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Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study

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The purpose of the present study was to describe in greater anatomical detail the changes in brain structure that occur during maturation between childhood and adolescence. High-resolution MRI, tissue classification, and anatomical segmentation of cortical and subcortical regions were used in a sample of 35 normally developing children and adolescents between 7 and 16 years of age (mean age 11 years; 20 males, 15 females). Each cortical and subcortical measure was examined for age and sex effects on raw volumes and on the measures as proportions of total supratentorial cranial volume. Results indicate age-related increases in total supratentorial cranial volume and raw and proportional increases in total cerebral white matter. Gray-matter volume reductions were only observed once variance in total brain size was proportionally controlled. The change in total cerebral white-matter proportion was significantly greater than the change in total cerebral gray-matter proportion over this age range, suggesting that the relative gray-matter reduction is probably due to significant increases in white matter. Total raw cerebral CSF volume increases were also observed. Within the cerebrum, regional patterns varied depending on the tissue (or CSF) assessed. Only frontal and parietal cortices showed changes in gray matter, white matter, and CSF measures. Once the approximately 7% larger brain volume in males was controlled, only mesial temporal cortex, caudate, thalamus, and basomesial diencephalic structures showed sex effects with the females having greater relative volumes in these regions than the males. Overall, these results are consistent with earlier reports and describe in greater detail the regional pattern of age-related differences in gray and white matter in normally developing children and adolescents.

To date, most studies of human brain development have focused on perinatal and early childhood periods when dramatic changes are occurring in the functionally developing neuropil. Most of the progressive and regressive events (e.g. synaptic reorganization, myelin deposition, and neuronal cell death) that contribute to human brain maturation occur in the perinatal period. MRI is particularly sensitive to many of these changes, especially changes in myelination, and many studies have focused on these phenomena (Holland et al. 1986, McArdle et al. 1987, Barkovich et al. 1988, Martin et al. 1988, Autti et al. 1994). Less dramatic, but functionally relevant, changes are known to be occurring later in childhood as well. For example, postmortem studies have revealed a protracted cycle of myelination, particularly in frontal and parietal regions (Yakovlev and Lecours 1967) continuing well into the third decade of life, and large increases in perihippocampal myelination between the first and second decades (Benes et al. 1994). Additionally, reductions in synaptic density have been reported to occur throughout adolescence in humans (Huttenlocher 1979, Huttenlocher and de Courten 1987) and in monkeys (Zecevic and Rakic 1991).

Recent studies have focused on the examination of these late brain maturational changes *in vivo* using MRI to assess for age-related changes in total brain volume and in the volumes of various cortical and subcortical structures (Jernigan et al. 1991; Pfefferbaum et al. 1994; Caviness et al. 1996; Giedd et al. 1996a, 1996b, 1999; Reiss et al. 1996; Giedd et al. 1997; Sowell and Jernigan 1998). In these studies, significant total brain volume increases have been observed between childhood and young adulthood (Jernigan et al. 1991, Giedd et al. 1999). Overall, cortical and subcortical gray matter shows evidence of volume reduction during this age range once the effects of brain size are controlled for (Jernigan et al. 1991, Pfefferbaum et al. 1994). When non-brain size corrected measures of gray matter are assessed, however, age effects appear to be non-linear where significant increases in volume are observed before adolescence and significant reductions are observed after adolescence (Giedd et al. 1999). On the whole, white-matter volumes appear to increase robustly enough between childhood and young adulthood that the effects are observed whether brain size correction is used (Pfefferbaum et al. 1994) or not (Giedd et al. 1999).

Regional and temporal differences are known to occur in the developmental processes (e.g. myelination, synaptic pruning) that result in cortical gray- and white-matter volume changes observed with MRI. Specifically, brain regions have been shown to mature in a pattern generally proceeding from inferior to superior, and from posterior to anterior structures (Yakovlev and Lecours 1967, Huttenlocher 1979, Huttenlocher and de Courten 1987). Findings from volumetric MRI studies have tended to reflect the postmortem studies given that cortical gray-matter volume reductions appear to be somewhat specific to the superior cortices of the frontal and parietal lobes relatively late in development (i.e. between childhood and adolescence; Jernigan et al. 1991, Sowell and Jernigan 1998). More recent volumetric studies with larger samples and longitudinal data have confirmed these results (Giedd et al. 1999).

Whole-brain voxel-based morphometry (VBM) has also been used to assess regional patterns of gray- and white-matter maturation and similar results have been observed where maturation in superior parietal and frontal cortical regions is

most prominent between 7 and 16 years of age (Sowell et al. 1999a). Another VBM study of normal development during this age range (4 to 17 years) has shown maturation in the internal capsule and in the frontotemporal pathways of the arcuate fasciculus (Paus et al. 1999). Notably, frontal cortices and striatal structures appeared to be changing most dramatically when individuals between 12 and 30 years of age were assessed (Sowell et al. 1999b). Again this finding is consistent with the postmortem studies given that the frontal cortices are the most superior and anterior, and would be expected to develop last.

The purpose of the present study was to conduct a more detailed assessment of volumetric changes that occur in the developing brain between 7 and 16 years. The methods were designed to improve upon those of most earlier reports where volumetric methods were used. First, a relatively high resolution imaging protocol with contiguous 4 mm sections was used and a higher resolution spatially registered T_1-weighted series (1.2 mm section thickness) was also collected as a reference for anatomical definition. Here we report age and sex effects for gray matter, white matter, and CSF in all cerebral lobes where tissue segmentation was used, and the regions were hand drawn based on an anatomically driven region definition protocol, rather than the stereotaxic criteria (Jernigan et al. 1991, Pfefferbaum et al. 1994, Reiss et al. 1996, Giedd et al. 1996b, Sowell and Jernigan 1998) or automated region definition protocols (Giedd et al. 1999) used in most previous studies of normative brain maturation.

Method

PARTICIPANTS

Thirty-five normally developing children and adolescents including 20 males and 15 females (see Table I for sex by age breakdown) were examined with MRI. All participants were recruited as normal control individuals for a large, multidisciplinary neurodevelopmental research center. As seen in Table I, the participants were fairly well distributed across the age range and by sex, though the females were slightly younger than the males on average (not statistically significant). All of the children were right handed, and 86% of them were white, 9% were African–American, and 5% were of Hispanic descent. These children were deemed medically and psychiatrically normal after extensive parent interviews, physical examinations, and neuropsychological testing. Children with any history of learning disability or developmental delay were excluded. Informed consent was obtained from all children and their parents and all experimental procedures were approved by the University of California, San Diego ethics committees. Neuropsychological test results for these children were all in the normal range and some of these results have been reported in relation to brain structural changes in another report (Sowell et al. 2001). It should be noted that none of these individuals were included in our earlier volumetric studies (Jernigan et al. 1991, Sowell and Jernigan 1998), though VBM analyses have been reported for some of the individuals studied here (Sowell et al. 1999a,b).

IMAGING PROTOCOL

Three whole-brain image series were collected for each participant. The first was a gradient-echo (SPGR) T_1-weighted series with: TR=24 ms, TE=5 ms, NEX=2, flip angle=45 degrees, field of view of 24 cm, section thickness of 1.2 mm, no gaps. The second and third series were fast spin-echo (FSE) acquisitions yielding two separate image sets: TR=3000 ms, TE=17 ms, ET=4 and TR=3800 ms, TE=102 ms, ET=8. For all series, the field of view was 24 cm. Section thickness for the FSE series was 4 mm, no gaps (interleaved). Imaging time for all series totaled approximately 30 minutes. Figure 1 displays representative spatially registered T_1-weighted (left), T_2-weighted (middle), and proton density (right) images (see Fig. 1).

