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A Predator-Prey Model of Human Cerebral Development

Robert W. Thatcher

NeuroImaging Labortory, Bay Pines VA Medical Center, St. Petersburg, Fl and the Department of Neurology, University of South Florida College of Medicine, Tampa, Fl .

Send Reprint Requests To:

Robert W. Thatcher, Ph.D.
NeuroImaging Laboratory
Research and Development Service - 151
Veterans Administration Medical Center
Bay Pines, Florida 33744
(727) 244-0240

INTRODUCTION

Recently, Edelman and colleaques (Edelman et al, 1987; Finkel and Edelman, 1989; Sporns et al, 1991; 1994) developed a neural population model of learning and memory in which competition and cooperation between populations of synapses determined the selection and survival of groups of neurons comprising neural networks. Their model primarily concerned the time domain of milliseconds to a few days of neural network interactions. Levay et al (1978) presented a neural population model of ocular dominance column development which was confined to the lateral geniculate cortical projections and a limited time domain. While these models are excellent in their focus on the short time domain of neural function and development, they do not address the long time domain of postnatal human cerebral development. In fact, there are currently no comprehensive neural population models of the postnatal ontogenesis of thalamo-cortical and cortico-cortical connections which operate over months and years.

The size and complexity of the nervous system makes it unlikely that changes in a single synapse result in significant change in the behavior of a interconnected neural network. It is more likely that significant changes in neural network behavior require changes in populations of synapses, defined as multiple synaptic modifications occurring simultaneously at multiple sites. The goal of the present paper is to develop a formal neural network model of human cerebral ontogenesis and to use the model to explain the development of human EEG coherence over the postnatal period from 1.5 to 16 years of age. This model will rely on developmental cytoarchitectural findings as well as on studies of electroencephalographic development.

Two different categories of electroencephalographic (EEG) analyses have been used to study lifespan human cerebral development: EEG power (Matousek and Petersen, 1973) and EEG coherence and phase (Gasser et al, 1988; Thatcher et al, 1987; Thatcher, 1991; 1992a; 1992b; Fox and Bell, 1990; McAlaster, 1992). Although EEG power measures differ from measures of EEG coherence, the application of these measurements to postnatal human development reveal two common or shared findings: 1- there is an exponential or logistic change

in EEG values from birth to approximately 6 years of age after which the rate of change slows and there is relative stability until late adulthood (Matousek and Petersen, 1973; Hudspeth and Pribram, 1991; 1992; Thatcher et al, 1987) and, 2- superimposed upon the dominant exponential or logistic developmental trajectories are oscillations in the range of 5 to 20% of the mean. Further, detailed comparisons of the development of EEG power and EEG coherence reveal common modes of oscillation and similar anatomical discontinuities over the human lifespan (Thatcher, 1991). For example, Hudspeth and Pribram (1991; 1992) and Thatcher et al, (1987) report similar 2 to 4 year periods of oscillation with similar onset times and amplitude changes in frontal, central, temporal and parietal-occipital regions. The oscillations are not random "noise" since they are very ordered with iterated anatomical sequences and dynamical phase relationships as well as prominent power spectral peaks (Thatcher, 1991; 1992a; 1992b). An intriguing finding is that the timing of the oscillations in EEG coherence and EEG power overlap the timing of stages in human cognitive development as specified by Piaget (Piaget, 1952; 1971; 1975) and others (Fischer and Pipp; 1984; Fischer, 1987; Case, 1985; 1987).

The spatial and temporal dynamics of the postnatal oscillations in EEG coherence exhibited highly organized features often observed in nonlinear dynamical systems, such as phase transitions or bifurcations, frequency doubling, in-phase and anti-phase transitions and competitive and cooperative dynamics (Gilmore, 1981; Thatcher et al, 1986; Thatcher, 1992a; 1994b; 1994c; Thom, 1975). The oscillations in the development of EEG coherence were also anatomically organized and involved anterior-posterior and medial-lateral gradients and were similar to the dynamics seen in biological population growth and in models of computational ecology. Based on these features, it was hypothesized that the postnatal EEG coherence oscillations involved synaptic competition which was driven by a propagated wave of nerve growth factor (i.e., a traveling wave) such that the leading edge of the wave resulted in the local production of a surplus of synaptic connections and/or increased synaptic strength of existing synapses while the trailing edge was followed by a pruning of excess connections and/or decreased synaptic strength of existing synapses (Thatcher, 1992a; 1992b; 1994a). It was

postulated that these dynamics, whether an increase in synaptic number or strength, were part of a process that shapes and sculpts the microanatomy of the brain over the lifespan of human development.

The purpose of the present study is to evaluate these hypotheses of human cerebral development by formulating a nonlinear dynamical model capable of characterizing the main features of the postnatal development of EEG coherence. This will be accomplished by: 1- evaluating the critical features of the EEG coherence developmental data and creating a qualitative model to explain the findings, 2- developing a formal mathematical model and then performing sensitivity analyses on the model and, 3- simulating the observed EEG coherence developmental trajectories through the appropriate selection of resource and control variables.

POSTNATAL OSCILLATIONS IN CORTICAL CYTOARCHITECTURAL DEVELOPMENT A- Oscillations in Neuronal Packing Density and Cortical Thickness

By the age of six years there is an estimated loss (i.e., cell death) of greater than 20% of the number of neurons present at birth (Cowen et al, 1984; O'Leary, 1987) while skull volume has increased from approximately 30% at birth to approximately 90% of adult value (Blinkov and Glezer, 1968). This large loss of neurons and simultaneous increase in skull volume results in a large decrease in neuronal packing density, with neuronal packing density Dn defined as:

EQ(1) $$D_n = \frac{N}{V}$$

where N is the number of neurons per unit volume V (e.g., cubic millimeters) (Rabinovicz, 1979; Blinkov and Glezer, 1968). Decreases in neuronal packing density are heterogeneous with different values and rates in different cortical regions (Bok, 1959; Blinkov and Glezer, 1968) as well as different onset times and rates of change in different cortical layers (Blinkov and Glezer, 1968; Huttenlocher, 1979; 1984; 1990; Huttenlocher and de Courten, 1987). For example, there are postnatal oscillations and discontinuous developments in the thickness of cortical gray

matter (Rabinovicz, 1979; Conel, 1955; 1959; 1963; 1967), the packing density of cortical neurons (Blinkov and Glezer, 1968; Rabinovich, 1979) and in cortical volume (Blinkov and Glezer, 1968; Schade and Groeningen, 1961). The latter measures of cerebral development demonstrate oscillations with specific periods and rhythmicities. An example of some of the differential changes in postnatal neuronal packing density and cortical thickness are shown in figure 1. Rhythmic increases and decreases in packing densities are evident in Figure 1 with the most pronounced changes occurring in the upper cortical layers (i.e., layers II and III).

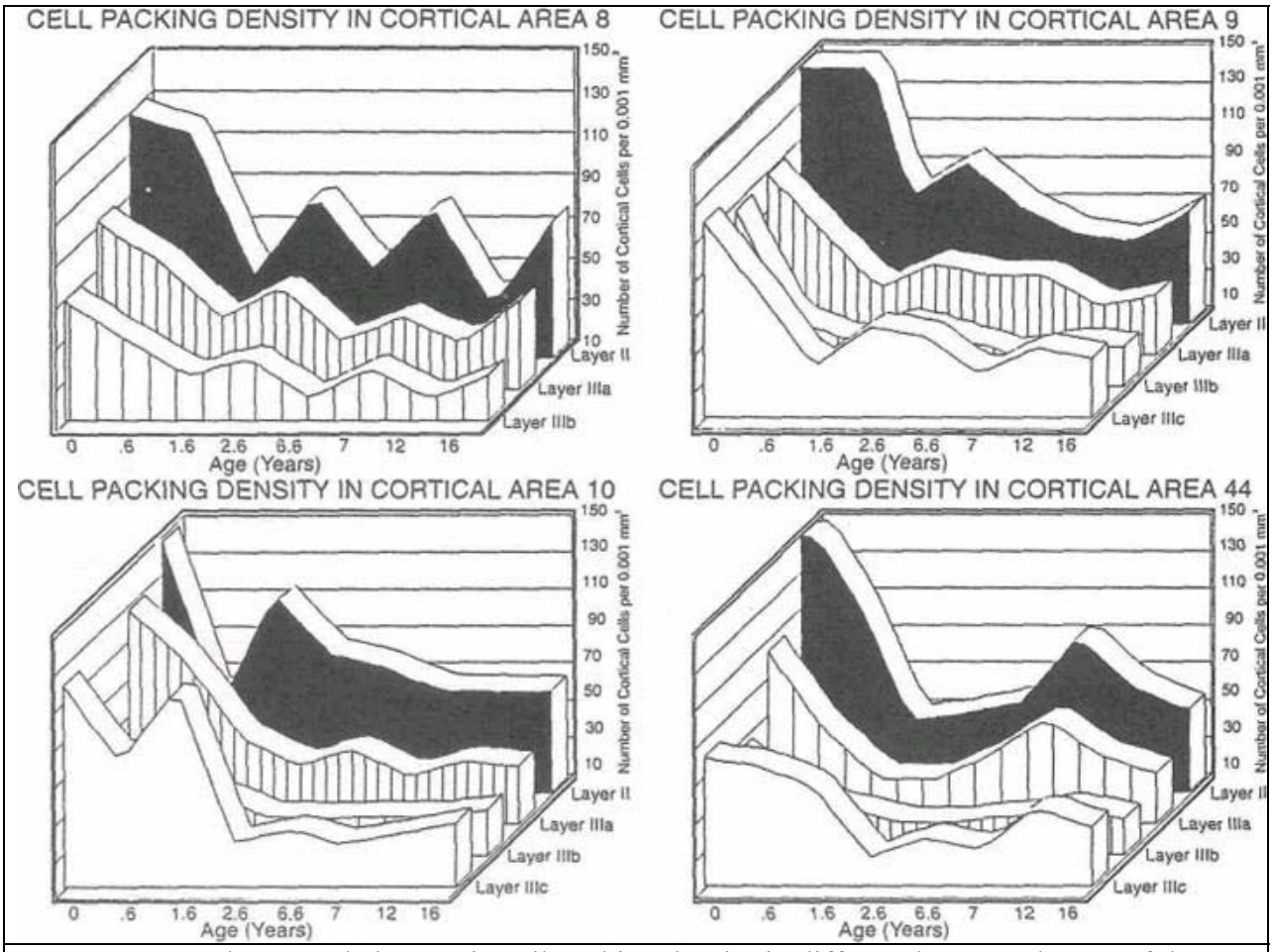

Figure 1 - Developmental changes in cell packing density in different layers and areas of the human frontal lobes (i.e., Broadman's Areas 8,9,10 & 44). The x-axis is age in yuears and the y-axis is number of cortical cells per 0.001 mm^3. Although the age samples are not at reular intervals, this figure illustrates two important phenomena: (a) the presence of postnatal oscillations in neuronal packing density and (b) that there are different postnatal rhythms in different cortical regions and in different cortical layers. Note. From The Human Brain (Table 229) by S. M. Blinkov and I. Glezer, 1968, New York: Plenum Press.

