

Brain development, gender and IQ in children

A volumetric imaging study

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Summary

Normal brain development during childhood is a complex and dynamic process for which detailed scientific information is lacking. MRI techniques, combined with methods for advanced image analysis, offer the potential to begin to construct a quantitative map of normal paediatric brain development *in vivo*. In this study we utilize volumetric analysis of high resolution brain images obtained from MRI to describe cerebral development and morphology in 85 normal children and adolescents ranging in age from 5 to 17 years. The results show that total cerebral volume is 10% larger in boys compared with girls. However, both boys and girls show little change in total cerebral volume after the age of 5 years. Increased cortical grey matter is the primary contributor to larger brain volume in boys, thus supporting the hypothesis that gender associated differences in brain size are related to differences in cortical neuronal density.

Prominent, age-related changes in grey matter, white matter and CSF volumes are evident during childhood and appear to reflect ongoing maturation and remodelling of the CNS. Both boys and girls show a similar pattern of cerebral asymmetry; a rightward prominence of cortical and subcortical grey matter and a leftward prominence of CSF is observed. IQ is positively correlated with total cerebral volume in children, in particular, with the volume of cortical grey matter in the prefrontal region of the brain. Subcortical grey matter also contributes to the variance in IQ, although to a lesser extent than cortical grey volume. Quantitative knowledge of the developing human brain will play an increasingly greater role in improving sensitivity and specificity in the interpretation of brain abnormalities in patients within the clinical environment, as well as in groups of children with suspected brain dysfunction in the research setting.

Keywords: brain; development; gender; IQ; MRI; childhood

Abbreviation: NF-1 = neurofibromatosis-1

Introduction

Although a number of investigators have described changes in cerebral morphology during adult life (Jernigan *et al.*, 1991a; Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995), there are relatively few imaging reports describing quantitative *in vivo* brain development in a large sample of normal, non-clinically referred children. Obtaining these data in a large normal population is important in order to unravel the complex and dynamic biological processes underlying brain development during childhood, as well as essential to the valid interpretation of imaging data derived from clinical paediatric populations with brain disorders.

Because of the scarcity of normal quantitative paediatric neuroimaging data, fundamental questions concerning cerebral development during early childhood remain unanswered at present. In this study, we utilize quantitative-volumetric analysis of high resolution MRIs to describe brain development and morphology in 85 normal children and adolescents ranging in age from 5 to 17 years. Methodological advantages of the research described in this report over previous quantitative imaging studies of children (Jernigan and Tallal, 1990; Jernigan *et al.*, 1991b; Pfefferbaum *et al.*, 1994) include a large, predominantly non-clinical population

of children, utilization of neuroanatomical imaging data from the entire cerebrum as opposed to a representative subset of the brain, use of contiguous slices in the imaging dataset versus datasets with interslice gaps, incorporation of standardized methods for tissue segmentation and stereotaxic division of the brain into more discrete cerebral regions, and the availability of IQ data on the majority of subjects. In this study, emphasis is placed on the elucidation of basic issues related to (i) gender-associated differences in cerebral structure or development which may be identifiable in young children, (ii) patterns of age-related changes in specific tissues or regions of the brain during childhood, and (iii) analysis of correlations between cerebral morphology and intellectual abilities. These issues are presented and discussed in light of our present knowledge of early brain development derived from post-mortem studies of children.

Methodology

Subjects

MRI scans were originally obtained from 100 normal children and adolescents between the ages of 5 and 17 years. Fifteen of these scans were identified as technically sub-optimal due to failure to include the entire cerebrum within the image dataset at the time of acquisition. The final subject group consisted of 64 females (mean age \pm SD, 10.6 ± 2.9 years) and 21 males (mean age \pm SD, 10.7 ± 2.8 years). The inclusion of larger numbers of female subjects relative to males was due to our recruitment of gender-matched normal controls for ongoing studies of female children with specific genetic conditions such as fragile X syndrome and Turner syndrome. All subjects were in good health and without evidence of neurological or psychiatric disorders. All subjects had normal IQ scores as determined by standard cognitive evaluation ($n = 69$), or satisfactory performance in a regular classroom setting ($n = 16$). The male and female groups were well-matched for handedness, with $\sim 15\%$ in each gender group left-handed, 83% right handed and 2% having mixed handedness. Most subjects ($n = 42$) were recruited from announcements in public and private schools and area newspapers. Control subjects were also recruited from the pool of normal siblings of subjects with fragile X syndrome, Turner syndrome or neurofibromatosis-1 (NF-1) participating in ongoing research at the Kennedy Krieger Institute ($n = 40$). All normal siblings of individuals with the fragile X syndrome ($n = 10$) were tested with DNA analysis (Rousseau *et al.*, 1991) and found to be negative for the fragile X mutation. All siblings of children with Turner syndrome or NF-1 were phenotypically normal; children in the latter group were also examined by a geneticist and ophthalmologist to rule out any physical stigmata of NF-1. Three subjects in this study were already scheduled to receive an MRI for evaluation of generalized headaches and were prospectively asked to participate in the research protocol (these scans were subsequently read as clinically normal). Subjects' informed consent was obtained

according to the guidelines of the Johns Hopkins Joint Commission on Clinical Investigation.

Imaging

MRIs were acquired on a General Electric 1.5 Tesla Signa Scanner. Scans utilized for the group analyses were derived from an axial spin-density, T_2 -weighted acquisition with the following parameters: TR = 3000, TE = 30/100, 5 mm slices angled parallel to the AC-PC (anterior commissure-posterior commissure) line. Three subjects had an interslice gap equal to 2.5 mm. The remaining 82 subjects had contiguous 5 mm images obtained with an interleaved protocol. Images were processed, then segmented into grey, white and CSF compartments as described below.

