

SEXUAL DIMORPHISM OF THE DEVELOPING HUMAN BRAIN

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Abstract

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1. Sexual dimorphism of human brain anatomy has not been well-studied between 4 and 18 years of age, a time of emerging sex differences in behavior and the sexually specific hormonal changes of adrenarche (the predominantly androgenic augmentation of adrenal cortex function occurring at approximately age 8) and puberty.
2. To assess sex differences in brain structures during this developmental period volumes of the cerebrum, lateral ventricles, caudate, putamen, globus pallidus temporal lobe, amygdala, and hippocampus, and midsagittal area measurements of the corpus callosum were quantified from brain magnetic resonance images of 121 healthy children and adolescent and examined in relation to age and sex.
3. Males had a 9% larger cerebral volume. When adjusted for cerebral volume by ANCOVA only the basal ganglia demonstrated sex differences in mean volume with the caudate being relatively larger in females and the globus pallidus being relatively larger in males. The lateral ventricles demonstrated a prominent sex difference in brain maturation with robust increases in size in males only. A piecewise-linear model revealed a significant change in the linear regression slope of lateral ventricular volume in males after age 11 that was not shared by females at that or other ages.
4. Amygdala and hippocampal volume increased for both sexes but with the amygdala increasing significantly more in males than females and hippocampal volume increasing more in females.
5. These sexually dimorphic patterns of brain development may be related to the observed sex differences in age of onset, prevalence, and symptomatology seen in nearly all neuropsychiatric disorders of childhood.

Key words: adolescent, brain, child, MRI, sex

Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD), Magnetic Resonance Imaging (MRI), Obsessive Compulsive Disorder (OCD), Physical and Neurological Examination for Subtle Signs (PANESS), Wechsler Intelligent Scale for Children - Revised (WISC-R), Wide Range Achievement Test (WRAT)

Introduction

Male/female differences have been reported for performance on cognitive tasks (Cairns *et al.*, 1985; Johnson and Meade, 1987; Gouchie and Kimura, 1991), brain physiology (Duke *et al.*, 1980; Gur *et al.*, 1995; Shaywitz *et al.*, 1995), and brain structure (Ho *et al.*, 1980; Witelson and Kigar, 1988; Witelson, 1989; Witelson, 1991; Cowell *et al.*, 1994; Kulynych *et al.*, 1994; Schlaepfer *et al.*, 1995; Murphy *et al.*, 1996). Few of these studies have involved children although the well-established differences in age of onset of puberty and differences in age of onset, incidence, symptomatology, and risk factors in nearly all neuropsychiatric disorders of childhood onset (American Psychiatric Association, 1994) make the pediatric population particularly pertinent for sexual dimorphism studies.

Part of the reason for the paucity of structural brain data of children and adolescents is that postmortem data is scarce for this age group. Mortality is low and autopsies are rarely performed. In vivo techniques such as computerized tomography and conventional radiography use ionizing radiation precluding their ethical use in the study of healthy children. The advent of magnetic resonance imaging (MRI), which provides excellent anatomical resolution without the use of ionizing radiation, opened the door for imaging of healthy children, although the high cost of the technology has made studies of healthy children sparse. The common practice of using as controls children referred for scans for clinical reasons whose scans were subsequently read as normal is problematic because indications for clinical MRI scans, such as head trauma or seizures, occur in higher frequency in children with neuropsychiatric disorders such as attention-deficit/ hyperactivity disorder (ADHD) (Szatmari *et al.*, 1989). Also, excluding scans of clinically healthy children who have abnormal scans confounds comparisons to clinical groups.

To provide normative data not confounded by these effects the Child Psychiatry Branch of the National Institute of Mental Health has been recruiting healthy children and adolescents from the community for participation in an MRI brain imaging project. In this study the authors report the effects of age and sex on brain morphometry in a sample of 121 subjects, ages 4 to 18 years, a subset of which has been described elsewhere (Giedd *et al.*, 1996 a,b,c).

