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# MATURATION OF HUMAN CEREBRUM OBSERVED IN VIVO DURING ADOLESCENCE

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## SUMMARY

In the present study using magnetic resonance imaging (MRI), age changes in the morphology of the cerebral cortex, greatest in the frontal and parietal convexities, were observed during adolescence. Results suggest that increases in cerebrospinal fluid (CSF) within the sulci of these cortical regions accompany grey matter decreases. Smaller reductions in volume are also observed in subcortical grey matter nuclei. These apparent grey matter volume reductions presumably reflect processes of late brain maturation. The changes may be related to decreasing neural plasticity.

## INTRODUCTION

As brain systems mature, 'regressive events' (Cowan *et al.*, 1984) strongly influence their final form. Many more neurons are produced than will survive, and the elimination of neurons, which usually occurs early in development, may selectively reduce the neuronal populations in ways that increase the functional specificity and efficiency of the remaining neurons (Changeux and Danchin, 1976; Purves and Lichtman, 1980; Cowan *et al.*, 1984). In later phases of neural maturation, fewer neurons are lost, but substantial changes occur in synaptic density (Huttenlocher, 1979; Huttenlocher *et al.*, 1982). The selection of synapses is probably related to neural activity occurring in functionally maturing neuropil (Easter *et al.*, 1985). In human brain maturation, most neuronal cell death and much synaptic reorganization is thought to occur very early in development, either *in utero* or during the first or second post-natal years. Clinical magnetic resonance imaging (MRI) reveals dramatic developmental changes in the brains of infants, and is especially sensitive to the process of myelination (Holland *et al.*, 1986; Lee *et al.*, 1986; McArdle *et al.*, 1987*a,b*; Barkovich *et al.*, 1988; Martin *et al.*, 1988). But evidence exists that maturational changes continue into late childhood (Easter *et al.*, 1985). Autopsy studies have indicated that late cycles of myelination (Yakovlev and Lecours, 1967; Kinney *et al.*, 1988) and continuing changes in cortical synaptic density (Huttenlocher, 1979) occur throughout childhood. Evidence for late childhood changes in cerebral blood flow (Kennedy and Sokoloff, 1957; Kennedy *et al.*, 1970), the electroencephalogram of deep sleep (Feinberg, 1982) and cerebral metabolic rate (Chugani and Phelps, 1986; Chugani *et al.*, 1987) confirm that these changes are accompanied

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by functional alterations. Unfortunately, the neuropathological evidence for late childhood changes in humans is based on the examination of relatively few individuals aged between 7 and 16 yrs.

Using clinical MRI and semi-automated morphometry, Jernigan *et al.* (1990) examined brain structure in normal subjects ranging in age from 8 to 80 yrs. While some of the variability in morphologic measures across this age range was attributable to slow degenerative changes in older individuals, substantial age differences were apparent, especially in cortical structures, between the children and the adult subjects. Jernigan and Tallal (1990) reported that volumetric measures of the cortical grey matter from MR images revealed substantial differences between children and young adults, with the adults showing less cortical grey matter relative to cerebral size. However, the sample included no individuals aged between 10 and 26 yrs, thus little information was available about the timing of the changes. Also, since global cortical volume was measured, no information about the regional distribution of the changes was available, and questions remained about the degree to which late myelination of white matter might explain the apparent cortical reductions. Simultaneous increases in cerebrospinal fluid (CSF) and decreases in cortical grey matter suggested that cortical volume loss might be occurring. The brains of 39 normal children and young adults (23 males, 16 females, aged 8–35 yrs) have now been examined in greater detail with particular emphasis on regional changes in cortical morphology. Twenty of the subjects participating in the present study (9 children and 11 adults) were also examined in the earlier study.

