

Human Cerebral Hemispheres Develop at Different Rates and Ages

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The development of the cerebral hemispheres was assessed by using measures of electroencephalographic coherence and phase in 577 children ranging in age from 2 months to early adulthood. Two categories of age-dependent change in electroencephalographic coherence and phase were noted: continuous growth processes that were described best by an exponential growth function, and discrete growth spurts that appeared in specific anatomical locations at specific postnatal periods. The left and right hemispheres developed at different rates and with different postnatal onset times with the timing of growth spurts overlapping the timing of the major developmental stages described by Piaget.

AMONG THE UNANSWERED QUESTIONS in developmental psychology are (i) do the left and right human cerebral hemispheres develop at different rates, and (ii) is human cerebral development a smooth and continuous function of age, or does it exhibit abrupt changes and critical growth periods? An issue related to the latter question is to what extent does human cognitive development occur ontogenetically, that is, by the genetically programmed unfolding of specific brain functions and specific brain connections? Behavioral analyses of child development often reveal "stages" of perceptual and cognitive development (1). Although there is behavioral support for distinct stages of human development, there is surprisingly little neurophysiological evidence of discontinuities and growth spurts during the early childhood and adolescent periods of human development.

Studies of neuron density, glial cell counts, and DNA and RNA weights have been largely devoted to prenatal and postnatal development from birth to about 3 years of age (2). These studies show that, by the age of 3 years neuron and glial counts are fixed and myelination is approximately 90% of adult values. An exception to this was provided in a developmental study that showed that the myelination of the subcortex was complete by 3 years (with the exception of the reticular formation), whereas myelination of the cerebral commissures was complete by 9 years of age and the myelination of the intracortical white matter continued throughout life or up to 60 years (the oldest person in the study) (3). Although in this last study different rates of myelin development were present in different cortical regions, there was no evidence of differences in the rate of development, or growth spurt onset times, between the cerebral hemispheres.

Some electrophysiological evidence for developmental staging of the human cerebral hemispheres has been provided by Ma-

tousek and Petersen (4) in a large cross-sectional study of human electroencephalographic (EEG) relative power. Subsequent analyses of the EEG relative power values obtained by Matousek and Petersen revealed a continuous growth function with sudden and significant increments in relative power occurring in specific cortical regions; they also indicated that the ages at which the increments occurred overlapped the Piaget periods of cognitive development (5). The Matousek and Petersen study was limited, however, by the use of EEG relative power and by the fact that data from the left and right hemispheres were averaged together. EEG relative power lacks the spatial resolution and network analysis advantages of measures such as EEG coherence and phase. Coherence is equivalent to the absolute value of the cross-correlation function in the frequency domain and reflects the number and strength of connections between spatially distant generators (6). Measures of phase provide estimates of lead and lag times between spatially separate but connected systems of generators as well as measures of frequency dispersion and conduction velocity (7). The advantages of EEG coherence and phase are that they reflect corticocortical connectivity properties of both short- and long-distance axonal systems and are relatively insensitive to volume conduction, especially at scalp distances greater than 7 cm (8).

The purpose of the present study was to use EEG coherence and phase network analyses to investigate cerebral hemispheric development in a large cross-sectional study of normal children ranging in age from 2 months to early adulthood. Our goal was to test a sufficiently large number of children so that developmental trends could be detected with adequate statistical reliability and statistical power. A total of 723 children were recruited from rural and urban areas of the state of Maryland as part of a U.S. Department of Agriculture study of the relations between nutrition and child development

(9). A variety of measures were obtained from each child. These included a neurological and developmental history, a full-scale intelligence test (IQ), and measures of school achievement, motor development, skull size, and handedness (9). In addition, 1 minute of eyes-closed EEG (obtained in a no-task or resting condition) was recorded from all 19 leads of the international 10/20 system of electrode placement. EEG coherence and phase were computed for all pairwise combinations of electrodes in the delta (0.5 to 3.5 Hz), theta (3.5 to 7 Hz), alpha (7 to 13 Hz), and beta (13 to 22 Hz) frequency bands (10). From the total of 723 children, a subset of 577 children were selected for analysis based on the criteria of (i) an uneventful prenatal, perinatal, and postnatal period; (ii) no disorders of consciousness; (iii) no head injury with cerebral symptoms; (iv) no history of central nervous diseases; (v) no convulsions of emotional, febrile, or other nature; (vi) no obvious mental diseases; and (vii) no abnormal deviation with regard to mental and physical development. The population included 58% males, 42% females, and 28.4% blacks, 71.6% whites. The range of full-scale intelligence quotient (IQ) of the children was from 70 to 160 with a mean of 106.4 and a standard deviation of 16.26.

