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Quantitative MRI of the Temporal Lobe, Amygdala, and Hippocampus in Normal Human Development: Ages 4–18 Years

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ABSTRACT

The volume of the temporal lobe, superior temporal gyrus, amygdala, and hippocampus was quantified from magnetic images of the brains of 99 healthy children and adolescents aged 4–18 years. Variability in volume was high for all structures examined. When adjusted for a 9% larger total cerebral volume in males, there were no significant volume differences between sexes. However, sex-specific maturational changes were noted in the volumes of medial temporal structures, with the left amygdala increasing significantly only in males and with the right hippocampus increasing significantly only in females. Right-greater-than-left laterality effects were found for temporal lobe, superior temporal gyrus, amygdala, and hippocampal volumes. These results are consistent with previous preclinical and human studies that have indicated hormonal responsivity of these structures and extend quantitative morphologic findings from the adult literature. In addition to highlighting the need for large samples and sex-matched controls in pediatric neuroimaging studies, the information from this understudied age group may be of use in evaluating developmental hypotheses of neuropsychiatric disorders. © 1996 Wiley-Liss, Inc.*

Indexing terms: child, adolescent, neuroanatomy, sex, maturation

The temporal lobes and related medial structures, such as the amygdala and the hippocampus, subserve functions of language, memory, and emotion (Nolte, 1993). Human capacity for these functions changes markedly from ages 4 to 18 years (Jerslid, 1963; Wechsler, 1974; Diener et al., 1985); however, because of the paucity of postmortem data or well controlled imaging studies of healthy children (Giedd et al., 1996), little is known about morphometric changes in these structures that parallel cognitive and behavioral development.

Electroencephalographic studies of adolescents and young adults indicate ongoing maturation of the temporal lobes during the second decade of life (Buchsbaum et al., 1992). To our knowledge, however, no in vivo quantitative morphologic studies of these structures have been carried out for children and adolescents. In one of the few postmortem studies of temporal lobe or related structures that included subjects from the child and adolescent age range, it was noted that myelination in a key relay zone of the hippocampal formation continues throughout adolescence (Benes et al., 1994).

With the use of magnetic resonance imaging (MRI), studies of normal aging in adults have indicated maturational changes for the temporal lobe and for medial temporal structures, which, in part, are sex specific. For instance, a recent study comparing brain morphology of 36 subjects aged 20–35 years to that of 33 subjects aged 60–85 years found age-related decreases in the amygdala for males and females but found a decrease in the hippocampus for females only (Murphy et al., 1996). A study comparing temporal lobe measures of 96 subjects aged 18–40 years to those of 34 subjects aged 41–80 years found an 8% decrease in temporal lobe volume for males (Cowell et al., 1994). However, these results may reflect processes at the extreme end of the aging process. A recent study that included 87 healthy adults aged 18–55 years reported larger superior temporal gyrus volumes in males but found no significant age effects (Flaum et al., 1996).

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Based on these reports and on animal and human studies that have indicated the responsivity of these structures to hormones (Morse et al., 1986; Gould et al., 1990; Murphy et al., 1993), we anticipated sex-specific maturational changes in the temporal lobe and in related medial structures for our child and adolescent sample, possibly with exaggerated effects concurrent with the hormonal changes of adrenarche or puberty.

Volumetric measures of the temporal lobe, superior temporal gyrus, amygdala, and hippocampus were acquired in 99 healthy children and adolescents aged 4–18 years. This study is part of an ongoing project at the Child Psychiatry Branch of the National Institute of Mental Health to examine the relationship between brain form and function in healthy and neuropsychiatrically impaired children and adolescents. Quantitative morphometry of the cerebrum, cerebellum, and basal ganglia for most of the subjects from this data set have been reported elsewhere (Giedd et al., 1996).

