

Sex Differences in Brain Maturation during Childhood and Adolescence

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Brain development during childhood and adolescence is characterized by both progressive myelination and regressive pruning processes. However, sex differences in brain maturation remain poorly understood. Magnetic resonance imaging was used to examine the relationships between age and sex with cerebral gray and white matter volumes and corpus callosal areas in 118 healthy children and adolescents (61 males and 57 females), aged 6–17 years. Gender groups were similar on measures of age, handedness, socioeconomic status and Full Scale IQ. Significant age-related reductions in cerebral gray and increases in white matter volumes and corpus callosal areas were evident, while intracranial and cerebral volumes did not change significantly. Significant sex by age interactions were seen for cerebral gray and white matter volumes and corpus callosal areas. Specifically, males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females. While these data are from a cross-sectional sample and need to be replicated in a longitudinal study, the findings suggest that there are age-related sex differences in brain maturational processes. The study of age-related sex differences in cerebral pruning and myelination may aid in understanding the mechanism of several developmental neuropsychiatric disorders.

Introduction

As evidenced by post-mortem studies, brain development during childhood and adolescence is characterized by regressive and progressive processes, such as synaptic and axonal pruning (Huttenlocher, 1979) and progressive myelination (Yakovlev and LeCours, 1967). The advent of quantitative magnetic resonance imaging (MRI) studies has advanced the study of child and adolescent brain development *in vivo*. Findings from cross-sectional studies suggest that cerebral gray matter (GM) volumes decrease progressively after age 4 (Jernigan and Tallal, 1990; Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994; Caviness *et al.*, 1996; Reiss *et al.*, 1996), perhaps in relationship to the regressive processes of synaptic and axonal pruning during development. Giedd and his colleagues have recently demonstrated in longitudinal studies that there are regionally specific nonlinear pre-adolescent increases followed by post-adolescent decreases in cortical GM (Giedd *et al.*, 1999a; Thompson *et al.*, 2000). On the other hand, findings from cross-sectional studies suggest that cerebral white matter (WM) volume (Pfefferbaum *et al.*, 1994; Caviness *et al.*, 1996; Reiss *et al.*, 1996) and the area of the corpus callosum (CC), the main interhemispheric commissure, increase significantly from childhood through late adolescence (Giedd *et al.*, 1996a). Recent results from longitudinal MRI studies of healthy children and adolescents have confirmed these age-related linear increases in cerebral WM and CC area (Giedd *et al.*, 1999a; Giedd *et al.*, 1999b; Thompson *et al.*, 2000). These observations may reflect *in vivo* evidence of age-related progressive events such as axonal growth and myelination.

It is well known that cognitive and emotional development differs between boys and girls [for review see (Nagy Jacklin and Martin, 1999)], though the timing, patterning and neurobiological parallels of such differential development remain poorly understood. Normal pubertal development is associated with marked increases in plasma levels of sex steroids (Ducharme and Forest, 1993). Preclinical studies suggest that sex steroid receptors are widely distributed throughout the brain and influence neurodevelopment [for review see (McEwen, 1981)]. Cognitive abilities, particularly visuo-spatial skills, differ between males and females (Hampson and Kimura, 1992; Kimura, 1996; Janowsky *et al.*, 1998). Sex differences in brain development may be related to the prevalence, course and treatment of several neuropsychiatric disorders, such as autism, attention deficit hyperactivity disorder and schizophrenia (Seeman, 1997; Cohen *et al.*, 1999).

We investigated the relationship between age, sex and cerebral GM and WM volumes and CC area using high-resolution MRI volumetric analyses in a large community sample of healthy, age-matched and sociodemographically similar male and female children and adolescents. We specifically investigated age-related sex differences in human brain maturational processes (age-related changes in cerebral GM and WM volumes and CC area).

Materials and Methods

Subjects

Sixty-one male and 57 female healthy children and adolescents (age range: 6.9–17 years) were recruited by advertisement from the community and underwent extensive clinical evaluations. The Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL), which includes a comprehensive post-traumatic stress disorder interview (Kaufman *et al.*, 1997), ruled out the presence of DSM-IV Axis I mental disorders. Socioeconomic status (SES) for each subject was completed using the Hollingshead Four Factor Index (Hollingshead, 1975). An abbreviated version of the Wechsler Intelligence Scale for Children (WISC-R) (i.e. Vocabulary, Digit Span, Block Design and Object Assembly) provided an estimate of Full Scale IQ (Wechsler, 1974). Handedness was determined using the 12 handedness items from the Revised Physical and Neurological Examination for Subtle Signs (PANESS) Inventory (Denckla, 1985), where eight out of 12 items were defined as right handed. There were no significant group differences on age, race, Tanner stage (Marshall and Tanner, 1969, 1970), SES, handedness, and Full Scale IQ. Males were significantly taller than females. The majority of subjects were above average on Full Scale IQ (median IQ: 116). The demographic characteristics of the groups are presented in Table 1.