Mean EEG coherence and phase were computed for each frequency band for 17 successive 1-year age groups ranging from 2 months to 26.42 years (11). The questions of primary concern were (i) do the left and right hemispheres develop at the same rate, and (ii) is there evidence of growth spurts (12) in the development of EEG coherence and phase and, if so, is the age of onset the same for the left and right hemisphere?

Efforts were made to control for differences in head size and full-scale IQ, which may occur as a function of age within the population of 577 children. Specifically, analyses of covariance (12) were conducted in which mean coherence and phase values were adjusted by all correlations between age and (i) head circumference, (ii) medial-lateral head size, (iii) anterior-posterior head size, and (iv) full-scale IQ. The results of the analyses of covariance demonstrated developmental trajectories for coherence and phase that were described best by an age-dependent exponential growth function $Y = BT^\alpha$, where Y is the EEG coherence or phase value, B is the intercept, T is the postnatal age in Julian years [that is, age in decimals (13)], and α is the proportional growth constant. This exponential growth

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equation provided a good fit for both EEG phase and coherence and generally showed a positive exponent (that is, $1 > \alpha > 0$) in which growth was most rapid in the early postnatal ages (that is, from birth to 6 years) with slower growth in the later postnatal ages.

Although the overall developmental trajectories could be accurately described by a continuous growth equation, there were many examples of growth spurts or sudden increases in the rate of growth (12). The growth spurts were present in both coherence and phase and were observed from a large number of deviations. There were clear spatial gradients in the amplitude of the growth spurts, which showed that only specific corticocortical relationships were statistically significant.

The data in Figs. 1, 2, and 3 are representative of the dominant and consistent intracortical developmental changes observed. Both the left and right frontal-occipital electrode pairs (Fp1-O1 and Fp2-O2) exhibited a slow increase in phase from birth

to about age 3 (Fig. 1A). However, from age 3 to 6 the left hemisphere showed a marked increase in phase that tended to level off from age 6 to adulthood. In contrast, EEG phase in the homologous right hemisphere did not show such a growth spurt during this period and instead increased slowly in phase with a slight growth spurt occurring between the ages of 8 and 10 years. Figure 1B plots the same data as in Fig. 1A as a percentage of adult phase values. The left frontal-occipital pairs achieved 90% of adult value by about 5 years. In contrast, the homologous right hemisphere did not achieve 90% of the adult value until about the age of 9 years. This is an example of the left hemisphere leading the right hemisphere in development. In Fig. 1C the same data as in Fig. 1A are displayed as biennial increments (that is, the difference in means between successive age groups, or $\bar{X}_i - \bar{X}_{i-1}$). A marked phase increment is evident in the left frontal-occipital pair, whereas a similar growth spurt is absent in the homologous right hemisphere.

Analyses of covariance showed a significant difference in mean alpha phase in the left frontal-occipital leads between ages 2 and 4 and between ages 2 and 5, but no significant differences during this period in the homologous right hemisphere. There was also a significant difference in mean alpha phase between the left and right hemisphere for the fourth- and fifth-year age groups.

Other examples of differences in the rate and timing of growth in the left and right hemispheres are shown in Fig. 2. Figure 2, A and B, shows biennial increments in EEG coherence from the left and right frontal derivations (that is, Fp1 and Fp2). The magnitude of the biennial increment in coherence in the right frontal region (Fp2-F4) was nearly three times that from the homologous left hemisphere (Fp1-F3), and a clear gradient of development was evident. That is, the magnitude of biennial increment follows the order Fp2-F4 > Fp2-C4 > Fp2-P4 > Fp2-O2, which represents a gradient of change that decreases with distance from the right hemisphere frontal pole (the Fp2

