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# Early organization of the nonlinear right brain and development of a predisposition to psychiatric disorders

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## Abstract

The concepts of self-organization, state changes, and energy flow are central to dynamic systems theory. In this work I suggest that to apply these general principles to the study of normal and abnormal development, these constructs must be specifically defined in reference to current knowledge of brain development. Toward that end, I present an overview of the properties of self-organizing developmental systems, and then propose a model of attachment dynamics as synchronized energy exchanges that cocreate nonlinear changes of state, discuss the roles of bioamines and energy-generating brain mitochondria in state regulation, and describe the energy-dependent imprinting of synaptic connectivity and neural circuitry in the infant brain. In this application of nonlinear concepts to developmental models of both resistance against and vulnerability to mental disorders, particular emphasis is placed upon the experience-dependent maturation of a system in the orbital prefrontal cortex that regulates psychobiological state and organismic energy balance. This frontolimbic system is expanded in the nonlinear right hemisphere that generates stress-regulating coping strategies, and it serves as the hierarchical apex of the limbic and autonomic nervous systems. Early forming microstructural alterations and energetic limitations of this regulatory system are suggested to be associated with a predisposition to psychiatric disorders.

Although there is now agreement within a wide spectrum of sciences that dynamic systems theory offers powerful insights into the organizational principles of all inanimate and animate systems, the application of its general tenets to specific problems of human psychology and biology has presented a difficult challenge. And yet this model of the mechanism of self-organization, of how complex systems that undergo discontinuous changes come to produce both emergent new forms yet retain continuity, clearly must be relevant to the study of normal and abnormal human development. In this paper, I will suggest that to more deeply integrate nonlinear principles into the discipline of developmental psychopathology, they must not be used as just metaphors but rather directly incorporated in their literal form into the core of the developmental

sciences. In particular, I will propose that current multidisciplinary knowledge regarding three systems concepts—state changes, self-organization, and the central role of energy flows—can more deeply elucidate the mechanisms by which early development indelibly influences all later function and dysfunction.

A fundamental focus of nonlinear dynamic theory is the modeling of complex patterns of *state changes* in all physical and biological systems. This clearly implies that the basic unit of analysis of the process of human development is not changes in behavior, cognition, or even affect, but rather the ontogenetic appearance of more and more complex psychobiological states that underlie these state-dependent emergent functions (Schore, 1994). Lydic (1987, p. 14) points out that “studies that ignore organismic state are analogous to the experiments of physics that ignore time” and that the ubiquity of state-dependent organismic changes “reminds us that biological

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systems are highly dynamic and notoriously nonlinear.” He then concludes that the prospects for future progress in our understanding of state phenomena must include a deeper explication of the role played by the brain systems that biochemically regulate all brain and bodily state phenomena—various discrete groups of bioaminergic neurons of the subcortical reticular formation that innervate wide areas of the brain through diffuse projections. The unique anatomical capacities of these systems to affect large areas simultaneously allow for their central involvement in global, state-associated brain functions.

The concept of psychobiological state lies at the common boundary of the psychological and biological sciences, and as such it can go far to overcome the myopia of “Descartes’s error,” “the separation of the most refined operations of mind from the structure and operation of a biological organism” (Damasio, 1994, p. 250). At all points of human development, but especially in infancy, the continually developing mind cannot be understood without reference to the continually maturing body, and their ongoing interactions become an important interface for the organizing self. This perspective necessitates an infusion of recent data from developmental psychobiology into the disciplines of developmental psychology and developmental psychopathology. Indeed, in a very recent text of this field, Michel and Moore (1995) declare that dynamic system theories are “good models on which to construct the developmental psychobiological approach” (p. 31).

A second core assumption of systems theory is that *self-organization* is characterized by the emergence and stabilization of novel forms from the interaction of lower-order components and involves “the specification and crystallization of structure” (Lewis, 1995). I will argue that this mechanism also describes how hierarchical structural systems in the developing brain self-organize. The developmental neurosciences are now identifying the “lower” autonomic and “higher” central brain systems that organize in infancy and become capable of generating and regulating psychobiological states. These homeostatic structures that maintain stability are primarily

lateralized in the early developing right brain (Chiron et al., 1997), which is, more so than the left, well connected into the limbic system and the mechanisms of autonomic and behavioral arousal, and their maturation is experience-dependent. In light of the ontogenetic principle that the most important information for the successful development of the human brain is conveyed by the social rather than the physical environment, I have proposed that “the self-organization of the developing brain occurs in the context of another self, another brain” (Schore, 1996, p. 60). This organization, like all aspects of human brain maturation, is nonlinear and shows discontinuous developmental patterns.

And lastly, another cardinal feature of nonlinear theory is that it assigns the sources of new adaptive forms to the self-organizing properties of systems that use *energy* in order to facilitate the cooperativity of simpler subsystem components into a hierarchically structured complex system (Thelen, 1989). This model therefore emphasizes the central roles of thermodynamics, the science of energy flow, and bioenergetics, the study of how energy is used for the work of establishing biological order, toward the understanding of the creation of new complex structural forms. The functional activity of the brain is an energy-requiring process. One of the most striking aspects of development is found in the growing brain’s rapidly increasing capacity to generate and sustain higher and higher levels of energy metabolism over the first 2 years of life.

The biosynthetic processes that underlie the proliferation of synaptic connections in the postnatally developing brain demand, in addition to sufficient quantities of essential nutrients, massive amounts of energy, so much so that the metabolic rate of the young child’s brain is significantly greater than adults (Kennedy & Sokoloff, 1957). Sequential increments in metabolic rates take place in various regions of the brain during postnatal development, and this accounts for the finding that the brain matures in discontinuous discrete stages (Martin et al., 1988). Because of the relationship between energy metabolism and physiological function, this event is central to

the emergence of “higher” brain systems and the appearance of more complex behaviors. A central principle of systems theory asserts that self-organization increases the rate of energy transfer, and the more ordered the complexity, the faster the energy flows (Goerner, 1995). In light of the fact that energy systems within the developing brain responsible for self-organization are themselves undergoing dramatic transformation, I will propose that knowledge of the gene–environment interactions responsible for the onset of aerobic energy metabolism in mitochondria, the preeminent source of biological energy in the brain, is relevant to an understanding of how neurons increase their synaptic connectivity and how energy fluxes organize new adaptive structures in development.

The energy metabolism of the brain is regulated and coordinated by biogenic amines that are delivered to widely distributed regions by ascending, unmyelinated projections from the brain stem. Ontogenetic changes in these monoaminergic systems result in progressive increases in organismic energy metabolism. These neuromodulators, in concert with different subtypes of their receptors that determine whether they augment local excitatory or inhibitory activity, alter and synchronize the input–output characteristics of brain cell populations in accord with changes in arousal. In human infancy these same bioagents that regulate central arousal and bodily states play an essential ontogenetic role—they also act as morphogenetic agents that induce the growth and organization of the developing brain. Most intriguingly, it is now evident that these bioamines are regulated by the interaction between caregiver and infant. Neurobiological studies can thus offer us valuable information about how social factors modulate the effects of state organization on development, that is, how early interpersonal experiences induce the bioenergetic changes that support the growth of brain interconnections and, therefore, more complex structures and emergent functions.