Procedures for removal of non-brain tissues and correction of pixel intensity non-uniformity artifact prior to tissue segmentation were based on methods described by Lim and Pfefferbaum (1989). Measurement of grey, white and CSF compartments were made after creating composite images from paired T_2 - and proton-weighted images. These composite images were produced by adding and subtracting, respectively, the early and late echo (paired) images. Tissue classification was determined in each slice using histogram-based segmentation algorithms which automatically establish one or more statistically optimal thresholds for separating tissue types (Otsu, 1979; Cho *et al.*, 1989). Manual adjustment of the selected threshold was available to the rater if the computer-determined values appeared grossly incorrect. Measurements of grey, white and CSF were made after tissue and fluid in the posterior fossa (brainstem and cerebellum) were manually excluded. CSF voxels comprising the lateral ventricles and subcortical grey voxels comprising the basal ganglia and thalamus were designated and segmented separately in each image slice. Lateral ventricle and subcortical regions were included in the overall and hemispheric grey, white and CSF volume measures but excluded from the 16 cerebral regional measures described below. The volume of a region of interest contained in a single slice was determined by multiplying the number of pixels comprising the region of interest in the slice by the slice thickness. The volume of the structure was then determined by summing the volumes of the region of interest in each slice in which it occurred.

In order to determine whether neuroanatomical differences associated with gender or age were localized to specific regions of the brain, volumes of hemispheric and subhemispheric regional grey matter, cerebral white matter, tissue (grey+white) and CSF, were determined after designation of five planes through the brain of all subjects. Operational definitions for placement of these planes were predetermined and based on a previously described regional stereotaxic coordinate system (Zipursky *et al.*, 1992). The anatomical location of the planes are further described and illustrated in Fig. 1. The projection of the five planes through the brain sections served to divide the brain into 16

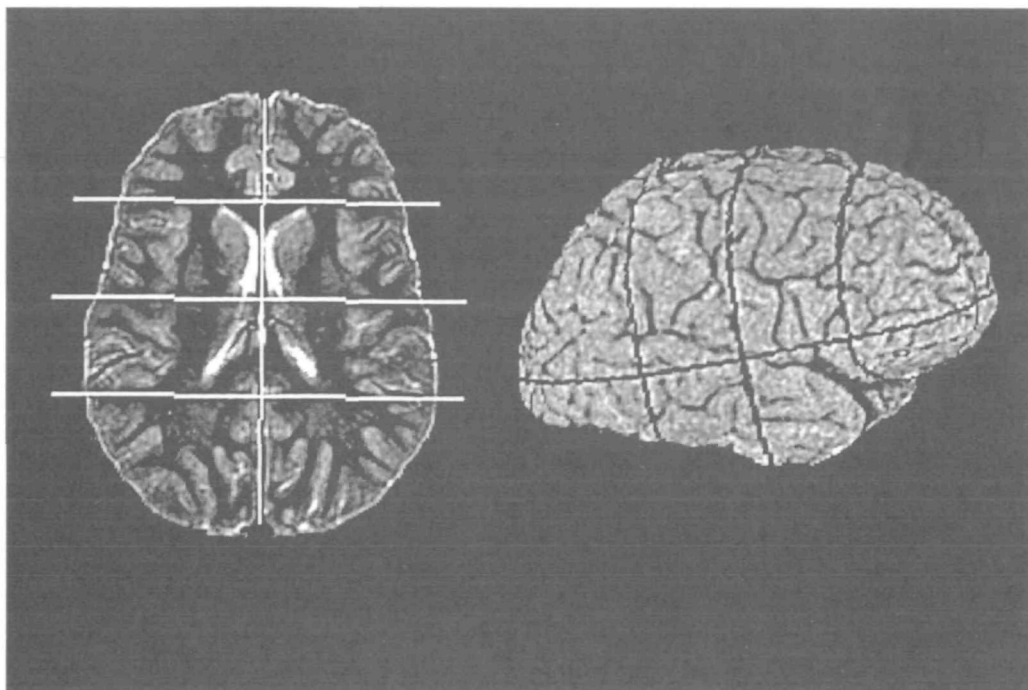


Fig. 1 The brain parcellation scheme used for analysis of subhemispheric regional volumes is illustrated in the figure. Images show the location of five planes projected through the brain in a transaxial slice and a three-dimensional surface rendering. The five planes consisted of (i) a midsagittal plane following the interhemispheric fissure dividing the brain into right and left hemispheres, (ii) a transaxial plane parallel to the orientation of the axial sections and along the AC–PC line dividing each hemisphere into superior and inferior regions, (iii) a coronal plane perpendicular to the transaxial plane and passing through the most anterior extreme of the genu of the corpus callosum, (iv) a coronal plane perpendicular to the transaxial plane and passing through the most posterior extreme of the splenium of the corpus callosum, and (v) a coronal plane perpendicular to the transaxial plane and passing through a point midway between the anterior and posterior callosal planes.

neuroanatomical sections. The resulting 16 subhemispheric brain areas roughly correspond to the following right and left cerebral regions: prefrontal, posterior frontal, orbital-frontal, parietal, superior parietal-occipital, inferior parietal-occipital, anterior temporal and mid/posterior temporal (Fig. 1). Because of the possible influence of slight variations in head tilt and slice location on volume determination of subhemispheric cerebral regions, all scans were visually inspected; 79 scans (60 females and 19 males) were determined to be correctly aligned to the AC–PC plane and were subsequently used in the analysis of subhemispheric regional morphology. The mean ages of the children comprising this subgroup (females, 10.6 ± 2.9 years; males, 10.5 ± 2.6 years) were very similar to those of the overall group.

Several procedural details were followed to eliminate observer bias in determining volumes of regions of interest. All scans were analysed interspersed among those from subjects having various developmental disorders (e.g. children with fragile X or Turner syndrome). Scans were processed so that images contained no subject information other than subject number, and the raters performing morphometric analyses did not know group membership of any subject. Previous description of specific definitions of neuro-

anatomical regions of interest as well as inter-rater reliabilities have been reported for all measures described in this study (Reiss *et al.*, 1993a, b, 1995). The average intraclass correlation corresponding to inter-rater agreement for cerebral regions of interest was 0.93.

Data analysis

Age was not significantly correlated with total cerebral volume (Fig. 2); therefore, ANOVA was used in the initial gender group comparisons for hemispheric and subhemispheric volumes of cerebral tissue (grey + white), grey matter, cerebral white matter, CSF and subcortical nuclei. The presence of significant gender differences for total cerebral volume (Table 1), and the possibility that age would be related to tissue- or region-specific volumes (Jernigan *et al.*, 1991b; Pfefferbaum *et al.*, 1994), led to the use of ANCOVA with both total cerebral volume and age as covariates in an additional set of gender comparisons. MANCOVA was also performed to determine whether there was a unique pattern of gender differences in the volumes of the subhemispheric regions.

