

Age-Related Changes in Frontal and Temporal Lobe Volumes in Men

A Magnetic Resonance Imaging Study

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Background: Imaging and postmortem studies provide converging evidence that, beginning in adolescence, gray matter volume declines linearly until old age, while cerebrospinal fluid volumes are stable in adulthood (age 20-50 years). Given the fixed volume of the cranium in adulthood, it is surprising that most studies observe no white matter volume expansion after approximately age 20 years. We examined the effects of the aging process on the frontal and temporal lobes.

Methods: Seventy healthy adult men aged 19 to 76 years underwent magnetic resonance imaging. Coronal images focused on the frontal and temporal lobes were acquired using pulse sequences that maximized gray vs white matter contrast. The volumes of total frontal and temporal lobes as well as the gray and white matter subcomponents were evaluated.

Results: Age-related linear loss in gray matter volume in both frontal ($r=-0.62$, $P<.001$) and temporal ($r=-0.48$, $P<.001$) lobes was confirmed. However, the quadratic function best represented the relationship between age and white matter volume in the frontal ($P<.001$) and temporal ($P<.001$) lobes. Secondary analyses indicated that white matter volume increased until age 44 years for the frontal lobes and age 47 years for the temporal lobes and then declined.

Conclusions: The changes in white matter suggest that the adult brain is in a constant state of change roughly defined as periods of maturation continuing into the fifth decade of life followed by degeneration. Pathological states that interfere with such maturational processes could result in neurodevelopmental arrests in adulthood.

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BRAIN MORPHOMETRY undergoes profound changes throughout the life span. Cross-sectional studies examining brain development in children and adolescents demonstrate increasing white matter volume and decreasing gray matter volume in later childhood and early adolescence.¹⁻⁴ These findings were recently confirmed in a prospective magnetic resonance imaging (MRI) study of brain development that demonstrated that white matter volume increases linearly between ages 4 to 20 years,⁴ a period characterized by increased myelination and axonal growth.⁵ Unlike the white matter changes, cortical gray matter changes were quadratic rather than linear and exhibited region-specific patterns of change within this age span. Gray matter reached maximum volume at approximately age 12 years in the frontal lobes but not until age 16 years in the temporal lobes; after these ages, gray matter volumes decreased.⁴

Postmortem data indicate that the pattern exhibited by gray matter is representative of brain maturation. This process initially involves cell growth, arborization, synaptogenesis, and cell proliferation, followed by neuronal pruning, resulting in an elimination of 40% of cortical synapses from the maximum childhood level to adult level and further decline in old age.^{6,7} Imaging studies confirm that after adolescence, cortical gray matter volume continues to decrease linearly throughout the life span.^{3,8-13} Postmortem data suggest that this decrease is primarily a result of large neuron shrinkage with minimal if any neuronal cell loss before age 55 years.¹⁴⁻¹⁶

Imaging studies of normal adult aging (aged ≥ 18 years) consistently show age-related enlargement of cerebrospinal fluid (CSF) spaces and the reciprocal reduction of total cerebral brain volume.^{3,11,12,17,18} These age-related changes are curvilinear, with cortical and ventricular CSF compartments remaining relatively stable up to age

SUBJECTS AND METHODS

SUBJECTS

Seventy healthy men aged 19 to 76 years were recruited from community volunteers. Each subject completed a clinical interview based on written standardized questions and administered by an experienced clinician-investigator (G.B.) to assess the history of medical, psychiatric, and substance dependence disorders. Selection criteria were as follows: no evidence of meaningful current or past psychiatric diagnosis or substance dependence based on *DSM-IV* criteria; no meaningful use of drugs or alcohol in the past year (amount of use did not meet *DSM-IV* criteria for substance dependence or abuse); no history or gross evidence of central nervous system impairment or any history of neurologic disorder (head trauma with loss of consciousness for >15 minutes); no history of chronic medical conditions likely to result in structural brain abnormalities (ie, stroke, transient ischemic attack, seizures, hypertension, diabetes); and self-report that no first-degree relatives have been treated for a major psychiatric disorder. These criteria excluded 3 subjects with a history of head trauma. One additional subject was excluded from analysis because he was a statistical outlier on the temporal lobe volume measure (>4 SDs greater than the mean of the other subjects). The remaining 70 participants averaged 38.6 years in age (SD, 15.6 years), 16.8 years of education (SD, 2.5 years; range, 12-22 years), and the ethnic composition comprised 44 white men, 15 African American men, 2 Hispanic men, and 9 Asian men. All subjects provided written informed consent approved by the local institutional review board prior to study participation.