This latter problem is, of course, a central focus of models of self-organization. To further explore this question, in this paper I will present an application of dynamic systems

theory to normal development, and then to a conceptualization of atypical development, but I will address the underlying mechanisms common to both. Within this framework, I will propose models of the nonlinear phenomena of attachment dynamics, of the roles of bioamines and mitochondria in self-organizational processes of synaptic connectivity, and of the energy-dependent imprinting of neural circuitry in the infant brain. In this application of self-organizational concepts to developmental models of both resistance against and vulnerability to mental disorders, I will particularly focus on the experience-dependent maturation of a frontolimbic system that regulates psychobiological states and organismic energy balance in a nonlinear fashion. This prefrontal system is expanded in the right hemisphere that plays a superior role in enabling the organism to cope actively and passively with stress. In the final section, I will suggest that early forming microstructural pathology and energetic limitations of this specific system are associated with a predisposition to later appearing psychiatric disorders. This work is a continuation of recent writings in which I contend that less than optimal gene–environment interactions that occur during the critical period of growth of this system produce a frontolimbic organization that is vulnerable to a spectrum of psychopathologies (Schore 1994, 1996).

### **Functional Properties of Self-Organizing Developmental Systems**

A fundamental property of any developing living system is that it is open to and interactive with its particular environment. This applies to the human infant, who actively seeks environmental input, adjusts to the variations of this input, transforms it with its organizing properties, and incorporates it into its developing form. In such reciprocal interchanges the dynamic activity of the developing system, in turn, produces changes in the proximal environment. As a result of these continuous self–environment interactions the system establishes dynamic equilibria both within itself, and between itself and its environment (Michel & Moore, 1995). It is important to

note that in the physical sciences dynamic systems theories imply that “the environment” is singularly the physical environment. But in the case of a living system, one that proceeds through development to ultimately attain a mature form that can pass on its genomes, these primordial interactions are with the social environment—others of its species, and in particular, the primary caregiver.

A central tenet of dynamic systems theory prescribes that in these early transactions the developing biological system is openly exchanging both energy and matter with the environment. Indeed, ongoing development requires an “open” system, one which inputs free energy from the environment, uses it for matter–energy transformations, and exports it in degraded form. As a result of incorporating the dissipation of energy and matter of its environment into itself, the developing system moves away from equilibrium and remains for periods of time in a state of disequilibrium, one that exhibits an increase in negative entropy. In this manner the flow of energy through the system creates conditions for strong deviations from thermodynamic equilibrium, and this results in the phenomenon of self-organization. When a system is “far-from-equilibrium” (Prigogine & Stengers, 1984) energy is continually dissipated in the very process that binds the elements of the system together, allowing the elements to “behave in a synchronous fashion, to couple with each other through ongoing feedback, and to act together in macroscopic entities rather than independent entities” (Lewis, 1995, p. 79).

As the patterns of relations among the components of a self-organizing system become increasingly interconnected and well ordered, it is more capable of maintaining a coherence of organization in relation to variations in the environment. Given a particular organization and a particular environmental context, the system prefers a certain range of states. A system passes through a succession of a finite number of states, but it must eventually reenter a state that it has previously encountered. These cycles of contiguous states represent the dynamic attractors of the system, and the path taken by the system from one state to another defines a “tra-

jectory” that describes the time evolution of the system. If the system is driven away from its stationary state, it will tend to return to that state; the time it takes to return to stationarity is a function of the stability of the system. The stability of a system is dependent upon its capacity to transition between, and thereby exist within, a range of possible states, and this property is a consequence of its dynamic processes.

Self-organization, the process whereby order and complexity create more order and complexity, proceeds hierarchically, as each level of self-organization builds on the level that precedes it. Different levels of organization are represented in hierarchical models of development, and maturation in infancy is best characterized by an alternation of rapid development and slower rates, even plateaus, which delimit “stages” (McGuinness, Pribram, & Pirnazar, 1990). Developmental change results from a series of states of stability and instability and phase transitions in the attractor landscape that irreversibly alter the trajectory of the system and allow for the organization of new states of matter-dissipative structures. These “points of bifurcation,” when new states can potentially evolve from preceding ones, occur in the context of a “mutually determining organism–environment interaction” (Schwalbe, 1991). During these intervals, the open system, due to increasingly complex interconnections within its components and the creation of feedback mechanisms, can now act not only on the output of an environmental system with which it is interacting, but also iteratively to amplify its own output, and so it is sensitive to fluctuations of both external and internal processes. Complex systems thus show sensitive dependence on initial conditions, the state of the system when fluctuations first initiate change, and small differences can be amplified into large effects over many cycles of iteration. These fluctuations drive the system to explore new states.

Most importantly, environmental perturbations that occur during points of bifurcation create nonlinear breaks in organization and discontinuous changes in system states. According to Schwalbe (1991, p. 276),

Chaos . . . arises at the point of phase transitions, when systems are “choosing” between different process structures. What occurs at these points is that random fluctuations in energy can be amplified throughout the entire system so that a new process structure is formed. Chaos in dynamical systems is thus a product of the same forces that create process structures and give rise to self-organization.

Nonlinearity, the source of rapid change and novel structure, is thus also the source of potential order and stability. It is now well established that nonlinearity can produce either positive (amplifying) or negative (dampening) feedback, stability or instability, convergence (coupling or entrainment) or divergence (Goerner, 1995). Along these same lines, Jackson (1991), in chaos research in the physical sciences, argues that “entrainment” of a dynamic system is a precondition to control of dynamic flows, and that this allows for “hierarchical systems to adapt to environmental changes” (p. 4839). Shinbrot, Grebogi, Ott, and Yorke (1993) report that chaotic systems are extremely sensitive to small perturbations and that these tiny feedback perturbations control their trajectories. These researchers experimentally demonstrate that small perturbations can be used both to stabilize regular dynamic behaviors and to direct chaotic trajectories rapidly to a “desired state.” They also show that, using only tiny perturbations, one can switch between a rich variety of dynamical behaviors as circumstances change. Referring to “the advantage of chaos,” they conclude that “incorporating chaos deliberately into practical systems therefore offers the possibility of achieving greater flexibility in their performance” (p. 411). These findings fit nicely with Thelen’s (1995) assertion that times of instability are essential to give a developing system flexibility to select adaptive capacities.

Developing organisms “internalize” environmental forces by becoming appropriately structured in relation to them and by incorporating an internal model of these exogenous signals they develop adaptive homeostatic regulatory mechanisms which allow for stability in the face of external variation. The

regulation of the organism, which maintains internal stability and output regulation and enables an effective response to external stimuli, therefore depends on the formation of a dynamic model of the external environment. Self-organizing systems are thus systems that are able capable of generating new internal representations in response to changing environmental conditions.

These abstract self-organizational principles apply in a general way to all living systems. The next question is, how do these overarching principles specifically apply to ontogeny of the human infant, itself described as “very nonlinear” (Thelen, 1989)? Schwalbe (1991) portrays the human as “a nonlinear dynamic system,” an inherently dynamic energy transformation regime that coevolves with its environment, one that self-organizes when exposed to an energy flux. In a scenario that resembles attachment dynamics, he postulates that the infant becomes “attuned to” an external object in its environment who consistently responds in a stimulating manner to the infant’s spontaneous impulsive energy dissipating behaviors.

