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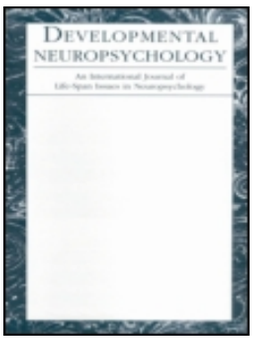

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Further MRI Evidence of Late Brain Maturation: Limbic Volume Increases and Changing Asymmetries During Childhood and Adolescence

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In this article, we extend earlier findings of age-related changes in brain morphology on magnetic resonance images to include measurements of the mesial temporal lobe as well as asymmetry measures in regional cortical and subcortical structures. The earlier sample was increased to include 57 children and young adults aged 8 to 35 years. The participants were studied using quantitative image analytic techniques. Estimated volumes of limbic and anterior diencephalic structures increased significantly with age; although inferior lateral cortex, superior cortex, caudate nuclei, thalamus, and lenticular nuclei all decreased significantly with age. Of the 7 regions measured, only the lenticular nucleus and anterior diencephalon showed significant changes in asymmetry with increasing age. It is hypothesized that some of these changes may be related to the changing levels of gonadal steroid hormones known to occur during this age range. They may also have important implications for the study of late developing higher cognitive functions and the loss of behavioral plasticity.

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Normal neurodevelopment between conception and maturity is characterized by both progressive (neuronal proliferation, cell migration, myelination) and regressive (cell death, axonal, and synaptic pruning) processes. Perhaps the most dramatic changes in brain morphology take place during the perinatal and infancy period and a number of magnetic resonance imaging (MRI) studies have described changes during this stage of neurodevelopment (Barkovich, Kjos, Jackson, & Norman, 1988; Holland, Haas, Norman, Brant-Zawadzki, & Newton, 1986; Martin, et al., 1988). Fewer MRI studies have focused on the subtler changes that occur in childhood and adolescence even though postmortem studies (i.e., Benes, Turtle, Khan, & Farol, 1994; Huttenlocher, 1979; Purves & Lichtman, 1980; Yakovlev & Lecours, 1967) suggest that maturational changes occur in many brain regions during this period.

Studies of cognitive development, much like studies of neurodevelopment, have largely focused on the infancy and early childhood ages with much less research devoted to normal development in the peripubertal age range. This is probably because the most dramatic changes in cognitive functioning occur earlier in life. For example, the emergence of previously nonexistent abilities (e.g., language) can be studied in infancy, whereas in studies of older children, perhaps only the somewhat less dramatic fine tuning of higher cognitive functioning can be observed. However, reports of relatively late brain maturation observed in vivo should help to establish the feasibility of studying the subtle changes in brain behavior relations that occur in the transitional stage of adolescence.

In a previous report, Jernigan, Trauner, Hesselink, and Tallal (1991) observed what appeared to be cortical thinning with increasing age in the dorsal frontal and parietal cortices in a group of 39 children and young adults. They also observed age-related reductions in the estimated volumes of caudate, lenticular, and thalamic nuclei. These changes were consistent with late regressive processes occurring in widespread cortical and subcortical structures, but such processes did not appear to be occurring simultaneously in the ventral cortical regions examined. In contrast to these volume reductions, Jernigan, Trauner, et al. observed a subtle but significant age-related increase in the volume of the anterior diencephalic region (which includes hypothalamic and septal nuclei), which they hypothesized was related to increasing levels of gonadal steroid hormones. More recently, Giedd et al. (1996) reported findings of age-related increases in lateralized measures of hippocampal and amygdala volumes in a group of 99 children ages 4 to 18 years. Specifically, in the girls, they observed a significant increase in the volume of the right hippocampus, and in the boys, they found significant increases in the volume of the left amygdala. Similar to Jernigan, Trauner, et al., Giedd and his colleagues concluded that the volume increases are consistent with the distribution of sex hormone receptors for these structures.

In this study, we attempt to characterize temporal limbic brain maturation in normal participants between the ages of 8 and 35 years. The MRI data for all 57 participants were collected between 1987 and 1991. We subsequently developed a

method for isolating the structures on the mesial surface of the temporal lobe (MTL) from the rest of the ventral cortical region examined in the previous study (Jernigan, Trauner, et al., 1991). Also, asymmetry ratios have been computed for the seven cerebral grey matter regions examined, and the association of these ratios with age is reported. The full set of anatomical analyses is reported here for an extended sample of 57 participants ranging in age from 8 to 35 years.

METHODS

Participants

Fifty-seven normal children and young adults, including 29 males and 28 females, were examined (see Table 1 for sex by age breakdown). Participants 21 years of age and younger were recruited as normal controls for a large, multidisciplinary neurodevelopmental research center. Participants from 23 to 35 years of age partic-

TABLE 1
Age by Sex Breakdown

Age (Years)	*Males*	*Females*
8	3	1
9	5	2
10	1	4
11	1	0
12	1	1
13	0	4
14	1	3
15	1	2
16	1	0
17	2	0
18	0	1
19	0	1
21	0	1
23	0	1
24	1	0
25	0	1
26	2	0
27	2	0
28	1	2
29	0	1
30	1	0
32	1	2
33	2	1
34	1	0
35	2	0
Total	29	28

ipated as controls in neuropsychiatric studies. All participants were screened by medical and psychiatric interviews (of parents or of participants themselves) for evidence of significant disease, substance abuse, developmental intellectual abnormality, or psychiatric illness. All adult participants were living independently in the community and were employed. Informed consent was obtained from all participants and from their parents when appropriate. The MR data from 37 of these participants were also examined in our earlier report (Jernigan, Trauner, et al., 1991). The 20 additional participants were added to increase the statistical power to detect age related changes using our new analyses. The new participants did not significantly differ from the original group by gender or age, and they participated in the same ongoing neurodevelopmental and neuropsychiatric studies.