## METHOD

### *Subjects*

Thirty-nine normal children and young adults (23 males, 16 females) were examined. Subjects 21 yrs of age and younger were recruited as normal controls for a large, multidisciplinary neurodevelopmental research centre. Subjects between 21 and 35 yrs of age participated as controls in neuropsychiatric studies. All subjects were screened by medical and psychiatric interviews (of parents or of subjects themselves) for evidence of significant disease (i.e. diabetes, heart disease), substance abuse, developmental intellectual abnormality, or psychiatric illness. All adult subjects were living independently in the community and were employed. Informed consent was obtained from all subjects and their parents when appropriate.

### *Imaging protocol*

MR was performed with a 1.5 Tesla super-conducting magnet (Signa; General Electric, Milwaukee) at the UCSD/AMI Magnetic Resonance Institute. Two spatially registered images (Fig. 1) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000 ms, TE = 25, 70 ms) 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 3-dimensional volume from which the signal value for a pixel is taken.

### *Image analysis*

The visual identification of cerebral structures in MR images is possible because of the tissue contrast between the grey matter structures and the surrounding white matter or CSF. However, measurements of volumes of cerebral structures must overcome several problems. First, because voxels at the edges of structures may contain mixtures of grey matter, white matter and CSF, sharply defined edges are not always

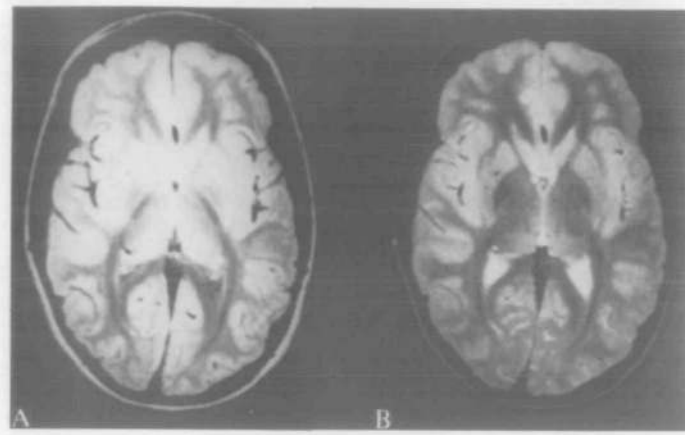


FIG. 1. Representative images from the standard protocol. A, axial section, SE 2000/25. B, axial section, SE 2000/70. Sections are 5 mm thick, matrix 256×256, with 2.5 mm gaps between images. A field of view of 24 cm was used.

present. This allows considerable scope for variability in subjective determinations of such boundaries (e.g. when tracing methods are used) leading to measurement unreliability in the computed volumes.

Visual identification of specific *cortical* structures on MRI presents additional challenges and depends upon the presence of visible gross morphologic features relative to which the boundaries of the cortical regions can be defined. Standard regional divisions for the cortex are based to a large extent on cortical gyral patterns, but the accurate localization of particular gyri or sulci, throughout a series of images, is often impossible. Furthermore, some boundaries, such as that between posterior temporal and inferior parietal cortex, are not clearly defined in gross morphological terms. Also, even when attempts are made to standardize head positioning, rotation of the head (relative to the standard plane) occurs in all three axes. This is especially likely when subjects are not sedated; they must be sufficiently comfortable in position to avoid movement during the imaging session. Careful inspection indicates that relatively small rotations substantially change the appearance of brain structures in the image plane, further complicating their visual identification; and, in addition, such rotations lead to spurious within-plane asymmetries of apparently comparable structures in the two hemispheres. Thus, manually tracing the structures in the sections where they are best visualized often leads to inaccurate volume and asymmetry assessments. The techniques described below were designed to address these problems.

To facilitate and standardize the determination of structural edges, our method involves a semi-automated classification of all pixels in the images on the basis of their signal characteristics on the two original images of each section. A detailed description of the pixel classification method has been reported (Jernigan *et al.*, 1990). Only a brief summary is provided here: for each axial brain section imaged, a computed matrix is produced. In this matrix, voxels are classified as most resembling (in signal strength) grey matter, white matter, CSF or signal hyperintensities (tissue abnormalities). The full series of axial images is analysed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Further manipulations to derive the specific structural measures for the studies reviewed here were then made using these 'pixel-classified' images. Trained operators, blind to subject age or gender, used a stylus-controlled cursor on the displayed images manually to separate cerebellar from cerebral areas, left from right hemispheres, and the cortical from subcortical regions.