The concept of energy, central to dynamic systems theory, is rarely used in developmental psychology. In a recent article on the self-organization of developmental paths, Lewis (1995) asks, “What is the best analogy for energy in psychological systems?” He points out that the energy flowthrough for self-organization has been conceived of as “information,” an idea that fits well with Harold’s (1986) formulation that information is a special kind of energy required for the work of establishing biological order. He then goes on to argue that information can be defined subjectively as that which is relevant to an individual’s goals or needs, an idea which echoes recent concepts of emotion as adaptive functions that guide attention to the most relevant aspects of the environment, and of emotional appraisals that monitor and interpret events in order to determine their significance to the self. Lewis concludes that there is no better marker of such information than the emotion that accompanies it, that emotions amplify fluctuations to act in self-organization, and that the processing of relevant infor-

mation in the presence of emotion may be analogous to the flowthrough of energy in a state of disequilibrium. Stability is a property of interpersonal attractors that maintain their organization by perpetuating equilibrium as well as resolving emotional disequilibrium.

In applying nonlinear systems concepts to development, Lewis emphasizes the salience of “dyadic self-organization,” which is epitomized by the creation of specific forms of communication between the mother and infant. When emotion is present in this dyadic interaction each partner’s behavior is monitored by the other, and this results in the coupling between the output of one partner’s loop and the input of the other’s to form a larger feedback configuration. These transactions represent a flow of interpersonal information accompanying emotion, and critical fluctuations, amplified by positive feedback, lead to disequilibrium and self-organization. Attachment patterns are posited to arise through consolidating interpretations (working models) of caretaking contingencies, and such representations take into account both emotional responses to caretaking fluctuations and maternal behavioral characteristics. Core attachment organizations stabilize with age and branch into attachment categories, and in this manner emotional experiences with caregivers set the course of the individual’s behavioral style and emotional disposition (Lewis, 1995).

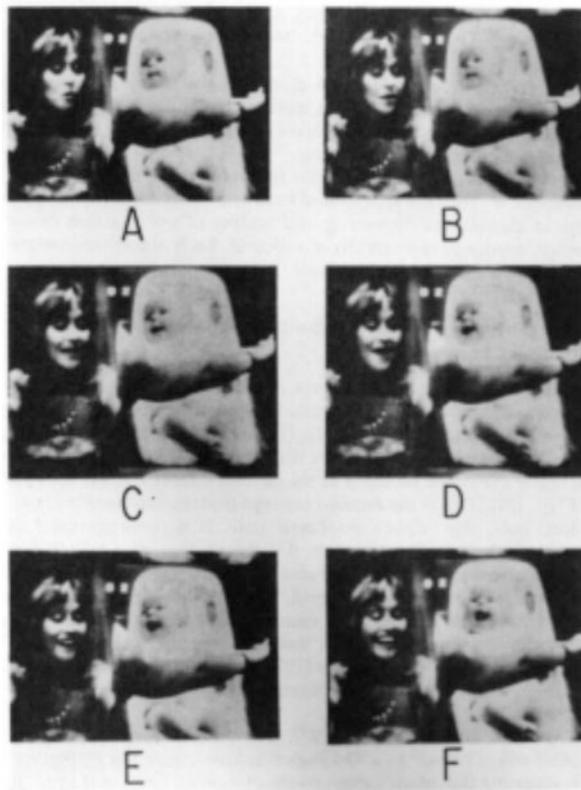
### **Nonlinear State Changes and Organization of Attachment Dynamics**

In previous work I have proposed that emotional transactions involving synchronized ordered patterns of energy transmissions (directed flows of energy) represent the fundamental core of the attachment dynamic (Schore, 1994). This conception, congruent with nonlinear dynamic models, focuses on reciprocal affective exchanges in which the caregiver psychobiologically regulates changes in the infant’s state. These interactions occur in sensitive periods of infancy, phases when energy is high in the infant and the parent for receptivity to each other’s cues and for adapting to each other. The creation of this dy-

namic system of “contingent responsivity” occurs in the context of face-to-face interactions, and it relies heavily upon the processing of visual and auditory (prosodic) information emanating from the most potent source of stimulation in the infant’s environment—the mother’s face. The human face is a unique stimulus whose features display biologically significant information.

Indeed, over the 1st year of life visual experiences play a paramount role in social and emotional development (Preisler, 1995; Wright, 1991). These face-to-face dialogs create a match between the expression of arousal-accelerating, positively valenced internal states. For this to happen, the mother must monitor the infant’s state as well as her own and then resonate not with the child’s overt behavior but with certain qualities of its internal state, such as contour, intensity, and temporal features. In physics, a property of resonance is sympathetic vibration, which is the tendency of one resonance system to enlarge and augment through matching the resonance frequency pattern of another resonance system. Dynamically fluctuating moment-to-moment state sharing represents an organized dialog occurring within milliseconds, and it acts as an interactive matrix in which both partners match states and then simultaneously adjust their social attention, stimulation, and accelerating arousal in response to the partner’s signals. In this mutually synchronized attunement of emotionally driven facial expression, prosodic vocalization, and kinesic behaviors, the dyad coconstructs a mutual regulatory system of arousal which contains a “positively amplifying circuit mutually affirming both partners” (Wright, 1991).

In such facial mirroring transactions (see Figure 1) the resonating caregiver facilitates a state transition, manifest in a change in patterns of “energetic arousal,” and a shift from quiet alertness (point A) into an intensely positive affective state (point F). Stern (1990) describes exchanges of smiles in escalating overlapping waves that propel the other into “higher orbit.” At resonance, energy transfer from the external agent to the resonant system is maximal (Katsuri, Amtey, & Beall, 1984).

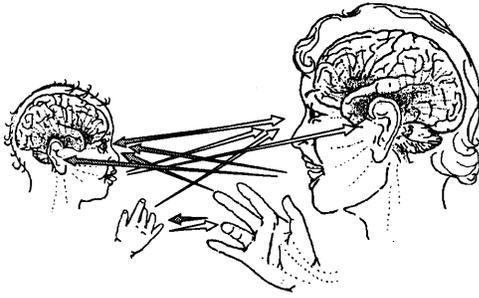


**Figure 1.** Photographs of a “mirroring” sequence. Mother and infant are seated face to face, looking at each other. At point A, mother shows a “kiss-face,” and infant’s lips are partially drawn in, resulting in a tight, sober-faced expression. At point B, mother’s mouth has widened into a slightly positive expression, and infant’s face has relaxed with a hint of widening in the mouth, also a slightly positive expression. At point C, both mother and infant show a slight smile, further widened at point D. At point E, the infant breaks into a “full gape smile.” At point F, the infant has shifted the orientation of his head further to his left, and upward, which heightens the evocativeness of the gape-smile. Total time under 3 s (Beebe & Lachmann, 1988).

In accord with complex systems theory, an environmental perturbation triggers a rapid and discontinuous change in state, one far-from-equilibrium that leads to the potential for achieving novel states of temporal stability. Schwalbe (1991) posits that the nonlinear self acts iteratively, so that minor changes, occurring at the right moment, can be amplified in the system, thus launching it into a qualitatively different state. The caregiver is thus modulating changes in the child’s energetic state, since arousal levels are known to be associated with changes in metabolic energy. Indeed, energy shifts are the most basic and fundamental features of emotion, discontinu-

ous states are experienced as affect responses, and nonlinear psychic bifurcations are manifest as rapid affective shifts.