MAGNETIC RESONANCE IMAGING PROTOCOL

The MRI examination used a 1.5-T instrument using previously published methods.²⁴ In brief, a coronal pilot sequence was used to align a sagittal MRI pilot sequence. The sagittal pilot sequence was then used to specify the position of the coronal image acquisition grid. The sagittal image containing the left hippocampus was used to define an oblique coronal acquisition plane perpendicular to the hippocampus. Two coronal sequences of the same brain slices were acquired: a transverse asymmetric dual spin echo Carr-Purcell-Meiboom-Gill sequence (repetition time, 2500 milliseconds; echo times, 30 and 90 milliseconds) and an inversion recovery (IR) sequence (repetition time, 2500 milliseconds; inversion time, 600 milliseconds; echo time, 30 milliseconds). Both sequences had 2 repetitions, 256 × 192 view matrix, 25-cm field of view, and produced coregistered 3-mm thick contiguous slices. These images provide excellent multiparameter visualization of the frontal and temporal lobes. The IR sequences provide the maximum gray vs white matter contrast available with MRI, improving the identification and quantification of these tissues.

IMAGE ANALYSIS

Imaging measures were obtained using an image workstation that read compact disks containing the original MRI data stored in digital format. Two raters who were blind to the clinical data quantified the frontal and temporal lobe regions of interest (ROI) using previously published methods.²⁴

The raters, using a calculated T2 image derived from the spin echo sequence, manually traced a rough contour surrounding the brain by maintaining the cursor on the bright CSF pixels and cutting through the brain to exclude subcortical gray and white matter and insular cortex (**Figure 1**). All pixels with T2 values in the CSF range (T2 >130 milliseconds) were then eliminated from the image using the "shrink image" function of the software. Thus, the resulting ROI contained only brain pixels. Once the brain ROI was quantified, it was pasted onto the IR image (depicted as the outside [brain/CSF] border in Figure 1). Then, the pixel intensities of the IR image were displayed in histogram form, and the gray matter histogram peak was eliminated. The resulting measure was the white matter area (depicted as the inside [gray/white] border in Figure 1). The gray matter area was obtained by subtracting the white matter area of each lobe from the total lobe area.

A contiguous 7-slice volume centered on the anterior commissure was used for data quantification. Volumes were computed by summing the products of each cross-sectional area with the slice thickness. Test-retest reliabilities for the ROI were good; the intraclass reliability coefficients (r_{xx}) were 0.85 and 0.86 for total temporal and frontal lobe volumes, respectively, and 0.82 and 0.90 for the temporal and frontal white matter, respectively.²⁴ Interrater reliabilities between the 2 raters were also high with intraclass reliability coefficients (r_{xx}) of 0.99 and 0.98 for total temporal and frontal lobe volumes, respectively, and 0.84 and 0.92 for frontal and temporal white matter volumes, respectively. Because gray matter volume is a calculated value based on total and white matter volume, reliability coefficients were not calculated for this brain variable.

STATISTICAL ANALYSIS

Linear and nonlinear relationships between age and brain structural volumes were examined with Pearson product moment correlation analyses and hierarchical polynomial regression analyses. Height was statistically controlled as a partial variable and introduced into all the analyses to adjust for variations in body size on the brain and its regions and control for the "secular effect" (the progressive trend toward increased body height and brain weight in the 20th century). To compare whether the peak of the quadratic age regression curves differed between 2 regions, a bootstrap replication analysis was employed.²⁵ One thousand bootstrap replication samples were created to serve as a sampling reference, and each replication was an individual random draw of 70 cases from the sample. All tests were 2-tailed, and the α level of significance was .05.

40 to 50 years and subsequently undergoing steep volume expansion.^{3,11}

Even though gray matter volume loss begins in mid adolescence, CSF and total cerebral brain volume remain stable until age 40 to 50 years.^{3,11,13} It is therefore logical to postulate that other tissues, namely the white

matter, should undergo concomitant expansion, similar in proportion to the gray matter loss, to maintain stable total cerebral and CSF volumes throughout early and middle adulthood. This white matter volume increase has yet to be demonstrated at the whole brain or lobar anatomic level. In fact, existing imaging studies consis-