Regression analyses were used to investigate the association of designated brain regions (or tissue) with age. Total

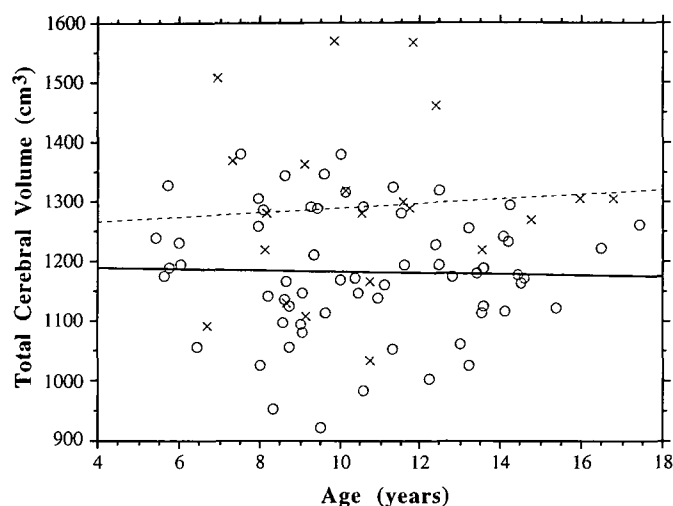


Fig. 2 Total cerebral volume in children ranging in age from 5 to 17 years is shown in the figure. Boys (crosses) and girls (open circles) show little change in this measure over the age range studied. Regression lines for boys (dashed) and girls (continuous) are also shown.

Table 1 Cerebral volumes (cm^3) in children

| Region | Male ($n = 21$) mean \pm SD | Female ($n = 64$) mean \pm SD | P |
|----------------------|---------------------------------------|---|-----------------------|
| Total cerebrum | 1290.6 \pm 147.4 | 1182.5 \pm 104.7 | ≤ 0.0005 |
| Right hemisphere | 643.9 \pm 72.6 | 591.1 \pm 52.5 | ≤ 0.0005 |
| Left hemisphere | 646.7 \pm 75.0 | 591.4 \pm 52.8 | ≤ 0.0005 |
| Total grey | 707.4 \pm 71.4 | 637.2 \pm 66.1 | $\leq 0.0001^*$ |
| Cortical grey | 674.8 \pm 67.8 | 605.6 \pm 64.0 | $\leq 0.0001^\dagger$ |
| Caudate nucleus | 11.1 \pm 1.9 | 10.7 \pm 1.6 | n.s. |
| Lenticular nucleus | 9.9 \pm 1.6 | 9.5 \pm 1.6 | n.s. |
| Thalamus | 11.6 \pm 2.2 | 11.4 \pm 1.8 | n.s. |
| White matter | 488.3 \pm 92.0 | 443.8 \pm 61.7 | ≤ 0.01 |
| Total CSF | 94.9 \pm 28.8 | 101.5 \pm 25.1 | n.s.* |
| Extraventricular CSF | 79.4 \pm 23.8 | 89.6 \pm 23.7 | n.s.† |
| Lateral ventricles | 15.5 \pm 9.5 | 11.9 \pm 5.7 | ≤ 0.05 |

Comparison of male and female group volumes for neuroanatomical regions of interest. All analyses were initially performed with ANOVA; analyses using ANCOVA with age and total cerebral volume as covariates were also used for all volume comparisons (other than total cerebrum) to determine whether a particular region contributed more heavily to gender differences in total cerebral volume. The P value shown for all variables in the table represents the significance level for the main effect of group (male versus female). *ANCOVA $P < 0.005$; †ANCOVA $P < 0.0025$; ‡ANCOVA $P < 0.0005$; n.s. = not significant.

cerebral volume, gender, age and gender by age interaction, were entered sequentially as independent variables in a series of hierarchical regression analyses with cortical grey matter, white matter, CSF and subcortical volumes as dependent variables. Because of the predictable (positive) correlation between the volumes of the dependent variables and total cerebral volume, total cerebral volume was entered into each regression analysis as an initial independent variable in order to measure, and remove, the contribution of overall cerebral

size to the volumes of the regions of interest. Gender, age, and gender by age interaction were entered, respectively, into the regression analysis in the second through fourth steps, and the independent (incremental) partial correlation squared (s^2) determined for each independent variable. The critical F value corresponding to the contribution of any of these three variables was set at ≥ 4.00 (corresponding to a P value of < 0.05 for the number of residual degrees of freedom in the model). As a means of validating the results obtained from the hierarchical regression analyses for grey and white matter, simple regression analyses were also performed with age as the independent variable and the region of interest volume:total cerebral volume ratio as the dependent variable in each gender group separately.

For analysis of gender-associated hemispheric differences in symmetry, a two (gender group) \times two (hemisphere: left versus right) mixed ANOVA was employed, with repeated measures on hemisphere. In addition, paired t test analyses were used to analyse left versus right hemisphere differences in the entire group of 85 subjects. Two-tailed tests of significance were used for all analyses used unless an *a priori* hypothesis had been stated in which case a one-tailed significance test was used. Alpha was set at $P < 0.01$ for all group comparisons in these repeated measures analyses.

The association of cerebral volume with IQ was investigated with stepwise and hierarchical regression analyses using specified neuroanatomical regions as independent variables.

Results

Cerebral volume in children-gender effects

Analyses shown in Table 1 indicate that absolute cerebral volume (grey + white + CSF) in boys is $\sim 10\%$ larger than that of girls ($P = 0.0004$). ANCOVA further suggests that in spite of the magnitudes of gender differences for cortical grey and white matter volumes being similar (11.4% and 10.0%, respectively), grey matter volume is a more consistent contributor to larger total cerebral volume in males than white matter volume (Table 1). Moreover, further examination of this issue indicated that the standard deviation for male white matter volume was larger than that for female white matter volume. Upon visually inspecting the distribution of this variable across genders, it became apparent that there was one (10-year-old) male for whom white matter volume was > 2 SDs (710.6 cm^3) from the mean of the entire male group. (No other volume from this individual was > 2 SDs from the group mean.) Reanalysis of volumes without this individual showed that gender differences were 11.0% and 7.5% for cortical grey and white matter, respectively. After exclusion of this subject, statistical analyses of gender differences for grey matter volumes remained significant for both total ($P \leq 0.0002$) and cortical grey ($P \leq 0.0001$) volumes. For white matter volume, the P value decreased to marginally significant ($P = 0.052$) when this single subject

was excluded. Reanalysis of the data also showed that, similar to the original analyses in which all subjects were included, the ANCOVA remained significant for cortical ($P \leq 0.001$) and total ($P \leq 0.05$) grey matter, and not significant for white matter ($P > 0.20$).

