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Objective: To model in vivo the dynamic interrelations of head size, gray matter, white matter, and cerebrospinal fluid (CSF) volumes from infancy to old age using magnetic resonance imaging (MRI).

Design: Cross-sectional, between-subjects using an age-regression model.

Setting: A Veterans Affairs medical center and community hospitals.

Participants: There were 88 male and female subjects aged 3 months to 30 years whose clinical MRI film had been read as normal and 73 healthy male volunteers aged 21 to 70 years who had an MRI performed specifically for this study.

Main Outcome Measures: These MRI data were quantified using a semiautomated computer technique for segmenting images into gray matter, white matter, and CSF compartments. The cortex was defined geometrically as the outer 45% on each analyzed slice, and the volumes of cortical white matter, gray matter, and CSF were computed. Subcortical (ventricular) CSF volume was computed for the inner 55% of each analyzed slice.

Results: In the younger sample, intracranial volume increased by about 300 mL from 3 months to 10 years. The same patterns of change in volume of each compartment across the age range were seen in both sexes: cortical gray matter volume peaked around age 4 years and decreased thereafter; cortical white matter volume increased steadily until about age 20 years; cortical and ventricular CSF volumes remained constant. In the older sample, brain volumes were statistically adjusted for normal variation in head size through a regression procedure and revealed the following pattern: cortical gray matter volume decreased curvilinearly, showing an average volume loss of 0.7 mL/y, while cortical white matter volume remained constant during the five decades; complementary to the cortical gray matter decrease, cortical CSF volume increased by 0.6 mL/y and ventricular volumes increased by 0.3 mL/y.

Conclusions: These patterns of growth and change seen in vivo with MRI are largely consistent with neuropathological studies, as well as animal models of development, and may reflect neuronal progressive and regressive processes, including cell growth, myelination, cell death, and atrophy.

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DRAMATIC CHANGE in the volume of the human brain occurs after birth. Brain weight increases fourfold from birth to about 10 years and then declines gradually during the remaining life span.[1-3] Changes in brain weight occur with changes in cerebral gray and white matter and cerebrospinal fluid (CSF) volumes. The timing of the volume changes in each tissue type are not necessarily coincident with each other, and thus gray and white matter and CSF volumes have dynamic interrelations throughout the course of development. Two types of neurodevelopmental events that occur after birth are likely to contribute to increases and decreases in brain volume: progressive phenomena, such as cell proliferation, arborization, and myelination,[3] and regressive phenom-

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SUBJECTS AND METHODS

SUBJECTS

Younger Sample

These subjects included 46 males and 42 females aged 3 months to 30 years. On average, the males were (mean±SD) 13.7±7.4 years old and the females were 14.7±7.5 years old. No other demographic information was available for these subjects. The MRI data for the younger sample were obtained retrospectively from four California clinics: 59 from the Stanford University Advanced Imaging Center; 15 from Good Samaritan Hospital, Los Gatos; seven from O'Connor Hospital, San Jose; and seven from the San Jose Kaiser Permanente Medical Center. The MRI data were chosen that were read clinically as normal from subjects free of definite or questionable central nervous system disorders, head trauma, seizures, atypical headache, psychosis, or dehydration, as stated in clinical radiology notes. Most subjects were referred for headache or dizziness. The total number of scans collected was 131, of which 90 could be quantified with our analysis technique. Reasons for not quantifying scan data included movement or position artifact, poor image quality, failure of the automatic segmentation algorithm, incomplete image data (eg, sagittal scan only or single echo scan), use of contrast agent, unknown diagnosis, and age older than 30 years. Two of the subjects with quantifiable MRI data were excluded because they were markedly deviant statistical outliers, having at least one brain measure approximately 5 SDs from the predicted values for their ages.

Older Sample

These subjects included 73 men aged 21 to 70 years old (mean, 44.1±13.8 years) who were recruited prospectively from the community to participate in this study of normal aging, as well as to serve as controls for neuropsychiatric studies. On average, this sample had 16.4±2.8 (range, 9 to 23) years of formal education and achieved a Wechsler Adult Intelligence Scale, Revised,[36] vocabulary age-scaled score of 12.3±2.4 (range, 7 to 18). The mean (±SD) score on a quantitative handedness scale was 26.7±15.3 (range, 14 to 69); scores range from 14 (extreme right-handedness) to 70 (extreme left-handedness).[37] Subjects responding to recruitment advertisements were initially screened by telephone interview. Those willing to participate and passing this screening process were invited into our laboratory where they were further screened by a psychiatrist for history of any psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia–Lifetime.[38] Subjects meeting criteria for current or past episodes of psychiatric illness were excluded. In addition, a research assistant conducted a lifetime alcohol-use interview modified from Skinner[39] and used in previous studies.[40] The sample of 73 was selected from a total group of 88 men; 15 subjects were excluded from the study for various reasons; six met Research Diagnostic Criteria[41] for substance abuse in the past year or had drunk more than 54 g/d of alcohol (equivalent of four "drinks" containing an average of 13.6 g of alcohol) for a period exceeding 1 month; one subject had no recorded alcohol history; one was diabetic; and one had technically unusable MRI data. In addition, six subjects were excluded based on the judgment of a clinical neuroradiologist who independently evaluated the MRI films of all subjects: one for marked ventriculomegaly and possibly arrested communicating hydrocephalus; one for colpocephaly; one for an infarction; one for posterior fossa fluid collection; and two for subarachnoid cyst. Data from subsamples of these 73 subjects have been reported before.[33,42,43]

PROCEDURE MRI SCAN ACQUISITION

All subjects in the adult sample were scanned using 1.5-T MRI scanners (General Electric Signa, Milwaukee, Wis). Scanning parameters and procedures used for the older sample have been described in detail.[35,42] Axial MRIs were acquired using a spin-echo sequence with a field of view of 24 cm and a 256×256 matrix. Acquisition was gated to every other cardiac cycle for an effective repetition time (TR) of greater than 2400 milliseconds with one excitation for each of 256-phase encodes. Early and late echoes were obtained at 20 and 80 milliseconds. All axial images were oriented in an oblique plane, perpendicular to the sagittal plane, and passing through the anterior commissure (AC) and posterior commissure (PC), which were identified from a midsagittal image. Beginning inferiorly at the base of the pons, 17 to 20 slices were collected, each 5-mm thick, with a 2.5-mm interslice skip to reduce cross talk. The older sample also had a limited coronal acquisition for another study; one slice from this sequence was used for head height measurement.

The MRI data for the younger sample were collected retrospectively. All of the analyzed images were acquired in the axial plane using early and late echo times of 30 and 80 milliseconds, respectively. Other acquisition parameters were not uniform across subjects. The image acquisitions used a spin-echo sequence with a modal field of view of 24 cm, with images from some subjects acquired with a 20-, 21-, or 22-cm field of view. The modal TR was greater than 2400 milliseconds, with some images having been acquired with TRs as short as 1800 milliseconds or as long as 3000 milliseconds. Beginning inferiorly at the base of the pons, 5-mm thick slices were collected, with most subjects having a 2.5-mm interslice skip. The interslice skip was 2.0 mm for 10 subjects, 1.5 mm for six subjects, and 1.3 mm for one subject. Quantitative volumetric MRI data from the younger sample were arithmetically adjusted for the differences in field of view and interslice skip.

MRI SLICE SELECTION CRITERIA AND QUANTIFICATION

All images were stored on magnetic tape, transferred to a laboratory microcomputer, and coded to allow processing to be

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performed "blinded" to subject identity, age, diagnosis, and neuroradiologist's report. For each data set, the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally, was identified as an index slice. Seven consecutive slices, beginning at the index slice and proceeding rostrally, were analyzed for each subject in the adult sample; six slices were analyzed for each subject in the younger sample. Slices superior to this were excluded because, in many subjects, they contained only CSF and partially volumed cortical tissue, making quantification unreliable; this problem was notable in the younger sample, which included children whose heads were considerably smaller than those of the adults. Slices inferior to the index slice were also excluded because their irregularly shaped skull boundaries precluded stripping of skull and soft tissue pixels from the images, a preprocessing requirement for automated tissue segmentation. The sum of brain tissue and CSF pixels on all slices used in quantification provided an estimate of intracranial volume, which was used for comparison with the coronally based head size estimate.

