The Human Brain Age 7–11 Years: A Volumetric Analysis Based on Magnetic Resonance Images

Volumetric magnetic resonance image (MRI)-based morphometry was performed on the brains of 30 normal children (15 males and 15 males) with a mean age of 9 years (range 7–11 years). This age range lies in a late but critical phase of brain growth where net volumetric increment will be small but when the details of brain circuitry are being fine-tuned to support the operations of the adult brain. The brain at this age is 95% the volume of the adult brain. The brain of the female child is 93% the volume of the male child. For more than 95% of brain structures, the volumetric differences in male and female child brain are uniformly scaled to the volume difference of the total brain in the two sexes. Exceptions to this pattern of uniform scaling are the caudate, hippocampus and pallidum, which are disproportionately larger in female than male child brain, and the amygdala, which is disproportionately smaller in the female child brain. The patterns of uniform scaling are generally sustained during the final volumetric increment in overall brain size between age 7–11 and adulthood. There are exceptions to this uniform scaling of child to adult brain, and certain of these exceptions are sexually dimorphic. Thus, with respect to major brain regions, the cerebellum in the female but not the male child is already at adult volume while the brainstem in both sexes must enlarge more than the brain as a whole. The collective subcortical

Introduction

The cycle of growth of the human brain is extended through approximately the first 1.5 decades of life after conception (Dekaban and Sadowsky, 1978; Kretschmann et al., 1986). The rate of growth is most rapid through in utero life and the first postnatal months. Growth remains rapid through the first several years after birth but declines sharply toward the end of the first decade of life. The cycle of growth is finally completed in adolescence. The present report is a volumetric analysis of the brains of primary school age children (age 7–11 years), equally divided among males and females. The age range of subjects lies in the final critical phase of brain growth where subsequent volumetric increments will be small. The analysis is based upon three-dimensional magnetic resonance image (MRI) acquisitions and an analytic procedure which has already been applied to a series of normal young adult brains (Filipek et al., 1994). Thus, the present series of data for the not-yet fully grown child’s brain is comparable with a published reference series which provides the adult expectations of growth. The analysis considers whether among 7–11 year old children as a group there are differences in the patterns of volumetric increase among separate structures of the brain and, if present, whether such different patterns are sexually dimorphic.

Materials and Methods

Subjects

Thirty subjects, aged 7–11 years (Fig. 1), were recruited as control subjects for a large NINDS-funded multicenter study of developmental language disorders in primary school age children. The mean age of the male and female subjects was 9.3 and 9.1 years respectively; this difference in ages was not statistically significant. Twenty-four of the subjects were strongly right-handed while 6 were non-right-handed (left-handed or mixed) (Oldfield, 1971). Approximately half of subjects were volunteers (n = 14) while the remainder were seen for evaluation of headaches (n = 16). All were born at term (37–45 weeks gestational age) following uncomplicated prenatal and perinatal courses, and their neurodevelopmental and medical histories were normal. None had a history of febrile or afebrile seizure, concussive head injury or psychiatric disorder. All had normal neurological examinations with head circumference within two standard deviations of the mean. Scores on the Vineland Maladaptive Behavior Scale (Sparrow et al., 1984), Connors teacher questionnaire (Goyette et al., 1978), and school achievement or Wide Range Achievement Test—Revised (Jastak and Jastak, 1984) were within two standard deviations of the age-appropriate mean. None had received special education services or private tutoring. The group was 87% Caucasian, 10% black, 3% Hispanic and 0% Asian. Children came from homes where English is the primary language. No subjects were admitted who might have had ventricular peritoneal shunt, cardiac pacemaker, vascular surgical clips or cochlear implants. Three children who had met historical and clinical criteria for controls for the study were excluded because their MRI studies were abnormal: small (2 cm) astrocytoma peripherally in the cerebellar folia, mesial temporal sclerosis, and Arnold-Chiari malformation. All subjects were imaged after informed consent and none required sedation.

Volumetric morphometry was undertaken by methods identical to those employed previously for a series of normal young adult brains (Filipek et al., 1994). This adult group consisted of 20 subjects (10 males, 10 females) with an age range 17–33 years. The majority (n = 15) were right-handed. We have assumed for purposes of child–adult comparison that the set of child subjects and the set of normal young adults of the prior analysis are representative of the same population and, therefore, that observed differences between age groups and gender within each age group are not due to sampling bias. We also assume that there is no age-related systematic bias in gray matter–white matter resolution in our T1 weighted images.