Methods

Subjects

From 748 responses to local advertisements 296 subjects were excluded by phone interview because of a history of learning disorder or ADHD in the child, sibling, or first degree relative; special service needs in school; current use of medications; or ongoing medical or psychiatric disorders. Of the remaining 452 subjects 230 were excluded based on responses to questionnaires mailed to their parents or teachers which included a medical history form, the Child Behavior Checklist (Achenbach and Edelbrock, 1983), and the Conner's parent and teacher forms (Werry et al. 1975; Goyette et al., 1978). This left 222 subjects who came in for face-to-face screening process which included a physical and neurological exam, a structured psychiatric interview using the Child and Parent Diagnostic Interview for Children - Revised (Welner et al., 1987), Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children - Revised (WISC-R) (Wechsler, 1974), the spelling subtest of the WRAT, and the reading achievement cluster of the Woodcock-Johnson Psychoeducational battery, and a clinical interview of the subject and parent(s) by a Child and Adolescent psychiatrist (JNG) which included a family history assessment. Ninety-one subjects were excluded during this process.

Once children made it to the point of scan acquisition they did quite well. Of 131 attempts 3 failed to complete scans because of anxiety or claustrophobia, and of the remaining 128, 7 scans were unsatisfactory because of excessive movement during the scan. Because of variation in scan quality not all measures were possible for all subjects. Sample sizes for the various measures were as follows: cerebrum - 121, lateral ventricles - 121, caudate - 114, putamen - 114, globus pallidus - 112, temporal lobe - 115, amygdala - 115, hippocampus - 115, and corpus callosum - 121.

All subjects were assessed by the 12 handedness items from the Physical and Neurological Examination for Subtle Signs (PANESS) inventory (Denckla, 1985). Subjects showing a right-hand preference on all 12 items were classified as right-handed.

Characteristics of the children and adolescents for whom MRI data were available are presented in Table 1. There were no group differences between males and females on age, height, weight, handedness, or IQ subtest scores. As can be seen from the WISC-R subtests the resulting sample is not average (which would be 10) on these measures. Vocabulary and Block Design subtests were chosen because a combination of these two subtests has been shown to have a 0.86 correlation with full scale IQ (Silverstein, 1985). The higher than average IQ scores are an expected consequence of our strict inclusion criteria, however it does pose some problems regarding the generalizability of our findings.

Table 1
 Characteristics of Healthy MRI Subjects (N = 121)

	Male	Female
Sample Size	71	50
^a Age (years)	10.6 (3.7) [4.3-18.0]	11.0 (3.8) [3.6-17.7]
^a Height (inches)	57.2 (9.3) [36.5-75.5]	57.2 (8.2) [41-71]
^a Weight (pounds)	89.1 (38.6) [32-208]	89.3 (34.6) [34-180]
^a Tanner Stage	2.1 (1.6) [1-5]	2.4 (1.6) [1-5]
Handedness	92% right	90% right
^a Vocabulary	13.7 (3.2) [6-19]	12.7 (2.5) [7-19]
^a Block Design	13.5 (3.7) [4-19]	12.7 (3.5) [3-19]
^a Digit Span	11.2 (3.0) [5-19]	11.4 (2.5) [4-16]

^a mean (standard deviation) [range]

No statistical differences between sexes on any of these variables.

The protocol was approved by the Institutional Review Board of the National Institute of Mental Health. Written assent from the child and consent from the parents were obtained.

MRI Protocol

All subjects were scanned on the same General Electric 1.5 Tesla Signa scanner using a spoiled gradient recalled echo in the steady state (3D SPGR) imaging sequence with echo time = 5 msec, time to repeat = 24 msec, flip angle = 45 degrees, acquisition matrix = 192 x 256, number of excitations = 1, and field of view = 24 cm. T1-weighted sagittal images with slice thickness of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane were obtained. Vitamin E capsules, two wrapped in gauze and placed in the meatus of each ear and a third capsule taped to the lateral aspect of the left inferior orbital ridge were used to help standardize head placement. If no slice of a multi-echo axial series clearly contained all three capsules, the patient was realigned until this criterion was met. As three non-linear points uniquely define a plane this procedure helps to identify a standardized coronal plane but still allows for rotation of the head within the coronal plane. To control for head alignment within the coronal plane, each subject's nose was aligned at the "12:00" position. It should be noted that external landmark based alignment criteria do not guarantee standardization of internal structures.

No sedation was used. Subjects were scanned in the evening to promote their falling asleep in the scanner. Younger children were allowed to bring blankets or stuffed animals into the scanner and have their parents read to them.