MATERIALS AND METHODS

Subjects

Healthy male (n = 53) and female (n = 46) subjects (mean age 11.8 years, S.D. 3.4 years, range 4.7–17.8 years) were recruited from the community over the last 5 years. Assessment included physical and neurological examinations, the 12 handedness items from the Physical and Neurological Examination for Subtle Signs (PANESS) inventory (Denckla, 1985) and clinical psychiatric interviews using the Child and Parent Diagnostic Interview for Children (Welner et al., 1987), the Child Behavior Checklist (Achenbach and Edelbrock, 1983), Conners' 48-item Parent and 39-item Teacher Questionnaires (Conners, 1973; Goyette et al., 1978), Vocabulary, Block Design, and Digit Span subtests of the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) for subjects under 16 years of age or the Wechsler Adult Intelligent Scale—Revised for subjects 16 or older (Wechsler, 1981), the spelling subtest of the Wide Range Achievement Test—Revised (Jastak and Wilkinson, 1984), and the Woodcock-Johnson Psycho-Educational Battery Reading Cluster Score consisting of Letter-Word Identification, Word Attack, and Passage Comprehension subtests; Woodcock and Johnson, 1977). Individuals with physical, neurological, or lifetime histories of psychiatric abnormalities were excluded. Subjects with first-degree relatives or with more than 20% of second-degree relatives with major psychiatric disorders were also excluded. Approximately five candidates were screened for every one accepted (Giedd et al., 1996). To enhance the independence of sample subjects, only one child per family was included in the data set. Male subjects were taller than the female subjects ($t = 2.37$; $P = 0.02$) and scored higher on the Vocabulary subtest of the WISC-R ($t = 1.99$; $P = 0.05$). There were no significant group differences for age, handedness, Tanner stage, Reading Cluster Score on the Woodcock Johnson test, or Digit Span and Block Design subtests of the WISC-R. Subject characteristics are shown in Table 1, where it can be seen that the subjects were above average (10 ± 3) on WISC-R subtests. Our strict inclusion criteria made this outcome likely, although it did limit the generalizability of these findings.

Subjects were scanned within 2 months of screening. From the scatterplot distributions in Figure 2, it can be seen that age distribution was not uniform, with fewer subjects in the youngest age quartile. The protocol was approved by the Institutional Review Board of the National Institute of Mental Health. Written consent from the parents and assent from the child were obtained.

TABLE 1. Characteristics of Healthy MRI Subjects[1]

Parameter	Female	Male
Sample size	46	53
Age (years)	11.2 (3.8)	12.2 (3.0)
Height (cm)	146.3 (20.6)	152.6 (18.6)*
Weight (kg)	41.5 (15.8)	46.3 (15.0)
Tanner stage	2.2 (1.5)	2.4 (1.6)
Handedness	90% right handed	90% right handed
Vocabulary	12.7 (2.5)	13.8 (2.8)*
Block design	12.7 (3.5)	13.6 (2.5)
Digit span	11.4 (2.3)	11.2 (2.4)

[1]Aged 4–18 years; n = 99.
*Male > Female; $P \leq 0.05$.

MRI acquisition

All subjects were scanned on the same GE 1.5 Tesla Signa Advance scanner (GE Signa version 5.4). Three-dimensional volumetric acquisition using spoiled-gradient recalled echo in the steady state yielded images with slice thicknesses of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane. Images were acquired from coronal, axial, and sagittal orientations to avoid possible multiplanar reformatting errors related to nonanisotropic voxels. Time to echo was 5 msec, time to repeat was 24 msec, flip angle was 4°, acquisition matrix was 192 × 256, number of excitations was 1, and field of view was 24 cm. Head positioning during the scan was standardized by assuring that three vitamin E capsules, one placed in the meatus of each ear and one taped to the left lateral inferior orbital ridge, were all visible on a single axial slice. If no slice clearly contained all three capsules, then the patient was realigned until this criterion was met. Head positioning in the remaining plane was standardized by positioning the subject's nose at the 12:00 position. The 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 to have their parents read to them. Three children aged 5, 7, and 11 who had been accepted for the study were unable to complete the scan due to claustrophobia or excessive anxiety. No sedation was used.

Image analysis

Clinical interpretation. All scans were evaluated by a clinical neuroradiologist. One subject was found to have increased T2 signal intensity in the area of the left semiovale. Another subject was noted to have increased T2 signal intensity in the right parietal lobe. Neither hyperintensity was deemed clinically significant, and, on clinical follow up, both subjects were asymptomatic. They were retained in the data set. No other gross abnormalities were reported.