Exclusion criteria were: (i) current or lifetime history of psychiatric disorders, including alcohol and substance use disorders; (ii) a significant medical, neurological or psychiatric disorder, or history of head injury or loss of consciousness; (iii) a history of prenatal confounds that may influence brain maturation, such as prenatal exposure to substances or pregnancy and birth complications; (iv) severe obesity or growth failure; (v) Full Scale IQ lower than 80; and (vi) positive trauma or maltreatment

Table 1

Demographic characteristics of healthy male and female child and adolescent MRI subjects

	Male	Female	Statistic	P
n	61	57	—	—
Age in years (range in years)	12.0 ± 2.3 (6.9–17.0)	11.8 ± 2.5 (7.3–16.3)	$t_{116} = 0.51$	0.61
Race: white/biracial/African American	51/6/4	40/12/5	Fisher's exact test	NS
Tanner stage I/II/III/IV/V	17/19/13/8/4	18/12/15/8/4	$\chi^2 = 1.62$	0.81
Weight (kg)	51.1 ± 18.1	44.9 ± 17.0	$Z_1 = 1.91$	<0.06
Height (cm)	156.2 ± 15.1	148.9 ± 16.6	$t_{116} = 2.50$	<0.02
SES (range)	42.0 ± 10.8 (18–64)	39.5 ± 8.5 (18–58)	$Z_1 = 0.89$	0.37
Handedness (right/left)	58/3	55/2	Fisher's exact test	NS
Full Scale IQ (range)	119.2 ± 17.0 (89–153)	117.0 ± 13.1 (90–145)	$Z_1 = 0.79$	0.43

SES = socioeconomic status; Z = Wilcoxon/Kruskal–Wallis test.

history. This study was approved by the Biomedical Institutional Review Board of the University of Pittsburgh. After a complete description of the study was given to the subject and parents, written informed consent was obtained. Subjects received monetary compensation for participation.

Magnetic Resonance Imaging

MRI was performed using a GE 1.5 Tesla Unit (Signa System, General Electric Medical Systems, Milwaukee, WI) running version 5.4 software located at the UPMC MR Research Center. The subject's head was aligned in a head holder. Foam padding was placed on both sides of the head and wrapped soft towels were placed under the chin with the use of chin and forehead straps to minimize head movement. The subject's nose was positioned at '12:00' for alignment in this plane. A gradient multi-echo localizing axial slice verified this plane. A sagittal series (using TE = 18 ms, TR = 400 ms, flip angle = 90°, acquisition matrix = 256 × 192, NEX = 1, FOV = 20 cm, slices = 21) verified patient position, cooperation and image quality. We required that the midsagittal slice shows full visualization of the cerebral aqueduct and the anterior and posterior commissures, in which a line was estimated requiring the anterior commissure–posterior commissure line to be within 3° of 180. If these criteria were not met, the subject was realigned until this criterion was met. Coronal sections were then obtained perpendicular to the anterior commissure–posterior commissure line to provide a more reproducible guide for image orientation. A three-dimensional spoiled gradient recalled acquisition in the steady-state pulse sequence was used to obtain 124 contiguous images with slice thickness of 1.5 mm in the coronal plane (using TE = 5 ms, TR = 25 ms, flip angle = 40°, acquisition matrix = 256 × 192, NEX = 1, FOV = 24 cm). Axial proton density and T2-weighted images were obtained to enable exclusion of structural abnormalities on MRI. A neuroradiologist reviewed all scans and ruled out clinically significant abnormalities.

Prior to the actual scanning procedure, subjects underwent a desensitization procedure in a simulation scanner, which reproduced the sights and sounds of the scanning environment. This method achieves increased patient cooperation and improvement in image acquisition due to reduced head movement artifact (Rosenberg *et al.*, 1997b). Subjects watched videos of their favorite movies during scanning. Subjects were motivated to remain still by allowing them to see their brain images after their scan (i.e. if they move, their brain pictures would be blurred). Subjects tolerated the procedure well and all scans were obtained with no or minimum head movement artifact (<6%). No sedation was used. Scanning was directly supervised by a child and adolescent psychiatrist (M.D.D.B.).