IMAGE ANALYSIS

Detailed descriptions of the image-analytic approach used in the present study are provided in another report (Jernigan et al. 2001), and will be summarized here. Trained anatomists who were blind to participant diagnosis, age, sex, or any other identifying information subjected each image data set to five image analysis procedures: (1) interactive isolation of intracranial regions from surrounding extracranial tissue; (2) three-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact; (3) reslicing of the volume to a standard orientation; (4) tissue segmentation using semi-automated algorithms; and (5) neuroanatomical region-of-interest analysis. Procedures 1 to 5 were specifically applied to the images from the registered FSE series, but registered resliced images from the SPGR volume were used to guide the anatomists at steps 1, 4, and 5. Three-dimensional filtering was conducted to reduce the non-biological signal drift that occurs because of inhomogeneity in the magnetic field. This step is essential for methods employing tissue classification. The method currently employed to segment the FSE images requires the operator to 'seed' the analysis by selecting samples of fully-volumed CSF, gray matter, and white matter from each of several brain areas. The signal values of the selected voxels were then used in regression analyses to produce coefficients for classifying remaining voxels as most similar to gray matter, white matter, or CSF.

In order to facilitate anatomical region definition, data sets were resliced in standardized planes defined relative to the decussations of the anterior and posterior commissures and the structural midline. This considerably improves the reliability of boundary determination and makes it possible to identify small structures more consistently. Registration of the T_1-weighted and spin-echo data sets was accomplished so that registered sections from both data sets were available to the operators when attempting to resolve anatomical boundaries.

Table I: Age and sex of participants

Age (y)	*Males*	*Females*
7	1	1
8	3	2
9	3	2
10	1	2
11	2	3
12	3	1
13	1	2
14	3	1
15	1	1
16	2	0
Age, mean (SD)	11.4 (2.8)	10.7 (2.3)

Anatomists circumscribe regions on segmented images which required them to draw fewer boundaries (e.g. the caudate nucleus is bound by the segmented CSF mesially, and the white matter of the internal capsule laterally) than would be necessary to defined the same region on raw imaging data sets.

Trained image analysts define brain structures using a stylus-controlled cursor as each tissue-segmented image section was presented on the computer screen. The cerebellum was first separated from the supratentorial cranium. Then, cortical regions are circumscribed in a predefined sequence using gyral landmarks as boundaries between lobes, and standardized rules where gyral landmarks were ambiguous. The primary hemispheric cortical structural measures obtained from MRI are volumes of the ventrolateral temporal lobe region, a mesial temporal lobe region (MTL), cingulate, insula, and frontal (excluding cingulate), occipital, and parietal lobes. Total frontal, temporal, parietal, and occipital lobes were drawn to include cortical gray matter, underlying white matter, and CSF. Briefly, frontal lobes are bound inferiorly and laterally by the central sulcus and posteriorly by the coronal section in which the decussation of the posterior commissure can be visualized. In more anterior brain regions (defined anterior to the coronal section containing the decussation of the posterior commissure) the lateral sulcus is the boundary between temporal and parietal lobes. The posterior temporal and parietal lobes were defined using stereotaxic rules (Jernigan et al. 2001). Finally, the occipital lobe was designated in all sections posterior to the splenium of the corpus callosum with the superior boundary as the calcarine sulcus more anteriorly and the parietooccipital fissure more posteriorly.

In addition to the lobar white matter and CSF measures, volumes of white matter and ventricular CSF in the deep subcortical zone were measured separately. The subcortical gray-matter structures include the caudate and lenticular nuclei, the thalamus, the nucleus accumbens, and a region referred to as the basomesial diencephalon (BMD) which includes septal nuclei, mammillary bodies and other hypothalamic structures, the bed nucleus of the stria terminalis, and the diagonal band of Broca. Interrater reliabilities for all measured gray matter regions can be seen in Table II. Detailed descriptions of the standard rules for defining each structure are reported in the work of Jernigan and colleagues (2001). Examples of fully processed images can be seen in Figure 2.

Table II: Interrater reliabilities for cortical and subcortical gray-matter regions

Region	*Pearson's r*
Cortical	
Frontal cortex	0.99
Cingulate cortex	0.97
Parietal cortex	0.97
Occipital cortex	0.92
Insular cortex	0.94
Lateral temporal cortex	0.99
Mesial temporal cortex	0.95
Subcortical	
Ventricles	0.99
Caudate nucleus	0.99
Lenticular nucleus	0.97
Thalamus	0.95
Basomesial diencephalon	0.98
Nucleus accumbens	0.98

STATISTICAL ANALYSIS

The effects of age on total supratentorial cranial volume, and total cerebellar volume were first assessed using Spearman's correlation coefficients and the effects of sex on these measures were assessed with the Mann–Whitney *U* (MWU) tests using the computer programme Systat 6.0 (SPSS). The effects of total supratentorial brain volume (i.e. volume including gray matter, white matter, and CSF and henceforth referred to as total brain volume), age, and sex were assessed for: (1) regional total lobar volume measures (i.e. volume including gray matter, white matter, and CSF); (2) regional lobar and mesial cortical gray matter volume; (3) regional lobar white matter volumes; (4) regional lobar and mesial cortical CSF measures; and (5) subcortical gray and CSF structures. To assess the effects of age on these measures that were not attributable to overall growth or variance in total

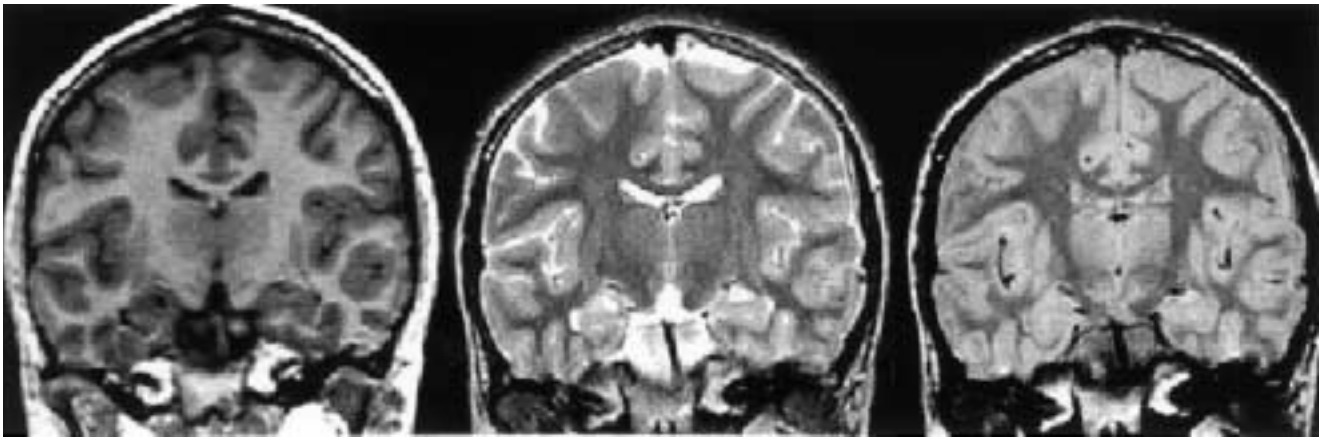

Figure 1: *Representative images from standard fast spin-echo and 3D protocols. Left: 3D gradient-echo (SPGR) T_1-weighted series with TR=24 ms, TE=5 ms, NEX=2, flip angle=45°; Middle: spatially registered FSE coronal section TR=3800 ms, TE=102 ms, ET=8; Right: coronal section, TR=3000 ms, TE=17 ms, ET=4.*

brain volume, proportional measures were also assessed (i.e. where each measure was entered as a proportion of total brain volume) with Spearman's correlation coefficients. The Spearman's correlation coefficient was chosen because it is sensitive to the effects of leverage and outliers which can occur with these volumetric data as well as to any monotone (not just linear) association between variables. Per cent change in total brain, total cerebellum, total gray matter, total white matter, and total CSF volumes was estimated by averaging the youngest (average volume of the seven 7-, 8-, and 9-year-olds) and the oldest (average volume of the eight 14-, 15-, and 16-year-olds) participants.