Magnetic Resonance Imaging

Magnetic resonance images were performed on either General Electric 1.5 T Signa (Milwaukee, WI) (n = 27) or Siemens 1.5 T (Iselin, NJ) (n = 3)
magnetic resonance systems. Image acquisitions included a T1-weighted sagittal scout series, a coronal T1-weighted sequence to rule out grossly recognizable pathology and a coronal volumetric T1-weighted spoiled gradient echo-imaging sequence for the morphometric analysis. When performed on GE systems, the following parameters were used for the volumetric acquisition: pulse sequence = 3D-SPGR or 3D-CAPR, Tr = 54–50 ms, Te = 5–9 ms, flip angle = 45–50°, FOV = 24–26 cm, slice thickness = 3.0–3.1 mm, number of slices = 60 contiguous, matrix = 256 x 256, number of excitations = 1. On Siemens systems, the following parameters were used for the volumetric acquisition: pulse sequence = 3D-FLASH, Tr = 40 ms, Te = 10 ms, flip angle = 40°, FOV = 30 cm, slice thickness = 3.1 mm, number of slices = 60 contiguous, matrix = 256 x 256, number of excitations = 1. We have previously reported (Filipek et al., 1991, 1994) that no significant effects on any of the measured volumes result from the use of the two different MR system manufacturers or resulting pulse sequences in our analyses (P > 0.309).

Image Analysis
Images from these normal children were analyzed concurrently with images of children with developmental disorders; the investigator was blind as to the classification of subjects. The image analysis routine, identical to that presented previously in detail (Filipek et al., 1989) involved positional normalization and segmentation of the entire brain into cerebrum, brain stem and cerebellum. The cerebrum was further subdivided into neocortex, hippocampus, central gray nuclei, caudate, putamen, pallidum and amygdala and central white matter according to conventions described and illustrated previously (Filipek et al., 1989, 1994). For each brain, volumes for each structure were computed from the imaging parameters and the number of voxels assigned to that structure in the course of the segmentation routines (Kennedy et al., 1989).

Symmetry Coefficient
Comparisons between the volumes of corresponding structures of the left (L) and right (R) cerebra are expressed as a symmetry index (SI; Galaburda et al., 1987) as:

\[
SI = \frac{(L - R)}{0.5(L + R)}
\]

Values of this index can, in principle, range from 0.0 (identical volumes in left and right) to ±2.0 (structure present on one side only). Positive values of the index correspond to left-sided while negative values of the index correspond to right-sided preponderance. Within a range of asymmetry of ~10%, a difference in value of the index of 0.01 will correspond to a 1% volumetric difference with respect to the average volume of the respective structure in the two sides.

Table 1

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean ± SE</th>
<th>Range</th>
<th>% of brain</th>
</tr>
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<tbody>
<tr>
<td>Brain</td>
<td>1312.3 ± 91.7</td>
<td>1128.2–1473.1</td>
<td>100.0</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>1136.8 ± 66.2</td>
<td>964.5–1269.5</td>
<td>86.5</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>140.0 ± 10.2</td>
<td>122.0–155.6</td>
<td>10.7</td>
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<tr>
<td>Brainstem</td>
<td>20.8 ± 2.1</td>
<td>17.8–25.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Ventricular system</td>
<td>14.7 ± 3.7</td>
<td>8.1–36.5</td>
<td>1.1</td>
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Results

Volumes and Proportions: Males and Females Together

The Principal Brain Regions

The average brain volume in the series of 30 male and female children is 1312 cm³ (Table 1). The cerebral hemispheres, exclusive of the lateral ventricles, constitute 86% (1137 cm³), the cerebellum 11% (140 cm³), while the brain stem and total ventricular system are only 2% (21 cm³) and 1% (15 cm³) respectively of total brain volume. Neither the volume of the total brain nor that of any individual brain structure increased systematically with age over the relatively narrow age span surveyed here (Table 3; Fig. 2A,C,E,G).