Total cerebral volume quantification. A technique that utilizes an active surface template of the brain to incorporate prior knowledge of brain anatomy to supplement MRI signal intensity characteristics was used to quantify the left and right cerebral hemispheres. This method models the brain surface as an elastically deformable structure while using successive iterations of an energy-minimization function to enforce constraints on curvature and topology. After this procedure, the brains were examined and edited slice by slice in the axial plane by experienced raters to remove

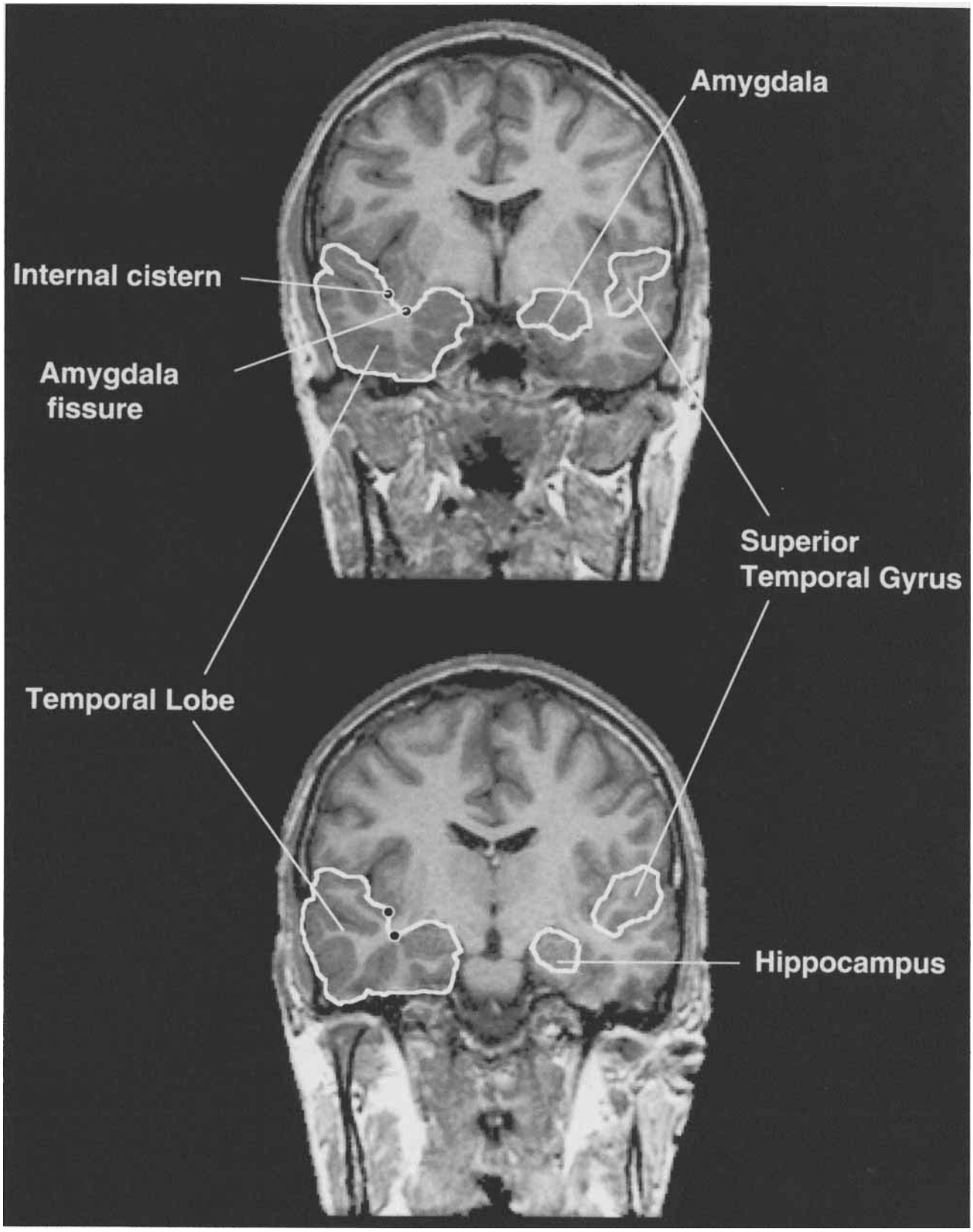

Fig. 1. Boundaries for measures of temporal lobe, superior temporal gyrus, amygdala, and hippocampus.