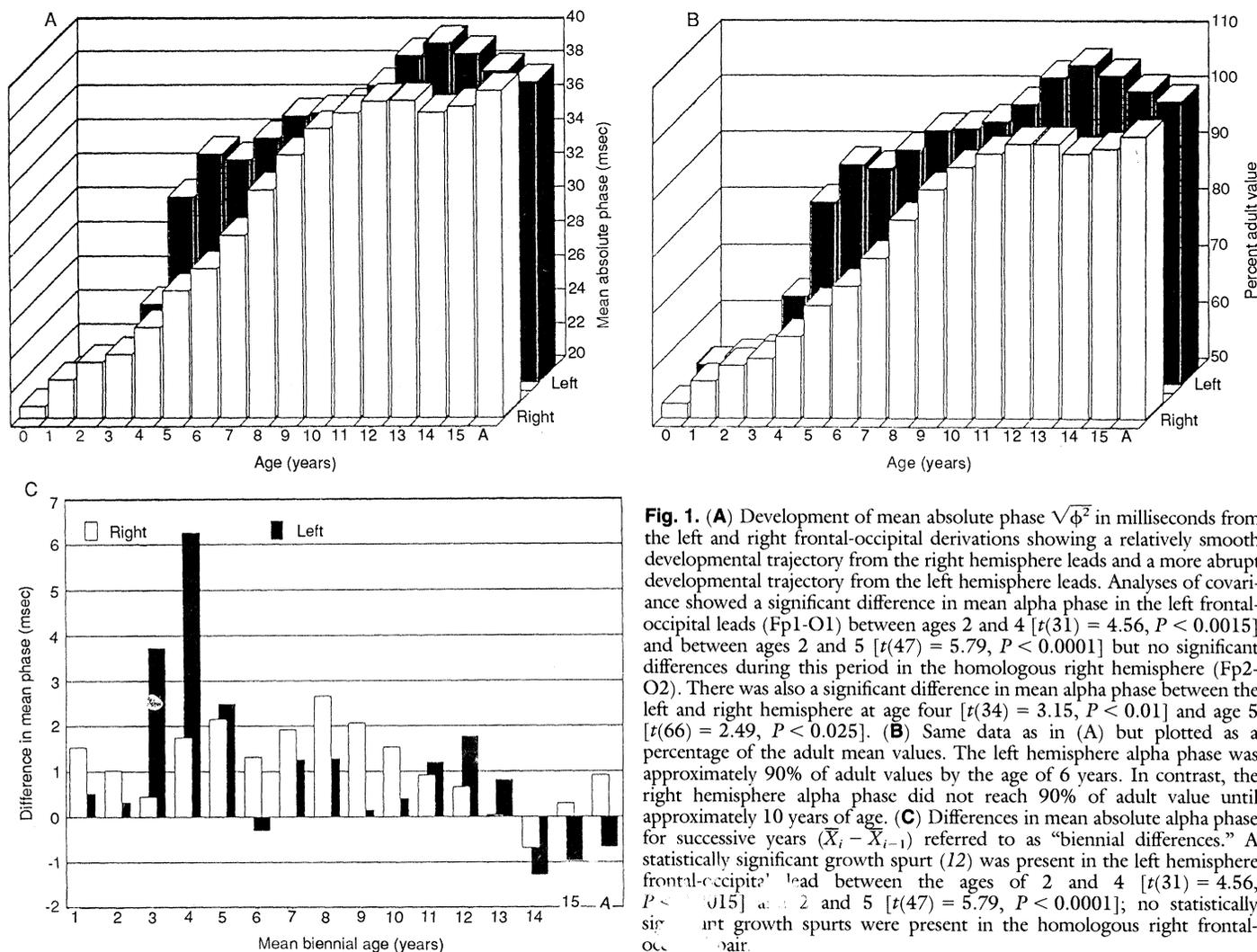


Fig. 1. (A) Development of mean absolute phase $\sqrt{\phi^2}$ in milliseconds from the left and right frontal-occipital derivations showing a relatively smooth developmental trajectory from the right hemisphere leads and a more abrupt developmental trajectory from the left hemisphere leads. Analyses of covariance showed a significant difference in mean alpha phase in the left frontal-occipital leads (Fp1-O1) between ages 2 and 4 [$t(31) = 4.56, P < 0.0015$] and between ages 2 and 5 [$t(47) = 5.79, P < 0.0001$] but no significant differences during this period in the homologous right hemisphere (Fp2-O2). There was also a significant difference in mean alpha phase between the left and right hemisphere at age four [$t(34) = 3.15, P < 0.01$] and age 5 [$t(66) = 2.49, P < 0.025$]. (B) Same data as in (A) but plotted as a percentage of the adult mean values. The left hemisphere alpha phase was approximately 90% of adult values by the age of 6 years. In contrast, the right hemisphere alpha phase did not reach 90% of adult value until approximately 10 years of age. (C) Differences in mean absolute alpha phase for successive years ($\bar{X}_i - \bar{X}_{i-1}$) referred to as "biennial differences." A statistically significant growth spurt (12) was present in the left hemisphere frontal-occipital lead between the ages of 2 and 4 [$t(31) = 4.56, P < 0.0015$] and 2 and 5 [$t(47) = 5.79, P < 0.0001$]; no statistically significant growth spurts were present in the homologous right frontal-occipital pair.