While some regions may have appeared to change with age in these statistical analyses and others did not, without a direct assessment of the difference in the rate of change in any given set of structures, regional differences could not be strongly inferred. Thus, additional analyses were performed where ratios of all possible pairings of two volumes within each data set (i.e. regional total lobar volume data set, cortical gray matter data set, white matter data set, CSF data set,

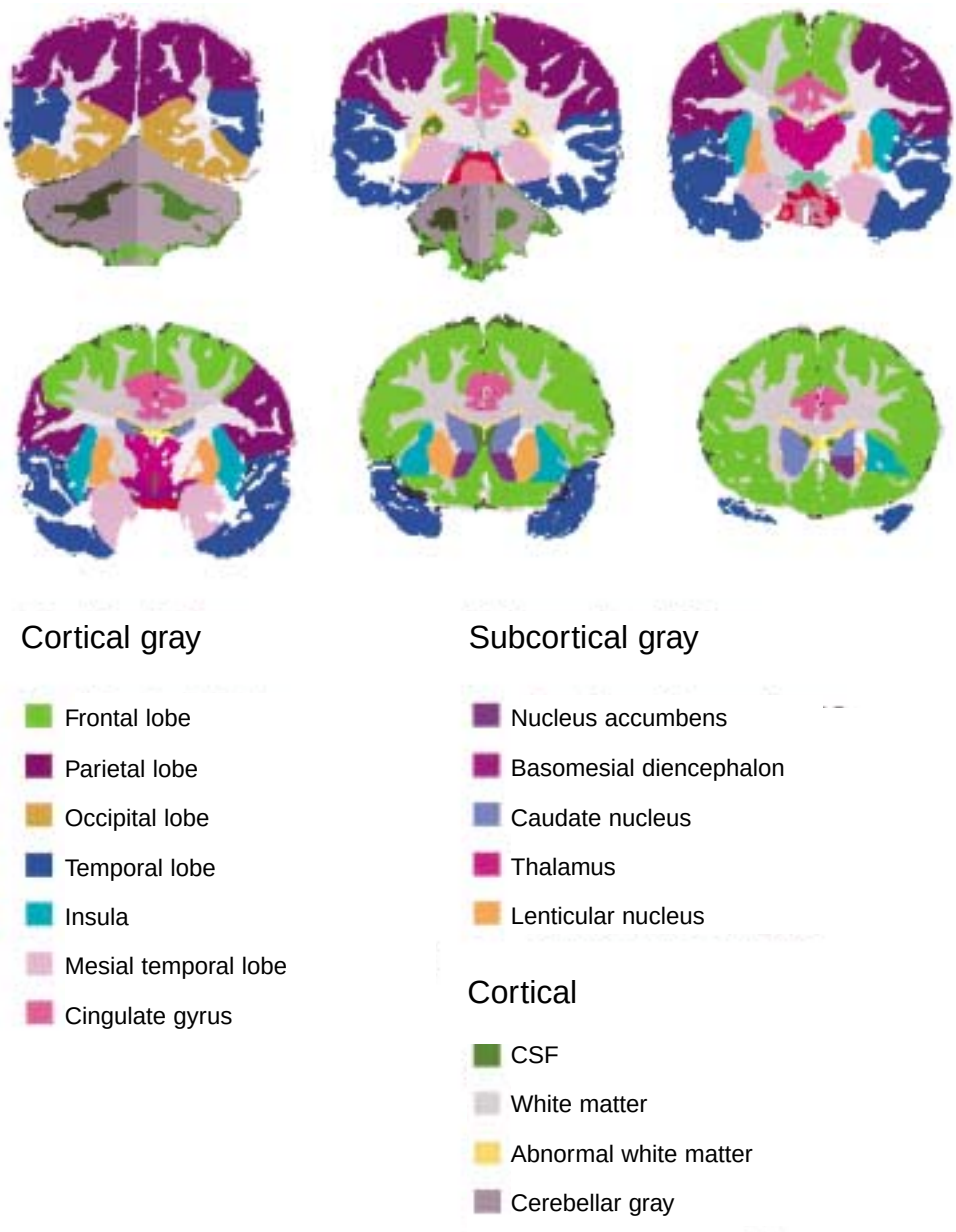

Figure 2: *Fully processed images from one 8-year-old female participant. Note that six, of the approximately 42, 4 mm resliced sections were chosen for presentation here. Color codings for each cortical gray-matter region are as follows: frontal cortex is green (with the cingulate region in pink), lateral temporal cortex is royal blue, parietal cortex is magenta, occipital cortex is mustard yellow, and mesial temporal cortex is light pink. White matter for each lobe can be seen in shades of gray, and the cortical CSF can be seen as the darkest colors around the edges of the brain. Ventricular CSF is seen in dark green. Subcortical structures include the caudate, periwinkle blue; thalamus, magenta; basomesial diencephalon, purple; lenticular nucleus, mustard yellow; and more anteriorly the nucleus accumbens, purple.*

subcortical data set) were assessed for correlations with age. A large Spearman's correlation coefficient indicates that one of the two volumes changed more rapidly than the other over the age range studied. These volume ratios are independent of whether or not one uses the proportional or raw volumes because, within a single participant the proportional constant (i.e. supratentorial cranial volume) is the same for both volumes. Thus the structure pair ratios were assessed for age effects only for the raw volumes within each data set.

Results

REGIONAL TOTAL CEREBELLUM AND LOBAR VOLUME

The analyses shown in Table III indicate that there is an age-related total brain volume increase within the age range studied here (Spearman's $r=0.317$, $p<0.05$) with the total volume of the older participants' brains being approximately 9.5% larger than the average of the younger participants' brains. A similar increase in volume was observed in the cerebellum (10% increase, Spearman's $r=0.347$, $p<0.05$), and the age effects for the ratio of cerebellar to total brain volume were not significant. This suggests that the supratentorial and infratentorial cranial vaults grow at comparable rates. Not surprisingly, regional total lobar volume measures are highly correlated with total brain volume. Only the subcortical region continues to grow in this age range above and beyond total brain growth as seen in the proportional measures ($r=0.537$, $p<0.01$), though the age effects for parietal- and occipital-lobe volumes are at trend level significance (i.e. $p<0.10$). The age effect for the ratio of subcortical volume to frontal lobe volume was significant ($r=0.487$, $p<0.01$) and the ratio of subcortical volume to temporal lobe volume was at trend level significance ($r=0.291$, $p<0.10$).

Also shown in Table III, male brain volumes tend to be larger than female brain volumes (MWU, $p<0.05$) by approximately 7%. The same pattern was observed in the cerebellum where the males had approximately 7% larger volume than the females (MWU=212, $p<0.05$). Regionally, only the frontal and parietal lobes and the subcortical region differ between males and females, but once the overall larger brain volume in the males is controlled with the proportional measures, sex effects in these regions are no longer present. Notably, however, girls have larger temporal lobes than boys (MWU=86, $p<0.05$) once the overall 7% male-larger brain volume difference is controlled with the proportional measure.

CORTICAL GRAY MATTER

The correlation between gray-matter volume and total brain volume is high in all regions measured (Table IV). For example the correlation between frontal lobe gray matter and total brain volume is 0.752 ($p<0.001$). Much of this association is due to individual differences in head size and shape. Thus, proportional gray-matter measures were used in some analyses so that age-related differences in relative gray-matter volume could be isolated from variability in gray-matter volume associated with individual differences in total brain volume. Table IV shows the results for assessment of age and sex effects on the raw and proportional cortical gray-matter volumes. The effects of age on the total gray matter and regional gray-matter raw volumes were not significant, but once total brain volume was controlled, a regional pattern of age-related proportional gray-matter relative volume loss was observed. Total proportional or relative gray-matter volume declines significantly in this age range ($r=-0.549$, $p<0.01$), with an approximately 9% decrease between the oldest and youngest participants. Regionally, robust relative gray-matter volume loss is observed in the frontal ($r=-0.581$, $p<0.001$) and mesial temporal lobes ($r=-0.507$, $p<0.01$) during this age range with less robust, but trend level significant proportional losses observed in the parietal ($r=-0.318$, $p<0.10$) cortices as well. The age correlations with ratio measures for cingulate/frontal and cingulate/mesial temporal gray-matter structure pairings were significant ($r=0.354$, $p<0.05$ and $r=0.395$, $p<0.05$ respectively). This suggests that the rate of change in cinguate cortex is different from (slower than) that in frontal and mesial temporal cortices. Graphical displays of the significant effects of age on relative measures of frontal, parietal, and mesial temporal gray matter can be observed in Figure 3.

