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LATE CHILDHOOD CHANGES IN BRAIN MORPHOLOGY OBSERVABLE WITH MRI

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Although several studies have been conducted of the brains of normal children using *in vivo* brain imaging, detailed studies have focused on neonates and infants. In one early CT study of the values for white and gray matter in normal subjects, a significantly lower difference between the two was noted in those under 15 years of age (Arimitsu *et al.* 1977). The authors suggested that the difference was likely to be due to increased white matter values of the children. Another CT study examining the CSF spaces in 34 children under six years of age suggested that there were enlarged and variable CSF spaces in children under two, but uniform and quite small spaces thereafter (Kleinman *et al.* 1983). Four normal children from 40 weeks postmenstrual age to five years were studied with magnetic resonance imaging (MRI) by Levene *et al.* (1982): striking changes in white-matter T_1 values were observed and interpreted as reflecting progressive myelination. These original observations were extended by Johnson *et al.* (1983) and Holland *et al.* (1986), who provided more information about the anatomical pattern of MRI changes accompanying myelination during childhood. Even greater specificity for the neonatal period has been provided by McArdle *et al.* (1987a, b), who described the changing pattern of gray-white differentiation and myelination from 29 to 42

weeks postconception. Barkovich and colleagues (1988) studied 82 normal infants and concluded that although the earliest changes related to myelination were visible on T_2 -weighted images, which provided more information about maturation in the first six to eight months, later brain myelination was best monitored with T_2 -weighted images.

These MRI studies have shown that early changes in water content and myelination are well visualized with this technique, but most describe an essentially normal adult appearance of the brain by age 10. In the present study, we used MRI to examine gross brain morphology in a group of normal children and young adults. A set of semi-automated measurements of morphological features was applied to the images.

Material and method

Nine children (five girls, four boys) aged eight to 10 years who were participants as normal controls in a large multidisciplinary study of neurodevelopmental disorders of language and cognition, served as subjects in this study. All were developing normally according to both medical and social histories, as well as on a full neurological examination and extensive behavioral testing. 15 adults (three women, 12 men) aged 25 to 39 years were recruited as control subjects for studies of psychiatric

Fig. 1. Representative images from standard protocol: **A** sagittal section, SE 600/20; **B** axial section, SE 2000/25 (PDW in text); **C** axial section, SE 2000/70 (T_2W in text); **D** coronal section, SE 2000/25 (PDW in text); **E** coronal section, SE 2000/70 (T_2W in text). All sections 5mm thick, matrix 256×256 . All series with 2.5mm gaps between images.

and neurological disorders and were also found to be normal based on medical and psychiatric interviews. All the adults and children were employed or attending school. Informed consent was obtained in all cases.

Imaging protocol

MRI was performed with a 1.5-T superconducting magnet (Signa; General Electric, Milwaukee) at the UCSD/AMI Magnetic Resonance Institute. A standard protocol was adopted for acquisition of the brain images to be analyzed by the Brain Imaging Laboratory in the Department of Psychiatry. Three consecutive spin-echo pulse sequences were used to obtain images in each of three orthogonal planes (Fig. 1). Using a T_1 -weighted (T_1W : TR = 600msec, TE = 20msec) sequence, sagittal images centered on the midsagittal plane were acquired to visualize the corpus callosum, brainstem and other medial-hemisphere surface landmarks. Subsequently, proton-density weighted

(PDW) and T_2 -weighted (T_2W) images were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000msec, TE = 25, 70msec). The sequence was used twice to obtain images of the entire brain in the axial and coronal planes for each subject. Slice thickness was 5mm, with a 2.5mm gap between successive slices in all instances. A 256×256 matrix and 24cm field of view were used in all examinations.