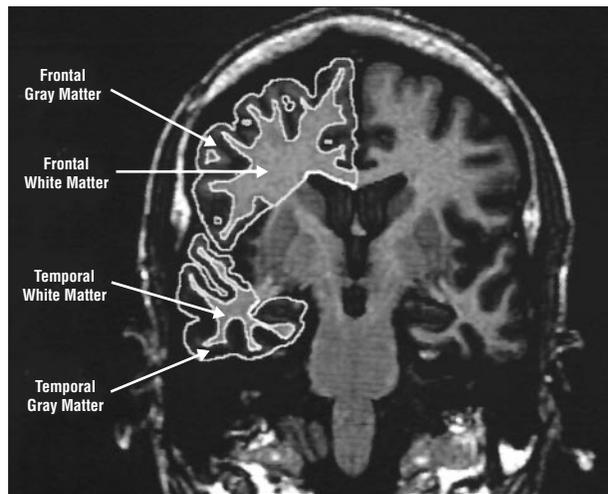


Figure 1. Oblique coronal inversion recovery image with drawings of frontal and temporal lobe gray matter and white matter regions of interest (ROI). The frontal and temporal lobe ROI are separated from the rest of the brain by linear cuts through the brain matter: medially, bisecting the corpus callosum; and laterally, from the superior fundus of the circular sulcus of the insula to the most superior and lateral point of the lateral ventricles, and from the inferior fundus of the circular sulcus of the insula through the temporal lobe stalk to the cerebrospinal fluid of the temporal horn.

tently report that white matter volume remains constant into the seventh decade, unaffected by the aging process.^{3,8-13}

The failure of imaging studies to detect age-related white matter volume increase in adulthood may be accounted for by methodological issues. These include the use of axial images aimed at studying the brain in its entirety^{3,8-10,13,17-19} rather than focusing on frontal and temporal lobes, which complete maturational changes later than the occipital lobe⁵⁻⁷ and are involved in behavioral plasticity and continued brain development.^{14-16,20-22} In addition, the use of automated procedures for gray and white matter segmentation and suboptimal contrast can contribute to misclassification of tissues,^{3,8-11,13,23} and slice thickness greater than 3 mm can increase partial volume effects.^{3,8-10,13,17}

The current study addresses these methodological concerns and focuses on examining the effects of the aging process on the frontal and temporal lobes. These structures continue maturing and developing (as defined by continued myelination) into the fourth and fifth decade⁵ and are clearly implicated in many age-related neuropsychiatric diseases such as schizophrenia and Alzheimer disease.

RESULTS

Examination of brain structural changes in men aged 19 to 76 years revealed significant linear age-related decreases in both frontal and temporal lobe volumes ($r = -0.43$, $P < .001$ and $r = -0.35$, $P = .003$, respectively). Segmenting the frontal and temporal lobes into cortical gray and white matter tissues revealed a significant linear decline in gray matter with age in both frontal ($r = -0.62$, $P < .001$) and temporal ($r = -0.48$, $P < .001$) lobes. These results are consistent with prior reports on brain volume changes with normal aging.^{3,8-12}

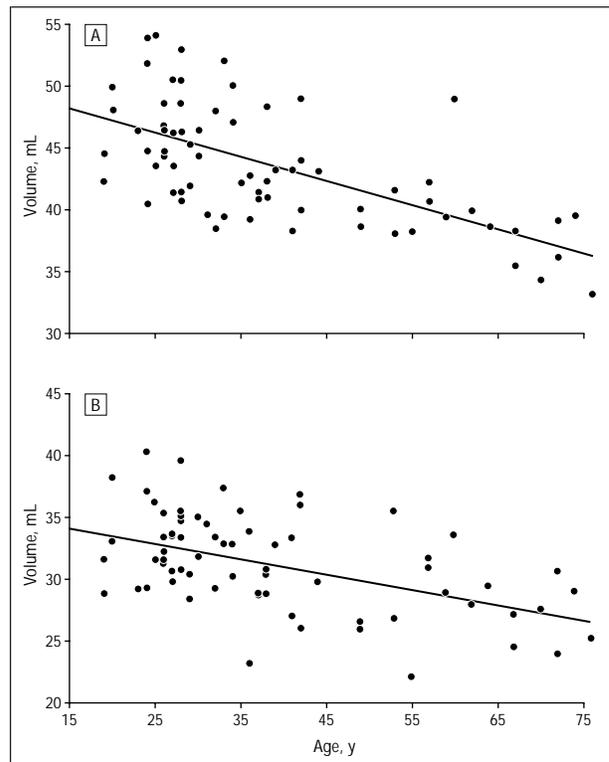


Figure 2. Regression of frontal (A) and temporal (B) lobe white matter volume on age in a sample of 70 normal adult men.

