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Relationship Between Head Circumference and Brain Volume in Healthy Normal Toddlers, Children, and Adults

Abstract

Objective: To quantify the relationship between brain volume and head circumference from early childhood to adulthood, and quantify how this relationship changes with age.
Methods: Whole-brain volume and head circumference measures were obtained from MR images of 76 healthy normal males aged 1.7 to 42 years.
Results: Across early childhood, brain volume and head circumference both increase, but from adolescence onward brain volume decreases while head circumference does not. Because of such changing relationships between brain volume and head circumference with age, a given head circumference was associated with a wide range of brain volumes. However, when grouped appropriately by age, head circumference was shown to accurately predict brain volume. Head circumference was an excellent prediction of brain volume in 1.7 to 6 years old children ($r = 0.93$), but only an adequate predictor in 7 to 42 year olds.
Conclusions: To use head circumference as an accurate indication of abnormal brain volume in the clinic or research setting, the patient's age must be taken into account. With knowledge of age-dependent head circumference-to-brain volume relationship, head circumference (particularly in young children) can be an accurate, rapid, and inexpensive indication of normalcy of brain size and growth in a clinical setting.

Key words
Head Circumference · MRI · Brain Volume

Introduction

Head circumference is commonly used as an indicator of brain size in infancy and early childhood. Postmortem studies of infants [1,3] and a CT-imaging study of neonates with medical complications [4] have found significant positive correlations between head circumference and brain size, but the oldest of these cases was 8 months. Knowing how the relationship between head circumference and brain size changes throughout childhood and adolescence is relevant to older patients whose head circumferences were abnormal in infancy or childhood. Similarly, at older ages, an abnormal brain size for a given head circumference may provide clues about the prior growth abnormalities. For example, an abnormally small brain size for a given head circumference in later childhood or adulthood might suggest that brain growth earlier in development was not abnormal, but that developmental volume loss was accelerated or later growth was retarded. To our knowledge, the normal relationship between head circumference and brain volume has not been empirically verified in older children and adults via postmortem or *in vivo* studies and there are no studies characterizing the potential change in the correlation of brain volume and head circumference with age. Thus, the accuracy and appropriateness of head circumference as a way to estimate brain size or brain growth throughout childhood and into adulthood remains unclear.

The main purpose of the present study was to quantify the relationship between whole-brain volume and head circumference from early childhood through adolescence and to investigate how this relationship changes with age. Additionally, this relationship in healthy adults was quantified for comparison with children and adolescents. In order to obtain a reliable and repro-

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ducible head circumference measure, an algorithm to obtain this measure from MR images was utilized.

Materials and Methods

Subjects were 76 healthy, normal males ranging in age from 1.7 to 42 years (mean age 15.5 ± 11.1 years, median age 11.5 years) recruited through advertisements in the community as a part of an ongoing autism study. Because the majority of people with autism are male, the majority of normal volunteers recruited for our study were also male, and only a small number of normal females were recruited. Therefore, normal female subjects were too few to analyze for the present purposes and so are not presented. Based on medical, family and educational history questionnaires, no subject showed evidence of developmental, educational, medical, psychological, or psychiatric abnormalities or deficiencies on a pre-MRI screening (as previously detailed [2]). The ethnic distribution was as follows: 72.4% Caucasians, 17.1% Hispanic, 3.9% Asian, 6.6% Other. Before testing, the procedure and design of the study were explained to each subject and informed consent was obtained. The study was approved by the Institutional Review Board of San Diego Children's Hospital Research Center. Before testing, procedures were explained to each subject and, for those subjects under 18 years of age, their parent. Informed consent was obtained from each subject or parent and subjects were paid for their participation.

Axial MR images (TR = 3000 ms, TE = 30 and 80 ms, 1 NEX, FOV = 20 cm, matrix = 256 × 256, 3 mm interleaved [no gaps]) were obtained with a 1.5-T GE Signa MR scanner, and digital MRI data were transferred to Silicon Graphics workstations for analysis. All children and adults were either scanned during natural sleep or remained awake during scanning. Each subject was coded so that the rater was blind to age, study group and subject identity (as previously described [2]). Brain volumes for 72 of the present study's 76 total subjects were available from a previous study [2]. The remaining four were obtained via the same method.

Head circumference measures were calculated from MR images for each of the 76 subjects using the following procedure. MR T_2-weighted images were compiled to render a 3-D image of the head, which was then re-sliced axially at the level and angle of maximal distance between frontal and occipital lobes. This plane generally included the occipital protuberance and the most prominent part of the forehead, superior to the eyebrows. The outer edge of the skin on this axial slice was manually traced to calculate the measure of the subject's head circumference. With this method, problems with manual measurements such as proper tape placement or thick hair do not influence the head circumference measurement.

Tape head circumference measurements for some subjects were available from clinical evaluations (n = 17). Clinical head circumferences that were obtained within 6 months of the date of the MRI scan were compared to head circumference measures from MR images (intraclass correlation coefficient = 0.95, $p < 0.001$). On average, MR head circumference measures were within 1% of clinical measures.

Statistical analysis was carried out (C. K., H. B.) using the SPSS statistical software. To test the relationship between head circumference and brain volume the following variables were regressed on whole brain volume measures: age, linear head circumference, and quadratic head circumference. Multiple regression analysis was computed with all three factors as independent variables and standardized regression coefficients were tested. The multiple R and associated F-test reported in the results below included all variables and the squared semipartial correlation of these variables are reported. Variables are reported as significant when a test of the standardized regression coefficient yielded a significant, $p < 0.05$ t-statistic for a variable, given the other two variables in the model. Separate tests of correlations between head circumference and brain volume were performed in three age groups according to age-related changes in brain growth and decline [2]: 6 years old and younger, 7 – 16 year-olds, and 17 – 42 year-olds.