Compared with cortical grey and white matter volumes, the size of subcortical nuclei were not significantly different between the two gender groups. However, girls did have proportionally greater amounts of extraventricular CSF, but not ventricular CSF.

Analyses were carried out to determine whether there was a unique pattern of gender differences in the volumes of the subhemispheric regions after statistically removing the influence of total tissue (or fluid) volume. A MANCOVA for the tissue (i.e. grey+white) volumes of the eight bilateral subhemispheric regions (i.e. prefrontal, posterior frontal, etc.) utilized gender as the grouping variable and total cerebral tissue volume as a covariate. (Bilateral volumes were used due to the absence of gender differences in cerebral asymmetry as shown by subsequent analyses below.) The MANCOVA was significant [Wilkes $F(8,69) = 2.92$, $P = 0.007$]; however, none of the eight individual ANCOVAs showed a significant gender effect. Three additional MANCOVAs were carried out for the eight cortical grey, eight cerebral white, and eight nonventricular CSF volumes, respectively. Similar to the first analysis, these three MANCOVAs used the overall volume of the respective tissue (or fluid) as the covariate. These analyses (not shown) did not reveal evidence for gender differences in regional tissue, cortical grey, cerebral white or non-ventricular CSF volumes of greater magnitude than those observed for the total tissue or fluid compartments, respectively. Thus, the relative proportion of tissue and fluid volumes comprising the brain is similar between males and females despite the 10% volume difference between the genders.

Change in cerebral volume with age

There was no observable change in total cerebral volume as a function of age in either male or female subjects (Fig. 2). Results from the hierarchical regression analyses (Table 2) showed that total cerebral volume predicted a significant proportion of the variance in the volumes of all constituent tissue and CSF variables evaluated. After removing the effect of total cerebral volume and gender on region of interest volume, age was found to predict a significant proportion of the variance in cortical grey matter volume (22%) and cerebral white matter volume (16%), such that increasing age was associated with decreasing grey matter volume and increasing white matter volume in children. Age was also observed to predict a small, but significant amount (7%) of the variance of extraventricular CSF (which increased with age), and lenticular and thalamic subcortical grey regions (which decreased with age). Consistent with ANCOVA results for gender comparisons, gender effects were small, yet significant, for cortical grey matter (males > females), and

extraventricular CSF (females > males), even after the effect of total cerebral volume and age had been removed. The gender-by-age interaction term was not found to be significant for any of the analyses, indicating that age-related effects for these brain regions were not different between boys and girls. Concordant with results from these hierarchical-stepwise regression analyses, the ratio of cortical grey volume to total cerebral volume showed a significant negative correlation with age for both boys ($R = -0.62$, $P \leq 0.002$) and girls ($R = -0.73$, $P \leq 0.0001$). An opposite pattern was observed for the ratio of total white matter volume to total cerebral volume ($R = 0.51$, $P \leq 0.01$ for males; $R = 0.72$, $P \leq 0.0001$ for females) which is observed to increase with age throughout childhood (Fig. 3).

Age predicted a significant proportion of the variance in the volumes of both total cortical grey matter and cerebral white matter. However, based on data suggesting region-specific differences in rates of cerebral maturation in the human brain, particularly for white matter (Lemire *et al.*, 1975), we also investigated whether regional age-related grey and white volume changes would be consistent with findings from the 'parent' tissue compartment. This question was addressed by analysing independent age effects on grey or white matter volumes of the eight bilateral subhemispheric cerebral regions; if present, these effects would be distinct from those explained by age associations with the total volume of cortical grey or cerebral white matter volume in the brain, and gender. Accordingly, the effects of gender and either total cortical grey or cerebral white volume (according to the variable being analysed) were first measured and removed in a hierarchical regression analysis. The effects of age and a gender-by-age interaction term on the grey and white volumes of each of the subhemispheric regions, were then examined. The results of these analyses (not shown) indicated that age, but not age by gender effects, were significant for white matter volume changes within the frontal lobe. Specifically, there was an increase in prefrontal white matter volume ($F = 7.0$, $P < 0.01$) and a decrease in orbital-frontal white matter volume ($F = 6.6$, $P < 0.02$) with increasing age which were independent of age-related changes in total white matter volume in the brain. No age or age-by-gender effects were observed for any regional cortical grey volume, indicating relative uniformity in age-related changes for cortical grey throughout the cerebrum in both boys and girls.

Cerebral asymmetry

The symmetry of right and left hemispheric tissue, grey, white, CSF (ventricular and extraventricular) and subcortical nuclei was examined for all 85 subjects; the symmetry of right and left subhemispheric cerebral regions was also analysed for the 79 subjects with scans correctly aligned to the AC-PC plane. No significant gender-by-hemisphere interactions emerged in these repeated measures ANOVAs,