#### *Definition of subcortical structures*

To delineate subcortical structures, the operators circumscribed pixels classified as subcortical grey matter that were visually determined to be in caudate nuclei, lenticular nuclei and diencephalic grey matter structures (including mammillary bodies, hypothalamic grey, septal nuclei and thalamus). They did not trace the edges of the structures, but designated polygons which included all grey matter pixels within the structures,

and excluded those grey matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as grey but clearly not in the structures, boundaries were manually constructed. Estimates of the volumes of the subcortical structures were made by summing the designated grey matter pixels across all sections.

#### *Definition of cerebral (cortical) regions*

To define anatomically consistent cerebral regions, a method was adopted for making subdivisions of the cerebrum relative to the centro-medial 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 3-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. Regions could then be constructed which resulted in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The two corpus callosum points were considered to lie in the true midsagittal plane. The orientation of this plane was then determined by computing a regression line through a series of visually selected brainstem midline points on different sections. The division of the cerebrum was based on two major planes (see Fig. 2): an *axial plane*, which is perpendicular in orientation to the midsagittal plane and passes through

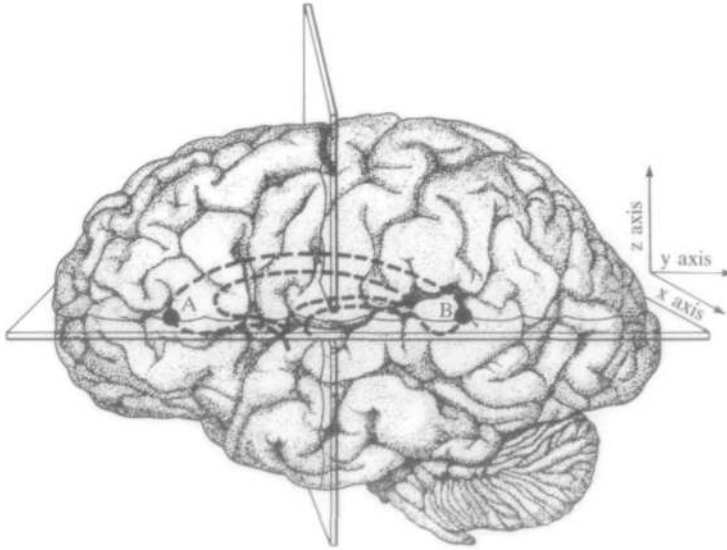


FIG. 2. Cerebral regions are defined as follows: Points A and B in the corpus callosum, shown above, are the most anterior midline point in the genu, and the most posterior midline point in the splenium, respectively. An axial plane passing through these two points is defined, as shown, perpendicular to the midsagittal plane. A coronal plane is defined perpendicular to the axial plane and passing through the midpoint between points A and B. Thus 4 cerebral zones are defined: inferior anterior, inferior posterior, superior anterior and superior posterior. Anterior temporal, orbito-frontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal and superior occipital cortex.

the two corpus callosum points, and a *coronal plane*, which is defined as perpendicular to the first plane and which passes through the midpoint between the two corpus callosum points. By computing new coordinates for each voxel relative to these planes, each is assigned to 1 of 4 zones: one, inferior to the axial plane and anterior to the coronal plane (IA); a second, inferior to the axial plane and posterior to

the coronal plane (IP): a third, superior to the axial plane and anterior to the coronal plane (SA); and a fourth, superior to the axial plane and posterior to the coronal plane (SP). Again, these defined planes are independent of the image plane, as a 3-dimensional rotation is first applied based on the positions of the landmarks described above. Anterior temporal, orbito-frontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal and a small portion of the superior occipital cortex.