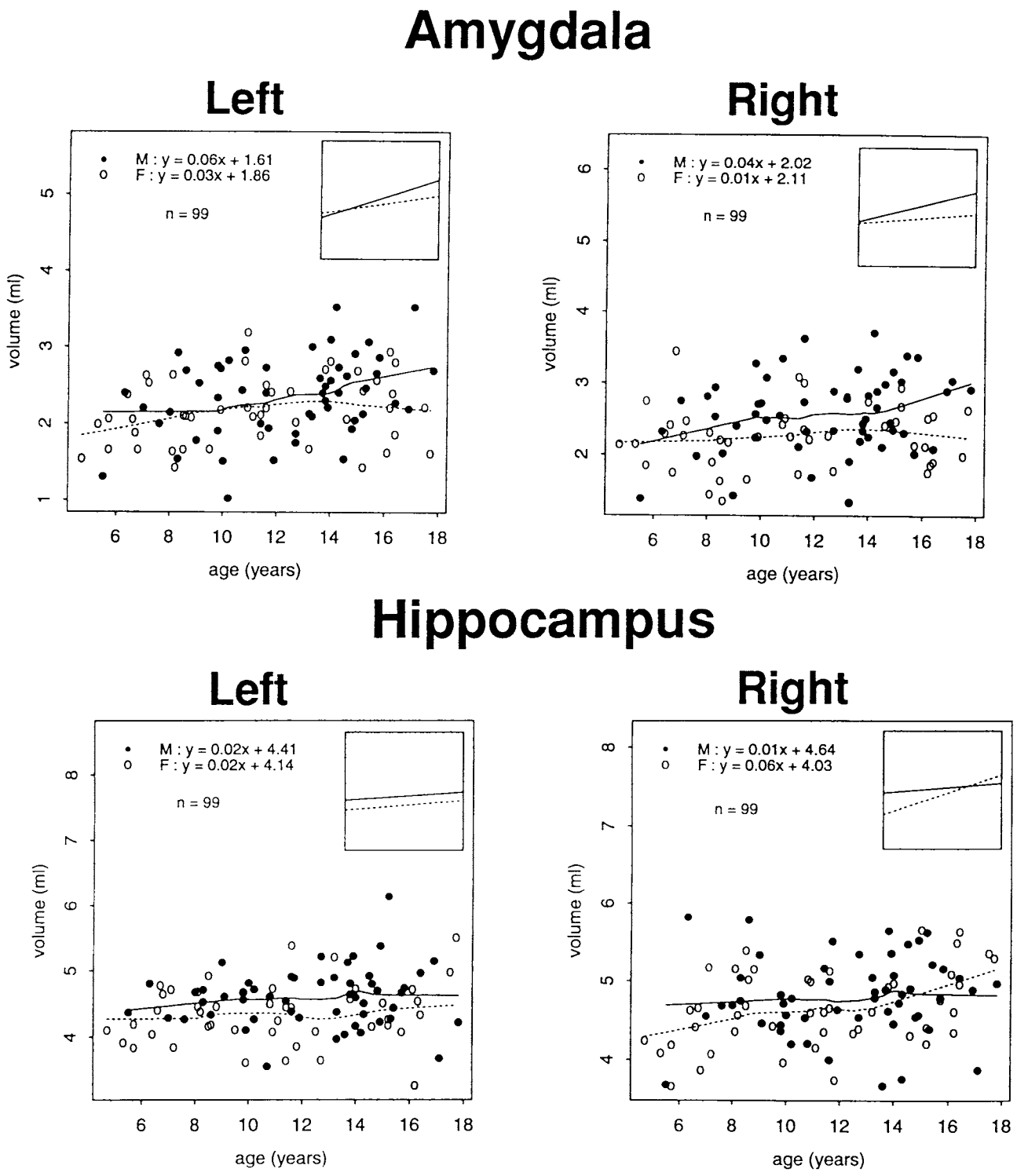

Fig. 2. Scatterplots by age and gender of left and right amygdala and hippocampal volume for children and adolescents (aged 4–18 years; n = 99). Nonlinear, local regression curve fitting is displayed. The boxes in each upper right corner show linear regression models for males (solid lines) and females (dashed lines).

remaining artifacts, such as patches of dura or eyeball. This technique has been validated by comparison to postmortem specimens. Intraclass correlations for the volumes of the edited brains were 0.99 for interrater reliability (A.C.V. and J.N.G.) and 0.95 compared to volumes derived from more conventional slice-by-slice hand tracing through all axial

slices on which brain matter is visible. Further details are provided elsewhere (Snell et al., 1995).

