Development and Psychopathology, 6 (1994), 565–596

Psychopathology of early frontal lobe damage: Dependence on cycles of development

ROBERT W. THATCHER
Veterans Administration Medical Center, and Departments of Neurology and Radiology, University of South Florida College of Medicine

Abstract
A new theory of frontal lobe development is presented in which the role of the human frontal lobes during normal development and the psychopathological consequences of early frontal lobe injury are explored. Analyses of the development of human electroencephalograph (EEG) coherence indicate that there are oscillations and cyclic growth processes along the mediolateral and anterior–posterior planes of the brain. The cycles of EEG coherence are interpreted as repetitive sequences of increasing and decreasing synaptic effectiveness that reflects a convergence process that narrows the disparity between structure and function by slowly sculpting and reshaping the brain's microanatomy. This process is modeled as a developmental spiral staircase in which brain structures are periodically revisited resulting in stepwise increases in differentiation and integration. The frontal lobes play a crucial role because they are largely responsible for the selection and pruning of synaptic contacts throughout the postnatal period. A mathematical model of cycles of synaptic effectiveness is presented in which the frontal lobes behave as gentle synaptic "predators" whereas posterior cortical regions behave as synaptic "prey" in a periodic reorganization process. The psychopathological consequences of early frontal lobe damage are discussed in the context of this model.

The field of developmental psychopathology is rapidly evolving and encompassing an ever wider understanding of both normal and abnormal development. Recently, Cicchetti (1993) emphasized that

> . . . developmental psychopathologists must be cognizant of normal pathways of development, discover deviations from these pathways, articulate the developmental transformations that occur as individuals progress through these deviant ontogenetic courses, and identify the factors and mechanisms that may deflect an individual out of a particular pathway. . . . (p. 474)

This perspective is reinforced by many developmental psychologists and biologists (Cicchetti, 1990; Sroufe & Rutter, 1984; Weiss, 1961, 1969; Zigler & Glick, 1986) who have emphasized organizational principals of development. According to this view, organizational principals provide a guiding theoretical orientation in which processes such as differentiation, hierarchical integration, and reorganization within and between behavioral and biological systems occur. One dynamic aspect of the organizational perspective is that individuals are shaped by both genetic and environmental factors whereby stage-salient unfolding

I am indebted to Dr. William Hudspeth for his readings and comments on the manuscript as well as to Ms. Rebecca A. Walker for her assistance in the typing and construction of the paper. I also am especially indebted to Dr. Dante Cicchetti for his comments and suggestions. This article was supported by a grant from the Henry M. Jackson Foundation No. JFC36285006. R. W. Thatcher, Principal Investigator.

Address correspondence and reprint requests to: Robert W. Thatcher, Ph.D., Neurology Service—151, Veterans Administration Medical Center, Bay Pines, FL 33504.

of biological capacities dynamically interact with environmental factors to direct and redirect the course of development (Cicchetti, 1993).

Another important aspect of the organizational perspective is the role and mechanisms of "sensitive periods" defined as windows of time during which environmental influences on development are enhanced (Bornstein, 1987, 1989; Greenough, Black, & Wallace, 1987). A "cyclic reorganization" theory of development was recently presented in which "sensitive periods" periodically and iteratively reoccur and development is described as a spiral staircase of ever increasing differentiation and integration (Thatcher, 1992b, 1994). The latter theory is based on computerized electroencephalograph (EEG) data from 436 children ranging in mean age from 6 months to 16 years. This theory postulates that during human development there are 2–4-year growth-spurt cycles in which each cycle is characterized by the production of a surplus of synaptic connections followed by a selective pruning of connections. In the left hemisphere, the cycles are composed of a developmental sequence governed by anterior–posterior and mediolateral gradients involving a sequential lengthening of intracortical connections between posterior sensory areas and frontal regions. The right hemisphere, in contrast, involves a sequential contraction of long-distance frontal connections to shorter distance posterior sensory connections. It is postulated that the left hemisphere expanding sequence reflects a process of functional integration of differentiated subsystems while the right hemisphere contracting sequence is a process of functional differentiation of previously integrated subsystems. These left and right hemisphere cycles are repeated throughout the life span and are believed to represent a process that iteratively narrows the gap between structure and function by slowly sculpting and refining the microanatomy of the brain.

In the present article, a new theory will be posited, in which the role of the human frontal lobes during development and the psychopathological consequences of frontal lobe injury will be explored. Special emphasis will be placed on the phenomena of frontal prepotency and delayed clinical expression following frontal lobe damage. These aspects of frontal lobe damage will be explained by the crucial role of the frontal lobes in the organization of spatiotemporal gradients that operate during postnatal development. The organizational aspect of the theory stems from the postulate that there is a commonality of gradients that operate over different time scales, from eons of phylogenetic and embryological time, to a period of years of the human life span, to a period of a few hundred milliseconds during conscious awareness (Thatcher & John, 1977). Interference with the normal operations of these gradients and cycles will have different psychopathological consequences depending on the phase of the cycles and the location and magnitude of brain injury.

Clinical Spatial Prepotency: An Example of a Spatial Hierarchy

A remarkable feature of childhood frontal lobe damage is that the earlier the age when frontal lobe damage occurs then the worse the long-term behavioral consequences (Kolb, 1989). This is contrary to the so-called Kennard effect, in which early childhood lesions have less severe effects on behavior than similar lesions occurring in adulthood (Finger & Wolf, 1988; Kennard, 1936). Another interesting observation is that the amount of tissue damaged is less important than the location of the damage. For example, studies by Kolb and colleagues (Kolb, 1984, 1989; Kolb & Whishaw, 1989) have shown that early hemidecortication of rats has less severe behavioral consequences at adulthood than bilateral frontal damage even though the amount of brain damage was less in the frontal lobe preparations. Human beings show a similar early childhood effect of frontal damage, when compared to other regions of the cerebral cortex (Ackerly, 1964; Ackerly & Benton, 1947). Studies by Grattan and Eslinger

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

(1991, 1992) and Eslinger, Grattan, Damasio, and Damasio (1992) review the consequences of early childhood frontal lobe damage on subsequent adolescent and adult development. In comparison to that of adults, childhood frontal lobe damage produces a more pervasive impairment, including "a persistent pattern of deficient decision making, hallmarked by capricious social and vocational judgment, rigidity, impulsivity, interpersonal conflict, and little ability to synthesize the lessons of experience" (Eslinger et al., 1992, p. 768). In the present paper, this aspect of early frontal lobe psychopathology will be explained by the crucial role of the frontal lobes in the selective elimination and reorganization of corticocortical connection systems.

Clinical Delays: An Example of a Temporal Hierarchy

In addition to the spatial prepotency of childhood frontal lobe injury in comparison to other cortical regions, there also are reports of a delayed onset of behavioral disorders following frontal lobe damage (Grattan & Eslinger, 1992). The speculations of Feinberg (1982) that schizophrenia and other emerging developmental disorders are due to a failure of cell death or synaptic loss suggests that delayed onset of mental and developmental disorders also are possible sequelae of early frontal lobe damage. However, it is unclear whether there is a true "delayed" onset of specific disabilities or simply a progressive disparity between expected and actual social and cognitive functioning that becomes increasingly evident over time as societal demands increase (Eslinger et al., 1992). A method of resolving this issue comes from recent studies that indicate that delayed onset of dysfunction is related to the arrest or slowing of neural maturation processes involved in modifications of frontal cortical connections during postnatal development (Blinkov & Glezer, 1968; Hudspeth & Pribram, 1990, 1991; Huttenlocher, 1984; Rabinovicz, 1979; Schade & Groeningen, 1961; Thatcher, 1991, 1992a, 1992b, 1994; Thatcher, Walker, & Giudice, 1987). In the present paper, this aspect of frontal damage will be explained by the operation of a spatial gradient that is involved in both embryological and ontogenetic development (Thatcher, 1992b, 1994).

Spatiotemporal Growth Gradients

A new view of the functional organization of the cerebral cortex is emerging from electrophysiological and magnetoencephalographic studies (Linas & Ribary, 1992; Thatcher, Toro, Pflieger, & Hallett, 1993; Thatcher, Wang, Toro, & Hallett, 1994). Whereas earlier studies tended to emphasize the functions of individual neurons in isolated cortical regions, current views of the functional organization of the cortex are focusing on the dynamics of distributed network processing in which the allocation of resources occurs through the rapid spatiotemporal self-organization of coherent regions of neural activity (Eckhorn et al., 1988; Gray, Konig, Engel, & Singer, 1989; John, 1963; Thatcher & John, 1977). Recent EEG and magnetoencephalography studies indicate that the rules that govern the self-organizational properties of the cortex involve traveling waves of neural activity. For example, Linas and Ribary (1992) recently showed a cyclic anterior–posterior traveling wave of coherent 40-Hz activity that is in continuous motion along mediolateral and anterior–posterior cortical directions. Other examples of mammalian traveling waves of coherent neural activity exhibiting specific preferred pathways have been noted in a wide number of studies (Gorbach et al., 1989; Lilly & Cherry, 1954, 1955; Nunez, 1981; Thatcher & John, 1977; Verzeano, 1972; Verzeano & Negishi, 1960, 1961). One of the notable aspects of these studies is that the traveling waves behave in an orderly fashion and exhibit specific spatial directions and velocities. The most commonly observed spatial directions are along the mediolateral and anterior–posterior anatomical axes of the cerebral cortex.

Goals of This Article

The goal of the present paper is to explore and theorize about the possible psychopathological importance of spatiotemporal gradients of human frontal lobe postnatal development. I first review the studies that establish the anatomical and neurophysiological presence of these gradients and then postulate a special role for the frontal lobes in postnatal synaptic pruning in which environmental influences and individual needs determine which synaptic connections will be stabilized. Next, the mechanisms for selective synaptic pruning and cortical stabilization by the frontal lobes are explored in an ecological neural network model in which the frontal lobes reorganize posterior cortical regions in a manner similar to "predators" in a predator–prey dynamic. Then I examine the fit of this model to EEG coherence data to help integrate and predict the meaning of the spatiotemporal gradients. Finally, based on this integration, I speculate on the behavioral and clinical consequences of early childhood frontal lobe damage.

Spatiotemporal Gradients in the Phylogenetic, Embryological, and Ontogenetic Development of the Frontal Lobes

Human beings are distinguished from nonhuman primates not only by the phylogenetic recency and size of the frontal lobes but also by the temporal sequence and patterning of its development (Carpenter & Sutin, 1983; Sanides, 1971). In fact, one of the most intriguing aspects of frontal lobe development are the parallels among its phylogenetic, embryological, and ontogenetic sequences of development (Thatcher, 1992b, 1994). An especially intriguing parallel is the presence of mediolateral and anterior–posterior gradients that spatially guide the phylogenetic, embryological, and ontogenetic development of the frontal lobes (Bayer & Altman, 1991; Carpenter & Sutin, 1983; Smart, 1983; Thatcher, 1992b, 1994). Intrinsic to the spatial gradients is a shared temporal gradient in which lateral cortex develops before medial cortex and frontal cortex develops before posterior cortex (Bayer & Altman, 1991; Carpenter & Sutin, 1983; Smart, 1983). Although these gradients have been observed in the EEG during the performance of cognitive tasks for many years (Lilly & Cherry, 1954, 1955; Linas & Ribary, 1992; Nunez, 1981; Rogers et al., 1991; Verzeano, 1972; Verzeano & Negishi, 1960, 1961), only recently have these same spatial gradients been observed in the ontogenesis of the human EEG (Hudspeth & Pribram, 1990, 1991; Thatcher, 1991, 1992b, 1994; Thatcher et al., 1987).

Spatiotemporal Gradients During Prenatal Brain Development

One of the wonders of human development is the process by which a few initial germinal cells so quickly develop into the human brain, which consists of over 100 billion neurons. Given the large number of neurons that comprise the infant brain, it has been estimated that during utero neurons are developing at a rate of over 250,000 neurons per minute (Cowan, 1979). This process is made even more remarkable by the fact that each germinal neuron must not only migrate to its terminal destination but also ultimately become connected to approximately 5,000–15,000 other neurons (Cragg, 1975). Recent research has shown that the development of the cortex in any mammalian species occurs in distinct sequences (Cowan, 1979; Rakic, 1985). The sequence is cell proliferation → cell migration → cell differentiation → dendritic and axonal growth → neuronal and synaptic death. Once the germinal cells migrate to their terminal location in the cortex, they next develop the characteristics of the cell type that they are to be (e.g., stellate or pyramidal), and then they begin to grow their dendrites and axons and form synapses. Detailed studies of brain development have shown that in most altricial mammals such as rat, cat, monkey, and humans, the stages of cell proliferation and migration are largely prenatal while much of the develop-

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

ment of the neuropil (i.e., axons and dendrites) and synaptic death occur during the postnatal period (Kolb, 1989).

Spatial Gradients of Prenatal Development

The appearance of prenatal spatial gradients of development are also remarkable (Diamond, Scheibel, & Elson, 1985). For example, shortly after conception a ball of cells grows symmetrically without a clear left or right or an anterior or posterior plane. However, at the first differentiation, spatial polarization occurs in which a disk with an anterior and posterior end and a medial and lateral plane appear. The inner layer (i.e., the endoderm) differentiates to form the skeleton and gut, while the outer layer of the disk (i.e., the ectoderm) differentiates to form the neural plate from which the entire nervous system develops. Shortly after the formation of the neural plate (e.g., about 16 days postconception), an indentation appears along the midline, which grows into a fold that becomes the neural groove. The neural groove becomes a hollow tube with the inside of the anterior end of the tube eventually becoming the forebrain ventricles and the middle and posterior ends becoming the spinal canal. The neural tube begins to close to form a roof in the center of the embryonic disc. Then, like two zippers moving in opposite directions, the roofing process continues in both an anterior and posterior direction (Diamond et al., 1985). This process represents one of the first examples of the two dominant prenatal spatial gradients, that is, the embryonic anterior–posterior and mediolateral gradients.