Imaging Protocol

MR was performed with a 1.5 Tesla super-conducting magnet (Signa; General Electric, Milwaukee). Two spatially registered images (Figure 1) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000 msec; TE = 25, 70 msec) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm with a 2.5 mm gap between successive sections in all instances. A 256 × 256 matrix and 24-cm field of view were used. No sedation was administered for the examinations. For the following discussion of image analysis, the term pixel will be used to refer to a single picture element (or signal value) from the image matrix. The term voxel will be used to refer to the corresponding three-dimensional volume from which the signal value for a pixel is taken.

Image Analysis

Four subcortical structures and three cortical regions were examined. The volumes of caudate nuclei, lenticular nuclei, the thalamus, and hypothalamic (including some septal nuclei) structures were computed, as were separate volumes of dorsal, lateral ventral, and MTL cortex (including uncus, amygdala, hippocampus, and parahippocampal gyrus). Detailed descriptions of the image-analytic approach used in this study are contained in several articles (Jernigan, Archibald, et al., 1991; Jernigan & Bellugi, 1990; Jernigan, Press, & Hesselink, 1990; Jernigan, Schafer, Butters, & Cermak, 1991; Jernigan & Tallal, 1990; Jernigan, Trauner, et al., 1991). Briefly, tissue segmented images are created by classifying each pixel location within a section of the imaged brain on the basis of its signal values in the two original images as most resembling cerebrospinal fluid (CSF), grey matter, white matter, or signal hyperintensity (tissue abnormality). These segmented images are then used to designate subcortical and cortical brain regions.

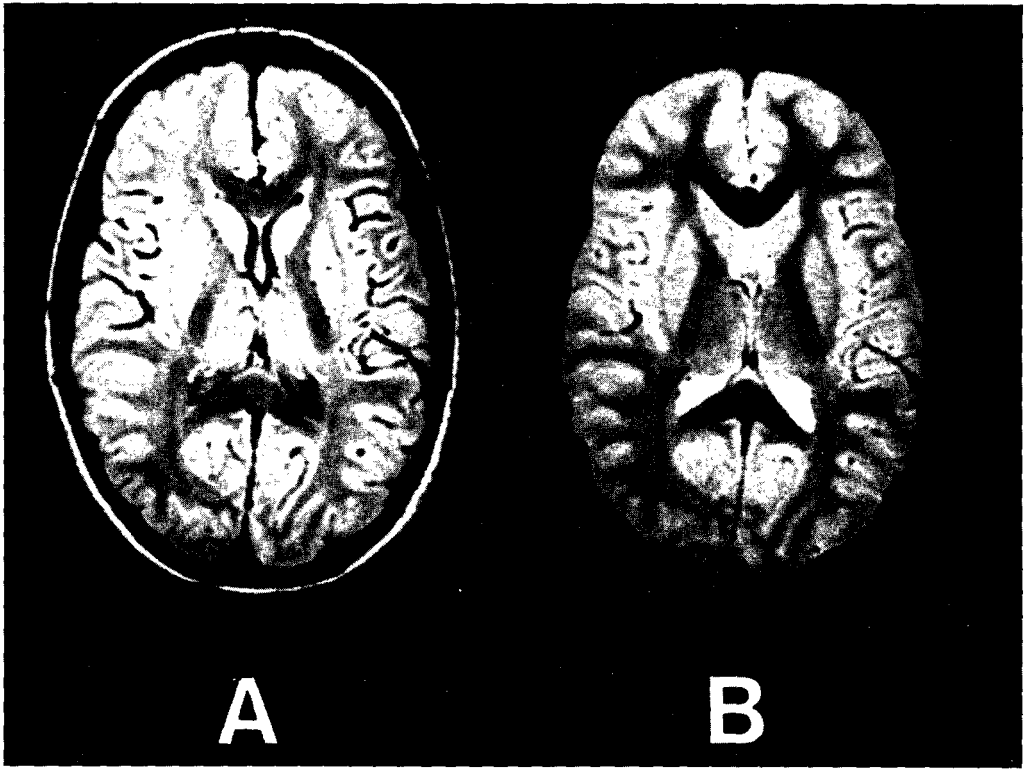

FIGURE 1 Representative images from the standard protocol: (A) axial section, SE 2000/25; (B) axial section, SE 2000/70. Sections are 5-mm thick, matrix 256 × 256, with 2.5- mm gap between sections. A field of view of 24 cm was used.