Temporal lobe/superior temporal gyrus quantification. The imaging data were imported into an image analysis program developed at the NIH (Rasband, 1993). Measures of the temporal lobe, superior temporal gyrus, amygdala, and hippocampal formation were all done by manual tracing in the coronal plane by a single experienced rater (A.C.V.) who was blind to any subject characteristics. The temporal lobe is discerned from the frontal and parietal lobes by the Sylvian fissure. The temporal stem was divided by a line connecting the most inferior point of the insular cisterns to the most lateral point of the hippocampal or amygdaloid fissure (Fig. 1). The posterior extent of the temporal lobes was defined by the coronal slice containing the posteriormost aspect of the corpus callosum (inclusive; Bilder et al., 1994). The superior temporal gyrus was identified by the gyral boundary in each of the coronal sections of the temporal lobes and extended posteriorly to the most posterior slice in which fibers of the fornix were visible (Shenton et al., 1992). The number of coronal slices to quantify the temporal lobes ranged from 30 to 40, with a mean of 34.6.

Amygdala/hippocampal formation quantification. Our designation of the hippocampal formation included the cornu ammonis, dentate gyrus, and subiculum. Each of these components has different histological characteristics and has topographically well ordered afferents and efferents (Nolte, 1993). However, precise delineation of boundaries, such as that between amygdala and hippocampus, can be difficult even at a histological level (Bergin et al., 1994). The coronal slice containing the most anterior portions of the mammillary bodies was used as a boundary to separate the amygdala from the hippocampus (Shenton et al., 1992; Bogerts et al., 1993). The posterior boundary of the hippocampal formation was the most posterior slice in which fibers of the fornix were visible (Cook et al., 1992; Shenton et al., 1992). The number of coronal slices used to quantify the amygdala averaged 6.1, and the number to quantify the hippocampus averaged 15.9.

Reliabilities for each of the structures were established by having two raters (A.C.V. and J.N.G.) initially measure ten subjects twice to determine intrarater and interrater-intraclass correlation coefficients (ICCs) and then by blindly introducing previously measured scans throughout the analysis to account for possible "drifts" in rater assessment. Interrater ICCs for the structures measured were as follows: temporal lobe, 0.98; superior temporal gyrus, 0.92; amygdala, 0.86; hippocampus, 0.87. Outlines of these structures are presented in Figure 1. Total image processing time for each subject was approximately 3 hours.

Statistical analysis

The SAS General Linear Model procedure was used to examine the total group and sex-specific effects of age on brain structure volumes (SAS Institute, 1990). Because total brain volume differed significantly between males and females (9% larger in males), sex differences were analyzed by using repeated-measures ANOVA and ANCOVA to adjust for total cerebral volume.

In addition, linearity and constant variance assumptions were relaxed by using a local regression procedure that retained the subtle nonlinearities in the data (Hastie and Tibshirani, 1990) to yield smooth, curvilinear, and sex-specific adaptive fits to the scatterplots of structure volumes by age. Males and females were analyzed separately, because single, classical, statistical models make linear and equal variance assumptions that are not always supported by our data. However, we have included results from the combined analyses (see Table 3) to allow comparison to previous reports.

TABLE 2. ANOVA and ANCOVA in Healthy Children and Adolescents[1]

		ANOVA			ANCOVA	
Structure	Parameter	*F* value	*P* value	Comment	*F* value	*P* value
Temporal lobes	Gender	19.1	0.0001	M > F	2.5	0.12
Temporal lobes	Side	20.7	0.0001	R > L		
Superior temporal gyrus	Gender	5.6	0.02	M > F	0.1	0.78
Superior temporal gyrus	Side	31.8	0.0001	R > L		
Amygdala	Gender	3.9	0.05	M > F	1.6	0.20
Amygdala	Side	9.3	0.003	R > L		
Hippocampus	Gender	2.6	0.11	M > F	1.3	0.25
Hippocampus	Side	27.0	0.0001	R > L		

[1]Adjusted for total cerebral volume. Aged 4–18 years; n = 99.