Image analysis

A detailed description of the method of image analysis is given in a separate paper (Jernigan *et al.* 1990). For each axial brain-section imaged, a computed matrix was produced in which pixels were classified as most resembling (in signal strength) gray matter, white matter, CSF or signal hyperintensities. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex. Blind to the subjects' ages or diagnoses,

Fig. 2. Representative, fully-processed images. Pixels are classified, zones manually designated. Gray matter pixels have been color-coded to display zone designations: right hemisphere cortical=yellow, subcortical=light blue; left hemisphere cortical=white, subcortical=magenta; and cerebellar=gray. CSF and white matter pixels in all zones are displayed in red and black, respectively; coded separately by zone so that regional measures may be computed. Three sections in upper row are from nine-year-old subject; those in lower row are from 32-year-old subject. Note slight increases in CSF and slight decrease in cortical thickness in older subject.

operators manually separated cerebellar from cerebral areas, and cortical from subcortical regions, using a stylus-controlled cursor on the displayed image. In this way separate estimates of the four classes of pixels could be made for these areas.

The fully processed images are illustrated in Figure 2. Subcortical and cortical fluid and hyperintensities were measured separately. Volumes of cerebellum and cerebrum were estimated by summing pixels in infratentorial and supratentorial zones, respectively, over all sections. Total cranial volume was computed by summing these volumes. Other measures were obtained by summing pixels in a given class, for each region, over all axial sections. These measures included cortical and ventricular CSF, and cortical and subcortical gray matter, all expressed as proportions of the supratentorial cranial volume. A ratio of total cerebral gray matter pixels to total cerebral white matter pixels was also computed.

An additional analysis of the structure of the cerebellar vermis was conducted, using a midsagittal section: this method was modified from that of Courchesne *et al.* (1987, 1988). Subjects were excluded if motion artefacts or an eccentric plane of section rendered the vermal landmarks indistinct. A suitable section, showing the primary and prepyramidal fissures, was obtained for all but two subjects, one child and one young adult. With the section displayed on the screen, an operator adjusted a numerical criterion until pixel values in the vermal area were all above the criterion, while the fluid surrounding the vermis was below it. No attempt was made to exclude the vermal sulci, most of which were partially volumed CSF and tissue. Then vermal lobules I-V were circumscribed, with a polygon designated using a stylus-controlled cursor, and vermal lobules VI-VII were similarly circumscribed. The number of pixels with values above the criterion and falling within the polygons were taken as the vermal I-V and vermal

TABLE I

Brain measures	Standardized regression coefficients	
	Sex	Age
Cranial volume	-0.37†	0.22
Cerebral volume	-0.34	0.17
Cerebellar volume	-0.41*	0.39*
Cortical CSF proportion	0.16	0.36
Ventricular CSF proportion	0.11	0.68**
Gray matter to white matter ratio	0.10	-0.77***
Cortical gray matter proportion	0.02	-0.84***
Subcortical gray matter proportion	0.08	-0.14
Vermal I-V area	-0.40†	-0.03
Vermal VI-VII area	0.18	0.48**
Vermal ratio	0.47*	0.42†

† $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Fig. 3. Illustration of vermal measurement technique. Primary and prepyramidal fissures are visually identified on midsagittal section displayed on console screen, as seen on left. With a stylus-controlled cursor, a polygon is designated which circumscribes first vermal lobules I-V, then vermal lobules VI-VII. On the right, all pixels designated as vermal I-V are shown in white, those designated vermal VI-VII in light gray. Areas reported here are total pixel counts of these regions.

VI-VII areas, respectively. A ratio of vermal VI-VII to vermal I-V was also computed. Figure 3 illustrates this method.

Statistical analysis

Multiple regression analyses were used to test for significant sex and age effects. Each morphological measure served as the dependent variable, with sex and age as predictors. A significant association between age and brain morphology required a statistically significant regression coefficient for age, with sex present in the prediction equation.

Results

Routine clinical readings of the MRI examinations were performed. A right cerebellar venous angioma was noted in a nine-year-old boy. Several tiny punctate foci of increased intensity were seen in the deep white matter in a 10-year-old girl. Mild atrophy was noted in a 35-year-old man, and moderate volume loss, with a single small punctate hyperintensity, in a 32-year-old woman. A single punctate focus of signal hyperintensity in the frontal lobe was seen in another 32-year-old woman. The remaining 19 examinations were deemed normal, except for comments on fluid in nasal cavities and occasional unusual appearances of the calvarium.

Results of the statistical analyses are summarized in Table I. Significant sex effects were observed on only two measures, the cerebellar volume area ($p < 0.05$) and the vermal VI-VII to I-V ratio ($p < 0.05$). The sex effect approached significance for cranial volume and the vermal I-V area. In all cases, females had smaller average values than males, except that the vermal ratio was larger in females.