Definition of Subcortical Structures

Trained image analysts delineated subcortical structures by circumscribing pixels previously designated as subcortical grey matter that were visually determined to be within caudate nucleus, lenticular nucleus, and diencephalic grey matter structures. The hypothalamus was then stereotactically separated from the rest of the diencephalic structures (see discussion of stereotactic methods later). The edges of the structures were not traced in the region definition procedure, but rather polygons were designated that included all grey matter pixels within the structures and excluded all grey matter pixels associated with other structures.

The voxels designated as within the caudate, lenticular, thalamic, and hypothalamic (including some septal nuclei) regions are highlighted in black in the representative, digitally processed images shown in Figures 2 A through D, respectively. It should be noted that, although the operators circumscribe the entire putamen and globus pallidus, areas within the lenticular nucleus containing significant iron deposits, particularly in globus pallidus, do not meet the signal criteria for grey matter and are, thus, not included in this region.

Definition of Cortical Structures

The definition of cortical structures is often challenging because these regions are most often bounded by specific gyri that are difficult to consistently identify on MR. Further, such limitations as head rotation within the field of view can make observed within-plane cortical (and subcortical) asymmetries nearly impossible to interpret. The techniques discussed next have been developed in this laboratory to address these concerns and are discussed more fully in other reports (Jernigan, Archibald, et al., 1991; Jernigan & Bellugi, 1990; Jernigan et al., 1990; Jernigan, Schafer, et al., 1991; Jernigan & Tallal, 1990; Jernigan, Trauner, et al., 1991).

To define anatomically consistent cortical regions, a method was adopted for making subdivisions of the cerebrum relative to the centromedial structural midline and two consistently identifiable points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating rotation angles using these landmarks, it was possible to perform a three-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. Cortical regions could then be constructed stereotactically, resulting in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The orientation of the midsagittal plane was first determined by computing a regression line through a series of visually selected brainstem midline points. The division of the cerebrum was then based on two major planes (see Figure 3): an *axial plane*, which is perpendicular in orientation to the midsagittal plane and passes through the two corpus callosum points, and a *coronal plane*, which is perpendicu-

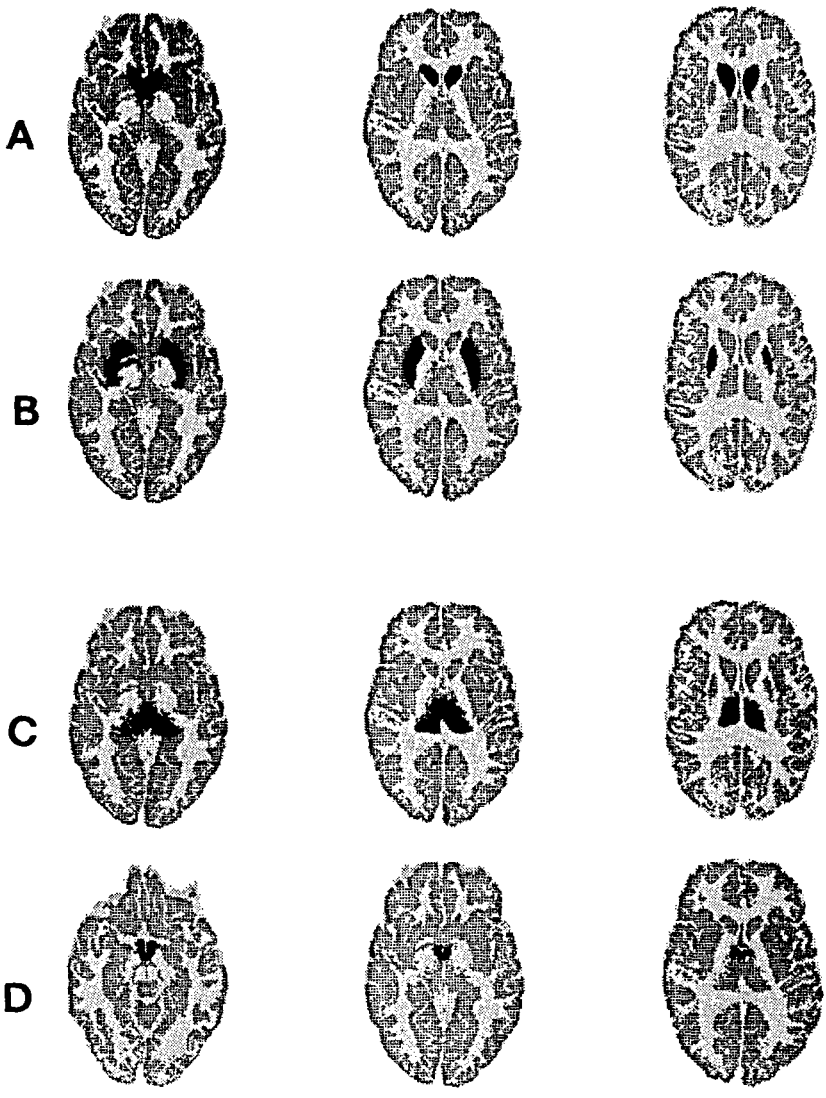

FIGURE 2 Representative processed images illustrating definition of subcortical grey-matter regions. Not all sections containing the subcortical regions of interest are shown here. Pixels within the (A) caudate nuclei, (B) lenticular nuclei, (C) thalamus, and (D) anterior diencephalon are highlighted in black.