Three-Compartment Image Segmentation

Each of the MRI slices was segmented into CSF gray matter, and white matter compartments using a semiautomated image analysis technique developed in our laboratory.[34,35] The technique consisted of the following steps. First, skull margins were identified, and skull and all pixels peripheral to it were stripped from each image. Then, to enhance CSF-tissue contrast, a composite image was created by subtracting the late echo image from the early echo image. This image was filtered using a homomorphic digital filter to reduce the effects of radiofrequency inhomogeneity, a low-frequency gradient in signal intensity across the image that violates the assumption of a level baseline needed for thresholding.[35] Trained research assistants blinded to subject identity and age identified the image intensity value above which all pixels could be considered tissue and below which all pixels could be considered CSF. For each subject, the most anterior and posterior points of the corpus callosum were also identified.

To enhance gray-white contrast, another set of composite images was created by adding together pixel intensity values for the early and late echo images. These composite images were also filtered to reduce radiofrequency inhomogeneity. Gray-white segmentation was achieved using an automated procedure[34] based on a nonparametric histogram analysis technique.[44] All pixels identified as tissue during manual thresholding were subjected to histogram analysis, which determined the threshold value separating gray from white matter. This was done separately for the inner 55% and outer 45% of each slice. On all slices, the outer two rows of pixels adjacent to subarachnoid space, which are susceptible to partial voluming and thus misclassification, were automatically set to gray matter values because anatomically these pixels most likely represent gray matter. This automatic gray-white thresholding technique was validated against our previously reported operator-driven thresholding method.[35]

Interrater reliability for four raters and 26 subjects was assessed with intraclass correlations[45] for the CSF, gray matter, and white matter ROI volumes. The reliabilities of the automatically determined gray matter and white matter segmentation were dependent on the operator-determined CSF-tissue thresholding. The reliabilities were high, ranging from 0.99 for cortical white matter to 0.997 for cortical gray matter.

The quality of the segmentation was judged blinded to age for each subject by comparing it with laser-printed images of the early and late echoes. Data for some subjects in the younger sample were excluded because the gray and white matter signals were isointense[15,19,46] and thus, as mentioned earlier, gray matter and white matter could not be distinguished with our automated algorithm. No subject in the older sample was excluded for poor segmentation quality.

Regional Divisions of Segmented Images

The images were divided according to anatomical landmarks and a priori geometric rules in an effort to achieve standardized regional divisions of the brain images. Each segmented brain slice was divided into an inner 55% region (to facilitate quantification of central CSF, which arose primarily but not exclusively from the ventricular system) and an outer 45% (to facilitate quantification of cortical tissue and sulcal volume). These proportions were empirically determined to maximize differentiation of ventricular from cortical sulcal CSF[27] in an efficient and consistent manner. Cortical tissue was further divided into gray matter and white matter to provide samples of the cortical gray matter mantle and underlying white matter. In this article, these samples are referred to as *cortical gray matter* and *cortical white matter*.

The subcortical region (inner 55%) was not separated into gray and white matter compartments because the automated method was prone to misrepresenting partially volumed white matter as gray matter in the subcortical regions, especially near the margins of the ventricles where hyperintensities were likely to appear.[24,47] Thus, only CSF and tissue were quantified in the subcortical compartment, and only the CSF volume was analyzed because the tissue measure was simply the complement of the CSF measure. **Figure 1** shows segmented MRIs divided into cortical and subcortical regions for a young child and for an older adult.

Head Size Estimation

We use the term *head size* as shorthand for, and interchangeably with, *intracranial volume*. It includes brain tissue, CSF-filled spaces (subarachnoid space, sulci, and ventricles), and blood-filled sinuses, recognizing that the skull, scalp, and hair also contribute to head size but are not germane to this measure. Brain growth drives the growth of the skull, and the ul-

timate volume of the skull (head size) reflects the maximal size of the brain. Thus, the head size measure is intended to reflect the maximum attained size of the brain, even if there is atrophy at the time of examination. Head size was estimated by modeling the intracranial volume as a sphere.[43] The diameter of the sphere was the height of the intracranial vault, which was based on a coronal slice passing through the temporal lobes. This coronal slice was located at the anterior commissure in a plane oriented perpendicular to the AC-PC line. Height of the intracranial vault was measured on a laser-printed coronal image for each subject. To derive a head height, raters drew a midline from the top of the superior sagittal sinus to the bottom of the temporal lobes, which was the inferior point at the intersection of the midline and a line drawn across the most inferior aspects of the temporal lobes. Half this height was used as the radius of the sphere, and the total area (tissue + CSF) of the index slice from the axial scan was used to estimate the area of a plane passing through the center of the sphere. The volume of the sphere, or intracranial space, was calculated as $4/3 \times$ radius $\times$ area of index slice. The approach provided an estimate of intracranial volume with measurement errors that were independent of the measurement errors associated with estimating the ROI volumes. Interrater reliability of the head height estimate for two raters independently rating 24 subjects, assessed with an intraclass correlation coefficient, was .97. For validity, the independent head size estimate correlated highly (r=.88) with the ROI-based intracranial volume estimate (ie, the sum of the tissue and CSF volumes from the seven axial slices analyzed) in the adult sample.

Coronal images were available for the adult sample but not for the younger sample. To estimate head heights in the younger sample, a method was developed to synthesize coronal images from the axial images such that the synthesized images were positioned similarly and scaled to the same dimensions as the actual coronal slices used to estimate head heights in the adult sample. Using information about slice thickness and spacing of the axial images, an interpolation algorithm was applied to the axial data set to synthesize the corresponding coronal images. For synthesized coronal images that did not have the most superior axial slices available for computation, a rater estimated the location of the top of the intracranial vault from a laser printout of the incomplete synthesized coronal image. The interrater reliability of the resulting head height estimate, based on independent ratings of 24 subjects by two raters and assessed with an intraclass correlation coefficient, was .81.

Head heights were measured in the younger sample using these synthesized coronal images. To assess the validity of the synthesized coronal images, head heights measured from actual coronal images and from synthesized coronal images were correlated for all 73 subjects in the adult sample. The correlation between these two head height measures was sufficiently high (r=.77, $P \leq .0001$) to further support the validity of this approach in the younger sample.

STATISTICAL ANALYSIS ASSESSMENT OF AGE TRENDS AND SEX DIFFERENCES

Linear and curvilinear age trends were assessed with hierarchical polynomial regression analyses. In such analyses, higher-order trends were tested for the predictive increments they afforded over and above lower-order trends. For example, the significance of a quadratic function ($y=\beta_0+\beta_1X+\beta_2X^2$) was tested by evaluating the increment in the multiple R^2 value it produced beyond that obtained when a linear function ($y=\beta_0+\beta_1X$) was used. Sex effects were also evaluated using hierarchical polynomial regression models that included a dummy-coded predictor variable representing sex (ie, male, 0; female, 1). Sex differences in the slopes of the age trends were evaluated by significance testing of the increment in the multiple R^2 value afforded by the addition of the sex times age product terms (ie, sex $\times$ age, sex $\times$ age^2, sex $\times$ age^3). Sex differences in the intercepts of the age trends, examined when the slopes were determined to be equivalent for males and females, were evaluated by significance testing of the increment in the multiple R^2 value afforded by the addition of the dummy-coded sex variable to the linear and higher-order terms in the regression model (for a further description of this statistical approach, see Pedhazur[48]).

