

# Development of Cortical Connections as Measured by EEG Coherence and Phase Delays

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**Abstract:** The purpose of this study was to explore human development of EEG coherence and phase differences over the period from infancy to 16 years of age. The electroencephalogram (EEG) was recorded from 19 scalp locations from 458 subjects ranging in age from 2 months to 16.67 years. EEG coherence and EEG phase differences were computed for the left and right hemispheres in the posterior-to-anterior direction (O1/2-P3/4, O1/2-C3/4, O1/2-F3/4, and O1/2-Fp1/2) and the anterior-to-posterior direction (Fp1/2-F3/4, Fp1/2-C3/4, Fp1/2-P3/4, and Fp1/2-O1/2) in the beta frequency band (13–25 Hz). Sliding averages of EEG coherence and phase were computed using 1 year averages and 9 month overlapping that produced 64 means from 0.44 years of age to 16.22 years of age. Rhythmic oscillations in coherence and phase were noted in all electrode combinations. Different developmental trajectories were present for coherence and phase differences and for anterior-to-posterior and posterior-to-anterior directions and inter-electrode distance. Large changes in EEG coherence and phase were present from ~ 6 months to 4 years of age followed by a significant linear trend to higher coherence in short distance inter-electrode distances and longer phase delays in long inter-electrode distances. The results are consistent with a genetic model of rhythmic long term connection formation that occurs in cycles along a curvilinear trajectory toward adulthood. Competition for dendritic space, development of complexity, and nonlinear dynamic oscillations are discussed. *Hum Brain Mapp* 29:1400–1415, 2008. © 2007 Wiley-Liss, Inc.

**Key words:** development of EEG coherence; EEG phase differences; cortical connections; two-compartmental model of cortico-cortical connectivity; complexity development

## INTRODUCTION

Neural dynamics involves the generation of electrical currents by populations of synchronously active neurons

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within local regions of the brain that are coupled through axonal connections to other populations of neurons (Braitenberg, 1978; Nunez, 1981, 1994; Schuz and Braitenberg, 2002). Anatomical analyses of the cerebral white matter have shown that there are three general categories of cortico-cortical connections: (1) intra-cortical unmyelinated connections within the gray matter on the order of 1 mm to 1 ~ 3 mm, (2) short-distance 'U' shaped fibers in the cerebral white matter located beneath the gray matter (10 mm to ~ 30 mm) and, (3) long distance fasciculi located in the deep white matter below the 'U' shaped fibers with distances from 30 to ~ 170 mm (Braitenberg, 1978; Schuz and Braitenberg, 2002). Measures of EEG coherence and phase delays from the scalp surface commonly detect the presence of two compartments with an approximate correspondence to the short distance 'U'

shaped and long distance fiber systems (Barry et al., 2005; Hanlon et al., 1999; McAlaster, 1992; Nunez, 1981, 1994; Pascual-Marqui et al., 1988; Shen et al., 1999; Srinivasan, 1999; Thatcher et al., 1986, 1998, 2007; Van Beijsterveldt et al., 1998). These studies show that EEG coherence when measured by a single common reference decreases as a function of distance from any electrode site thus characterizing the 'U' shaped fiber compartment and coherence increases as a function of distance beyond ~10–12 cm which characterizes the long distance fascicular compartment. Studies of changes of EEG coherence with distance are usually explained by a decrease in the number of connections as a function of distance from any given population of neurons while increased coherence with distance is explained by an increase of connections between two populations through axons and fasciculi of the deep cerebral white matter (Braitenberg, 1978; Hanlon et al., 1999; McAlaster, 1992; Nunez, 1981, 1994; Schuz and Braitenberg, 2002; Srinivasan, 1999; Thatcher et al., 1986, 1998, 2007). Understanding of the differential rates of development of the local versus distant cortical connections has been advanced by genetic analyses of identical twins in which short distance coherence measures are ~55% determined by environmental factors and ~45% by genetics whereas the long distance coherence measures are greater than 75% determined by genetic factors (van Baal et al., 2001; Van Beijsterveldt et al., 1998).

A deeper understanding of cortical coupling is possible by studying the maturation of EEG coherence and phase differences in the short versus the long distance compartments. EEG phase difference is an analytical measure of the time difference between coupled oscillators (Bendat and Piersol, 1980). EEG coherence is a statistical measure of the consistency of phase differences over some sample space and is a measure of "phase synchrony" or "phase stability" between spatially distant generators (Bendat and Piersol, 1980; Nunez, 1981; Otnes and Enochson, 1972). EEG phase differences are often the opposite of coherence by systematically increasing while EEG coherence decreases as a function of inter-electrode distance (Thatcher et al., 1986, 1987). The increase in phase differences as a function of inter-electrode distance are due to many potential sources such as longer conduction delays as a function of distance or slower average synaptic rise times or longer average synaptic integration times. An important advantage of measures of spontaneous EEG phase difference is that phase delays can eliminate volume conduction because volume conduction, in the absence of a defined dipole source, is defined by phase difference = 0 every where in the volume while network properties are measured by large phase differences. Because myelination and synaptic growth occur during human development, a study of the maturation of both coherence and phase differences may help unravel the relative contributions of the various sources of phase differences.

In the present study, EEG coherence and phase differences will be analyzed using similar methods previously

published in which the spatial heterogeneity of scalp recorded EEG coherence and phase is measured along two parallel lines with scalp electrodes equally spaced in the anterior-to-posterior and posterior-to-anterior directions (Thatcher et al., 1986, 1998). This method of EEG coherence measurement is a normalization procedure in which all electrode reference and analysis procedures are experimentally analyzed as a function of interelectrode direction, interelectrode distance, hemispheric symmetry, and frequency. Inflation of EEG coherence by reference electrodes was controlled in the present study (Fein et al., 1988; Rappelsberger, 1989) because a single common reference or a linked ear reference was held constant while only electrode direction, distance, hemisphere symmetry, and frequency were systematically compared. This method of EEG coherence measurement is also a direct test of a two compartmental model of EEG coherence in which dynamic differences and interactions between short distance interelectrode distances (e.g., 6 cm) versus long interelectrode distances (e.g., 18–24 cm) have been measured (Hanlon et al., 1999; McAlaster, 1992; Nunez, 1981, 1994; Pascual-Marqui et al., 1988; Srinivasan, 1999; Thatcher, 1992, 1994, 1998; Thatcher et al., 1986, 1987, 1998; van Baal et al., 2001; Van Beijsterveldt et al., 1998).

Finally, the studies by Thatcher et al. (1987) and Thatcher (1994, 1998) reported oscillations in EEG coherence over the age range from birth to 16-years; however there was no parallel study of EEG phase differences in this same population. Therefore, another purpose of the present study is to explore oscillations in the maturation of both coherence and phase differences in order to further understand the development of human cortical connectivity. The null hypotheses tested in this study were: (1) there are no left and right hemispheric differences in the development of coherence or phase; (2) there are no differences as a function of direction, (3) there are no differences as a function of inter-electrode distance, and (4) there are no changes as a function of age.

## METHODS

### Subjects

A total of 458 subjects ranging in age from 2 months to 16.67 years (males = 257) were included in this study. The subjects in the study were recruited using newspaper advertisements in rural and urban Maryland (Thatcher et al., 1987, 2003, 2007). The inclusion/exclusion criteria were no history of neurological disorders such as epilepsy, head injuries, and reported normal development and successful school performance. None of the subjects had taken medication of any kind at least 24 h before testing in this study. All of the school age children were within the normal range of intelligence as measured by the WISC-R and were performing at grade level in reading, spelling, and arithmetic as measured by the WRAT and none were classified as learning disabled nor were any of the school aged children in special education classes.