Cycles of Prenatal Development

The emergence of one of the first "cyclic" processes that is embedded in the anterior–posterior and mediolateral gradients begins at approximately 23 days postconception. The cycle is illustrated in Figure 1, where the germinal neuroepithelia (A) of the neural tube lies between the lumen (F) and the outer limiting membrane (E^1). At about 23 days postconception, a cyclic spatial growth process occurs in which the neuroepithelial cells alternate in activity between cell division or mitosis (A^1) and synthesis of the genetic material DNA (A^2). The spatial cycle is where the neuroepithelial cell near the lumen divides → the nucleus of each newly formed daughter cell moves laterally away from the lumen of the neural tube toward the outer limiting membrane → the nucleus then undergoes DNA synthesis or generation → the nucleus moves medially back toward the lumen and, to repeat the cycle, then the cell becomes mitotic again (Diamond et al., 1985). The cycle time of this spatial process is approximately 4–24 hours per cycle, and the process continues over a period of days until a large compliment of neuroepithelial cells are produced after which differentiation of the neuroepithelial cells to neuroblasts (G) begins. The neuroblasts migrate laterally away from the lumen to form a new, outer mantle layer (C), which becomes the gray matter of the brain and spinal cord. As the neuroblasts differentiate into mature neurons, their axons form the marginal layer (D), which becomes the white matter of the brain and spinal cord. As with the earlier stages of embryogenesis, the precise timing of the development and migration of cells to different cortical regions occurs along mediolateral and anterior–posterior spatial gradients. Figure 2 shows the standard neuroanatomy textbook view of early human embryogenesis in which migration to the frontal and lateral cortical regions occurs before migration to the medial and posterior cortical areas. Detailed analysis of the operation of the anterior–posterior and mediolateral spatial gradients have also been provided for the embryogenesis of the mouse (Smart, 1983) and rat (Bayer & Altman, 1991) brains. All mammalian species appear to exhibit dominant embryological brain development gradients along the anterior–posterior and mediolateral spatial planes.

Because the embryological sequence of neural development depends on cell migration occurring first, it must be the case that the sequence of synapse formation followed

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

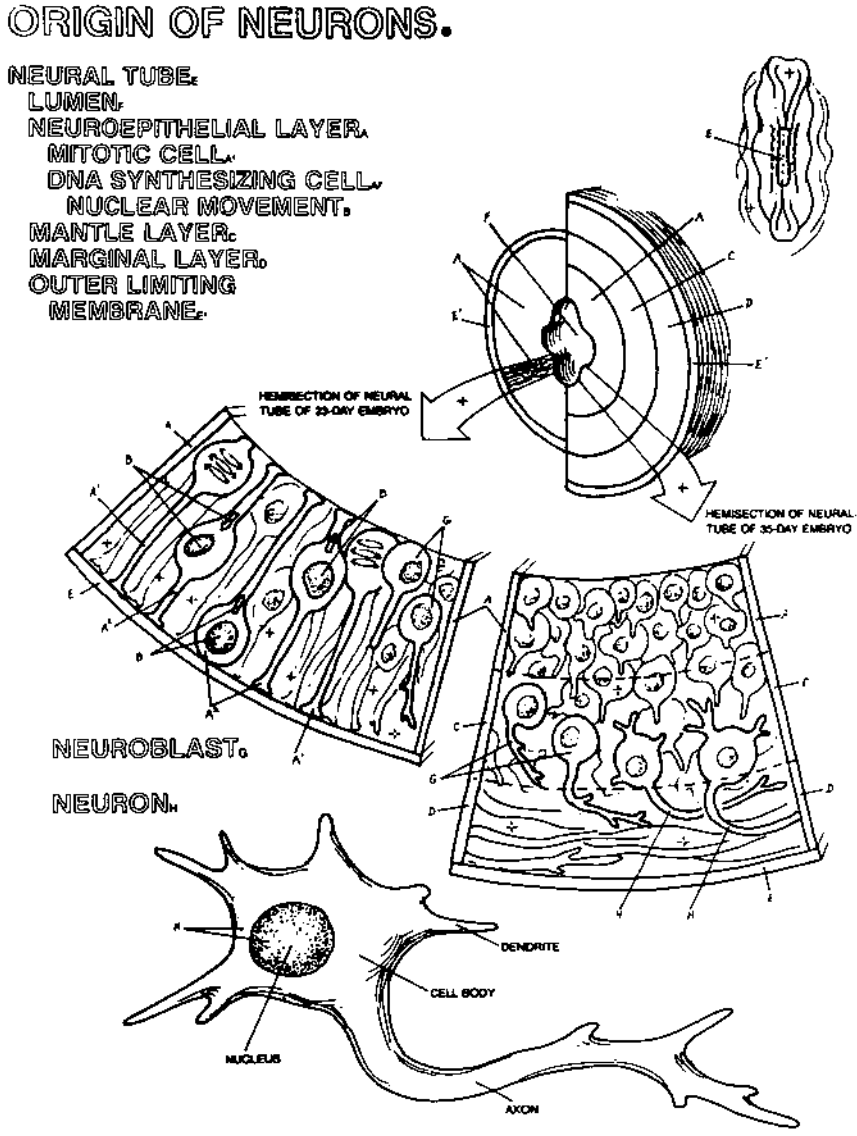


Figure 1. Diagram of a cross-section of the human neural tube of a 23-day and 35-day embryo. Middle left is a hemisection of the neural tube at 23 days, and middle right is a hemisection of the neural tube at 35 days. The emergence of one of the first "cyclic" processes that is embedded in the anterior–posterior and mediolateral gradients is illustrated where the germinal neuroepithelia (A) of the neural tube lies between the lumen (F) and the outer limiting membrane (E^1). At about 23 days postconception, a cyclic spatial growth process occurs in which the neuroepithelial cells alternate in activity between cell division or mitosis (A^1) and synthesis of the genetic material DNA (A^2). The spatial cycle is where the neuroepithelial cell near the lumen divides → the nucleus of each newly formed daughter cell moves laterally away from the lumen of the neural tube toward the outer limiting membrane → the nucleus then undergoes DNA synthesis or generation → the nucleus moves medially back toward the lumen and then repeats the cycle every 4–24 hours. From *The Human Brain Coloring Book* (pp. 3–4) by M. C. Diamond, A. B. Scheibel, and L. M. Elson, 1985, New York: Barnes & Noble.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

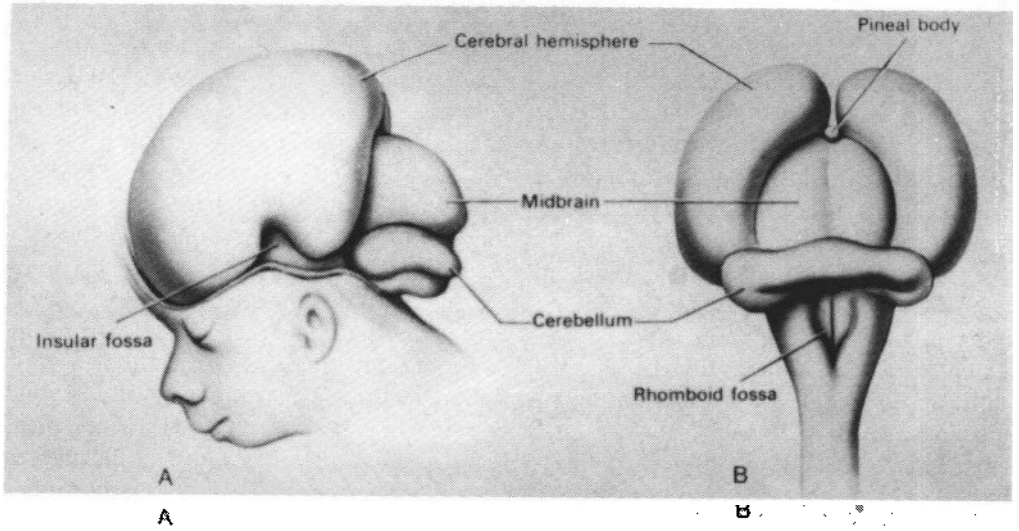


Figure 2. Drawings of the cerebral vesicle and brain stem in a 12-week fetus. (A) Lateral view. (B) Posterior view. From *Human Neuroanatomy* (p. 79) by M. B. Carpenter and J. Sutin, 1983, Baltimore, MD: Williams & Wilkins.

by synaptic death is also influenced by anterior–posterior and mediolateral spatial gradients. Therefore, it is reasonable to suggest that the recent findings of a postnatal overproduction of synapses followed by pruning of synapses (Huttenlocher, 1984, 1990; O'Leary, 1987; O'Leary, Stanfield, & Cowan, 1981) also follows anterior–posterior and mediolateral spatial gradients. This is important given the magnitude of these postnatal processes in which there is an overproduction of synapses by as much as a factor of 2 (Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986) with as much as 50% of the early synapses lost by adulthood (Huttenlocher, 1990). The importance of this process is underlined by suggestions that a failure of postnatal cell death or synaptic loss may lead to retardation (Kolb, 1989) or the emergence of other developmental disorders such as schizophrenia (Feinberg, 1982).

Spatiotemporal Gradients of Postnatal Brain Development

Because of the expense and difficulty of human anatomical studies, there is a paucity of detailed anatomical information about synaptic overproduction and pruning during human postnatal development. What work has been done has been accomplished largely by Huttenlocher and colleagues (Huttenlocher, 1979; Huttenlocher & de Courten, 1987; Huttenlocher, de Courten, Garey, & Van der Loos, 1982). These workers primarily studied the human visual and frontal cortex, although the age range and the sample sizes are limited. Their data show age-dependent discontinuities in synaptic density in which high synaptic densities are achieved at approximately 1 and 7 years for visual and frontal cortex, respectively. At these ages, synaptic density is about twice that for adults. Unfortunately, the human neuroanatomical data is too sparse to observe mediolateral and anterior–posterior gradients of synaptic development.

In contrast to anatomical experiments, computerized EEG analyses of the development of the human cortex are noninvasive and less expensive, thus allowing for the use of large sample sizes and analyses over the entire human life span (Hudspeth & Pribram, 1991; Matousek & Petersen, 1973; Thatcher et al., 1987). These studies clearly show cyclic patterns of cortical development in which the different regions of the cortex develop at different rates and ages.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

In the Thatcher et al. (1987) study, there were many examples of rapid and significant increments in EEG coherence that were characterized as growth spurts, and the time and sequencing of the growth spurts exhibited a striking similarity to the timing and sequencing of power peaks in the Matousek and Petersen (1973) EEG data as analyzed by a number of people including Epstein (1980), Thatcher (1980), Fischer (1987), and Hudspeth and Pribram (1990, 1991). A number of the authors of the EEG power studies speculated about the temporal relationship between the EEG growth spurts and the Piaget stages of development (Fischer, 1987; Hudspeth & Pribram, 1990, 1991). Analyses of EEG coherence and phase have an advantage over power analyses because coherence is sensitive to the magnitude and existence of corticocortical connections (Lopes da Silva, Pijn, & Boeijinga, 1989; Nunez, 1981; Pascual-Marqui, Valdes-Sosa, & Alvarez-Amador, 1988; Thatcher, Krause, & Hrybyk, 1986; Tucker, Roth, & Blair, 1986). Although EEG relative power also exhibits spatiotemporal gradients, in the section to follow we will only discuss the details of the development of human EEG coherence.

Corticocortical Connections and EEG Coherence

The Thatcher (1992b, 1994) studies used measures of EEG coherence to estimate changes in the maturation of corticocortical connections; accordingly, a brief introduction to the mathematical and neurophysiological foundations of EEG coherence is necessary to provide a basis by which the conclusions of these studies can be understood. 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 (Bendat & Peirsol, 1980; Glaser & Ruchkin, 1976; Otnes & Enochson, 1972). The application of coherence measures to the human scalp EEG have shown that EEG coherence reflects the coupling between neocortical neurons (Lopes da Silva et al., 1989, 1991; Nunez, 1981, 1989; Thatcher, McAlaster, Lester, Horst, & Cantor, 1983; Tucker et al., 1986). Recently, a "two-compartmental" model of EEG coherence was developed (Pascual-Marqui et al., 1988; Thatcher et al., 1986) based on 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 that represent the majority of white matter fibers. These two systems exhibit two different network properties. System B, due to reciprocal connections and invariant apical dendrite terminations, is involved in long-distance feedback or loop systems. In contrast, 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 (Braitenberg, 1978; Pascual-Marqui et al., 1988; Thatcher et al., 1986).

The following mathematical equation was developed to describe the magnitude and slope of decline of human EEG coherence with interelectrode distance (Pascual-Marqui et al., 1988; Thatcher et al., 1986):

$$\text{coherence} = A_i e^{-kd} + B_i e^{kd} \sin kd, \quad (1)$$

where A_i, B_i, and k are functions of frequency, and d is scalp interelectrode distance in centimeters. The first term on the right side of Equation 1 corresponds to the operation of the A system while the second term corresponds to the operation of the B system.

While the moment-to-moment changes in EEG coherence with interelectrode distance can be understood by Equation 1, changes in the development of coherence

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

over long spans of time (i.e., months and years) requires additional consideration. One consideration is that developmental changes in EEG coherence in a large group of subjects reflects changes in the mean coupling constants 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: (a) the number of corticocortical connections between neural assembles, and (b) the synaptic strength of connections between neural assemblies (the terms *corticocortical connections* and *intracortical connections* are considered synonymous). This relationship is described in Equation 2:

$$\text{coherence} = (C_{ij} \times S_{ij}), \qquad (2)$$

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. Equation 2 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 (Pascual-Marqui et al., 1988; Thatcher et al., 1986, 1987). For example, 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. The neurophysiological mechanisms responsible for the changes in the numbers or strengths of connections include 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; Huttenlocher, 1984). Currently, measures of EEG coherence cannot discern among these various possibilities.

Cycles of Postnatal Development

In the Thatcher et al. (1987) and Thatcher (1992b, 1994) studies, growth spurts were defined by peaks of velocity in mean EEG coherence or those postnatal ages where there was a maximum increase in mean coherence as measured by the first derivative. 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 described in Thatcher (1992b, 1994), only positive first derivative values were counted as growth spurts. This was decided based on the fact that postnatal synaptogenesis often involves a sequence of overproduction of synapses followed by a pruning of synapses (Cowan, 1979; Huttenlocher, 1984, 1990; O'Leary, 1987; O'Leary et al., 1981; Rakic et al., 1986). Accordingly, the positive first derivative peaks are expected to correspond to the overproduction phase while the negative peaks are expected to correspond to the pruning phase.