In light of the facts that in these interchanges the infant’s and mother’s homeostatic systems are “open” and linked together (Hofer, 1990; Kalin, Shelton, & Lynn, 1995) and are “semipermeable to regulation from the other” (Pipp, 1993), the transition embedded in the psychobiological attunement of the dyad involves an alteration in the infant’s bodily state. These interactions increase over the 1st year, since the baby’s ability to adjust the amount of interaction with mother in accordance with internal states increases with phys-



**Figure 2.** Channels of face-to-face communication in protoconversation. Protoconversation is mediated by eye-to-eye orientations, vocalizations, hand gestures, and movements of the arms and head, all acting in coordination to express interpersonal awareness and emotions. Adapted from Trevarthen (1993).

iological and psychological maturity. An essential attachment function is to promote the synchrony or regulation of biological and behavioral systems on an organismic level. Damasio (1994) concludes that primordial representations of body states are the building blocks and scaffolding of development. The infant's core sense of self is bodily based, and since body processes abide by the laws of nonlinear dynamics (Goldberger, Rigney, & West, 1990), the emerging self is grounded in biologically mediated self-organizing properties (Pipp, 1993). Even more specifically, synchronized gaze transactions induce changes in the infant's bodily states by maternal regulation of the child's autonomic nervous system, and this interactive mechanism represents a mutual entrainment of the mother's and infant's brains, including a coupling of the activation of subcortical areas responsible for the somatic components of emotion.

In support of this model, Trevarthen (1993) argues that the epigenetic program of brain growth requires brain-brain interaction and occurs in the context of a traffic of visual and prosodic auditory signals which induce instant positive emotional states in both infant and mother (see Figure 2). The resonance of the dyad ultimately permits the intercoordination of positive affective brain states. Trevarthen concludes that "the affective regulations of brain growth" are embedded in the context of

an intimate relationship, and that they promote the development of cerebral circuits.

### **Central Role of Bioamines in Regulation of Energy Metabolism of Developing Brain**

In her recent writings, Thelen (1995) asserts that dynamic systems theory needs to be more closely tied into a theory of brain development that addresses the fundamental question, how is the brain molded through experience? Although nonlinear systems theory has been used to model brain functions, the problem of what causes the infant brain to change, of how this organization is influenced by the interaction of genetic programming and environmental history, has not received much attention. Yet, Cicchetti and Tucker (1994) now emphasize that the identification of the brain's self-organizing mechanisms is a primary challenge of science and that indeed it may reveal the best description of development. These authors also point out that certain interactions between an "open homeostatic system" and the environment are critical to the differentiation of brain tissue and that particular environmental experiences during sensitive periods are necessary for the induction of certain developmental changes that result from the maturation of the infant brain.

This leads to the fundamental questions, what specific kinds of experiences induce brain maturation and how does this early experience influence the "social construction" (Eisenberg, 1995) of the human brain? Toward that end I have proposed that attachment experiences essentially represent affective transactions in which the caregiver modulates changes in the infant's arousal levels and thereby in its energetic state. This is accomplished by her psychobiological regulation of neurohormones and catecholaminergic neuromodulators in the infant's developing brain (Hofer, 1990). In the context of face-to-face interactions the mother triggers production of corticotropin releasing factor (CRF) in the infant's paraventricular hypothalamus that, in turn, raises plasma concentrations of noradrenaline, activates the sympathetic nervous system, increases oxygen consumption and en-

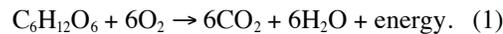
ergy metabolism, and generates a state of emotional excitement. CRF, which controls endorphin and ACTH production in the anterior pituitary, also activates the ventral tegmental system and augments the activity of the other catecholamine, dopamine, thereby elevating dopaminergic arousal and an elated state in the infant.

These same catecholamines are known to be centrally involved in the regulation of brain metabolic energy levels, morphogenesis, and the maturation of cortical areas during different developmental stages (Berntman, Dahlgren, & Siesjo, 1978; Lauder & Krebs, 1986). For this reason, the energy transformations occurring in attachment bond formation are vitally important for the infant's continuing neurobiological development. Since the ascending bioaminergic "reticular" systems that are responsible for various states of arousal are in an intense state of active growth in infancy, the regulatory transactions embedded in the emotional relationship are occurring at a time when the infant's circuitry of the biological hardware of arousal is expanding. In fact, there are specific postnatal critical periods and developmental sequences for the appearance of the biogenic amines dopamine and noradrenaline. Central catecholaminergic neurons undergo an accelerated development in mammalian infancy, and their proliferating axonal terminals hyperinnervate distant cortical territories. In these same periods various types of regional catecholaminergic receptors are amplified, especially the D1 dopamine receptor that is found throughout the prefrontal cortex and limbic system associated with memory, learning, and cognitive processing (Huang, Zhou, Chase, Gasella, Aronin, & DiFiglia, 1992), as well as the beta noradrenergic receptor that is activated in states of emotional excitement (Cahill, Prins, Weber, & McGaugh, 1994). These events are experience-dependent, and they account for the evolution of an increasing tolerance for higher levels of arousal over the course of the 1st year.

During early critical periods, biogenic amines, the same agents that regulate emotion and motivation throughout the life span, play an important role in the responsiveness of the cortex to environmental stimulation and in the

regulation of the temporal framework of developmental processes. These neuromodulators influence the ontogeny of cortical circuitry and have long-lasting effects on synaptic plasticity and on biochemical processes that mediate developmental influences (Foote & Morrison, 1987). Their activation of both glycogenolysis, a cascade of biochemical reactions that trigger the release of glucose in conditions of intense activity, and the pentose phosphate pathway, a pathway that mediates biosynthetic processes, underscores their preeminent role in the regulation of energy substrate availability in the developing brain.

Catecholamines modulate cerebral circulatory systems and the blood-brain barrier that delivers and exports metabolic substrate to the brain, thereby regulating the responsiveness of large areas of the brain to inputs in a coordinated manner (see Schore, 1994 for a detailed discussion). The growth and organization of the brain is highly dependent upon the continued availability of substrate, and in postnatal periods its production of energy shifts from anaerobic to aerobic oxidative metabolism, thereby enabling a significant increase in output that can sustain the very large energy requirement of brain cells for differentiation and the formation of connections. The brain's main metabolic fuel is glucose, which in the presence of oxygen undergoes complete combustion to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ :



The free energy liberated in this exergonic reaction is partially trapped as adenosine triphosphate (ATP), the main source of energy in living matter, in glycolysis and oxidative phosphorylation (Erecinska & Silver, 1989). ATP is generated both in glycolysis, a process located in  $\text{Na}^+, \text{K}^+$ -ATPase activity, especially at the plasma membrane surrounding the cell and in synaptic nerve endings (Erecinska, Nelson, & Silver, 1996), and in oxidative phosphorylation, the preeminent supplier of ATP in biological systems. This latter process occurs in mitochondria and reflects the activity of cytochrome oxidase, the enzyme that supports the high aerobic energy metabolism of the brain (Wong-Riley, 1989). The activity

of these enzymes is coordinated (Hevner, Duff, & Wong-Riley, 1992) and influenced by catecholamines (Van der Krogt & Belfroid, 1980), and since they act as regulators, the effects of their action involve large amplification factors. The major inactivation of biogenic amines is performed by monoamine oxidase, an enzyme located solely in mitochondria.