Sex effects are not significant for any of the raw cortical gray-matter volumes. However, once the effects of brain size are controlled, females have more gray matter in the mesial temporal cortices than the males (MWU=80, $p<0.05$), and they tend to have more lateral temporal cortical gray matter as well.

CEREBRAL WHITE MATTER

Like the gray-matter measures, the cerebral white-matter volumes for each region were all highly correlated with total brain volume (Table V). Age-related increases were significant

Table III: Effects of total brain volume, age, and sex on lobar volume

Brain region	*Effect of brain volume* Spearman's r	*Effect of age* Spearman's r	*Effect of age on proportion* Spearman's r	*Effect of sex* MWU	*Effect of sex on proportion* MWU
Total brain volume	NA	0.317[b]	NA	224[b]	NA
Total cerebellar volume	NA	0.347[b]	NA	212[b]	NA
Total frontal volume	0.905[d]	0.186	–0.251	219[b]	163
Total parietal volume	0.842[d]	0.393[a]	0.060	229[c]	170
Total temporal volume	0.796[d]	0.162	–0.006	167	(0.366)[b]
Total occipital volume	0.669[d]	0.298[a]	0.056	203[a]	155
Subcortical volume	0.695[d]	0.537[c]	0.416[b]	218[b]	159

[a] $p<0.10$, [b] $p<0.05$, [c] $p<0.01$, [d] $p<0.001$.

MWU, Mann–Whitney *U* test; NA, not applicable. Note: female larger than male pattern sex differences are shown in parentheses.

for white matter overall (r=0.438, p<0.05), and in frontal, parietal, and occipital lobar regions, but not in the temporal lobes. There was an approximately 20% increase in raw white-matter volume between the youngest and the oldest participants. Once brain size was controlled, frontal, parietal, and occipital lobes still had significant age-related increases in white matter, and temporal-lobe white matter did not change above and beyond overall brain growth in this age range. White-matter structure paired ratios were at trend level significance for frontal versus occipital white matter (r=–0.336, p<0.10) and significant age affects for temporal versus occipital white matter (r=–0.385, p<0.05) were

Table IV: Effects of total brain volume, age, and sex on cortical gray matter

Cortical gray matter region	*Effect of brain volume Spearman's r*	*Effect of age Spearman's r*	*Effect of age on proportion Spearman's r*	*Effect of sex MWU*	*Effect of sex on proportion MWU*
Total gray matter	0.828[d]	0.072	–0.549[c]	193	(110)
Frontal lobe (excluding cingulate)	0.752[d]	–0.017	–0.581[d]	199	(129)
Cingulate	0.520[c]	0.217	–0.037	(149)	(114)
Parietal lobe	0.583[d]	0.035	–0.318[a]	200[a]	(133)
Insula	0.518[c]	0.031	–0.221	(139)	(104)
Lateral temporal lobe	0.739[d]	0.111	–0.195	156	(93)[a]
Mesial temporal lobe	0.552[c]	–0.083	–0.507[c]	(168)	(80)[b]
Occipital lobe	0.606[d]	0.042	–0.162	185	(144)

[a] p<0.10, [b] p<0.05, [c] p<0.01, [d] p<0.001.

MWU, Mann–Whitney U test. Note: female larger than male pattern sex differences are shown in parentheses.

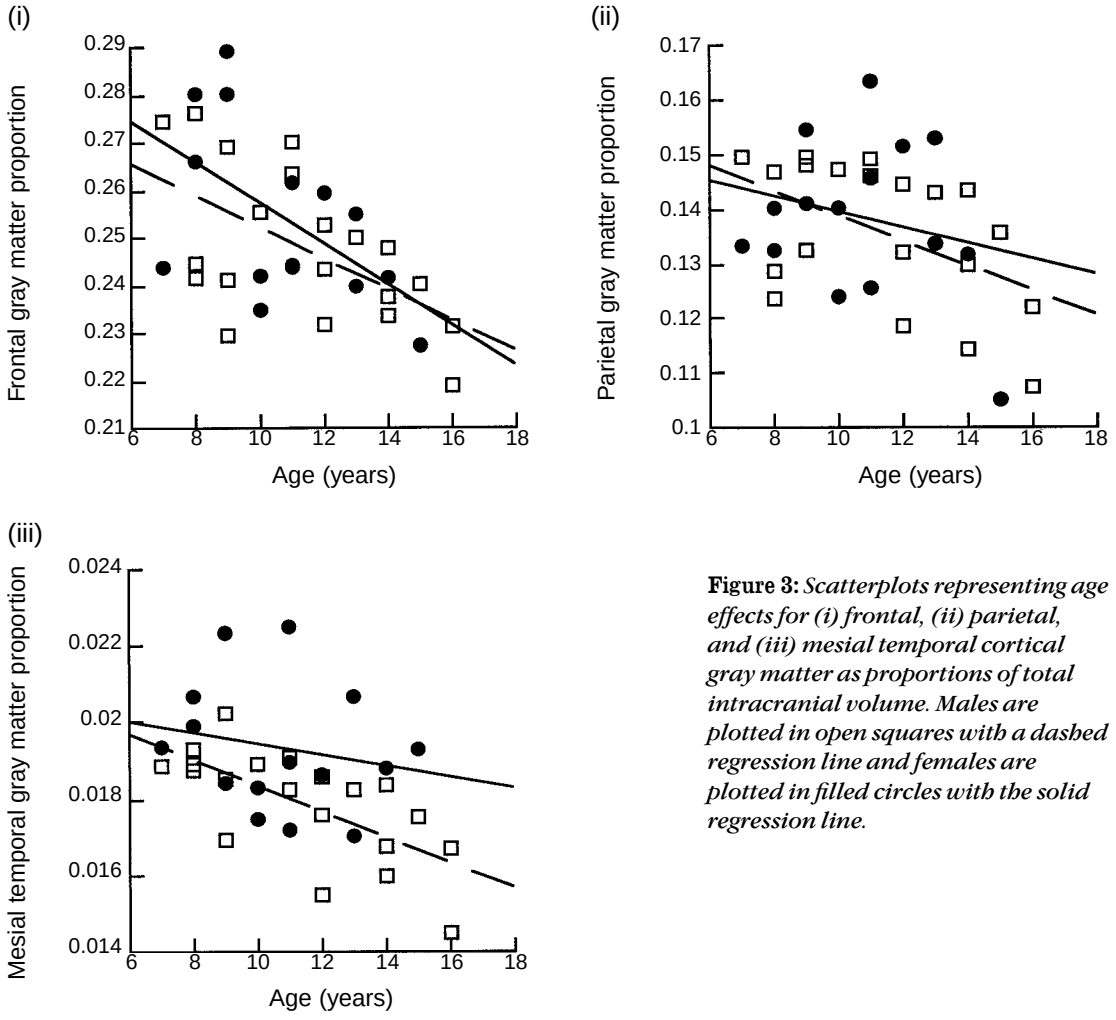

Figure 3: *Scatterplots representing age effects for (i) frontal, (ii) parietal, and (iii) mesial temporal cortical gray matter as proportions of total intracranial volume. Males are plotted in open squares with a dashed regression line and females are plotted in filled circles with the solid regression line.*

observed. These results suggest that the rate of decline in white-matter volume within the occipital lobe is greater than that of the temporal lobes and the rate of change in the frontal lobes is greater than that in the occipital lobes. Figure 4a is a set of graphical displays of the significant effects of age on the raw frontal, parietal, and occipital white-matter volumes and Figure 4b shows the significant proportional measures for the same structures. Once the effects of brain size were controlled, sex effects were not significant for any of the cortical white-matter measures. Tissue segmented image volumes from one representative 7 year old and one representative 15-year-old participant are shown in Figure 5. Volume differences between the 7 year old and the 15 year old shown in Figure 5 tend to be representative of average differences between children and adolescents where the largest volume difference is in white

Table V: Effects of total brain volume, age, and gender on cortical white matter

Cortical white matter region	*Effect of brain volume Spearman's r*	*Effect of age Spearman's r*	*Effect of age on proportion Spearman's r*	*Effect of sex MWU*	*Effect of sex on proportion MWU*
Total white matter	0.573[d]	0.438[b]	0.410[b]	201[a]	171
Frontal lobe	0.573[d]	0.347[b]	0.293[a]	205[a]	175
Parietal lobe	0.624[d]	0.535[c]	0.452[c]	212[b]	184
Temporal lobe	0.437[d]	0.275	0.216	166	(145)
Occipital lobe	0.470[c]	0.463[c]	0.417[b]	201[a]	175

[a] $p<0.10$, [b] $p<0.05$, [c] $p<0.01$, [d] $p<0.001$.
MWU, Mann–Whitney *U* test. Note: female larger than male pattern sex differences are shown in parentheses.