Image Analysis

All scans were evaluated by a clinical neuroradiologist. One subject was found to have increased T2 signal intensity in the right parietal lobe and another subject was noted to have increased T2 signal intensity in the area of the left semiovale. Neither of these findings was deemed clinically significant and both subjects were asymptomatic on clinical follow-up. The data from these scans was retained in the analysis. The decision to retain the subjects was made prior to quantification of the brain structures, however the subjects with anomalous T2 signal intensities were not outliers on any of the measures. No other gross abnormalities were reported for any subject.

The MRI images were processed and analyzed using a variety of computer platforms and software packages the details of which are described elsewhere (Giedd et al., 1996 a,b,c).

The brain was separated from the intracranial cavity using a program that models the brain as an active surface template which then conforms to the individual brain through a series of energy minimization functions (Snell et al., 1996). The output of this program was then edited to remove artifacts related to eyeballs or patches of dura to yield our measures of left and right cerebral hemisphere.

The midsagittal cross-sectional area of the corpus callosum and seven subdivisions were quantified using a semi-automated program developed by JCR (Rajapakse et al., 1996). The program is written in C language and is available upon request.

Ventricular volume was quantified using a simple thresholding function available in NIH Image (Rasband, 1993).

The measures of the caudate, putamen, globus pallidus, amygdala, hippocampus, temporal lobes were done using the manual tracing feature available in NIH Image. Left and right sides of the structures were quantified separately. Inter-rater (JNG and ACV) correlation coefficient measurement reliability's for the quantified structures were as follows: cerebrum, 0.99; lateral ventricles, 0.99; caudate, 0.88; putamen, 0.84; globus pallidus, 0.82; temporal lobe, 0.98; amygdala, 0.86; hippocampus, 0.87; corpus callosum, 0.92.

Statistical Analysis

The sex-specific effects of age on brain structure volumes were assessed using the SAS General Linear Model procedure (SAS Institute, 1990). Sex differences were analyzed using repeated measures ANOVA. Because cerebral volume differed significantly between males and females an ANCOVA analysis was also performed to adjust for this difference. To graphically display the variability and non-linear nature of the developmental data scatterplots of cerebral volume and lateral ventricular volume by sex are presented fitted with a local regression procedure that retained the subtle non-linearities in the

data (a "super-smoother", see Hastie and Tibshirani, 1990) to yield smooth, curvilinear adaptive fits to the data.

Results

Variability

Variability of structure size was high for all structures examined, even in this well-screened group of healthy children. The degree of variability can be appreciated from the scatterplots by age of total cerebral volume and lateral ventricular volume presented in Figures 1 and 2.

Sex differences in mean size

Mean cerebral volumes were approximately 9% larger for males ($t = 18.44$, $p < 0.0001$), which was significant even after adjustment for height ($F = 6.78$, $p = 0.004$) and weight ($F = 6.53$, $p = 0.004$). As seen in Table 2, when adjusted for total cerebral volume (ANCOVA) the mean volumes of the basal ganglia demonstrated sexual dimorphism with the caudate relatively larger in females ($F = 9.95$, $p = 0.002$) and the globus pallidus relatively larger in males ($F = 11.8$, $p = 0.008$).

Sex differences in maturation

Total cerebral volume did not change significantly with age. However, various subcomponents of the brain did demonstrate age-related changes. Lateral ventricular volume increased robustly in males (slope of regression line = 0.72 ml/yr, $p = 0.0001$) with females showing a trend toward increasing volume with age (slope of regression line = 0.47 ml/yr, $p = 0.06$). Interestingly, the increase for males occurred almost entirely after age 11 (Fig. 2). A piecewise-linear model revealed a significant change in slope after age 11 ($p = 0.03$) not shared by females at that or other ages. For males only there was a significant decrease in left globus pallidus volume (slope of regression line = -0.02 ml/yr, $p = 0.05$) and a trend for a decrease in left caudate volume (slope of regression line = -0.03 ml/yr, $p = 0.09$). Amygdala volume increased robustly for males (slope of regression line = 0.14 ml/yr, $p = <0.0001$) and less so for females (slope of regression line = 0.06 ml/yr, $p = 0.05$), whereas hippocampal volume showed more robust increases in females (slope of regression line = 0.10 ml/yr, $p = 0.001$ and slope of regression line = 0.07 ml/yr, $p = 0.04$ for females and males respectively). (See Table 3: for data regarding left and right sides). Midsagittal cross-sectional area of the corpus callosum increased for both males and females (slope of regression line = 7.1 mm²/yr, $p = 0.007$ for males and slope of regression line = 10.1