Levels of  $\text{Na}^+, \text{K}^+$ -ATPase increase dramatically in early development during periods of neuronal arborization (Bertoni & Siegel, 1978), and cytochrome oxidase activity, regulated by oxygen concentrations, increases and peaks at the time of most rapid growth and maturation (Wong-Riley, 1989). During the critical period of a brain region, growth in neurons occurs essentially in dendrites, and is manifest in heightened levels of synaptogenesis.  $\text{Na}^+, \text{K}^+$ -ATPase and cytochrome oxidase are heightened in dendrites, and this accounts for the fact that dendritic metabolism makes the largest contribution to the metabolic activity of the brain. In postnatal development mitochondria are associated with the presynaptic and postsynaptic processes of developing synapses. In these same time periods catecholamines induce dynamic changes in the shape and branching patterns of dendrites and the growth of dendritic spines. These spines have the greatest energy requirements and density of mitochondria in the brain, and they act as potential sites of synaptic contact which modulate rapid changes in the nervous system throughout the course of its development.

It is now well established that the size and complexity of dendritic arbors increase in development and that dendritic growth and synaptogenesis of the postnatally developing brain is "experience-sensitive." Indeed, the neurodevelopmental processes of dendritic proliferation and synaptogenesis which are responsible for postnatal brain growth are critically influenced by events at the interpersonal and intrapersonal levels. As mentioned, the events embedded in interpersonal transactions can be very fast acting, yet structure-inducing. Indeed, modifications of dendritic spines occur "within minutes of a stimulus train that lasts for a fraction of a second" (Lynch, 1986, p. 7). Dopamine, regulated within rapid

mother-infant affective transactions, activates excitatory NMDA receptors (Knapp, Schmidt, & Dowling, 1990) and modulates the excitability of prefrontal neurons by altering dendritic spine responses to excitatory inputs (Smiley, Levey, Ciliax, & Goldman-Rakic, 1994). Excitatory sensory input, including visual input, is required for the increases in mitochondrial cytochrome oxidase-driven oxidative metabolism in spines of growing dendrites of the developing cerebral cortex (Wong-Riley, 1979). Most intriguingly, catecholamines initiate protein synthesis and the maturation of energy transduction in mitochondria (Houstek, Kopecky, Baudysova, Janikova, Pavelka, & Klement, 1990), and infant animals exposed to early environments that allow for social experiences show larger mitochondrial populations, an indicator of metabolic energy activity, as well as increased dendritic volume, in developing cortical areas (Sirevaag & Greenough, 1987).

#### **Energy-Dependent Imprinting of Neural Circuits During Critical Periods of Infancy**

A central tenet of dynamic systems theory holds that at particular critical moments, a flow of energy allows the components of a self-organizing system to become increasingly interconnected, and in this manner organismic form is constructed in developmental processes. These moments occur in instances of imprinting, the very rapid form of learning that irreversibly stamps early experience upon the developing nervous system and mediates attachment bond formation. It is now thought that a stimulus which elicits a high level of catecholamine-generated arousal facilitates the imprinting process and exerts an enduring influence on neural development (a perfect description of the emotionally expressive face of the attachment object), and that certain types of early learning experiences associated with new levels of arousal lead to rapid increases in the volume of hemispheric blood flow. Both imprinting and arousal are associated with increased metabolic activity, and both are regulated by cate-

cholamines, agents that have pronounced effects on cerebral oxidative energy metabolism and cerebral blood flow.

During very early development, the neonatal cerebral metabolic rate that sustains early cortical function is very low. But as infancy proceeds, blood flow, known to correlate with changes in arousal, and to be an indicator of regional oxidative metabolism, rises to maximal levels and then declines (Kennedy, Grave, Jehle, & Sokoloff, 1972). Kennedy suggests that the peak elevation in early infancy specifically reflects the increased energy demands associated with biosynthetic processes essential for growth and development of differentiating cortical structures and their emergent functions. In this period of intense growth, the metabolic activity that supports this growth is heightened, so much so that the young child's cerebral metabolic rate consumes one-half of the total body oxygen consumption (Kennedy & Sokoloff, 1957).

In a similar dynamic scenario, Purves and LaMantia (1990) demonstrate that mitochondrial cytochrome oxidase-rich zones in the cerebral cortex increase in number in development, and propose that the pattern of high metabolic activity in these areas demarcates modular circuits. They further suggest that novel circuits are constructed in a critical period of postnatal life, that modular and processing units are added progressively during the period of brain growth and maturation, and that modular circuit formation wanes in the later stages of postnatal development. They conclude that critical periods, "epochs in early life when the brain is particularly sensitive to the effects of experience" represent the normal duration of the construction of cytochrome oxidase-labeled circuits.

Indeed the dramatic transformations of energy production which occur in particular portions of the maturing nervous system during specific postnatal temporal intervals represent the physiological basis of developmental stage and critical period phenomena, and these events allow for the onset of increasing complexity of structure and efficiency and integration of function, just as described by dynamic systems theory. In recent writings (Schore, 1994, see chapters 11 and 36) I have

proposed that the onset of a critical period of growth in a differentiating brain region is defined by a sudden switch from anaerobic to aerobic energy metabolism. A mature neuron has greater energy-consuming demands than an immature neuron, and this transformation is expressed, at the intracellular level, by a replication of the mitochondrial genome, a rapid multiplication of mitochondrial biogenesis, an elevation of environmentally regulated mitochondrial protein synthesis, and a significant increase in cytochrome oxidase levels. These fast onset, discontinuous changes that occur within "the period of rapid mitochondrial proliferation" (Pysh, 1970) result in an augmentation of cellular energy metabolism, since glycolysis alone only produces 2 mols of ATP per mol of glucose, while oxidative phosphorylation produces 36 (Erecinska & Silver, 1989).

The increased number and onset of aerobic metabolism in mitochondrial populations within maturing regions of the infant's developing brain allow for the generation of significantly higher levels of biological energy that are available for "morphogenesis," the generation of new forms during growth and development, that is for the processing of genetic information, biosynthesis, and the transport of building blocks to their final destination (Harold, 1986). The transient increase in the division and production of new mitochondria peaks just when the dendrites are growing out, a fact that may account for the finding that in a developing system, postsynaptic neurons respond initially to excitatory inputs by heightening their energy metabolism (Mjaatvedt & Wong-Riley, 1988). I suggest that during the critical period growth of a particular region, the peaks of heightened energy metabolism described by Wong-Riley, Purves and LaMantia, and Kennedy represent a coordinated flow of energy through the components of a system that is now synaptically coupling into a circuit. This directed energy is continually dissipated in the very process that binds the elements of the system together; that is, it allows for the coordinated onset of mitochondrial energy metabolism among the neurons, glia, and endothelial cells within contemporaneously differentiating cortical columns.

Most importantly, the dramatic increase in the number of mitochondria during a critical period results in larger and larger flows of energy within more and more interconnected elements that can be used for self-organizational processes.