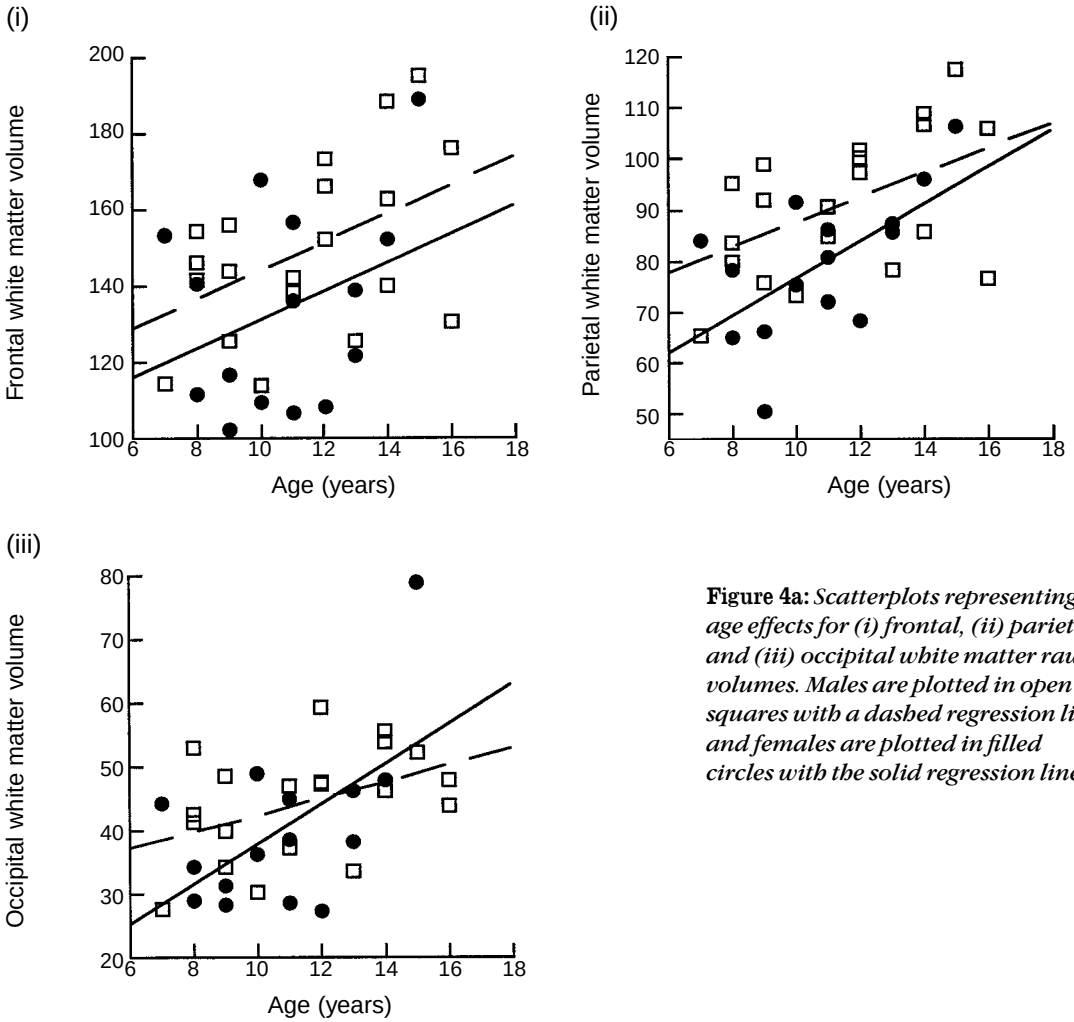

Figure 4a: *Scatterplots representing age effects for (i) frontal, (ii) parietal, and (iii) occipital white matter raw volumes. Males are plotted in open squares with a dashed regression line and females are plotted in filled circles with the solid regression line.*

matter (19%) with a relatively small difference in total gray-matter volume (8%).

Notably, the age effect for the ratio of total gray-matter volume to total white-matter volume is significant (r=–0.457, p<0.01) indicating that the white-matter increase in this age range is significantly greater than any change in gray matter.

CORTICAL FLUID

As shown in Table VI, total CSF volume is correlated at trend level significance with total brain volume (r=0.317, p<0.10), though no single regional cortical CSF measure is. Age effects are significant for an increase in total raw CSF volume over this age range (r=0.418, p<0.05), and the older participants have

Table VI: Effects of total brain volume, age, and sex on cortical CSF

Cortical CSF region	*Effect of brain volume Spearman's r*	*Effect of age Spearman's r*	*Effect of age on proportion Spearman's r*	*Effect of sex MWU*	*Effect of sex on proportion MWU*
Total CSF	0.317[a]	0.418[b]	0.316[a]	200	185
Frontal lobe (excluding cingulate)	0.250	0.337[b]	0.247	194	184
Cingulate	0.066	0.227	0.168	186	177
Parietal lobe	0.248	0.327[a]	0.306[a]	203[a]	198
Insula	–0.047	0.385[b]	0.318[a]	160	150
Lateral temporal lobe	0.180	0.385[b]	0.295[a]	169	157
Mesial temporal lobe	–0.162	0.103	0.025	(134)	(120)
Occipital lobe	0.058	0.309[a]	0.260	193	189

[a] p<0.10, [b] p<0.05, [c] p<0.01, [d] p<0.001.

MWU, Mann–Whitney U test. Note: female larger than male pattern sex differences are shown in parentheses.