A consistent feature of Blinkov and Glezer's data and Conel's (1955; 1959; 1963; 1967) data is that the upper cortical layers (e.g., II and III) tend to exhibit larger amplitude of oscillation in neuronal packing density than the lower layers (e.g., IV, V and VI). As shown by Rabinovich (1979), rhythmic increases and decreases in cortical thickness are also present in different cortical layers. Cyclic changes in cortical thickness may reflect cyclic changes in dendritic ramification, in the size of neurons and/or in the numbers of glia cells and pre-synaptic terminals. The important point is that there is evidence indicating a dynamic and cyclical alteration in the cytoarchitecture of the human cerebral cortex during the postnatal period which can most easily be understood as a consequence of changes in dendritic ramification and in the regional density of synapses.[1]

Relations Between Synaptogenesis, Dendrite Length and Packing Density

It seems reasonable that both axons and dendrites develop in a coordinated or interrelated manner. For example, synapse differentiation on developing dendrites is closely correlated with developing afferent axons, suggesting a preferential growth of these elements toward one another (Becker, 1991). This indicates that synaptic contacts increase the probability of dendritic differentiation, such that dendritic growth would likely extend into rich synaptic fields and retract from impoverished ones (Henrikson and Vaughn, 1974). Vaughn (1989) postulated that synapses are initially formed on dendritic filopodia and growth cones and then as the dendrite differentiates and radially lengthens along its glial guide (Rakic, 1985) the synapses become located on the differentiated segments. It is further postulated by Vaughn (1989) that synaptotrophic processes induce dendritic branching such that the direction of dendritic growth is toward the highest concentration of axons during both prenatal and postnatal periods.

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[1] This position is contrary to the 'Concurrent Development' hypothesis of Rakic et al (1986). However, Rakic et al (1986) and subsequent studies by his group (Zecevic and Rakic, 1991; Bourgeois, et al, 1994) relied strongly on the assumptions of linear regression which may have prevented observing oscillations in their own data. For example, significant nonlinear regression fits and strong fourier components can be obtained by fourier analysis and nonlinear regression of the published data in Rakic et al (1986) and the other papers cited above (Thatcher unpublished observations). An interesting aspect of the 'concurrent' hypothesis is that it is all-or-none, that is, either cerebral development involves a single event or it involves multiple events and, therefore, measurable temporal oscillations do not support a concurrent hypothesis.

A more quantitative analysis of available dendritic surface area is based upon the studies of Bok (1959), Jerison (1973) and Wright, (1934) which demonstrated an inverse relationship between dendritic length L and cortical neuron packing density, i.e.,

EQ(2) $L = \frac{1}{D_n}$ and $D_n = \frac{N}{V}$,

Where N = the number of neurons per unit volume V. If we assume that each dendrite is conic and/or cylindrical in shape, then dendritic length is directly related to dendritic surface area S (e.g., the equation for surface area of the sides of a cylinder and a conic is $S = 2\pi rL$). Thus, there is a direct relationship between the surface area of dendritic arborization in squared microns and neuronal packing density in the number of neurons per cubic millimeter or $S = \frac{1}{D_n}$,

as per equations 1 & 2. We can extend these relations and define synaptic packing density in which the density D_S of synapses per unit somato-dendritic surface area is:

EQ(3) $D_S = \frac{N}{S}$,

where N is the number of synapses and S is somato-dendritic surface area in mm^2 .

Postnatal Development of Pyramidal Cell Dendrites

As emphasized by Von Economo (1926), many factors can influence cell packing density. Three of the most important measures are: 1- cranial volume (determined by skull expansion), 2-neural cell body size (or volume) and, if we assume that the development of the vasculature and glia are to support the development and function of neurons then, 3- dendritic length and dendritic ramification. In order to specifically measure the contribution made by dendrites, Schade and Groeningen (1961) studied the growth and arborization of the dendrites of the human frontal cortex by measuring the number of dendrites leaving the cell body, the number of points of ramification of the dendrites and the number of dendrite endings within zones of concentric circles separated by 25 u. They found that the total number of dendrites increased

from birth until about two years and then remained unchanged. However, the number of points of ramification within the zones as well as dendritic length increased after birth and throughout the early childhood and adolescent periods up to adulthood. For example, the degree of ramification of pyramidal cell dendrites increased by a factor of 13.6 times from birth to adulthood, while the total length of the pyramidal cell dendrites increased by a factor of 33 times (Schade and Groeningen, 1961). This represents a very considerable increase in the total dendritic surface area and, thus, an increase in the area available for synapse formation from birth to adulthood. Since dendritic surface area and/or arborization is inversely related to neuronal packing density (EQ 3), these data support the assumption that the amount of dendritic arborization and synaptic packing density is not a constant and fixed postnatal value, but dendritic surface area changes in a nonlinear manner in both the temporal and spatial domains as a function of postnatal age.

POSTNATAL OSCILLATIONS IN HUMAN EEG DEVELOPMENT

A- Cortico-Cortical Connections and EEG Coherence

Coherence is mathematically analogous to a cross-correlation in the frequency domain. It is a measure of the degree of "phase synchrony" or "shared activity" between spatially separated generators (Otnes and Enochson, 1972; Bendat and Peirsol, 1980; Glaser and Ruchkin, 1976). The application of coherence measures to the human scalp EEG have shown that EEG coherence reflects the coupling between neocortical neurons (Lopez da Silva et al, 1989; Nunez, 1981; Tucker et al, 1986; Thatcher et al, 1983). Recently, a "two-compartmental" model of EEG coherence was developed by Braitenberg (1978), Nunez (1981) and Thatcher et al (1986). A two-compartmental equation was developed based upon Braitenberg's (1978) two-compartment analysis of cortical axonal fiber systems in which compartment 'A' is composed of the basal dendrites that receive input primarily from the axon collaterals from neighboring or 'short distance' pyramidal cells, while compartment 'B' is composed of the apical dendrites of cortical pyramidal cells that receive input primarily from 'long-distance' intracortical connections. The

short distance 'A' system primarily involves local interactions on the order of millimeters to a few centimeters, while the long distance 'B' system involves long-range interactions on the order of several centimeters which represent the majority of white matter fibers. These two systems exhibit two different network properties. System 'A', due to the variable depths of the basal dendrites, is not involved in reciprocal loop processes but rather in a diffusion type of transmission process. In contrast, system 'B', due to reciprocal connections and invariant apical dendrite terminations, is involved in long distance feedback or loop systems (Thatcher et al, 1986; Pascual-Marqui et al, 1986; Braitenberg, 1978).

The following mathematical equation was developed to describe the magnitude and slope of decline of human EEG coherence with interelectrode distance (Thatcher et al, 1986):

EQ(4) $$Coherence = A_i e^{-kd} + B_i e^{kd} \sin kd \ ,$$

where A_i , B_i are amplitude parameters and k and d are parameters of frequency (Hz) and scalp interelectrode distance in centimeters, respectively. The first term on the right side of equation 4 corresponds to the operation of the short-distance 'A' system while the second term corresponds to the operation of the long-distance 'B' system.

While the magnitude of EEG coherence with interelectrode distance can be understood by a two-compartmental model, changes in the development of coherence over long spans of time (i.e., months and years) requires additional consideration. The developmental changes in EEG coherence in a large group of subjects reflects changes in the mean coupling between connected neuronal networks. For example, if we assume that volume conduction has been controlled, then we can postulate a relationship between EEG coherence and two primary factors: 1-the number of cortico-cortical connections between neural assembles, and 2- the synaptic strength of connections between neural assemblies (the terms cortico-cortical connections and intracortical connections are considered synonymous). This relationship is described as:

EQ(5) $$Coherence = C_{ij} \times S_{ij}$$

where C_{ij} is a 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. The later equation provides a logical means by which developmental changes in EEG coherence can be interpreted in terms of changes in the number and strength of connections between assemblies of neurons (Thatcher et al, 1986; 1987). For example, according to EQ 5, increased coherence is due to either an increase in the number and/or strength of connections and, conversely, decreased coherence is due to a decreased number and/or reduced strength of connections. Among the neurophysiological mechanisms that could be responsible for the changes in the numbers or strengths of connections are: axonal sprouting, synaptogenesis, mylenation, expansion of existing synaptic terminals, pruning of synaptic connections, presynaptic changes in the amount of neurotransmitter and changes in the postsynaptic response to a given neurotransmitter (see discussions by Purves, 1989; and Huttenlocher, 1984).

Growth Spurts and Oscillations in EEG Coherence Development

I have previously defined growth spurts in EEG coherence as age specific peaks of velocity or those postnatal ages where there was a maximum increase in mean coherence as measured by the first derivative of the developmental time series (Thatcher; 1992a, 1993). The point of maximum increase in EEG coherence (i.e., peak velocity) was considered to reflect either an increase in the number and/or strength of connections between two or more intracortical systems as per equation 5. The criteria for defining a peak in velocity as a growth spurt was: 1- only EEG coherence trajectories that loaded > .80 on a factor were evaluated and, 2- the first derivative must exhibit a positive peak. The criteria of "in phase" developmental trajectories was generally satisfied by a significant loading on a given factor (Thatcher, 1991). That is, each factor represents the commonality between developmental trajectories of EEG

coherence and, therefore, by definition a factor reflects "in phase" activity by a positive loading and anti-phase by a negative loading. High loading trajectories were consider important since they reflect shared activity between specific intracortical connection systems and not localized or spurious changes. The velocity or first derivative was selected rather than the second derivative (acceleration) or peaks in mean coherence itself because the first derivative reflects the developmental point in time when growth or change in coherence is at a maximum. The second derivative reflects the time of onset of a growth spurt as well as points of inflection. However, the second derivative is more susceptible to noise and may or may not eventually lead to a positive first derivative peak or to a significant increase in mean coherence. Mean coherence values represent the target or end-point of the growth spurt as measured by the first derivative. However, the end point is when growth or change is at zero or at a peak or trough before the next growth spurt.