Since these bioenergetic transformations are coordinated over long distances, they also underlie the critical period construction of a neural circuit—a self-contained neuronal network which sustains a nerve impulse by channeling it repeatedly through the same network. In a discussion of the stabilization of excitatory Hebbian cell assemblies, Singer (1986) suggests that pathways are formed between elements that have a high probability of being active at the same time. This selection process serves to develop assemblies of reciprocally coupled neurons that allow for the organization of a reverberating circuit. He also states that these experience-dependent processes rely both on cortical sensory processing of information from the “outer” world and on internally generated signals involving catecholamines from the reticular formation which reflect the central state of the organism during a postnatal period.

Hudspeth and Pribram (1992) propose that a maturation period has three phases: an accelerating edge that reflects a changing state in the brain region; a peak that reflects the attainment of a new state; and a decelerating edge, in which a stable equilibrium within the state is established. I deduce that the peak phase is identical to the metabolic peak described above, and that in its critical period of maturation a particular brain region is an object of an energy flux which creates conditions for strong deviations from thermodynamic equilibrium that result in self-organization. The last phase may be related to the fact that in a developing system neurons initially receive excitatory inputs that heighten energy metabolism followed by inhibitory inputs that lower metabolism. This developmental shift from excitation to inhibition may reflect an early overexpression of excitatory NMDA glutamate receptors to later maturing inhibitory GABAergic systems. Glutamate is metabolized in mitochondria, and GABA-T, the

enzyme that degrades GABA, is located in this organelle. Overall, these phenomena are more accurately described by the second law of thermodynamics, which deals with the efficiency with which energy is used and the amount of useful work to which the energy is put, rather than to the first law, the conservation of energy.

In light of the facts that energy metabolism peaks in a critical period of a developing brain region when dendrites are growing and neurons are attaining a new state of organization, and that dendritic spines have the greatest energy requirements in the brain, I would characterize their local cellular environment at this specific time as a “far-from-equilibrium system.” It is now held that energy-regulating bioamines modulate ion channels in dendrites and that excitatory events occurring in dendrites within a “narrow time window” produce a “much bigger response” than outside this window, thereby allowing for interactions among synapses to be “highly nonlinear” (Johnston, Magee, Colbert, & Christie, 1996). Expanding upon these ideas, I suggest that although dendritic spines represent a unique site for receiving communications from other cells, these points of interface with the local environment, especially in critical periods, also potentially expose the neuron to a state of “oxidative stress,” thereby making the cell vulnerable to excitotoxic “apoptotic” or “programmed cell death” (Margolis, Chuang, & Post, 1994).

Apoptosis plays a crucial role in the early development and growth regulation of living systems. This same mechanism may underlie the developmental process of circuit pruning, the selective loss of connections and redistributions of inputs that allow for the appearance of an emergent function. Regressive events such as cell death and the elimination of long axon collaterals and dendritic processes are essential mechanisms of brain maturation. A large body of evidence supports the principle that cortical networks are generated by a genetically programmed initial overabundant production of synaptic connections, which is then followed by a process of competitive interaction to select those connections that are most

effectively entrained to environmental information. "Parcellation," the activity-dependent fine tuning of connections and winnowing of surplus circuitry, dominates the third maturational phase described by Hudspeth and Pribram.

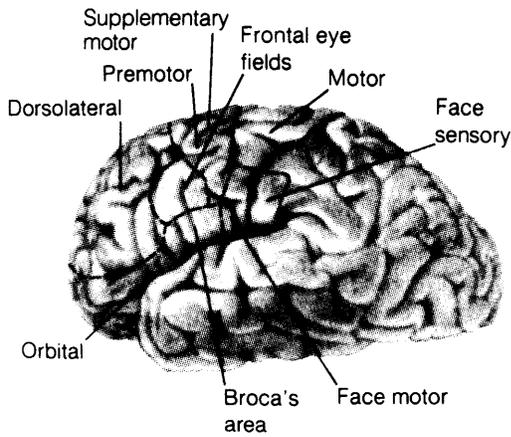
Parcellation is responsible for the selective loss of synapses that determines the microcircuitry within a cortical region, and this same mechanism of functional segregation also allows the developing brain to become increasingly complex, a property of a self-organizing system. Furthermore, this process has been described as analogous to natural selection. Changeux and Dehaene (1989) point out that the "Darwinian" selective stabilization of surviving synapses that have functional significance in a particular environment occurs in cortical areas during postnatal sensitive periods. These findings imply that maternal behavior, the preeminent source of environmental information for the infant, functions as an agent of natural selection that shapes the trajectory of the infant's emerging self. They may also bear upon the mechanism of "maternal effects" (Bernardo, 1996), the influence of the mother's experiences on her progeny's development and ability to adapt to its environment.

Studies of the infant brain thus have direct implications for a more precise elucidation of dynamic systems theories. A fundamental postulate of this model holds that a condition of chaos exists when a system must move from a previously ordered, yet obsolete adaptive state to a more flexible state in order to be better adapted to novel aspects of a currently changing environment. The term "self-organization" can be imprecise and misleading, because first, despite the implications of the two words used to describe this process, self-organization occurs in interaction with another self—it is not monadic but dyadic. And second, the organization of brain systems does not involve a simple pattern of increments but rather changes in organization. Development, the process of self-assembly, thus involves both progressive and regressive phenomena, and is best characterized as a sequence of processes of organization, disorganization, and reorganization.

### **Organization of Regulatory System in Orbitofrontal Cortex That Manifests Chaotic Dynamics**

According to chaos theory, the stabilization of reverberating circuits in early development allows for the organization of a network that can amplify minor fluctuations over cycles of iteration, and thereby influences the system's trajectory. This reexcitatory activity launches the system into a different state, but it also facilitates the "persistence" of a memory trace, an important advance, since "attractors might be thought of as either as memories held by the neural network or as concepts" (Kaufmann, 1993, p. 228). As previously mentioned, these attractors maintain the system's organization by acting as adaptive homeostatic regulatory mechanisms that allow for stability in the face of external variation. Of particular importance to the regulation of nonlinear emotional states are cortical-subcortical circuits, especially those that directly link cortical areas that process current information about changes in the external social environment with subcortical information about concurrent alterations in internal bodily states.

In earliest human infancy, before most areas of the cortex are even myelinated, limbic areas of the amygdala are dominant in the processing of emotional information. A critical period for the maturation of particular rapidly developing temporolimbic and cortical association areas onsets in the middle of the 1st year. By the end of this year the orbitofrontal region of the prefrontal cortex (see Figure 3), an area that contains neurons that fire in response to faces, first become preeminently involved in the processing of interpersonal signals necessary for the initiation of social interactions and in the regulation of arousal and body states, properties that account for its central involvement in attachment neurobiology. The orbitofrontal system matures in the last half of the 2nd year, a watershed time for the appearance of a number of adaptive capacities. These advances reflect the role of the frontal lobe in the development of infant self-regulatory behavior (Dawson,