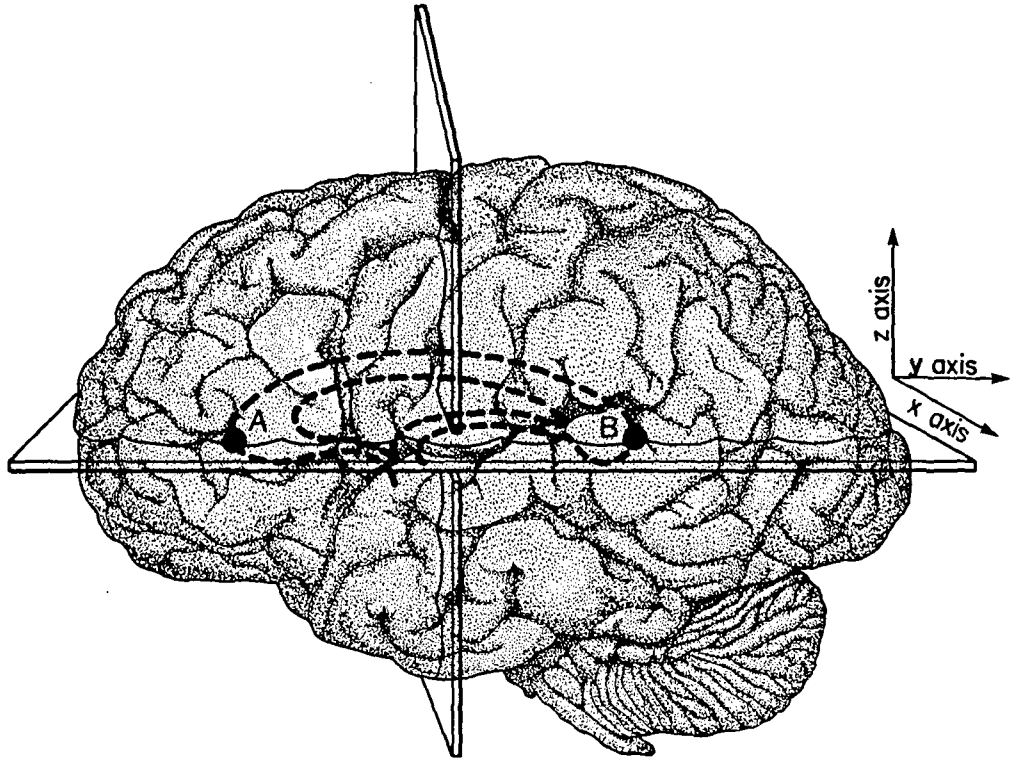

FIGURE 3 Cerebral regions are defined as follows: Points A and B in the corpus callosum, shown here, are the most anterior midline points in the genu and the most posterior midline point in the splenium, respectively. An axial plane passing through these two points is defined, as shown, perpendicular to the midsagittal plane. A coronal plane is defined perpendicular to the axial plane and passing through the midpoint between Points A and B. This coronal plane divides the cerebrum into an anterior and a posterior zone.

lar to the first plane and passes through the midpoint between the two corpus callosum points. New coordinates for each voxel were then computed relative to these planes. Cerebral regions were then defined either entirely manually or with the use of a combination of manual and stereotactic procedures.

Volumes of the infratentorial and supratentorial cranial vaults were estimated, as in the previous studies (Jernigan & Tallal, 1990; Jernigan, Trauner, et al., 1991), by summing infratentorial or supratentorial voxels (including CSF, hyperintensities, and grey and white matter) over all sections. The cortical grey matter voxels designated as the MTL region are highlighted in black in representative images shown in Figure 4A. The region includes hippocampus, amygdala, uncal cortex, and parahippocampal gyrus. All other cortical grey matter voxels inferior to the *axial* plane shown in Figure 2 were assigned to the inferior (or ventral) lateral cortical region (Figure 4B). All cortical grey matter voxels superior to this plane constituted the superior, or dorsal, cortical region (Figure 4C). Additionally, each structure was measured separately for each hemisphere, for the purpose of examining asymmetries. Asymmetry ratios of the left hemisphere to the right hemisphere (L/R) volumes were computed for each structure. Analyses conducted using the hemispheric difference divided by the combined left and right volumes for each structure (L–R/L+R) yielded virtually identical results to those presented here.

Statistical Analysis

Because little is known about brain maturation in this age range, we chose statistical analyses that are descriptive in nature. The magnitude of the independent effects of age and gender on the morphologic variables were estimated separately using multiple linear regression analyses. Effects of these variables on the cortical grey matter volumes were estimated adjusting for variation due to the size of the cranial regions from which the volumes were taken. This was accomplished by entering the regional cranial volumes in the multiple regressions as additional predictors so that any observed effects of age or gender could be assumed to be independent of (not attributable to) variation in region size. Similarly, the age and gender effects on the subcortical grey matter volumes were estimated after removing variance due to total supratentorial cranial volume. Asymmetries in the cortical and subcortical regions were also entered into regression equations using age and gender as predictor variables. However, because the asymmetries were measured as ratios of the left to the right regional grey matter volume, no correction for variation due to cranial size was necessary. In these analyses, the magnitude of the independent effect of a variable is reflected in that variable's regression coefficient (β) in the presence of the other predictors. Probabilities given for each coefficient estimate the likelihood that such a value would occur by chance if the predictor was unrelated to the criterion variable. Wherever a significant age or gender effect was observed, the age by gender interaction was tested for significance.