Age-related increases in brain volume variability have been evident in previous studies of normal aging across the adult life span.[24,27,28,32] Ordinary least-squares regression assumes that the variance is constant or "homoscedastic" across the range of the predictor variable. Weighted least-squares regression takes heteroscedasticity in the data into account. Although we used ordinary least-squares regression for most of our analyses, weighted least-squares analysis was used in the final age-regression analyses in the older sample to increase the precision (ie, efficiency) of the parameter estimates on which the brain ROI volume age norms were based.[49] In other work from our laboratory, these norms serve as a reference for evaluating brain changes associated with diseases such as alcoholism.[33] A procedure based on the test of Glejser[50] for heteroscedasticity provided estimates of the ROI SDs specific for each age, which served as weights in the weighted least-squares age-regression analyses in the older sample.

Correction for Normal Variation in Head Size

In volumetric quantification of brain tissue from MRI data, head size differences among subjects are an important source of variation, reflecting processes that determine somatic size in general: large people have larger heads and brains than small people, and thus because of their larger somatic size, on average, men have larger heads and brains than women.[2,3] The proportion of the different tissue types may change with head size differences.[43] In the adult age range, where head size reflects maximal brain size attained, and where atrophy is reflected as a decrease in tissue and an increase in CSF volume in a static

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intracranial space,[51] some between-subject variance can be removed by correcting for head size statistically. Head size correction can facilitate the detection of brain changes caused by aging or disease.[43] In growing children, in whom increases in brain volume are normally accommodated by a similar increase in intracranial volume, head size is a marker of the state of growth and development. Thus, unlike the situation in adults, head size correction of volumetric MRI brain measurements in children could potentially obscure or even remove the developmental trends targeted for study.

Thus, in the older sample, the volumetric brain ROI measures were corrected for head size variation as follows: pixel counts were transformed into milliliters, which formed the volumetric measures (ie, raw data) of cortical gray matter, cortical white matter, and CSF for the brain ROIs measured. Linear regressions of the brain measures on head size provided predicted ROI volumes for a given head size. Residual values (ie, head size–corrected data) were then calculated for each subject by subtracting the predicted scores, based on the subject's head size, from the observed scores. In the younger sample, the ROI measures were not corrected for head size. In addition, to examine changes in the relative proportions of cerebral gray matter, underlying white matter, and CSF during the period of brain growth and development, we calculated the volume of each of the three tissue compartments as a proportion of head size and expressed these proportion scores over age in the first decade of life.

ena, such as cell death, synaptic and axonal pruning, and atrophic processes.[4]

Cell growth, arborization, synaptogenesis, and cell proliferation are likely to contribute notable increases in cortical gray matter volume during the first 5 to 10 years of life.[3,5] Reduction of gray matter volume proceeds with pruning, which is the normal elimination during childhood of about 40% of cortical synapses.[6] In humans, different regions of cortex may undergo neuronal pruning at different times and rates. For example, pruning is ongoing in layer III of prefrontal cortex from about the ages of 5 to 16 years, and in visual cortex from about the ages of 1 to 12 years.[6-8] In contrast, pruning in subhuman primates may proceed simultaneously throughout the cortex.[9,10]

In addition to developmental processes affecting gray matter volume are those affecting white matter volume. Likely contributors to increases of white matter volume after birth are myelination and axonal growth. Neuropathological and animal studies suggest that these processes may continue through maturation to adulthood.[3,11] Many developmental studies have used magnetic resonance imaging (MRI) to assess myelination and the growth of white matter.[12-19] Consistent with the neuropathological studies is the report by Holland et al[15] showing that white matter tracts are well defined by 1 year of age; myelination proceeds most rapidly for about the first 3 years of life but continues into early adolescence.

Evidence for the functional ramifications of normal neuronal progressive and regressive processes stems from cross-sectional studies of sleep architecture and of brain metabolism in children examined with positron emission tomography (PET) and single photon emission computed tomography (SPECT). Marked increases in slow-wave sleep amplitude occur from infancy to about 8 years followed by a marked decrease in adolescence and leveling off during adulthood.[20] A PET study of children aged 5 days to 15 years[21] revealed that, before age 9 years, brain metabolism was generally high; in older children, however, brain metabolism decreased by 50%. Because glucose use is largely attributable to activity of synaptic processes, low brain metabolism in normal subjects, as measured by PET, is thought to reflect low synaptic density, in this case, associated with adolescent synaptic pruning.[22] More recently, a cross-sectional study of regional cerebral blood flow using SPECT in healthy children provided support for the metabolic peak at about age 5 to 6 years.[23]

Results from a series of cross-sectional MRI studies by Jernigan et al[24-26] provide evidence for age-related volume differences in brain morphology that are consistent with these cortical maturational declines observed in functional studies. Specifically, in normal volunteers aged 8 to 80 years, the superior portion of frontal and parietal cortical gray matter volume declined progressively from 8 years onward, accompanied by a complementary increase in cortical CSF volume. Earlier childhood in vivo growth patterns in volumes of cortical gray matter, white matter, and CSF were not well documented and discontinuities in cross-sectional sampling over the age range from infancy to old age make it difficult to adequately model age-related changes in these brain volumes. Cross-sectional quantitative computed tomographic studies have demonstrated in vivo enlargement of cortical and ventricular CSF-filled spaces with normal aging.[27-31] Quantitative MRI studies have extended this observation by revealing a complementary relation of CSF-volume enlargement and gray matter volume decrease, without white matter volume change, with aging in adults.[24,32-34]

The goals of the current cross-sectional study were threefold. First, to replicate the findings of Jernigan et al using a similar semiautomated segmentation technique to quantify volumes of gray matter, white matter, and CSF and a similar geometric approach to differentiating cortical from subcortical regions of interest (ROIs).[34,35] Second, to extend those findings to include younger subjects. Last, to use samples of brain gray matter, white matter, and CSF to model the progressive and regressive phenomena of maturation and aging. To this end, we collected prospective MRI data on healthy community volunteers who spanned five decades of the adult age range (21 to 70 years). We also acquired retrospective MRI data from clinical sources on children and young adults (age 3 months to 30 years) who

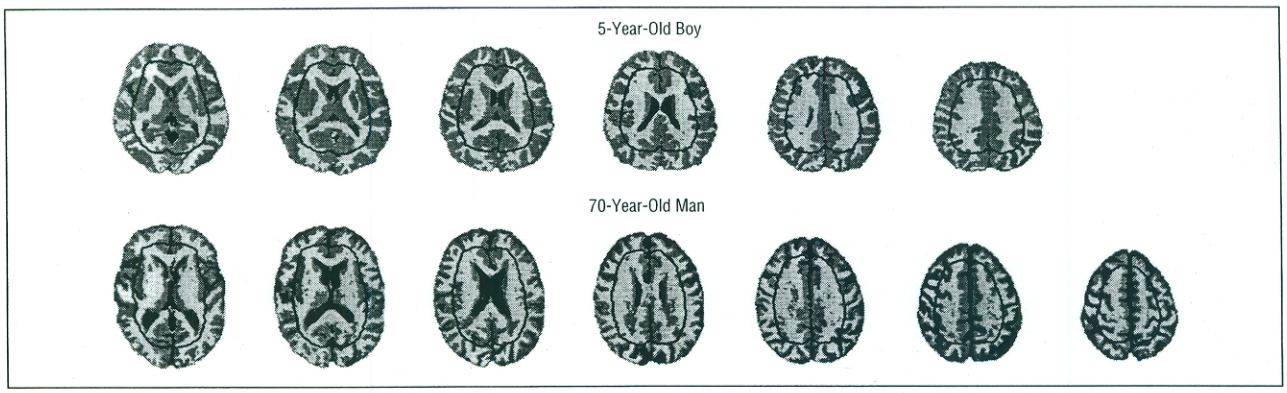

Figure 1. *Examples of segmentation maps of the axial slices that were used to estimate tissue volumes. Solid areas indicate cerebrospinal fluid; dark gray, gray matter; and light gray, white matter. The area outside the black ring indicates the outer 45% of each magnetic resonance image slice, the volumes of which composed the cortical measures. The cerebrospinal fluid pixels inside the black ring (inner 55%) composed the ventricular measures. Six slices were used in the younger sample and seven were used in the adult sample.*

were referred for clinical MRIs but whose MRI films had been read clinically as normal. Using the quantitative MRI data from both samples in this cross-sectional study, we attempted to answer the following questions: (1) Do cortical gray matter and white matter grow and regress at the same rate? and (2) Does one tissue type contribute disproportionately to the ultimate brain size and head size achieved after birth?