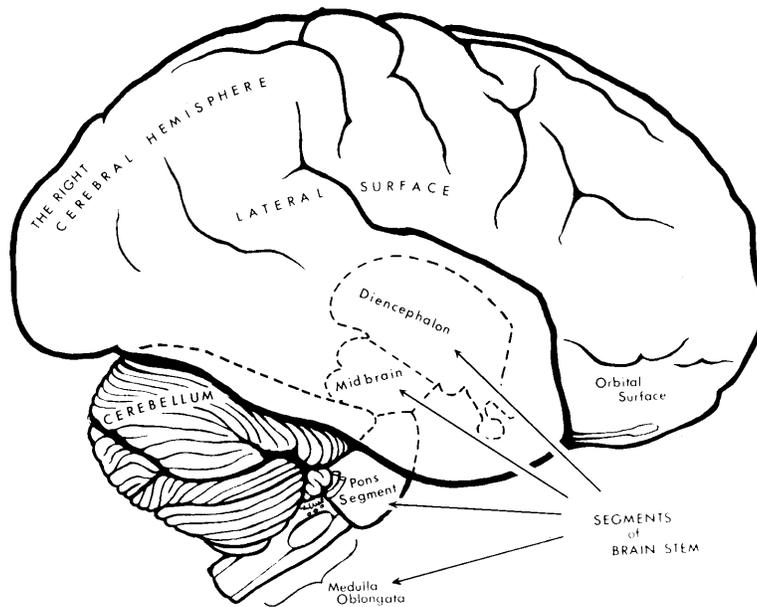
**Figure 3.** Boundaries of functional zones of the human cerebral cortex, showing the orbital and dorsolateral prefrontal areas (from Kolb & Whishaw, 1990).

1994) and are relevant to Cicchetti and Tucker's (1994) assertion that the homeostatic, self-regulating structures of the mind are the major stabilities in the chaotic dynamics of psychological and neural development. Because orbital activity is essentially implicated in maintaining organismic homeostasis, the operational nature of this prefrontal cortex is best described as a nonlinear dynamic system.

The functional properties of this structural system can only be understood in reference to its unique neuroanatomical characteristics. This ventromedial frontal cortex is "hidden" in the ventral (areas 11–14 and 47) and medial (areas 24, 25, and 32) surfaces of the prefrontal lobe (Price, Carmichael, & Drevets, 1996). Because of its location at the interface of cortex and subcortex (see Figure 4), the orbital prefrontal cortex acts as a "convergence zone" and is one of the few brain regions that is "privy to signals about virtually any activity taking place in our beings' mind or body at any given time" (Damasio, 1994, p. 181). In addition to receiving input from all sensory association areas of the posterior cortex as well as outputs to motor areas in the anterior cortex and ventral striatum, it uniquely projects extensive pathways to limbic areas in the anterior cingulate, insula, temporal pole, central nucleus of the amygdala, and olfactory areas, to glutamate responsive *N*-methyl-D-aspartate (NMDA) receptors of mesocortico-

limbic dopamine neurons in ventral tegmental areas of the anterior reticular formation, and to subcortical drive centers in the paraventricular hypothalamus that are associated with the sympathetic branch of the autonomic nervous system. This excitatory limbic circuit, the ventral tegmental limbic forebrain–midbrain circuit, is involved with the generation of positively valenced states associated with motivational reward. Orbitofrontal regions also send axons onto subcortical targets in parasympathetic autonomic areas of the hypothalamus, and to noradrenergic neurons in the medullary solitary nucleus and the vagal complex in the brain stem caudal reticular formation, thereby completing the organization of another limbic circuit, the lateral tegmental limbic forebrain–midbrain circuit that activates the onset of an inhibitory, negatively valenced state (see Schore, 1994).

The orbital corticolimbic system, along with the amygdala, insular cortex, and anterior cingulate, is a component of the "rostral limbic system" (Devinsky, Morrell, & Vogt, 1995). But even more, it sits at the hierarchical apex of the emotion-generating limbic system, and regulates not only anterior temporal and amygdala activity, but indeed all cortical and subcortical components of both the excitatory and inhibitory reverberating circuits of the limbic system. But in addition, it acts as a major center of CNS hierarchical control over the energy-expending sympathetic and energy-conserving parasympathetic branches of the ANS, thereby regulating, respectively, ergotropic high arousal and trophotropic low arousal bodily states (Gellhorn, 1970). With such autonomic connections, it plays an important cortical role in both the nonlinear mechanisms of visceral regulation (Skinner, Molnar, Vybiral, & Mitra, 1992) and the feedback from bodily systems, what Damasio (1994) calls "somatic markers." These reciprocal connections with autonomic areas allow for an essential orbitofrontal role in the control of emotional behavior (Price, Carmichael, & Drevets, 1996), the representation of highly integrated information on the organismic state (Tucker, 1992), and the modulation of energy balance (McGregor & Atrens, 1991).



**Figure 4.** Relationships of brain stem structures to the orbital surface of the right hemisphere (from Smith, 1981).

By being directly connected into heteromodal areas of the cortex as well as into both limbic circuits, the sensory perception of an environmental perturbation can be associated with the adaptive switching of bioaminergic-peptidergic regulated energy-expending and energy-conserving bodily states in response to changes (or expected changes) in the external environment that are appraised to be personally meaningful (Schore, in press-a). These rapid acting orbitofrontal appraisals of the social environment are accomplished at levels beneath awareness by a visual and auditory scanning of information emanating from an emotionally expressive face, and they act as nonconscious biases that guide behavior before conscious knowledge does (Bechara, Damasio, Tranel, & Damasio, 1997). The paralimbic orbitofrontal cortex performs a “valence tagging” function, in which perceptions receive a positive or negative affective charge. The orbitofrontal system, the “administrator of the basolimbic forebrain circuitry” (Nelson, 1994), is a central component of the mechanism by which “forebrain circuits concerned with the recognition and interpretation

of life experiences are capable of influencing virtually all, if not all, regulatory mechanisms in the body” (Wolf, 1995, p. 90).

In such organism–environment interactions there is a sensitive dependence on initial conditions, and these heightened affective moments represent “points of bifurcation” of the potential activation of the two limbic circuits. Marder, Hooper, and Eisen (1987) demonstrate that “a given circuit might easily express a variety of states, depending on the presence or absence of one or more peptides or amines” (p. 223). Not only the output of each circuit, but also the interaction between the circuits is influenced by one or more bioaminergic neurotransmitters, thereby allowing for an adaptive flexible control of multiple states or output patterns. Indeed, in the orbitofrontal areas, dopamine excites and noradrenaline inhibits neuronal activity (Aou, Oomura, Nishino, Inokuchi, & Mizuno, 1983). Mender (1994) points out that in a competitive system, steep gain increases in response to stimulus input, combined with arousal, can create explosive bursts of neural activity and hence discontinuous jumps between discrete aggre-

gate states of neuronal networks. As a result, distributed aggregates of neurons can shift abruptly and simultaneously from one complex activity pattern to another in response to the smallest of inputs. It is interesting to note that dopamine neurons involved in emotional states show a “nonlinear” relationship between impulse flow and dopamine release, and shift from single spike to “burst firing” in response to environmental stimuli that are associated with a quick behavioral reaction (Gonon, 1988), and that this effect is induced by medial prefrontal activity (Gariano & Groves, 1988).