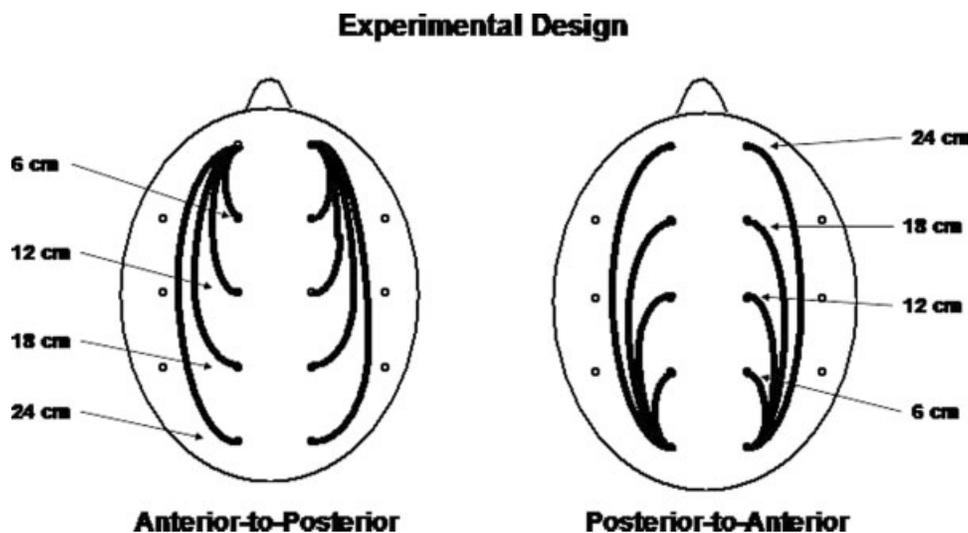


Figure 1.

Experimental design. Left head diagram shows the location of electrodes for the computation of coherence and phase differences in the anterior-to-posterior direction. Right head diagram shows the location of electrodes in the posterior-to-anterior

direction. Local distances (6 cm) are in adjacent electrode combinations (O1/2-P3/4 and Fp1/2-F3/4). Longest distance (24 cm) electrode combinations are Fp1/2-O1/2.

### EEG Recording

The EEG was recorded from 19 scalp locations based on the International 10/20 system of electrode placement, using linked ears as a reference. Eye movement electrodes were applied to monitor artifact and all EEG records were visually edited to remove any visible artifact. Each EEG record was plotted and visually examined and then edited to remove artifact using the Neuroguide software program (NeuroGuide, v2.3.8). Split-half reliability tests were conducted on the edited EEG segments and only records with >90% reliability were entered into the spectral analyses. The amplifier bandwidths were nominally 0.5–30 Hz, the outputs being 3 db down at these frequencies. The EEG was digitized at 100 Hz and up-sampled to 128 Hz and then spectral analyzed using the fast fourier transform (FFT) (Otnes and Enochson, 1972).

### Coherence and Phase Computations

Power spectral analyses were performed on 2–5 min segments of EEG recorded during an resting eyes closed condition. Epoch length was 2 s or 256 points with a cosine taper window resulting in a 0.5 Hz resolution from 1 to 30 Hz. A 25% sliding window method of Kaiser and Stermann (2001) was used to compute the FFT in which successive two-second epochs were advanced by 500 ms steps to minimize the effects of the FFT windowing procedure.

The cross-spectrum was used to compute EEG coherence and phase differences in the frequency range from 13 to 25 Hz for anterior-to-posterior electrodes Fp1/2-F3/4; Fp1/2-

C3/4; Fp1/2-P3/4; and Fp1/2-O1/2 and for posterior-to-anterior electrodes O1/2-P3/4; O1/2-C3/4; O1/2-F3/4; and O1/2-Fp1/2. Figure 1 is a diagram of the anterior-to-posterior and posterior-to-anterior electrode combinations. This recording arrangement provides a stable recording matrix and test of spatial homogeneity by using five equally spaced electrodes per hemisphere with increasing distance between electrodes in the anterior-to-posterior and posterior-to-anterior directions. Factors used in the analysis of variance were: (1) Hemisphere, (2) Direction, (3) Inter-electrode distance, and (4) Age.

Phase differences are analytical measures and can be computed for every instant of time (Oppenheimer and Schaefer and 1975). In contrast, coherence is a measure of the consistency of the analytical phase differences over some interval of time and is equivalent to a squared correlation coefficient and is dependent on the number of degrees of freedom used to estimate the consistency of the phase differences (Bendat and Piersol, 1980; Otnes and Enochson, 1972, 1978). When the phase difference in successive epochs is constant then coherence = 1 and when phase differences are random then coherence = 0. Coherence is mathematically defined as:

$$\Gamma_{xy}^2(f) = \frac{(G_{xy}(f))^2}{(G_{xx}(f)G_{yy}(f))},$$

where  $G_{xy}(f)$  is the cross-power spectral density and  $G_{xx}(f)$  and  $G_{yy}(f)$  are the respective autopower spectral densities (Otnes and Enochson, 1978). The computational procedure to obtain coherence involved first computing

the power spectra for  $x$  and  $y$  and then computing the cross-spectra. Since complex analyses are involved this produced the average cospectrum ('r' for real) and quad-spectrum ('q' for imaginary). Then coherence

$$\Gamma_{xy}^2(f) = \frac{\sum_N [r_{xy} + q_{xy}]^2}{\sum_N G_{xx}G_{yy}}$$

was computed.

The average phase angle  $\Theta_{xy}$  between two channels in each 2 s epoch is the arctangent of the ratio of the average quaspectrum to the average cospectrum or  $\Theta_{xy} = \text{Arctan} \frac{q_{xy}}{r_{xy}}$  which was computed in radians and transformed to degrees (Otnes and Enochson, 1972, 1978; Bendat and Piersol, 1980). Signed phase  $-\pi$  to  $+\pi$ , confounds direction with magnitude of phase differences because spontaneous EEG involves continuous oscillations of electrical activity around loops of neurons with no beginning or end to emphasize the fact that spontaneous EEG has no starting point by which a "lead" or "lag" relationship can be defined. Relatively complicated directed transfer function (DTF) using Multivariate Auto-Regression are capable of extracting phase difference magnitude and direction (Kamiński and Blinowska, 1991). However, in the absence of DTF, a simple coherence and phase analysis can not separate magnitude and direction. For this reason, the absolute phase difference in degrees was computed by squaring and then taking the square root of the phase angle or  $\sqrt{\Theta_{xy}^2}$ . Absolute phase ranges from 0 to 180° and eliminates negative integers and represents absolute phase difference by the set of zero and positive integers  $\geq 0$  (John et al., 1977; Thatcher et al., 1986, 1987, 2005).

### Sliding Averages

To increase temporal resolution 1-year sliding averages of EEG coherence and EEG phase differences were computed. The procedure involved computing averages over a 1 year period, e.g., birth to 1 year, then recomputing a mean from 0.25 to 1.25 years, then a mean age from 0.5 to 1.5 years, etc. This resulted in a 75% overlap of subjects per mean with totally unique subjects at 1 year intervals. The sliding average procedure produced 64 equally spaced mean values with a 0.25 year (or 3 month) time resolution and spanning the mean age from 0.44 to 16.22 years.

### Spectral Analyses

As explained in the previous section, the sliding averages produced 64 equally spaced mean values of coherence and phase differences in each electrode pairing (at 3 month or 0.25 year resolution) from 0.44 to 16.22 years. This resulted in a developmental time series of equally spaced mean ages for coherence and phase differences which were then spectrally analyzed. After detrending, the

FFT was used to analyze the frequency spectrum of the developmental trajectories of coherence and phase differences (Systat II, 2004). The number of time points = 64, and the epoch length = 16.22 years. This produced a frequency resolution of 6 months and a maximum frequency of 32 cycles/epoch. The units of frequency were cycles per lifespan (cpl) and wavelength ( $\lambda$ ) = Lifespan (16 years)/cpl. The magnitude of the spectrum plotted on the  $y$ -axis was coherence/cycle/lifespan (Fig. 5) and phase (degrees)/cycle/lifespan (Fig. 6).

## RESULTS

### Development of EEG Coherence

Figure 2 shows the development of mean EEG coherence from 0.44 to 16.22 years of age. The top row are the anterior-to-posterior electrode combinations and the bottom row are the posterior-to-anterior combinations. The left column are the left hemisphere mean EEG coherence values and the right column are the right hemisphere values. In all instances there was higher coherence in short distance interelectrode combinations (6 cm) than in longer inter-electrode distances with intermediate mean coherence at intermediate inter-electrode distances. Also, all inter-electrode distances exhibit oscillations in mean EEG coherence over the age range. It can be seen that there is a large increase in coherence in all four inter-electrode distances from 0.44 to ~ 4 years of age. There are clear developmental trends toward higher coherence as a function of age, especially in the short inter-electrode distances and there are also differences in EEG coherence in the anterior-to-posterior versus the posterior-to-anterior directions in both left and right hemispheres. For example, 12 cm inter-electrode distance (Fp1/2-C3/4) exhibits higher coherence in the anterior-to-posterior direction than in the posterior-to-anterior (O1/2-C3/4) direction. Mean coherence in the 24 cm long inter-electrode distance was nearly flat as a function of age and while exhibiting oscillations, nonetheless also exhibited the lowest coherence values.