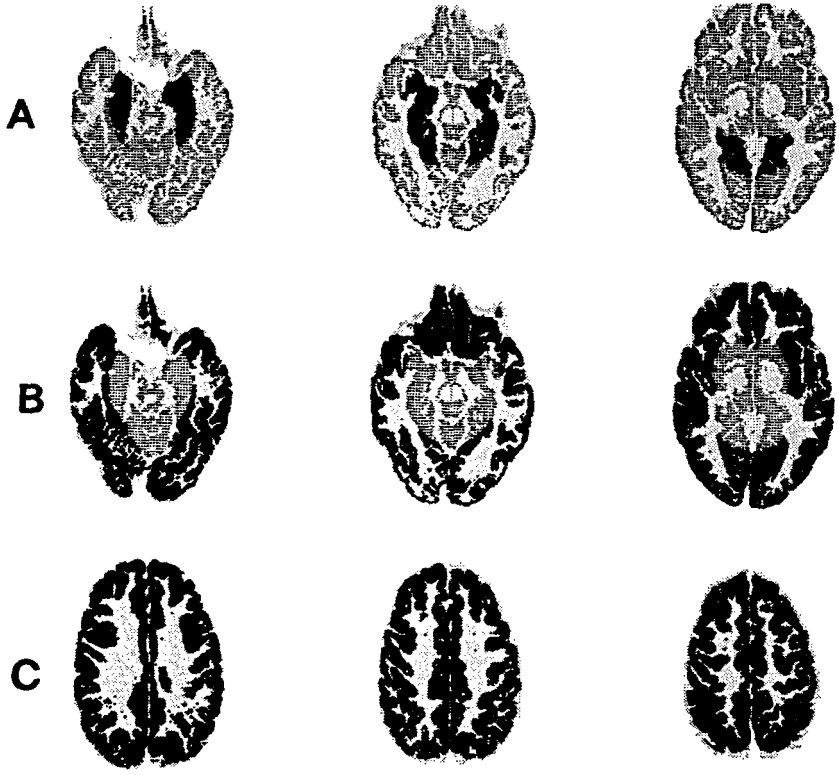

FIGURE 4 Representative processed images illustrating the definition of cortical regions. Not all sections containing the cortical regions of interest are shown here. Pixels within the (A) mesial temporal lobe, (B) ventral lateral cortex, and (C) superior cortex are highlighted in black.

RESULTS

Analyses of the inferior and superior supratentorial cranial regions yielded results that were similar to those observed in Jernigan, Trauner, et al. (1991) with fewer participants. Once the highly significant effects of gender were controlled for, there was evidence for a trend toward an increase with age in the volume of the superior cranial region ($\beta = .226$, $p = .069$) and no evidence for change with age in the volume of the inferior cranial region ($\beta = -.074$, $p = .541$). No age by gender interaction was observed for either cranial region. It should be noted that in the previous study (Jernigan, Trauner, et al., 1991) the anterior portion of the superior cranial region increased significantly with age, whereas the age-related increase in the posterior portion only approached significance. In this study, separate analyses were not conducted for the two regions.

The analyses of the cortical grey matter volumes are summarized in Table 2. As expected, the regional cortical volumes were highly associated with the volumes of the total cerebral regions from which they were measured, except, surprisingly, in the MTL region. No gender effects were observed once the effects of cranial volume were removed. Consistent with the previous study (Jernigan, Trauner, et al., 1991), the cortical grey matter in the superior region significantly decreased in volume with age ($p < .001$). Although the volume of the cortex in the inferior region appeared to remain constant across this age range in the previous study, when the MTL was measured separately from the lateral cortical region, both regions showed significant age effects.

Specifically, once the surface of the MTL was isolated from the lateral cortex, it could be observed that the MTL was actually significantly increasing in volume with age, whereas the more lateral cortex was significantly decreasing across the age range. Scatterplots illustrating the age-related changes in the inferior lateral cortex and in the MTL are shown in Figure 5. To visualize the age effects of interest in these variables, the irrelevant variability due to overall cerebral volume has been removed. That is, a residual cortical volume for each participant was computed for each region by subtracting the predicted cortical volume based on region volume. No Age × Gender interaction was observed for any of the three cortical regions.

Analyses for the subcortical grey matter structures are presented in Table 3. Again, as expected, the volumes of the subcortical structures were highly associated with the total cerebral volume, except in the anterior diencephalon in which only a trend toward significance was observed. After adjusting for the size of the supratentorial cranium, no gender effects were observed. As reported in the previous study, significant reductions in volume were observed in the caudate, lenticular nuclei, and thalamus, whereas there was a significant increase in the volume of the anterior diencephalon. No Age × Gender interactions were observed.