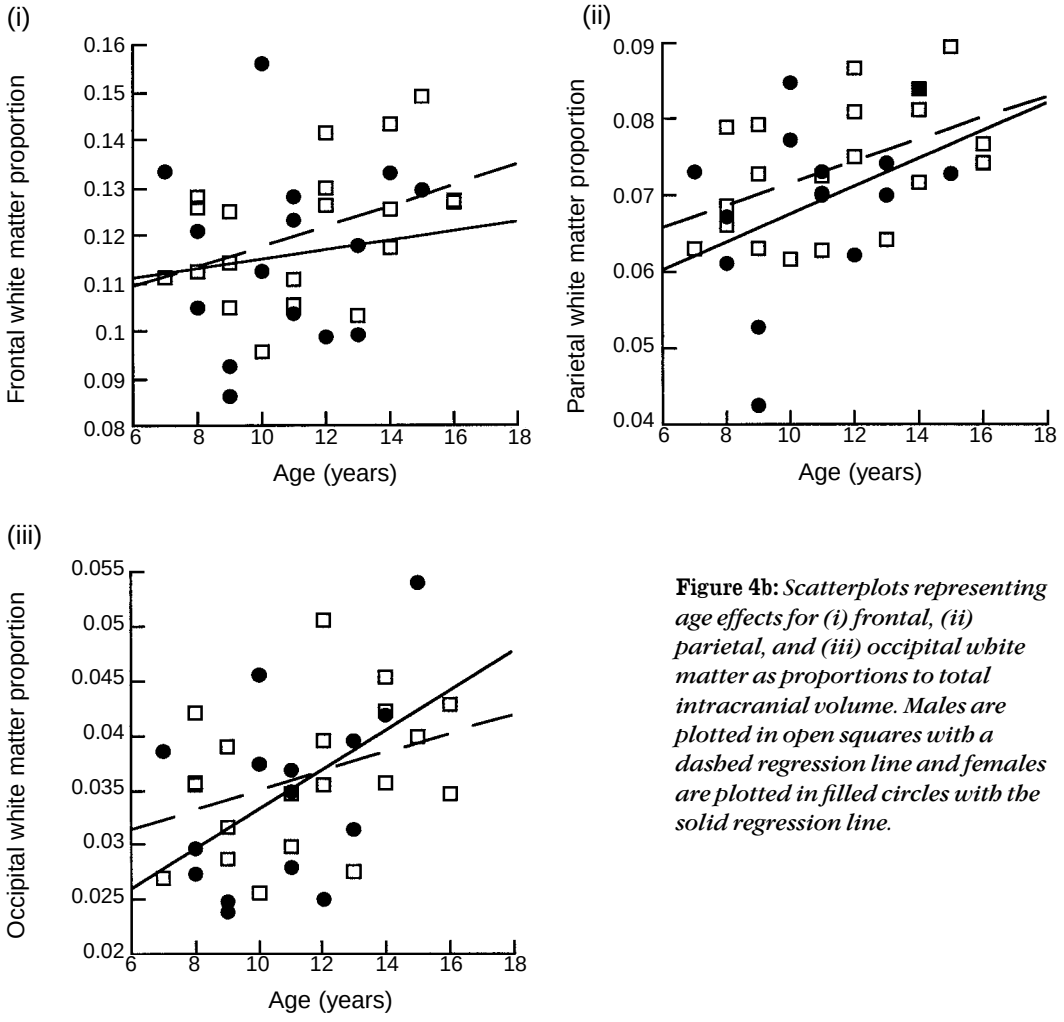

Figure 4b: *Scatterplots representing age effects for (i) frontal, (ii) parietal, and (iii) occipital white matter as proportions to total intracranial volume. Males are plotted in open squares with a dashed regression line and females are plotted in filled circles with the solid regression line.*

approximately 50% more CSF than the younger participants. Regionally, CSF age effects are greatest in frontal (r=0.337, p<0.05), insular (r=0.385, p<0.05), and lateral temporal cortices (r=0.385, p<0.05), and they are at trend level significance in the parietal lobes (r=0.327, p<0.10). Once the effects of brain size were controlled, age effects for CSF were found to be less robust, though still at trend level significance (r=0.316, p<0.10). The age-effect for the ratio of insular to mesial temporal CSF was significant, indicating a more rapid CSF increase in the insular cortex (r=0.474, p<0.01) over the 7 to 16 years age range studied. Sex differences were not significant for total or regional, raw, or proportional CSF measures.

SUBCORTICAL GRAY MATTER AND VENTRICULAR CSF

With the exception of the thalamus, all subcortical regions were significantly correlated with total brain volume. Similar to the cortical gray matter, none of the subcortical gray-matter structures changed significantly with age until the effects of total brain volume were controlled in the proportional measures. The proportional volumes of the thalamus and lenticular nuclei both decreased significantly with age (r=–0.438, p<0.05 and r=–0.364, p<0.05). Interestingly, sex effects were significant for the proportional measures of caudate (MWU=89, p<0.05), thalamus (MWU=71, p<0.01), and basomesial diencephalon (MWU=89, p<0.05) where the females actually had larger volumes in these regions than the males. Raw and proportional ventricular volumes increased significantly with age (r=0.348, p<0.05 and r=0.462, p<0.01 respectively). Ratio measures of the various subcortical gray-matter structures were not significant, suggesting a relatively uniform decrease in volume with increasing age. However, ratios of ventricular volume to the volumes of basomesial diencephalon (r=–0.412, p<0.05), lenticular nuclei (r=–0.464, p<0.01), thalamus (r=–0.487, p<0.01), and nucleus accumbens (r=–0.481, p<0.01) were all significant suggesting the increase in ventricular CSF is more rapid than the decline in the volumes of subcortical gray matter structures. Figure 6a

Table VII: Effects of total brain volume, age, and sex on subcortical structures

Subcortical gray matter/ CSF region	*Effect of brain volume Spearman's r*	*Effect of age Spearman's r*	*Effect of age on proportion Spearman's r*	*Effect of sex MWU*	*Effect of sex on proportion MWU*
Caudate	0.428[b]	0.005	–0.307[a]	152	(89)[b]
Thalamus	0.222	–0.192	–0.438[b]	(122)	(71)[c]
Basomesial diencephalon	0.376[b]	0.052	–0.189	(143)	(89)[b]
Nucleus accumbens	0.417[b]	0.076	–0.047	184	163
Lenticular nuclei	0.417[b]	–0.054	–0.364[b]	205[a]	(141)
Lateral ventricles	0.348[b]	0.462[c]	0.443[c]	195	186

[a] p<0.10, [b] p<0.05, [c] p<0.01, [d] p<0.001.
MWU, Mann–Whitney U test. Note: female larger than male pattern sex differences are shown in parentheses.

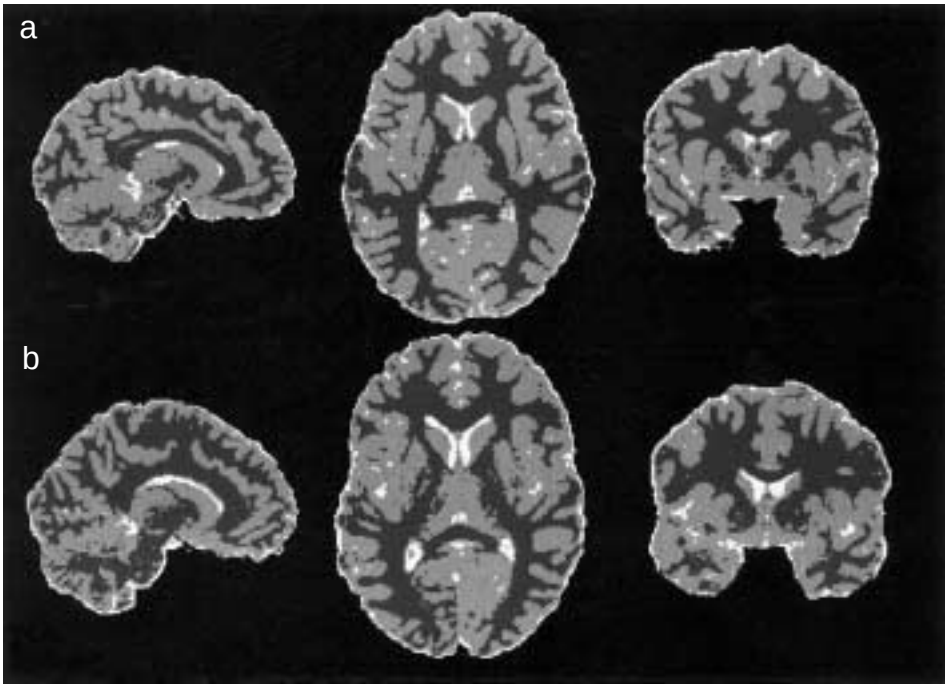

Figure 5: *Representative spatially registered, tissue segmented images from one (a) 7-year-old individual and one (b) 15-year-old individual. All voxels that segmented as gray matter are shown in light gray, and white-matter voxels are shown in dark gray. CSF is shown in white. Note the 15-year-old's brain is 12% larger than the 7 year old's brain. The older participant has 19% more white matter and only 8% more gray matter, despite the overall volume difference.*

contains graphical displays of the significant age effects on brain size corrected caudate, thalamic, and lenticular gray-matter measures and Figure 6b contains scatterplots of significant age effects on raw and proportional ventricular volumes.

Estimated mean volumes in mL for the cortical gray-matter, white-matter, and CSF volumes can be seen in Table VIII, and similar estimated mean volumes for subcortical measures can be seen in Table IX. Note that the raw volume estimates in Table IX apply to participants across the whole age range for structures that do not show significant age effects. Volume estimates for different ages in structures that do change with age can be obtained from the scatter plots of raw volumes (Figs 4a, 6b).