A four point least squares procedure was used to compute the first derivative (i.e., velocity) or instantaneous rate of change in EEG coherence means from the 436 children in each developmental time series (Savitzky and Golay, 1964). The first 4 points (mean ages of .513 to 1.292 years) were used to estimate the derivatives, and these points were set to zero. Therefore, no estimates of growth spurts prior to 1.495 years of age were made. Figure 2 shows the velocity curves from the sub-groupings of electrode pairs that had the highest loadings (e.g., > .80) on the first five factors in the theta frequency band. These factors accounted for a total of 65.7% of the variance. Factor 1 accounted for 22.3% of the variance, factor 2 accounted for 12.9% of the variance, factor 3 accounted for 10.4% of the variance, factor 4 accounted for 10.8% of the variance and factor 5 accounted for 9.3% of the variance (Thatcher, 1991). Left temporal-frontal and left parietal-frontal developmental trajectories loaded on factor 1, right temporal-frontal developmental trajectories loaded on factor 2, bilateral local frontal trajectories loaded on factor 3, left occipital frontal trajectories loaded on factor 4,

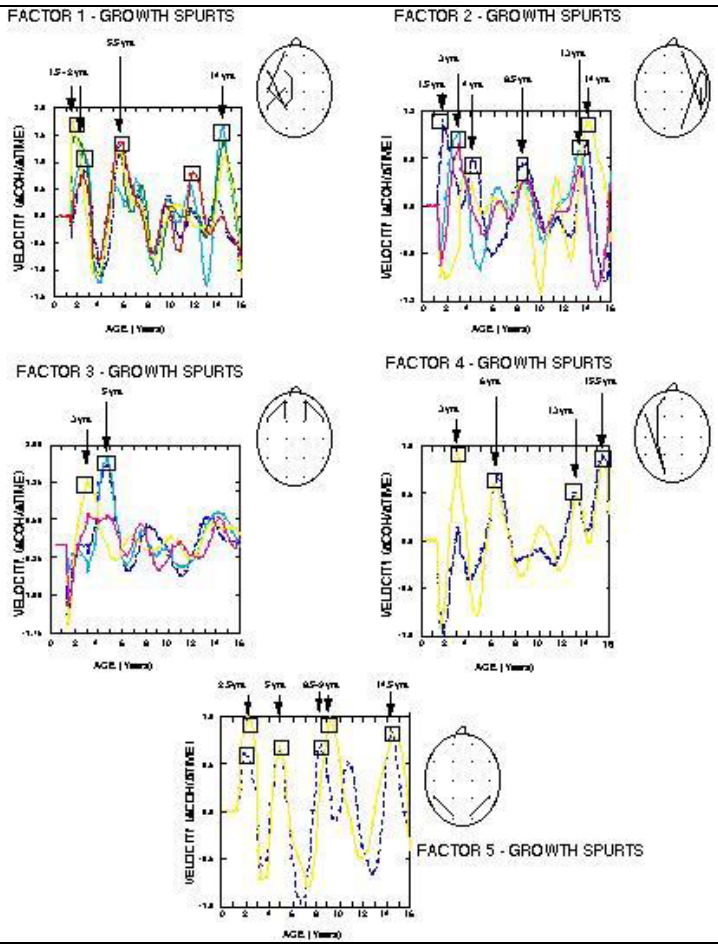

Figure 2 -The velocity curves or the first derivatives (Mean Coherence/Time) of the developmental trajectories of mean EEG coherence from the sub-groupings of electrode pairs that had the highest factor loadings (e.g., > .80) (Thatcher, 1991). Growth spurts were defined by a positive peak in the first derivative (i.e., a postnatal time of maximum growth) in multiple interelectrode combinations. Since each of the trajectories loaded heavily on a factor (i.e., > .80) this was considered sufficient evidence that a trajectory represented "in-phase" or anatomical synchrony of growth. Adapted from Thatcher, 1994a.

and bilateral posterior cortical trajectories loaded on factor 5. Periodic "in-phase" activity was present at different ages for each of the 5 factors. The fact that multiple electrode combinations were often involved indicated that the "growth spurts" or "in-phase" activity reflected the involvement of relatively large numbers of neuronal systems over relatively short periods of time (e.g., 6 months to 1 year).

Phase Transitions About Ages 6 and 10 Years Postnatal

As seen in figure 3 between the age of 5 to 7 years and 9 to 11 years a sudden change in the mean trajectory occurred. This sudden changes in the developmental trajectories, referred to

as phase transitions or bifurcations, involved the sequence from in-phase to out-of-phase oscillations in the left hemisphere at age 6 to 7 and from out-of-phase to in-phase oscillations at age 9 to 11 in the right hemisphere (see arrows). The phase transitions were widespread and were

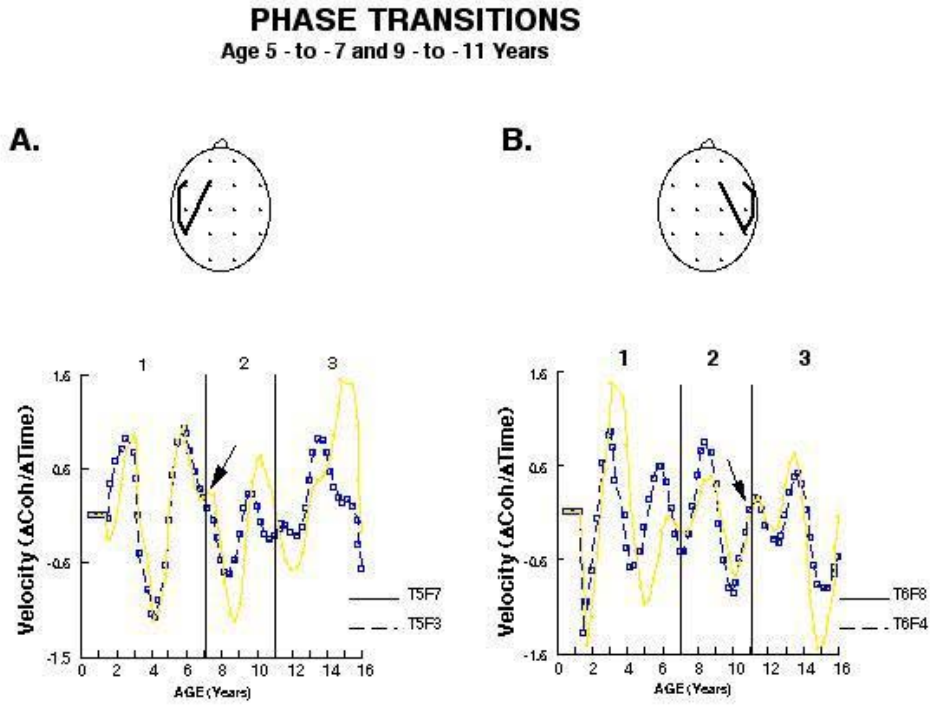

Figure 3 - (A) Velocity curves (Mean Coherence/Time) from left hemisphere dorsal medial-frontal to lateral-temporal (F3-T5) and from lateral frontal to lateral-temporal (F7-T5). The developmental trajectories were "in-phase" from 1.5 years to approximately 5 years (cycle 1). At approximately 7 years (see arrow) the trajectories began to exhibit "out-of-phase" relations. The 'X' axis is age in Julian years (see (6) for method of computing Julian years).

(B) Velocity curves (Mean Coherence/Time) from right hemisphere dorsal medial-frontal to lateral-temporal (F4-T6) and from lateral frontal to lateral-temporal (F8-T4). The developmental trajectories were "out-of-phase" from 1.5 years to approximately 9 years (cycle 3). At approximately 9 to 11 years (see arrow) the trajectories began to exhibit "in-phase" relations. The 'X' axis is age in Julian years (see Thatcher et al, 1987 for method of computing Julian years).

observed in numerous pairs of interelectrode combinations. However, they were most pronounced and consistent from lateral and medial frontal cortical regions. A spatial gradient in

the velocity of EEG coherence was evident for phase transitions in the lateral to medial plane. In the left hemisphere, for example, the age 7 phase transition was marked by two poles of apparently competing intracortical systems; pole one was lateral-frontal to lateral-temporal (F7-T5) and the second pole was medial frontal to lateral-temporal (F3-T5). Prior to age 5, both intracortical poles were in-phase, however, around age 6 to 7 the medial and lateral fronto-temporal systems phase shifted and formed two separate sub-systems (see fig. 4A).

A phase transition with a spatial gradient was also present in the right lateral and right medial fronto to lateral temporal regions during the age 9 to 11 year period (see Fig. 4B). This right hemisphere phase transition, however, was different than the earlier left hemisphere phase transition since it was marked by an apparent integration or phase synchrony of previously differentiated or asynchronous right lateral-temporal trajectories. Another example of the phase transition at age 5 to 7 is seen in 4 from the left fronto-parietal electrodes (i.e., F7-P3). Mean %coherence (i.e., coherence x 100) versus age is shown in fig. 4A in which there are oscillations around a homeoretic line (dashed line) and a slow decline in coherence from 1.5 to approximately 5 years. At approximately 6 years there is a large jump in mean %coherence

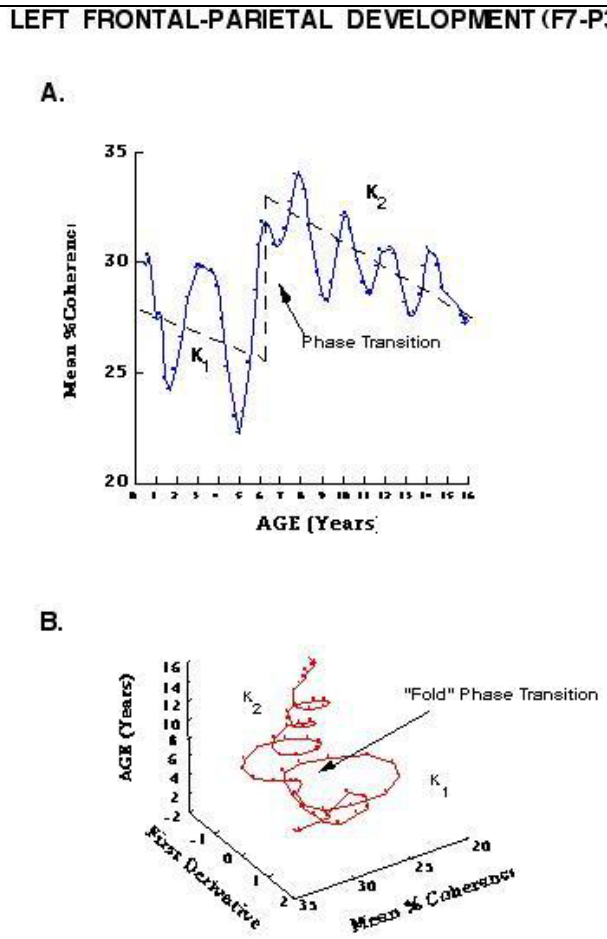

Figure 4 - (A) Mean %EEG coherence (i.e., coherence x 100) in the theta frequency band from left lateral frontal-parietal regions (i.e., F7-P3) from 6 months to age 16. Two modes of oscillation, mode one from birth to approximately age 5 and mode two from approximately age 7 to age 16, are fit by regression lines K_1 and K_2 . The phase transition between the two developmental states of equilibria is represented by the line connecting K_1 to K_2 . (B) is a two-dimensional phase portrait represented in three dimensions by extending the phase space over age. This figure demonstrates that there are two-limit cycles or phase states of EEG coherence oscillation the left fronto-parietal (i.e., P3-F7) which are spirals with different radii and frequencies over the lifespan. Adapted from Thatcher, 1991.

with a new set of damped oscillations and a second homeorhetic line from age 7 to 16. Figure 4B shows this phase transition in phase space where the first derivative (Y axis) is plotted against mean %coherence (X axis) and the age axis (Z axis) is extended. The phase transition is seen as a "cusp" between the age of 5 and 7 years (Thom, 1975; Gilmore, 1981).