lead). This indicates the presence of a growth spurt in the right frontal pole that may involve short-distance fibers (probably less than 6.65 cm, which is the average Fp2-F4 electrode distance at age 5). The homologous left hemisphere frontal derivations show a statistically nonsignificant increment during the 4- to 6-year period.

Two other features of Fig. 2, A and B, were commonly present. One was the topographic scatter of coherence change from birth to about age 3 years, which disappeared, however, and was replaced by rhythmic

and phase-locked developmental trajectories, which spanned the age from 3 to adulthood. A second commonly observed feature was weak growth spurts around the ages of 11 to 13 years and 16 years to adulthood (Fig. 2, A and B). These later growth spurts were often not statistically significant. Nonetheless, they were consistently present in both the left and right hemispheres with bilateral frontal pairings exhibiting the earliest and largest biennial increments.

Figure 3, A and B, shows phase differ-

ences of posterior temporal lobe (T5 and T6) calculated by biennial differences from birth to adulthood. A very pronounced increment in EEG phase was present in the left temporal-frontal electrode pairs (Fig. 3A) between the ages of 4 and 6 years, but a corresponding growth spurt was not present in the homologous right temporal-frontal electrode pairs (Fig. 3B) during this same period. In contrast to the left hemisphere, the right temporal-frontal pair (T6-F8) showed a growth spurt during the period from age 8 to 10 years (Fig. 3B). A corresponding growth