Asymmetry Analyses

Each asymmetry measure was computed as a ratio of the left to the right hemisphere; thus, numbers greater than one represent a left-larger asymmetry, and num-

TABLE 2
Regression Analyses for Cortical Regions

	Effect of Cerebral Size		*Effect of Gender*		*Effect of Age*	
	β	*p*	β	*p*	β	*p*
Dorsal cortex	.799	.000	.017	.832	−.585	.000
Mesial temporal lobe	.211	.133	−.187	.186	.286	.025
Ventral lateral cortex	.836	.000	.094	.289	−.214	.008

TABLE 3
Regression Analyses for Subcortical Regions

	Effect of Cerebral Size		*Effect of Gender*		*Effect of Age*	
	β	*p*	β	*p*	β	*p*
Caudate nucleus	.551	.000	.101	.448	−.309	.011
Lenticular nucleus	.455	.000	−.029	.806	−.570	.000
Anterior diencephalon	.279	.063	.135	.357	.283	.032
Thalamus	.357	.006	−.135	.283	−.528	.000

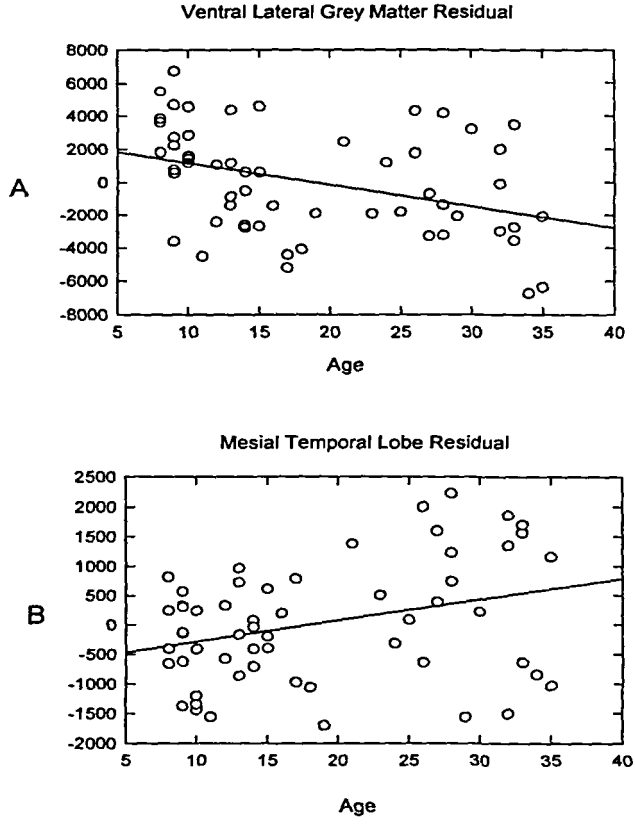

FIGURE 5 Scatterplots of age by the (A) ventral lateral cortex volume and (B) the mesial temporal lobe volume. Both measures are residual scores after adjustment for the overall volume of the inferior cerebrum.

bers less than one represent a right-larger asymmetry. Asymmetry analyses of the total supratentorial cranial vault indicate that the right hemisphere is slightly larger than the left with an asymmetry ratio of .99 ($t = -7.01$, $p < .01$). The results of the cortical grey matter asymmetry analyses are presented in Table 4. As can be observed, only the MTL grey matter ratio was significantly different from 1.0, and the value of .94 suggests a right-larger asymmetry ($t = -.408$, $p < .01$). The ratios for the other two cortical regions showed tendencies toward asymmetry as well. Analyses conducted with only right-handed participants ($n = 51$) yielded the same results as those observed in the full sample except that the trends toward asymmetry in the dorsal and inferior lateral cortex were no longer present.

The results for the asymmetry analyses for the subcortical regions are presented in Table 5. A significant right-larger asymmetry was observed in the anterior diencephalon, whereas a significant left-larger asymmetry was observed in the thalamus. No evidence for significant asymmetry was observed in either the caudate or the lenticular nuclei. Exclusion of the left-handed participants did not change the results of the subcortical asymmetry analyses.

Regression analyses for the cortical asymmetries are shown in Table 6. No age or gender effects were observed in the three cortical regions. Analyses conducted excluding the left-handed participants were virtually identical to those including the entire sample.

TABLE 4
Asymmetry Analyses for Cortical Regions

Anatomical Region	*Estimated Mean Volumes in Milliliters (Left/Right)*	*Asymmetry Left/Right (SD)*	*t*	*Probability*
Mesial temporal lobe cortex	18.9/20.1	.944 (.104)	–4.08	.00
Ventral lateral cortex	105.5/103.7	1.020 (.080)	1.89	.07
Dorsal cortex	184.8/186.9	.990 (.043)	–1.78	.08

TABLE 5
Asymmetry Analyses for Subcortical Structures

Anatomical Region	*Estimated Mean Volumes in Millliliters (Left/Right)*	*Asymmetry Left/Right (SD)*	*t*	*Probability*
Caudate	6.4/6.4	.999 (.082)	–0.12	.90
Lenticular	7.0/6.9	1.021 (.122)	1.29	.20
Hypothalamus	1.1/1.4	.772 (.192)	–8.95	.00
Thalamus	6.8/6.3	1.084 (.141)	4.48	.00

Table 7 contains the results of the regression analyses for the subcortical asymmetries. No gender effects were observed. A trend toward a change with age in the thalamic asymmetry was observed ($\beta = .241$, $p = .07$), and the relation between age and the caudate asymmetry ratio was not significant. Significant age-related changes in the asymmetry ratios were observed in the anterior diencephalon and in the lenticular nucleus. Analyses excluding left-handed participants yielded a significant change with age in the thalamus asymmetry ratio ($\beta = .293$, $p < .05$), but the results for the other three subcortical measures did not change from the results including the entire sample displayed in Table 6.