Discussion

This study describes regional brain structural changes associated with late childhood development in greater anatomical detail than has been provided in previous volumetric studies. The findings are generally consistent with earlier reports of relative volume reductions in gray matter and volume increases in white matter between childhood and adolescence. We also found evidence for subtle increases in brain volume, with a 9.5% difference between the youngest and oldest participants studied here. This finding is consistent with some studies in the literature (Jernigan et al. 1991, Pfefferbaum et al. 1996), but not with others (Reiss et al. 1996). The cerebellum shows a comparable volume increase over the age range studied. For the first time, we report that the changes in cerebral gray-matter volume across this age range are actually significantly less rapid than changes in cerebral white matter. Perhaps increased myelination plays a more prominent role in the dynamic changes in tissue observed between childhood and adolescence than other cellular events, such as synaptic pruning, which would presumably result in a more prominent or rapid reduction in gray matter. The brain structural changes we observe are most likely maturational in nature, though we cannot rule out that individual differences in environmental influences may also affect changes in brain structure (i.e. nutritional factors, environmental enrichment, educational changes) in this cross-sectional sample.

The continued brain growth that occurs between childhood and adolescence is relatively subtle when compared with the dynamic changes that occur in the gray- and white-matter tissues within it during the same age range. Our results show that the growth during this age range is probably carried, to a large extent, by the robust increase in white

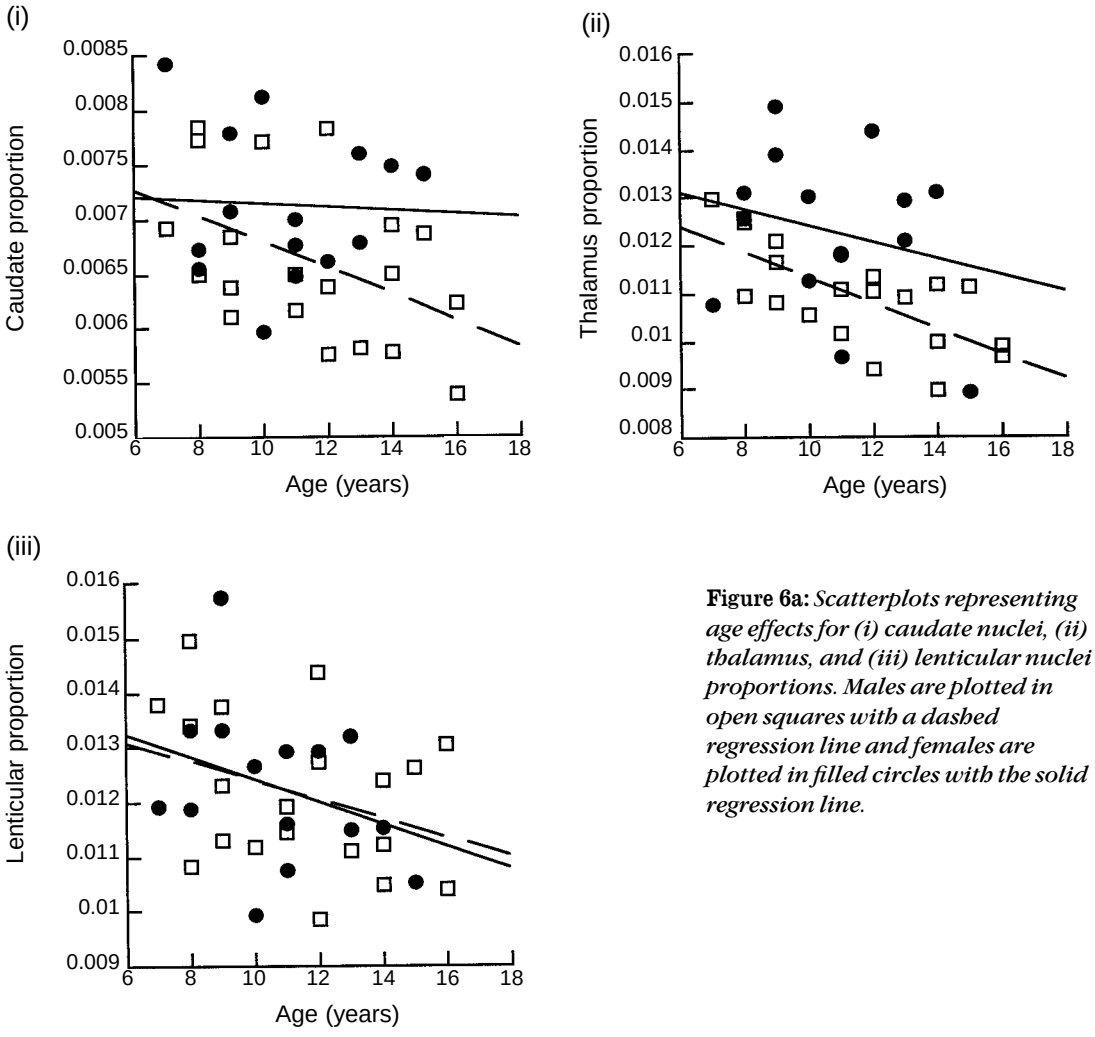

Figure 6a: *Scatterplots representing age effects for (i) caudate nuclei, (ii) thalamus, and (iii) lenticular nuclei proportions. Males are plotted in open squares with a dashed regression line and females are plotted in filled circles with the solid regression line.*

matter, given that the sum increase in white matter is larger than the sum increase in total brain volume. Concurrent relative decreases in other brain tissues (i.e. gray matter) offset, to some extent, the increases in white matter, and this limits the overall increase in cranial size. Notably, the decreases in gray matter can only be observed between childhood and adolescence once the effects of brain size increase have been controlled for. An increase in total CSF is also observed here such that the older participants have approximately 100% more CSF than the younger participants. CSF comprises approximately 2% of total intracranial supratentorial volume in the 7 to 9 year old participants, and approximately 4% of the total intracranial supratentorial volume in the 14 to 16 year old participants. Thus, while the percentage change in CSF between childhood and adolescence seems somewhat high (100% increase), the actual volume change is quite small relative to gray- and white-matter changes (9% and 20% respectively).

Evidence was found for regional variability in the progressive and regressive events that occur in brain development, which would be expected given postmortem human studies (e.g. Yakovlev and Lecours 1967). Age effects were significant for relative or raw volume changes in gray matter, white matter, and CSF only in the frontal and parietal lobes, which provides some evidence for regional specificity with more dynamic changes in these regions in the 7 to 16 year age range. Relative gray matter for mesial temporal lobes also significantly decreased, and the occipital lobes showed significant increases in raw white-matter volume. Overall, the temporal lobes appeared to change the least with significant changes only in the CSF, but not in gray or white matter, which comprise much larger percentages of total brain volume. This is consistent with VBM analyses in the same participants where gray-matter density decreases (and probably white-matter density increases) were most prominent in dorsal frontal and parietal lobes, and least prominent in the more ventral cortices of the temporal lobes (Sowell et al. 1999a). These results are also consistent with earlier volumetric studies (Jernigan et al. 1991, Giedd et al. 1999).

Other evidence for regional specificity comes from the assessment of age effects on the paired ratios of cortical gray matter, cortical white matter, and cortical CSF regions. The ratio of frontal to cingulate cortices was significant for age effects, as was the measure of mesial temporal to cingulate cortices. Similarly, for cortical white-matter regions, the age effects for the ratios of frontal to occipital, and temporal to occipital white matter were significant. Taken together, these results indicate statistical evidence for differences in the rate of change with age between various cortical regions. The gray matter in frontal and mesial temporal lobes changes more rapidly than in the cingulate. The white matter in the frontal lobes changes more rapidly than the white matter in the occipital lobes, which changes more rapidly than the white matter in the temporal lobes. Again, only the frontal and parietal lobes show evidence for change in gray matter, white matter, and CSF measures.

Caudate, thalamus, and lenticular nuclei also showed evidence for age-related proportional volume reduction, although the age effects for paired subcortical structure ratios were not significant. This may suggest a lack of regional specificity of volume reductions in subcortical structures observed in this age range.