Cyclic Micro-Cycles of Development

Figure 5 is a summary of the ages and durations of "in-phase" activity for the five factor groupings shown in Figure 1. [2] An iterative and sequential anatomical pattern of growth spurts

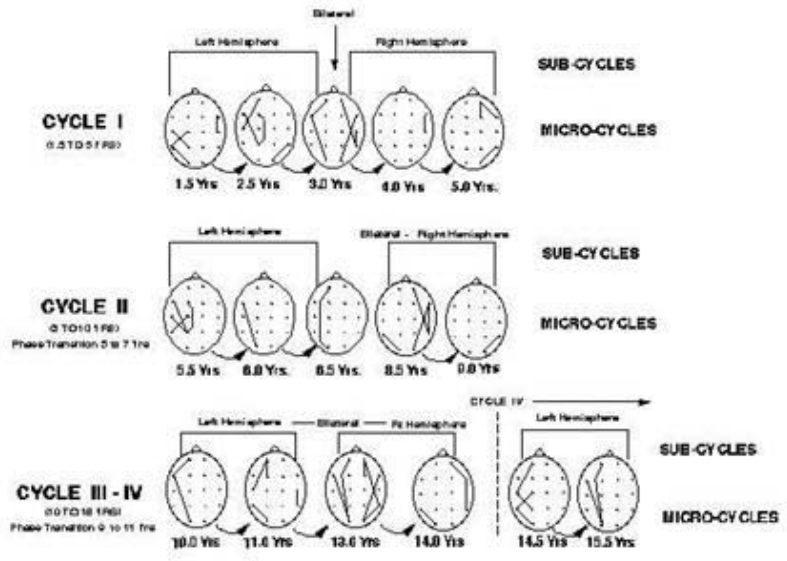

Figure 5 - Representation of the sequence and anatomical distribution of the growth spurts shown in figure 1. Lines connecting two electrode locations correspond to the electrode locations in figure 1 for the various developmental trajectories that loaded (> .80) on the first five factors (Thatcher, 1991). Micro-cycles were defined by a developmental sequence involving a anterior-posterior lengthening of interelectrode distances and a lateral-medial rotation that cycles from the left hemisphere to bilateral to right hemisphere in approximately 4 year periods. The micro-cycles were grouped into sub-cycles and the sub-cycles were grouped into cycles as defined by the age 5-7 and age 9-11 bifurcations.

[2] Although most of the first derivative peaks were single points, several peaks were broad involving more than one point. Therefore, for clarity only approximate ages of first derivative peaks are represented in the text and figures. Since Julian ages were used (Thatcher et al, 1987) the designation of the age of a first derivative peak was the six month period it was nearest to.

was evident. For example, at age 1.5 years growth spurts were relatively localized (e.g., 6 cm interelectrode distances) and confined to the left parietal and left central to left lateral-temporal regions. At age 2.5 years there was a lengthening along the anterior-posterior dimension (e.g., 12 cm interelectrode distances) with a lateral-to-medial rotation of parietal-frontal relations to include left parietal to left dorsal medial-frontal regions (i.e., P3-F3 and T3-F1). At age 3 years there was a further lengthening of intracortical relations along the anterior-posterior dimension (e.g., 18 to 24 cm interelectrode distances) with continued involvement of dorsal medial-frontal to posterior cortex. This sequence of lengthening along the anterior-posterior dimension and rotation along the lateral-to-medial dimension between 1.5 and 3 years was repeated again between ages 5.5 to 6.5 years and finally again between 14.5 to 15.5 years and is referred to as "micro-cycles" of cortical development. The label of a pattern as a micro-cycle or a sub-cycle is used to emphasize the presence of a cyclical pattern. The important point, whether a sequence is labeled as a micro-cycle or a sub-cycle, or as a stage or sub-stage is that sequential developmental processes were nested within cyclic anatomical patterns.

Each EEG coherence growth spurt was marked by a different set of differentiated and integrated intracortical sub-systems that represented an iterative sequence of cortical re-organizations. That is, there was a sequential reordering of different sub-groupings of cortical connection systems at specific postnatal ages. For example (see Fig. 6), the left parietal-temporal pattern (i.e., P3-T3) at 1.5 years was repeated at 5.5 years and again at 14.5 years, the left frontal pole-occipital pattern (i.e., 01-F1) at 6.5 years was repeated at 13 and 15.5 years; the bilateral occipital-posterior temporal pattern (i.e., 01/2-T5/6) at 2.5 years was repeated at 5 and 14.5 years; and the right frontal-posterior cortical pattern (F2-T6 and F8-02) at 3 years was repeated at 8.5 years and 13 years, etc.

A NONLINEAR SYNAPTOGENIC MODEL OF CEREBRAL DEVELOPMENT

The results of the developmental EEG studies (Epstein, 1980; Matousek and Petersen, 1973; Thatcher et al, 1987; Thatcher, 1991; 1992a; 1993) raise a number of critical questions. Among these questions are: 1- What are the physiological bases for the oscillations in human EEG over the developmental lifespan?, 2- what are the mechanisms by which growth spurts in EEG occur? 3- what is the nature of the phase transitions that occur between brain regions that exhibit different oscillations and, 4- If lifespan oscillations reflect important physiological processes then do different modes and locations of oscillation contribute to the development of different aspects of human cognition? To begin the search for the answers it is reasonable to begin with fundamental biological and ecological models which are capable of explaining the presence of oscillations in populations of neurons. Among the most adaptable ecological models are where two populations are competing for a common food supply (Volterra, 1926; Gause, 1934; Gause and Witt,1935) and/or population models involving prey-predator relationships (Lotka, 1925; Volterrra, 1926; Nicholson and Bailey, 1935; Soloman, 1949; Holling, 1959; 1966). These two models are mathematically related, primarily by the strength of the competitive coupling (Real, 1977; Berryman, 1981; Getz, 1984). In order to adapt these models to cortical development we must assume: 1- a common niche for synapses is the somato-dendritic surface area expressed in squared microns (see Eqs 1 to 3), 2- cortico-cortical connection systems can compete and/or cooperate for the available somato-dendritic surface area upon which synaptic connections are formed, 3- competing and/or cooperating cortico-cortical connection systems from different brain regions can coexist within a given cortical region, such that displacement of connections from region 1 by connections from region 2 can occur. In order to specify the dynamics of synaptic population interaction, three levels of analysis are considered: 1- the synaptic level, 2- the axonal-dendritic level and 3- the synaptic population level.

The Synaptic Level

It is generally agreed that the mature synapse represents the end point of a continuous and dynamic process of growth and degeneration in which both postsynaptic and presynaptic mechanisms operate in the embryogenesis, maintenance and regression of synapses (Purves, 1988). On the one hand, mature neuronal networks are believed to be genetically specified in which the environment merely triggers pre-established programs and sequentially stabilizes specific synaptic connections (Weisel, 1982). A growing number of scientists believe that genetic programs only grossly specify synaptic configuration with the activity of the nervous system largely specifying the fine details of connectivity (Zucker, 1981; Brown et al, 1982; Purves and Lichtman, 1985). One of the strongest proponents of the latter view is Changeux and Danchin (1976) who postulate that genetic mechanisms specify main categories or sets of connections by producing a surplus or redundant number of synapses and that activity dependent factors select which of this redundant set will become stable and survive. According to this model, the genetic program allows for an initial overproduction of synapses but during maturation a significant fraction regress. They argue that when synaptic contacts first form they exist under three states: labile (L), stable (S) and regressed (D). The labile state may become either stabilized (L-->S) or irreversibly regressed (L-->D) with re-growth represented by (not -->L). A critical feature of Changeux and Danchin's (1976) model is that the transitions of synapses from labile to stable or labile to regressed are regulated in an "epigenetic" manner by both pre-synaptic and post-synaptic activities. While the molecular mechanisms are not precisely known, it is widely believed that environmentally driven neurotransmitters are involved in the anterograde or presynaptic side (Purves, 1988; Lo and Poo, 1991) and genetically driven nerve growth factors are involved in the retrograde or postsynaptic side (Changeux and Danchin, 1976; Vogel and Davies, 1991; Montague et al, 1991). Of course other factors emitted by nerve terminals must also be considered, such as ATP and some enzymes or polypeptide hormones (Becker, 1991; Raffioni et al, 1993) which provide "energy" for development. For the development of complex patterns of synapses on somas and dendrites, internal "coupling factors" are postulated as a way to explain the regular spacing of synapses (Stent, 1973). Thus, for

simplification one can postulate that while environment and genetics interact on both the pre and postsynaptic sides, the presynaptic side is more strongly influenced by environmental factors and the postsynaptic side is more strongly influenced by genetic factors. We can represent the relation between synapses and the supply of energy necessary to sustain their existence, such as trophic nerve growth factor NGF or ATP, etc., as:

EQ(6) $$D_e = \frac{N}{E} \quad ,$$

where N = the number of synapses and E is the concentration of subsistence and maintenance substance such as NGF and D_e is the density of subsistence and maintenance substance per unit synapse (see equations 24 and 25 for more detailed definitions).

The Axonal-Dendritic Level

Figure 6 (top) is a representation of two synaptic populations A and B converging on a common somato-dentritic area C. The projections A and B represent multiple axons with multiple branches containing multiple synaptic connections. There are shared spatial locations on the dendrites of C in which the synaptic species from population A cooperates and/or competes for occupancy with the synaptic species from population B. The bottom illustration is an example of cortico-cortical connection systems representing A, B and C, e.g., lateral frontal to parietal cortico-

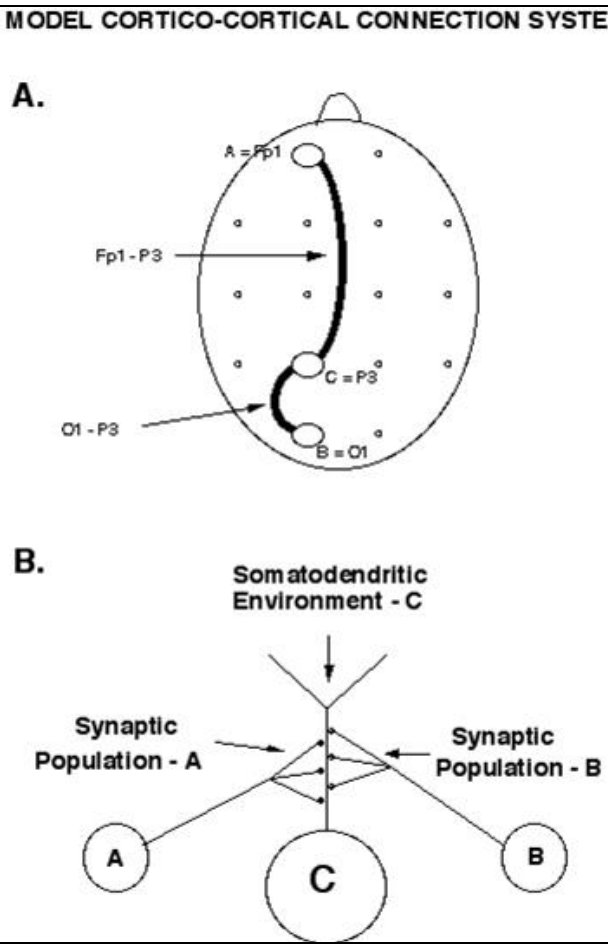

Figure 6 - A model of cortico-cortical connection development. Top (A) is a diagram of left frontal pole regions (i.e., Fp1) which is competing with left occipital (i.e., O1) for synaptic influence on the parietal cortex. That is, connections from Fp1 and O1 converge onto P3 where they compete for the available synaptic binding sites on the dentrites and/or cell body of parietal neurons. Bottom (B) An expansion of the synaptic environment for the competing connection systems shown in (A). The carrying capacity for synaptic influence is a function of the amount of parietal dendro-somatic area upon which synapses can form and the amount of trophic growth factor. Synapses originating from the frontal and occipital regions converge onto the parietal dendro-somatic surface where they compete for contact and influence of the parietal neurons. Adapted from Thatcher, 1994b.

cortical connections (F7-P3) are A, occipital to parietal cortico-cortical connections (O1-P3) are B and C is the somato-dendritic domain of the left parietal region (P3) where the cortico-cortical connections A and B converge. It is at this location of convergence that competition for available dendritic space and limited energy resources emerges (see equations 24 and 25).