White matter volume did not exhibit a linear association with age in either region ($P > .48$). In fact, the quadratic function of the polynomial regression approach emerged as the best representation of the relationship between age and white matter volume changes in both frontal ($P < .001$) and temporal ($P < .001$) lobes (**Figure 2**). All the analyses were repeated, controlling for education and ethnicity to ensure that the observed changes in brain tissue matter were not better accounted for by other demographic characteristics, but adjusting for these 2 potential confounding variables did not meaningfully alter any of the results.

The age at which the white matter tissue reaches maximum volume, derived from the quadratic curves, was calculated to be 44.6 years for the frontal lobes and 47.5 years for the temporal lobes. A bootstrap replication analysis²⁵ confirmed that maximum white matter volume is reached at a later age in the temporal lobe vs the frontal ($P = .01$).

Since this is the first report, to our knowledge, to demonstrate gross increases in white matter volume after age 20 years, secondary follow-up analyses were conducted to investigate the age-related brain tissue changes in younger adults. This sample consisted of the youngest 52 subjects younger than the age at which maximum white matter volumes are reached. In the frontal lobes, significant age-associated loss in gray matter was observed ($r = -0.34$, $P = .01$) with concurrent significant increase in white matter tissue ($r = 0.52$, $P < .001$), while total frontal lobe volume remained unchanged ($r = 0.20$, $P = .16$). Temporal lobe gray matter volume demonstrated a negative trend with age ($r = -0.23$, $P = .10$) and

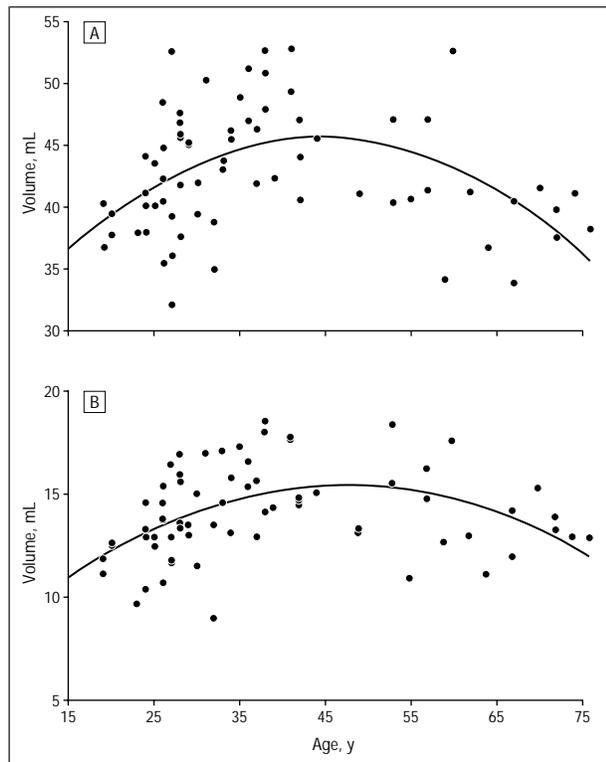


Figure 3. Regression of frontal (A) and temporal (B) lobe gray matter volume on age in a sample of 70 normal adult men.

temporal white matter volume increased significantly with age ($r=0.53$, $P<.001$). As with the frontal lobes, the opposing gray and white matter volume changes canceled each other, resulting in no age-related change in total temporal lobe volume ($r=0.09$, $P=.52$).

COMMENT

The most striking observation of the current study is the quadratic age-related pattern of white matter volume changes (Figure 2). Contrary to previously published imaging studies reporting static white matter volume after adolescence,^{3,8-13} the data suggest that white matter volumes of frontal and temporal lobes continue to increase into the fifth decade and decline thereafter. The rate and pattern of white matter change seems to be regionally specific as it reaches peak volume at about age 44 years in the frontal lobes and age 47 years in the temporal lobes. The regionally specific pattern of white matter development in adulthood is similar in temporal order and magnitude to the regionally specific pattern of gray matter volume expansion and contraction occurring in childhood and adolescence.⁴ This temporally parallel pattern observed in the 2 lobes suggests a maturational continuum between the gray matter volume peaks occurring in adolescence and the white matter peaks occurring in midlife.

Several limitations of our study must be acknowledged prior to further interpretation. First, only data from men were presented, and the educational attainment of the participants exceeds usual norms; therefore, the results cannot be generalized to women or less-educated groups.