Table 2 Influences of total cerebral volume, gender and age on region- and tissue-specific volumes (cm³)

| Dependent variable | Regression step | Independent variable(s) | B(β)* | sr ² | P |
|-----------------------|-----------------|-------------------------|---------------|-----------------|----------|
| Cortical grey matter | 1 | Total cerebral volume | 0.695 | 0.571 | <0.00001 |
| | 2 | Gender | -0.087 | 0.022 | <0.05 |
| | 3 | Age | -0.382 | 0.223 | <0.00001 |
| | 4 | Gender \times age | -0.124 | 0.000 | n.s. |
| Cerebral white matter | 1 | Total cerebral volume | 0.826 | 0.653 | <0.00001 |
| | 2 | Gender | -0.111 | 0.002 | n.s. |
| | 3 | Age | 0.229 | 0.163 | <0.00001 |
| | 4 | Gender \times age | 0.241 | 0.002 | n.s. |
| Ventricular CSF | 1 | Total cerebral volume | 0.277 | 0.110 | <0.002 |
| | 2 | Gender | 0.627 | 0.012 | n.s. |
| | 3 | Age | 0.812 | 0.000 | n.s. |
| | 4 | Gender \times age | -1.107 | 0.038 | n.s. |
| Extraventricular CSF | 1 | Total cerebral volume | 0.485 | 0.118 | <0.002 |
| | 2 | Gender | 0.294 | 0.119 | <0.001 |
| | 3 | Age | 0.138 | 0.052 | <0.025 |
| | 4 | Gender \times age | 0.122 | 0.000 | n.s. |
| Caudate nucleus | 1 | Total cerebral volume | 0.498 | 0.219 | <0.0001 |
| | 2 | Gender | 0.542 | 0.008 | n.s. |
| | 3 | Age | 0.416 | 0.004 | n.s. |
| | 4 | Gender \times age | -0.663 | 0.014 | n.s. |
| Lenticular nucleus | 1 | Total cerebral volume | 0.433 | 0.182 | <0.0001 |
| | 2 | Gender | 0.763 | 0.002 | n.s. |
| | 3 | Age | 0.553 | 0.054 | <0.025 |
| | 4 | Gender \times age | -1.079 | 0.038 | n.s. |
| Thalamus | 1 | Total cerebral volume | 0.477 | 0.181 | <0.0001 |
| | 2 | Gender | 0.487 | 0.019 | n.s. |
| | 3 | Age | 0.111 | 0.067 | <0.01 |
| | 4 | Gender \times age | -0.508 | 0.008 | n.s. |

The table shows the standardized regression coefficients (β) and incremental partial correlations squared (sr^2), corresponding to the association between the volume of the dependent variable (a designated tissue or region) and the specified independent variables. The sr^2 indicates the proportion of variance in the volume of the dependent variable predicted by the independent variable; n.s. signifies that the F value for the independent variable did not reach statistical significance ($P < 0.05$). The independent variables were entered sequentially in individual hierarchical regression analyses in the order shown in the table. *Beta coefficients (β) for each independent variable are derived from the final step in the regression analysis.

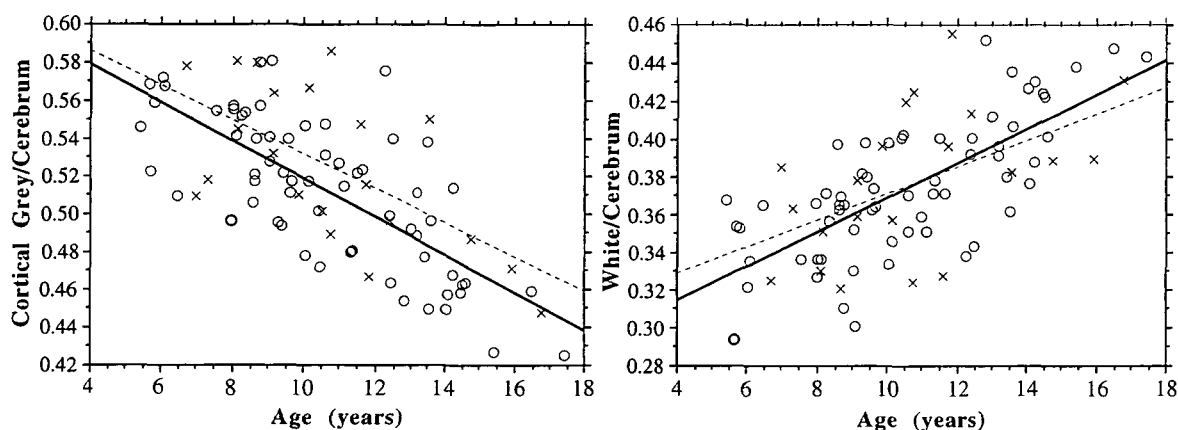


Fig. 3 Age-related changes in the proportions of cortical grey matter and cerebral white matter are shown in the figure. Boys (crosses, dashed line) and girls (open circles, continuous line) show significant changes in both variables over the age range studied.

providing no evidence for gender-associated symmetry differences for the regions examined.

Following this initial analysis, paired t tests (using right versus left volumes) were utilized to determine the presence of brain asymmetries across the entire group of boys and

girls. These analyses revealed a number of cerebral asymmetries which, although modest in absolute volume, were statistically significant. These included a right > left pattern for the caudate ($t = 4.8$; $P < 0.0001$), lenticular nucleus ($t = 4.4$; $P < 0.0001$), and cortical grey ($t = 3.9$;

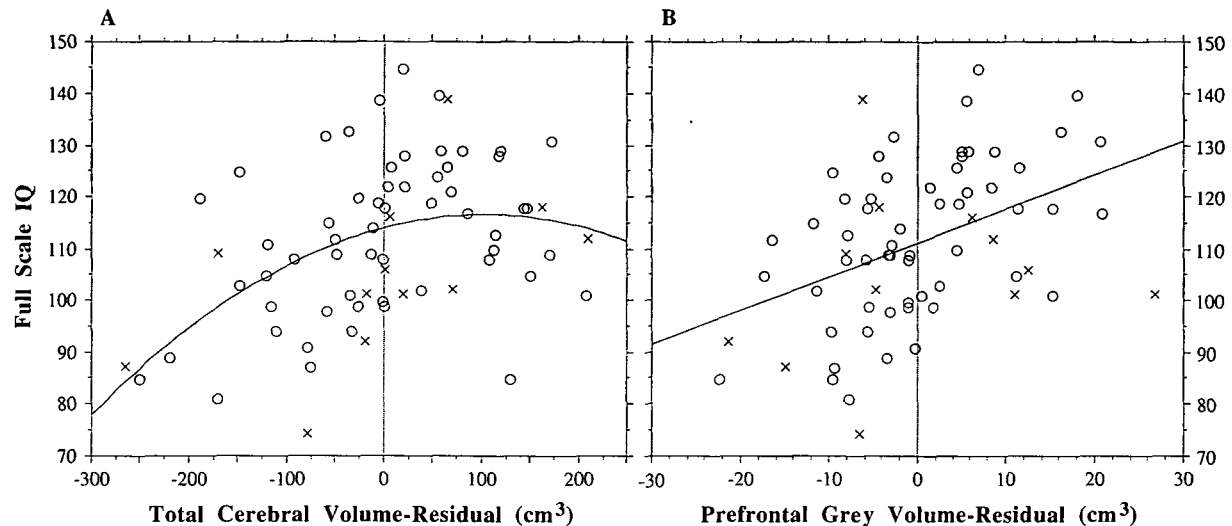


Fig. 4 The scattergrams show the association of full scale IQ with the residual total cerebral volume variable (A) and the residual prefrontal grey matter volume variable (B). Both neuroanatomical variables represent the 'residual' volume of the respective region after the effect of gender has been statistically removed.