Image Analysis

The imaging data were transferred from the MRI unit to a computer workstation (PowerMacintosh, Apple Computer) and analyzed using the IMAGE software (version 1.52) developed at the NIH (Rasband, 1996) that provides valid and reliable volume measurements of specific structures using a manually operated (hand tracing) approach. All measurements were made by trained and reliable raters who were blind to subject information. Intraclass correlation of inter- and intrarater reliability for independent designation of regions on segmented images obtained from 20 subjects were 0.99 and 0.99 for intracranial volume

(J.H. and K.F.), 0.99 and 0.99 for cerebral volume (J.H. and K.F.), and 0.99 and 0.99, respectively, for cerebral GM and WM volumes (J.H. and K.F.). Intra- and inter-rater reliability from 20 subjects were 0.99 and 0.98, respectively, for total CC area (J.H. and A.M.B., and J.H. and J.N.). These methods were previously described by our group (De Bellis *et al.*, 1999, 2000a,b).

Intracranial volumes were calculated by first manually tracing the intracranial volume of each coronal slice after exclusion of skull and dura, then summing these areas of successive coronal slices, including GM and WM and cerebral spinal fluid (CSF) volumes, and multiplying by slice thickness. These measures included frontal, parietal, temporal, occipital cortex, subcortical structures, cerebellum and brainstem.

Cerebral volumes were measured after manual exclusion of CSF volumes, cerebellum and brainstem in the same manner and included cortical and subcortical structures.

Total cerebral GM and WM volumes were calculated using a semi-automated segmentation algorithm. This computerized segmentation technique is both labor intensive and manually operated. It uses an interactive method where mathematically derived cutoffs for GM-WM-CSF partitions from histograms of signal intensities are used to individually select GM, WM, and CSF areas from each coronal slice. GM and WM and CSF areas are thus separately calculated and multiplied by slice thickness for individual subjects' GM, WM, and CSF volumes. In this way, we can minimize the inherent limitations on qualifying WM signal hypointensities as GM on T1-weighted MRI scans by visual inspection of slices (i.e. so that hypointensity artifacts in the CC or cerebral WM are not calculated as GM). This approach has been validated using both a stereological technique for brain morphometric measurements and a phantom with known absolute volumes (Keshavan *et al.*, 1995), and has been used in several published neuroimaging studies (Keshavan *et al.*, 1994b; Rosenberg *et al.*, 1997a; De Bellis *et al.*, 1999). Total cerebral GM and WM volume measures included cortical and subcortical WM and GM volumes.

The CC area was measured from a single midsagittal section selected as the slice showing full visualization of the anterior and posterior commissures and the cerebral aqueduct [as described in a diagram published previously (De Bellis *et al.*, 1999)].

Data Analysis

Data distributions were examined for normality and outliers before applying linear models. Linear regression models were undertaken for gender groups, age, and age by group interactions, and for the main effects of group and age on the dependent variables using covariates as described. To control for the known sex differences, cerebral volume was covaried for GM, WM and CC analyses. All significance testing involving the main hypothesis was two-tailed, with alpha < 0.05.

Results

Age-related Changes between Genders

The sex by age interaction term was significant for cerebral GM and WM volumes and CC area (see Fig. 1). The slopes of these changes significantly differed between male and female subjects