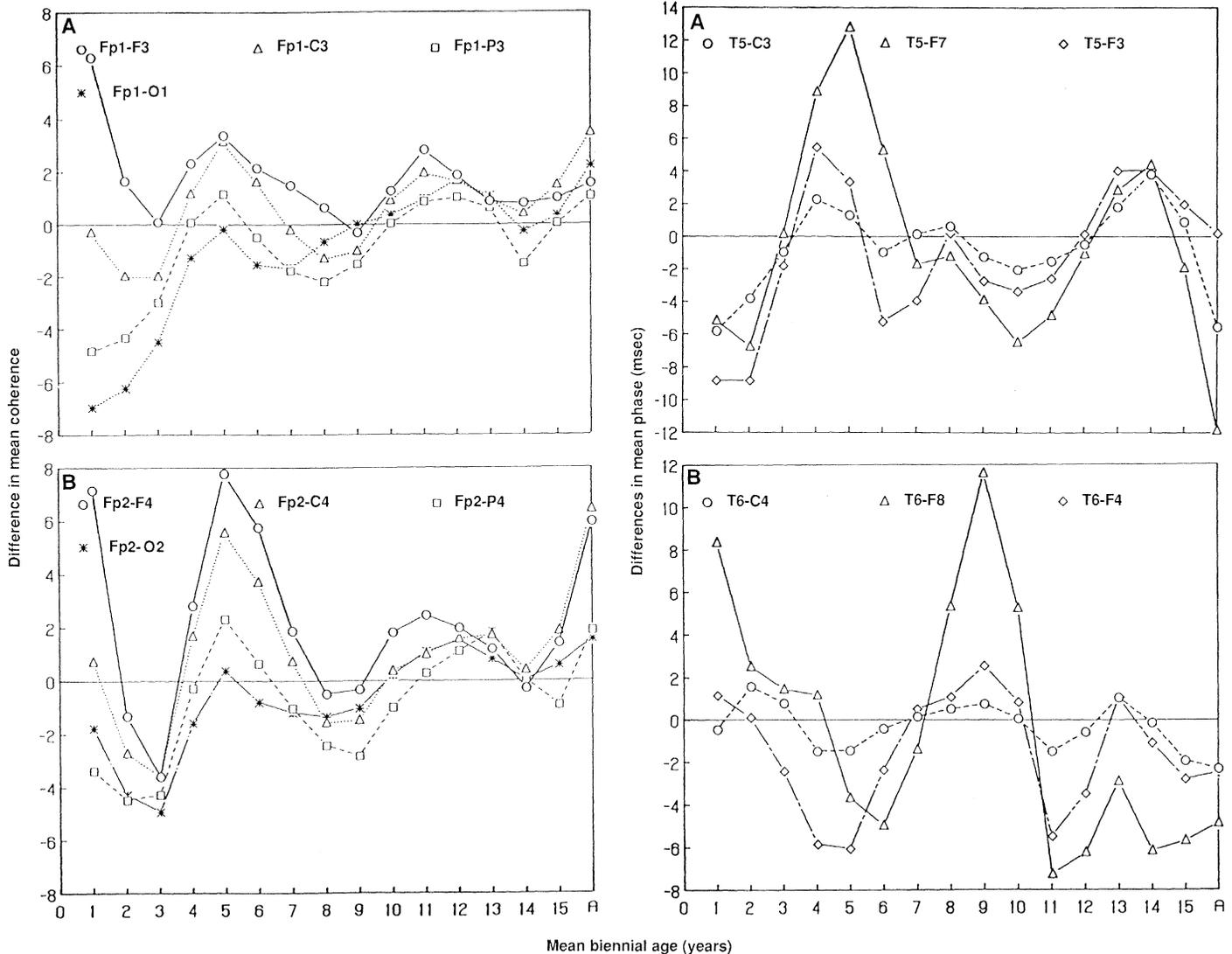


Fig. 2 (left). Biennial differences in mean coherence from the left and right hemisphere frontal electrode pairings. **(A)** A typical rhythmic pattern of development from the left frontal intrahemispheric derivations. A statistically significant growth spurt (11) occurred between birth and age 5 in the Fp1-O1 derivation [$t(46) = 7.05, P < 0.0001$]. All other statistically significant growth spurts occurred between ages 10 and 13 [Fp1-F3, $t(94) = 4.03, P < 0.001$; Fp1-C3, $t(94) = 3.56, P < 0.001$], and between age 13 and adulthood [Fp1-F3, $t(48) = 3.52, P < 0.01$]. **(B)** A typical rhythmic pattern of development from the right frontal intrahemispheric derivations. Statistically significant growth spurts were present between ages 3 and 5 [Fp2-F4, $t(76) = 4.91, P < 0.0008$; Fp2-C4, $t(76) = 5.03, P < 0.0001$; Fp2-P4, $t(76) = 3.0, P < 0.03$]; between ages 9 and 13 [Fp2-F4, $t(90) = 4.89, P < 0.0006$; Fp2-C4, $t(91) = 4.12, P < 0.004$; Fp2-P4, $t(90) = 3.81, P < 0.008$], and between age 14 and adulthood [Fp2-C4,

$t(38) = 3.04, P < 0.03$]. The most prominent biennial peak at age 5 exhibited a spatial gradient of change in the order Fp2-F4 > Fp2-C4 > Fp2-P4 > Fp2-O2, which indicates that the origin of the differences was in the right frontal pole (near Fp2). **Fig. 3 (right).** Biennial differences in mean absolute phase lags between the left and right hemispheric temporal pairings. **(A)** Left temporal phase development in which a statistically significant growth spurt was present in the left temporal-frontal derivation (T5-F7) between age 2 and 5 [$t(47) = 3.37, P < 0.01$] and between age 14 and adulthood [$t(38) = 3.66, P < 0.01$]. **(B)** Right temporal phase development, which was distinctly different in pattern to that observed from the homologous left temporal derivations. Statistically significant growth spurts were present in the right temporal-frontal derivation (T6-F8) between the ages of 6 and 9 [$t(77) = 3.6, P < 0.01$] and between ages 6 and 10 [$t(81) = 3.24, P < 0.01$].

spurt was absent in the left temporal pairs during this same period (Fig. 3A).

Certain consistent and stable patterns of EEG development were evident. In general, there were five dominant growth periods in intrahemispheric corticocortical coupling from birth to adulthood. The first, from birth to 3 years of age, was a topographically scattered developmental change, which primarily, but not exclusively, involved a decrease in coherence and phase (Figs. 2 and 3). Beyond 3 years of age a much more uniform and synchronized pattern of development was observed. The second period, from age 4 to 6, involved a change in the left frontal-occipital coupling, the left frontal-temporal coupling, and a localized right frontal pole pairing (Figs. 1 and 2). The third growth period, from age 8 to 10, involved connections between the right hemisphere temporal-frontal regions. The fourth and fifth growth periods, which occurred during the periods from about age 11 to 14 and from age 15 to adulthood, respectively, were bilateral in nature and involved primarily, but not exclusively, frontal lobe connections.