mm²/yr, $p = 0.001$ for females), driven by increases in the posterior sections. Neither the total nor any of seven subdivisions of midsagittal corpus callosum area demonstrated sexual dimorphism. When adjusting by ANCOVA for total cerebral volume only the genu was sexually dimorphic being relatively larger in females ($F = 6.12$, $p = 0.015$). Temporal lobe volumes did not differ between the sexes, with or without adjustment for total cerebral volume.

Table 2

ANOVA and ANCOVA (adjusting for total cerebral volume) for Brain Structures by Sex and Side (right and left) in Healthy Children and Adolescents ($N = 121$)

Region	ANOVA			ANCOVA		
	F Value	P Value	Comment ^a	F Value	P Value	Comment
Cerebrum						
sex	18.44	<0.0001	M > F			
side	45.25	<0.0001	R > L			
Ventricles						
sex	0.91	0.34		0.70	0.40	
side ^b	7.10	0.009	L > R			
Caudate						
sex	1.11	0.29		9.95	0.002	F > M
side ^b	45.6	<0.0001	R > L			
Putamen						
sex	9.86	0.002	M > F	2.96	0.09	M > F
side ^b	109.6	<0.0001	L > R			
Globus Pallidus						
sex	15.55	<0.0001	M > F	11.80	0.0008	M > F
side ^b	0.21	0.64				
Amygdala						
sex	2.41	0.12		0.07	0.80	
side ^b	11.61	0.0009	R > L			
Hippocampus						
sex	1.12	0.29		0.32	0.57	
side ^b	13.35	0.0004	R > L			

^a F = Female, M = Male, R = Right, L = Left

^bside does not change with ANCOVA

Total Cerebral Volume vs Age for Healthy Children and Adolescents (N=121)