RESULTS

The two subject samples differed in MRI scanners, acquisition parameters, and quantification (ie, number of slices used in volume estimates and nature of the coronal images used in the head height estimate). These differences precluded combining the two samples in statistical analyses. In addition, the variability in TR, field of view, and interslice skip thickness among subjects in the younger sample led us to examine whether any of these MRI acquisition parameters showed any relations with age. Conceivably, relations between age and certain MRI acquisition parameters could confound true age-related brain changes with artifactual brain differences owing to MRI parameter variation. The results showed that TR and field of view were not significantly correlated with age, whereas interslice skip showed a moderate positive age relation (Spearman's r=.41, $P \leq .001$), where smaller interslice skips were used in younger children. The use of different interslice skips at different ages was understandable given the differences in somatic size and head size that are associated with early development. In this study, the interslice skip thickness and the slice thickness were used in calculating the volumetric estimates of the brain ROIs. Because the use of smaller interslice skips at earlier ages may have facilitated the sampling of similar brain regions in children at various points in development, the interslice skip correlation with age was unlikely to have introduced spurious correlations between age and brain measurements.

YOUNGER SAMPLE (3 MONTHS TO 30 YEARS) HEAD SIZE ASSOCIATIONS WITH AGE AND SEX

Based on the assumption that brain growth drives intracranial volume growth during development,[52] age-related increases in head size were examined prior to the consideration of brain volume changes. Using hierarchical polynomial regression analysis, head size was regressed on age and a dummy-coded variable representing sex. The results indicated a significant cubic trend (P=.012) that did not differ in form for male and female subjects (P=.889). However, a significant difference in the intercepts of the cubic functions (P=.003) showed male subjects to have slightly larger heads than female subjects across the age range. On average, male head size was larger by 70 mL. The cubic function for the male and female subjects combined shows a rise in head size from birth, peaking at about age 10 years, followed by a leveling off (**Figure 2**, top [dashed line]). This initial rise in intracranial volume was reminiscent of the gamma function that previous researchers have used to fit neurodevelopmental data.[7,20,22,23,53] Accordingly, a gamma function was also used to model the head size changes with age (Figure 2, top [solid line]). Both functions suggested a marked increase in intracranial volume (by approximately 300 mL) from 3 months to 10 years of age.

The growth trend in head size agrees with prior research showing increases in brain weight until about age 10 years, followed by a cessation of growth.[1] To improve our modeling of this early developmental process, we divided the sample by age into a younger group (3 months to 10 years; n=30) and an older group (11 to 30 years; n=58). Separate polynomial regression analyses were performed within each of these groups, and the results are graphed in Figure 2, bottom. In the younger group, a significant linear function emerged (r=.42, P=.02) showing a steady increase in head size from age 3 months to 10 years, with no significant higher-order trends. In the older group, none of the examined age

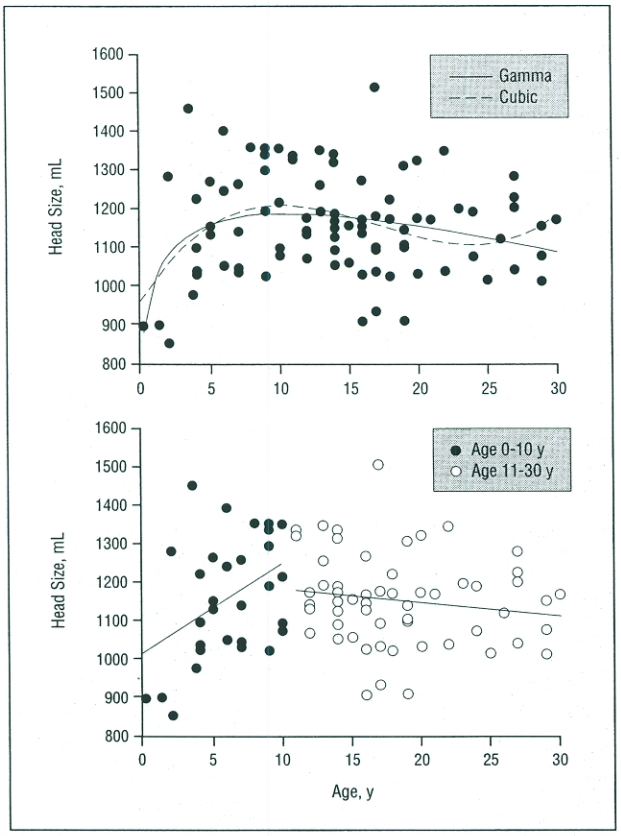

Figure 2. *Regression of head size on age on the younger sample (n=88). Top, Gamma and cubic functions. Bottom, Linear functions shown for age ranges of 0 to 10 years and 11 to 30 years.*

trends was significant (linear r=.14, P=.3), indicating essentially no age-related changes in head size between the ages of 10 and 30 years (Figure 2, bottom).

Volume Associations With Age Sex Differences

Potential sex differences in the relations between the brain measures and age from 3 months to 30 years were examined using hierarchical polynomial regression analyses. Raw measures of cortical gray matter, cortical white matter, and CSF volumes were regressed on age and sex using linear, quadratic, and cubic models. Results showed no significant sex differences in the slopes or shapes of linear or higher-order age functions for any measure examined.

The next question pertaining to sex differences considered whether the intercepts of the age functions were equivalent, given that no sex differences were noted in the slopes or shapes of the age functions. Significant sex differences in the intercepts of the cubic (P=.011), quadratic (P=.011), and linear (P=.012) age functions were found for cortical gray matter volume, with male subjects showing greater gray matter volumes at a given age than female subjects; however, these intercept differences did not persist when head size differences between male and female subjects were considered by using head size as a covariate in the analyses. Furthermore, no significant sex differences were found in

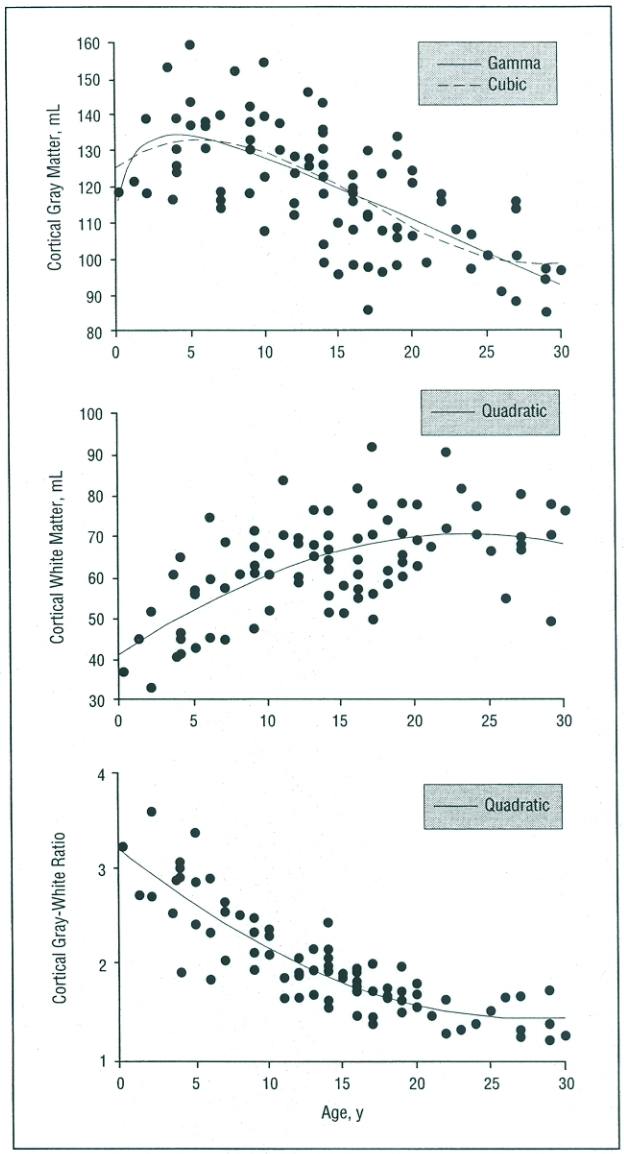

Figure 3. *Regression of cortical gray and cortical white matter volumes on age in the younger sample (n=88). Top, Gamma and cubic functions for cortical gray matter volume. Center, Quadratic function for cortical white matter volume. Bottom, Ratio of cortical gray matter to cortical white matter volumes.*