These results indicate a sequencing of different anatomical systems during postnatal cortical development. It is significant that the timing of the EEG changes observed in the present study, as well as in the Matousek and Petersen study (4), overlap quite well with the timing for the Piaget theory of human cognitive development (5). Although "staging" or discontinuous theories of cognitive development are reasonably well accepted, they nonetheless lack neurophysiological validation. One value, therefore, of the present findings is in the degree to which they may add neurophysiological and anatomical insight into the mechanisms of human cognitive development.

The present data do not lend themselves to a simple "left-right maturational gradient" hypothesis (14), since different regions of the left and right hemisphere developed at different times and different rates. For example, the left frontal-occipital and left frontal-temporal regions developed earlier than the homologous right frontal-occipital and right frontal-temporal regions (Figs. 1 and 2A). However, the right frontal pole developed earlier than the homologous left frontal pole (Fig. 2, A and B). It is well established that the two cerebral hemispheres carry out qualitatively different functions, especially in adulthood (15). Thus, maturation of long-distance fiber systems in homologous brain regions does not necessarily represent the maturation of homologous functions or even homologous cellular connections. The microanatomy of the two cerebral hemispheres may well be different and maturation

changes in coherence and phase may represent different processes at different times. The present findings provide evidence of differential rates of human cerebral development, and they provide some answers to the questions initially posed: that relatively specific anatomical connections within the left and right human cerebral hemispheres develop at different rates and at different postnatal onset times. Furthermore, the strength and the specificity of the patterns in the data strongly favor the ontogenetic hypothesis of human cortical development in which there is a genetically programmed unfolding of specific corticocortical connections at relatively specific postnatal ages.