Table I shows the results of a linear fit of the mean coherence as a function of age for all electrode pairings. It can be seen in Table I that 6 cm inter-electrode distances exhibited a positive slope of the linear fit to age while the 24 cm inter-electrode distances exhibited a negative slope. The only exception was in the posterior-to-anterior direction at 6 cm where the slope was essentially flat.

Multivariate analyses of variance (MANOVA) were conducted with the factors being direction (anterior-to-posterior vs. posterior-to-anterior), left hemisphere versus right hemisphere and distance (6, 12, 18, and 24 cm). No significant left versus right hemisphere effect was present ( $F = 2.094$ ,  $P < 0.1526$ ). However, there was a significant direction effect ( $F = 11.598$ ,  $P < 0.0001$ ) including a significant Bonferroni post hoc test ( $P < 0.000686$ ) and a significant distance effect ( $F = 2969.8$ ,  $P < 0.0001$ ) including a

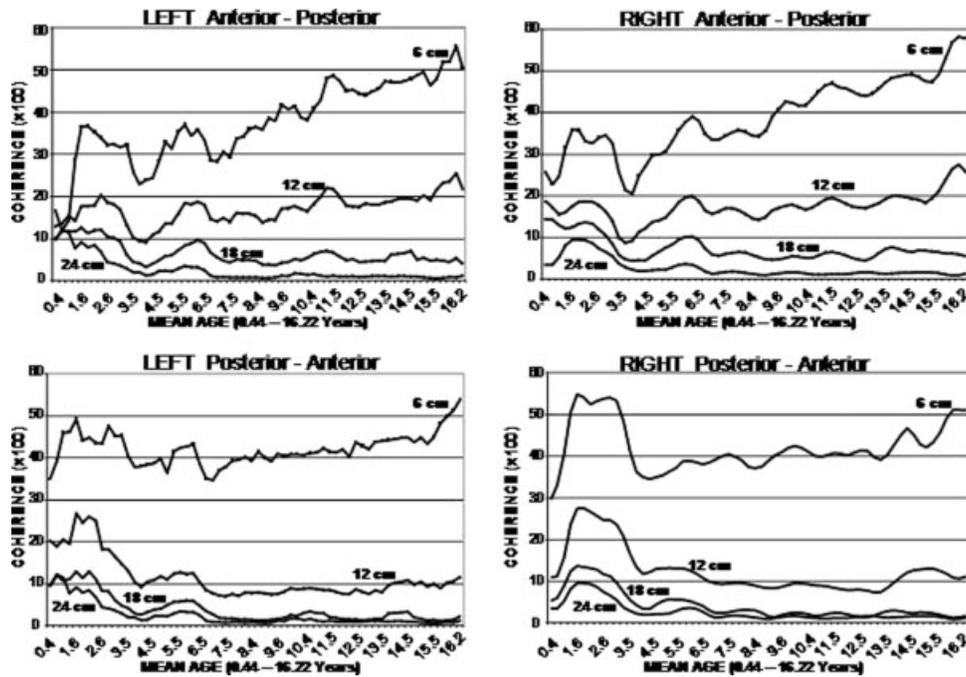


Figure 2.

Mean EEG coherence values ( $\times 100$ ) from 0.44 years of age to 16.22 years of age. Top row are from the anterior-to-posterior electrode combinations and bottom row are from the posterior-to-anterior electrode combinations (see Fig. 1). The left column

is from the left hemisphere and the right column is from the right hemisphere. It can be seen that coherence increases in the short inter-electrode distance (6 cm) and decreases in the long inter-electrode distance (24 cm) as a function of age.

significant Bonferroni post hoc test ( $P < 0.000001$ ) for all pair-wise distance differences.

### Development of EEG Phase Differences

Figure 3 shows the development of mean phase differences from age 0.44 to 16.22 years. The top rows are the anterior-to-posterior electrode combinations and the bottom rows are the posterior-to-anterior combinations. The left column is the left hemisphere mean EEG phase difference values and the right column is the right hemisphere values (see Fig. 1). In general there are higher phase differences in long distance inter-electrode combinations (24 cm) than in short inter-electrode distances with intermediate mean phase differences at intermediate inter-electrode distances. Similar to coherence, all inter-electrode distances exhibited oscillations in mean phase differences over the age range. Unlike coherence, however, EEG phase differences in the short distance (6 cm) declined as a function of age and exhibited a negative slope whereas the intermediate (18 cm) and long distance (24 cm) inter-electrode combinations exhibited positive slopes and increasing phase differences as a function of age.

Table II shows the results of a linear fit of the mean phase differences as a function of age for all electrode pairings. It can be seen in Table II that 6 cm distances exhib-

ited a negative slope of the linear fit to age while the 24 cm distances exhibited a positive slope.

There also were differences in EEG phase in the anterior-to-posterior versus the posterior-to-anterior directions

**TABLE I. Regression analyses of coherence development: Short distance positive slopes and long distance negative slopes**

Left anterior-posterior				
Slope	1.81	0.47	-0.34	-0.43
Intercept	22.56	13.15	9.28	6.07
Correlation	0.884	0.650	-0.617	-0.714
Significant	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Left posterior-anterior				
Slope	0.28	-0.71	-0.54	-0.43
Intercept	39.79	17.44	8.52	6.07
Correlation	0.343	-0.656	-0.758	-0.714
Significant	$P < 0.01$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Right anterior-posterior				
Slope	1.75	0.44	-0.36	-0.34
Intercept	24.16	13.73	10.28	5.50
Correlation	0.908	0.604	-0.599	-0.695
Significant	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Right posterior-anterior				
Slope	0.08	-0.71	-0.56	-0.34
Intercept	41.50	18.01	9.12	5.50
Correlation	0.062	-0.601	-0.756	-0.695
Significant	No Sig.	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$

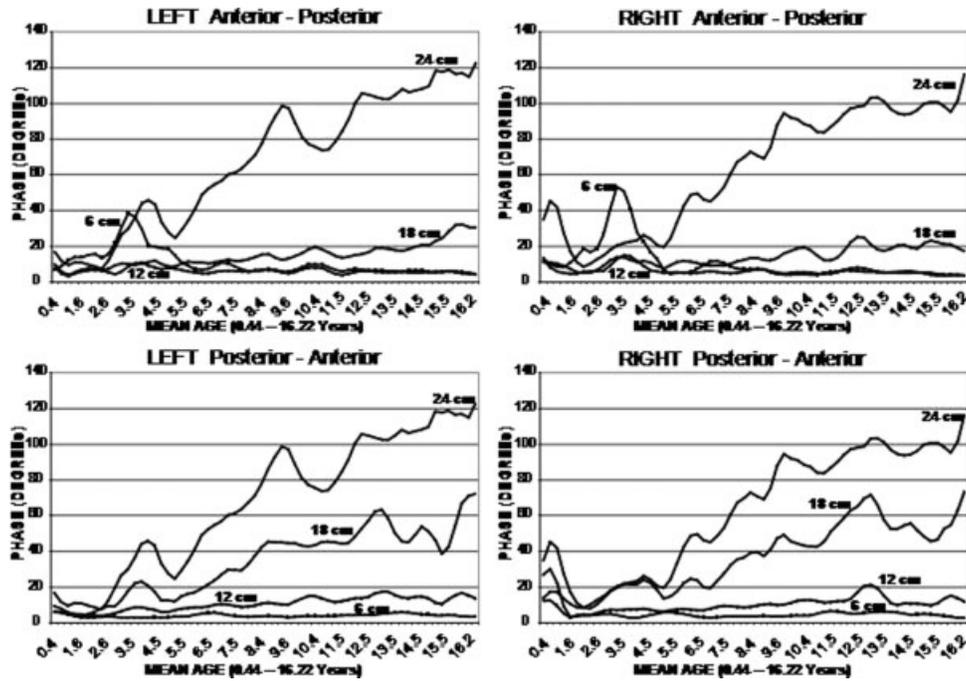


Figure 3.

