Title
LATE CHILDHOOD CHANGES IN BRAIN MORPHOLOGY OBSERVABLE WITH MRI

Permalink
https://escholarship.org/uc/item/3119v0cz

Journal
DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY, 32(5)

ISSN
0012-1622

Authors
JERNIGAN, TL
TALLAL, P

Publication Date
1990-05-01

Peer reviewed
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
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 ($T_1W$: $TR = 600\text{msec}, TE = 20\text{msec}$) sequence, sagittal images centred 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 ($TR = 2000\text{msec}, TE = 25, 70\text{msec}$). 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 $256 \times 256$ 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,
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

<table>
<thead>
<tr>
<th>Brain measures</th>
<th>Standardized regression coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td>Cranial volume</td>
<td>-0.37</td>
</tr>
<tr>
<td>Cerebral volume</td>
<td>-0.34</td>
</tr>
<tr>
<td>Cerebellar volume</td>
<td>-0.47*</td>
</tr>
<tr>
<td>Cortical CSF proportion</td>
<td>0.16</td>
</tr>
<tr>
<td>Ventricular CSF proportion</td>
<td>0.11</td>
</tr>
<tr>
<td>Gray matter to white matter ratio</td>
<td>0.10</td>
</tr>
<tr>
<td>Cortical gray matter proportion</td>
<td>0.02</td>
</tr>
<tr>
<td>Subcortical gray matter proportion</td>
<td>0.08</td>
</tr>
<tr>
<td>Vermal I-V area</td>
<td>-0.40*</td>
</tr>
<tr>
<td>Vermal VI-VII area</td>
<td>0.18</td>
</tr>
<tr>
<td>Vermal ratio</td>
<td>0.47*</td>
</tr>
</tbody>
</table>

*p < 0.10; **p < 0.05; ***p < 0.001.

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 vermally-VII to I-V ratio (p < 0.05). The sex effect approached significance for cranial volume and the vermally-V area. In all cases, females had smaller average values than males, except that the vermally 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 vermally-VII area (p < 0.05), but not in vermally-V area, and the resulting increase in the ratio of vermally-VII to I-V approached significance. Figure 5 shows the distribution of the vermally 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...
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 role 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 role 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.

Accepted for publication 22nd June 1989.

Acknowledgements
The authors are especially grateful to Drs. Eric Courchesne, Gary Press and John Hesselink for their help in evaluating the images, and for demonstrating the methods for measuring the vermis. This research was supported by the NINCDS Multidisciplinary Research Center for the Study of the Neurological Basis of Language, Learning and Behavior Disorders in Children, grant number NS22343.

Authors' Appointments
*Terry L. Jernigan, Ph.D., Staff Psychologist, VA Medical Center; Assistant Professor of Psychiatry and Radiology, UCSD School of Medicine. Paula Tallal, Ph.D., Co-Director, Center for Molecular and Behavioral Neurosciences, Rutgers University.

*Correspondence to first author at V-116B, VA Medical Center, 3350 La Jolla Village Dr., San Diego, CA 92161.

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 Hirn morphologie im späten Kindesalter

RESUMEN
Cambios en la morfologia cerebral al final de la infancia, observables con la RM
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 substancia gris en relación con la substancia blanca y en especial en el manto corticoc el cual se torna substancialmente más delgado a la RM 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 cerebelsco sugiere que aumentos significativos tienen lugar en el área vermián neo-cerebellese a lo largo de las edades estudiadas y que la relación entre las áreas vermiánneas neocerebelleosas y palneo-cerebelleosas puedan tambien aumentar.

References