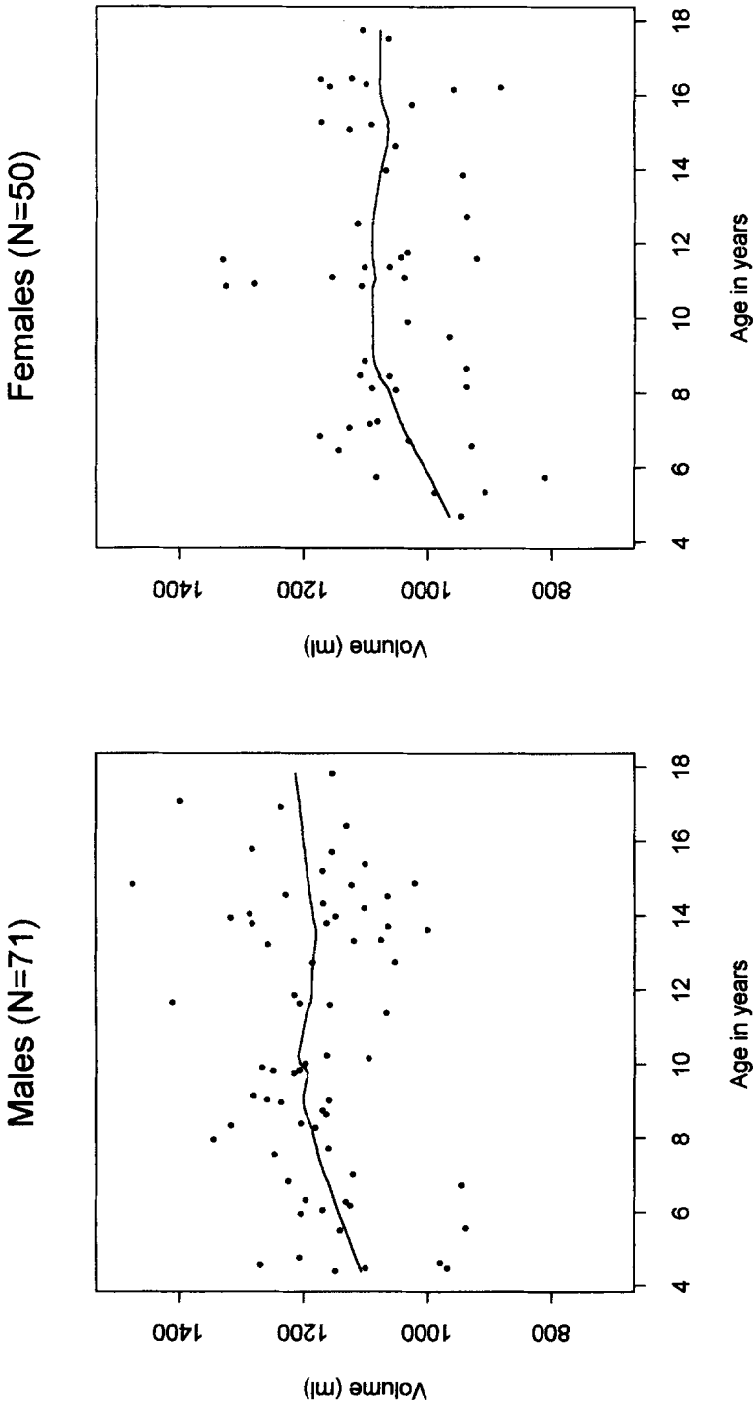


Fig 1. Scatterplots by age of total cerebral volume for male and female healthy children and adolescents (N = 121).

Lateral Ventricular Volume vs Age for Healthy Children and Adolescents (N=121)