Mean EEG phase differences (degrees) from 0.44 years of age to 16.22 years of age. Top row are from the anterior-to-posterior electrode combinations and bottom row are from the posterior-to-anterior electrode combinations. The left column is from the

left hemisphere and the right column is from the right hemisphere. It can be seen that phase differences increase in the long inter-electrode distance (24 cm) and decrease in the short inter-electrode distance (6 cm) as a function of age.

in both left and right hemispheres. For example, the 12 cm inter-electrode distance exhibited higher differences in the posterior-to-anterior direction (O1/2-C3/4) than in the anterior-to-posterior direction (Fp1/2-C3/4). The 24 cm long inter-electrode distance exhibiting oscillations and a steady increase in phase difference as a function of age, especially at ages greater than ~ 4 years of age.

MANOVA were also conducted for phase difference with the factors being direction (anterior-to-posterior vs. posterior-to-anterior), left hemisphere versus right hemisphere and distance (6, 12, 18, and 24 cm). No significant left versus right hemisphere effect was present ( $F = 0.2767, P < 0.0599$ ). However, there was a significant overall direction effect ( $F = 14.547, P < 0.0001$ ) including a significant Bonferroni post hoc test ( $P < 0.000144$ ) and a significant overall distance effect ( $F = 482.34, P < 0.0001$ ) including a significant Bonferroni post hoc test ( $P < 0.000001$ ) for all pair-wise distance differences accept between 6 and 12 cm.

### Developmental Oscillations

Examination of Figures 2 and 3 shows ultra-slow oscillations with inter-peak intervals of ~ 2 to 3 years. Phase shifts between Fp1-F3 and Fp1-O1 and other pairing can be seen in Figure 3 in which the short distance phase differences peak at ~ 3.6 years of age while the long inter-electrode distance (24 cm) reaches a peak at ~ 4 years of

age. After 4 years of age the 6 cm inter-electrode distance phase difference declines from about 40° at age 3.6 to about 5° at age 16.22 years while the 24 cm inter-electrode

**TABLE II. Regression analyses of phase difference development: Short distance negative slopes and long distance positive slopes**

	6 cm	12 cm	18 cm	24 cm
Left anterior-posterior				
Slope	-0.98	-0.10	1.27	7.71
Intercept	18.78	6.88	3.96	3.15
Correlation	-0.613	-0.326	0.903	0.969
Significant	$P < 0.0001$	$P < 0.01$	$P < 0.0001$	$P < 0.0001$
Left posterior-anterior				
Slope	0.06	0.73	3.82	7.71
Intercept	3.47	4.38	1.77	3.15
Correlation	0.309	0.905	0.933	0.969
Significant	$P < 0.05$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Right anterior-posterior				
Slope	-1.29	-0.23	0.93	6.72
Intercept	21.45	8.15	6.24	7.30
Correlation	-0.552	-0.445	0.840	0.933
Significant	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Right posterior-anterior				
Slope	-0.07	0.26	3.70	6.72
Intercept	5.22	8.58	5.28	7.30
Correlation	-0.168	0.239	0.918	0.933
Significant	No sig.	No sig.	$P < 0.0001$	$P < 0.0001$

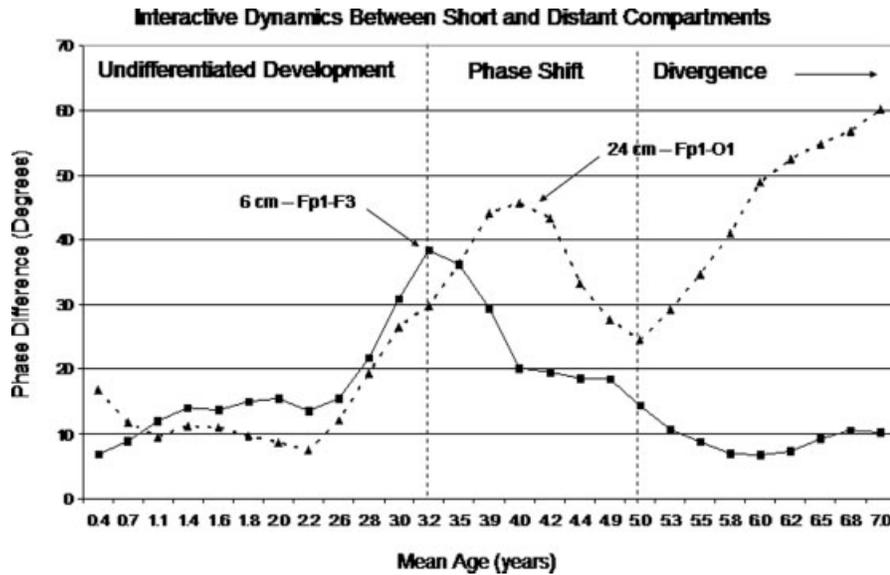


Figure 4.

Mean phase differences between 0.44 and 7.04 years of age. Undifferentiated developmental trajectories for short (6 cm) and long (24 cm) measures until the mean age of 3.16 years and then opposite directions of change occurred between 3 and 5

years of age in the short (6 cm) versus long (24 cm) distant peaks. After 5 years of age phase in the short and distant systems diverges (see Fig. 3, top left). Dashed line = Fp1-O1 and solid line = Fp1-F3.

distance phase difference steadily increases from about 20° at age 5 years of age to 120° at 16.22 years.

Figure 4 is the same as the top left chart in Figure 3 and shows EEG phase delays in Fp1-F3 (6 cm-dashed line) and Fp1-O1 (24 cm-solid line) from mean age of 0.44 years to the mean age of 7.04 years. It can be seen that the short and long distance compartments exhibit similar phase differences from 0.44 to 3.2 years and then there is a phase shift between 3.2 and 5 years of age followed by steady divergence where phase differences increase as a function of age in the long inter-electrode distance and decrease in the short inter-electrode distances. There appears to be a competitive type of dynamic between the short and distant connections with a ~ 1 year shift between the short and long distance systems between ~ 3 and 4 years of age (see Fig. 4).

Oscillations in both the 6 and 24 cm inter-electrode distances were present; however, the magnitude of oscillations in phase differences were much larger in the 24 cm inter-electrode distances. A cross-correlation of the 6 versus 24 cm time series of means showed a maximal time shift of 1.5 years with the 6 cm inter-electrode distance leading the 24 cm inter-electrode distance.

Spectral analyses of the developmental time series of coherence from 0.4 to 16.2 years for the 6 and 24 cm inter-electrode distances are shown in Figure 5. The top row is the anterior-to-posterior electrode combinations and the bottom row is the posterior-to-anterior combinations. The left column is the left hemisphere FFT values and the right column are the right hemisphere values (see Fig.

1). In general there was greater developmental spectral energy in the short inter-electrode distance (6 cm) in comparison to the long inter-electrode distance (24 cm). Most of the developmental spectral energy was in the ultraslow frequency range of 1 cycle/lifespan (i.e., a wavelength of 16 years) to ~ 12 cycles/lifespan (i.e., a wavelength of 1.33 years). The highest peak frequency was 31 cycles/lifespan (i.e., a wavelength of 0.51 years or 6.12 months).

Spectral analyses of the developmental time series of phase differences from 0.4 to 16.2 years for the 6 and 24 cm inter-electrode distances are shown in Figure 6. The top row of Figure 6 is the anterior-to-posterior electrode combinations and the bottom row are the posterior-to-anterior combinations. The left column is the left hemisphere FFT values and the right column is the right hemisphere values (see Fig. 1). In comparison to coherence a distinctly different pattern of oscillatory energies were present in phase. For example, in general there was greater spectral energy in the long inter-electrode distance (24 cm) in comparison to the short inter-electrode distance (6 cm) which is the opposite of coherence development (see Fig. 5). Similar to coherence, phase difference development exhibited most of the spectral energy in the ultraslow frequency range of 1 cycle/lifespan (i.e., a wavelength of 16 years) to ~ 12 cycles/lifespan (i.e., a wavelength of 1.33 years). The highest peak frequency was 31 cycles/lifespan (i.e., a wavelength of 0.51 years or 6.12 months).