The Cerebrum

The total cerebral volume is ~67% gray matter structures and 33% white matter (Table 2). The neocortex, mean volume 700 cm³, is 62% of the total volume of the cerebrum. The neocortex constitutes 92% of the total gray matter volume of the cerebrum and is variably some 60–165 times the size of the other cerebral gray structures. Of the other cerebral gray matter structures, the central gray nuclei are largest at 21 cm³, but this is only ~3% of the total cerebral gray matter. None of the other cerebral gray structures measured in this analysis contributed >1% of the total cerebral gray matter. The ratio of total cerebral gray matter (neocortex, hippocampus, basal ganglia, amygdala, central gray nuclei) to central white matter in the cerebrum is 2.0:1.

Volumetric Comparison: Male and Female Brains

The whole brain of the female child is ~93% the volume of the brain of the male child at this age (Table 5; Fig. 3). This difference in volume of the entire brain is uniformly scaled among the major brain regions: cerebrum, cerebellum and brain stem. Within the cerebrum (MANOVA P < 0.04), the neocortex, central gray nuclei, putamen (collectively 94% of the cerebral gray matter) and the central white matter of the female brain are also variably 92–95% their volumes in the male brain (Table 5; Fig. 4). Exceptions to this pattern of uniform scaling are the...
Figure 2. Scatter plots of the volumes by age of brain (A,B), neocortical (C,D), caudate (E,F) and white matter (G,H) volumes where male values are represented by open squares and female values by closed triangles. Series A,C,E,G are for the age range 7–11; series B,D,F,H are for the young adult age range. For each plot a linear regression line with regression equation and $R^2$ are provided.
caudate, hippocampus, pallidum and amygdala. The caudate, hippocampus, and pallidum are similar in size in male and female, i.e. they are disproportionately large in the female brain. The volume of the amygdala in the female, by contrast, is only 84% its volume in the male brain, i.e. the amygdala is disproportionately small in the female brain. In Table 6 we list the volumes of sets of related structures: neocortex and hippocampus, both cortical structures; the total of subcortical gray structures; the total set of subcortical ganglionic structures, the cerebral basal ganglia (caudate, putamen and pallidum); and the 'limbic' hippocampus and amygdala. These groupings of structures in the female child brain, like the separate structures, are variably 92–95% the volumes of the corresponding structure groups in the male child brain.

**Symmetry of Bilateral Cerebral Structures**

All structural asymmetry coefficients measured were <0.10 (10%). Values of 0.05 (5%) or greater were found only for the pallidum and putamen (Table 4). Significant volumetric asymmetry favoring the left side was observed for the pallidum for the full series of 30 brains (left 6% greater than right), but a statistically significant asymmetry of pallidum was not observed in the brains of either the female or male children considered separately. Significant volumetric asymmetries favoring the right side are observed for the cerebral white matter (right 3% greater...
Figure 4. Mean volumes of major cerebral regions (neocortex, NCTX; central white matter, CWM; central gray nuclei, CGN; caudate, CAUD; putamen, PUT; pallidum, PALL; amygdala, AMYG; hippocampus, HIPPO) in boys and girls, mean age 9 years (range 7–11 years). Standard deviations of mean values are provided in Table 5. *Differences significant at $P < 0.04$; **differences significant at $P < 0.002$ (Table 5).

Figure 5. Mean volumes of brain and major brain regions (cerebrum, CER; cerebellum, CBL; brainstem, BST; ventricular system, VNT) in boys and girls, mean age 9 years (range 7–11 years) as a percentage of volumes of adults of the same sex. The accented horizontal line at 100% corresponds to the mean adult values. Standard deviations of mean values for children are provided in Table 5 and for adult values in Filipek et al. (1994). *Differences significant between child and adult values at $P < 0.04$ (Table 5).

Table 4

<table>
<thead>
<tr>
<th>Cerebral symmetry indices: male and female children</th>
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<tr>
<td>Child ($n = 30$)</td>
</tr>
<tr>
<td>Neocortex</td>
</tr>
<tr>
<td>White matter</td>
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<tr>
<td>Central gray nuclei</td>
</tr>
<tr>
<td>Caudate</td>
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<tr>
<td>Putamen</td>
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<td>Pallidum</td>
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<td>Hippocampus</td>
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<td>Amygdala</td>
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* $P < 0.007$ corresponding to Bonferroni correction for eight observations.