Figure 3 shows the first derivatives or velocity curves of mean EEG coherence from subgroupings of electrode pairs from the Thatcher (1991, 1992b, 1994) studies. The postnatal ages of the positive first derivatives are indicated by the arrows.

Figure 4 is a summary of the ages and durations of peak first derivatives in mean EEG coherence that were shown in Figure 3. An iterative and sequential anatomical pattern of growth spurts 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., 18–24-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

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

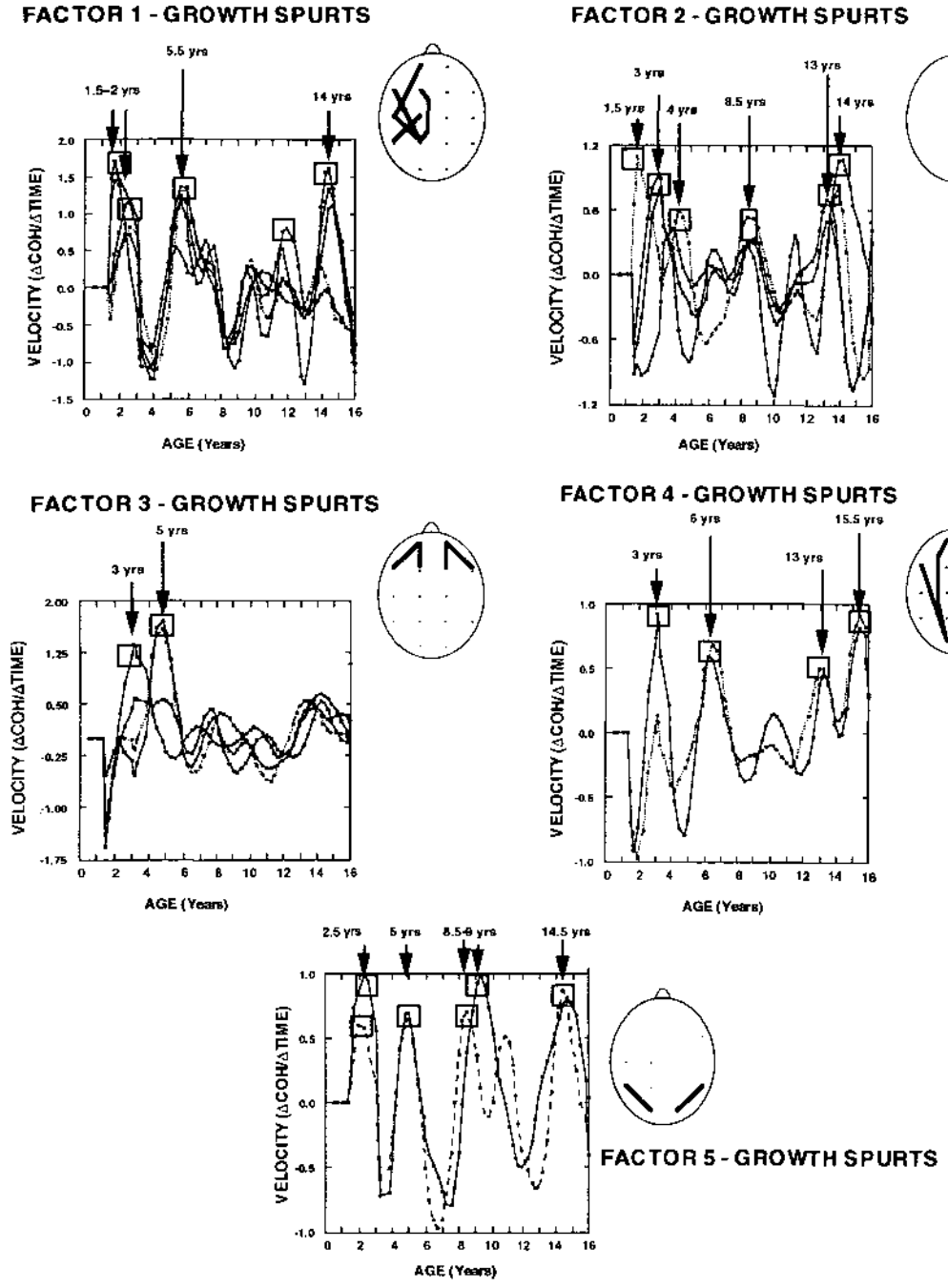


Figure 3. Velocity curves or the first derivatives (mean coherence/time) of the developmental trajectories of mean electroencephalograph coherence from the subgroupings of electrode pairs that had the highest factor loadings (e.g., > .80) (Thatcher, 1991). Growth spurts were defined by a positive peak in the first derivative (i.e., a postnatal time of maximum growth) in multiple interelectrode combinations. From "Cyclic Cortical Reorganization: Origins of Cognitive Development" by R. W. Thatcher, in *Human Behavior and the Developing Brain* (p. 237), edited by G. Dawson and K. Fischer, 1994, New York: Guilford Publications. Copyright 1994 by The Guilford Press. Reprinted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

between 1.5 and 3 years was repeated again between ages 5.5 and 6.5 years and finally again between 14.5 and 15.5 years and is referred to as microcycles of cortical development.

Anatomical Poles of Development

Anatomical poles are defined by one or more of the following factors: (a) they are the dominant spatial dimensions or anatomical axes of EEG coherence development, (b) they exhibit developmental organizing properties, and (c) they exhibit spatial gradients. The dominant patterns of the developmental trajectories of EEG coherence over the period from 1.5 to 16 years indicate three "poles" of development from which there are gradients or organizational structure. The poles are anterior–posterior, mediolateral, and, left–right hemisphere.

Postnatal Anterior–Posterior Gradients of Development

An anterior–posterior pole of development was evident by (a) a frontal-to-posterior dominance of corticocortical relations in both the left and right hemispheres (Thatcher, 1991; Thatcher et al., 1987) and (b) a developmental sequence from short-distance anterior–posterior interelectrode combinations (e.g., P3-T3 or T5-C3) to longer distance anterior–posterior electrode combinations (e.g., P3-F7 or P3-F1) to even longer anterior–posterior electrode combinations (e.g., O1-F1). An example of the anterior–posterior pole of EEG coherence development is shown in Figure 5.

Postnatal Mediolateral Gradients of Development

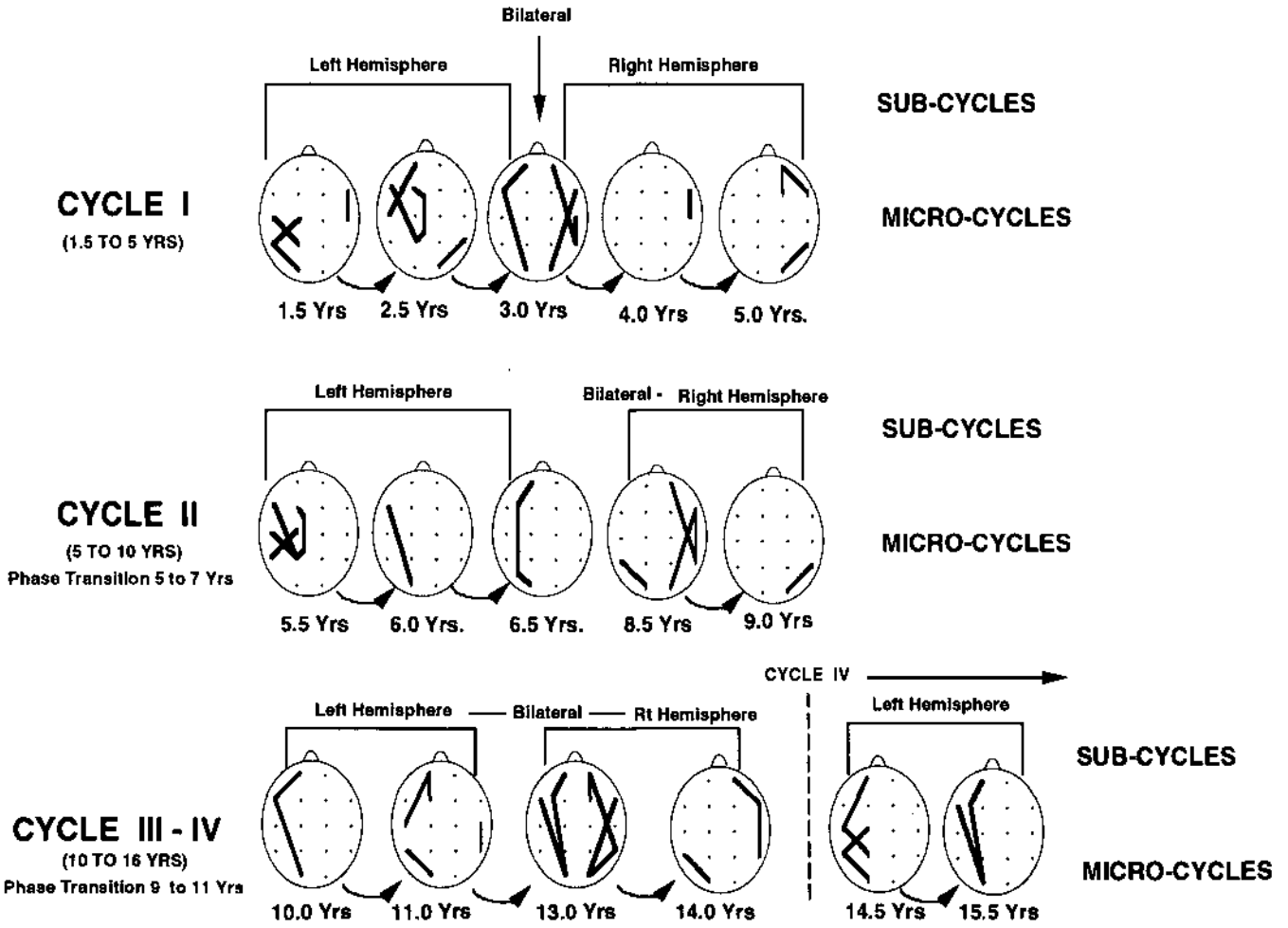
A mediolateral pole of development was evident by (a) differential rates of development of the lateral (i.e., F7/8 and T3/4) as opposed to the dorsal medial frontal regions (F3/4 and C3/4) (see Figures 5a and 5b); (b) a rotational sequence with a direction from lateral to medial in the left hemisphere and a direction from medial to lateral in the right hemisphere; (c) interhemispheric lateral frontal and lateral temporal regions exhibited 180° phase reversals, whereas interhemispheric dorsal medial frontal regions did not (Thatcher, 1994); and (d) dorsal medial interhemispheric trajectories were mostly synchronous, whereas lateral interhemispheric trajectories were mostly asynchronous (see Thatcher, 1994). An example of mediolateral poles of EEG coherence development are shown in Figure 6.

Postnatal Left Versus Right Hemisphere Development

A left versus right hemisphere pole of development was evident by (a) a sequence of predominantly left hemisphere growth spurts followed by predominantly right hemisphere growth spurts; (b) a sequential lengthening of corticocortical connections in the left hemisphere as opposed to a sequential contraction of corticocortical connections in the right hemisphere; and (c) a tendency toward integration of short- to long-distance connections in the left hemisphere, whereas the right hemisphere exhibited a tendency toward differentiation of long-distance connections into shorter distance connections. An example of left hemisphere expansion and right hemisphere contraction is shown in Figure 7.

Nonlinear Dynamics of Frontal Lobe Development

The dynamics of the bifurcations or phase transitions observed in the EEG coherence data 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 3–4 years, 5–7 years, and 9–11 years satisfy many of Gilmore's catastrophe flags (Gilmore, 1981) and exhibit characteristics of a "fold" or "cusp" catastrophe (Thom, 1975; van der Maas & Molenaar, 1992). A clear example of a cusp catastrophe is seen



in Figure 8, in which the P3-F7 EEG coherence trajectory exhibits a fold and frequency shift between 5 and 7 years. The Gilmore (1981) catastrophe 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 catastrophe suggests that the underlying dynamics can be modeled by gradient systems and vector fields of the form $\mathbf{x} = -\nabla U(x)$ for $\mathbf{x}$ in $\mathbb{R}^k$ in which competition and cooperation between forces are responsible for the dynamics and the stable equilibria (Gilmore, 1981; Thompson & Stewart, 1986).

Dominance of Frontal Lobe Connections During Postnatal Cerebral Development

The developmental trajectories of EEG coherence and phase were dominated by frontal lobe interactions (Thatcher, 1991, 1992b, 1994; Thatcher et al., 1987). Each postnatal age of development was marked by a different frontal to posterior or frontal to temporal or frontal to central cortical interactions. Also, the developmental trajectories were different for the left and right hemispheres, and they were different for ventral versus dorsal frontal regions (Thatcher, 1994). A common finding was the presence of competition between interhemispheric lateral frontal regions but not between interhemispheric medial frontal regions. As suggested elsewhere (Thatcher, 1992b, 1994), this finding may reflect differences in the anatomy of ventral-lateral versus dorsal-medial-frontal cortex (Abbie, 1940; Dart, 1934; Pandya & Barbas, 1985; Sanides, 1971).