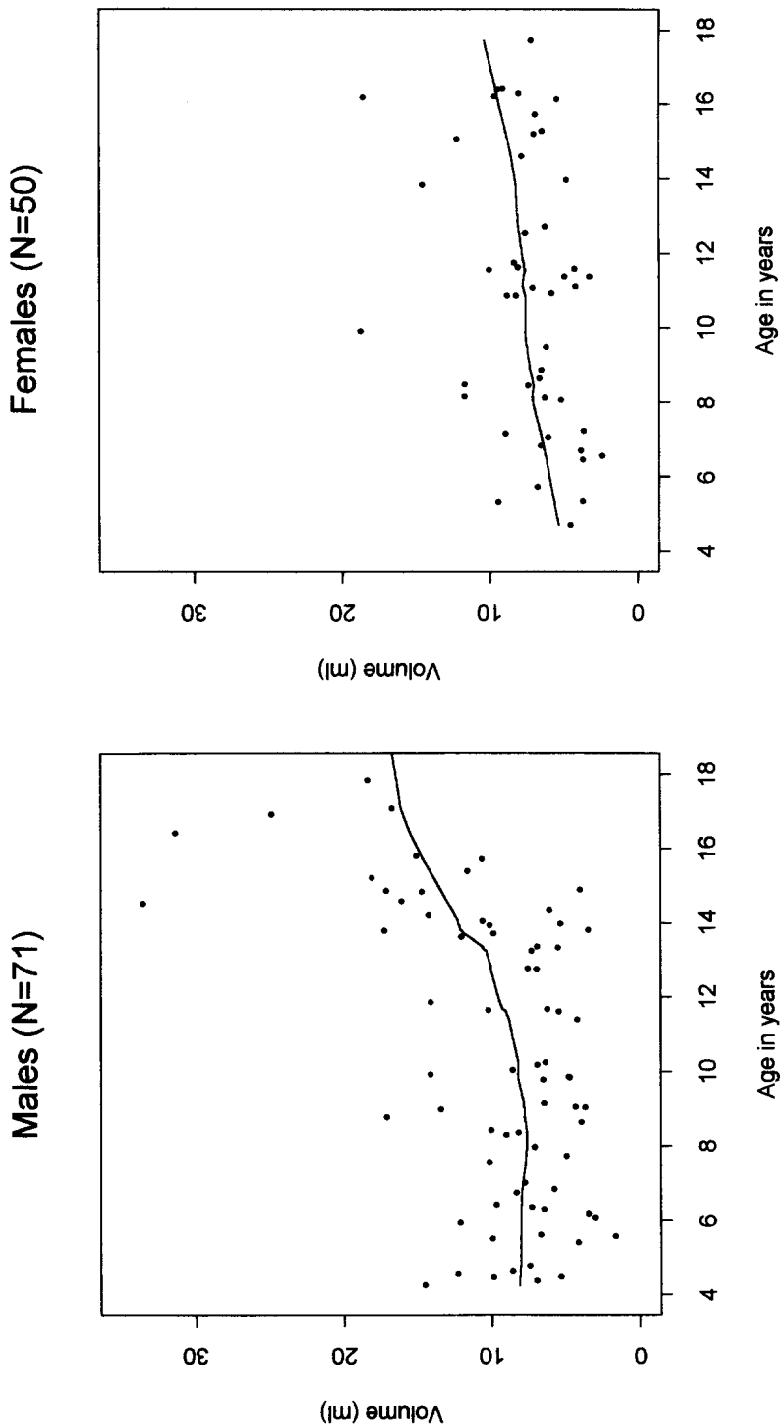


Fig 2. Scatterplots by age of lateral ventricular volume for male and female healthy children and adolescents (N = 121).

Table 3

Linear Regression of Brain Structure Size with Age by
Sex and Side in Healthy Children and Adolescents (N=121)

Region		Male		Female	
		slope in ml/yr	P value	slope in ml/yr	P value
Cerebrum	Right	0.93	0.64	3.1	0.12
	Left	1.1	0.58	2.7	0.19
Lateral Ventricles	Right	0.38	<0.0001	0.22	0.09
	Left	0.34	0.0007	0.25	0.06
Caudate	Right	-0.01	0.43	0.01	0.83
	Left	-0.03	0.09	0.01	0.83
Putamen	Right	0.01	0.41	-0.02	0.28
	Left	0.01	0.42	-0.03	0.18
Globus Pallidus	Right	-0.01	0.14	-0.01	0.25
	Left	-0.02	0.05	-0.003	0.64
Amygdala	Right	0.07	0.0002	0.03	0.14
	Left	0.08	<0.0001	0.03	0.09
Hippocampus	Right	0.05	0.01	0.05	0.01
	Left	0.02	0.26	0.05	0.0004
Corpus Callosum ^a		7.1	0.007	10.1	0.001

^aCorpus callosum is a midsagittal area measure (mm²)

Handedness

No effects of handedness or sex-by-handedness interactions were found in this study but due to the small number of adextrals (5 males, 5 females) no conclusions can be drawn.

Laterality

Although there were significant left-right differences (right-greater-than-left cerebral hemisphere, caudate, amygdala, and hippocampus; left-greater-than-right lateral ventricular volume and putamen), there were no sex-by-side or age-by-side interactions.

Discussion

Determinants of sexual dimorphism

The X chromosome, hormones, and the environment may all contribute to sexual dimorphism of brain structures. Based on an MRI study of Turner's syndrome the X chromosome appears to be involved in determining the adult size of the caudate, lentiform nucleus, thalamus, and cortical gray matter (Murphy et al., 1993). Hormonal effects seem to influence overall brain size and cerebral asymmetries (Kelley, 1988). Environmental influences such as infections, toxins, trauma, stress, adequacy of nutrition, or degree of enriched environment also play a role in determining structure size (Diamond et al., 1964; Jacobson, 1991).

The most robust sexually dimorphic brain feature in this pediatric population, as in adults, was total cerebral volume. On average male brains were approximately 9% larger than female brains, which was consistent across all ages examined (Fig. 1). The magnitude of this difference is similar to that found in adult postmortem (Dekaban and Sadowsky, 1978; Ho et al., 1980) and in vivo imaging studies (Flaum et al., 1995).

Given the myriad of factors that determine brain structure size, and findings of enlarged brains in patient groups such as Fragile X syndrome (Reiss et al., 1994) and autism (Piven et al., 1995), size difference should not be interpreted as imparting any sort of functional advantage or disadvantage. The fact that gross structural size may be insensitive to sexual differences in receptor density or connectivity between different neurons further emphasizes the complexity of interpreting the implications of size differences in brain structures.