Discussion

We consider here two themes related to the neuroanatomical volumetric patterns of the brain of the child, age 7–11 years. First, there are significant differences in the patterns of volumetric change of cerebral gray matter structures in comparison to cerebral white matter structures between childhood and adulthood. In addition, this pattern of volume change is different among certain of the gray matter structures. Second, the brain of the male and female child are not only different in their overall sizes, but there are also sexually dimorphic distinctions in the patterns of volume change of white matter and certain of the gray matter structures. The analysis also establishes that there is minimal volumetric asymmetry of bilaterally represented forebrain structures in the child's brain. This holds even with the neocortex, which is of different shape in the two hemispheres (Rademacher et al., 1993; Filipek et al., 1994). As discussed elsewhere (Filipek et al., 1994), volumetric symmetry with shape asymmetry argues that the development of neocortical shape is regulated independently of those processes which determine volume.

Prior to considering these principle themes arising from the present findings, however, we will consider in more detail certain of the technical issues related to image acquisition, processing and analysis which bear upon the validity of our observations. We emphasize at the outset that there is general accord between our quantitative findings and those of other analyses based upon differing methods and approaches, including postmortem as well as MRI-based volumetric analyses (Anton, 1903; Jaeger, 1914; Dekaban and Sadowosky, 1978; Kretschmann et al., 1979, 1986; Jernigan et al., 1990, 1991; Reiss et al., 1991, 1993; Pfefferbaum et al., 1994), and this reassuringly reinforces our sense that our approaches have been sound. The MRI-based analyses, among those cited above,
confirm that overall brain volume has approached its maximum value at the end of the first decade of life. Admittedly, none of these cited studies deal specifically with whether there is age-related overall volume change in the 7-11 year age range.

Our analysis fails to detect significant progression in total brain volumes or in the volumes of separate brain structures across the 7-11 year old age span of our childhood study population, despite the fact that these volumes are known to be changing slightly during this interval. Similarly, our earlier analysis failed to detect significant decline in brain volume across the age span of young adult (17-33 year old) population although decline by a few percentage points may occur in that age span. We view this as reflecting the limited sensitivity of analyses such as ours which are cross-sectional, rather than longitudinal, and which are based upon relatively small population samplings. On the other hand, mean brain volumes and the mean volumes of certain brain structures for the 7-11 age group of the present analysis and the young adult sampling of the prior analysis do differ significantly. We assume that these differences are manifestations of volumetric changes that occur in the interval years. Thus, though our two samplings are not suitable for defining an overall growth function spanning age 7 and 37, the two populations in comparison, as 'snapshots', highlight the direction and magnitudes, but not rates, of volumetric changes that must occur 'sometime' in the interval. Whereas these volumetric changes might be subsumed under the general concept of 'growth', we draw attention to an uncomfortable fit between the notion of growth, implying a monotonically progressive process, and the volumetric changes actually observed here which in some instances appear to be regressive. We will review evidence from the experimental literature that substantiates this interpretation and actually
identifies a set of concurrent progressive and regressive cellular events that plausibly may be viewed as underlying the net volumetric changes associated with maturation of brain structure in the developing human brain.

In principle, there are a number of sources of potential error in the data acquisition and analysis system employed here. These include image artifacts (intensity drift, motion and pulsatile phase artifacts, susceptibility effects), errors in segmentation, and the use of multiple scanners with variation in imaging sequence parameters. Our use of a semi-automated segmentation system gives the segment the flexibility to adjust for the majority of minor image anomalies such as intensity artifacts due to susceptibility changes and phase artifacts. Images which possess an unacceptable level of artifact are not analysed, and the imaging is reperformed. The majority of the user intervention in the segmentation process is 'operationalized' to minimize subjective decision-making (Filipek et al., 1994). All segmentation results are reviewed by a trained neuroanatomist. Systematic effects due to the use of multiple scanners is not likely to be a major error source. This and previous studies (Filipek et al., 1991, 1994) have demonstrated no significant differences in volumes determined using the scanners and parameters similar to ones used in this study. Finally, previously reported error analyses estimate the degree of volumetric error to be in the 5-10% range, depending on structure size and shape complexity (Kennedy et al., 1989; Filipek et al., 1990).