the intercepts of either linear, quadratic, or cubic age functions for any of the other brain measures considered. Thus, other than the cortical gray matter difference, which appeared to be tightly coupled with head size differences, no consistent tissue or CSF volume differences were noted between males and females across the first three decades of life.

Raw Data

Age trends in the volumes of the raw MRI data (ie, uncorrected for head size) were examined for CSF, cortical gray matter, and cortical white matter in the younger sample. Based on the aforementioned analyses, which showed no sex effects other than a quantitative sex difference in cortical gray

matter explainable by somatic size differences, males and females were combined into a single sample. Hierarchical polynomial regression analyses were used to model linear and higher-order age trends. For brain tissue relations with age, a linear function was significantly improved on by a quadratic function for cortical white matter volume (P=.002), and a cubic function improved on the quadratic function for cortical gray matter (P=.053). The cubic function describing the change in cortical gray matter with age is presented in **Figure 3**, top (dashed line). As with the age-related changes in head size, a gamma function was also used to model the cortical gray matter volume differences across the age range. Compared with the cubic, the gamma function (Figure 3, top [solid line]) depicts a steeper initial rise in cortical gray matter and suggests a peak gray matter volume at about age 4 years. Both functions suggest a gradual decline in cortical gray matter during the second and third decades of life.

The significant quadratic function depicting cortical white matter volume changes with age (Figure 3, center) shows that cortical white matter volume steadily increases from birth to about age 20 years, after which it levels off. To consider the dynamic interplay between the white matter and gray matter changes, the ratio of cortical gray to white matter volume was calculated for each subject and then was plotted against age. When submitted to a hierarchical polynomial regression analysis, the quadratic function (Figure 3, bottom) best described the changes in the gray-white volume ratio with age (P=.0001). This function shows that from age 3 months to 20 years, the cortical gray-white ratio declines steeply, reflecting the earlier finding of a simultaneous decrease in gray matter and increase in white matter during most of this period. From age 20 to 30 years, the decline in the gray-white ratio is less steep, reflecting the earlier finding that gray matter volume continues to decrease, whereas white matter volume stabilizes by about age 20 years.

For CSF volume differences associated with age, the cortical and the ventricular measures exhibited different age relations. Hierarchical polynomial regression analyses showed that the cortical CSF volume exhibited a significant quadratic trend (P=.002) but a nonsignificant cubic trend (P=.862). The significant quadratic trend (**Figure 4**, top) shows that sulcal CSF volume remains stable to about age 20 years, after which it begins to increase. In contrast, ventricular CSF volume showed no significant linear (Figure 4, bottom) or higher-order age relations from birth to age 30 years.

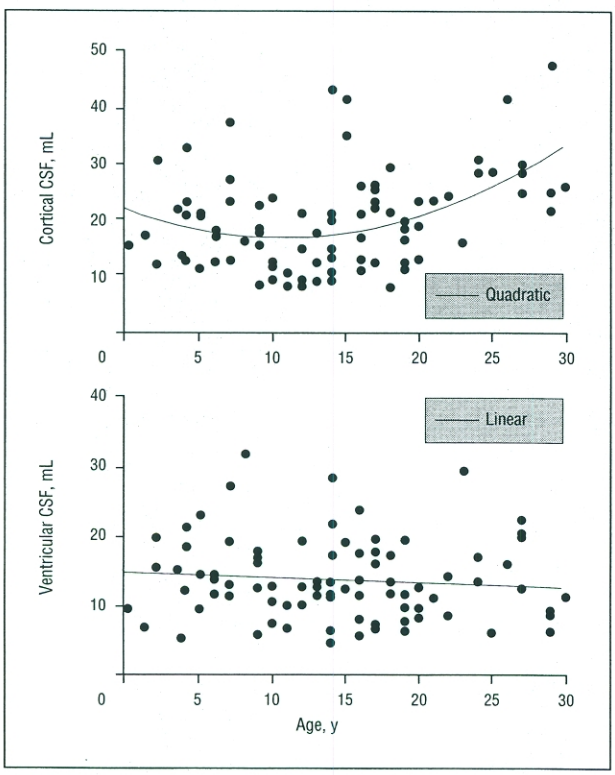

Figure 4. *Regression of cerebrospinal fluid (CSF) volume on age in the younger sample. Top, Quadratic function for cortical CSF volume. Bottom, Linear function for ventricular CSF volume.*

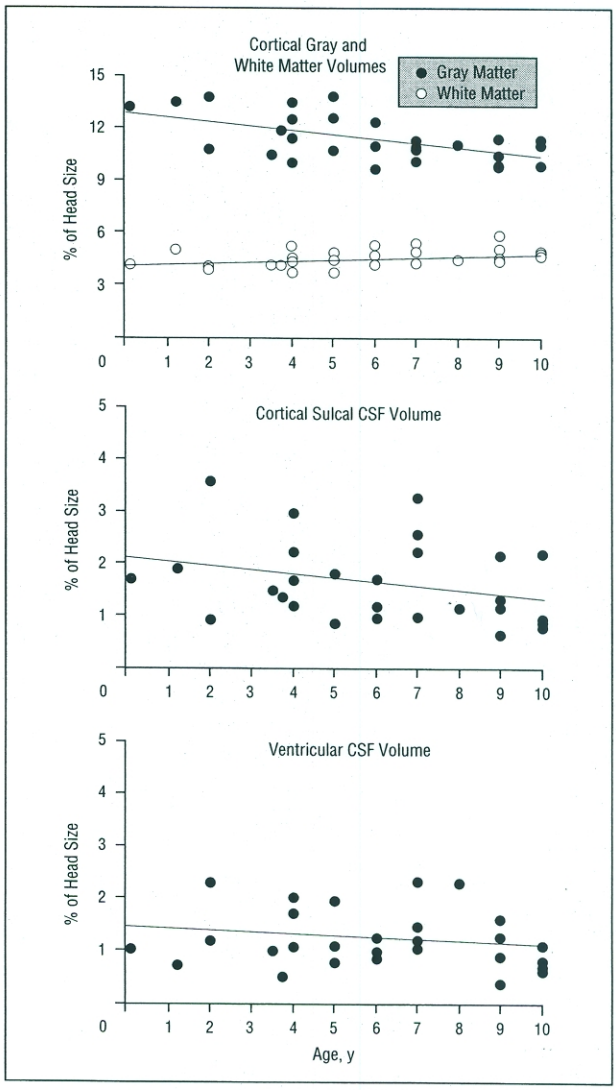

Figure 5. *Linear regressions on age of four brain regions expressed as percentages of head size in the first decade of life (n=30). Top, Cortical gray matter and cortical white matter volumes. Center, Cortical sulcal cerebrospinal fluid volume. Bottom, Ventricular cerebrospinal fluid volume.*