The fully processed images are illustrated in Fig. 3. The colour coding for different pixel classes is

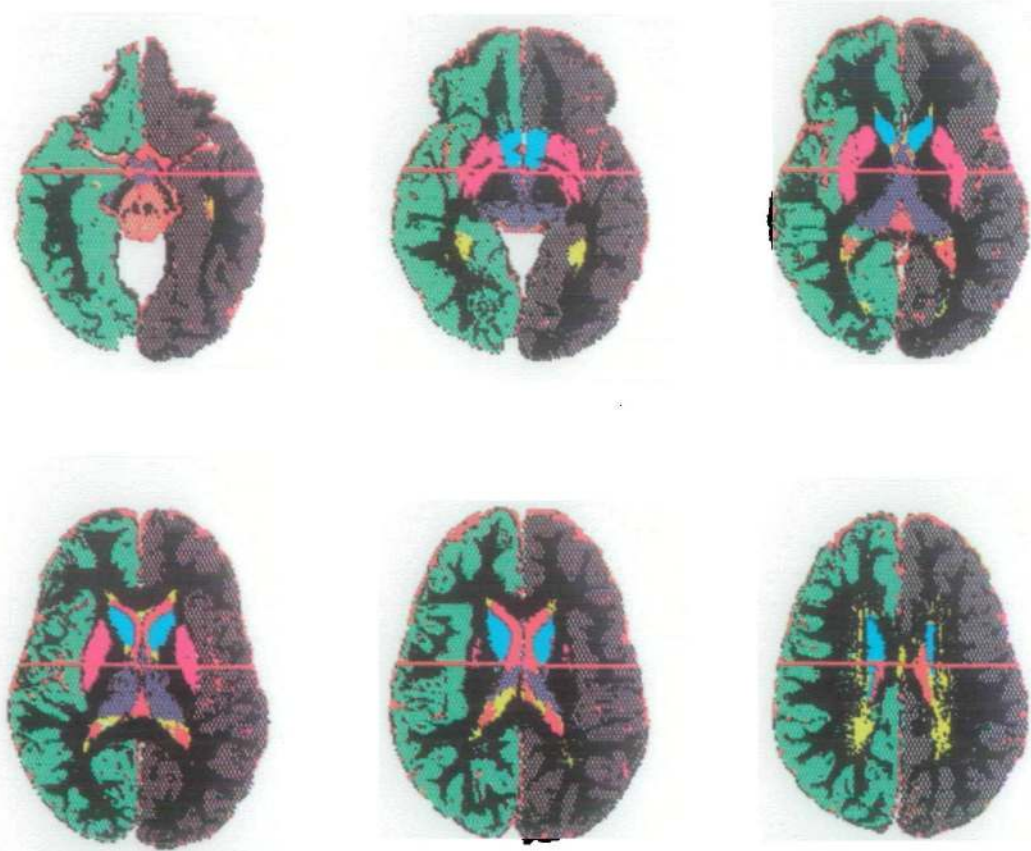


FIG. 3. Representative fully processed images. The different pixel classes are colour coded as follows: right-hemisphere cortical grey matter is green, and left-hemisphere cortical grey matter is grey. Diencephalic areas are purple, caudate nuclei are blue and lenticular nuclei are magenta. The red line running through each section indicates the position of the coronal dividing plane. The sections on the top row are below and the sections on the bottom row above the axial dividing plane. This set of images was chosen because the imaging plane is parallel to the axial dividing plane and virtually no rotation of the head in the coronal or sagittal planes occurred. Note that, due to 3-dimensional image rotation, in typical sets of images, the separation of inferior from superior zones would not coincide with a section boundary, but would occur within a section.

described in the figure legend. The red line running through each section indicates the position of the coronal dividing plane. Because this plane passes through the diencephalic grey matter regions and divides the functionally distinct hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus

(lying posteriorly), the corresponding anterior and posterior diencephalic volumes were computed separately. It should be noted that 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. Fluid and white matter are shown in red and black, respectively; however, subcortical and cortical fluid are measured separately.