Patterns of Volumetric Change in the Brain
The brain of the child aged 7-11 years has completed ~95% of its overall cycle of volumetric increase (cf. Table 5 and 6; Fig. 5). The brain will achieve the final 5% of its adult volume over an interval of time which is nearly as long as the time required for the initial 95% of volumetric acquisition (Dekaban and Sadowosky, 1978; Kretschmann et al., 1986).

The present analysis documents a substantial dissociation in the relative stages of volume increase of gray matter and white matter in the child's brain. We suggest that in the 6 years of development preceding the age of the present subjects the modes of volume increase of gray and white matter are different, but both are approaching their transition to their adult volumes. The volumes of the collective gray matter structures of the forebrain of the 7-11 year old child are already at their adult values (Tables 5 and 6; Figs 6 and 7). Certain of the subcortical gray matter structures, e.g. the caudate, putamen and amygdala in the male child and the pallidum in the female child, are measured at even greater volumes in the brain age 7-11 years than in the adult brain. Collectively, subcortical gray structures, variously grouped, are larger than their adult values; this is not the case in the female where collective groupings of subcortical gray structures are indistinguishable from adult female values (Fig. 7). The only cerebral 'gray matter structures' larger in adult than in the 7-11 year old child are the hippocampus in both male (not statistically significant) and female (statistically significant) and the amygdala (statistically significant) in female. The central white matter of the cerebrum, by contrast to the gray matter, is only ~85% of its anticipated volume in the adult brain (Filipek et al., 1994). The hippocampus, as parcellated here, includes a substantial proportion of white matter fiber systems (fimbria, fornix, commissure) which are also likely to be volumetrically small relative to adult volume, resulting in an apparent 'hippocampus' volume that is reduced relative to the adult volume.

Taken together, these findings suggest that prior to age 7 the relative rate of volume increase of gray matter structures has been significantly greater than that of white matter. This disparity has been of sufficient degree that gray matter structures have equaled or even overshot the anticipated adult volumes while white matter structures have lagged behind the overall rate of brain volume increase. The expected course beyond this stage of transition is a stabilization in the total volume of gray matter and even a reduction in that of basal ganglia. There will be continued increase of white matter volume.

In broad outline, findings with other recent MRI-based morphometric analyses (Jernigan and Tallal, 1990; Jernigan et al., 1991; Pfefferbaum et al., 1994) and pathoanatomic analyses undertaken in the course of the present century (Anton, 1903; Jaeger, 1914; Dekaban and Sadowosky, 1978; Kretschmann et al., 1979; Kretschmann et al., 1986) of the developing brain accord with the findings of the present study. In particular the MRI-based analyses confirm that overall brain volume has approached its maximum value at the end of the first decade of life although none of these studies specify the age-related overall volume change in the 7-11 year age range.

In accord with the present analyses these studies find that the rate of volume increase of gray matter structures is substantially in advance of that of the cerebral white matter, and that the brain of the male is of larger volume that that of the female (Jernigan and Tallal, 1990; Jernigan et al., 1991; Pfefferbaum et al., 1994). Cortical gray matter may reach its maximum volume as early as 4 years of age while white matter volume increase may continue through the end of the second decade of life (Pfefferbaum et al., 1994). That the ratio of gray to white matter declines, reflecting both a reduction in gray matter and an augmentation of white matter volumes beyond the first decade of life, was solidly established by these prior MRI-based (Jernigan and Tallal, 1990; Jernigan et al., 1991; Pfefferbaum et al., 1994) and more limited pathoanatomic analyses (Anton, 1903; Jaeger, 1914; Miller et al., 1980; Thompson et al., 1985). Thus, recorded ratio changes in the cerebral gray to white matter volume from the end of the first to the end of the second decade have been from 1.8 to 1.3 (Jernigan and Tallal, 1990), from 1.5 to 1.2 (Anton, 1903; the brain of a single 11 year old female and a single 34 year old male); and from 1.5 to 1.4 (Jaeger, 1914; the brain of a single 11 year old child, sex not specified, and a single 27 year old female). The ratio of gray to white matter for a set of sex and female brains at the outset of the third decade is given as 1.3 by Miller et al. (1980). In a pathoanatomic analysis limited to the superior aspect of the frontal lobe (rostral to and above the foramen of Monro; Thompson et al., 1985) this ratio was ~2.0 at the end of the first decade and ~1.8 at age 16. As with the present analysis there is a reduction in the volume of the caudate, lenticular and thalamic nuclear masses occurring during the second decade of life (Jernigan et al., 1991).