Multiple Regression of Volumetric Brain Measures on Age and Head Size*

	Predictor Variables				
	Age		Head Size		
Brain Volumetric ROI	β†	Squared Semipartial Correlation‡	β	Squared Semipartial Correlation	Multiple R^2
			Younger Sample (n=88)		
Cortical gray matter	−0.64	.413¶	0.58	.331¶	.742¶
Cortical white matter	0.56	.315¶	0.58	.337¶	.654¶
Cortical sulcal CSF	0.36	.128‖	−0.26	.066§	.194¶
Lateral ventricular CSF	−0.06	.004	0.19	.035	.039
			Older Sample (n=73)		
Cortical gray matter	−0.65	.420¶	0.44	.193¶	.584¶
Cortical white matter	0.09	.009	0.69	.473¶	.490¶
Cortical sulcal CSF	0.60	.354¶	0.14	.02	.384¶
Lateral ventricular CSF	0.43	.187¶	0.37	.138‖	.344¶

*ROI indicates region of interest; CSF, cerebrospinal fluid.
†Standardized partial regression coefficient.
‡Indicates the proportion of brain ROI variance accounted for independently by each predictor.
§$P \leq .01$.
‖$P \leq .001$.
¶$P \leq .0001$.

VOLUMES RELATIVE TO HEAD SIZE DURING THE FIRST DECADE OF LIFE

During the first decade of life (3 months to 10 years; n=30), cortical tissue volumes correlated with head size (gray matter, $r=.68, P \leq .0001$; white matter, $r=.84, P \leq .0001$), whereas CSF volume did not correlate (cortical CSF, $r=-.29, P=.12$; ventricular CSF, $r=.19, P=.33$). As the brain grows and the intracranial vault expands during development, the question arises as to whether the CSF, cortical gray matter, and cortical white matter compartments expand at equal rates relative to each other, with their representation within the total intracranial vault remaining constant. The answer to this question depended on the rate of growth of the brain tissue and CSF compartments relative to the rate of head size growth. Accordingly, we addressed this question by examining age-related changes in the ratios of the brain ROI measures to the head size estimate. The proportion of head size occupied by cortical gray matter volume decreased linearly with age during the first decade of life ($r=-.53$, $P=.003$) (Figure 5, top), whereas the cortical white matter proportion increased linearly ($r=.48, P=.008$) (**Figure 5**, top). No higher-order age trends reached significance for these tissue proportions. The proportion of head size occupied by cortical CSF showed a nonsignificant trend toward linear decline over the first decade of life ($r=-.28$, $P=.135$) (Figure 5, center), whereas the ventricular CSF proportion remained essentially constant ($r=-.13, P=.483$) (Figure 5, bottom). Thus, cortical white matter volume appears to increase faster than head size, occupying an increasing proportion of the expanding intracranial vault. In contrast, cortical gray matter volume is decreasingly represented, and CSF for cortical and ventricular volumes together maintains essentially the same representation in the expanding intracranial vault during the first decade.

Another analysis undertaken to assess the relative contributions of cortical gray matter, cortical white matter, and CSF to head size growth during the first decade of life was a multiple regression of head size on these three cortical measures. Results showed significant improvements in the prediction of head size for cortical gray matter volume (R^2 change=.10, $P=.001$) and cortical white matter volume (R^2 change=.34, $P \leq .0001$) when entered as the last predictor into the regression equation. In contrast, cortical CSF volume failed to improve the head size prediction when entered last into the equation (R^2 change=.01, $P=.199$). The standardized regression equation showed that head size increased 0.70 standard units for every unit increase in cortical white matter volume, 0.38 standard units for every unit increase in gray matter volume, and 0.13 standard units for every unit increase in sulcal CSF volume. These results attest to the independent contributions of cortical gray matter volume and especially of cortical white matter volume to the expansion of the intracranial vault during development.

ACCOUNTING FOR BRAIN VARIATION

The preceding analyses described age-related trends in head size and brain volume growth. The association between head size variation and brain size variation is mediated not only by common developmental trends but also by individual differences in somatic size at any given period of development. A series of multiple regression analyses were conducted to assess whether head size variation and age could account for independent aspects of the variation in brain tissue or CSF volumes. The results (**Table**) showed that head size

and age each accounted for independent components of the variance of cortical gray matter, cortical white matter, and cortical sulcal CSF volumes. However, neither age nor head size could account for variance in ventricular CSF volume when controlling for the other.

OLDER SAMPLE (21 TO 70 YEARS) VOLUME ASSOCIATIONS WITH AGE

The older sample included men aged 21 to 70 years and therefore permitted an assessment of the aging brain over the adult life span after most of the earlier neurodevelopmental processes had ceased to exert their influence. In the adult age range, no further growth in head size was expected, and therefore any observed head size variation likely reflected individual differences in hereditary, constitutional, and environmental determinants rather than differences in developmental stage. Thus, as expected, head size and age were uncorrelated (r=.05, P=.65). Nevertheless, head size variation is a significant source of between-subject brain volume variation. In the older sample, head size showed positive linear correlations with the cortical tissue volume measures (gray matter, r=.41, P=.0004; white matter, r=.69, P=.0001) and with the lateral ventricle volume (r=.4, P=.0005), but not with the cortical CSF volume, which showed a weak nonsignificant head size correlation.

Removal of head size variation from the brain volume measures would be expected to remove noise from the data, possibly allowing a clearer view of the age trends for different ROIs without altering the form of the age function.[43] The age-related changes in brain tissue and CSF volumes were assessed using hierarchical polynomial age regression analyses of both the raw and the head size–corrected brain data. Because the significant age trends that emerged were the same for the raw and head size–corrected data, only the results based on the head size–corrected data are presented herein. For the cortical tissue measures, cortical gray matter volume showed a significant linear decline (r=−.71, $P\leq$.0001) and a quadratic trend approaching significance (P=.073) (**Figure 6**, top left), with an average decrease in cortical gray matter volume of 0.7 mL/y, whereas cortical white matter volume remained stable across the five decades (r=.13, P=.28) (Figure 6, top right). For CSF measures, the cortical CSF volume and the ventricular CSF volume exhibited quadratic age trends (cortical, r=.63, P=.061; ventricular, r=.52, P=.031) (Figure 6, bottom left and right), with an average increase