The cortical grey matter voxels and the cortical sulcal CSF voxels within each of the 4 zones were summed separately, as were the totals of all intracranial voxels (including brain and CSF) within each zone.

Ten full sets of images were analysed twice several weeks apart. The repeat analyses were conducted blind and completely independently of the first analyses. Thus, reliability of the method could be determined for the volume measures. Reliability coefficients (Pearson  $r$ ) were as follows: supratentorial volume, 0.99; infratentorial volume, 0.99; ventricular CSF, 0.99; cortical CSF, 0.99; cortical grey matter, 0.88; caudate, 0.93; diencephalon, 0.87; and lenticular nuclei, 0.73.

#### Statistical analysis

The statistical analyses were descriptive. 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 and CSF 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. In these analyses the magnitude of the independent effect of a variable is reflected in that variable's regression coefficient in the presence of the other predictors. Probabilities given for each coefficient estimate the likelihood that such a value would occur by chance when in fact the predictor is unrelated to the criterion variable.

## RESULTS

In preliminary analyses, the supratentorial cranial volume and the volumes of the 4 subregions were examined for evidence of continuing growth during this age range. The results are presented in Table 1. The supratentorial volume is considerably smaller in female subjects ( $P = 0.001$ ). Controlling for the gender effect, the age increase is small ( $P = 0.08$ ). Examination of the results for the different regions, however, suggests that some continuing growth may take place in the superior frontal region ( $P = 0.009$ ). The gender effect is present and comparable in size in inferior cerebral regions, somewhat less pronounced in the superior posterior region, and not observed in the superior anterior region.

TABLE 1. REGRESSION ANALYSES ON CRANIAL VOLUMES

	<i>Effect of gender</i>		<i>Effect of age</i>	
	$\beta$	$P$	$\beta$	$P$
Total supratentorial cranium	-0.483	0.001	0.252	0.076
Cranial regions				
Inferior anterior	-0.492	0.002	-0.096	0.519
Inferior posterior	-0.468	0.003	-0.010	0.948
Superior anterior	-0.185	0.221	0.408	0.009
Superior posterior	-0.365	0.018	0.281	0.064

$\beta$  = standardized regression coefficient;  $P$  = significance level for  $\beta$ .

The analyses of the cortical grey matter volumes are summarized in Table 2. In all 4 regions the cortical grey matter volume is, predictably, highly associated with the volume of the total cerebral region from which it was measured. After adjusting for

TABLE 2. REGRESSION ANALYSES FOR REGIONAL CORTICAL GREY MATTER VOLUMES

	<i>Effect of regional volume</i>		<i>Effect of gender</i>		<i>Effect of age</i>	
	$\beta$	<i>P</i>	$\beta$	<i>P</i>	$\beta$	<i>P</i>
Cortical region						
Inferior anterior	0.909	0.000	0.064	0.495	0.026	0.754
Inferior posterior	0.779	0.000	0.045	0.722	-0.136	0.227
Superior anterior	0.937	0.000	0.060	0.513	-0.593	0.000
Superior posterior	0.830	0.000	0.010	0.925	-0.559	0.000

$\beta$  = standardized regression coefficient; *P* = significance level for  $\beta$ .

regional volume differences, however, no gender effect is observed for any cortical volume. There is no evidence for age-related change in the cortical volumes from either of the 2 inferior cortical regions; however, substantial age decreases are measured in both the superior anterior ( $P < 0.001$ ) and superior posterior ( $P < 0.001$ ) regions.