Contrasting 'Tempos of Gray and White Matter Volumetric Change'
The interpretation of the present and prior volumetric findings that there are contrasting tempos of gray and white matter volume increase has solid support in experimental observations in non-human primates where the actual cell biological correlates have been specified in substantial detail. On a more limited basis certain of these cell biological correlates have also been characterized in the developing human brain.

In monkey, the period of gestation is ~5.5 months and puberty occurs at 3 years of age postnatally, compared to 9 months and
-13 years in human. These 'timemarks' provide an approximate equivalence of the developmental time line for man and monkey (Bourgeois and Rakic, 1993; Bourgeois et al., 1994).

**Gray Matter—Cellular Events of Development**

The primate neocortex expands rapidly in volume through the perinatal period (Bourgeois and Rakic, 1993; Bourgeois et al., 1994). The thickness of the prefrontal cortex of the rhesus reaches its maximum value (2.3 mm), and the neuropil reaches its maximum proportion of the cortex (84%) at 2 months after birth (Bourgeois et al., 1994). A waxing of the total volume of the neocortical neuropil correlates closely with the cycle of progression and recession of cortical thickness (Bourgeois et al., 1989; Zecevic et al., 1989; Bourgeois and Rakic, 1993: Bourgeois, 1994 #96). Cortical thickness, neuropil and synaptic density maintain values close to the maximum through the next 2 years as the monkey approaches puberty toward the end of the third year of life. These values then decline in parallel over several years to reach adult levels which are only 50-70% (depending upon neuropil component) the maximum values observed at 2 months (Bourgeois et al., 1994).

The human cerebral cortex follows a developmental path similar to that of the rhesus though with differences in tempo (Huttenlocher, 1979, 1987, 1994; Huttenlocher et al., 1982). By extrapolation from the analyses in monkey, however, the state of development of the human brain age 7-11 years is comparable to that of the monkey between 2.5 and 3 years of age. As with the monkey, the complement of neurons becomes fixed and the principal cortical efferent neurons achieve their full dendritic arborization much earlier (Becker et al., 1984; Mrzljak et al., 1992; Huttenlocher, 1994). This level of development would probably have been passed in the third year of postnatal life as the total brain reaches 80% its adult volume (Dekaban and Sadowsky, 1978; Kretschmann et al., 1986). Only minimal neuronal and dendritic enlargement would continue as late as the sixth year of life (Conel, 1939-1967; Becker et al., 1984; Mrzljak et al., 1992).

The profile of human neocortical synaptogenesis, as with the rhesus monkey, surges in the early postnatal period to attain synaptic densities that are as much as 150% the adult synaptic densities (Huttenlocher et al., 1982; Huttenlocher, 1990). The temporal profile of synaptic density in the developing human prefrontal cortex parallels closely that in rhesus if the elapsed time of development is expressed as a fraction of the entire developmental interval rather than as absolute time. Thus, the peak synaptic densities achieved toward the end of the first postnatal year are largely sustained until the approach to puberty. They then decline through adolescence to the adult level (Bourgeois et al., 1994; Huttenlocher, 1994; Rakic et al., 1994). General neocortical glucose utilization as an indirect index of synaptic activity, determined from birth through adult life by positron emission tomography, follows closely this profile of prefrontal synaptic density. Thus, maximum signal intensities which are twice those of the normal adult brain are achieved in the first two years of life. These high values are sustained up until the age of 9 and then decline gradually through adolescence to adult values (Chugani and Phelps, 1986; Chugani et al., 1987; Chugani 1994).

By inference, the cerebral gray matter structures of the human cerebral are at maximum volumes with maximum synaptic density at the age of the present subjects. The gray matter structures of the cerebral at this age range, at the zenith of growth and differentiation, would be at the threshold of entry into decremental or regressive process. Ultimately, these latter processes would bring the brain to its definitive configuration and, one assumes, bear major responsibility for fine-tuning circuitry to definitive states of functional competence.