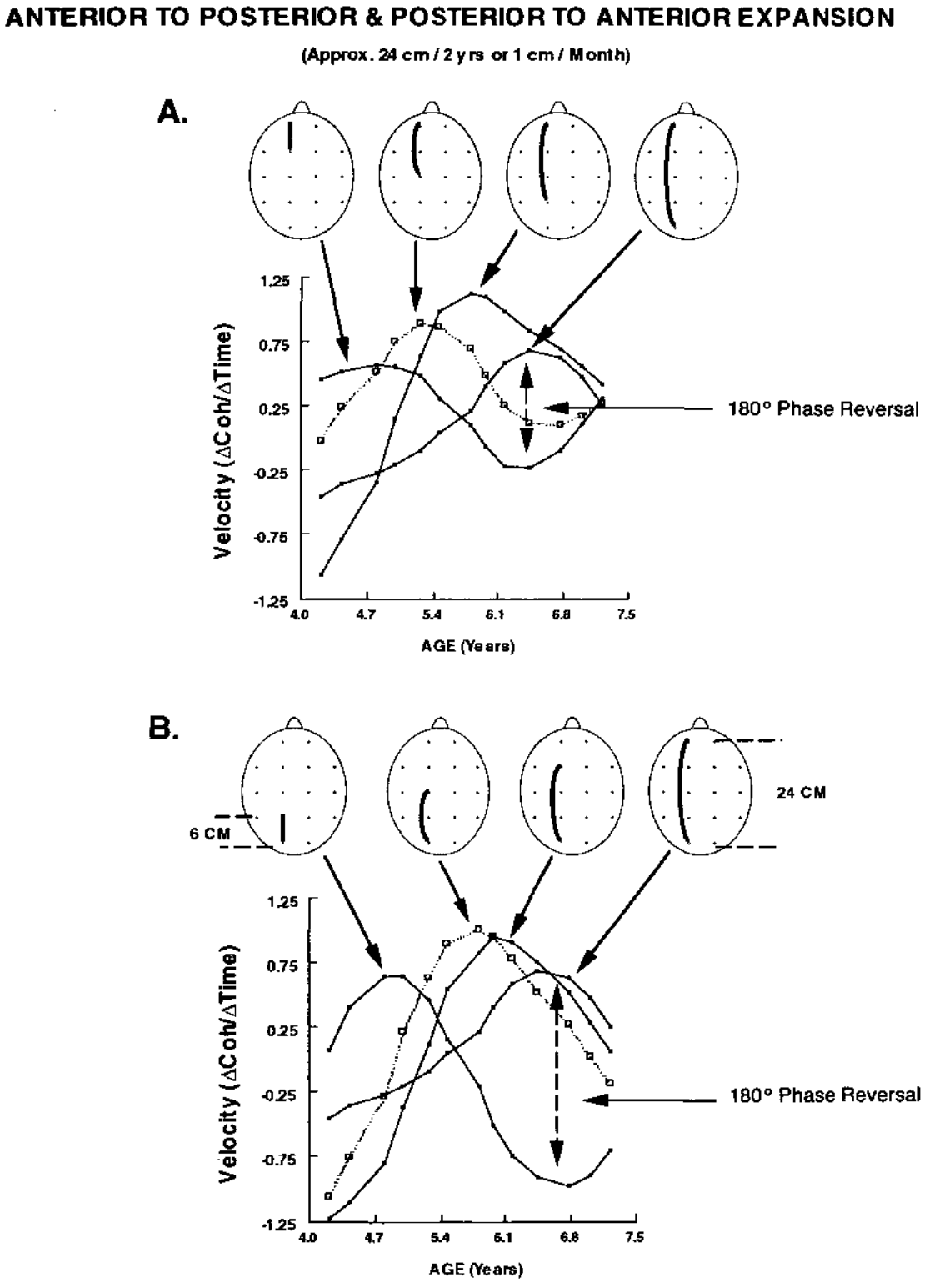
Finally, some mention should be made about the role of the frontal lobes in the long-distance versus short-distance competition observed in the EEG coherence and phase data (Thatcher, 1991, 1992b, 1994; Thatcher et al., 1987). Competition, as evidenced by 180° phase reversals, have been observed in local frontal with respect to long-distance occipital–parietal regions (e.g., F1-F7 vs. P3-F7); however, more frequent and larger magnitude competition was noted from local occipital–parietal with respect to long-distance frontal regions (e.g., P3-O1 vs. P3-F7). These data indicate that long-distance frontal connections tend to compete, and even displace, short-distance posterior cortical connections. As mentioned previously, this process may reflect a dynamic reorganization of increasing differentiation and integration and a developmental progression toward increasing frontal influence and frontal modulatory control of posterior cortical regions.

A Theory of Cyclic Frontal Lobe Development

The essence of the theory of cyclic cortical development is that the iterative growth spurts and patterns of development during the postnatal period reflect a convergence process that narrows the disparity between structure and function by slowly sculpting and reshaping the brain's microanatomy to eventually meet the demands and requirements of an adult world (Thatcher, 1992b,

Figure 4. Diagrammatic representation of the sequence and anatomical distribution of the growth spurts shown in Figure 3. Lines connecting two electrode locations correspond to the electrode locations in Figure 3 for the various developmental trajectories that loaded (> .80) on the first five factors (Thatcher, 1991). Microcycles were defined by a developmental sequence involving an anterior–posterior lengthening of interelectrode distances and a mediolateral rotation that cycles from the left hemisphere to bilateral to right hemisphere in approximately 4-year periods. The microcycles were grouped into subcycles and the subcycles were grouped into cycles as defined by the age 5–7 and age 9–11 bifurcations. From "Cyclic Cortical Reorganization: Origins of Cognitive Development" by R. W. Thatcher, in *Human Behavior and the Developing Brain* (p. 241), edited by G. Dawson and K. Fischer, 1994, New York: Guilford Publications. Copyright 1994 by The Guilford Press. Reprinted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press



https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

1994). According to this notion, an individual's gross anatomical structure is established early in development and the postnatal iterative sculpting process is used to fine-tune anatomical structure to meet the needs of diverse and unpredictable environments. The sculpting process unlocks or tailors the functional potential of the stable gross anatomy according to individual needs and environmental demands. According to this theory, the frontal lobes are especially critical in the synaptic sculpting process for the purposes of resource allocation whereby environmental demands are matched by the cortical resources capable of meeting those demands.

Figure 9 is a diagrammatic representation of the structure of cycles and subcycles as observed in the EEG coherence data, and they correlate with cognitive development. For continuity, the Fischer (Fischer, 1980; Fischer & Farrar, 1987) and Case (1985, 1987) descriptions of cognitive development are used in Figure 9. It should be kept in mind, however, that the label of an anatomical organization of growth spurts as a subcycle or a microcycle is somewhat arbitrary. The particular divisions used in Figure 9 are to emphasize the presence of cyclical patterns of predominantly left, bilateral, and right hemispheric development. The important point, whatever divisions of age one chooses, is that sequential developmental processes are nested within cyclic anatomical patterns.

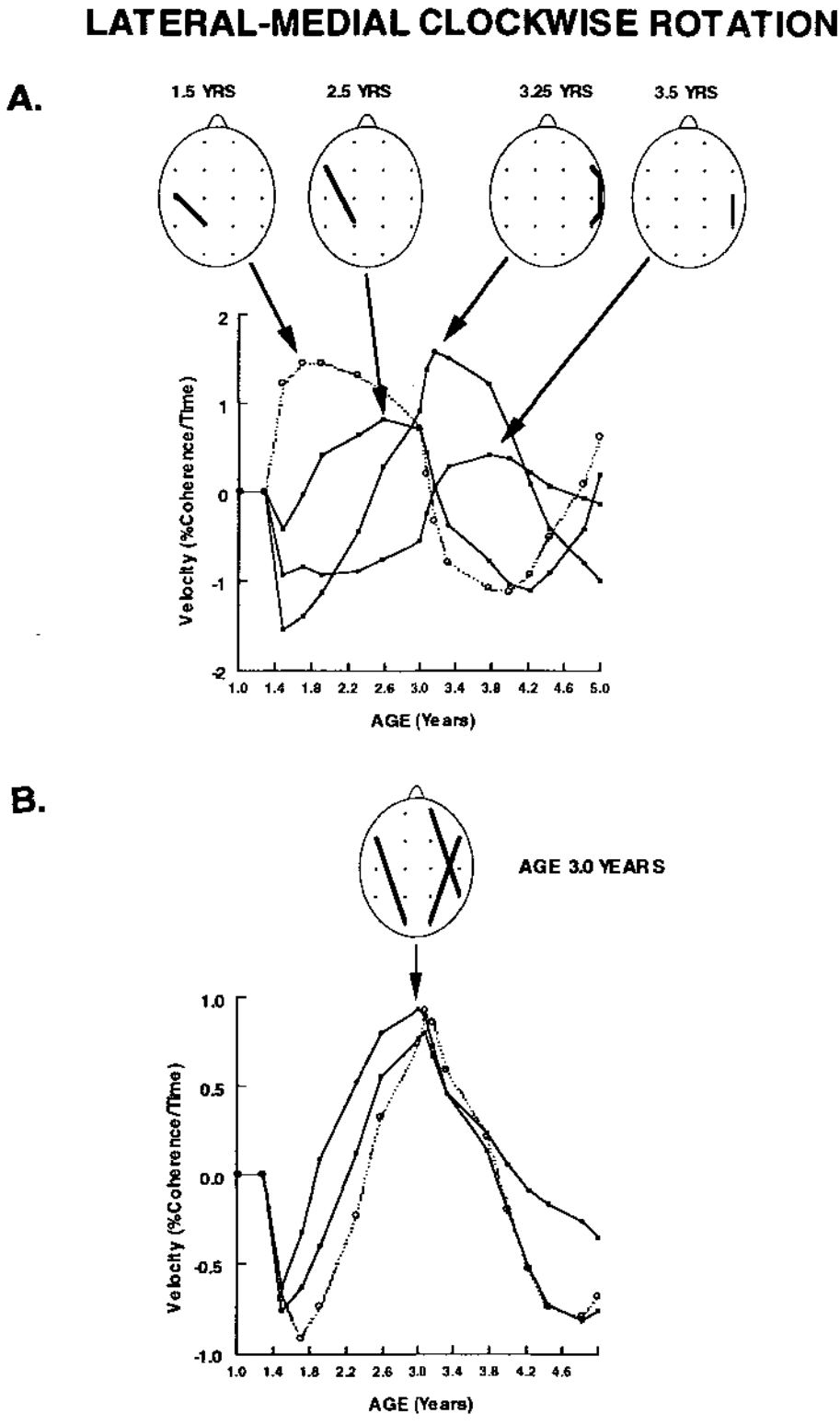
According to the theory, the oscillations in the mean EEG coherence data are due to delays between the activation and termination of trophic growth factors that are signaled by biochemical mechanisms activated by spatial limits. As shown in Figure 10, the engine that drives this process is a traveling wave, which is postulated to arise from left hemisphere lateral cortical regions and to rotate clockwise at a rate from approximately 1.0 to 0.5 cm/month (i.e., assumes 24-cm excursion in the mediolateral direction over a 2–4-year period). According to Equation 2, the leading edge of each cyclic wave front involves the local production of a surplus of synaptic connections and/or a periodic reinforcement of existing connections, while the trailing edge involves the elimination or pruning of excess connections and/or a reduction in synaptic strength. It is suggested in the present paper that the frontal lobes are largely responsible for selecting and influencing the extent to which environmental factors determine which synaptic connections will survive or be reinforced and which will be pruned and/or neglected. A local increase in synaptic effectiveness is defined in Equation 2 as either an increase in the number of connections and/or an increase in the strength of existing connections.

An Ecological Neural Model of Frontal Lobe Development

In the following sections, an ecological model of synaptogenesis will be explored to

Figure 5. (A) Expanding sequence of anterior–posterior growth spurts that occur in the mediodorsal plane. This process begins at approximately age 4.5 years in the left frontal pole–dorsal frontal region, then expands at approximately age 5.3 to the left frontal pole–central region, then expands at approximately age 6.0 to the left frontal pole–parietal region, and, finally, expands at approximately age 6.5 years to the left frontal pole–occipital region. A 180° phase reversal between the short-distance intracortical electrode pair (i.e., F1-F3) and the long-distance intracortical electrode pair (i.e., F1-O1) is evident around age 6.5 years. (B) Complementary and nearly simultaneous expanding sequence to that observed in (A) but in the posterior–anterior direction. This process begins at approximately age 4.5 in the left occipital–central region at approximately age 5.75 years, then expands to the left occipital–dorsal frontal at approximately age 6.0 years, and, finally, expands to the left occipital–frontal pole at approximately age 6.5 years. A 180° phase reversal between the short-distance intracortical electrode pair (i.e., O1-P3) and the long-distance intracortical electrode pair (i.e., O1-F1) is again evident around age 6.5 years. Adapted from "Cyclic Reorganization During Early Childhood" by R. W. Thatcher, 1992, *Brain and Cognition, 20*, p. 28. Copyright 1992 by Academic Press. Adapted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press



https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

explain how the frontal lobes operate to cyclically sculpt and select which synaptic influences will be pruned and which will survive.

Let us begin with a search of plausible neural population models that are capable of explaining the presence of oscillations in the development of EEG coherence. For purposes of simplicity, changes in the number of synapses will be emphasized; however, the model will work for modulation of the strength of synapses without a change in the number of synapses. Among the most adaptable biological models are where two populations are competing for a common food supply (Gause, 1934; Gause & Witt, 1935; Volterra, 1926) and/or population models involving prey–predator relationships (Holling, 1959, 1966; Lotka, 1925; Nicholson & Bailey, 1935; Soloman, 1949; Volterra, 1926). These two models are mathematically related, primarily by the strength of the competitive coupling (Berryman, 1981; Getz, 1984; Real, 1977). To adapt these models to cortical development, we will assume the following: (a) a common niche for synapses is the somato-dendritic surface area expressed in squared micrometers, (b) corticocortical connection systems can compete and/or cooperate for the available somato-dendritic surface area upon which synaptic connections are formed, and (c) competing and/or cooperating corticocortical connection systems from different brain regions can coexist within a given cortical region, such that displacement of connections or reduced connection strength from Region 1 by connections from Region 2 can occur.

Figure 11A is a representation of a competing and/or cooperating corticocortical connection system representing the lateral frontal to parietal corticocortical connections (Fp1-P3 or A), the occipital to parietal corticocortical connections (O1-P3 or B), and the somato-dendritic domain of the left parietal region (P3) where the corticocortical connections A and B converge at C. Figure 11B is a representation of the synaptic populations A and B converging on the somato-dendritic area C as depicted in Figure 11A. The projections A and B contain multiple synaptic connections, and 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.

Figure 12 is a representation of the mathematical interactions within and between corticocortical synaptic systems as depicted in Figure 11. There are three major kinds of interactions between synaptic connection systems: (a) competition, (b) cooperation, and (c) predator–prey. Each of these categories of interaction can be depicted by the sign and magnitude of the interaction coefficients α_{ii} which are divided into intrasynaptic interaction coefficients (e.g., α_{11} and α_{22}) or into intersynaptic interaction coefficients (e.g., α_{12} and α_{21}).