To further examine the age effects observed in the anterior diencephalon and in the lenticular nucleus, separate regression analyses were conducted for the right and left sides of the region of interest. In the anterior diencephalon, the left side increased with age once gender and cerebral size were controlled for ($\beta = .352$, $p < .01$), whereas the right side did not change with age ($\beta = .173$, $p > .10$). Figure 6A illustrates the regression lines for the left and right anterior diencephalon. The left and right volumes were normalized to their respective hemispheric cranial vaults. As can be seen in Figure 6A, the anterior diencephalon becomes relatively more symmetrical with age, with the smaller left side appearing to increase more rapidly in volume with increasing age.

TABLE 6
Regression Analyses for Cortical Asymmetries

	Effect of Age		*Effect of Gender*	
Anatomical Region	β	*p*	β	*p*
Mesial temporal lobe	−.016	.904	.105	.445
Ventral lateral cortex	.006	.967	−.047	.730
Dorsal cortex	.071	.606	.058	.672

TABLE 7
Regression Analyses for Subcortical Asymmetries

	Effect of Age		*Effect of Gender*	
Anatomical Region	β	*p*	β	*p*
Caudate nucleus	.067	.626	.011	.935
Lenticular nucleus	−.300	.026	.043	.745
Hypothalamus	.291	.030	−.062	.639
Thalamus	.241	.071	−.148	.264

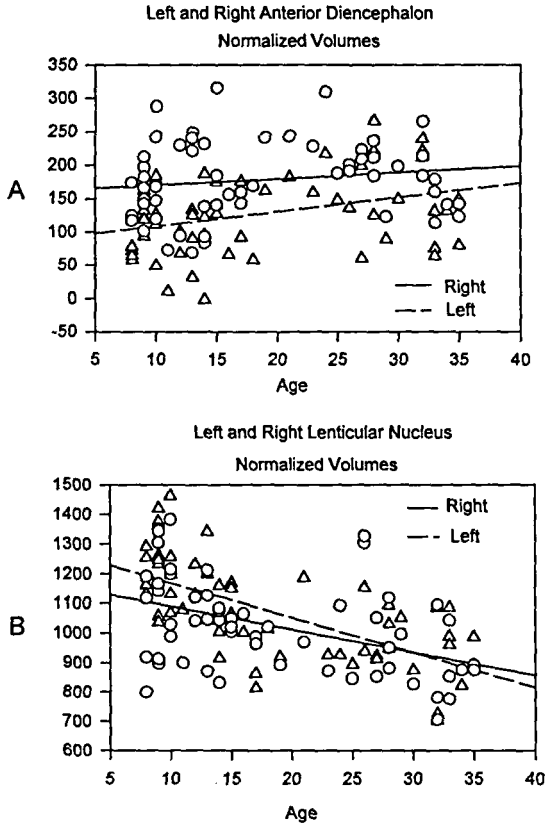

FIGURE 6 Scatterplots of age by the (A) left and right anterior diencephalon and (B) the left and right lenticular nucleus volumes (normalized to their respective hemispheric cranial vaults). Open triangles represent values for the right hemisphere, and open circles represent values for the left hemisphere for both Plots A and B.

For the lenticular nucleus, both the left and right sides decreased significantly with age once gender and hemispheric cerebral size were accounted for ($\beta = -.653, p < .01$ and $\beta = -.411, p < .01$, respectively). Figure 6B is a graphical display of the regression lines for the normalized left and right lenticular nuclei volumes. As can be seen, the left lenticular nucleus normalized volume was larger than the right in the youngest participants, and this pattern reversed with a right-larger pattern in the adults. Thus, even though there is no evidence for significant left- or right-larger asymmetry when the participants are collapsed across the age range (see Table 5), a reversal from left-larger to right-larger apparently results from more rapid shrinkage in the volume of the left lenticular nucleus across this age range.

DISCUSSION

These results suggest that dynamic, and regionally specific, changes are occurring in cortical and subcortical structures across the peripubertal age range. Although most regions appear to be decreasing in volume with increasing age, a few structures actually increase in volume. Specifically, as discussed in the previous study (Jernigan, Trauner, et al., 1991), the dorsal cortex dramatically decreases in volume across the age range. However, the volume of the inferior cortex does not remain constant as the earlier study indicated. Rather, the lateral cortices in the ventral region decrease in volume, whereas the limbic structures in the MTL actually appear to be increasing in volume with age.

Jernigan, Trauner, et al. (1991) hypothesized that the reductions they observed in the dorsal cortical volume were related to decreases in synaptic density found during the same age range in human autopsy material (Huttenlocher, 1979). Marked reductions in cortical synaptic density have also been reported in monkeys at a comparable stage of development by Rakic and his associates (Zecevic & Rakic, 1991). The subcortical volume reductions noted in this and the previous report may have a similar basis.