**Central White Matter—Cellular Events of Development**

The development profile of white matter reflects both the development of the axonal systems, elaborated by neurons, and the formation of myelin sheaths by oligodendroglial elements. Axonal elaboration precedes the processes of myelination, but with substantial overlap. In monkey, the corpus callosum is the major cortico-cortical fiber system of the cerebrum in which the developmental events have been explored in detail (Lamantia and Rakic, 1990). The initial axons to cross the midplane do so early in the second trimester (Rakic and Yakovlev, 1968), decussation is high during the remainder of fetal life, and the maximum number of callosal axons, 3.5 times the adult number, is achieved by birth. The decline toward the adult number of axons is initiated rapidly during the first three postnatal weeks, and this initial phase of rapid loss is followed by a somewhat slower pace of elimination with the final adult number reached at ~6 months of age.

Callosal axon myelination, initiated in fetal life (Lamantia and Rakic 1990), continues strongly through the end of the first postnatal year (Lamantia and Rakic, 1990; Gibson, 1991). There is an overlapping phasing of axonal elimination and myelination which suggests that the myelinated axons are not those which are eliminated (Lamantia and Rakic, 1990). The total area of the commissure increases progressively postnatally and the maximum area is achieved with approach to puberty, i.e. by 2.5-3 years of age.

The commissure in the human brain enlarges in its cross-sectional area in late fetal life, reaching a maximum area of ~180 mm² at 33 weeks gestation (Clarke et al., 1989). There follows a sharp decline through birth into the end of the second postnatal month to an area of ~150 mm². Subsequently it increases again to a value of ~550-575 mm² by age 5. The remaining 10-20% of areal growth in approach to the adult state appears to occur between 5 and 14 years of age (Clarke et al., 1989). As with the development of this axonal system in monkey, the terminal phase of growth probably reflects enlargement of axons and expansion of the gial composition of the commissure. It is probably not due to further modification of the number of axonal elements of which it is constituted (Lamantia and Rakic, 1990).

As with the monkey brain, myelination of the human brain is initiated prenatally, though the major bulk of myelin is formed through a protracted postnatal period (Yakovlev and Lecours, 1967; Rorke and Riggs, 1969; Gilles et al., 1983; Gibson, 1991). By extrapolation from observations in monkey, where the axonal complement is probably fixed at 6 months postnatally, that in the human brain is probably fixed by 2-3 years of age. The lipid constitution of human forebrain myelin (Moser, 1972; Martinez, 1986) and its proton resonance as revealed in magnetic resonance imaging (Barkovich and Kjos, 1988; Barkovich et al., 1988; Dietrich et al., 1988; Bird et al., 1989; van der Knaap and Valk, 1990; van der Knaap et al., 1991) has also become essentially indistinguishable from adult values by age 2-3. The development of myelin sheaths of the forebrain central white matter, as reflected in density of histochemical staining, continues to advance strongly through the first postnatal decade. It progresses more gradually well into adult life, particularly for fiber systems within cortex and in other gray matter structures.
Sexual Dimorphism

The brain of the 7–11 year old female child is ~93% the volume of the male child at this age (Table 5) (see also Jernigan and Tallal, 1990; Jernigan et al., 1991; Pfefferbaum et al., 1994). This difference in volume of the entire brain is uniformly scaled to 93–95% among the major brain regions: cerebrum, cerebellum and brain stem. Within the cerebrum, the neocortex, central gray nuclei, putamen and the central white matter of the female brain are also variably 92–95% their volumes in the male brain (Tables 5 and 6). Thus, for a set of structures comprising ~98% of the total volume of the brain, the relative volumes in female and male child are scaled uniformly to the overall size of the female and male brains. Exceptions to this pattern of uniform scaling of volumes of female to male brain are the caudate, hippocampus, pallidum and amygdala, which collectively represent only 2% of brain volume. The caudate, hippocampus, and pallidum are indistinguishable in size in male and female, i.e. they are scaled disproportionately larger in the female brain. The volume of the amygdala in the female, by contrast, is only 84% its volume in the male brain, i.e. the amygdala is scaled disproportionately smaller in the female brain.

These patterns of volumetric scaling of female and male brain in the 7–11 year old child are largely sustained with brain growth to adulthood. Thus, the volumes of the brain of the female and male child are 95 and 96% respectively of the volume of the adult brain of the same sex (Table 5; Fig. 5). The cerebrum of the female and male child and the cerebellum in the male child are also 95% their volumes in the adult brain of the same sex. The cerebellum of the female child, by contrast, is already at its adult volume. The brain stem of the female and male child, on the other hand, are relatively behind the volumetric increase of the entire brain at only 87 and 91% of their corresponding adult volumes.