The results of similar analyses for the cortical sulcal CSF volumes in these regions are presented in Table 3. Again, the volumes are corrected for regional volume, and

TABLE 3. REGRESSION ANALYSES FOR REGIONAL CORTICAL CSF VOLUMES

	<i>Effect of regional volume</i>		<i>Effect of gender</i>		<i>Effect of age</i>	
	$\beta$	<i>P</i>	$\beta$	<i>P</i>	$\beta$	<i>P</i>
Cortical region						
Inferior posterior	0.309	0.103	0.248	0.193	0.126	0.448
Inferior anterior	0.303	0.106	0.276	0.143	0.048	0.771
Superior anterior	-0.031	0.840	0.253	0.077	0.606	0.000
Superior posterior	-0.021	0.897	-0.017	0.911	0.582	0.000

$\beta$  = standardized regression coefficient; *P* = significance level for  $\beta$ .

again no independent effects of gender on the volumes are observed. However, definite age-related increases are observed in the volumes computed from both of the superior cortical regions ( $P < 0.001$  for both regions). A scatterplot illustrating the age-related changes in the superior cortex is shown in Fig. 4. For this figure, a superior cortical grey matter measure was computed by combining the anterior and posterior cortical volumes. As shown in the regression analyses, this volume was highly positively correlated with the total superior region volume. This correlation yields a formula for predicting the superior cortical volume from the regional volume. To adjust for the irrelevant variability in regional volume, a residual cortical volume was computed. That is, the volume was expressed as a deviation from the cortical volume predicted from the total regional volume. Thus the variability in this new cortical volume measure is



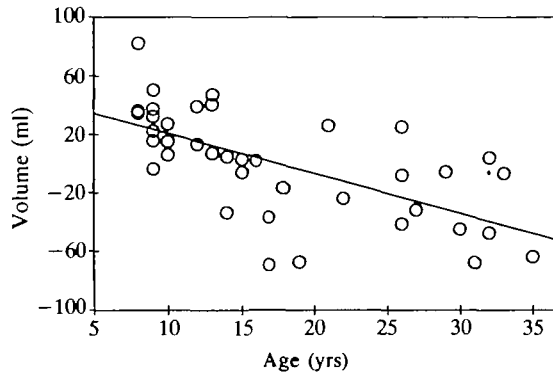


FIG. 4. Scatterplot of superior cortical grey matter volumes across age. The measure is a residual score after adjustment for total volume of the 2 superior supratentorial regions. The formula, taken from a regression of superior regional volume on superior cortical grey volume, is as follows: residual superior cortical volume = superior cortical grey volume  $- [151.52 + (0.00196 \times \text{superior regional volume})]$ . Values decrease with increasing age.

unrelated to regional volume. Inspection of Fig. 4 shows that the measure is strongly related to age.

The analyses of subcortical grey matter volumes and ventricular CSF are summarized in Table 4. After adjusting for the size of the supratentorial cranium, no gender effects

TABLE 4. REGRESSION ANALYSES FOR SUBCORTICAL STRUCTURES

	<i>Effect of cranial size</i>		<i>Effect of Gender</i>		<i>Effect of age</i>	
	$\beta$	<i>P</i>	$\beta$	<i>P</i>	$\beta$	<i>P</i>
Caudate	0.623	0.001	0.143	0.384	-0.402	0.010
Lenticular nucleus	0.321	0.066	-0.121	0.460	-0.563	0.000
Anterior diencephalic grey	0.070	0.700	0.210	0.233	0.470	0.005
Posterior diencephalic grey	0.310	0.099	-0.075	0.669	-0.447	0.008
Ventricular CSF	0.042	0.815	0.158	0.362	0.494	0.003

$\beta$  = standardized regression coefficient; *P* = significance level for  $\beta$ .

are observed. There is evidence for reduction with increasing age in both basal ganglia measures ( $P = 0.01$  for caudate,  $P = 0.000$  for lenticular nucleus), and in the posterior diencephalic measure, which includes mostly thalamus ( $P = 0.008$ ). Surprisingly, there is an apparent increase with age in the volume of the anterior diencephalic grey matter (consisting of hypothalamic grey matter, septal nuclei and some very anterior parts of the thalamus). The volume of ventricular CSF increases across this age range ( $P = 0.001$ ).