Tables III and IV are summaries of the cycles per lifespan (cpl) and the wavelength (16 yrs/cpl) of the spectral

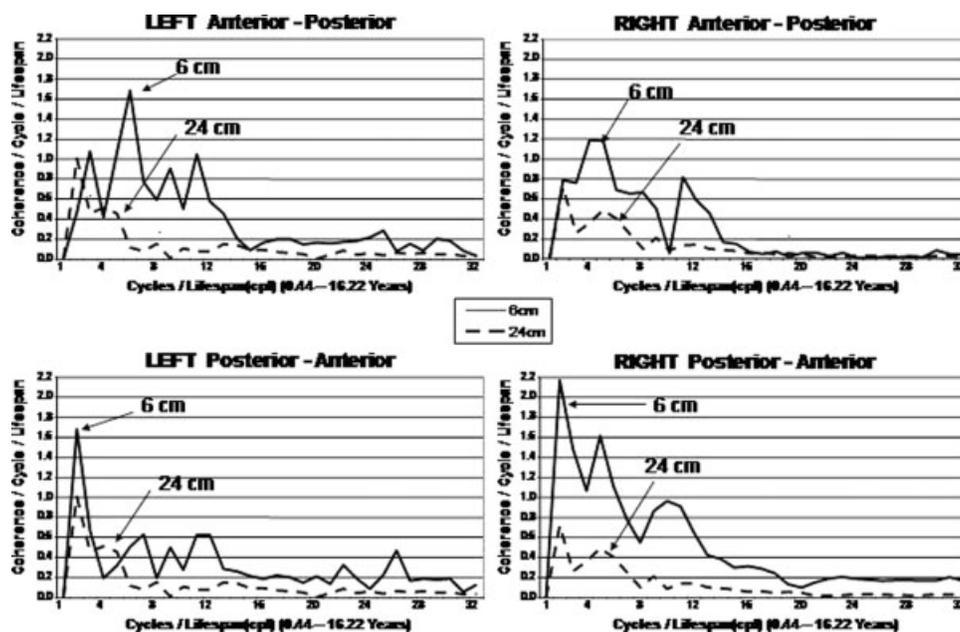


Figure 5.

Fourier spectral analyses of the developmental trajectories of mean coherence from 0.44 to 16.22 years of age in short (6 cm) (solid line) and long (24 cm) (dashed line) inter-electrode distances in the anterior-to-posterior and posterior-to-anterior directions. The greatest spectral energy was in the short distance inter-electrodes (6 cm) and at ultraslow frequencies.

peaks in the FFT analyses of the mean coherence and mean phase difference developmental trajectories from 0.44 to 16.22 years. Table III shows the FFT peak values in the anterior-to-posterior direction for both coherence (Top) and phase differences (Bottom) and Table IV shows the values in the posterior-to-anterior direction. It can be seen that short (6 cm) and distant (24 cm) are different for coherence versus phase in both directions. In general there are more spectral peaks and greater power in the short distant inter-electrode connections in coherence than there are in phase differences at 6 cm. The opposite is true for the development of phase differences which exhibited more spectral peaks and greater power in the long distance inter-electrode connections than are in coherence at 24 cm.

## DISCUSSION

The results of this study are consistent with two-compartmental models of cerebral connectivity in which there is a local or short distance compartment that is distinctly different than the long distance compartment (Barry et al., 2005; Braitenberg, 1978; Hanlon et al., 1999; McAlaster, 1992; Nunez, 1981; Pascual-Marqui et al., 1988; Schultz and Braitenberg, 2002; Shen et al., 1999; Srinivasan, 1999; Thatcher et al., 1986, 1987, 1998; Van Beijsterveldt et al.,

1998). The postnatal development of EEG coherence and EEG phase were different in both the short and long distance compartments. EEG coherence increased as a function of age in the short inter-electrode distance while EEG coherence in the long inter-electrode distances declined as a function of age. The opposite was observed for EEG phase differences which increased as a function of age in the long inter-electrode distances and declined in the short inter-electrode distances. Postnatal development of EEG coherence and EEG phase were also different in the anterior-to-posterior direction in comparison to the poster-to-anterior direction even though the inter-electrode distances were the same. In addition, oscillations were prevalent in all electrode combinations in both EEG coherence and EEG phase maturation with growth spurts at specific postnatal ages. The latter finding is consistent with previous publications on the subject of cyclic reorganization using EEG coherence and phase measures (Hanlon et al., 1999; Isler et al., 2005; McAlaster, 1992; Thatcher, 1994; Thatcher et al., 1987; van Baal et al., 2001; Van Beijsterveldt et al., 1998). Finally, only weak hemispheric differences in the maturation of EEG coherence and phase were found, although there were differences in the timing of growth spurts and oscillations between the two hemispheres. All five null hypotheses enumerated in the introduction were rejected by the findings in this study.

### Lifespan Spectral Analysis of Phase

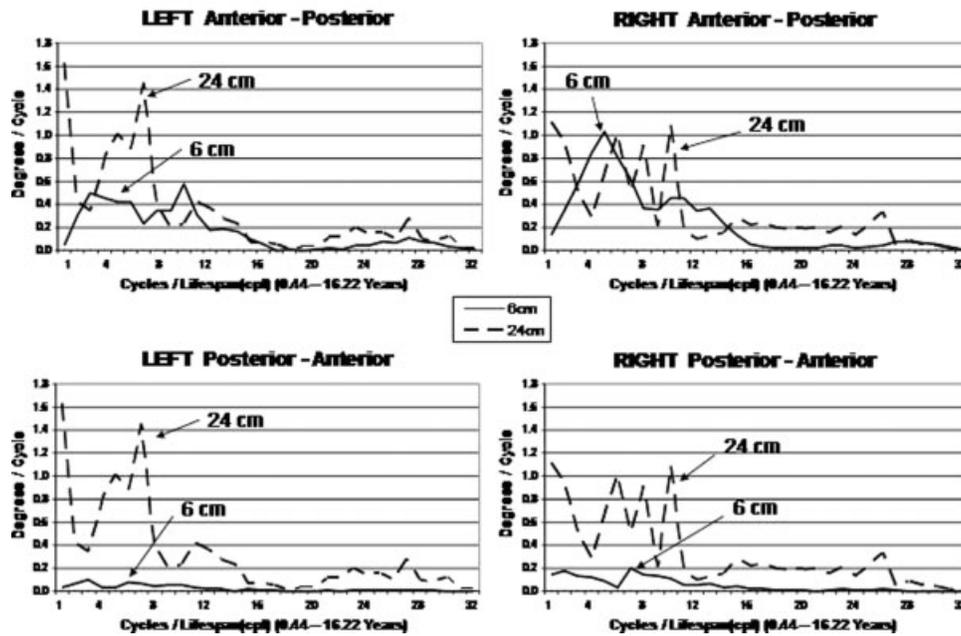


Figure 6.

Fourier spectral analyses of the developmental trajectories of mean phase differences from 0.44 to 16.22 years of age in short (6 cm) (solid line) and long (24 cm) (dashed line) inter-electrode distances in the anterior-to-posterior and posterior-to-anterior directions. The greatest spectral energy was in the long distance inter-electrodes (24 cm) and at ultraslow frequencies.

#### Limitations of the Present Study

One limitation of the present study is the focus on only the beta frequency band (13–25 Hz). Delta, theta, and alpha frequency bands are important; however, due to the complexity of the analyses of coherence and phase delay it was not feasible to present all of the frequency bands in a single paper. Further, there was noticeable consistency across frequency bands and the preliminary analyses of the delta, theta, and alpha frequency bands do not contradict the beta frequency findings in this study. We plan to publish analyses of other frequency bands in subsequent studies. Another limitation is the use of only a small set of electrodes and not the entire 171 possible combinations when using 19 recording electrodes. However, there is a considerable advantage to limiting analyses to a small set of geometrically identical inter-electrode distances that vary only in the direction of comparison. For example, analyses of spatial heterogeneity and volume conduction effects can be concisely conducted (Thatcher et al., 1986, 1998). We also examined the full set of 171 electrode combinations and again nothing in these analyses contradicts the findings in the present study and we plan to publish a more extensive analysis of these data in a future study. We do not consider the use of a linked ear reference as a serious limitation based on the studies of Rappelsberger

(1989), Kamiński et al. (1997), and Essl and Rappelsberger (1998). Rappelsberger (1989) and Essl and Rappelsberger (1998) after many analytic comparisons concluded that linked ears was a valid and useful reference in the measurement of coherence although digital averaging of the ears is an optimal reference. Most importantly, however, the issue of a linked ear reference is irrelevant because none of the oscillations and developmental effects observed in this study can be explained by a reference. Finally, a limitation is the absence of longitudinal developmental data to minimize the within subject variance over age. However, large sample sizes required for longitudinal studies are expensive and difficult to conduct, especially over a 16 year lifespan and the cross-sectional data generally approximate longitudinal data as the sample size increases. This is supported by longitudinal genetic studies of van Baal et al. (2001) that tested the EEG cross-sectional findings from Thatcher et al. (1987) and Thatcher (1992, 1994) and the van Baal et al. (2001) longitudinal coherence findings confirmed the prior cross-sectional coherence findings.