Neural Population Level

Given the factors and arrangements at the synaptic and axonal-dendritic levels described in sections IV-A and B a mathematical model of the ontogenesis of synaptogenesis was developed. This model is based upon modifications of the Lotka-Volterra equations as described by Milsum (1968), Gilpin and Ayala (1973) and Berryman (1981). The following sections represent an adaptation of Berryman's (1981;1990) population dynamics model as applied to cortico-cortical synaptic systems. Figure 7 is a representation of the dynamical interactions within and between cortico-cortical synaptic systems as depicted in Figure 6. There are four major kinds of relations and interactions between synaptic connection systems: 1- independent, 2- competition, 3- cooperation and 4- predator/prey. Which of these categories of interaction can be depicted by the sign and magnitude of the interaction coefficients a_{ii} which are divided into intra-synaptic interaction coefficients, e.g., a_{11} and a_{22}, or into inter-synaptic interaction coefficients, e.g., a_{12} and a_{21}. Independence is when a_{12} and $a_{21} = 0$, competition is when a_{12} and a_{21} are both negative, cooperation is when a_{12} and a_{21} are both positive and predator/prey is when a_{12} is negative and a_{21} is positive (see equations 27 to 30).

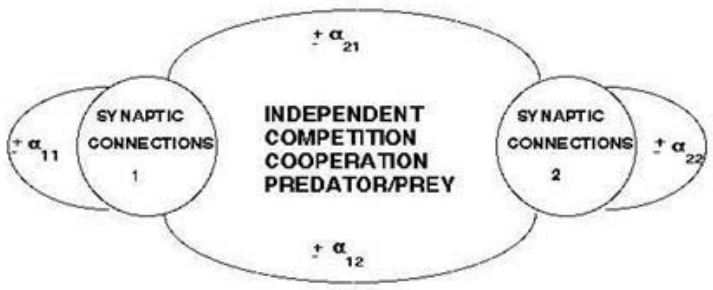

Figure 7 - Ecological model in which synapses arising from two different cortical regions interact for influence on a third cortical region. The interaction can be of four types: 1- Independent, 2- Cooperative, 3- Competitive and 4- Predatory/Prey, depending upon the sign and magnitude of the interaction coefficients a_{ii} which are divided into intra-synaptic interaction coeffcients, e.g., a_{11} and a_{22} , or into inter-synaptic interaction coefficients, e.g., a_{12} and a_{21} . Adapted from Thatcher, 1994b.

In the sections to follow the details of how these population interactions are modeled for cortical synaptic connections will be established by an examination of the mathematical structure of neural population dynamics.[3]

Nonlinear Dynamics of Intra-Synaptic Interactions

[3] This model is an adaptation of standard ecological models that are used in the POPSYS software program (Berryman, 1990) involving rabbits and foxes and other animal species. The same ecology terminology and the same mathematics as used in POPSYS is applied to the ecology of synaptic formation and brain developmental dynamics in the model that follows.

We will define a population of synapses as a group or set of synapses with a common origin and a common somato-dendritic termination point. In other words, axonal terminations which arise from neural cell bodies in location A and terminate on location C represent a population of synapses (see Figure 6). Let the number of synaptic connections in a population at time t be represented by N(t) and those present one time period previously by N(t-1). Further, let the number of synaptic connections grow or increase at an average rate of b over the time interval t-1 to t. It follows that the number of synaptic connections present in the population at time t must be

EQ(7) $N_{(t)} = N_{(t-1)} \times b$

If we start at time zero with a population of N(0) synaptic connections, and assuming that the rate of growth does not change, then we can calculate the growth of synaptic connections over several time increments by the equation

EQ(8) $N_{(t)} = N_{(t-1)} \times b^{\Delta t}$

where Δt is the number of time increments. We can write equation (8) in its more familiar exponential form by taking natural logarithms, setting $B = \log_e(b)$ and taking antilogs to arrive at:

EQ(9) $N_{(t)} = N_{(t-\Delta t)} \times \exp(B \times \Delta t)$

Equation (9) is a solution of the well-known differential equation of exponential growth or the "Malthusian law" as described in Equation 10.

EQ(10) $\frac{dN}{dt} = N \times B$

In addition to growth of synaptic connections we must assume that connections die or are displaced. To incorporate this feature into the model a growth parameter r is defined as:

EQ(11) $r = b - d$

where r is the rate of change in synaptic connections, b is the birth or creation of synaptic connections and d is the death or displacement of synaptic connections. We can substitute R = $\log_e(r)$ for B in equation (9) when $\Delta t = 1$ to yield

EQ(12) $N_{(t)} = N_{(t-1)} \times \exp(R)$

Using equation (12) we can calculate population growth as a stepwise, or recursive, process and estimate the rate of change by

EQ(13) $R = \log_e \left[N_{(t)}\right] - \log_e \left[N_{(t-1)}\right]$

where R = the rate of growth and $N_{(t)}$ and $N_{(t-1)}$ are the estimated densities of synaptic connections at two sequential points in time.

Limits To Growth

It is obvious that populations of synapses can not grow indefinitely and must eventually be limited by shortages of trophic nerve growth factor (NGF), space or other essential resources. This idea can be formalized by considering a population of N synaptic contacts in which each individual synapse requires W units of a critical resource, say a trophic nerve growth factor, to keep it alive and to be replaced when it dies. If the total nerve growth factor available per unit time is F, there will be surplus trophic growth factor for synaptic growth when F is larger than the subsistence demand of the population W x N. In other words, the population will grow (i.e., R > 0) when the demand/supply ratio is less than unity, i.e., (W x N)/F < 1. In contrast, the population will decline (i.e., R < 0) when W x N/F > 1, and the population will remain constant at steady state equilibrium (i.e., R = 0) when the demand/supply ratio is unity, i.e., (W x N)/F = 1. We can see from equation (12) that the population will also be in equilibrium when R = 0,

because exp[0] = 1 and, therefore, $N_{(t)} = N_{(t-1)}$. A simple expression for the relationship between rate of growth R and the demand/supply ratio (W x N)/F is

EQ (14) $$R = A - C \times \left(\frac{W \times N}{F} \right)$$

where A is the intercept of the line with the R-axis at N = 0 and C is the slope of the line. Since R = 0 when (W x N)/F = 1 then A = C when R = 0 (i.e., 0 = A - C or A = C). Because A = C when R = 0, equation 8 can be written

EQ (15) $$R = A - \left(\frac{A \times W \times N}{F} \right) \text{ or } R = A \times \left(1 - \frac{W \times N}{F} \right)$$

We can further reduce the number of parameters in this equation by letting the equilibrium value of N = K which occurs when R = 0, so that

EQ (16) $$0 = A \times \left(1 - \frac{W \times K}{F} \right) \quad \text{or K = F/W}$$

In other words, the equilibrium density, K, is equal to the supply of essential resources F divided by the subsistence demand W. This parameter reflects the density of synapses that can be sustained indefinitely by a constant supply of nerve growth factor and available somato-dendritic space and is referred to as the "carrying capacity of the synaptic environment" (K). Substituting K for F/W in equation (15) yields

EQ (17) $$R = A \times \left(1 - \frac{N}{K} \right)$$

This equation expresses R, the rate of change in the number of synapses, as a function of the synaptic density, N, and the carrying capacity of the synaptic environment, K.

Genetics as "Experience Independent" and Environment as "Experience Dependent" Development

The synaptic carrying capacity can be modeled to contain dynamical properties itself. This is important in order to account for both genetical and environmental aspects of development as they may operate at sub-cellular or DNA levels as well as extracellular levels. The approach we choose to model the dynamics of genetics and environment is based upon Greenough and colleague's "experience-dependent and independent" models of cortical development (Greenough et al, 1987; Black and Greenough, 1986) in which the carrying capacity could be modified depending upon the supply and demand of nerve growth factor (NGF) and somato-dendritic surface area. Let us assume that the carrying capacity of the synaptic environment K is a function of both the concentration of nerve growth factor and the available somato-dendritic space upon which synapses can be formed or K = NGF + SPACE. Let us further assume that the ratio between the supply and demand of these components is controlled by both experience dependent and experience independent influences at all levels of development and that environment and genetics are always interrelated and additive. We can model such a relationship by representing experience independent and experience dependent influences on different axes of a complex variable Z, where Z = x + iy with experience independent influences represented by the x or real variable and the experience dependent influences represented by the imaginary variable iy.

However, for the sake of simplicity, in the following sections the complex representation of experience dependent and experience independent influences will not be formally modeled or simulated. Although this is necessary given the limits of space, it should be noted that interesting and complicated dynamics evolve from these equations when the complex variable is used. For the moment, let us substitute the functional relationship (EQ17) for R in equation (12), in which we get a discrete-time analog of the well-known Verhulst (1938) logistic equation,

EQ (18) $$N_{(t)} = N_{(t-1)} \times \exp\left(A \times \left(1 - \frac{N_{(t-1)}}{K}\right)\right)$$

more commonly seen as the differential equation

EQ (19) $$\frac{dN}{dt} = R \times N \times \left(1 - \frac{N}{K}\right)$$, where R = A.

The logistic is a fundamental equation of linear population dynamics, containing the basic elements of positive feedback population growth and negative feedback constraints on growth. It assumes that R is linearly related to population density, that negative feedback occurs without a time delay and, that the system is characterized by a single equilibrium point. These assumptions are overly restrictive and do not allow for the richness of behavior observed in the development of cerebral cytoarchitecture and the developmental EEG literature. In order to adapt equations (18 and 19) we need to account for synaptic growth in a variable environment which involves delayed nonlinear negative feedback. We also need to account for "stages" or "discontinuities" in development as represented by two or more equilibria or domains of attraction.

Based upon Gilpin and Ayala (1973) and Berryman's (1990) formulation, we can adapt equation (EQ 18) to describe synaptic growth far from equilibrium in a variable or stochastic environment as

EQ (20) $$R = A \times \left(1 - \left(\frac{N_{(t-1)}}{K}\right)^{Q}\right) + V[0, S]$$

where V is a standard deviate of a normally distributed variable with mean 0 and standard deviation S. Increasing the value of S will increase the amount of random "noise" in the environment. We can also adapt equation (18) so that the slope of the feedback function is not constant, and in fact, is proportionally stronger at either high or low densities (i.e., is nonlinear). For example, when competition is strong near to the carrying capacity then the R function will get steeper as it approaches the carrying capacity, i.e., it will be convex. When negative feedback is more intense at low synaptic densities then the R-function will have a concave form. We can represent nonlinear feedback by adding an exponent Q to the demand/supply ratio,

where Q is referred to as the coefficient of curvature of the logistic equation. When Q > 1 the R-function will become convex and when Q < 1 it will become concave (Berryman, 1990).