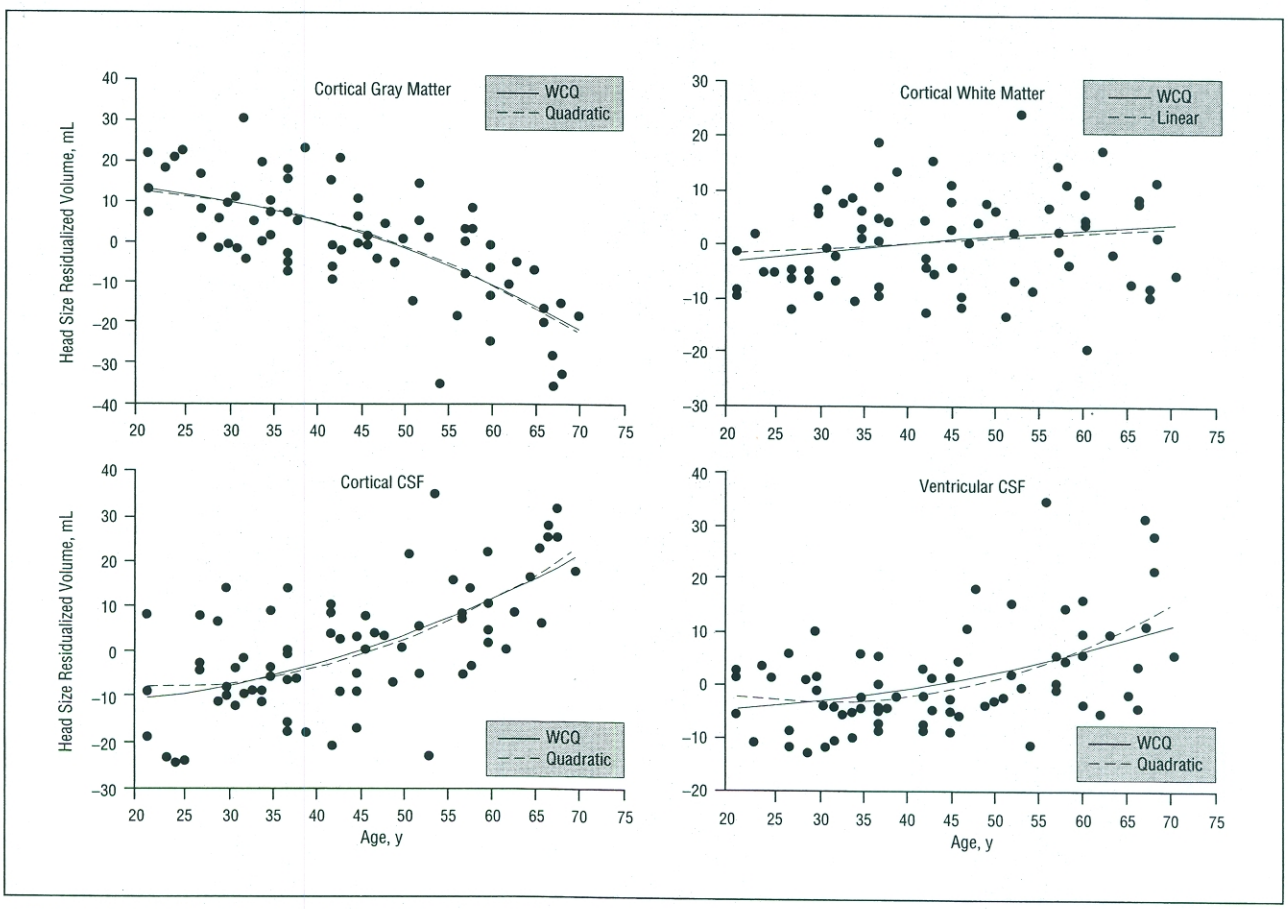

Figure 6. *Regression of head size–residualized brain region volumes on age in the adult sample (n=73). Top left, Unconstrained quadratic and weighted constrained quadratic (WCQ) functions for cortical gray matter volume. Top right, Unconstrained linear and WCQ functions for cortical white matter volume. Bottom left, Unconstrained quadratic and WCQ functions for cortical cerebrospinal fluid (CSF) sulcal volume. Bottom right, Unconstrained quadratic and WCQ functions for ventricular CSF volume.*

in cortical CSF of 0.6 mL/y and an average increase in ventricular CSF of 0.3 mL/y. Thus, the decline of cortical tissue volume in normal aging is primarily the replacement of cortical gray matter volume with CSF.

Modeling Normal Aging With Polynomial Functions

These results, as well as those from previous studies,[24,27,28] have shown that, depending on the tissue type and region measured, estimates of brain volume may change in a linear or a curvilinear fashion with age. Using a polynomial regression approach, quadratic functions often emerge as the best representation of curvilinear age trends. However, in the age range of 20 to 70 years, quadratic curves sometimes exhibit inflection points that do not make biological sense. The quadratic age curves found for the CSF volumes (Figure 6) demonstrate this inflection point problem: the curves inflect at approximately age 20 years, suggesting the biologically implausible trend of CSF increases before and after age 20 years. Such inflections are undesirable given that a major objective of age regression analysis is to model normal aging and to derive age-normalized data with which to compare patient groups with each other and normal controls.[24,27] Further, the analyses of the data from the younger sample do not support this result, ie, a CSF volume increase as one looks back from age 20 years to birth. Our solution was to represent curvilinear age trends using a quadratic polynomial regression model constrained to permit only monotonic changes from age 10 years onward. This age constraint was chosen based on postmortem studies suggesting that adult brain weight is substantially achieved by about age 10 years.[1] This constraint received additional corroboration from the significant cubic age trend found for head size in the younger sample (Figure 2), showing a peak in head size growth near age 10 years. In addition to imposing a constraint, we used a weighted least-squares regression model to consider possible increases in variance with age, as described herein. The solid lines in the graphs in Figure 6 depict the weighted constrained quadratic regression model. For the cortical tissue measures, the constrained quadratic is nearly linear, whereas for the CSF measures, the constrained quadratic regression lines do not show the inflection points that characterize the unconstrained quadratic model. Thus, the constrained quadratic model was flexible enough to fit linear and curvilinear data trends and did not produce biologically implausible curve inflections.

Accounting for Brain Volume Variation

As with the younger sample, an analysis of the raw brain data in the older sample was conducted to determine the relative contributions of both head size and age as independent sources of brain volume variation (Table). Multiple regression analyses showed that in predicting cortical gray matter and ventricular CSF volume, head size and age were each able to make significant incremental predictions above the other. In contrast, for cortical white matter, only head size could independently account for white matter variance when age was controlled for; age did not significantly contribute to the prediction of cortical white matter volume after controlling for head size. The reverse pattern was observed when predicting cortical CSF: age, but not head size, accounted for a significant incremental proportion of variance in CSF volume.

COMMENT

These analyses of quantitative MRI data, collected cross-sectionally, suggest patterns of change in human cortical gray matter, cortical white matter, and sulcal and ventricular CSF volumes during the age range from 3 months to 70 years. Head size increased to about age 10 years. Cortical gray matter volume peaked at age 4 years and then decreased throughout the adult age-range sampled. Cortical white matter volume increased through late adolescence (age 20 years) and remained stable thereafter. Cortical sulcal and ventricular CSF volumes increased curvilinearly throughout adulthood.

On average, head size of boys was larger than that of girls by about 70 mL. Both sexes, nevertheless, followed the same growth trend, showing significant intracranial enlargement until about age 10 years. This in vivo observation agrees with postmortem studies describing an increase in brain weight until about age 10 years, with the brains of boys being heavier than those of girls by about 160 g.[1]

The growth in gray matter volume, as observed with MRI, peaked at about age 4 years and then declined steadily throughout the life span, as inferred from the two age samples. Limited sampling under this age because of difficulties in segmenting isointense gray from white matter in the very young necessitates caution in interpreting these data. Despite these limitations, the timing of the rise and fall of cortical gray matter volume is consistent with findings from three different research paradigms, reviewed earlier: neuropathology of synaptic counts in the frontal cortex,[6] electrophysiology of sleep slow-wave amplitude,[20] and brain metabolism and blood flow as studied with PET[21] and SPECT.[23] These studies provide converging evidence for peaks in gray matter volume, cerebral metabolism, and neuronal activity to occur around age 4 to 10 years, followed by a decline during adolescence and young adulthood. These observations may actually reflect the processes of cortical cell growth overlapping with pruning and cell death.

Patterns of cortical gray and white matter volume growth, as estimated from geometrically defined samples, differed. This study reports on only cortical white matter because of current limitations in techniques for segmentation of subcortical white and gray matter. However, the

data are consistent with pathological studies of developmental myelination,[11] showing a steady rise in volume from birth to about age 20 years. From then onward to age 70 years, white matter volume did not fluctuate (see also Jernigan et al[32]). Increases in cortical gray matter volume to about age 4 years and increases in cortical white matter volume during the first decade of life differentially contribute to intracranial vault expansion, with white matter contributing more than gray matter. The dynamic interplay of gray matter and white matter volumes during the course of development to age 30 years was demonstrated by the quadratic decline of the gray-white matter ratio. In particular, age-related changes in the gray-white matter ratio suggested that the growth in white matter exceeded that of gray matter during the first 5 years, followed by a decline in gray matter volume accompanied by continued growth in white matter until about age 20 years, when white matter volume leveled off. This observation is consistent with that of Martin et al[17] who reported that gyration preceded myelination in their sample of 50 children aged 8 months to 4.6 years. The white matter measured in our study includes only those regions immediately mesial to the cortical mantle and thus represents only a subsample of the entire mass of brain white matter; however, it is likely to include white matter regions engaged in axonal growth and myelination and may still provide useful clues to modeling white matter changes in other parts of the brain.

