE subjects. The regions, suggesting that this region is resistant to atrophy in the healthy aged. The AD subjects had less total and gray matter PFC volume than did YHE subjects. The AD group had less total prefrontal cortex (PFC) and gray matter PFC volume than did the YHE group. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates P<.05. A. The AD group had less total prefrontal cortex (PFC) and gray matter PFC volume than did the YHE group. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates P<.05. B. Comparison of regional volumes. Subjects with AD had significantly less volume in the inferior PFC region, but in no other region, compared with YHE subjects. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates P<.05. C. Scattergram of inferior PFC region corrected for ICV. The AD subjects had significantly less inferior PFC volume than did YHE subjects. Circles represent individual subjects. Bars represent group means. Asterisk indicates P<.05. D. Regional volumes did not differ significantly between YHE and AD subjects when examined as a ratio to all other regions combined. Regions are described in the “Regions of Interest Analysis” subsection of the “Materials and Methods” section. Data are presented as mean±SEM.

Figure 3. Comparison of volumetric measures between younger healthy elderly (YHE) subjects and subjects with Alzheimer disease (AD). Volumes are presented as percentage of total intracranial volume (ICV) to correct for head size. Regions are described in the “Regions of Interest Analysis” subsection of the “Materials and Methods” section. A. The AD group had less total prefrontal cortex (PFC) and gray matter PFC volume than did the YHE group. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates P<.05. B. Comparison of regional volumes. Subjects with AD had significantly less volume in the inferior PFC region, but in no other region, compared with YHE subjects. Data are presented as mean±SEM. Mean absolute regional volumes are presented in cubic centimeters above each bar. Asterisk indicates P<.05. C. Scattergram of inferior PFC region corrected for ICV. The AD subjects had significantly less inferior PFC volume than did YHE subjects. Circles represent individual subjects. Bars represent group means. Asterisk indicates P<.05. D. Regional volumes did not differ significantly between YHE and AD subjects when examined as a ratio to all other regions combined. Regions are described in the “Regions of Interest Analysis” subsection of the “Materials and Methods” section. Data are presented as mean±SEM.

We used volumetric analysis of the PFC to determine whether degeneration in healthy aging and AD is selective to particular regions within the PFC. The OHE group had less total and white matter PFC volume than did the YHE group, as previously reported in a smaller sample (Figure 3A). The AD subjects had significantly less volume in inferior PFC (r0.2) but not in any other PFC region (for all, P>.18) (Figure 3B-C). There were no differences between YHE and AD subjects when each region was analyzed as a proportion of all other regions combined, although there was a trend for the orbital region to be greater in AD subjects compared with YHE subjects (P=.07) (Figure 3D) in relation to all other regions.

COMMENT

We used volumetric analysis of the PFC to determine whether degeneration in healthy aging and AD is selective to particular regions within the PFC. The OHE group had less total and white matter PFC volume than did the YHE group, as previously reported in a smaller sample of partially overlapping subjects. The OHE group had a greater proportion of orbital regional volume to all other regions, suggesting that this region is resistant to atrophy in the healthy aged. The AD subjects had less total and gray matter PFC volume than did YHE subjects. The AD subjects had significantly less inferior PFC volume compared with YHE subjects, suggesting that this region is more susceptible to degeneration with AD. Our measurements of total prefrontal volume are smaller but in the range of previously published measurements using a similar procedure (eg, approximately 140 cm3 in a healthy sample of young subjects; mean age, 30.4 years).

A previous study found loss of volume in orbital PFC, although the age range (18-77 years) and anatomical boundaries in that study differed from those in the current study. The orbital region in the previous study contained some of the inferior region described herein. Thus, differences in findings are likely related to subject selection (age) and the region measured.

An alternate interpretation of the findings of orbital preservation in YHE subjects is that this measurement reflects other biological differences. Subjects who remain neurologically healthy into late aging could have a greater orbital ratio throughout their life span, and this preservation could decline with the development of AD. The latter theory is in accord with findings of a previous histological study demonstrating that the orbital region (Brodmann area 11) showed preserved neural density with increasing age. A quantitative neuropathological study of healthy older adults would be useful to understand whether cellular changes differ in the orbital region compared with other PFC regions.
Volumetric preservation does not provide information about the functionality of the tissue. Preservation could also be due to pathologic mechanisms such as neuronal hypertrophy or gliosis as opposed to simple resistance to degeneration. Although these subjects were extremely healthy for their age, it is possible that at least some of the older subjects have clinically asymptomatic neuropathologic AD. Still, although subjects with preclinical AD might exist in the OHE group, this contamination is probably not responsible for the results seen in the current data, as the OHE and AD subjects differed in patterns of degeneration compared with the YHE subjects.

Regions more strongly connected to sites of primary degeneration with AD were expected to show greater volumetric differences in AD subjects compared with YHE subjects due to anterograde or retrograde degenerative processes. The orbital region of the prefrontal cortex was expected to show the greatest degeneration with AD due to connectivity with temporal lobe structures that degenerate in the early stages of the disease process, but this is not what we found. Our study was limited because approximately one third of the posterior aspect of orbital cortex was likely excluded in our measurements because of the use of the genu of the corpus callosum as a posterior landmark. Thus, degeneration could be prominent in the more posterior sector of the orbital region, as this area has the densest connectivity with temporal lobe structures. Also, degeneration in certain regions across time could be hidden in a cross-sectional study because of the confound of group differences in premorbid brain volume. Alternatively, it is possible that temporal lobe regions connected to the inferior PFC are more prone to degeneration compared with areas connected to orbital PFC.

The PFC measurements were not related to disease severity in the AD subjects (MMSE score; data not shown). Thus, it is unclear how prefrontal degeneration is related to cognitive decline. Still, the MMSE is a global scale of disease severity and thus not likely to contribute to understanding more subtle cognitive changes related to prefrontal function. Studies are currently under way in our laboratory examining the relationship between regional volumes and cognitive performance on tasks demonstrated to depend critically on different PFC regions in OHE subjects.

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Corresponding author and reprints: David H. Salat, PhD, Athinoula A. Martinos Center, Department of Radiology, Bldg 149, 13th St., Mail Code 149 (2301), Charlestown, MA 02129-2060 (e-mail: salat@nmr.mgh.harvard.edu).

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