For purposes of examining the fit of the model to the mean EEG coherence developmental data from Thatcher (1992b, 1994), the following mathematical equation was used. Using the notation of Berryman (1990), we can write one equation for the developmental synaptic dynamics, which

Figure 6. (A) Sequence of expanding and contracting growth spurts that reflect a clockwise anatomical rotation. The process begins at approximately age 1.5 years in the left temporal–parietal region, rotates and extends at approximately age 2.5 years to the left lateral frontal–parietal region, then rotates at approximately age 3.2 years to the right lateral frontal–posterior temporal region, and, finally, rotates and contracts to the right lateral temporal–posterior temporal region at age 3.5–4 years. (B) Long-distance corticocortical growth spurts that are present near the dorsal-medial cortex around the age of 3.0 years. Age 3.0 represents the "12 o'clock" or "north pole" of the lateral-to-medial rotational vector and is characterized by a phase lag of about 0.25 years between long-distance left hemisphere frontal connections and long-distance right hemisphere frontal connections. From "Cyclic Reorganization During Early Childhood" by R. W. Thatcher, 1992, *Brain and Cognition*, *20*, p. 36. Copyright 1992 by Academic Press. Reprinted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

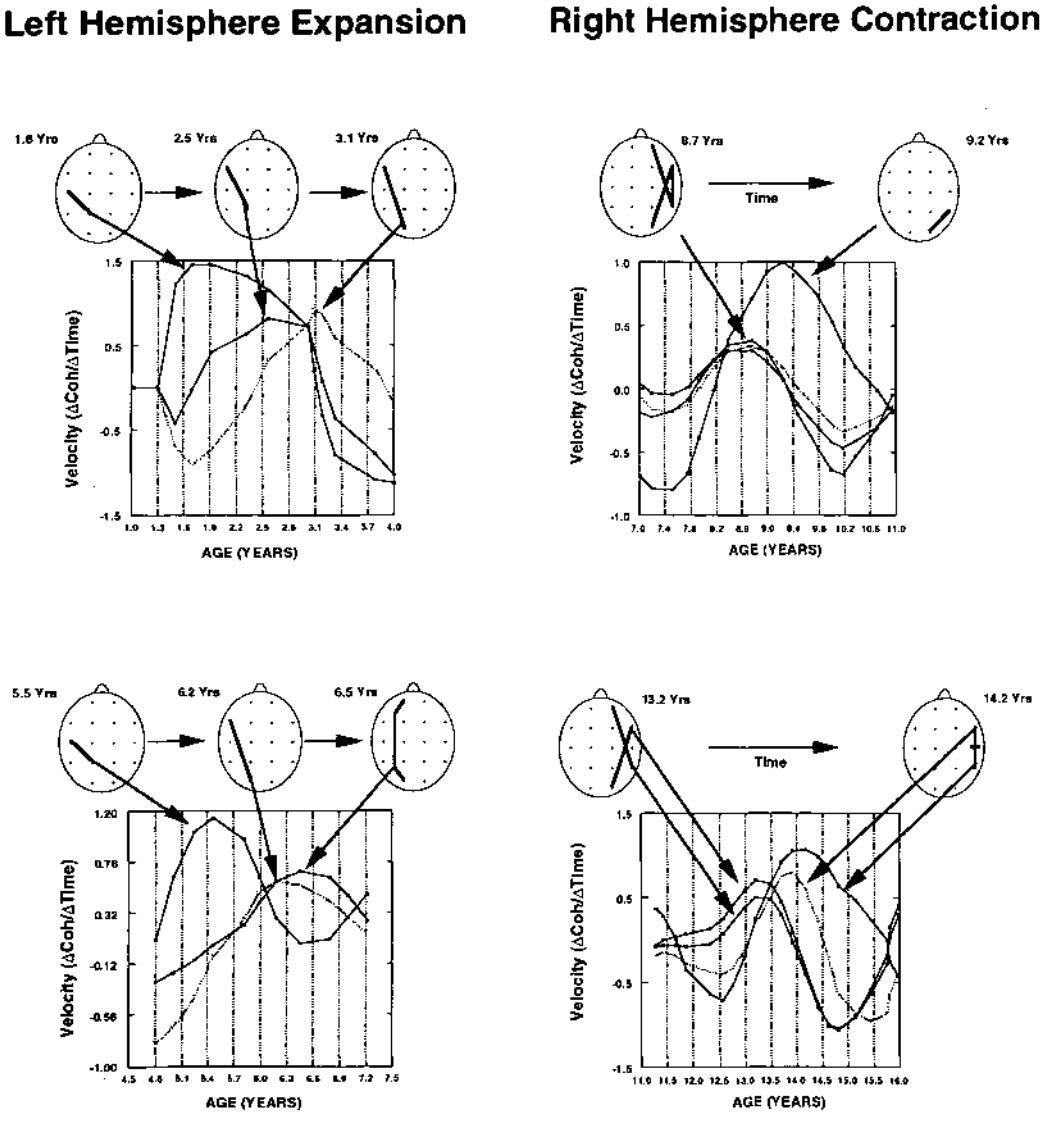


Figure 7. Left column shows examples of left hemisphere expansion sequences from short-distance intracortical connection systems to longer distance systems (see Figure 4). Right column shows examples of right hemisphere contraction sequence from long-distance intracortical connection systems to shorter distance systems (see Figure 4). Adapted from "Cyclic Cortical Reorganization: Origins of Cognitive Development" by R. W. Thatcher, in *Human Behavior and the Developing Brain*, edited by G. Dawson and K. Fischer, 1994, New York: Guilford Publications. Copyright 1994 by The Guilford Press. Adapted by permission.

includes a nonlinear term of coefficient of curvature and terms for carrying capacity:

$$R_i = A_i\left[1 - \left(\frac{N_i}{K_i}\right)^{Q_i}\right] - \frac{\alpha_i N_i}{N_i + E_i} \quad (3)$$

where R_i is the rate of change in the number of synapses, as a function of (a) the maximum per-capita rate of increase of the population in a given environment A_i, (b) the current synaptic density, N_i, and (c) the carrying capacity of the synaptic environment, K_i. The carrying capacity K_i limits the growth of the population because when $N = K$ then $R = 0$. Q_i is the coefficient of curvature to reflect nonlinear properties of the R function, α_i is the intrasynaptic effect

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

of N_i and N_j on themselves as well as the intersynaptic effect between N_i and N_j, and E_i is the concentration of trophic nerve growth factor that can modulate the number of synapses and/or the strength of synapses.

Fit of Model to EEG Coherence Development

A stepwise procedure was used to evaluate individual and combinations of mean EEG coherence development and to determine the best fit of the data. The first step was to evaluate the dynamics, stability, and sensitivity of the population model for single corticocortical connection systems. In these analyses, the EEG coherence trajectories were evaluated for (a) the presence of two or more equilibria (i.e., the presence of a separatrix and basins of attraction), (b) the magnitude of time delays, and (c) the magnitude and direction of nonlinearity as measured by the coefficient of curvature of fit (Berryman, 1990). The second step was to evaluate the dynamics of pairs of EEG coherence trajectories using the model of two populations competing, cooperating, and/or in a predator–prey mode of interaction. 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 also determined. The type of two-population interaction that 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 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^2s at T_3 or T_2 ranged from 41.78% in F3-C3 to 99.9% in F1-F3. The phase-space trajectories were characterized by (a) sigmoid-type logistic growth or (b) limit cycle behavior, or (c) 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 bifurcation occurred primarily in the local right frontal regions (e.g., F2-F8; F2-F4) and in the right fronto-temporal regions (F2-T6; F2-T4). Between the ages of 5 and 7 years, the separatrix bifurcation occurred primarily in the left frontotemporal and left frontoparietal regions and a third group of separatrix bifurcations were seen in the right frontotemporal regions around the ages of 9–11 years.

Frontal Cortical Regions as Predators and Posterior Cortical Regions as Prey

The mode of interaction between EEG corticocortical developmental systems could be explained most frequently and with the highest amount of variance accounted for in the predator–prey mode (e.g., 86.7% in the left hemisphere and 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. The least frequent modes of interaction were the independent and cooperative modes, respectively. Clear differences in the anatomical distribution of the various modes were present. In general, the predator–prey modes occurred in the anterior–posterior plane with frontal regions being the predators and the posterior cortical regions the prey. The independent and cooperative modes tended to occur in the mediolateral plane, and the competitive modes occurred, primarily, in right local frontal and right frontotemporal regions.

Figure 13 shows an example of actual mean EEG coherence data (A) and simu-

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

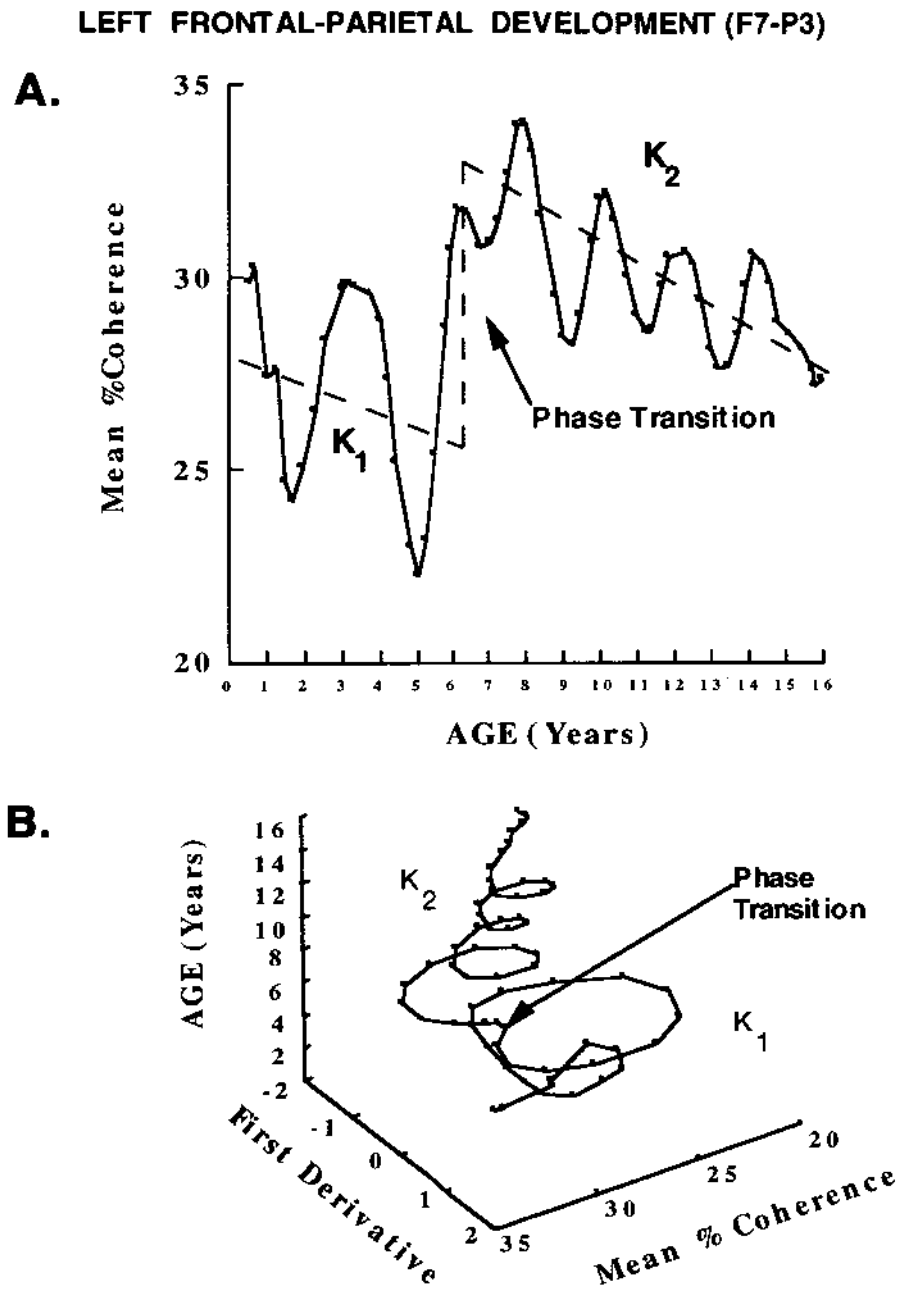


Figure 8. (A) Mean %EEG coherence (i.e., coherence × 100) in the theta frequency band from left lateral frontal-parietal regions (i.e., F7-P3) from 6 months to age 16 years. Two modes of oscillation, mode one from birth to approximately age 5 and mode two from approximately age 7 to age 16, are fit by 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) 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 in the left frontal-parietal (i.e., P3-F7) which are spirals with different radii and frequencies over the life span. Adapted from "Maturation of the Human Frontal Lobes: Physiological Evidence for Staging" by R. W. Thatcher, 1991, *Developmental Neuropsychology*, *7*(3), p. 413. Copyright 1991 by Lawrence Erlbaum Associates, Inc. Adapted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