Results

Fig. 1 shows the relationship between head circumference and brain volume across ages 1.7 to 42 years. Head circumference ranged from 48.6 to 62.3 cm and whole-brain volume ranged from 1028.2 to 1590.8 ml. Head circumference and age were significant predictors of whole brain volume (F [3, 68] = 28.4, $p < 0.001$, multiple $R = 0.745$, contributions to R^2: linear head circumference, 0.41; quadratic head circumference, 0.02; age, 0.28; standard error of estimate, ± 83.5).

Fig. 1 b shows the relationship of head circumference and brain volume in the following age groups: 6 years old and younger, 7 to 16 years old, and 17 to 42 years old. In children 6 years old and younger, head circumference ranged from 48.6 to 56.1 cm and brain volume ranged from 1028.2 to 1590.8 ml. Both linear and quadratic head circumference were significant predictors of whole brain volume, but age did not significantly contribute to predicting whole brain volume with head circumference in the model (F [3, 18] = 37.2, $p < 0.001$, multiple $R = 0.928$, contributions to R^2: linear head circumference, 0.33; quadratic head circumference, 0.04; age, 0.01; standard error of estimate, ± 59.1 ml).

For 7 through 16 years olds, head circumference ranged from 52.6 to 58.7 cm and brain volume ranged from 1147.3 to 1542.9 ml. In this age group, linear head circumference and age significantly contributed to predicting brain volume, although the model was less strongly predictive than in the younger age group (F [3, 20] = 5.37, $p < 0.01$, multiple $R = 0.67$, contributions to R^2: linear head circumference, 0.40; quadratic head circumference, 0.01; age 0.14; standard error of estimate, ± 75.8 ml).

In adults aged 17 to 42 years old, head circumference ranged from 55.2 to 62.3 cm and brain volume ranged from 1080.6 to 1504.9 ml. In this age range, only head circumference was a significant predictor of brain volume (F [3, 22] = 6.54, $p < 0.01$, multiple $R = 0.69$, contributions to R^2: linear head circumference, 0.45, quadratic head circumference, 0.05; age= 0.04; standard error of estimate, ± 77.3 ml).

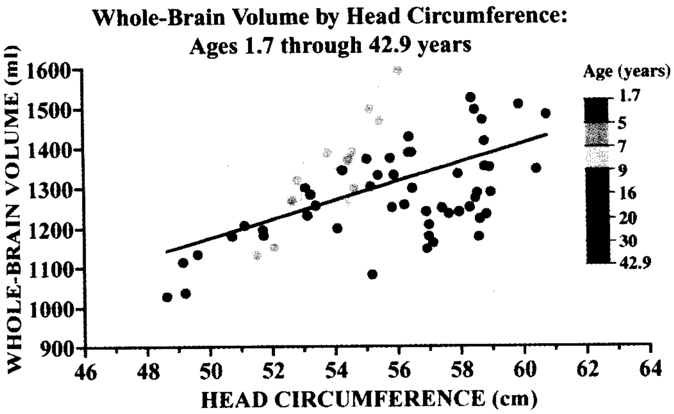

Fig. 1 Relationship of head circumference and whole-brain volume with best-fit curves. Age is represented with a color scale. **a** For ages 1.7 through 42 years the best-fit curve is shown.

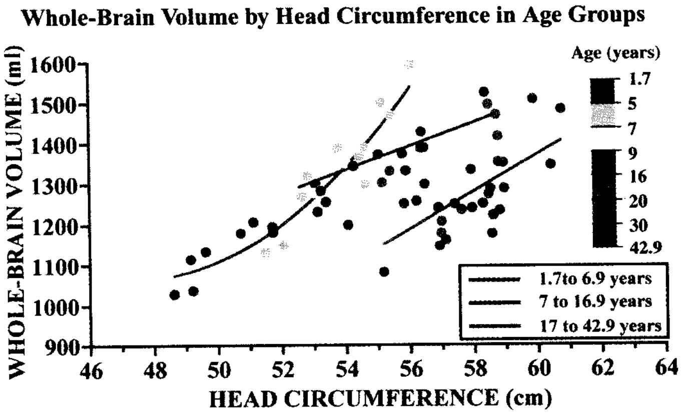

Fig. **1 b** Best-fit curves for three age groups are shown: ages 1.7 through 6 years (red line), 7 through 16 years (green line), and 17 through 42 years (blue line). Note that at mid-range head circumference, there is a wide range of brain volumes with the larger brain volumes belonging to the younger subjects.

Discussion

The accuracy and appropriateness of head circumference as an index of brain volume is dependent on age. For children 6 years old and younger, the correlation between head circumference and brain volume was very strong; thus, head circumference can be used as a relatively accurate reflection of a very young child's brain volume. For our subjects aged 7 through 16 years, the strength of the correlation between head circumference and brain volume decreased. Developmental changes in growth rate and skull thickness probably contribute to this general decrease in correlation as age also becomes a significant predictor in this age range. Our adult age group included ages 17 through 42 years because whole-brain volume stops increasing at around 16 years of age [2]. The average brain volume for children aged 7–16 years with head-circumference measures between 55.0 and 58.0 cm was 1368.1 ml, and yet the average *adult* brain volume (17–42 years) for that same head circumference range was only 1231.4 ml, demonstrating the importance of age when estimating brain volume from head circumference. The relationship between brain volume and head circumference in adult normals can provide important reference information for infants and children with unusual head circumferences as they age, and for retrospective brain-growth information in older patients with unusual head circumference or brain volume.

In conclusion, reliable estimates of brain volume can be made from head circumference measures when age-appropriate. Considering the ease and cost-effectiveness of measuring the head circumference of a young patient, this method of estimating brain volume in a developing young child is useful.

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