$P = 0.0002$), and a left > right pattern for ventricular ($t = 2.6$; $P = 0.01$) and nonventricular CSF ($t = 3.5$; $P = 0.0007$). For subhemispheric regions, tissue (grey+white) volumes showed a right > left pattern for prefrontal ($t = 4.0$; $P = 0.0001$), posterior frontal ($t = 3.9$; $P = 0.0002$) and parietal regions ($t = 2.8$; $P = 0.007$) and a left > right pattern for the inferior parietal-occipital region ($t = 4.3$; $P < 0.0001$). When subhemispheric tissue volumes were analysed separately, cortical grey showed a pattern of regional asymmetry identical to that observed for regional tissue volumes (all t s > 4.0; all P s < 0.0001 for the four regions), whereas only the inferior parietal-occipital region showed significant left > right volume in the analysis of white matter ($t = 3.3$; $P < 0.0014$).

Association of cerebral volume with IQ

For the 57 girls and 12 boys for whom cognitive testing data were available (the IQ subgroup), there was no gender associated statistical difference in mean (\pm SD) full scale IQ score (113 ± 15 for girls; 105 ± 17 for boys). The ages of the boys and girls comprising this subgroup were similar to those of the entire sample (10.6 ± 2.7 for girls, 10.1 ± 2.7 for boys). The volumes of neuroanatomical regions for the known-IQ subgroup were also analysed to ensure the representativeness of the sample; these volumes did not significantly differ from those of the overall group (analyses not shown). So that the entire group of boys and girls could be analysed together in subsequent regression analyses focusing on IQ, the effect of gender on total cerebral volume was statistically removed. This was accomplished by creating a residual cerebral volume variable which represents the amount of deviation from the regression line derived from the correlation of gender (coded as 0 = male, 1 = female) with total cerebral volume.

In an initial regression analysis, residual total cerebral

volume was observed to predict ~20% of the variance in IQ ($R^2 = 0.207$; $P = 0.0005$); the best curve fit for these data was a second order polynomial (Fig. 4A) suggesting that IQ increased with larger cerebral volume to a point, then reached a plateau, and perhaps decreased with the largest volumes. In order to determine which of the tissue compartments were most responsible for the IQ/brain volume correlation, residual variables were also created for total grey matter, white matter and CSF. These variables were generated from the regression of the respective tissue compartment with gender and age. Age was included as an independent variable in the creation of these three residual volume variables, since we had previously demonstrated significant age correlations with grey, white and non-ventricular CSF compartments, as described above. A stepwise regression was utilized to determine which of the three residual variables (grey, white, CSF) would predict a significant portion of the variance in IQ. Only the residual grey matter variable was included in the final regression model as a statistically significant predictor ($n = 69$, $R^2 = 0.156$; $P = 0.0008$), indicating that after removing the effects of gender and age, grey matter volume predicted ~15% of the variance in IQ in this population of normal children; specifically, larger total grey matter volume predicted higher IQ scores.

To further specify the particular tissue components predicting IQ variance, the stepwise regression was repeated for the two sub-compartments comprising the total grey matter volume, cortical grey and subcortical grey. As described above, residual variables were created with the respective tissue compartment and age. Since the total grey matter volume was comprised predominantly of cortical grey matter (95%), a hierarchical regression was utilized to determine whether subcortical grey volume would predict any variance in IQ after cortical grey volume was entered into the model in an initial step. The results showed that

both the cortical grey ($R^2 = 0.143$; $P < 0.002$) and subcortical grey ($sR^2 = 0.073$; $P < 0.025$) residual volumes predicted a significant portion of the variance in IQ.

To investigate whether particular brain regions were more highly correlated with general cognitive ability than others, the association of subhemispheric cortical grey volumes with IQ were investigated in a subgroup of 64 children (11 boys and 53 girls) who had both IQ data and correctly aligned scans. This subgroup was also representative of the overall group with respect to age and cerebral volumes (analyses not shown). Residual volume variables were generated from the regression of the respective subhemispheric regional grey volume (e.g. orbital-frontal) with both gender and age to remove the effect of these independent variables. The volumes of the corresponding right and left grey regions were summed for these analyses. A stepwise regression was utilized to determine which of the eight subhemispheric regions would predict a significant portion of the variance in IQ. Only the prefrontal cortical grey volume was entered into the final regression model ($n = 64$, $R^2 = 0.186$; $P = 0.0004$). This indicated that after removing the effects of gender on subhemispheric volume, the prefrontal regional grey volume predicted nearly 20% of the variance in IQ (Fig. 4B).

Discussion

Gender differences

Imaging and post-mortem studies of adult brains consistently point to gender differences in overall brain size with adult males having, on average, a 10% greater volume than females (Dekaban, 1978; Ho *et al.*, 1980; Filipek *et al.*, 1994; Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995). Our study extends this finding to a large group of children as young as 5 years of age, a result which strongly suggests the presence of early gender-associated differences in cerebral development and organization.

While the specific learning and behavioural correlates of gender differences in cerebral volume await elucidation, a clue as to the cytoarchitectonic basis of this neuroanatomical finding was recently described by Witelson *et al.* (1995). This group reported that the neuronal density of the granular layers of the cerebral cortex was significantly higher in females, compared with males, within the portion of the superior temporal cortex known as the planum temporale. In our study, increased cortical grey matter was the most consistent contributor to brain volume differences in our child subjects, thus supporting the hypothesis of gender associated differences in brain size being related to differences in cortical neuronal density.