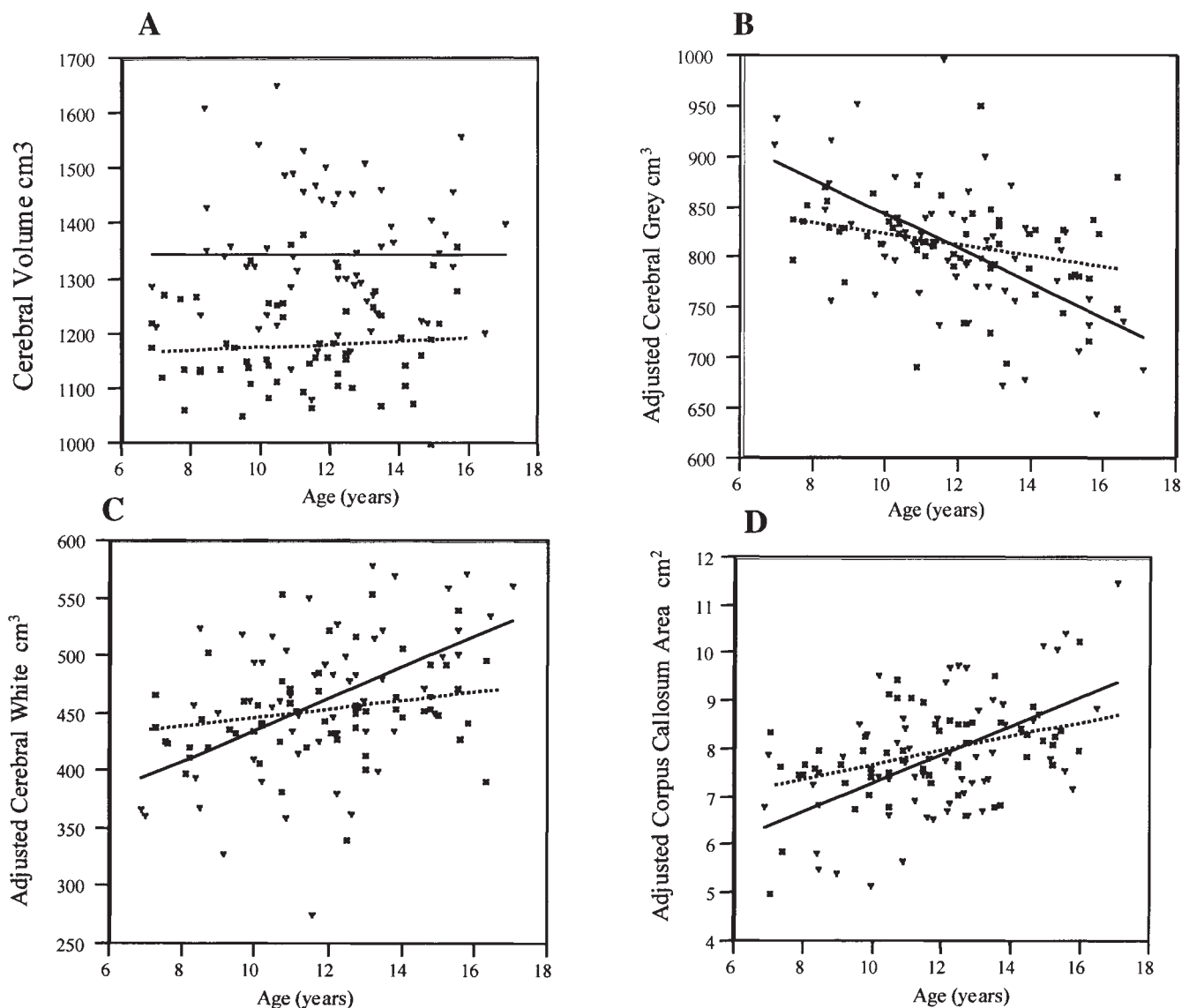


Figure 1. Scatterplots of cerebral volume (A), cerebral GM (B) and cerebral WM (C) volumes and CC areas (D) by age and sex in healthy male ($n = 61$) (solid lines, individual points = \square) and female ($n = 57$) (dashed lines, individual points = \triangle) children and adolescents. Cerebral GM and WM volume and CC area means were adjusted for cerebral volume. For males, the linear regression lines with regression equation and R^2 were: cerebral vol. = $1342.75 + 0.14768 \text{ age}$, $R^2 = 0.00$; GM = $1013.89 - 17.2084 \text{ age}$, $R^2 = 0.35$; WM = $300.208 + 13.519 \text{ age}$, $R^2 = 0.24$; and CC = $4.34662 + 0.2962 \text{ age}$, $R^2 = 0.27$. For females, the linear regression lines with regression equation and R^2 were: cerebral vol. = $1158.53 + 2.5461 \text{ age}$, $R^2 = 0.005$; GM = $876.772 - 5.30581 \text{ age}$, $R^2 = 0.08$; WM = $407.774 + 3.92078 \text{ age}$, $R^2 = 0.06$; and CC = $6.10137 + 0.14767 \text{ age}$, $R^2 = 0.17$.

(see Table 2). Thus girls showed significant developmental changes with age but at a slower rate than boys. Specifically, males had an $\sim 19.1\%$ reduction in GM volume between 6 and 18 years of age compared with a 4.7% reduction in females. On the other hand, males had a 45.1% increase in WM and a 58.5% increase in CC area compared with 17.1 and 27.4% increases, respectively, in females.