Equation (20) is self-regulatory if it is assumed that there is none or only a negligible delay between the time that the population N reaches its limit K and the time for the establishment of the appropriately corrected value of the synaptic productive rate. However, as pointed out by Hutchinson (1957), if there is a time lag T so that the rate dN/dt at time T is determined by the

delay N (t - T), then oscillations will be present in the equation. We can incorporate time-lags into the logistic equation by letting R be a function of N(t - T), where T is the delay in the negative feedback response; i.e.,

EQ (21) $$R = A \times \left(1 - \frac{N(t-T)}{K}\right) + V[0,S]$$

Finally, we can use Tong's (1978) and Berryman's (1990) formulations to adapt equation (20) to contain two equilibria or basins of attraction which are separated by an unstable equilibrium point, sometimes referred to as an escape threshold or separatrix. To accomplish this we use the Berryman's equation 10 (Berryman, 1990) that generalizes the logistic R-function as:

EQ (22) $$R = A_i \times \left(1 - \frac{N(t-1)}{L_i}\right) \times \left(1 - \left(\frac{N(t-1)}{K_i}\right)^{Q_i}\right) + V(O,S)$$

i = 1 when N(t - 1) > E

i = 2 when N(t - 1) < E

where L and K are the carrying capacities of the lower and upper equilibrium states respectively, E is the escape threshold or separatrix and the subscript i indexes the parameters of the upper (i = 1) and lower (i = 2) equilibria. Thus, when synaptic density is above the escape threshold, E, trajectories are drawn towards the upper equilibrium, and when density is below the threshold,

trajectories are attracted to the lower equilibrium. In nonlinear dynamics the separatrix E forms the unstable point of a saddle to which trajectories move toward limit sets or basins.

Nonlinear Dynamics of Intra and Inter-Synaptic Interactions

A crucial aspect of this model concerns the availability and demand for resources, which are defined by the number of synapses and the availability of dendritic space upon which synapses are formed and the availability of trophic growth factors. It is the interrelations between demand for and availability of these resource that determines the nature of the nonlinear dynamics of the model. The same as for any ecological model of predatory/prey, competition and cooperation (Berryman, 1990).

To explore this aspect of the model let us first write equation (17) as:

EQ (23) $$R = A - \beta N_{(t-1)} \quad ,$$

where β = A/K is the negative effect of a set of cortico-cortical synaptic connections on its own rate of increased connectivity. We can call this an intra-synaptic effect because it represents the effects of intra-specific competition between members of the same cortico-cortical connection system. However, because there is a finite amount of resources from which synapses can be formed it is necessary to modify equation (23) to take into account both dendritic space and the amount of trophic nerve growth factor. Therefore, let us extend equation (23) so that

EQ (24) $$R_i = A_i - G_i \frac{N_i}{S_i} - H_i \frac{N_i}{E_i},$$

where N_i is the density of the ith set of cortico-cortical connections, G_i is a measure of the demand for somato-dendritic space for that set of connections, H_i is a measure of the demand for food or trophic growth factor for that set of connections, S_i is a measure of the available somato-dendritic space for that set of connections and E_i is the amount of trophic growth factor available for that set of synaptic connections i. In this variation of the logistic model, the

carrying capacity can be determined by both available somato-dendritic surface area (S_i) expressed in mm^2 and/or the concentration of trophic nerve growth factor (E_i) expressed in micromoles, while the parameters G_i and H_i specify the demands of the average synapse for these resources, respectively.

As described in more detail in section H, the concepts of competition, cooperation and predator/prey interactions between two populations emerge by expanding equation 24 to two interrelated equations and varying the ratios of the various elements of equation 24. For example we can write equation 24 for two populations as equation 25a and 25b:

EQ (25a) $$R_1 = A_1 - G_1 \frac{N_1}{S_1} - H_1 \frac{N_1}{N_o}$$

EQ (25b) $$R_2 = A_2 - G_2 \frac{N_2}{S_2} - H_2 \frac{N_2}{N_1}$$

These equations state that the rates of growth of the two populations R_1 and R_2 vary as a function of their respective intercepts A_1 and A_2 minus the respective demands for space G_1 and G_2 and the ratio of the density of synapses (N_1 and N_2) to the available dendritic space (S_1 and S_2). Most importantly, R_1 and R_2 are also related to the respective demand for food (and/or trophic factor) H_1 and H_2 and the ratio of the density of synapses (N_1, N_2, N_o) to the available food as supplied by population N_2 to N_1 in equation 25b and between population N_1 and a basic trophic level N_o in equation 25a. In other words, the rate of growth of population two is dependent upon the density of synapses of population one, since population one serves as a source of food for population two.

Competition, Cooperation and Predator/Prey Interactions Between Cortico-Cortical Synaptic Connections

A simplification of the model shown in equations 24 and 25 can yield a product model of competition, cooperation and predator/prey. For example, let us consider that somato-dendritic

space and nerve growth factor for the intra-specific interactions of a given population of cortico-cortical connections are constant and set β in equation 23 to α_{ii} where:

EQ (26) $$\alpha_{ii} = \frac{G_i}{S_i} + \frac{H_i}{E_i}$$

which allows us to reduce equation (24) to equation (23)

With this simplification it is possible to introduce the effect of another or different set of cortico-cortical synaptic connections. We will use the notation of Berryman (1990) to describe the interaction coefficients α_{ii} to be consistent with figure 7:

EQ (27) $$R_1 = A_1 - \alpha_{11} N_1, t-1 \pm \alpha_{12} N_2, t-1$$

where α_{11} is the coefficient or weighting for the intra-specific effect of N_1 on itself and α_{12} is the coefficient or weighting for the effect of the second set of synaptic connections, N_2 , on the rate of increase of N_1 , or the inter-specific effect. The sign of the coefficient α_{12} determines whether the interaction between sets of synaptic connections is competitive, cooperative or exploitive. Equation (27) is a variation of the Lotka-Volterra equation in which predator/prey interactions are dependent upon the product of predator to prey. However, as pointed out by Berryman (1990) there are problems with the simplified product model of equation (27). For example, according to equation (27) the rate of increase in synaptic connections is dependent only on the density of the other set of synaptic connections and does not take into consideration the possibility that growth of a given synaptic connection system may depend upon its own density and not just the density of another synaptic system. In other words, the rate of change in synaptic connections can also be expressed as a ratio of predators to prey or $\frac{N_2}{N_1}$ as in equations 25. We will call this the ratio dependent variation of the model and the formulation in equation (27) as the product dependent variation of the model. In subsequent analyses of the model both the product dependent and the ratio dependent forms of the model will be evaluated and

compared to determine which is the best fit and possibly to infer which dynamic is most prevalent in the development of cortico-cortical connection systems. In the equations to follow, however, only the ratio dependent variation will be presented. In order to derive the product dependent variation one simply changes the ratio (e.g., $\frac{N_2}{N_1}$) to a single species as in equation (27). By setting both dendritic space and the nerve growth trophic levels constant the equations can be simplified to the ratio of the two synaptic connection systems where one is either cooperating or competing with the other. For this purpose, let us set the exploited population as N_1 and the exploiting population as N_2. In this manner competition, cooperation and predator/prey interactions can be described by three similar equations that differ only in the ratio that determines the inter-specific interaction. For example, beneficial effects are signified by the ratio of a population of synaptic connections to a population of benefactor connections, $\frac{N_1}{N_2}$ and harmful effects are represented by the ratio of the exploiting synaptic population (i.e., N_2) to the synaptic population that is displaced or exploited (e.g., the prey), $\frac{N_2}{N_1}$. The following three equations described these interrelated conditions.

Competition Between Cortico-Cortical Synaptic Systems

Competition can be represented as follows:

EQ (28a) $$R_1 = A_1 - \alpha_{11} N_1 - \alpha_{12} \frac{N_2}{N_1}$$

EQ (28b) $$R_2 = A_2 - \alpha_{22} N_2 - \alpha_{21} \frac{N_1}{N_2}$$

Equations 28a and 28b are symmetrical in that each set of synaptic connections has a negative effect on the other so that the two equations are structurally balanced. As described by Berryman (1990) Zero growth isocline analyses in which R =0 for each synaptic connection group show the conditions of stability and instability in equations 28a and 28b. For example,

competitive coexistence is possible only when $\alpha_{11}\alpha_{22} > \alpha_{12}\alpha_{21}$, for all other conditions competitive annihilation or exclusion will occur in which one synaptic species or group of synaptic connections is succeeded by more successful competitors.

Cooperation Between Cortico-Cortical Synaptic Systems

Cooperation between two sets of cortico-cortical synaptic connections is described with the following two equations:

EQ (29a) $$R_1 = A_1 - \alpha_{11}N_1 - \alpha_{12}\frac{N_1}{N_2}$$

EQ (29b) $$R_2 = A_2 - \alpha_{22}N_2 - \alpha_{21}\frac{N_2}{N_1}$$

The only difference between the equations for competition and the equations for cooperation is the ratio of synaptic densities that determines the inter-specific interaction (Berryman, 1990). As in the case of competition, the feedback structure of cooperation is symmetrical but involves positive rather than negative interactions between the two sets of synaptic connections. However, this has no effect on the overall feedback structure of the system because the product of the two positive interactions also produces a positive feedback loop.

Predator/Prey Relations Between Cortico-Cortical Synaptic Systems

The equations for exploitation or predator-prey interactions are represented by the following two equations:

EQ (30a) $$R_1 = A_1 - \alpha_{11}N_1 - \alpha_{12}\frac{N_2}{N_1}$$ (Prey population)

EQ (30b) $$R_2 = A_2 - \alpha_{22}N_2 + \alpha_{21}\frac{N_2}{N_1}$$ (Predatory population)

Notice that the inter-specific effect on the exploited population is determined by the same predatory/prey ratio. These two ratio-dependent equations represent, more generally, sets of

synaptic connections that are harmed by the interaction (i.e., competing with or being exploited by). In the predator/prey relationship the feedback structure is asymmetrical because one set of synaptic connections benefits while the other suffers from the association. This produces an overall negative feedback loop that has a stabilizing effect on the two synaptic connection's interaction. However, an intrinsic time-lag in the feedback loop can give rise to cyclical oscillations characteristic of many predator-prey interactions.

We can expand equations 28, 29 & 30 to explicitly include supply and demand for dendritic space as well as the supply and demand for trophic nerve growth factor as per equations 24 and 25. We can also write a general model (Berryman, 1990) for the ratio dependent equations in terms of their carrying capacities and the nonlinear coefficients of curvature, Q's such as

EQ (31) $$R_i = A_i\left[1-\left(\frac{N_i}{K_i}\right)^{Q_i}\right]-\frac{\alpha_{ij}N_j}{N_i+F}$$

where N_j and N_i represent the exploiting and exploited populations, respectively. The three types of interactions expressed by this general equation are represented in figure 7. This equation was derived by Dr. Alan Berryman and operational in his POPSYS software which is the software that I used to evaluate the non-linear dynamical models of cerebral development. [4]

FIT OF MODEL TO EEG COHERENCE TRAJECTORIES:

The POPSYS software programs provided by Alan Berryman and Jeffrey Millstein (Berryman, 1990) were used in all of the developmental analyses in this study. We used the stepwise procedure as described in the POPSYS manual (Berryman, 1990) to evaluate coherence changes in individual electrode pairs and combinations of EEG coherence developmental

[4] I am indebted to Dr. Berryman and Dr. Millstein's POPSYS software in which the basic ecological mathematical models were tested with a few key strokes. Also, Dr. Berryman's equations were easily applied to synaptic development because of his excellence as a teacher.

trajectories and to determine the best fit of the data to both the product dependent and the ratio dependent variations of the model. The first step was to evaluate the dynamics, stability and sensitivity of the population model for single cortico-cortical connection systems. In these analyses intrahemispheric EEG coherence trajectories in the theta frequency band (right hemisphere = 28 , left hemisphere = 28) were evaluated for the presence of two or more equlibria (i.e., the presence of a separatrix and basins of attraction, see EQ 22), the magnitude of time delays and the magnitude and direction of nonlinearity as measured by the coefficient of curvature. The second step was to evaluate the two population dynamics of EEG coherence developmental trajectories in short/short distance electrode pairings (e.g., F1-F7 vs F1-F3; N = 14) and short/long distance electrode pairings (e.g., F1-F3 vs F1-O1; N = 30) in both the left and right hemisphere. The goal was to evaluate the goodness of fit to the EEG coherence trajectories using the model of two populations as independent, competing, cooperating and/or in a predator-prey mode of interaction (see Fig. 7). This involved a least squares regression analysis to fit the R-function, using both the product dependent variation and the ratio-dependent variation, followed by simulation of the best fitting model using deterministic and stochastic simulations. The mode of interaction as competitive, cooperative, predator/prey or independent (i.e., no significant interaction) was determined based upon Equation 31. The type of two-population interaction each pair of EEG coherence trajectories fell into was determined by the sign of the coefficients, the R^2 and the probability values (i.e., $P < .05$). Once the category of interaction was determined (excluding the independent interactions), the dynamics of the model were further evaluated by isocline analyses in which the structure of the isoclines, the phase-space trajectories and the time-series plots were compared.