Unexpectedly, after covarying for overall cerebral volume and age, extraventricular CSF volume was found to be increased in the female subject group compared with the age-matched sample of boys. While an obvious explanation for this phenomenon is not apparent from our data, this finding could also have been influenced by the presence, in

girls, of larger amounts of cisternal CSF which was included in the non-ventricular CSF volume measure in this study. Future studies will need to separate out the cisternal compartment from sulcal and ventricular CSF in order to address this issue.

Age effects

Post-mortem studies show that the human brain attains adult weight by early childhood, usually by age 5–10 years (Lemire *et al.*, 1975). Our finding no evidence of growth in total cerebral volume in either boys or girls between the ages of 5 and 17 years is consistent with these data. In contrast to total cerebral volume, cortical grey and cerebral white matter volumes are quite dynamic throughout childhood. Loss of cortical grey volume and gain in white matter volume with age were demonstrated in this study, both as a change in the grey or white matter to cerebral volume ratio, and as a function of change in absolute (raw) cortical grey or cerebral white matter volume. Age-related decline in cortical grey volume in normal children as young as 5 years old is consistent with the findings of other imaging investigations of smaller groups of older children and adult populations (Jernigan *et al.*, 1991a, b; Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995). Our findings are also consistent with a recent imaging study performed on scans obtained retrospectively from a clinically referred sample of children (Pfefferbaum *et al.*, 1994).

The finding of decreasing subcortical grey matter volume with age in our population is consistent with a previous investigation of a smaller group of normal children (Jernigan *et al.*, 1991b) and suggests that regressive events aimed at refinement of neuronal connections through cellular and synaptic pruning (Cowan *et al.*, 1984) occur normally in cortical and, to a lesser extent, subcortical grey matter regions during early childhood. Similarly, increase in brain myelinization in the first and second decades of life is likely to be a primary contributor to expansion of the volume of the white matter compartment in the age group sampled in this study. It is of interest that this expansion was particularly prominent in the prefrontal region of the brain. This region is known to undergo considerable myelinization during late childhood and young adulthood and is implicated in higher order (executive) regulation of cognitive functions in humans (Cummings, 1993).

Brain asymmetry

In addition to discrepant cerebral volume, recent evidence for sexual dimorphism of the human brain with respect to cerebral asymmetry, has been described in age groups as young as the foetus (de Lacoste *et al.*, 1991). However, consistent with data obtained from adults (Zipursky *et al.*, 1990), we found no evidence of brain asymmetry differences between boys and girls, suggesting that the method for brain parcellation used in this study may be too unrefined for any

gender differences in cerebral volume to be identified, if they exist. However, when analysing the group of children altogether, evidence for brain asymmetry was present. Findings of a subtle rightward preponderance of prefrontal tissue and leftward preponderance of inferior parieto-occipital tissue is consistent with post-mortem and early imaging studies describing cerebral hemisphere asymmetry in the human brain (Chiu and Damasio, 1980; Bear *et al.*, 1986). Rightward preponderance of cortical grey (Filipek *et al.*, 1994) and the caudate nucleus (Castellanos *et al.*, 1994) has also been reported in adults and children, respectively. Leftward preponderance of ventricular and extraventricular CSF was also observed in our child subjects, the former being consistent with findings from studies of the adult brain (Zipursky *et al.*, 1990). Taken together, findings of rightward preponderance of cortical and subcortical grey, and leftward preponderance of CSF, support a hypothesis of differential development and maturation of the two cerebral hemispheres in humans (de Lacoste *et al.*, 1991).

In contrast to other findings of cerebral asymmetry, our observation of rightward preponderance of the lenticular nucleus in normal children is not consistent with previous studies from our laboratory and others (Peterson *et al.*, 1993; Singer *et al.*, 1993). Although variation in scan acquisition parameters may have contributed to this phenomenon (5 mm thick, double echo scans in the present study versus 3 mm thick, inversion recovery scans in Singer *et al.* (1993)), it is more likely that disparate methods for segmenting and measuring lenticular nucleus volume is the primary cause of divergent results. Specifically, manually drawn boundaries were utilized to circumscribe the lenticular nucleus regions of interest in both previous studies showing left-prominent asymmetry of this region (Peterson *et al.*, 1993; Singer *et al.*, 1993). In these studies, lenticular nucleus regions of interest were inclusive of all tissue types (i.e. grey matter, white matter, grey/white volume-averaged pixels, and vasculature) contained within the manually drawn boundaries. In contrast, in the present study, semi-automated, histogram-based threshold determination was used to classify and measure only grey matter pixels within the lenticular nucleus region of interest. Anatomical admixture of grey and white matter leads to volume averaging of pixels in an MRI and a decreased likelihood of these volume averaged pixels being categorized as grey matter in a threshold/histogram-based segmentation process. Due to the presence of a high proportion of intermixed grey and white matter and iron deposits normally occurring within the lenticular nucleus region (particularly the globus pallidus), the total volume of the lenticular nucleus would be expected to represent a different and more restricted tissue composition in the present study. This hypothesis is supported by the finding that the mean lenticular nucleus volume in the present study was ~30% less than that reported in our previous study utilizing manually drawn boundaries (Singer *et al.*, 1993).

The fact that asymmetry measures of the lenticular nucleus are reversed when measuring grey matter volume versus total

volume, suggests that asymmetry of particular tissue types may be particularly prominent for this region of the brain. This possibility is being further explored in our laboratory with probabilistic tissue segmentation procedures which can assign and measure partial tissue compositions to the same pixel in an image (Subramaniam *et al.*, 1996). These discrepancies in study results also point out the need for close inspection of study methodology as a potential source of variation in findings from clinical imaging studies of similar populations of subjects.

Brain volume/IQ correlations

Our data indicate that a modest, yet significant positive correlation exists between brain volume and IQ in this sample of young normal children. This result is consistent with findings reported in normal adults with respect to both the general magnitude of the correlation (Willerman *et al.*, 1991; Andreasen *et al.*, 1993; Egan *et al.*, 1994; Wickett *et al.*, 1994), and the importance of grey matter as the primary tissue compartment driving the statistical association (Andreasen *et al.*, 1993). In addition, our subhemispheric-regional analysis further specifies this correlation by implication of prefrontal grey as the cortical region most important in the prediction of variance in IQ. This is an intriguing finding as the prefrontal cortex is believed to be a regulatory centre for brain activities related to selective attention, working memory, inhibition and other executive functions (Cummings, 1993; Williams and Goldman-Rakic, 1995). If confirmed by subsequent studies, the finding of a particularly strong correlation between prefrontal cortex and IQ would provide important insights into our current construct of human cognition and its measurement. Ongoing studies in our laboratory are aimed at further investigating correlations between particular brain regions and more specific cognitive and neuropsychological measures.