#### Volume Conduction Versus Network Measures

Volume conduction is an electrical field produced at near the speed of light by an electrical dipole and thus

**TABLE III. Summary of developmental cycles and wavelengths: Anterior-to-posterior direction**

Coherence			
6 cm		24 cm	
CPL	$\lambda$ (yrs)	CPL	$\lambda$ (yrs)
Left			
2	8.00	4	4.00
3	5.33	8	2.00
5	3.20	13	1.23
8	2.00	22	0.73
10	1.60		
25	0.64		
29	0.55		
Right			
2	8.00	2	8.00
4	4.00	5	3.20
8	2.00	9	1.78
11	1.45		
23	0.70		
30	0.53		

Phase difference			
Left			
3	5.33	2	8.00
10	1.60	4	4.00
29	0.55	7	2.29
		11	1.45
		14	1.14
		16	1.00
		21	0.76
Right			
5	3.20	2	8.00
10	1.60	5	3.20
15	1.07	8	2.00
29	0.55	10	1.60
		14	1.14
		18	0.89

exhibits approximately zero phase lag everywhere in the field (Malmivuo and Plonsey, 1995; Nunez, 1981). Theoretically, large phase differences can be produced by volume conduction when there is a deep and temporally stable tangential dipole that has a positive and negative pole with an inverse electrical field at opposite ends of the human skull. In this instance, phase difference is maximal at the spatial extremes and approximates zero half way between the two ends of the standing dipole. However, this is a special situation that is sometimes present in evoked potential studies but is absent in spontaneous EEG studies. In the case of spontaneous EEG there is no time locked event by which to synchronize potentials that result in a standing dipole, instead, there is an instantaneous summation of millions of ongoing rhythmic pyramidal cell dipoles with different orientations averaged over time. To explain the results of the present study based on volume conduction there must be a single standing dipole that exhibits a zero phase delay at its midpoint and oscillates and rotates differentially from anterior-to-posterior and

posterior-to-anterior. To test this particular volume conduction model we examined absolute and signed phase histograms and failed to find a zero point or phase reversals. Figure 7 shows the results of the histogram analysis at 24 cm for signed and absolute phase differences in which it can be seen that there are clear and distinct modes at  $\sim \pm 11^\circ$  to  $20^\circ$  and  $\pm 160^\circ$  to  $170^\circ$  and the variance of phase is systematic. As seen in Figure 7, absolute phase is the folding of the signed phase at zero thus eliminating direction as discussed in the coherence and phase computations section. As mentioned previously, EEG phase was different in the anterior-to-posterior direction in comparison to the poster-to-anterior direction even though the inter-electrode distances were the same, thus further disconfirming a standing dipole model.

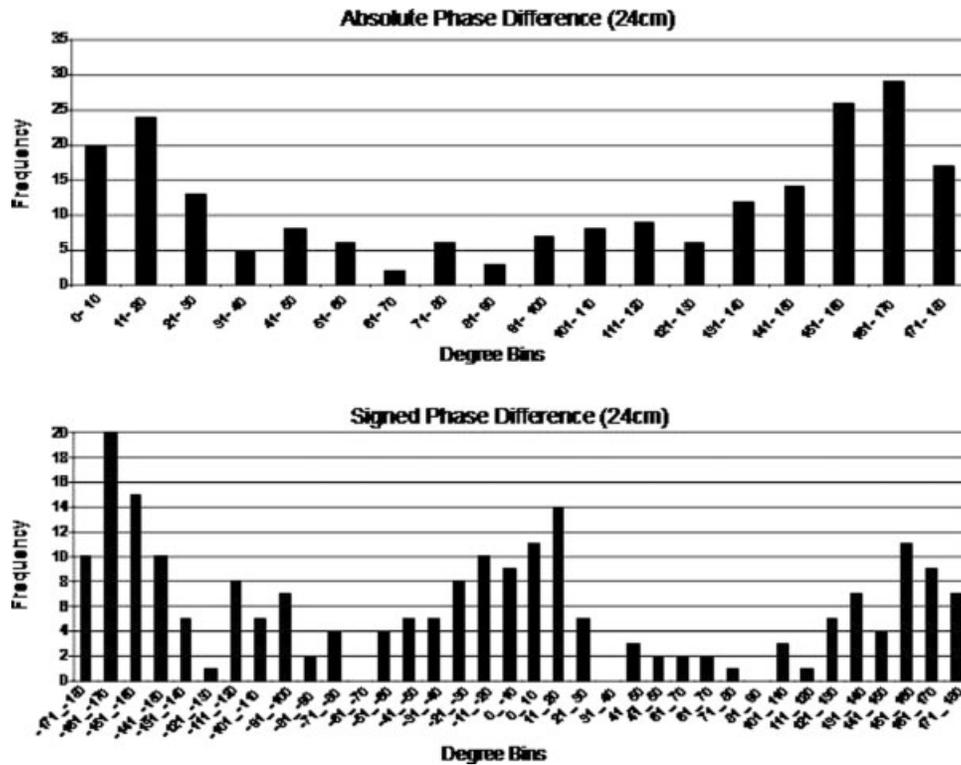
Skull volume is sometimes mentioned in regard to EEG amplitudes and volume conduction (Nunez, 1981); however, skull volume has been shown not to be relevant in the computation of coherence (Srinivasan, 1999). This is because coherence is a measure of phase consistency inde-

**TABLE IV. Summary of developmental cycles and wavelengths: Posterior-to-anterior direction**

Coherence			
6 cm		24 cm	
CPL	$\lambda$ (yrs)	CPL	$\lambda$ (yrs)
Left			
2	8.00	2	8.00
7	2.29	4	4.00
9	1.78	8	2.00
11	1.45	13	1.23
22	0.73		
26	0.62		
30	0.53		
Right			
2	8.00	2	8.00
5	3.20	5	3.20
10	1.60	9	1.78
16	1.00	12	1.33
23	0.70		
31	0.52		

Phase difference			
Left			
3	5.33	2	8.00
4	4.00	4	4.00
7	2.29	5	3.20
10	1.60	7	2.29
		11	1.45
		14	1.14
		21	0.76
		27	0.59
Right			
2	8.00	2	8.00
4	4.00	5	3.20
7	2.29	8	2.00
8	2.00	10	1.60
13	1.23	14	1.14
		16	1.00
		18	0.89



**Figure 7.** Histogram of absolute phase differences (top) and signed phase differences (bottom) at 24 cm in the age group 10–16.67 years.

pendent of magnitude and the near speed of light involved in spontaneous EEG means that changes in the size of the volume conductor are essentially irrelevant (Feynman et al., 1963; Malmivuo and Plonsey, 1995).

While skull volume and a standing dipole model can not explain the oscillations and developmental trends in the present study, nonetheless, some degree of “inflation” of coherence values due to zero-phase lag volume conduction is always present when using a common reference to compute coherence and phase. Although the mean phase differences were  $>0$  in this study, the variance was large enough to include zero phase lag and thus some degree of inflation was likely inflating the coherence values, especially at 6 cm distances. Zero-phase lag removed coherence is a promising method to quantitatively eliminate the “inflation” of coherence due to volume conduction (Nolte et al., 2004; Pascual-Marqui, 2007). The present article crudely achieves zero phase lag removed coherence by virtue of the side-by-side plotting of the development of coherence and phase in which mean phase is  $>0$ . However, it is not possible to completely remove zero-phase lag volume conduction without partial correlation coefficient methods and other analytical methods (Marzetti et al., 2007). While such studies are planned for the future it should be noted that the main findings in this study are

changes over age in which the reference electrode and all other conditions are constant and thus can not be explained by volume conduction even if there was some inflation of the absolute values of coherence.