Although the volumes of the brain of the male and female child are equally scaled to their adult volumes, the present observations suggest that the final phase of brain volume increase, which occurs after 11 years of age, is significantly dimorphic. In particular, the terminal patterns of volume increase of cerebral gray and white matter structures is different between the two sexes (Tables 5 and 6; Fig. 6) with projected increases in volumes of the collective gray matter structures of the forebrain of an average of 14.7 cm³ in the male, and in the female a reduction of 9.5 cm³. In male and female alike, these reductions are ~20% of the net volumetric change in brain volume occurring after age 11. Thus in the male there is an increase of 75.9 cm³ in the volume of the cerebral central white matter compared to an increase of 59.0 cm³ in the female. This white matter increment in the male cerebrum corresponds to 98% and in the female to 119% of the total net volumetric changes to occur though the teenage years in the two sexes.

Whereas the general volumetric disparities in male and female brain have been previously considered to reflect allometric scaling to differential body size (Pfefferbaum et al., 1994), this issue was not approached directly. Nor has this possibility been dealt with in the present analysis where values for body weight and height of the subjects were not recorded. From at least two points of view, the allometric 'explanation' of different brain size in male and female is unsatisfactory in any event. First of all, within species, in contrast to across species, body and brain size are weakly if at all correlated (Jerison, 1987). More particularly, the absence of bone weight to brain weight correlation holds in humans (Peters, 1991). Secondly, quantitative cytopathological analysis (limited thus far to the temporal plane) finds that there is an 11% greater packing density of neocortical neurons in the female than in the male brain (Witelson et al., 1995). The difference is found to be highly significant in granular cortical layer IV with a trend also in granular layer II. Thus, the female brain may not only be smaller than that of the male, but broadly acting developmental mechanisms which regulate neuronal somatic size, dendritic arborization and/or the elaboration of other elements of the neocortical neuropil may differ in the two sexes.

The developmental mechanisms which underlie the multifaceted morphological differences between female and male brains are in all likelihood attributable directly to the differential effects of sex hormones or the interactive roles of sex steroids with other trophic substances such as peptide growth factors or transmitter substances (Gorski 1985a; Celotti et al., 1987; Garcia-Segura et al., 1988; Toran-Allerand et al., 1991, 1992; Miranda et al., 1994). The limited number of sexually dimorphic differences thus far recognized in the human brain may represent a grossly incomplete perspective. Thus, no structure of the central nervous system may be exempt from sexually dimorphic modulatory effects of sex steroids. A variety of regional variations in the prominence of such effects are known principally from experiments in rodents (Gorski, 1984, 1985b; McCarthy et al., 1990, 1991; Langub and Watson, 1992; Grattan and Selmanoff, 1993). It remains to be seen whether these differences are general to all mammalian species or are species specific.

It is, perhaps, particularly relevant with respect to the late sexually dimorphic pattern of volume increase of cerebral central white matter to be anticipated with approach to puberty that estrogens are powerfully trophic for glial cells as well for as neuronal elements. Estrogens increase the density of GFAP fibers produced by astrocytes without altering the numbers of glial cells per se (Tranque et al., 1987; Garcia-Segura et al., 1988; Perez et al., 1990, 1993). Estrogen receptors are abundant upon the myelin-forming oligodendroglia elements and are probably part of a tonic drive to myelination of axonal systems in peripubertal and postpubertal life.

MRI-Based Morphometry and the Developing Brain: A Prospectus

The present analysis illustrates the application of MRI-based volumetric morphometry to the human brain at a stage of development when volumetric increase is nearly complete. It has delineated differential patterns of gray and white matter development and provided additional evidence that certain of these patterns are different in the male and female brain. The potential applications of this methodology to the developing brain extend well beyond their utility for characterization of normal structure and developmental process. Substantial applications may be expected in the larger realm of developmental disorders of obscure etiology and pathology where traditional non-quantitative diagnostic criteria have failed to identify structural correlates of disability (Jernigan et al., 1991; Reiss et al., 1991; Jenike et al., 1995). Delineation of such structural correlates may be expected both to provide new hypothesis with respect to the disordered workings of the brain.
and the cellular and molecular biological mechanisms underlying abnormal development.

Notes

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