The volume of cortical CSF remained stable (or was undetectably small with these measures) from age 3 months to 20 years, when it increased in an accelerating fashion over the five decades of adulthood studied. The increase in cortical CSF complementary to the decrease in cortical gray matter volume has been documented.[32,33] Ventricular CSF volume started to show significant enlargement around age 30 years, when it too increased in an accelerating fashion with aging. It is plausible that the increase in CSF volume and the decrease in gray matter volume in the aging brain reflects atrophic processes, including cell shrinkage and loss, as well as possible cellular compacting (increased neuronal packing density). According to Kemper,[51(p10)] gross morphological correlates of this atrophic process are gyral atrophy and ventricular dilation. The term *gyral atrophy* is preferred to *cortical atrophy*, since it is not clear whether the cortex, the underlying white matter, or both are responsible for the change. The data from our study suggest that these complementary functions do indeed signal cortical atrophy.

The trends in volume changes over age in the adult sample are consistent with those reported by Jernigan et al.[24,32] Those studies and this one show a linear decline in gray matter volume, no change in white matter volume, and an increase in CSF volume described best by a quadratic function. However, our analyses also highlighted the problem of biologically implausible inflection points in quadratic polynomial age trends, particularly in the CSF volume measurements. When brain changes associated with normal aging in a control group are to serve as a reference for evaluating brain changes associated with disease, it is desirable to model age-related brain changes in a statistically accurate yet biologically valid manner. Our solution has been to use a constrained quadratic regression model, with the constraint being that only monotonic changes in brain volume may occur after age 10 years. We also used weighted least-squares regression to guard against violations of the assumption of homoscedastic variances over the adult age range. As demonstrated in the older sample, this method preserves the form of the age-trend while avoiding statistical artifacts that do not make biological sense.

The contributions of age and head size to the variation of CSF and cortical tissue volumes, evaluated with multiple regression analyses, depended on the developmental period under study and provided hints about the onset and termination of various neurodevelopmental processes. Cortical white matter volume, as estimated from our geometrically defined tissue sample, expanded with age to about 20 years, after which it remained at its maximum volume, suggesting a termination time of progressive processes contributing to white matter growth, such as myelination and axonal growth. Moreover, white matter volume was a strong correlate of head size, suggesting that white matter growth is a major contributor to the expansion of the intracranial vault and that white matter volume may be a stable reflection, throughout the adult life span, of the maximally attained intracranial volume and of somatic size more generally. Our automated measures of white matter volume have two principal limitations: the boundaries are defined geometrically rather than anatomically, and the measures represent only a sample of total brain white matter volume. Despite these shortcomings, the increase in cortical white matter volume during childhood and adolescence is predictable from neuropathological studies of brain development.[11] Similarly the stability of white matter volume over the adult age range is also predictable from neuropathological studies of aging.[54]

Other than the modest rise in cortical gray matter from infancy to about age 4 years, suggesting the termination period for progressive processes, such as synaptogenesis and arborization, cortical gray matter showed a remarkably consistent decline throughout the life span. Despite the continuing age-related changes in this tissue compartment, a strong relation between cortical gray matter and head size is established early on and persists in a somewhat attenuated form into late adulthood. This relation suggests an early role for gray matter in intracranial volume expansion and a marker of individual differences in somatic size. Because no obvious inflection was noted in the cortical gray matter volume decline, age-related changes in gray matter offered no suggestions of a possible demarcation point between the maturational process of neuronal pruning and the atrophic processes of normal aging. Similarly, cortical sulcal CSF volume, which showed no relation to head size in adulthood and a weak counterintuitive relation in childhood, exhibited increases with age in the younger and older samples. These CSF increases could be attributable to pruning, atrophy, or both

of these regressive processes, again suggesting no obvious separation point. However, a possible demarcation is suggested by the age-related changes in ventricular volume. In the younger sample, lateral ventricular CSF volume was not associated with head size or with age. The processes that govern ventricular size early in life are apparently independent of the primary neurodevelopmental events and of general somatic size constraints. The onset of ventricular enlargement between age 20 to 30 years, reflected by a significant age relation in the older sample, suggested a possible marker for the onset of atrophy. Regardless of the processes underlying atrophy, whether they be cell loss or cell shrinkage,[5] the tissue (presumably cortical gray matter) volume reduction associated with ventricular enlargement proceeds in such a way that ventricular size develops an association with head size in later life. Perhaps the constraints imposed by a fixed intracranial volume do not play a role in determining ventricular size until the process of atrophy begins.

The MRI signals of gray matter and white matter are notoriously isointense during the first year of life, depending somewhat on the MRI acquisition sequence. In the younger sample, 20% (8/41 cases) of the MRI data excluded were from children younger than 1 year whose MRIs could not be segmented into gray and white matter compartments successfully with our automatic algorithm. This attrition rate significantly limited our ability to sample data from very young children and infants. Moreover, the discrimination of the gray and white pixels from the MRIs by the automatic algorithm was increasingly difficult in children at younger ages. This poor gray-white matter differentiation at very early ages is well documented and may be attributable to the incomplete myelination of the brains of young children.[15,19,46] Marked decreases in water content and increases in whole brain cholesterol concentration are coincident with myelination, which occurs most rapidly up to about age 3 years.[14,55] At this time, the brain also takes on a more adult-looking gyral pattern.[17]

Ideally, studies of normal development should involve healthy subjects prospectively recruited from the community rather than patients selected from medical clinics. Although our older sample filled this requirement, our younger sample did not, principally because of obvious difficulties in recruiting and scanning very young children solely for research. This type of retrospective recruitment is susceptible to subject selection bias. For example, for clinical subjects to be declared to have "normal" brain MRI readings, they must be well within the normal range; thus, such scans may actually be "supernormal."[56] In addition, the use of clinical scans in the younger sample gave us less control over imaging parameters (eg, interslice skip, field of view, and TR), as well as other sources of imaging variability, such as differences in MRI scanners and differences in head tilt among younger subjects who may have had difficulty maintaining a uniform head position in the scanner. All of these uncontrolled variables undoubtedly introduced measurement error or "noise" into the MRI brain data in the younger sample. However, to the extent that this measurement error was random with respect to the variables of theoretical interest, particularly age, the error was sufficiently small to allow the emergence of clear and biologically plausible developmental trends. The only source of measurement error that showed a systematic relationship with age was interslice skip, which, as suggested in the "Results" section, was consistent with age-related somatic size differences. The use of a uniform number of slices to derive volumetric brain estimates in children of different ages and stages of development could introduce a systematic age bias in the sample of brain encompassed by these slices, with younger children having a greater proportion of their brain subsumed within the sample than older children. The use of smaller interslice skips in younger children was likely to have helped offset this potential age bias. In addition, even if there was more variability in head tilt among the younger sample, it would have a less significant effect on volumetric measurements than on single slice area estimates, especially if the measured ROI is completely encompassed by the brain slices used in volumetric quantification.[57] Despite the potential study limitations, the results of the younger sample clearly reflected the results of developmental studies of brain morphology based on other in vivo and postmortem analyses and animal models.

This quantitative MRI study suggests that cortical gray and white matter grow and regress at different rates and make different magnitude contributions to the ultimate maximal brain size. The pattern of brain development observed with MRI in this cross-sectional study is consistent with that reported in neuropathological studies of humans and animals, which, by definition, are cross-sectional. Thus, in vivo MRI may provide a valid tool for longitudinal studies of brain development and for investigating neurodevelopmental models of major neuropsychiatric diseases, including schizophrenia.

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