Significant cerebral changes with age included a decrease in the ratio of gray matter to white matter ($p < 0.001$), a decrease in the cortical gray matter proportion ($p < 0.01$), and an increase in the ventricular fluid proportion ($p < 0.05$). These results are illustrated in Figure 4.

In the posterior fossa, significant increases with age were observed in cerebellar volume ($p < 0.05$) and vermal VI-VII area ($p < 0.05$), but not in vermal I-V area, and the resulting increase in the ratio of VI-VII to I-V approached significance. Figure 5 shows the distribution of the vermal measurements.

Discussion

These results suggest that although the age-related increase in the size of the cerebrum is, at most, slight in late childhood, striking changes occur in the cerebral gray matter. The ratio of gray to white matter declines significantly, which is attributable to marked decreases in cortical gray matter with no observable change in subcortical gray matter. In at least three previous studies, gray to white

Fig. 4. Distributions of values across age-range on measures of cerebral morphology: (left) ratio of gray matter to white matter decreases; (center) proportion of cerebrum that is cortical gray matter decreases; (right) proportion of cerebrum that is ventricular CSF increases.

Fig. 5. Distributions of values across age-range for areas of vermal lobules I-V and VI-VII and for vermal ratio: (left) vermal I-V areas show no significant change; (center) vermal VI-VII areas increase with age; (right) vermal ratio also increases.

matter ratios have been computed for children's brains. In two German neuropathology studies by Anton (1903) and Jaeger (1914), reviewed by Miller *et al.* (1980), gray to white ratios were measured using planimetry and averaged approximately 2.3 at age three, declining in adulthood to about 1.1 to 1.4. More recently, Thompson *et al.* (1985) used CT imaging to measure these ratios in the frontal lobes: they obtained quite similar values, with a change from about 2.2 to about 1.8 over the age-range from 20 months to 16 years. Our values, using *in vivo* MRI measurements, are consistent

with the neuropathology reports and suggest a reduction from about 1.8 in eight-year-olds to 1.3 in adults.

It is possible that late myelination of peripheral areas of white matter results in apparent thinning of the cortical mantle. It has been suggested that this would explain the thinning of the cortical mantle noted on MRI in qualitative descriptions by Holland *et al.* (1986). Barkovich *et al.* (1988) also noted late progression of myelination into peripheral occipital and frontal areas, resulting in cortical thinning; however, they were studying children under two years of age.

The reduction of the proportion of cortical gray matter is strongly associated with the increase in ventricular CSF ($r = -0.73$, $p < 0.001$), and in fact is also correlated with increases in cortical sulcal CSF ($r = -0.44$, $p < 0.05$) and total CSF ($r = -0.52$, $p < 0.01$). This suggests that some cellular constituents may be lost in association with these late maturational changes. It is possible that some form of 'pruning' within the cortical structure occurs during adolescence, with important functional implications.

Prompted by recent studies by Courchesne *et al.* (1987, 1988), which showed significant differences in vermal morphology in autistic subjects, we used similar methods to examine the posterior fossa structures of our subjects. In the studies by Courchesne and colleagues, vermal I-V areas were comparable to those of controls; however, vermal VI-VII areas were reduced, and in some cases the hypoplasia was pronounced. Our results suggest that while the paleocerebellar vermal lobules I-V approach their full size by at least age eight, the neocerebellar lobules continue to grow, so the relationship of neocerebellar to paleocerebellar areas may change in late childhood. An alternative explanation, that the shape, rather than the size, of the cerebellum changes, resulting in altered cross-sectional appearance of the lobules, seems less likely but cannot be ruled out. Continuing growth of the larger neocerebellar areas, even with no growth of paleocerebellar areas, should be reflected in an over-all increase in cerebellar volume, and such an increase was observed in our study.

One limitation of the present study is

the lack of subjects between 10 and 25 years of age, so it is unclear whether the changes occur linearly or precipitously. The possibility that puberty may play a rôle in triggering the changes is intriguing, and studies examining brain morphology in adolescents are under way.