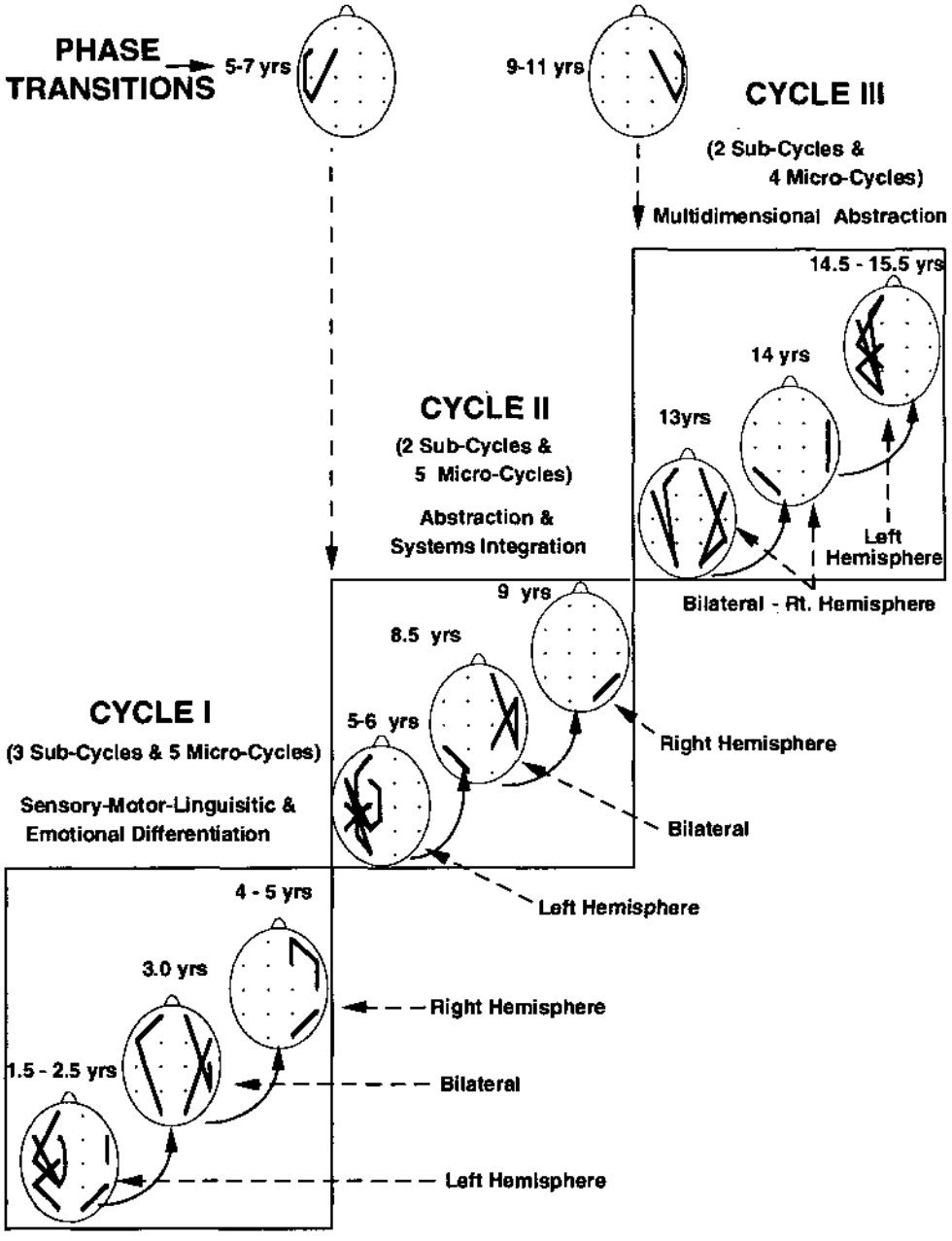


Figure 9. Diagrammatic representation of the predominant developmental cycles and subcycles of neocortical reorganization. Designation of left, bilateral, or right hemisphere is to emphasize the predominant growth spurts during a given age range as shown in Figure 4 (e.g., there are six left and two right hemisphere growth spurts between ages 1.5 and 2.5 years as the cycle moves from predominantly left to bilateral). Furthermore, microcycles are not included; instead, the microcycles are combined into their respective subcycles from Figure 4. This figure is to illustrate the combination of punctuated equilibria and the presence of a spiral staircase of cyclic reorganization during postnatal cerebral development. The verbal descriptions of the stages of cognitive development are from Fischer (1980), Fischer and Farrar (1987), and Case (1985, 1987). Adapted from "Cyclic Cortical Reorganization: Origins of Cognitive Development" by R. W. Thatcher, in *Human Behavior and the Developing Brain* (p. 252), edited by G. Dawson and K. Fischer, 1994, New York: Guilford Publications. Copyright 1994 by The Guilford Press. Adapted by permission.

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

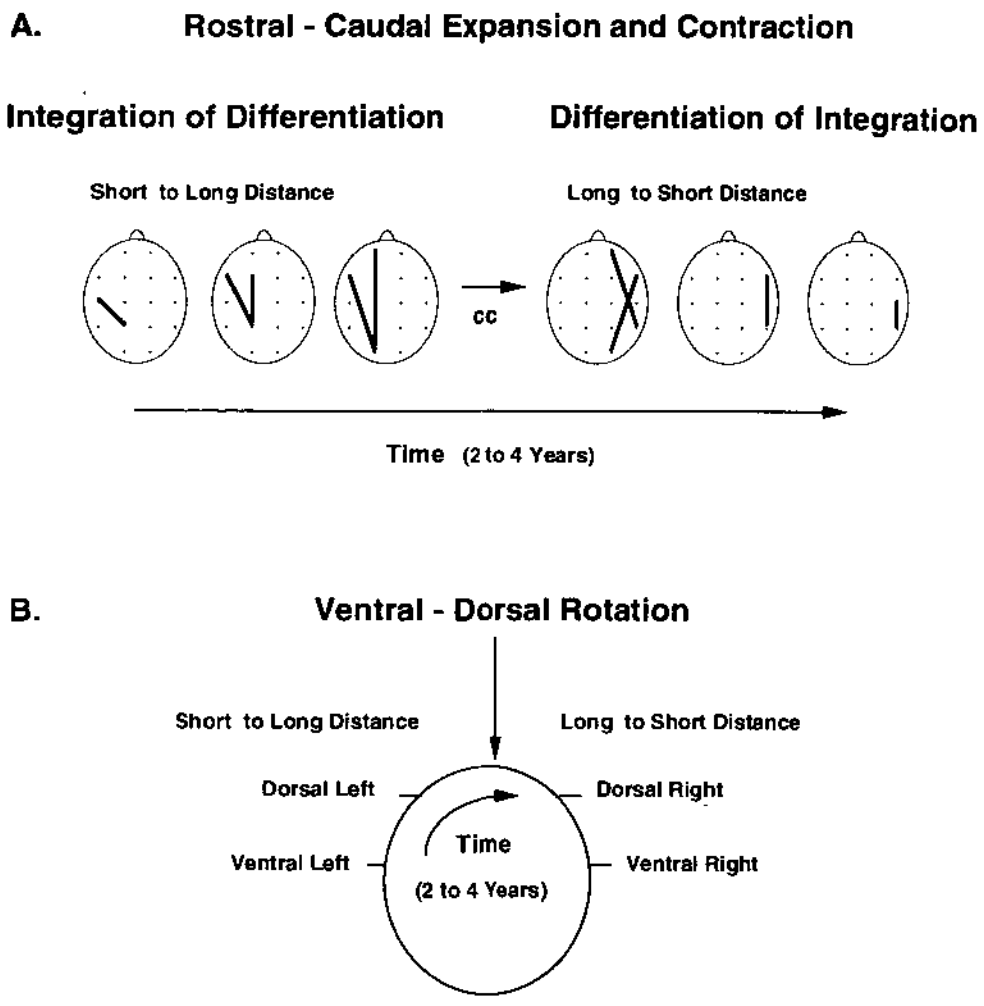


Figure 10. (A) Diagrammatic representation illustrating the anterior–posterior sequence of development in the left and right hemispheres. The left hemisphere exhibited a sequential lengthening of intracortical connection systems, described as a developmental process of integrating differentiation. The right hemisphere exhibited a sequential shortening of the intracortical connection systems, described as a developmental process of differentiating integration (see Figures 4–6). (B) Diagrammatic representation illustrating the mediolateral sequence of development. The sequence begins at left lateral cortex, then intrahemispherically expands to left dorsal medial cortex, then projects through the corpus callosum to the right dorsal medial cortex, and then intrahemispherically contracts in the right lateral cortex (see Figures 1, 4, and 8). Adapted from "Cyclic Reorganization During Early Childhood" by R. W. Thatcher, 1992, *Brain and Cognition*, *20*, p. 42. Copyright 1992 by Academic Press. Adapted by permission.

lated data (B) for Fp1-P3 and O1-P3 competitive dynamics. In this case, the least-squares regression fit of the model to the actual mean EEG coherence data had an R^2 for P3-O1 = 97.41% and for Fp1-P3 = 94.97%. According to the model, there is a continuous cycling of synaptic abundance followed by synaptic pruning in both frontal and posterior cortical regions. However, the mechanisms of pruning are somewhat different because the frontal regions are directly responsible for the synaptic organization and reorganization in posterior cortical regions. The synaptic sequence, as dia-

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

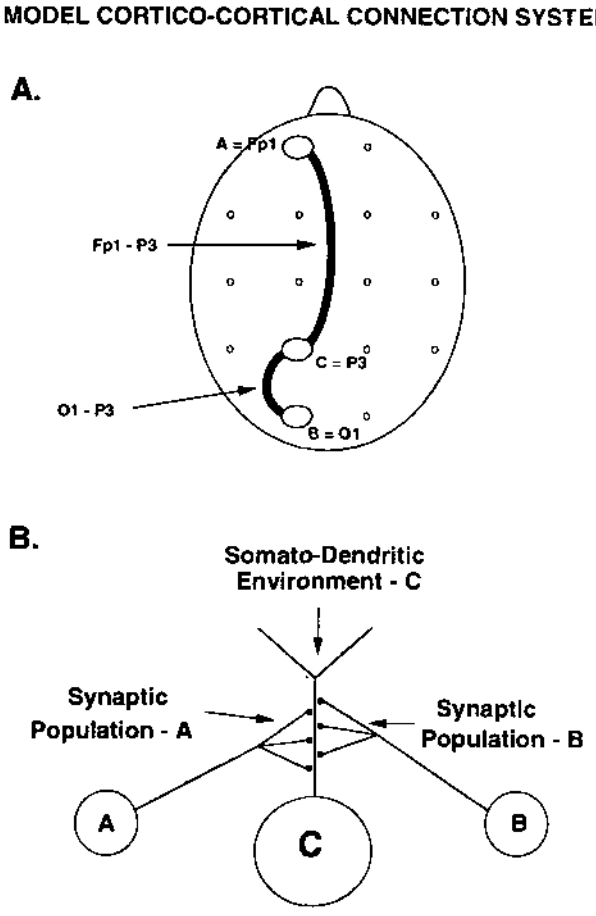


Figure 11. Model of corticocortical connection development. (A) Diagram of left frontal pole region (i.e., Fp1), which is competing with left occiptal (i.e., O1) for synaptic influence on the parietal cortex. That is, connections from Fp1 and O1 converge onto P3 where they compete for the available synaptic binding sites on the dentrites and/or cell body of parietal neurons. (B) 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 dendrosomatic 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 dendrosomatic surface, where they compete for contact and influence of the parietal neurons.

grammed in Figure 13B, is as follows: Stage 1, 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 2, 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 3, at 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 4, at

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

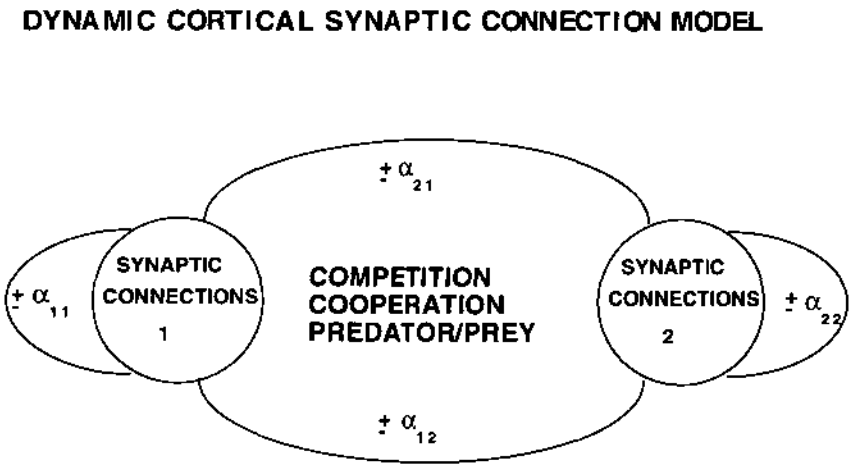


Figure 12. Ecological model in which synapses arising from two different cortical regions interact for influence on a third cortical region. The interaction can be of four types: (a) independent, (b) cooperative, (c) competitive, and (d) predator–prey, depending on the sign and magnitude of the interaction coefficients α_{ij}, which are divided into intrasynaptic interaction coefficients (e.g., α_{11} and α_{22}) or into intersynaptic interaction coefficients (e.g., α_{12} and α_{21}).

approximately 5.5 years, is 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."

The adaptation of an ecological predator–prey model to cortical synaptogenesis does not require the exact specification of the predator–prey type because identical mathematical forms pertain to each of the four different categories of interaction. However, given the long 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 analog.

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 cycles of synaptic effectiveness? One interpretation is that the frontal regions control or significantly influence the cycles of synaptic influence in 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 spatial 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; Fischer & Pipp, 1984). According to the present model, sensitive periods reflect the nonlinear manifestation of an underlying and continuous growth process (Thatcher, 1992a, 1992b, 1994).