Global Characteristics: Limit Cycles and Bifurcations

The phase space trajectories were characterized by: 1- sigmoid type logistic growth or, 2- limit cycle behavior or, 3- spiral trajectories that tended to converge toward a limit cycle. Many of the trajectories could be characterized as two or more equilibria separated by an escape

threshold or separatrix. From 1.5 to 5 years of age the separatrix occurred primarily in right frontal and right fronto-temporal regions around the ages of 3 to 4 years. Between the ages of 5 to 7 years the separatrix occurred primarily in the left fronto-temporal and left fronto-parietal regions and a third group of separatrix bifurcations were seen in the right fronto-temporal regions around the ages of 9 to 11 years. Because of the complexity of the analyses, especially, when two or more separatrixes were involved, the following presentation will concern only the range from 1.5 to 5 years of age. This age range only contained, at most, one separatrix and it provides for a detailed and simplified analysis.

The fit of all of the EEG developmental trajectories were statistically significant ($P < .05$) using the single population equations. In 100% of the cases time delays at T_3 and/or T_2 yielded higher R^2 values than at a time delay of T_1. The highest R^2's at T_3 or T_2 ranged from 41.78% in F3-C3 to 99.9% in F1-F3.

Frontal Cortical Regions as Predators and Posterior Cortical Regions as Prey

The mode of interaction between EEG cortico-cortical developmental systems could be explained most frequently and with the highest amount of variance accounted for in the predator/prey mode (e.g., 37/44 = 86.05% in the left hemisphere and 21/44 = 48.5% in the right hemisphere). The next most prevalent mode of interaction was of the competitive type, although competitive interactions occurred exclusively in the right hemisphere (12/44 = 27.2% of right hemisphere pairings and 0% of left hemisphere pairings). The least frequent mode of interaction were the independent (5/44 = 11.63% of left hemisphere and 6/44 = 13.63% of right hemisphere) and cooperative modes (2/44 = 4.65% of left hemisphere pairings and 4/44 = 9.09% of right hemisphere pairings), respectively. Clear differences in the anatomical distribution of the various modes were present. In general, the predator/prey modes occurred in the anterior-to-posterior plane with frontal regions only being the predators and only the posterior cortical regions the prey. The independent and cooperative modes tended to occur in the medio-lateral

plane and the competitive modes occurred, primarily, in right local frontal and right fronto-temporal regions.

Figure 8 shows an example of actual mean EEG coherence data (A) and simulated data (B) for Fp1-P3 and O1-P3 competitive dynamics (see fig. 6). In this case the least squares regression fit of the model to the actual mean EEG coherence data had an R for P3-O1 = 97.41% and for Fp1-P3 = 94.97%. According to the model there is a continuous cycling of synaptic abundance

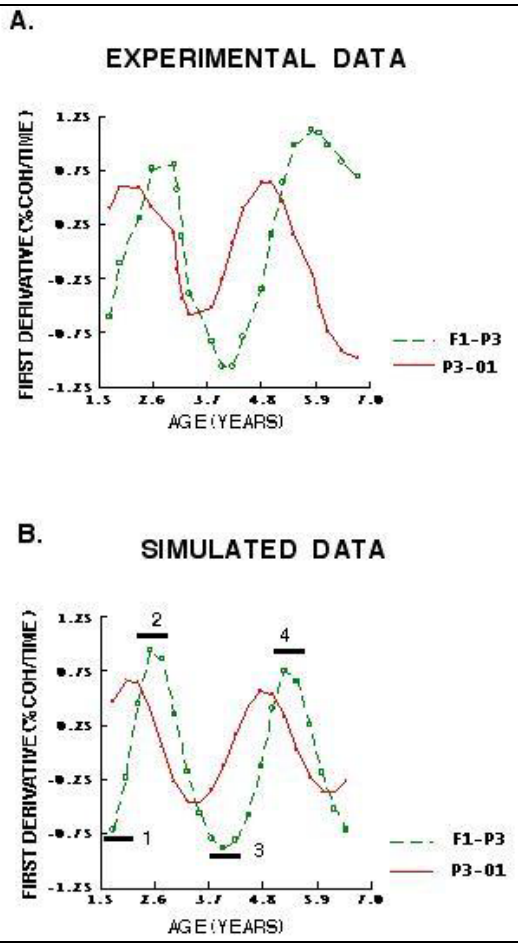

Figure 8 - Comparison of (A) actual first derivatives of mean EEG coherence from the frontal-parietal (F1P3) and parietal-occipital (P3O1) regions to (B) simulated first derivative values based upon the Predator/Prey model described by equation 31. The least squares regression fit of the model (EQ 25) to the actual mean EEG coherence data had an R^2 for P3-O1 = 97.41% and for Fp1-P3 = 94.97%. Adapted from Thatcher, 1994b.

followed by synaptic pruning in both frontal and posterior cortical regions. However, it is believed that the mechanisms of pruning are somewhat different since the frontal regions are

directly responsible for the synaptic organization and reorganization in posterior cortical regions (Thatcher, 1994b). The synaptic sequence, as diagrammed in Figure 8B is: **Stage one** at approximately 1.5 years is when long distance frontal-posterior synaptic influences are at a low while, at the same time, short distance posterior cortical synaptic influences are at a high or surplus. At this age there is minimal frontal cortical reorganization of posterior regions with previously formed frontal connections being influential; **Stage two** at approximately 2.5 years, is when short distance posterior cortical synaptic influences are on the decline while long distance frontal-posterior synaptic influences are increasing and becoming significantly more influential on posterior cortical neural networks; **Stage three** at age approximately 3.8 years, appears when long distance frontal synaptic influence and reorganization is at a maximum, however, there is a diminishing supply of "virgin" local posterior cortical synapses, thus frontal influence begins to decline and, **Stage four** at approximately 5.5 years, when long distance frontal-posterior cortical synaptic influences are on the decline, short distance posterior cortical influences are on the rise, that is, restocking the supply of posterior cortical synapses that the frontal lobes can later "replace" or "reorganize".

DISCUSSION

The results of the model simulations and regression fits to the trajectories of EEG coherence development demonstrate the feasibility of applying an ecological model of predator/prey interaction to explain the dynamics of human cerebral development. For example, in the single population analyses statistically significant regression fits ranged from 33% to 99% of the variance. The adequacy of the two population model was also established by the accuracy of the simulations and the consistency of the signs of the coefficients in which 86.36% of the total number of regression fits were statistically significant ($P < .05$), while 86.05% and 47.7% of the left and right hemispheres models, respectively, were of a predator/prey type with frontal regions always being the predator and posterior cortical regions always being the prey. Attempts

were made to reverse the signs of the coefficients and to force the posterior cortical regions to be the predator, however, the fit process always failed to converge.

Cytological Analogs of Synaptic Predation

The three primary forms of ecological interactions are cooperation, competition and predator/prey. Of these the predator/prey interactions are the most pervasive and stable, being present in a very wide range of biological situations and levels of interaction. The pervasiveness and stability of predator/prey interactions stems from the maintenance of a dynamic equilibrium through the mutual dependence of both cooperation and competition of the two interacting species. There are four types of ecological predation, each of which is equivalent when expressed in their simplest mathematical forms. *Herbivores* are animals that prey on plants or their fruits or seeds, and although the plants eaten are often not killed they may nevertheless be damaged. *Carnivores* prey on herbivores or other carnivores. *Parasitism* is a variant on predation, and involves the parasite laying eggs on or near the host which results in reduced fertility, fecundity and growth rates of the host. Finally, *cannibalism* is a form of predation involving just one species, with predator and prey often being the adults and young, respectively. It is important to note that prey death is not always necessary for predator reproduction, especially in the case of parasites and herbivores.

The adaptation of an ecological predator/prey model to cortical synaptogenesis does not require the exact specification of the predator/prey type since identical mathematical forms pertain to each of the four different categories of interaction. However, given the long time cycle times of cerebral dynamics (e.g., months and years) a somewhat gentle form of predation, similar to a herbivore or parasite would represent a more appropriate ecological model. According to this model, synaptic reorganization would involve a displacement and/or absorption of existing synapses by successfully competing synapses.

Cycles of Development: The Issue of Discontinuous Development

According to the model the frequency of oscillation in EEG coherence developmental trajectories is a function of the time delay t, the rate of growth r, the carrying capacity K and the stochastic noise or variability (V,0) (see EQ 22). The parametric evaluation of the model showed 91.3% of the time delays were 3 steps, 8.7% were two steps and 0% were only a time delay of 1 step. Three step time delays are characteristic of predator/prey interactions where there are intervening biological variables governing the predator/prey interaction. One and two step time delays are more characteristic of competitive and cooperative dynamics. An important feature of the frequency of oscillations in EEG coherence was their relative invariance within a phase period, e.g., from birth to age 7 or age 7 to 16, with sudden shifts in frequency usually occurring when there were sudden changes in the homeorhetic mean value of oscillation such as in Figure 4. Such coordinated changes in frequency and the homeorhetic mean can occur very simply by changing the carrying capacity. As specified in section IIB, carrying capacity would be most strongly influenced by changes in skull growth and/or cell packing density. It is significant that dendritic surface area is inversely related to neuronal packing density (Bok,1959; Jerison, 1973; Wright, 1934) (see Eqs 1, 2 and 3). By the age of six years there is measurable cortical neuronal cell death (Cowen et al, 1984; O'Leary, 1987) while skull volume has increased from approximately 30% at birth to approximately 90% of adult value by age 6 (Blinkov and Glezer, 1968). The postnatal loss of neurons and simultaneous increase in skull volume results in a large decrease in neuronal packing density (Rabinovicz, 1979; Blinkov and Glezer, 1968). However, neuronal packing density, and thus the cortical dendritic surface areas available for synaptogenesis, reaches an asymptote near the age of 6 years. The transition from rapid growth to asymptotic stability in which limits in synaptogenesis are at a new high, may contribute to a shift in the global equilibria of the EEG trajectories observed around the age of 5 to 7 years. A decrease in cortical packing density due to skull growth near the time of puberty may contribute to the second transition or bifurcation observed around the age of 10 to 11 years.