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8. In the case of cortical EEG the magnitude of coherence can be modeled by coherence = $C_n \times S$, where C_n is the number of connections between neural systems and S is the driving strength of those connections. Phase can be modeled by phase = $E_n \times D$, where E_n is the number of elements in a neural loop and D is the delay between the elements (for example, axonal conduction delays, synaptic delays, and dendrosomatic integration times). In this way, EEG coherence and phase can be interpreted in terms of neurophysiological network properties such as axonal conduction velocities, interneuronal densities, and the ratio of long- versus short-distance connections (7).
9. Further details of the population and the testing categories and procedures are described in: R. W. Thatcher et al., *Arch. Environ. Health* **37**, 159 (1982); and R. W. Thatcher et al., in *Cognitive Processing in the Right Hemisphere*, A. Perecman, Ed. (Academic Press, New York, 1983), pp. 125-146.
10. A transorbital eye channel (electrooculogram or EOG) was used to measure eye movements. All scalp recordings were referenced to linked ear lobes. Amplifier bandwidths were nominally 0.5 to 30 Hz, the outputs being 3 db down at these frequencies. The EEG activity was digitized at a sample rate of 100 Hz by a PDP 11/03 data acquisition system. An on-line artifact rejection routine was used, which excluded segments of EEG if the voltage in any channel exceeded a preset limit determined at the beginning of each session to be typical of the subject's resting EEG and EOG. A second-order recursive digital filter analysis was used to compute the auto and cross-spectral power density for each channel (6). The procedure involved the use of a first difference prewhitening filter: $y(i) = x(i) - x(i-2)$ and a two-stage (four pole) Butterworth band-pass filter [for mathematical equations see (6)]. Frequency bands, including the center frequencies (f_c) and one-half power values (B) were delta (0.5 to 3.5 Hz; $f_c = 2.0$ Hz; and $B = 1.0$ Hz), theta (3.5 to 7.0 Hz; $f_c = 4.25$ Hz; and $B = 3.5$ Hz), alpha (7.0 to 13.0 Hz; $f_c = 9.0$ Hz; and $B = 6.0$ Hz), beta (13 to 22 Hz; $f_c = 19$ Hz; and $B = 14.0$ Hz). Degrees of freedom = $2BwT_r$, where Bw = the bandwidth and T_r the length of the record (for example, for 20 seconds of EEG there are 160 degrees of freedom) and the start-up and trail-off periods of the filter are 2 divided by bandwidth in hertz or 0.5 second for a 4-Hz bandwidth. The artifacting routines precluded EEG segments less than 0.8 second in length, and the range of total EEG length per subject varied from 16 to 60 seconds (mean, 42 seconds; SD, 13.61). Coherence is defined as $\gamma_{xy}^2(f) = [G_{xy}(f)]^2 / [G_{xx}(f) G_{yy}(f)]$, where $G_{xy}(f)$ is the cross-spectral power density and $G_{xx}(f)$ and $G_{yy}(f)$ are the respective auto spectral power densities. Coherence was computed for all pairwise combinations of the following 16 channels (O1, O2, P3, P4, T5, T6, T3, T4, C3, C4, F3, F4, F7, F8, Fp1, Fp2) for each of the four frequency bands. The computational procedure to obtain coherence involved first computing the spectral power for x and y and then the normalized cross-spectra. Since complex analyses are involved, this produced the cospectrum (r' for real) and quadspectrum (q' for imaginary). Then coherence was computed as: $\gamma_{xy}^2 = (r_{xy}^2 + q_{xy}^2) / G_{xx} G_{yy}$ and the phase difference, in milliseconds, was computed as: phase = $159.1549 \tan^{-1}(q/r) / f_c$, where f_c is the center frequency.
11. To increase the number of subjects and thus statistical power, no attempt was made to separate subjects on the basis of variables such as sex and handedness; therefore, the present population is heterogeneous with respect to these variables. The mean age and sample size for each group were: 0.2 to 0.99 (mean, 0.49 year; SD, 0.23; $n = 16$); 1.0 to 1.99 (mean, 1.5 years; SD, 0.26; $n = 18$); 2.0 to 2.99 (mean, 2.59 years; SD, 0.27; $n = 17$); 3.0 to 3.99 (mean, 3.31 years; SD, 0.25; $n = 46$); 4.0 to 4.99 (mean, 4.43 years; SD, 0.28; $n = 20$); 5.0 to 5.99 (mean, 5.44 years; SD, 0.33; $n = 36$); 6.0 to 6.99 (mean, 6.45 years; SD, 0.32; $n = 36$); 7.0 to 7.99 (mean, 7.49 years; SD, 0.3; $n = 47$); 8.0 to 8.99 (mean, 8.4 years; SD, 0.29; $n = 41$); 9.0 to 9.99 (mean, 9.49 years; SD, 0.3; $n = 47$); 10.0 to 10.99 (mean, 10.38 years; SD, 0.28; $n = 51$); 11.0 to 11.9 (mean, 11.41 years; SD, 0.28; $n = 44$); 12.0 to 12.99 (mean, 12.53 years; SD, 0.29; $n = 49$); 13.0 to 13.99 (mean, 13.51 years; SD, 0.28; $n = 49$); 14.0 to 14.99 (mean, 14.43 years; SD, 0.29; $n = 29$); 15.0 to 15.99 (mean, 15.42 years; SD, 0.3; $n = 15$), and 16.0 to 26.42 (mean, 19.15; SD, 0.43; $n = 16$). For purposes of plotting the age versus the mean EEG variables, including biennial ages, the data points were smoothed by means of a Blackman Window low-pass filter with a 0.05-Hz cutoff frequency. The software algorithm was provided by Asystant, Macmillan Software Co.
12. Growth spurts were defined as a statistically significant ($P < 0.05$) difference between mean coherence or between mean phase for two different age groups, after adjusting for head circumference, medial-lateral head size, anterior-posterior head size, and IQ [General Linear Model (GLM)-Analysis of Covariance, SAS, Statistical Analysis Systems, Triangle Park, NC, 1985]. The degrees of freedom include the four covariates and, since there was a statistically significant overall F in the ANCOVAs, the method of planned comparisons was used to test statistical significance for selected means. The specific age groups used for statistical comparison were identified from the biennial difference curves as adjacent maxima and minima (that is, peak-to-peak differences). For example, in Fig. 2B peak-to-peak comparisons were made between age 3 and 5 since these ages represented adjacent maxima and minima.
13. Julian years are defined as the decimal fraction of age and are computed as Julian years = age in years + [(30.4 × number of months + day of month)/365].
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16. We acknowledge the help of M. Lester, D. Cantor, M. Hrybyk, P. Krause, and R. McAlaster in the data collection phase of the project. Supported by USDA grants (HRD0200) and NIH (RR08079-0951).

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