Genetic Versus Environmental Influences

As defined earlier, the positive first derivatives of mean EEG coherence change were defined as reflecting the increased synaptic influence phase while the negative first derivative was defined as reflecting a de-

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

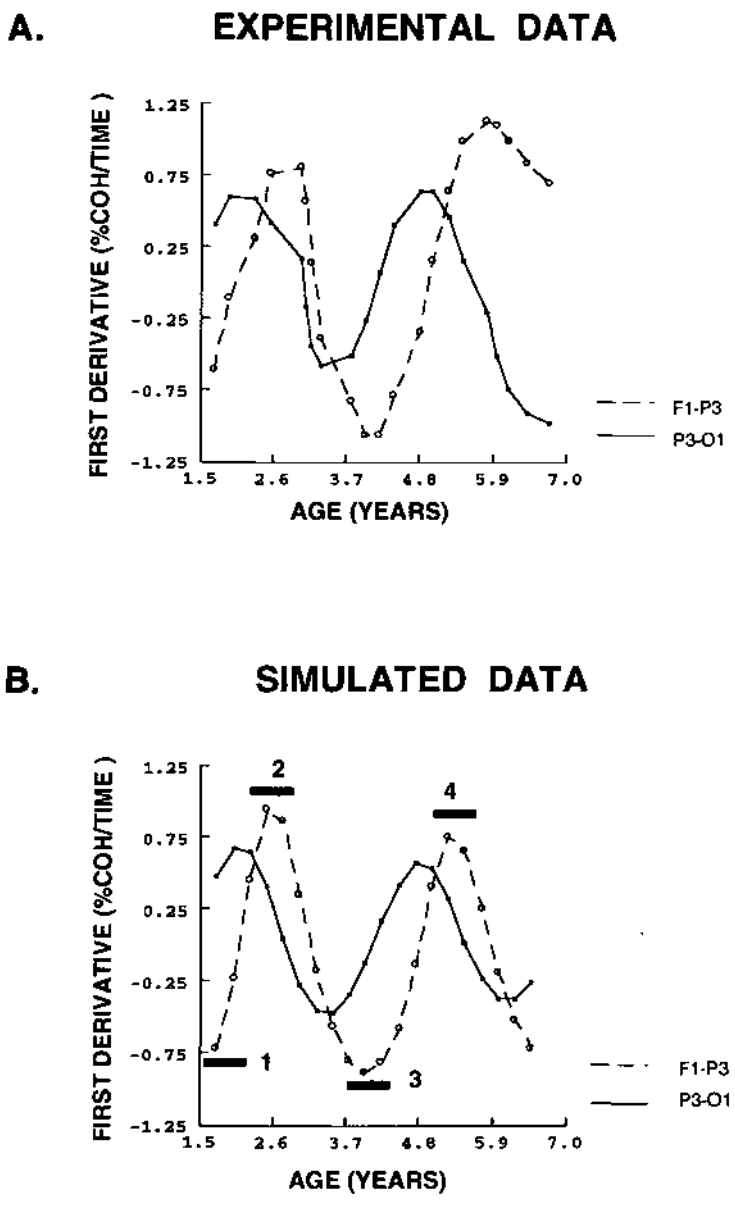


Figure 13. Comparison of (A) actual first derivatives of mean EEG coherence from the frontoparietal (F1-P3) and parietal-occipital (P3-O1) regions to (B) simulated first derivative values based on the predator–prey model described by Equation 4. The least-squares regression fit of the model (Equation 4) to the actual mean EEG coherence data had an R^2 for P3-O1 = 97.41% and for Fp1-P3 = 94.97%.

creased synaptic influence (Thatcher, 1992b, 1993, 1994). One would expect that genetic factors would have a strong impact on the positive synaptic influence phase and that environmental factors would have a strong impact on the declining synaptic influence 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 en-

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

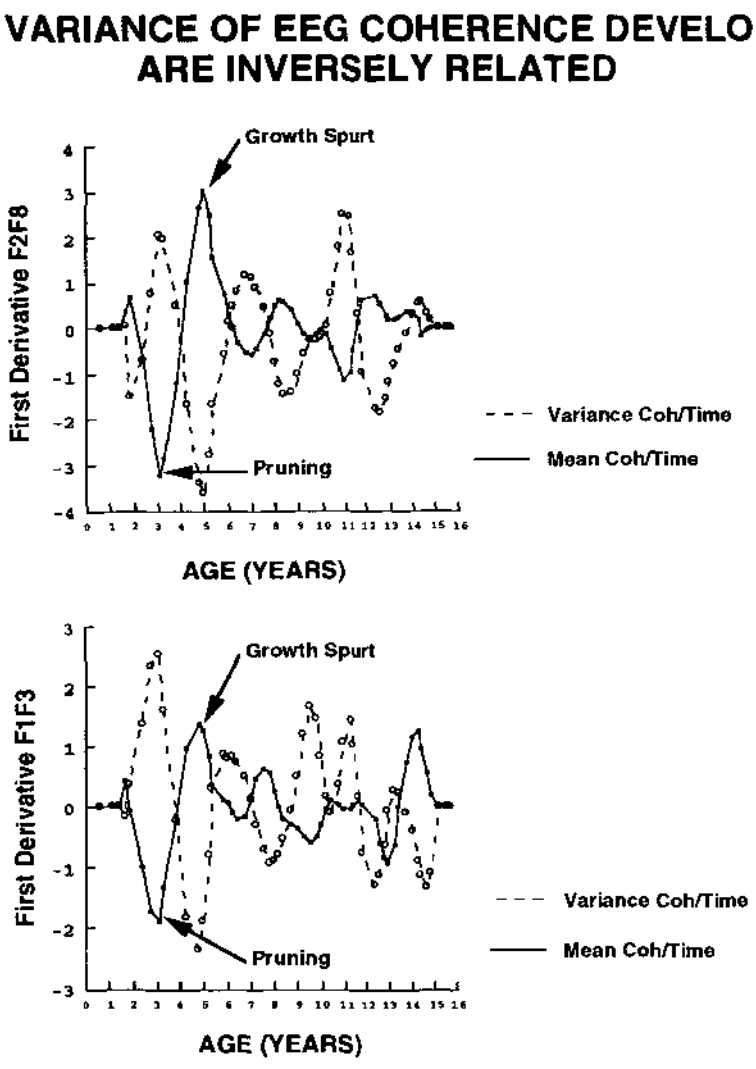


Figure 14. The first derivatives of the mean and variance of EEG coherence from male children for two different cortical regions (A = F2F8, and B = F1F3). A 180° phase reversal is strongly present in which variance is greatest during the negative first derivatives or the synaptic pruning phases and it is small during the positive first derivatives or the synaptic surplus phases (from Hanlon, 1994).

vironments one would expect greater variance in the first derivative of EEG coherence during the pruning phase than during the surplus phase. Figure 14 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° 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 13B 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 10 (i.e., the F1-P3 and O1-P3 model). Both frontal and

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

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 depends on 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 "restocking" of the supply of posterior cortical synapses that the frontal lobes can subsequently "replace" or "reorganize" based on environmental exigencies.

Theoretical Consequences of Early Childhood Frontal Lobe Injury

Based on the preceding data and ecological modeling, the following are theoretical explanations of some of the more intriguing and unique aspects of early childhood frontal lobe damage as reviewed in the introduction. All of these explanations stem from the general theory of postnatal cyclic cortical reorganization, which is comprised of at least three basic postulates: (a) there are postnatal wave processes that operate along spatial gradients and contain a periodic sequence of increasing and decreasing synaptic effectiveness; (b) the frontal lobes play a dominant role in the synaptic selection process by periodically reorganizing the synaptic environment of posterior cortical regions, which slowly brings larger cellular domains under the control of the frontal lobes and incrementally alters the functions of these regions; and (c) this process contributes to behavioral and cognitive development as a cascading spiral, in which higher and higher levels of abstractions occur and more sophisticated skills emerge during the postnatal period (Case, 1987; Fischer, 1980; Thatcher, 1994).

Prepotency of Early Frontal Lobe Damage

It follows directly from the preceding theory of cyclic cortical reorganization that injury to the frontal regions will have a profound effect on a wide number of postnatal neural maturational processes. Unlike posterior cortical regions, the frontal lobes serve as a dominant organizer of neural networks that are sculpted and shaped to meet the demands of society and the needs of the individual. Given Postulate (b) of the theory specifying the dominant postnatal developmental role of the frontal lobes, it follows that not only will skill acquisition in general be affected (i.e., the higher level cognitive and social functions of the frontal lobes will be diminished or arrested), but also, most importantly, there will be reduced information or knowledge acquisition in general. Furthermore, the model predicts the finding of a progressive and cumulative disparity between expected and actual social and cognitive functioning as the child develops (Eslinger et al., 1992; Grattan & Eslinger, 1992). For example, given the dominant and organizing role of the frontal lobes, one would expect that the earlier the frontal lobe damage, then the more profound and pervasive the cognitive and social deficits. A similar progressive and cumulative deficit would not be expected from posterior cortical regions because only the frontal cortex is the "predator" or "organizer" of long-distance corticocortical connections. In fact, compensatory reorganization is more likely to follow posterior cortical damage when, at least, unilateral frontal regions are left intact.

Delayed Clinical Expression of Frontal Lobe Damage

A theoretical explanation of a delayed expression following frontal lobe damage stems primarily from the sequential synaptic overproduction and synaptic pruning process and the competitive dynamics involved in this process. According to the predator–prey model, the frontal lobes are crucial in the pruning process, which occurs sequentially in different regions of the cortex. A generalized reduction or arrest of the pruning process would result in a cumulative overproduction of synaptic terminals and a resultant interference in the dynami-

cal reorganization process, which may require several years before behavioral consequences are observed. Reduced or arrested frontal lobe predation of posterior cortical synaptic systems could result in increased intrasynaptic competition within the posterior cortical regions, which may result in a reduction in frontal-to-posterior cortical connections. The length of delay before behavioral consequences emerge would depend on the severity and spatial extent of frontal lobe damage. The delay interval would be a function of the rate of synaptic growth R, the carrying capacity of the somato-dendritic synaptic systems K, and the magnitude of the frontal lobe predator action N_j/N_i (see Equation 3). Such a model would be consistent with Feinberg's (1982) speculation that schizophrenia is due to a failure of cell death or synaptic loss.

Injury Before, During, or After Growth Spurts

Based on the cyclic cortical reorganization theory, the time of frontal cortical injury and the location will have different behavioral consequences. In general, if injury occurs to an active predatory frontal region (e.g., lateral or ventral or dorsal depending on timing), then there would be reduced frontal sculpting or pruning of specific posterior cortical regions that were previously connected to the specific frontal region. This would result in an excess of posterior cortical synapses with a consequent increased intrasynaptic competition in the posterior cortex but also, possibly, increased predation at a subsequent time from a healthy frontal cortical region. This could result in compensatory reorganization, depending on which frontal regions are affected and what age the injury occurs. This may be why bilateral frontal damage has more severe long-term behavioral consequences than unilateral frontal damage (Kolb, 1989).

Injury Before or After Bifurcations and Phase Transitions

The cyclic reorganization theory is a dynamical equilibrium model in which there are relatively large shifts in equilibria (called bifurcations and phase transitions) at specific postnatal ages. The age periods from 5 to 7 and 9 to 11 contain two of the most pronounced bifurcations of phase transitions. Such processes are characterized as punctuation marks in a dynamical process in which large-scale reorganizations occur and new stable equilibria states are reestablished (Thatcher, 1994). In biological systems, stabile state equilibria are maintained by biological regulation involving negative and positive feedback, and damage to the regulator mechanisms can result in catastrophic behavior such as a complete collapse in the function of the system or in cyclic instability (Berryman & Stenseth, 1984). It therefore follows that the exact long-term consequences of frontal lobe damage will depend on the magnitude and location of the injury as well as the time relationship between the injury and naturally occurring developmental bifurcations. For example, if injury occurs during periods of relative instability such as the rising phase of the bifurcation, then catastrophic events may occur where future development is totally arrested or a markedly different or pathological frontal lobe equilibrium emerges. On the other hand, if frontal lobe injury occurs during a period of relative stability (e.g., after the peak of the bifurcation when a new stable equilibrium has been established), then the long-term consequences of the injury may be less severe. In general, however, frontal lobe damage, whatever the age of occurrence, should result in reduced regulability or increased instability in neural network functions. Based on this model, quite complicated effects of injury may result depending on exactly when and where the injury occurs with respect to the nonlinear aspects of the developmental processes.

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

https://doi.org/10.1017/S0954579400004697 Published online by Cambridge University Press

pruning represents a sensitive period in anatomically localized and interconnected brain regions. Thus, sensitive periods are continually occurring because 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 overproduction of synapses and the environmentally driven maintenance and pruning of synaptic connections. As emphasized in previous sections, it is predicted that the frontal lobes play a crucial role, especially in the process of synaptic pruning and synaptic selection.

References

Abbie, A. A. (1940). Cortical lamination in the monotremata. *Journal of Comparative Neurology, 72*, 429–467.

Ackerly, S. S. (1964). A case of prenatal bilateral frontal lobe defect observed for thirty years. In J. M. Warren & K. Ackert (Eds.), *The frontal granular cortex and behavior* (pp. 192–218). New York: McGraw-Hill.

Ackerly, S. S., & Benton, A. L. (1947). Report of case of bilateral frontal lobe defect. *Proceedings, Associations for Research in Nervous and Mental Disease, 27*, 479–504.

Bayer, S. A., & Altman, J. (1991). *Neocortical development*. New York: Raven Press.

Bendat, J. S., & Piersol, A. G. (1980). *Engineering applications of correlation and spectral analysis*. New York: John Wiley & Sons.

Berryman, A. A. (1981). *Population systems: A general introduction*. New York: Plenum Press.

Berryman, A. A. (1990). *Population dynamics: A workbook for POPSYS software*. Pullman, WA: Ecological Systems Analysis.

Berryman, A. A., & Stenseth, N. C. (1984). Behavioral catastrophies in biological systems. *Behavioral Science, 29*, 127–135.

Blinkov, S. M., & Glezer, I. I. (1968). *The human brain in figures and tables*. New York: Plenum Press.

Bornstein, M. H. (Ed.). (1987). *Sensitive periods in development: Interdisciplinary perspectives*. Hillsdale, NJ: Erlbaum.

Bornstein, M. H. (1989). Sensitive periods in development: Structural characteristics and causal interpretation. *Psychological Bulletin, 105*, 179–197.

Braitenberg, V. (1978). Cortical architectonics: General and areal. In M. A. B. Brazier & H. Petsche (Eds.), *Architectonics of the cerebral cortex*. New York: Academic Press.

Carpenter, M. B., & Sutin, J. (1983). *Human neuroanatomy*. Baltimore, MD: Williams & Wilkins.

Case, R. (1985). *Intellectual development: Birth to adulthood*. New York: Academic Press.

Case, R. (1987). The structure and process of intellectual development. *International Journal of Psychology, 22*, 571–607.

Cicchetti, D. (1990). The organization and coherences of socioemotional, cognitive, and representational development: Illustrations through a developmental psychopathology perspective on Down syndrome and child maltreatment. In R. Thompson (Ed.), *Nebraska Symposium on Motivation: Socioemotional development* (Vol. 36, pp. 259–366). Lincoln: University of Nebraska Press.

Cicchetti, D. (1993). Developmental psychopathology: Reactions, reflections, projections. *Developmental Review, 13*, 471–502.

Cowan, W. M. (1979). The developing brain. In *The brain* (pp. 56–69). San Francisco: Freeman.

Cragg, B. G. (1975). The development of synapses in the visual system of the cat. *Journal of Comparative Neurology, 160*, 147–166.

Dart, R. A. (1934). The dual structure of the neopallium: Its history and significance. *Journal of Anatomy, 69*, 3–19.