RESULTS

The variability of size was high for all structures examined in this well screened group of healthy children (see Fig. 2). Despite this, sex, maturational, and laterality effects were seen.

Sex

Cerebral volumes, as reported previously (Giedd et al., 1996), were approximately 9% larger for males ($t = 5.6$; $P < 0.0001$), even after adjustment for height and weight ($F = 27.5$; $P < 0.001$). Similarly, for all temporal lobe structures measured, male volumes were approximately 10% larger. When they were adjusted for total cerebral volume (ANCOVA), the temporal lobe measures did not show sexual dimorphism. Table 2 shows sex and side (left or right) ANOVAs and ANCOVAs corrected for total cerebral volume. No interactions between sex and side were found.

Maturational change

Similar to the previously reported total cerebral volumes (Giedd et al., 1996), neither the right, nor the left, nor the total temporal lobe volume increased significantly with age for either sex. In females, the right hippocampal volume showed a significant increase with age (slope of regression line = 0.72 mm^2/year; $P = 0.004$), whereas, in males, the left amygdala volume increased (slope of regression line = 0.72 mm^2/year = 0.06; $P = 0.01$). However, the slopes of the left or right amygdala or hippocampus did not significantly differ from each other within each sex. Table 3 shows the linear regression slopes with age for specific structures.

Scatterplots of the amygdala and hippocampus with respect to sex and age are presented in Figure 2. Both linear and nonlinear summaries are displayed. A prominent feature that is evident from the scatterplots is the enormous variation in structure size. The hypothesis of increased maturational changes around the time of puberty is not supported by these relatively linear regression results.

Asymmetries

The temporal lobe, superior temporal gyrus, amygdala, and hippocampus all exhibited a right-greater-than-left asymmetry (Table 2), which did not change with age.

TABLE 3. Linear Regression of Temporal Lobe and Medial Temporal Structures With Age by Gender and Side in Healthy Children and Adolescents[1]

	Right						Left					
	Male		Female		Total		Male		Female		Total	
Structure	Slope	*P*	Slope	*P*	Slope	*P*	Slope	*P*	Slope	*P*	Slope	*P*
Temporal lobe	0.47	0.32	−0.10	0.79	0.32	0.32	0.61	0.27	0.13	0.68	0.48	0.14
Superior temporal gyrus	−0.15	0.33	0.04	0.75	−0.007	0.94	−0.08	0.60	0.03	0.77	0.001	0.99
Amygdala	0.05	0.07	0.01	0.41	0.06	0.08	0.06	0.01	0.03	0.11	0.07	0.03
Hippocampus	0.01	0.60	0.06	0.004	0.08	0.09	0.02	0.45	0.02	0.37	0.05	0.16

[1]Aged 4–18 years; n = 99.

DISCUSSION

To our knowledge, this is the first large, normative, morphologic study of the temporal lobe and related medial temporal structures in children and adolescents. All of the structures that were measured demonstrated a high degree of variability. Total temporal lobe volume was stable while amygdala volume increased, only in males, and hippocampal volume increased, only in females. This pattern is consistent with the distribution of sex hormone receptors for these structures, with the amygdala having a predominance of androgen receptors (Clark et al., 1988; Sholl and Kim, 1989) and the hippocampus having a predominance of estrogen receptors (Morse et al., 1986).

The hormonal responsivity of the hippocampus in females is supported well by both animal and human studies. Gonadectomized adult female rats have decreased fiber outgrowth and altered density of dendritic spines in the hippocampus, which can be reversed with hormone replacement (Morse et al., 1986; Gould et al., 1990). In humans, women with gonadal hypoplasia were also noted to have decreased hippocampal volume (Murphy et al., 1993).