### Local Versus Distant Connections

An interesting finding in this study is that the development of EEG phase differences were the opposite of EEG coherence (see Figs. 2 and 3, Tables I and II). Why would EEG phase differences in the long inter-electrode distances increase as a function of age? There are no published studies demonstrating delayed conduction such as reduced conduction velocities or reduced myelin concentration in cortico-cortical connections from birth to age 16. Thus, reduced conduction velocity is not a reasonable explanation of the finding of increased phase delays in long distance connections. Increased variance of phase in distant connections also can not explain a larger mean phase difference since the digital sample lengths used to compute the cross-spectrum were essentially the same and, in any case, random noise produces zero mean phase differences and certainly random noise can not produce increased mean phase differences. In the absence of other explanations, the finding of phase shifts and competitive dynamics

(see Fig. 4) suggests an inverse relationship between the short and distant connection systems because of some type of competitive dynamic. If we assume that conduction velocity is not a critical factor to explain the findings in this study, then we can postulate a single unifying concept of an increase in the number of synaptic connections in the local systems and a reduction of synaptic connections in the distant systems as being primarily responsible for both the decrease in EEG coherence in distant connections and increased coherence in local connections. The unifying concepts is an increase in the number of connections in local domains results in an increased local processing/integration time and therefore longer phase delays between separated local domains. It is known that cortico-cortical connections arise primarily in layer III and terminate primarily on layers I–III and V–VI of cortical pyramidal cells and short distance connections primarily terminate closer to cell bodies in layer III (Barbie and Levitt, 1995; Jones, 1984; McConnel and Kaznowski, 1991; Schmahmann and Pandya, 2006). Competition for available dendritic space for synapse formation with the short distance connections “winning” the competition could cause the longer distant connections to be located further away from the cell body and thus resulting in longer phase delays in the distant connection system.

This conclusion is consistent with standard nonconduction volume models of EEG coherence (i.e., phase differences  $>0$ ) in which the magnitude of EEG coherence is mathematically modeled as equal to the average number of connections times the average strength of the connections:

$$C_{ij} = N_{ij} \times S_{ij} \quad (1)$$

where  $N_{ij}$  is a local connection matrix of the number or density of connections between neural systems  $i$  and  $j$ , and  $S_{ij}$  is the synaptic strength of those connections. Phase delays can be modeled by the number of elements in a loop times the delay between elements, where delays are due to axonal conduction velocity, synaptic rise times and dendritic integration times:

$$P_{ij} = K_{ij} \times D_{ij} \quad (2)$$

where  $K_{ij}$  is a distant connection matrix of the number or density of connections between neural systems  $i$  and  $j$ , and  $D_{ij}$  is the delay between elements in a loop. A relationship between the local and distant connection systems could be combined to model competitive, cooperative and predator/prey dynamics (Barryman, 1981; Thatcher, 1998) as:

$$R_1 = N_{ij} - K_{ij}/N_{ij} \quad (3)$$

-Competition

$$R_2 = K_{ij} - N_{ij}/K_{ij} \quad (4)$$

$$R_1 = N_{ij} - K_{ij}/N_{ij} \quad (5)$$

-Predatory/Prey

$$R_2 = K_{ij} + N_{ij}/K_{ij} \quad (6)$$

where  $R_1$  is the rate of growth of connections in the local connection system and  $R_2$  is the rate of growth of connections in the distant connection system. Further mathematical details of the effects of changing the sign and ratios of the two connection systems is described in Thatcher (1998). These generic equations are presented as models and further analyses are required to determine the best fit of the equations to the data in this study.

Because of the ultraslow frequencies and long time span from  $\sim 6$  months of age to 16 years of age a simple explanation of increased local coherence and increased distant phase differences is an increase in the number of local connections which are at the expense of the number of distant connections located on the distal regions of the dendrites. That is, the average number of connections  $N$  in local domains increases in Eq. (1) and  $K$  decreases in Eq. (2). After the age of  $\sim 4$  years there is a reduction in the average number of connections in the long distance system while there is an increase in the number of connections in the short distance compartments of the cerebral cortex. From infancy to about 3 years of age, there were relatively low levels of spatial differentiation and beyond  $\sim 4$ –5 years of age there was a steady increase in local coherence and distant phase differences (see Figs. 2–4). The findings are generally consistent with models of coupled nonlinear oscillators operating over long periods of time (Buzaski, 2006; Freeman et al., 2003, 2006) as well as studies of the degree of local clustering versus the degree of separation of clusters of connected neurons (Watts and Strogatz, 1998). According to this model, increased phase differences in long distance connections is not due to conduction velocity changes but rather it is due to increased processing/integration time in local neural domains and/or increased dendritic distance of synaptic termination from the cell body. Similarly, the finding of reduced coherence in long inter-electrode distances is consistent with a periodic pruning or reduction in the number of connections.

### Thalamo-Cortical Versus Corticocortical Connections

The earlier discussion concentrated on the development of cortical synaptic connections which also involve thalamo-cortical influences (Lopes da Silva, 1995; Steriade, 1995; Thatcher and Purpura, 1972, 1973). The moment-to-moment synchronization of cortical pyramidal cells occurs by thalamic inputs and re-entrant cortico-thalamic circuits (Steriade, 1995), therefore, thalamo-cortical interactions are fundamental to the genesis of EEG rhythms. Importantly, thalamic cortical afferents constitute only  $\sim 3$ –5% of pyramidal cell synaptic contacts which are limited primarily to layer IV of the neocortex (Carpenter and Sutin, 1983; Schuz and Braitenberg, 2002). Thus, although thalamo-

cortical inputs are important for the synchronization of cortical cells, nonetheless, thalamo-cortical inputs are too sparse to account for the findings in this study. Also, the role of the thalamus in ultra-slow oscillations of different EEG frequencies and coherences during human development has not been studied to this date. Nor has the possible role of the thalamus in the sudden appearance of growth spurts in EEG coherence and phase differences. It is difficult to conceive of a model of thalamic control of the development of phase differences that did not include cortical synaptic connectivity especially when considering the dependence of the thalamus on the neocortex to produce spatially resonant electrical activity (Buzsáki, 2006). Nonetheless, thalamo-cortical and cortico-thalamic interactions are likely involved in the phenomena observed in this study at some level.

### Development of Complexity

The finding of an increase in short distance coherence simultaneously with a decrease of coherence in the long distant connections is also consistent with models of complexity in which there is a parallel increased integration in local domains and increased differentiation in long distance connections as a function of age. Tononi et al. (1994) used quantitative models of information theory and stochastic processes to define complexity in connected neural networks. They showed that highly complex neural networks were characterized by neurons that were organized into densely linked groups that were sparsely and reciprocally interconnected. The findings in this study are consistent with the Tononi et al. (1994) mathematical model of complexity where functional segregation and global integration are critical parameters. Specifically, increased integration because of increased number of connections within local domains of neurons is linked to increased differentiation and pruning of long distance connections involving more precise reciprocal linkages between local and distant systems.

A neural network model is applied to the findings of this study in Figure 8 top which shows the standard two compartmental model of EEG coherence for local and distant connections and the bottom of Figure 8 is the application of the two compartmental model to the Tononi et al. (1994) information theory of optimal neural network complexity. The distant connections are between local connection systems and are the differentiated long association systems of the neocortex, e.g., the frontal-occipital fasciculus, uncinate fasciculus, the arcuate fasciculus, and the cingulum which are the major long association fibers of the human brain that terminate primarily on layers I-III, V, and VI of the neocortex (Barbie and Levitt, 1995; Jones, 1984; McConnell and Kaznowski, 1991; Schmahmann and Pandya, 2006). Local synaptic connections tend to terminate closer to the cell body in layer III and are likely to be competing for dendrite membrane space for synaptogenesis (Jones, 1984). The brain development complexity curve

at the bottom of Figure 8 represents the dynamics of development that were observed in this study (see Figs. 2 and 3 and Tables I and II) in which there was increasing coherence in local connection systems (e.g., O1/2-P3/4 and Fp1/2-F3/4) that represents increased local integration. In contrast, the distant connection systems (O1/2-Fp1/2) differentiates resulting in selective pruning and refined connectivity during maturation. The combination of increased local integration and increased distant differentiation gives rise to increased brain complexity and increased efficiency. The arrows pointing to different ages are illustrative only and designed to indicate nonlinear rates of growth at different ages which fall on the continuum of complexity as measured by Tononi et al. (1994). The right half of the brain complexity curve indicates states of declining complexity which may occur with pathology, aging and states of nonoptimal organization.