Diamond, M. C., Scheibel, A. B., & Elson, L. M. (1985). *The human brain coloring book*. New York: Barnes and Noble.

Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., & Reitboek, H. J. (1988). Coherent oscillations: A mechanism of feature linking in the visual cortex? *Biological Cybernetics, 60*, 121–130.

Epstein, H. T. (1980). EEG developmental stages. *Developmental Psychobiology, 13*, 629–631.

Eslinger, P. J., Grattan, L. M., Damasio, H., & Damasio, A. R. (1992). Developmental consequences of childhood frontal lobe damage. *Archives of Neurology, 49*, 764–769.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence. *Journal of Psychiatric Research, 17*, 319–334.

Finger, S., & Wolf, C. (1988). The "Kennard effect" before Kennard: The early history of age and brain lesions. *Archives of Neurology, 45*, 1136–1142.

Fischer, K. W. (1980). A theory of cognitive develop-

ment: The control and construction of hierarchies of skills. *Psychological Review, 87*, 477–531.
Fischer, K. W. (1983). Developmental levels as periods of discontinuity. In K. W. Fischer (Ed.), *Levels and transitions in children's development* (pp. 23–45). San Francisco: Jossey-Bass.
Fischer, K. W. (1987). Relations between brain and cognitive development. *Child Development, 57*, 623–632.
Fischer, K. W., & Farrar, M. J. (1987). Generalizations about generalization: How a theory of skill development explains both generality and specificity. *International Journal of Psychology, 22*, 643–677.
Fischer, K. W., & Pipp, S. L. (1984). Processes of cognitive development: Optimal level and skill acquisition. In R. J. Sternberg (Ed.), *Mechanisms of cognitive development* (pp. 45–80). New York: Freeman.
Gause, G. F. (1934). *The struggle for existence*. Baltimore, MD: Williams & Wilkins.
Gause, G. F., & Witt, A. A. (1935). Behavior of mixed populations and the problem of natural selection. *American Naturalist, 3*, 596–609.
Getz, W. M. (1984). Population dynamics: A per-capita resource approach. *Journal of Theoretical Biology, 108*, 623–643.
Gilmore, R. (1981). *Catastrophe theory for scientists and engineers*. New York: John Wiley & Sons.
Glaser, E. M., & Ruchkin, D. S. (1976). *Principles of neurobiological signal analyses*. New York: Academic Press.
Gorbach, A. M., Tsicalov, E. N., Kuznetsova, G. D., Shevelev, I. A., Budko, K. P., & Sharaev, G. A. (1989). Infrared mapping of the cerebral cortex. *Thermology, 3*, 108–112.
Grattan, L. M., & Eslinger, P. J. (1991). Frontal lobe damage in children and adults: A comparative review. *Developmental Neuropsychology, 7*, 283–326.
Grattan, L. M., & Eslinger, P. J. (1992). Long-term psychological consequences of childhood frontal lobe lesion in patient DT. *Brain and Cognition, 20*, 185–195.
Gray, C. M., Konig, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature (London), 338*, 334–337.
Greenough, W., Black, J., & Wallace, C. (1987). Experience and brain development. *Child Development, 58*, 539–559.
Hanlon, H. W. (1994). *Differences in female and male development of the human cerebral cortex from birth to age 16*. Unpublished dissertation.
Holling, C. S. (1959). The components of predation as revealed by a study of small mammal predation of the European pine sawfly. *The Canadian Entomologist, 91*, 293–320.
Holling, C. S. (1966). The functional response of invertebrate predators to prey density. *Memoirs of the Entomological Society of Canada, 48*, 1–86.
Hudspeth, W. J., & Pribram, K. H. (1990). Stages of brain and cognitive maturation. *Journal of Educational Psychology, 82*, 881–884.
Hudspeth, W. J., & Pribram, K. H. (1991). Physiological indices of cerebral maturation. *International Journal of Psychophysiology, 2*, 19–29.
Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex: Developmental changes and effects of aging. *Brain Research, 163*, 195–205.
Huttenlocher, P. R. (1984). Synapse elimination and plasticity in developing human cerebral cortex. *American Journal Mental Deficiencies, 88*, 488–496.
Huttenlocher, P. R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia, 28*, 517–527.
Huttenlocher, P. R., & de Courten, C. (1987). The development of synapses in striate cortex of man. *Human Neurobiology, 6*, 1–9.
Huttenlocher, P. R., de Courten, C., Garey, L., & Van der Loos, H. (1982). Synaptogenesis in human visual cortex – Evidence for synapse elimination during normal development. *Neuroscience Letters, 33*, 247–252.
John, E. R. (1963). *Mechanisms of memory*. New York: Academic Press.
Kennard, M. A. (1936). Age and other factors in motor recovery from precentral lesions in monkeys. *Journal of Neurophysiology, 1*, 477–496.
Kolb, B. (1984). Functions of the frontal cortex of the rat: A comparative review. *Brain Research Reviews, 8*, 65–98.
Kolb, B. (1989). Brain development, plasticity and behavior. *American Psychologist, 44*, 1203–1212.
Kolb, B., & Whishaw, I. Q. (1989). Plasticity in the neocortex: Mechanisms underlying recovery from early brain damage. *Progress in Neurobiology, 32*, 235–276.
Lilly, J. C., & Cherry, R. (1954). Surface movements of click responses from the acoustic cerebral cortex of the cat: The leading and the trailing edges of a response figure. *Journal of Neurophysiology, 17*, 521–532.
Lilly, J. C., & Cherry, R. (1955). Surface movements of figures in the spontaneous activity of anesthetized cerebral cortex: The leading and trailing edges. *Journal of Neurophysiology, 18*, 18–32.
Linas, R. R., & Ribary, U. (1992). Rostrocaudal scan in human brain: A global characteristic of the 40-Hz response during sensory input. In E. Basar & T. H. Bullock (Eds.), *Induced rhythms in the brain* (pp. 147–154). Boston: Birkhauser.
Lopes da Silva, F. (1991). Neural mechanisms underlying brain waves: From neural membranes to networks. *Electroencephalography and Clinical Neurophysiology, 79*, 81–93.
Lopes da Silva, F., Pijn, J. P., & Boeijinga, P. (1989). Interdependence of EEG signals: Linear vs. nonlinear associations and the significance of time delays and phase shifts. *Brain Topography, 2*, 9–18.
Lotka, A. J. (1925). *The elements of physical biology*. Baltimore, MD: Williams & Wilkins.
Matousek, M., & Petersen, I. (1973). Frequency analysis of the EEG background activity by means of age dependent EEG quotients. In P. Kellaway & I. Petersen (Eds.), *Automation of clinical electroencephalography* (pp. 75–102). New York: Raven Press.
Nicholson, A. J., & Bailey, V. A. (1935). The balance of animal populations. *Proceedings of the Zoological Society of London, 3*, 551–598.
Nunez, P. (1981). *Electric fields of the brain: The neurophysics of EEG*. New York: Oxford University Press.
Nunez, P. L. (1989). Generation of human EEG by a

combination of long and short range neocortical interactions. *Brain Topography, 1*(3), 199–215.

O'Leary, D. D. M. (1987). Remodelling of early axonal projections through the selective elimination of neurons and long axon collaterals. In G. Bock & M. O'Connor (Eds.), *Selective neuronal death* (pp. 113–142). New York: John Wiley & Sons.

O'Leary, D. D. M., Stanfield, B. B., & Cowan, W. M. (1981). Evidence that the early postnatal restriction of the cells of origin of the callosal projection is due to the elimination of axon collaterals rather than to the death of neurons. *Developmental Brain Research, 1*, 607–617.

Otnes, R. K., & Enochson, L. (1972). *Digital time series analysis*. New York: John Wiley & Sons.

Pandya, D. N., & Barbas, H. (1985). Supplementary motor area structure and function: Review and hypotheses. *Behavioral and Brain Sciences, 8*, 595–596.

Pascual-Marqui, R. D. S. L., Valdes-Sosa, P. A., & Alvarez-Amador, A. (1988). A parametric model for multichannel EEG spectra. *International Journal of Neuroscience, 125*, 73–86.

Purves, D. (1988). *Body and brain: A trophic theory of neural connections*. Cambridge: Harvard University Press.

Rabinowicz, T. (1979). The differentiate maturation of the human cerebral cortex. In F. Falkner & J. Tanner (Eds.), *Human growth: Neurobiology and nutrition* (pp. 97–123). New York: Plenum Press.

Rakic, P. (1985). Limits of neurogenesis in primates. *Science, 227*, 1054–1056.

Rakic, P., Bourgeois, J., Eckenhoff, M., Zecevic, N., & Goldman-Rakic, P. S. (1986). Concurrent overproduction of synapses in diverse regions of primate cerebral cortex. *Science, 232*, 232–234.

Real, L. (1977). The kinetics of functional response. *The American Naturalist, 111*, 289–300.

Rogers, R. L., Baumann, S. B., Papanicolaou, A. C., Bourbon, T. W., Alagarsamy, S., & Eisenberg, H. M. (1991). Localization of the P3 sources using magnetoencephalography and magnetic resonance imaging. *Electroencephalography and Clinical Neurophysiology, 79*, 308–321.

Sanides, F. (1971). Functional architecture of motor and sensory cortices in primates in the light of a new concept of neocortex development. In C. R. Noback & W. Montana (Eds.), *Advances in primatology* (pp. 137–208). New York: Academic Press.

Schade, J. P., & Groeningen, V. V. (1961). Structural development of the human cerebral cortex. *Acata Anatomica, 47*, 79–111.

Smart, I. H. M. (1983). Three dimensional growth of the mouse isocortex. *Journal of Anatomy, 137*, 683–694.

Soloman, M. E. (1949). The natural control of animal population. *Journal of Animal Ecology, 18*, 1–35.

Sroufe, L. A., & Rutter, M. (1984). The domain of developmental psychopathology. *Child Development, 55*, 19–46.

Thatcher, R. W. (1980). Neurolinguistics: Theoretical and evolutionary perspectives. *Brain and Language, 11*, 235–260.

Thatcher, R. W. (1989, February). Nonlinear dynamics of human cerebral development. Paper presented at the First International Conference on Mechanisms on Mind, E. R. John (Organizer), Havana, Cuba.

Thatcher, R. W. (1991). Maturation of the human frontal lobes: Physiological evidence for staging. *Developmental Neuropsychology, 7*(3), 397–419.

Thatcher, R. W. (1992a). Are rhythms of human cerebral development "traveling waves"? *Behavior and Brain Sciences, 14*(4), 575.

Thatcher, R. W. (1992b). Cyclic cortical reorganization during early childhood development. *Brain and Cognition, 20*, 24–50.

Thatcher, R. W. (1993, March). Cyclic cortical morphogenesis: A nonlinear synaptic population model. Abstract presented at the biennial meeting of the Society for Research in Child Development, New Orleans.

Thatcher, R. W. (1994). Cyclic cortical reorganization: Origins of cognition. In G. Dawson & K. Fischer (Eds.), *Human behavior and the developing brain* (pp. 232–268). New York: Guilford Press.

Thatcher, R. W., & John, E. R. (1977). *Functional neuroscience: Foundations of cognitive processing*. Hillsdale, NJ: Erlbaum.

Thatcher, R. W., Krause, P., & Hrybyk, M. (1986). Corticocortical association fibers and EEG coherence: A two compartmental model. *Electroencephalography and Clinical Neurophysiology, 64*, 123–143.

Thatcher, R. W., McAlaster, R., Lester, M. L., Horst, R. L., & Cantor, D. S. (1983). Hemispheric EEG asymmetries related to cognitive functioning in children. In A. Perecuman (Ed.), *Cognitive processing in the right hemisphere* (pp. 125–146). New York: Academic Press.

Thatcher, R. W., Toro, C., Pflieger, M. E., & Hallett, M. (1993). *Multimodal registration of EEG, PET and MRI: Analyses of neural network switching*. Berkeley, CA: Society of Magnetic Resonance in Medicine: Functional MRI of the Brain.

Thatcher, R. W., Walker, R. A., & Giudice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science, 236*, 1110–1113.

Thatcher, R. W., Wang, B., Toro, C., & Hallett, M. (1994). Human neural network dynamics using multimodal registration of EEG, PET and MRI. In R. Thatcher, M. Hallett, T. Zeffiro, E. John, & M. Huerta (Eds.), *Functional neuroimaging: Technical foundations* (pp. 269–278). Orlando, FL: Academic Press.

Thom, R. (1975). *Structural stability and morphogenesis*. Reading, MA: W. A. Benjamin.

Thompson, J., & Stewart, H. (1986). *Nonlinear dynamics and chaos*. New York: John Wiley & Sons.

Tucker, D. M., Roth, D. L., & Blair, T. B. (1986). Functional connections among cortical regions: Topography of EEG coherence. *Electroencephalography and Clinical Neurophysiology, 63*, 242–250.

van der Maas, H. L. I., & Molenaar, P. C. M. (1992). A catastrophe theoretical approach to stagewise cognitive development. *Psychological Review, 99*, 395–417.

Verzeano, M. (1972). Pacemakers, synchronization, and epilepsy. In H. Petsche & M. A. B. Brazier (Eds.), *Synchronization of EEG activities in epilepsies* (pp. 154–188). New York: Springer-Verlag.

Verzeano, M., & Negishi, K. (1960). Neuronal activity in cortical and thalamic networks. *Journal of General Physiology, 43*(Suppl.), 177.

Verzeano, M., & Negishi, K. (1961). Neuronal activity

in wakefulness and in sleep. In G. E. W. Wolstenholme & M. O'Connor (Eds.), *The nature of sleep* (pp. 108–126). London: Churchill.

Volterra, V. (1926). Variazioni e fluttuaxioni del numero d'individui in specie animali conviventi. *Memorial R. Academic Lincei Series, 6*(2), 26–43.

Weiss, P. (1961). Deformities as cues to understanding development of form. *Perspectives in Biology and Medicine, 4*, 660–669.

Weiss, P. (1969). The living system: Determinism stratified. In A. Koestler & J. Smythes (Eds.), *Beyond reductionism* (pp. 25–36). Boston: Beacon Press.

Zigler, E., & Glick, M. (1986). *A developmental approach to adult psychopathology*. New York: Wiley.