The finding that subcortical grey matter volume predicts a small, yet significant portion of the variance in IQ is not consistent with a recent study of 67 normal adults (Andreasen *et al.*, 1993) in which a statistical association was not found. Nevertheless, our ongoing imaging studies of paediatric neurogenetic groups with cognitive deficits (Singer *et al.*, 1993; Denckla *et al.*, 1996; Reiss *et al.*, 1995) consistently point to the potential importance of subcortical regions in the pathogenesis of cognitive and neurobehavioural disorders in children. The study of these homogeneous neurogenetic groups also reveals circumstances in which larger than normal brain volume is not associated with superior cognitive function. Examples include children with NF-1 and the fragile X syndrome; both disorders are known to be associated with suboptimal cognitive function and larger-than-normal overall, or regional brain volumes (Reiss *et al.*, 1995; von Deimling *et al.*, 1995). The possibility that increases in brain size exceeding an optimal range may be associated with decreased cognitive function is also suggested by the finding that a quadratic function best modelled the association between

cerebral volume and IQ in the present study (Fig. 4A). However, this presumption awaits confirmation with a larger sample as the statistical improvement resulting from a quadratic fit over a linear correlation, although significant [F (for R^2 change) = 4.41; $P < 0.05$], appeared to depend on a small number of subjects with large cerebral volume and relatively lower IQ.

Consistency of data with previous studies

Procedures utilized for subject ascertainment, scan acquisition and image analysis in the present study helped to avoid many of the methodological problems of previous quantitative imaging studies of children. In the largest of these studies, Pfefferbaum *et al.* (1994) analysed MRIs from 88 individuals, ranging in age from 3 months to 30 years (mean = 14 ± 7 years), for gender differences and age-related changes in neuroanatomy. Many of the findings of this study were similar to the results presented here, particularly with respect to the male > female difference for cortical grey matter volume, and the presence of age-related changes in grey and white matter volumes during childhood. This correspondence in results is of particular interest, as the core methods for image processing and segmentation were quite similar across studies. Comparison of cross-study results for many other variables of interest was not possible, as analyses of symmetry, subcortical volumes, regional cortical volumes and brain/IQ correlations were not reported in Pfefferbaum *et al.* (1994).

Subtle differences between our findings and those reported by Pfefferbaum *et al.* (1994) were also observed. For example, they failed to detect gender differences in white matter volume, or an age-related increase in extraventricular CSF in subjects aged <20 years. These differences are likely to be due to methodological problems inherent in retrospective studies. All of the scans used in the Pfefferbaum study were obtained *post hoc*, from patients who had been referred clinically for an imaging study for suspected neurological problems, including head trauma, seizures, psychosis and dehydration. Although these scans were judged to be normal by standard (qualitative) radiological assessment, many of the aforementioned indications for imaging are known to be associated with quantitative morphological abnormalities of the brain (Cook *et al.*, 1992; Zipursky *et al.*, 1992; Gale *et al.*, 1995; Yaffe *et al.*, 1995). In addition, because of the retrospective nature of this study, scan acquisition procedures could not be standardized across subjects. As a result, scans included in the analysis had variable pulse sequences, and had an interslice gap equal to one-half the slice thickness. Most important, only six representative slices were used for analysis of each of the brain volume variables. As Pfefferbaum *et al.* (1994) also discuss, these factors could have affected the accuracy of their results.

In the only other study of normal neuroanatomy in a large number of children, Jernigan *et al.* (1991b) analysed MRI scans from 39 normal control subjects ranging in age from

8 to 35 years, including 26 subjects in the age range of the study presented here. Although these investigators used different methods for cortical and subcortical parcellation and tissue segmentation, many similarities in study results exist. For example, cerebral volume was significantly smaller in female subjects in the Jernigan *et al.* (1991b) study. In addition, cortical and subcortical grey matter volumes were, after adjusting for brain volume and gender, observed to decrease with age; however, cortical changes were restricted to the superior portion of the cerebrum, a finding not replicated in the present study (analyses not shown). Extraventricular CSF volumes were observed to increase with age, but only in the inferior regions of the cerebrum. White matter volumes, symmetry and IQ correlations were not reported.

Limitations

Although this study was conducted with a predominantly non-clinical group of children, potential biases resulting from recruitment strategies utilizing school and newspaper announcements, and siblings of children with genetic disorders, cannot be ruled out. Accordingly, conclusions regarding normal brain development in children must be considered provisional until confirmed by investigation of a more random sample of children from the normal population. Similarly, although the cerebral parcellation procedure used in this study presents clear advantages over the analysis of total or hemispheric cerebral volumes only, the definitions for the cerebral regions of interest are relatively gross and subject to effects resulting from differences in brain shape across subjects. Accordingly, studies utilizing finer, more functionally precise regions of interest are needed to build upon the results presented here.

Conclusions

Despite attainment of overall adult size by ~5 years of age, maturation of the human cerebrum is a dynamic and complex process, with gender differences, structural asymmetry, and uneven region-specific development being detectable throughout childhood. Structural components of the human brain are modestly correlated with cognitive abilities, a finding that may reflect the action of many potential influences on brain development, ranging from environmental to genetic effects. We predict that quantitative knowledge of normal brain development in children will play an increasingly greater role in improving sensitivity and specificity in the interpretation of brain abnormalities in patients within the clinical environment, as well as in groups of children with suspected brain dysfunction in the research setting.

Continued analyses of these and other data are ongoing in our laboratory and include examination of the association between more specific neuropsychological measures and brain volumes, analysis of higher-resolution scans which

permit a more fine-grained stereotaxic parcellation technique (Subramaniam *et al.*, 1996), longitudinal analysis with serial brain scans, and analyses of gender differences, age effects and IQ correlations for structures within the posterior fossa.

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