Second, the sample of this cross-sectional study was not derived using random selection from the normative population; therefore, interpretation of the observed age-related differences between age group means as “changes” or “increases” must be made with caution.²⁶ For simplicity and ease of conceptualization, the results are discussed as changes or increases over time; however, conclusions regarding the developmental course of the changes and their application to individuals will need further definition through longitudinal studies. Third, the brain variables were analyzed without examining for left-right asymmetry. Finally, the volume measures were obtained on only a sample of the total frontal and temporal lobes and cannot be generalized to the entire brain. However, the specificity of the regions quantified maximizes the inclusion of the frontal and temporal neurocortical zones (regions Yakovlev and Lecours^{5(p49)} referred to as the supralimbic and paralimbic zones) involved in continued maturation into middle age and excludes areas (internal capsule and subcortical gray matter) that are postulated to complete the myelination cycle by the third decade.⁵

The cortex undergoes profound changes with aging, consisting primarily of shrinkage of large neurons and increase in the proportion of small neurons,¹⁴⁻¹⁶ visualized in this and other studies^{3,8-13} as a reduction in the volume of cortical gray matter (**Figure 3**). Frontal and temporal lobe white matter volume expansion into the fifth decade suggests an increase of myelination and/or interconnectivity of these lobes. Postmortem studies have shown that associative neocortex of the human frontal and temporal cortices continues to develop (as judged by continued myelination of the white matter of these regions) up to the fifth decade and beyond,^{5,27,28} suggesting that after this age, degenerative processes may cancel out any myelination-related white matter volume increase on MRI. An increase in myelination and/or interconnectivity could facilitate the synchronous integration of information across the many spatially segregated associative neocortex regions involved in higher cognitive functions.^{21,22} The speed of neural transmission depends on the structural properties of the connecting fibers, including axon diameter and the thickness of the insulating myelin sheath.²⁹

The present in vivo evidence of increasing white matter volume with age in the frontal and temporal lobes supports the concept of continued brain maturation into the fifth decade. The results could be analogized to the Internet phenomenon in which increasing computer interconnectivity and/or accelerated speed of connections facilitate an increase in capacity and utility. The development of better emotional regulation, response inhibition, and possibly the concept of wisdom commonly associated with the mid- and late-life periods^{30,31} may be manifestations of this quantifiable brain maturation process. This interpretation suggests that the brain could experience neurodevelopmental arrest, even in adulthood, if pathological states (eg, brain trauma, schizophrenia, severe stress, substance abuse) alter the normal age-related pattern of structural changes. Finally, the data suggest that during the life span, the brain is in a constant state of change roughly defined as periods of development and maturation.

tion followed by degeneration and that, biologically speaking, the societal concept of a stable or unchanging adult brain may not be valid.

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Correction

Error in Figures and Legends. In the article titled "Age-Related Changes in Frontal and Temporal Lobe Volumes in Men: A Magnetic Resonance Imaging Study," published in the May issue of the ARCHIVES (2001;58:461-465), **Figure 2** and **Figure 3** appeared in reverse order. Below are the corrected figures and legends. The ARCHIVES regrets the error.

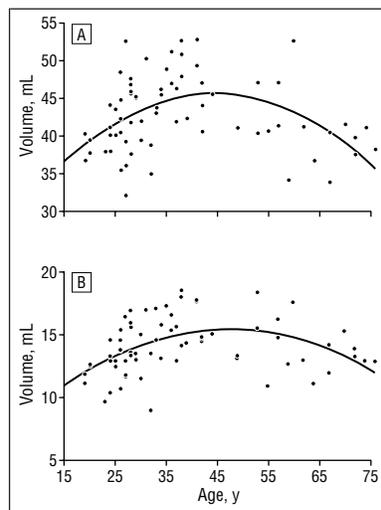


Figure 2. Regression of frontal (A) and temporal (B) lobe white matter volume on age in a sample of 70 normal adult men.

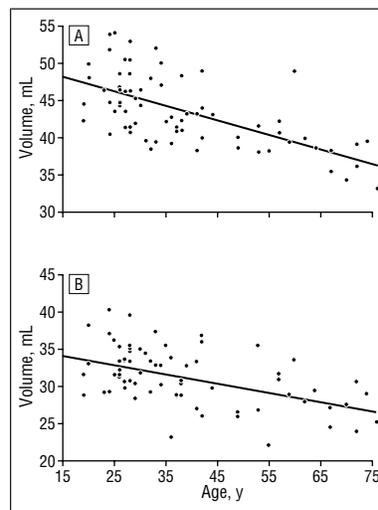


Figure 3. Regression of frontal (A) and temporal (B) lobe gray matter volume on age in a sample of 70 normal adult men.