### Differences in the Anterior-to-Posterior Versus the Posterior-to-Anterior Direction

The strongest difference between the anterior-to-posterior versus the posterior-to-anterior direction of electrode placement are the coherence and phase values of the intermediate inter-electrode distances. The development of EEG coherence in the anterior-to-posterior direction exhibits higher coherence values in intermediate inter-electrode distances (e.g., 18 cm) whereas there is little difference between the intermediate and long inter-electrode distance in the posterior-to-anterior direction. If we consider the coherence connectivity model in equation one where coherence = number of connections times the strength of connections, then the direction factor can be explained by assuming an increase in the number of connections between the frontal pole and the sensory motor cortex or between Fp1/2 and C3/4. For example, intermediate inter-electrode distances exhibited higher coherence in the anterior-to-posterior direction (i.e., Fp1/2-C3/4) because there are more connections between the frontal lobes (Fp1/2) and the sensory motor strip (C3/4) than between the occipital lobes and the sensory motor strip (i.e., the posterior-to-anterior direction). Similarly, the lower coherence in O1/2-C3/4 in contrast to Fp1/2-C3/4 is due to fewer connections between the occipital lobes and the sensory motor strip than between the frontal lobes and the sensory motor strip.

EEG phase developmental trajectories are the opposite of EEG coherence developmental trajectories in the intermediate inter-electrode distances (see Fig. 3). For example, intermediate inter-electrodes exhibited larger EEG phase differences in the posterior-to-anterior direction than in the anterior-to-posterior direction. If we assume again that increased phase delay is proportional to an increased number of connections, then the difference in direction can be explained by assuming that there are a larger number of local connections in the occipital lobes than in the frontal lobes. That is, the frontal-parietal relationship (Fp1/2- P3/

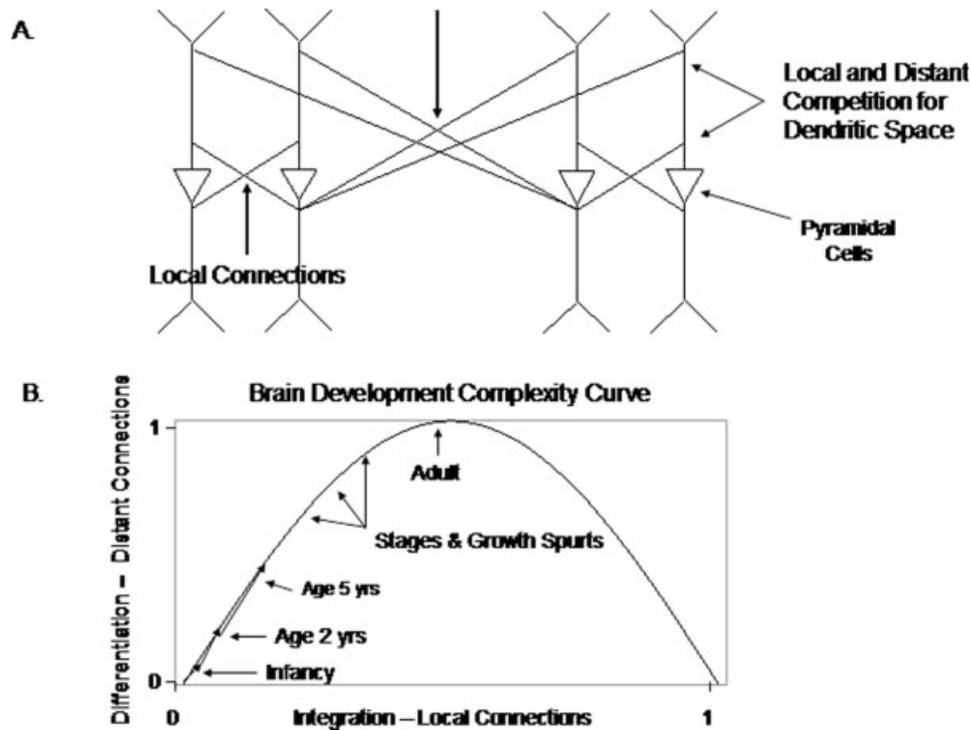


Figure 8.

Top (A) illustrates the two compartmental model of coherence and Bottom (B) represents the Tononi et al. (1994) information theory and stochastic processing model of network complexity. The findings in this study of increased coherence in short distance domains and declining coherence in long distance domains is consistent with a competitive model of synaptogenesis (Thatcher, 1998) as well as the Tononi et al. (1994) model of brain complexity. Increased coherence indicates increased local

integration while lengthened phase delays and declining coherence in the distance connections indicates increased differentiation during maturation. The combination of increased local integration and increased distant differentiation gives rise to increasing complexity during human development. The different length arrows on the complexity curve indicate growth spurts and different rates of complexity maturation.

4) has shorter phase delays in comparison to the occipital-frontal relationship (O1/2-F3/4) because of a larger number of connections in the local occipital cortex in comparison to the local frontal cortex. This explanation is consistent with the higher packing density in the occipital lobes compared to the frontal lobes (Carpenter and Suttin, 1983) and it is consistent with the coherence model in equation one used to explain the difference in the maturational trajectories of EEG coherence and phase (see Local versus distant connections section).

### Ultralow Oscillations and Competitive Dynamics

The Fourier transform of the EEG coherence and EEG phase developmental trajectories demonstrated significant ultralow oscillations over the lifespan of 16 years. The mean frequency of oscillation was different in the anterior-to-posterior and posterior-to-anterior directions and for left and right hemispheres. However, common frequencies of

oscillation were observed in all electrode combinations. The strongest spectral magnitudes for EEG coherence and phase development were repetitive cycles at wavelengths between 5 and 2 years using detrending in the FFT analysis. The highest frequency of oscillations were 6 month wavelengths and the higher frequency oscillations exhibited the lowest power. Cross-correlation analyses indicated a competitive relationship between short and long distance connections (see Fig. 4). An important fact is that there was a diversity of different environments and experiences in the lives of all of the 458 subjects in this study. In other words, the regularity of growth spurts and the strength of the repetitive cycles of coherence and phase differences can not be explained by a common environmental factor. The most likely explanation is that a common genetic factor is responsible for the regular rhythms and slopes of change in mean coherence and mean phase over a 16 year period. The findings in this study are consistent with earlier studies demonstrating ultralow oscillations and

growth spurts in EEG coherence (Hanlon et al., 1999; McAlaster, 1992; Thatcher, 1992, 1994, 1998; Thatcher et al., 1987) as well as genetic studies of the ultraslow rates of development of local versus distant coherence measures (Van Beijsterveldt et al., 1998; van Baal et al., 2001). The studies by Van Beijsterveldt et al. (1998) and van Baal et al. (2001) demonstrated different genetic contributions to local versus distant connections in which there is more genetic influence on distant connections than on local connections but both compartments dynamically evolve with growth spurts at specific ages. Reduced long distant connections in expanding neural networks often leads to increased complexity and efficiency (Buzaski, 2006). When considering efficiency and complexity models then the present findings support the view that genetics cyclically produces an excess of synaptic connections followed by pruning of the excess connections based on experience. This process is relatively slow and occurs over decades of the human lifespan.

In summary, the results are consistent with a genetic model of rhythmic long term connection formation that occurs in cycles along a curvilinear trajectory toward adulthood. Studies of the prenatal and postnatal development of cortical synapses have shown competitive and predator-prey type dynamics (Edelman, 1987; Finkel and Edelman, 1989; Levay et al., 1978; Sporns et al., 1991, 1994; Thatcher, 1994, 1998). It would be consistent with these studies to conclude that periodic increased connections and reduction of connections is linked to the periodic genetic reshaping of cortical connectivity during postnatal development.

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