Traditionally, neocerebellar regions have been linked to fine motor functions, and these findings may have relevance for the development of this aspect of behavior. In recent articles by Leiner *et al.* (1987) and Dow (1988), evidence has been summarized for a possible rôle of the human neocerebellar structures in mental and linguistic manipulations as well, so the late development of these neocerebellar regions may also have important implications for cognitive, and even affective, functions in late childhood and early adulthood. Further studies are needed to reveal the specific relationships, if any exist, between developing brain function and these late morphological changes.

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SUMMARY

Quantitative studies of brain morphology in groups of normal children aged eight to 10 years and of young adults aged 25 to 39 years revealed continuing maturation of the brain over this age-range. There was some evidence of slightly increasing brain volume, but the most striking changes occurred in the gray matter to white matter ratio, and especially in the cortical mantle, which becomes substantially thinner on MRI between the age of eight and adulthood. An increase in the volume of the cerebral ventricles occurred in close association with the decrease in cortical gray matter. Analyses of the morphology of the cerebellar vermis suggest that significant increases occur in the neocerebellar vermal area over this age-range, and that the ratio of neocerebellar to paleocerebellar vermal areas may also increase.

RÉSUMÉ

Modifications tardives de l'enfance dans la morphologie cérébrale observée par IRM

Des études quantitatives de morphologie cérébrale dans des groupes d'enfants normaux âgés de huit à dix ans et de jeunes âgés de 25 à 39 ans ont montré une maturation continue du cerveau durant l'intervalle d'âge. Il y avait quelques indications d'une légère augmentation du volume cérébral mais

la modification la plus frappante se situait dans le rapport entre substance grise et substance blanche, spécialement au niveau du cortex qui devient substantiellement plus fin à l'IRM entre huit ans et l'âge adulte. Un accroissement du volume des ventricules cérébraux apparaissait en étroite association avec la diminution de la matière grise corticale. Les analyses de la morphologie du vermis cérébelleux suggèrent un accroissement significatif de l'aire néo-cérébelleuse du vermis durant la période considérée, et que le rapport des aires vermiennes néo-cérébelleuses sur les aires vermiennes paléo-cérébelleuses peut aussi s'accroître.

ZUSAMMENFASSUNG

Im MRI darstellbare Veränderungen der Hirnmorphologie im späten Kindesalter

Quantitative Studien der Hirnmorphologie bei normalen Kindern im Alter zwischen acht und 10 Jahren und jungen Erwachsenen zwischen 25 und 39 Jahren zeigten eine kontinuierliche Hirnreifung in diesem Altersbereich. Es gab Hinweise für eine leichte Zunahme des Hirnvolumens, die auffälligsten Veränderungen jedoch zeigten sich im Verhältnis von grauer zu weißer Substanz und besonders im Hirnrindenbereich, der im MRI von acht Jahren bis zum Erwachsenenalter deutlich dünner wird. Eine Volumenzunahme der Hirnventrikel stand in enger Relation zur Abnahme der grauen Hirnsubstanz. Analysen der Morphologie des Vermix cerebellaris deuten auf eine signifikante Zunahme im neocerebellären Bereich in diesem Alter hin, und auf eine Zunahme des Verhältnisses von neocerebellärem zu paleocerebellärem Vermixbereich.

RESUMEN

Cambios en la morfología cerebral al final de la infancia, observables con la IRM

Estudios cuantitativos de la morfología cerebral en grupos de niños normales de ocho a 10 años y de jóvenes adultos de 25 a 39 años, revelaron una maduración continua del cerebro a lo largo de estos márgenes de edad. Había evidencia de un aumento ligero del volumen cerebral, pero los cambios más sobresalientes tuvieron lugar en la sustancia gris en relación con la sustancia blanca y en especial en el manto cortical el cual se torna substancialmente más delgado a la IRM entre los ocho años y la edad adulta. Un aumento en el volumen de los ventriculos cerebrales tuvo lugar en estrecha relación con la disminución de la corteza gris. El análisis de la morfología del vermis cerebeloso sugiere que aumentos significativos tienen lugar en el área vermiana neocerebelosa a lo largo de las edades estudiadas y que la relación entre las áreas vermianas neocerebelosas y paleocerebelosas puedan también aumentar.

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