After covarying for the effects of Full Scale IQ, the sex by age interaction term remained significant for cerebral GM [$F(1,112) = 7.00$, $P = 0.009$] and WM [$F(1,112) = 7.18$, $P < 0.009$] volumes. A suggestive but nonsignificant difference was seen in the sex by age interaction term for CC area [$F(1,112) = 3.69$, $P < 0.06$].

To explore the relationship between Tanner stage of pubertal development and cerebral GM and WM volumes and CC area, separate analyses were undertaken by substituting Tanner stage for age. In this case, the sex by Tanner stage interaction term were significant for cerebral GM [$F(1,107) = 2.75$, $P = 0.03$] and

cerebral WM volumes [$F(1,107) = 2.78$, $P = 0.03$] and CC area [$F(1,107) = 2.43$, $P = 0.05$].

Age

Overall, cerebral GM volume showed the expected significant decrease, while cerebral WM volume and corpus callosal area showed the expected significant increase with age (see Fig. 1 and Table 2). Goodness-of-fit regression models of these structures indicated that the relationships with age were linear. Intracranial and cerebral volumes did not significantly increase with age (see Fig. 1).

Gender

Males had larger intracranial and cerebral volumes than females by 11 and 12%, respectively [$F(1,115) = 55.90$, $P < 0.0001$]. These effects remained after correction for height [$F(1,115) = 57.69$, $P < 0.0001$]. Cerebral GM and WM volumes and CC areas

Table 2

Means and linear regression of brain structures of healthy male and female child and adolescent MRI subjects

Structures	Males (mean \pm SD)	Females (mean \pm SD)	Group (males > females)	Age	Sex \times age
Intracranial volume (cm ³)	1581.94 \pm 137.54	1409.86 \pm 92.64	$F(1,115) = 63.03; P < 0.0001$	$F(1,115) = 0.86; P = 0.35$	
Cerebral volume	1344.53 \pm 123.41	1188.50 \pm 85.70	$F(1,115) = 63.49; P < 0.0001$	$F(1,115) = 0.13; P = 0.72$	
Cerebral GM	850.75 \pm 97.41	767.96 \pm 71.50	$F(1,114) = 1.72^a; P = 0.19$	$F(1,114) = 25.07^a; P < 0.0001$	$F(1,113) = 8.13^b; P = 0.005$
Cerebral WM	493.79 \pm 80.79	420.34 \pm 49.52	$F(1,114) = 1.41^a; P = 0.24$	$F(1,114) = 23.44^a; P < 0.0001$	$F(1,113) = 7.32^b; P < 0.008$
CC (cm ²)	8.04 \pm 1.28	7.69 \pm 0.93	$F(1,114) = 0.13^a; P = 0.72$	$F(1,114) = 33.27^a; P < 0.0001$	$F(1,113) = 3.94^b; P < 0.05$

^aLinear regression adjusting for sex, age and cerebral volume.^bLinear regression adjusting for sex, age, sex and age interaction, and cerebral volume.

did not differ between gender groups after adjustment for cerebral volumes (see Table 2).

Discussion

In this neuroimaging study, boys showed significantly greater loss of GM volume and an increase in both WM and CC area compared with girls over a similar age range. Consequently, girls showed significant developmental changes with age but at a slower rate than boys. Consistent with earlier cross-sectional studies (Jernigan and Tallal, 1990; Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994; Caviness *et al.*, 1996; Giedd *et al.*, 1996a,b; Reiss *et al.*, 1996) and recent longitudinal investigations (Giedd *et al.*, 1999b; Rapoport *et al.*, 1999; Thompson *et al.*, 2000), significant age-related decreases in cerebral GM and increases in cerebral WM volumes and CC areas were evident in the overall sample, while intracranial and cerebral volumes did not change significantly. While these data are from a cross-sectional sample and need to be replicated in a longitudinal study, the results suggest that there are age-related sex differences in brain maturation. GM decreases are likely to reflect dendritic pruning processes, since GM is largely composed of cells and dendrites; there is no evidence of large scale cell loss (apoptosis) during late childhood and adolescence (Oborai *et al.*, 1998). WM increases could be due either to myelination, increases in axonal size, glial proliferation or a combination of these.