Finally, the correlations between the regional cortical grey matter and CSF measures, and between the subcortical grey matter measures and the ventricular CSF measure are summarized in Table 5A and 5B respectively. The coefficients are partial correlations controlling for regional volume (for the cortical measures) or the supratentorial volume (for subcortical measures). There are moderate correlations between superior cortical

TABLE 5A. PARTIAL CORRELATIONS OF REGIONAL CORTICAL GREY MATTER VOLUMES WITH REGIONAL CORTICAL CSF VOLUMES CONTROLLING FOR REGIONAL VOLUMES

Region	<i>r</i>	<i>P</i>
Inferior anterior	-0.08	0.63
Inferior posterior	-0.21	0.20
Superior anterior	-0.56	0.00
Superior posterior	-0.54	0.00

TABLE 5B. PARTIAL CORRELATIONS OF SUBCORTICAL GREY MATTER VOLUMES WITH VENTRICULAR CSF VOLUME CONTROLLING FOR SUPRATENTORIAL CRANIAL VOLUME

	<i>r</i>	<i>P</i>
Caudate	-0.52	0.00
Lenticular	-0.40	0.01
Anterior diencephalon	0.15	0.37
Posterior diencephalon	-0.37	0.02

*r* = partial correlation coefficient; *P* = significance level for *r*.

grey volumes and the CSF volumes from the adjacent sulci, but no correlation for the inferior zones. Also, the peri-ventricular subcortical structural volumes show some degree of correlation with the ventricular measure.

Estimated volumes for the measured brain structures are given in Table 6.

## DISCUSSION

Jernigan and Tallal (1990) reported a decline in the cortical grey matter proportion in adults relative to children. Expressing the cortical volume as a proportion, either of the cranial volume or of a regional volume, is a method often used to improve the sensitivity of the cortical measure by removing the effects of irrelevant variation in head size from one subject to the next. A decreasing proportion is interpreted as evidence for thinning of the cortex. However, such a proportion will decrease with age even though the cortical volume remains constant, if the cranial or regional volume is increasing. The results of the present study suggest that an increase in the cranial volume may occur over this age range, especially in the superior prefrontal region. This small increase is consistent with evidence that the cranial sutures do not completely fuse until after 30 yrs of age (Hodges, 1971), and with radiological observations of increases in cerebral size during late childhood (Ethier, 1971). Given a cranial volume increase, the cortical proportion may be an inappropriate measure of cortical thickness. The multiple regression method used here provides estimates of the independent effects of brain size differences, gender and age on the cortical volumes. Thus, the significant age-decreases reported here are not due to increasing brain size. They occur because (statistically) an older person with a given brain size has less cortical grey matter than a younger person with the same brain size.

TABLE 6. MEAN (STANDARD DEVIATION) VOLUMES FOR ANATOMICAL MEASURES IN MILLILITRES

	<i>Mean</i>	<i>(SD)</i>
Total Supratentorial Cranium	1296.63	(122.61)
<b>Cranial regions</b>		
Inferior anterior	201.13	(26.08)
Inferior posterior	307.97	(37.66)
Superior anterior	319.30	(44.05)
Superior posterior	468.38	(56.17)
<b>Regional cortical grey matter volumes</b>		
Inferior anterior	105.20	(15.15)
Inferior posterior	150.72	(28.03)
Superior anterior	155.78	(20.35)
Superior posterior	229.37	(29.72)
<b>Regional cortical CSF volumes</b>		
Inferior anterior	17.12	(4.37)
Inferior posterior	16.52	(4.34)
Superior anterior	27.09	(9.63)
Superior posterior	35.66	(13.40)
<b>Subcortical structures</b>		
Caudate	13.10	(2.03)
Lenticular nucleus	14.57	(2.26)
Anterior diencephalic grey	2.59	(0.73)
Posterior diencephalic grey	13.89	(2.75)
Ventricular CSF	16.70	(5.36)