In general, the dynamics of intracortical development modeled in this study support modern neo-Piagetian models of cognitive development (Fischer, 1980; Fischer and Pipp, 1984;

Fischer and Farrar, 1987; Case, 1985; 1987; Pascual-Leon, 1976; van Geert, 1991). Specifically, children's thought processes proceed through time-bound cycles between birth and 16 years of age with each cycle divided into a number of subcycles and the structure of one cycle or subcycle hierarchically emerges from those of the previous cycle or subcycle (Case, 1985; 1987). While Fischer and Case differ in the exact timing of cycles and in their emphasis on the relative importance and meaning of different cycles, these two workers have done a commendable job of formulating cyclical theories of behavioral development. The data from the present study strongly supports Fischer's and Cases's theories by pointing out some of the physiological processes that may underlay the emergence of "stages" of child development. One of the most important contributions by the neo-Piagetian's, especially Fischer and Case, is their perception of "cycles" as opposed to simply "stages" of child behavioral development. A "cycle" is defined by events that repeat themselves in the same order and over approximately the same interval of time. In contrast, a "stage" is a discrete process or step. There are many examples in biology whereby cycles of growth give rise to an outward manifestation of stages. For example, organisms that construct nests or hives on a seasonal basis, often produce step like structures. It is argued in the present paper that the presence of stages in cognitive development are merely the outward manifestation of underlying cycles of brain growth and that the underlying neurophysiological gradients and cycles are the engines that drive cognitive development. Thus, human cognitive development contains both continuous and discontinuous processes. One possible source of the stages in cognitive development is the fact that different regions of the brain development at different ages. Although a cyclic process drives differential anatomical development, the outward manifestation of qualitatively different behaviors is due, in part, to the growth of different neural structures at different ages.

Bifurcations, Phase Transitions and Punctuated Equilibria

The dynamics of the bifurcations or phase transitions are similar to those observed in competitive nonlinear oscillator systems in which opposing forces imperceptibly build up until a

sudden differentiation or bifurcation occurs (Thom, 1975). The sudden changes in mean EEG coherence observed at 3 to 4 years (see Thatcher, 1992b), 5 to 7 years and 9 to 11 years satisfy many of Gilmore's catastrophy flags (Gilmore, 1981) and exhibit characteristics of a "fold" or "cusp" catastrophy (Thom, 1975; van der Maas and Molenaar, 1992). A clear example of a cusp catastrophy is seen in figure 4, in which the P3-F7 EEG coherence trajectory exhibits a fold and sudden jump between 5 and 7 years. The Gilmore (1981) catastrophy flags of "modality", "sudden jump", "hysteresis" and "frequency shifts" were present in many of the EEG coherence developmental trajectories. The presence of a bifurcation or catastrophy suggests that the underlying dynamics can be modeled by gradient systems and vector fields of the form $\mathbf{x} = -U(x)$ for $\mathbf{x}$ in R^k in which competition and cooperation between forces are responsible for the dynamics and the stable equilibria (Gilmore, 1981; Thompson and Stewart, 1986). The presence of formal catastrophy dynamics is also important for modeling "schemata" development using the ideas and notation of Rumelhart and colleagues (Rumelhart et al, 1986).

Functional Interpretation of Frontal Lobe Synaptic Competition and Predation

What is the functional significance of the frontal regions being exclusively the predators and fierce competitors in the dynamic cycle of synaptic surplus followed by synaptic pruning? One interpretation is that the frontal regions control or significantly influence the pruning phase of the synaptic development of posterior cortical regions. That is, frontal synaptic influence significantly determines which synapses will survive and which will be lost during the developmental sculpting process. A hierarchical integration of cortical resources periodically occurs forming a frontal lobe mediated spiral of ever cascading competencies. This process is nonlinear in both space and time and is manifested behaviorally by relatively sudden changes in cognitive competence. The appearance of discontinuous development is often characterized as "sensitive periods" or "growth spurts" (Cicchetti, 1990; 1993; Fischer, 1983). According to the

present model, "sensitive periods" reflect the nonlinear manifestation of a underlying and continuous growth process (Thatcher et al, 1992a; 1992b; 1994a).

Genetic versus Environmental Influences

As defined earlier, the positive first derivatives of mean EEG coherence change were defined as reflecting the synaptic surplus phase while the negative first derivative was defined as reflecting the synaptic pruning phase (Thatcher, 1992a; 1993; 1994a). One would expect that genetic factors would have a strong influence on the synaptic surplus phase and that environmental factors would have a strong influence on the synaptic pruning phase. That is, genetics has the less variable task of turning genes on and off, while the environment and the demands placed on the individual are highly variable and complex. It follows that because the individuals in these studies lived in diverse environments one would expect greater variance in the first derivative of EEG coherence during the pruning phase than during the surplus phase. Figure 9 shows two examples of the relationship between the variance of the first derivative of mean EEG coherence versus the actual first derivatives of mean EEG coherence. A 180^0 phase reversal is strongly present in which variance is greatest during the negative first derivatives or the synaptic pruning phases, while it is small during the positive first derivatives or the synaptic surplus phases. High EEG coherence variance of the negative first derivative is precisely what is expected if environmental factors dominate the pruning phase, while genetic factors dominate the surplus phase.

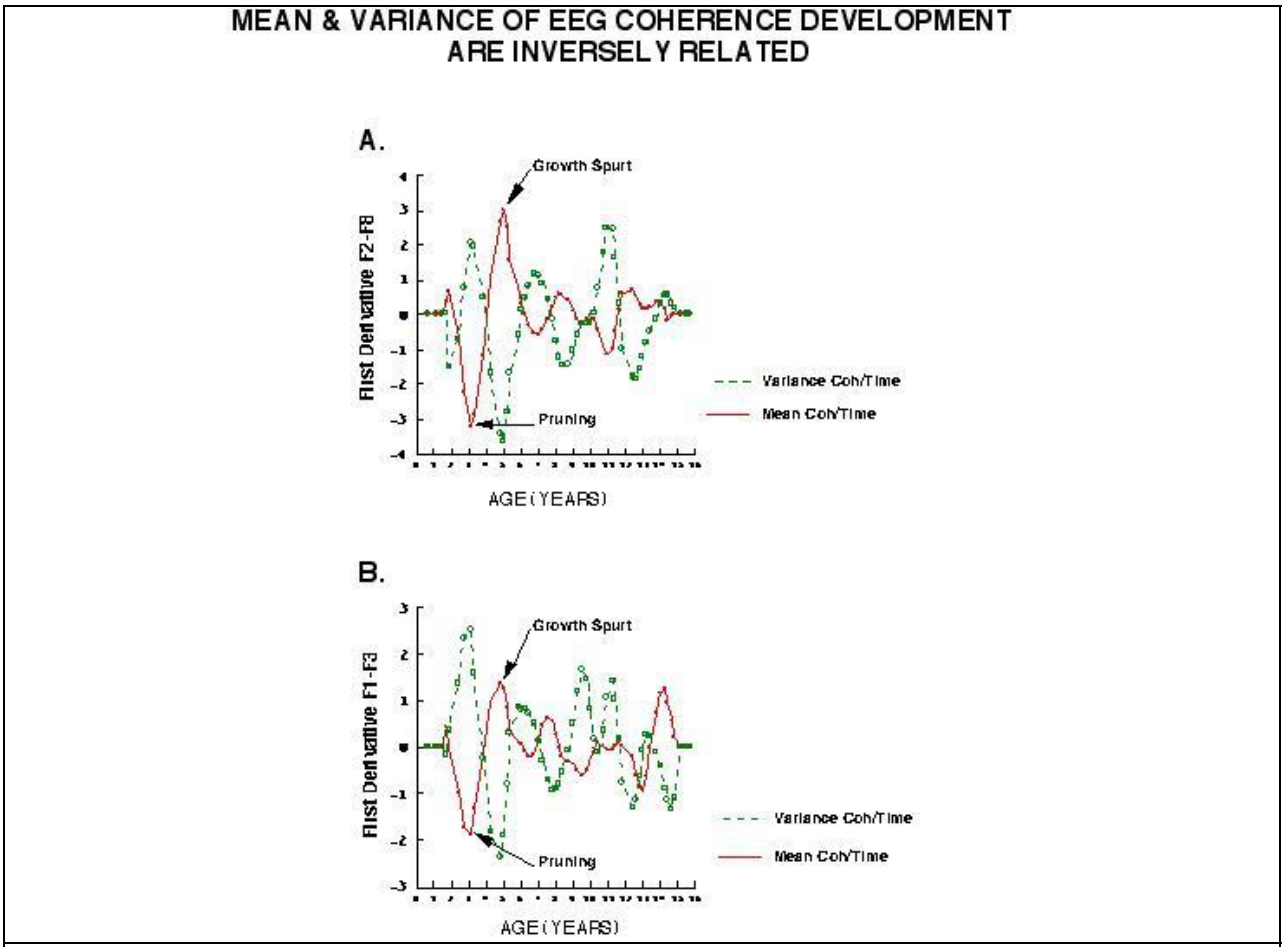

Figure 9 - The first derivatives of the mean and variance of EEG coherence from male children for two different cortical regions (A = F2F8, and B = F1F3). A 180^0 phase reversal is strongly present in which variance is greatest during the negative first derivatives or the synaptic pruning phases while it is small during the postive first derivatives or the synaptic surplus phases. Adapted from Thatcher, 1994b.

Figure 9B illustrates the proposed cycle of synaptic surplus followed by synaptic pruning in which the pruning phase is strongly influenced by the frontal lobes according to the model in figure 6 (i.e., the F1-P3 and O1-P3 model). Both frontal and posterior cortical regions exhibit cycles of synaptic surplus followed by synaptic pruning; however, the frontal regions directly displace or remove posterior cortical synapses whereas the posterior cortical regions do not displace the frontal synapses. Instead, the growth of frontal synapses is dependent upon the presence of posterior cortical synapses. Thus, when there is a reduced supply of posterior cortical synapses, then frontal synaptic influences decline and vice versa. The posterior cortical synaptic surplus phase is a type of "re-stocking" of the supply of posterior cortical synapses that

the frontal lobes can subsequently "replace" or "reorganize" based upon environmental exigencies.

Neural Plasticity, Sensitive Periods and Psychopathology

The cyclic reorganization model of human brain development explicitly integrates neural plasticity with sensitive periods. That is, each cycle of synaptic surplus followed by pruning represents a "sensitive period" in anatomically localized and interconnected brain regions. Thus, sensitive periods are continually occurring since they are driven by a diffusion wave of anatomically circulating nerve growth factor. A staging or discontinuous aspect of this process arises because of inherent nonlinearities in both space and time. Spatially the nonlinearities arise because of the segregation of differentiated function in distributed ensembles of neurons. The functionally differentiated anatomy of the brain guarantees spatial nonlinearities as the wave of growth hormone sweeps across domains of cells. Thus, stages or "sensitive periods" are present because functionally differentiated regions of the brain develop at different ages. A stage-plateau sequence in cognitive development is an outward manifestation of both the continuous and discontinuous aspects of the process. Each stage or period represents rapid synaptic growth within functionally differentiated neural systems and, as a consequence, neural plasticity involves the genetically driven over production of synapses and the environmentally driven maintenance and pruning of synaptic connections. As emphasized in previous sections, it is predicted that the subcortical synaptic drives upon the frontal lobe as well as cortico-cortical connections with the frontal lobes along plays a crucial role in development, especially in the process of synaptic pruning and synaptic selection.

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