Unfortunately, few studies of the MTL and anterior diencephalic structures have been reported in the human postmortem literature. However, several animal studies in the literature discuss regionally specific trophic effects induced by the introduction of gonadal steroid hormones (for a review, see Jones, 1988). Some of the highest concentrations of steroid hormone receptors in rats are found in the hippocampus, amygdala, hypothalamus, and septal nuclei (Rainbow, Parsons, McLusky, & McEwen, 1982; Stumph & Sar, 1978), all of which are within our anterior diencephalic and MTL regions. Perhaps the increase in circulating gonadal steroid hormones that occurs at puberty has organizational effects on the morphology of the human brain. It is also possible that maturation in the anterior diencephalon or MTL precedes the increase in levels of gonadal steroid hormones. In any event, the only two grey matter regions measured in our study that increase in volume during the peripubertal age range (MTL and anterior diencephalon) are found in animal studies to contain high concentrations of hormone receptors. Given this, it does not seem unreasonable to hypothesize that these morphological changes may be related to hormonal factors.

Other maturational changes in the region of the MTL have been shown to occur during this age range. Benes et al.'s (1994) human postmortem study is of particular relevance because they examined the brains of 164 participants from 0 to 76 years of age, including many participants in the peripubertal age range. Specifically, they studied the extent of myelination along the surface of the hippocampal formation at the level of the subiculum, presubiculum, and parasubiculum (referred to as the superior medullary lamina) using a computer-assisted quantitative technique. Benes et al. found a 95% increase in the area

of myelination of the superior medullary lamina in the 1st and 2nd decades of life. Notably, when the authors corrected their measure for overall changes in cerebral size (e.g., area of myelination expressed relative to brain weight), they still found a 92% area increase between groups of participants aged 0 to 9 and 10 to 19 years. They describe in detail the known connectivity of the subicular and presubicular region, indicating that at least some of the axons myelinating in this region in adulthood could originate from the cingulate gyrus. Thus, Benes and her colleagues speculate that the functional significance of the increased myelination that they observe could be related to corticolimbic integration thought to be involved in the regulation of emotional behaviors with greater cognitive maturity.

It is likely that continued myelination is occurring in the superior medullary lamina in our sample of normal participants given that Benes et al.'s (1994) postmortem findings are so robust in such a large group of participants. It is not clear how increased myelination in a brain region would result in an increase in tissue quantified as grey matter on MRI, unless additional trophic changes occur, however it is possible that the two observations are related. Notably, Giedd et al. (1996) also observed volume increases in certain MTL regions in vivo. However, the image analysis methodologies differed significantly from the present methods. Specifically, Giedd and his colleagues did not use tissue segmentation or try to differentiate between grey and white matter in their measures of MTL structures. Perhaps both imaging studies are consistent with Benes et al.'s postmortem findings of increased area of myelin staining during the first and second decades (and beyond). For example, Benes et al. noted that their observations could result from "either de novo myelination of previously unmyelinated axons or increased numbers of myelin lamellae surrounding fibers that already have a myelin sheath" (p. 482). Regardless of whether the former or the latter form of increased myelination is occurring, the change in density of myelination in the MTL would most likely be reflected in the intensity of the MR signal. Clearly myelin does occupy space within the cranial cavity, and it is possible that what we are observing in this study is an increase in myelination that increases the volume of the structure but does not sufficiently change tissue signal characteristics to change the classification of the grey matter voxels. Further study will be needed to address this issue.

Analyses of regional cortical asymmetries in this age range revealed some interesting patterns. Of the three cortical asymmetry ratios, only the MTL ratio is significantly different from 1.0, with the right hemisphere being larger than the left. The right-larger than left hemisphere asymmetry in the MTL is consistent with an earlier report (Giedd et al., 1996). Of the four subcortical structures, the anterior diencephalon is the most dramatically asymmetrical with the right considerably larger than the left side. There is some evidence that the thalamus is also significantly asymmetrical and in the opposite direction from the anterior diencephalon. Finally, we find that both the lenticular nucleus and the anterior diencephalon have asymmetry ratios that change with increasing age.

The association of age with anterior diencephalic asymmetry in this study suggests a hemisphere-specific change in these structures with age. Given the age of the participants, the question arises again whether the results could be related to hormonal effects. One possibility is that, in the human, the left and right sides of the hypothalamus are differentially sensitive to hormones, a phenomenon found to occur in the developing rat brain (Nordeen & Yahr, 1982). In a review of their hypotheses regarding cerebral lateralization, Geschwind and Galaburda (1985) implicated testosterone in the development of brain asymmetry. Thus, it is not inconceivable that our asymmetry findings are related to hormonal factors as well.

It is difficult to explain why no gender effects and no age by gender interactions were observed in our study given that many theories of hormonal action on brain development stem from observed sex differences (see Geschwind & Galaburda, 1985; Toran-Allerand, 1984). The most parsimonious explanation would be that our participants were not evenly distributed by gender across the age range, leaving us with little power to find such differences.

It is beyond the scope of this anatomical study to address questions regarding the functional significance of these apparent late maturational changes in brain morphology. However, noninvasive brain imaging methods provide the means for conducting prospective studies of brain maturation that include detailed functional and neuroendocrine assessments. Future research should help to establish more solid links, if they exist, between levels of gonadal steroid hormones, changes in cognitive abilities and other behavioral indexes, and changing brain morphology during the peripubertal age range.

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