The increase in hippocampal volume in females is consistent with a postmortem study (Benes et al., 1994) of 164 psychiatrically normal individuals (newborn to age 76 years) showing that myelination in the subicular and presubicular regions of the hippocampus continue throughout adolescence and into adulthood. When adjusted for total brain weight, the area of myelination doubled between the first and second decades in this key relay zone. A sexually dimorphic effect was also noted with females who showed a greater degree of myelin staining during the interval of 6–29 years but showed no significant differences thereafter. This is consistent with a recent MRI study of 20 young adults showing proportionately larger hippocampal volumes in females (Filipek et al., 1994).

In addition to receptors for gonadal steroids, the hippocampus and amygdala are rich in receptors for adrenal steroids, thyroid hormone, and nerve growth factor (Gould et al., 1991; Amaral et al., 1992). As well as its direct effects on hippocampal development, estrogen may influence development by blocking the neurodegenerative effects of glucocorticoids (Sapolsky et al., 1985; Miller et al., 1989; Sapolsky, 1990). The diversity of afferent and efferent connections to the many distinct nuclei of the amygdala and the hippocampus as well as the complexity of their various neurochemical systems make the prediction of functional correlates of gross volume changes difficult.

Several limitations of this study should be noted. First, the use of internal medial landmarks (e.g., the mammillary bodies) to define structural boundaries does not consider cytoarchitectonic or sulcal/gyral information. With regard to right/left asymmetries, the right cerebral hemisphere tends to be shifted anteriorly compared to the left (Bilder et al., 1994), and this would favor the observed right-greater-than-left asymmetries of the amygdala, superior temporal gyrus, and temporal lobe.

This phenomenon, however, would not account for a right-greater-than-left hippocampal volume, because the posterior boundary of the hippocampus (ascending fibers of the crux of the fornix) was determined on a per-hemisphere basis, and the location of the boundary between the amygdala and the hippocampus farther posteriorly on the right should serve to decrease the relative size of the right hippocampus. The use of sulcal and gyral landmarks on three-dimensional reconstructed images to define these structures would be preferable, because it would be more sensitive to developmental changes in the Sylvian fissure and the inferior sulcus of the superior temporal gyrus, and it would provide a more valid index of asymmetry. This further analysis is planned.

The interpretation of volumetric changes is complicated by the myriad of factors contributing to structure size, including the number and size of neurons and glial cells, packing density, vascularity, and matrix composition. These parameters, in turn, are affected by genetics, environment, hormones, growth factors, and nutrients in the developing nervous system (Diamond et al., 1964; Jacobson, 1991). Despite this complexity, there are suggestions of a relationship between hippocampal size and memory function in birds, where food-storing species have larger hippocampal volumes than related species of nonfood-storing birds (Krebs et al., 1989; Sherry et al., 1989). Mammals also show a relationship between spatial memory and hippocampal size (Sherry et al., 1992). For instance, males of a polygamous vole species that explore large areas in search of mates and that perform better on laboratory measures of spatial ability have significantly larger relative hippocampal volumes than their female counterparts. This sexual dimorphism of hippocampal size is not seen in the monogamous vole species, which does not show male-female differences in spatial ability (Jacobs et al., 1990). Such relationships are less striking in humans, although correlations between left hippocampus volume and memory for stories have been noted (Lencz et al., 1992; Goldberg et al., 1994).

The stability of the total temporal lobe volume with age for our sample mirrors findings from the adult literature in which temporal lobe volumes decrease at a much slower rate than other brain regions (Coffey et al., 1992; Murphy et al., 1995). However, stability over time in gross size of a structure may not be sensitive to qualitative changes in connectivity or tissue composition.

Anomalies of temporal lobe and medial temporal lobe structures have been reported for a variety of psychiatric

disorders, including affective disorders (Swayze et al., 1992), autism (Bachevalier, 1994), and, most consistently, schizophrenia (Swayze et al., 1992; Bogerts et al., 1993), which is increasingly understood as a neurodevelopmental disorder (Weinberger, 1994). These disorders have marked sex differences in age of onset, symptomatology, and risk factors. Our sex-specific maturational differences may have relevance to the expression of these disorders.

The high variability of structural volumes necessitates large sample sizes and/or longitudinal studies to quantify accurately the heterochronous developmental curves in this population. A longitudinal study of these subjects is underway to validate these cross-sectional results. The sex specificity of these findings should underscore the importance of sex-matched samples in developmental neuroimaging studies.

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