To our knowledge, this is the first study showing sex differences in both cerebral GM and WM maturational processes in childhood and adolescence. Results from a recent longitudinal MRI study of child and adolescent brain development also described sex differences in the rate of linear WM increase, with greater age-related increases in males than females (Giedd *et al.*, 1999a). These results are similar to those of this cross-sectional study reported here. Giedd *et al.* (Giedd *et al.*, 1999a) did not find sex differences in the nonlinear rate of pre-adolescent increases and post-adolescent decreases seen in regional GM over this developmental period. Subcortical GM measures were not included in this latter study, which may have contributed to the differences in findings. However, several cross-sectional investigations of human aging have suggested that there may be greater age-related atrophy in males compared with females (Gur *et al.*, 1991; Kaye *et al.*, 1992; Cowell *et al.*, 1994; Murphy *et al.*, 1996; Coffey *et al.*, 1998; Xu *et al.*, 2000). Significant sex by age interactions were found for sex differences in regional volumes in two of these studies (Cowell *et al.*, 1994; Murphy *et al.*, 1996). Recently, significantly larger ventricular volumes and smaller cerebral GM and WM volumes in older compared with younger people and in men compared with women were reported in a cross-sectional study of 116 adults, aged 59–85 years (Resnick *et al.*, 2000). However, significant sex by age interactions were not seen and no detectable changes upon repeat MRI on cerebral GM

and WM volumes measures after 1 year follow-up were seen in this restricted age range (Resnick *et al.*, 2000).

Previous cross-sectional MRI studies of children showed no significant sex differences in the slopes or shapes of linear or higher-order age functions for cerebral GM and WM volume and CC area measures (Jernigan and Tallal, 1990; Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994; Giedd *et al.*, 1996a; Reiss *et al.*, 1996). Relatively small sample sizes, the known wide range of inter-individual variation in cerebral structures, unequal samples of boys and girls, the use of clinic based populations as controls and the wide age range of subjects studied may have contributed to these negative findings.

Normal pubertal development is associated with a 26-fold increase in testosterone plasma levels in males and a 10-fold increase in estradiol plasma levels in females (Ducharme and Forest, 1993). Findings from animal studies suggest that sex steroids influence neurodevelopment. Estradiol positively influences hippocampal cell proliferation (Tanapat *et al.*, 1999), number of dendritic spines (Gould *et al.*, 1990) and synaptogenesis (Woolley *et al.*, 1996), and delays synaptic pruning in other brain regions (Naftolin *et al.*, 1990). On the other hand, testosterone (Martini and Melcangi, 1991) may be associated with myelinogenesis. The results from this study may suggest that the earlier maturation in females may lead to an estrogen-mediated delay in dendritic pruning. The findings reported here, of significant sex by Tanner stage interaction terms for cerebral GM and cerebral WM volumes and CC area, support the idea of a hormonal influence on these brain maturational processes.

The results of this study are limited by its cross-sectional design and need to be replicated with longitudinal data to truly demonstrate if the growth curves are different for boys and girls. Other limitations of this investigation may have contributed to these findings. These include (i) a wide range of inter-individual variation in cerebral structures between subjects of similar age; (ii) the use of highly functioning subjects, whose results may not be generalizable; and (iii) the use of a methodological approach that only estimates gray and WM tissue separation as there are no universally accepted or validated GM–WM separation methods published to date. However, the inclusion of a large group of healthy, high functioning and clinically well characterized child and adolescent subjects, who were well matched on important variables and very cooperative during the scanning procedures, was an important strength in this study.

Thus, if these findings are confirmed with longitudinal data, the observed differences in patterns of brain maturation between boys and girls are likely to be of considerable pathophysiological significance in neuropsychiatry. It has been proposed that neuropsychiatric illnesses, such as schizophrenia, with a typical adolescent onset may be mediated by excess elimination of synapses (Feinberg, 1982; Keshavan *et al.*, 1994a). This theory has received recent support from neuropathological

studies (Glantz and Lewis, 2000). The rapid rate of peri-adolescent pruning in males may underlie the early age of onset and increased illness severity in male schizophrenic patients (Seeman, 1997; Cohen *et al.*, 1999). It was also found that maltreated male children and adolescents with post-traumatic stress disorder showed more evidence of adverse brain development than maltreated females with post-traumatic stress disorder, an illness that may be seen as environmentally induced (De Bellis *et al.*, 1999). Further research is needed to examine whether estrogens have a protective effect against certain neuropsychiatric disorders (i.e. schizophrenia or post-traumatic stress disorder) and whether this is mediated by the hormonal effects on cerebral pruning processes. Age-related sex differences in cerebral pruning and myelination warrant further investigation and may aid in understanding the mechanism of several developmental neuropsychiatric disorders.

Notes

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