The present results suggest that the changes are localized in the superior cortical regions (comprised mostly of the frontal and parietal convexities). No evidence was found for significant change in the inferior cortical regions. Yakovlev and Lecours (1967) described continuing myelination after the first decade in the intracortical neuropil of what they referred to as the supralimbic areas. These regions make up a considerably larger proportion of our superior than our inferior regions. Thus, apparent cortical thinning in these regions could be due to late peripheral arborization of myelin. If, however, the cortical changes observed here were simply due to decreases in signal values within pixels near the edge of the cortical rim (associated with myelination), then no concurrent increases in CSF overlying these cortical regions would be expected. However, the regional pattern of age correlations for cortical CSF closely resembles that for cortical grey matter. The grey matter/CSF correlations show that the apparent cortical decreases are associated with visually subtle, but closely related, increases in adjacent sulcal CSF. This suggests that loss of constituents of the cortical neuropil accompanies the apparent cortical thinning, some of which may be due to myelination. An alternate explanation is that maturational changes coinciding with late myelination in these areas are associated with other biochemical processes in the cortex leading to the local accumulation of CSF.

Secondary analyses suggest that morphologic changes in this age range are not confined to cortical structures. The posterior diencephalic measure, consisting mostly of the thalamus, appears to undergo a subtle reduction in volume. Basal ganglia structures also appear to decrease in volume. However, because increasing iron deposition over this age range would reduce the apparent volume of these structures using the present

methods, these observations must be interpreted with caution. Such an explanation is especially likely for the changes observed in lenticular nucleus, where accumulation of iron has been amply demonstrated (Drayer *et al.*, 1986; Drayer, 1988). It is less likely to account for the caudate reductions. Furthermore, the fact that increases in CSF in the adjacent ventricles occur in association with the apparent reductions in caudate and thalamus, strengthens the argument for actual volume reductions of these structures.

The increase in the anterior diencephalic structures is entirely unexpected. The region measured is comprised of a set of small structures difficult to separate at the resolution achieved in the present images. Interpretation of increasing volume in these structures during adolescence should await replication. It is of interest, however, that animal studies have shown post-natal anatomic variation induced by gonadal steroids (*see* Arnold and Gorski, 1984, for review); and that receptors for these hormones are concentrated in some of the structures within our anterior diencephalic region, such as hypothalamic nuclei and septum (Stumpf and Sar, 1978; Rainbow *et al.*, 1982). Two recent MR studies (Hayakawa *et al.*, 1989; Elster *et al.*, 1990) have provided evidence that a growth spurt occurs in the pituitary gland at approximately the same age that we observe increasing anterior diencephalic volume. Taken together, these results suggest that pubertal hormonal changes may be accompanied by related brain structural alterations.

Huttenlocher (1979) has observed reductions in synaptic density in human frontal cortex during roughly the same age range as the changes reported here. It is possible that both observations reflect maturation of specific cortical structures during adolescence. In the present study, no change is observed within this age range in inferior cortical areas, suggesting regional variation in human cortical maturation. Other evidence for regional variation comes from Huttenlocher *et al.* (1982, 1987) who have suggested that changes in synaptic density in the occipital lobe are completed earlier than those in the frontal cortex. This appears to be in conflict with the findings in monkeys (Rakic *et al.*, 1986) which indicate that synaptic density declines in diverse cortical regions simultaneously.

Structural changes within these cortical regions could play an important role in such functional changes during adolescence as those that have been observed with sleep EEG (Feinberg *et al.*, 1977) and brain metabolism (Kennedy and Sokoloff, 1957; Chugani and Phelps, 1986; Chugani *et al.*, 1987). Purves (1988) has suggested that modification of central connectivity may be necessary during the rapid somatic growth of adolescence, and thus long-persisting neural plasticity may be needed to accommodate these changes.

Morphologic changes observed in the present study may also relate to pubertal alterations of higher cognitive and affective functions, or to the decrease in cortical plasticity thought to occur during late childhood and adolescence. Finally, they may be relevant in the pathogenesis of major psychiatric disorders, such as schizophrenia, which have a characteristic onset in late adolescence (Feinberg, 1982, 1982/1983, 1987). These speculations suggest hypotheses that may be testable *in vivo* in behavioural studies using MRI and morphometric techniques.

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