Sexual dimorphism of the basal ganglia

Except for the basal ganglia the brain size difference appears to be relatively uniform. That is, when brain structure sizes are adjusted for total cerebral volume using ANCOVA only the basal ganglia demonstrate sexual dimorphism in mean structure size. For the basal ganglia the caudate were relatively larger in females, while the globus pallidus remained relatively larger in males. The sexual dimorphism of the basal ganglia is interesting in light of the frequent implication of basal ganglia involvement in neuropsychiatric disorders such as ADHD (Hynd et al., 1991; Castellanos et al., 1994; Castellanos et al., 1995) and Tourette's syndrome (Peterson et al., 1993; Singer et al., 1993; Hyde et al., 1995) which have a much higher incidence in males. Obsessive compulsive disorder (OCD), which has an approximately equal incidence for males and females in late adolescence and adulthood, may be more common in boys in early childhood (Swedo et al., 1989). Also, a developmental subtype of OCD which demonstrates a more treatment refractory course and neurological/basal ganglia abnormalities is more common in young

boys (Blanes and McGuire, 1997).

Sex differences in the amygdala and hippocampus

Sexual differences of maturational patterns were also noted, most prominently for the lateral ventricles, but also for the amygdala and hippocampus. The amygdala and hippocampus findings are consistent with the preponderance of androgen receptors in the amygdala (Clark *et al.*, 1988) and of estrogen receptors in the hippocampus of rats (Sholl and Kim, 1989). Further evidence of a relationship between estrogen and hippocampal volume in rodents is the decreased fiber outgrowth and altered density of dendritic spines in the hippocampus of gonadectomized adult females that is reversed with hormone replacement (Morse *et al.*, 1986; Gould *et al.*, 1990). Similarly, in humans women with gonadal hypoplasia have been found to have smaller hippocampi than controls (Murphy *et al.*, 1993).

Relevance to psychopathology

These sexually dimorphic patterns of brain development may interact with as yet uncharacterized environmental forces to yield the striking sex differences seen in most developmental neuropsychiatric disorders (American Psychiatric Association, 1994) and in some late adolescent/adult onset disorders, such as schizophrenia, which is increasingly viewed as a neurodevelopmental disorder (Bloom, 1993; Weinberger, 1995).

Differences in brain morphometry between subjects with schizophrenia and controls have included medial temporal lobe structures such as the amygdala and hippocampus as well as the basal ganglia and prefrontal and parietal association cortices, temporal lobe, superior temporal gyrus, and thalamus - but by far the most robustly replicated brain finding in schizophrenia is increased ventricular volume (Weinberger, 1995).

The most consistent phenomenological sex difference in schizophrenia is earlier age of onset in males, which was first reported by Kraepelin and has been replicated in more than 60 studies.

In our sample mean ventricular volume, adjusted or unadjusted for total cerebral volume, was not different between sexes, however healthy adolescent males have a significantly sharper rate of increase than healthy adolescent females (Fig. 2). Although enlarging ventricles may be a nonspecific sign of brain pathology, the authors speculate that the excess of males in adolescent onset schizophrenia may reflect some exaggeration of the normal brain maturational process.

Variability

Minimum sample size required to detect a difference between two groups can be calculated from a given structures coefficient of variation and the mean ratio of the two groups. The large variability in brain structure sizes reported in this study and the subtleness of sex and diagnostic differences call for large sample sizes in pediatric neuroimaging studies. For example, using the empirically-derived

coefficient of variation for the globus pallidus of 0.15 one can calculate, that to detect a 10% difference (with a 5% type I error and 80% power) one would need 38 subjects per group (Lange et al., 1997). To detect a 5% difference the number of subject needed per group exceeds 100.

This is far more than has traditionally been reported in the pediatric neuroimaging literature. The high variability also emphasizes the need for longitudinal studies to adequately characterize the heterochronous nature of most developmental curves. Such longitudinal studies, supported by high rescan reliability's for MRI brain measures (Giedd et al., 1995), are currently underway.

Conclusions

Brain structure sizes are highly variable, even in well-screened healthy children and adolescents. Boy's brains and girl's brains differ most notably in overall size, with male brains being approximately 9% larger across all age spans. This should not be interpreted as imparting any sort of functional advantage or disadvantage. When adjusting for the overall size of the brain only the basal ganglia remain sexually dimorphic with the caudate being relatively larger in girls and the globus pallidus being larger in boys. Other structures such as the amygdala and hippocampus, as well as the lateral ventricles, demonstrate sexually specific differences in maturation. These sex differences in the normal development of the brain may interact with as yet uncharacterized environmental or genetic influences to account for the sex differences in age of onset, prevalence, and symptom profiles observed in nearly all neuropsychiatric disorders of childhood.

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