Sex differences were observed in total cranial volume, where the boys' brains were approximately 7% larger than the girls'. Once the cranial size difference between males and females was accounted for, only the gray matter in the temporal lobes showed evidence for sex differences (significant mesial temporal-lobe sex effects and trend level significant lateral temporal-lobe effects) where the females actually had larger volumes in these regions than the males. This effect is not consistent with an earlier report where no sex differences were observed in temporal lobes once brain size differences were controlled for (Giedd et al. 1996). However, in the earlier report, tissue segmentation was not used and our results show sex differences only for the segmented gray matter, and not for white matter. The differences in gray and white matter may have counterbalanced each other in the earlier report. Significant sex effects were also observed in subcortical regions where females had larger thalami, larger caudate nuclei, and larger basomesial diencephalic regions once cranial size differences were controlled for. Larger caudate nuclei

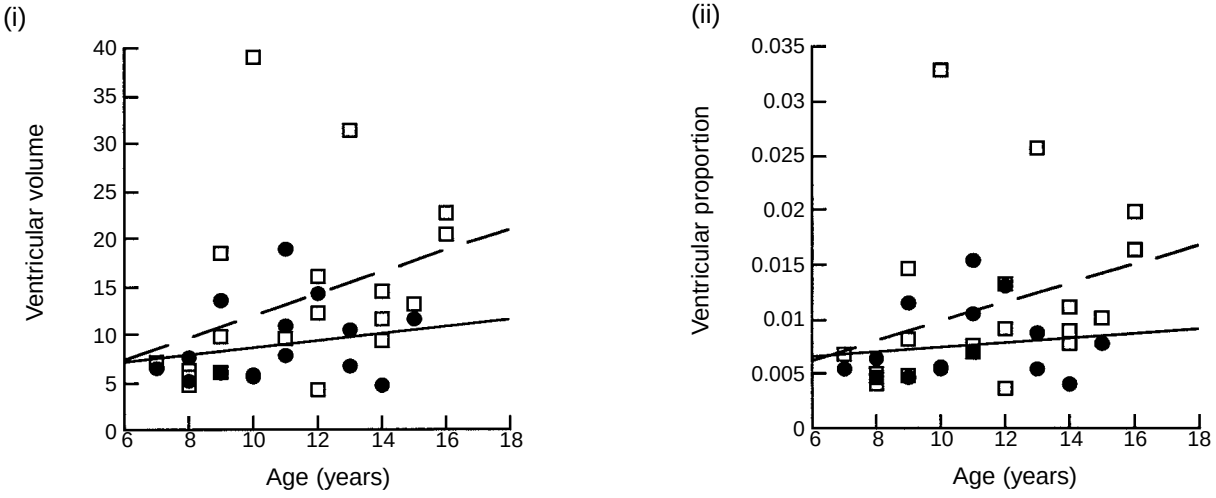

Figure 6b: *Scatterplots representing age effects for (i) ventricular raw and (ii) proportional volumes. Males are plotted in open squares with a dashed regression line and females are plotted in filled circles with the solid regression line.*

in girls than in boys has also been reported by another research group (Giedd et al. 1997). Unfortunately, our examination of sex effects suffers from a lack of statistical power when males and females are analyzed separately, thus all analyses for age effects included all participants, male and female. Observation of sex differences may also be confounded given that the males may have been somewhat overrepresented in the upper end of our age range (and volumes decrease with age such that older participants have smaller gray-matter volumes), which could account for the larger subcortical gray-matter volumes in females. Nonetheless, our results are consistent with at least one other report, attesting to their validity (Giedd et al. 1997).

Previous studies have reported volume increases in mesial temporal lobe gray-matter structures between 8 and 35 years of age (Giedd et al. 1996b, Sowell and Jernigan 1998). This was not the case in the current study, in which a volume reduction in mesial temporal-lobe structures was observed. In order to further assess this apparent discrepancy, analyses were conducted using data from the previously published report (Sowell and Jernigan 1998) which contained a completely different sample of participants than those studied for the current report. Correlational analyses were conducted for the 31 participants in the earlier study who were under the age of 17 years and age effects for the proportional mesial temporal lobe gray-matter volume measure were not significant in the younger sample ($r=0.172, p=0.35$). The fact that volume reduction in mesial temporal-lobe gray matter is observed between 7 and 16 years in this study, and significant volume increases were observed in a different sample which extended to participants in the young adulthood age range, suggests that age-related changes in this structure may be non-linear, with proportional volume decreases occurring between childhood and adolescence followed by volume increases much later and only after puberty.

Table VIII: Estimated mean gray-matter, white-matter, and CSF volumes in mL for cortical regions. Note that white matter was not measured for all areas

Cortical brain region	*Mean (SD) gray-matter volume*	*Mean (SD) white-matter volume*	*Mean (SD) CSF volume*
Frontal	237.5 (34.4)	142.9 (25.0)	12.9 (7.3)
Cingulate	28.4 (4.2)	–	0.4 (0.3)
Parietal	163.7 (18.9)	86.0 (14.9)	5.2 (3.4)
Insular	18.1 (2.1)	–	0.4 (0.4)
Lateral temporal	126.8 (16.9)	58.9 (14.1)	2.8 (1.7)
Mesial temporal	22.2 (2.5)	–	0.8 (0.3)
Occipital	112.7 (16.5)	42.8 (10.8)	1.4 (1.2)

Table IX: Estimated mean (SD) volumes in mL for subcortical regions

Subcortical brain region	*Estimated volume*
Ventricles (CSF)	11.6 (7.7)
Caudate nucleus (Gray)	8.2 (1.0)
Lenticular nucleus (Gray)	14.6 (1.7)
Thalamus (Gray)	13.7 (1.6)
Basomesial diencephalon (Gray)	5.0 (0.7)
Nucleus accumbens (Gray)	2.9 (0.5)

The results reported here are largely complementary to results reported in an earlier VBM study (Sowell et al. 1999a) given that frontal and parietal cortex seem to change the most dramatically regardless of which method is used. While the VBM analyses allowed a more detailed spatial assessment of brain changes without the time and labor intensiveness of defining regions of interest, it was unclear from the VBM results whether maturational changes were due more to changes in gray matter, or to changes in white matter. Volumetrics, on the other hand, can show with certainty which tissue type is most affected by the maturational processes we measure with MRI and tissue segmentation; the results from the present study have shown that white-matter changes are probably more responsible for the brain maturational changes observed in the earlier VBM report (Sowell et al. 1999a). The volumetric analyses conducted here also allowed assessment of regional differences which were unbiased by potential problems that occur in the spatial normalization used in the VBM analyses (given that all volumetric analyses were conducted in native image space). Thus, in combination VBM and volumetric analyses have revealed more about brain development than either would have alone and the two different methods of image analysis have shown us a similar pattern of brain maturation during childhood and adolescence.

Overall, the results from this study provide further evidence that dynamic brain changes can be observed *in vivo* during childhood and adolescence. We would expect structural changes in the brain to relate to improved cognitive abilities during this age range. This is particularly the case if our observations are related to increased myelination because increased myelination is related to improved conductivity between different brain regions. Owing to the fact that we observe most prominent changes (perhaps due to increased myelination with maturation) in frontal and parietal cortices during the age range studied, we might expect improvement on cognitive tasks subserved by these brain regions. This has been shown in one recent study where improvement on a task of verbal learning and organization was found to be related to maturation specifically in the frontal lobes (Sowell et al. 2001). Similar relations between cingulate cortex and tasks of attention have been observed (Casey et al. 1997) providing further evidence that the structural changes observed are related to improved cognitive abilities.

Studies of normal brain maturation in the late childhood and adolescent age range are relatively few in number when compared with the large number of brain morphological studies of disease states in childhood. The interpretation of numerous studies of brain development in children with severe neuropsychiatric disorders (e.g. fetal alcohol syndrome, Tourette syndrome, Williams syndrome) has been considerably limited by the paucity of *in vivo* normative data in the later childhood and adolescent age range. Additionally, anomalies of brain structure have been noted in many neuroimaging studies of psychiatric disorders (e.g. schizophrenia) that are increasingly understood as neurodevelopmental disorders. A better understanding of normal neurodevelopment could help elucidate the pathogenesis of disorders such as schizophrenia, in which aberrant brain development is thought to occur before the onset of psychotic symptomatology (Weinberger 1995).

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