Bertalanffy (1974) asserts that a small change in an anterior “higher” controlling center “may by way of amplification mechanisms cause large changes in the total system. In this way a hierarchical order of parts or processes may be established” (p. 1104). I suggest that the orbitofrontal cortex represents this controlling center and that it is intimately involved in the mechanism by which affect acts as an “analog amplifier” that extends the duration of whatever activates it (Tomkins, 1984). In accord with chaos theory, “Tiny differences in input could quickly become overwhelming differences in output” (Gleick, 1987, p. 8). These “tiny differences” refer to extremely brief events perceived at levels below awareness—although facially expressed emotions can be appraised within 30 ms, spontaneously expressed within seconds, and continue to amplify within less than a half minute, it can take hours, or days, or even weeks or longer for certain personalities experiencing extremely intense negative emotion to get back to a “normal” state again.

Chaotic behavior within the excitatory and inhibitory limbic circuits is thus expressed in sudden psychobiological state transitions. Orbitofrontal activity is associated with affective shifts, the alteration of behavior in response to fluctuations in the emotional significance of stimuli (Dias, Robbins, & Roberts, 1996). In optimal frontolimbic operations, these shifts from one emotional state to another are experienced as rhythms in feeling states and are fluid and smooth, a flexible capacity of a coherent dynamic system. The adaptive

aspects of these nonlinear phenomena is stressed by Hofer (1990, p. 74):

To accomplish various age-specific tasks, the brain must be able to shift from one state of functional organization to another and thus form one mode of information processing to others within an essentially modular structure. These organized states constitute an important component of motivational systems, and they can be considered to provide the neural substrates of affect—both the internal experience of affect and the communicative aspects that are embedded in the form and patterning of the behavior that is produced during these states.

The activity of this prefrontal system is responsible for the regulation of motivational states and the adjustment or correction emotional responses. It is specialized for generating and storing cognitive interactive representations (internal working models) that contain information about state transitions, and for physiologically coding that state changes associated with homeostatic disruptions will be set right. The infant’s memory representation includes not only details of the learning cues of events in the external environment, but also of reactions in his internal state to changes in the external environment. The dampening of emotional discomfort and the performance of previously rewarded actions are now thought to be specifically stored in infant procedural memory (Meltzoff, 1995). Regulated emotional states represent desired attractors that maintain self-organization by perpetuating emotional equilibrium and resolving emotional disequilibrium. Chaotic variability in brain self-regulatory activity is thus necessary for flexibility and adaptability in a changing environment. According to Ciompi (1991) under certain conditions feedback processes in “affective cognitive systems” are capable of “provoking sudden non-linear jumps, far away from equilibrium, leading to chaotic conditions or to the formation of new ‘dissipative structures’” (p. 98). Very recent work indicates that the orbitofrontal system is specialized for “cognitive–emotional interactions” (Barbas, 1995) and that neurons in the right prefrontal cortex with balanced excit-

atory and inhibitory inputs show chaotic behavior (van Vreeswijk & Sompolinsky, 1996).

### Right Brain as Nonlinear System

The fact that the orbital prefrontal area is expanded in the right hemisphere (in contrast to the later maturing nonlimbic dorsolateral prefrontal area which is larger in the left—White, Lucas, Richards, & Purves, 1994) has been suggested to account for the dominance of this hemisphere in the processing of emotional information (Falk, Hildebolt, Cheverud, Vannier, Helmkamp, & Konigsberg, 1990). The early developing right cerebral cortex plays an important role in the processing of individual faces early in life, in the infant's recognition of arousal-inducing maternal facial affective expressions, and in its response to the prosody of motherese. In describing the greater involvement of the right hemisphere in infancy, Semrud-Clikeman and Hynd (1990, p. 198) point out that

The emotional experience of the infant develops through the sounds, images, and pictures that constitute much of an infant's early learning experience, and are disproportionately stored or processed in the right hemisphere during the formative stages of brain ontogeny.

Indeed, the right hemisphere is centrally involved in human bonding and attachment (Henry, 1993) and in the development of reciprocal interactions within the mother–infant regulatory system (Schore, 1994, 1997). In earlier work I presented a substantial body of multidisciplinary evidence which indicates that the high intensity affective communications that culminate in the development of the attachment system are essentially right-hemisphere-to-right-hemisphere arousal-regulating energy transmissions between the primary caregiver and infant. Attachment dynamics continue in ongoing development, and the ventromedial region of the right cortex that neurobiologically mediates these dynamics plays a crucial role in the processing of information emanating from the human face

throughout the life span (Sergent, Ohta, & MacDonald, 1992).

Descending projections from the prefrontal cortex to subcortical structures are known to mature during infancy, and the “primitive” right hemisphere, more than the left, has dense reciprocal interconnections with limbic and subcortical structures, and contains an increased emphasis on paralimbic networks. These reciprocal right frontal–subcortical connections, especially with bioaminergic and hypothalamic subcortical nuclei, account for the unique contribution of the right hemisphere in regulating homeostasis and modulating physiological state in response to internal and external feedback. The representation of visceral and somatic states is under primary control of the right hemisphere, and the somatic marker mechanism, tuned by critical learning interactions in development, is more connected into the right ventromedial area. Wittling and Pfluger (1990) conclude that the right hemisphere is dominant for “the meta-control of fundamental physiological and endocrinological functions whose primary control centers are located in subcortical regions of the brain” (p. 260). This cortical asymmetry is an extension of an autonomic asymmetry—at all levels of the nervous system the right side of the brain stem provides the primary central regulation of homeostasis and physiological reactivity (Porges, Doussard-Roosevelt, & Maiti, 1994).

Expanding upon these neurophysiological and neuroanatomical relationships, Porges demonstrates that the right vagus is involved in the regulation of emotion and communication. He also discusses the relationship between “shifts” in emotion regulation and oxygen demands within the ANS. In his most recent work (1995) he presents a neuroanatomical schema in which he proposes that the input site into this right brain circuit of emotional regulation is the nucleus of the solitary tract. This site, in turn, is fed by unnamed higher central structures that promote either immediate mobilization of energy resources or calming. I deduce that the orbitofrontal cortex and the central amygdala, which both send axons directly into the noradrenergic neurons

of the nucleus of the solitary tract and into the hypothalamus, are these structures. Indeed, orbitofrontal–vagal interconnections are demonstrated in studies showing that vagal stimulation induces a cortical evoked response only in the orbitoinsular cortex, and that orbitofrontal stimulation triggers an almost instantaneous inhibition of gastrointestinal motility, respiratory movements, and somatic locomotor activity, and a dramatic precipitous fall in blood pressure (see Schore, 1994).

In other words, Porges' right brain circuit of emotion regulation is identical to the inhibitory lateral tegmental noradrenergic limbic circuit that is hierarchically dominated by the right orbitofrontal cortex. As opposed to sympathetically driven "fight–flight" active coping strategies, parasympathetically mediated passive coping mechanisms expressed in immobility and withdrawal allow for conservation-withdrawal, the capacity that improves survival efficiency through inactive disengagement and unresponsiveness to environmental input in order "to conserve resources." In contrast to "problem focused coping," which entails direct action on the self or on the environment to remove the source of stress, this "emotion focused coping" is directed toward the reduction of the emotional impact of stress through psychological processes (Folkman & Lazarus, 1980).

With regard to the other ventral tegmental dopaminergic limbic circuit, psychopharmacological research shows that emotionally stressful experiences result in greater dopaminergic activation of the right over the left prefrontal cortex (Fitzgerald, Keweller, Glick, & Carlson, 1989). In a recent study of the mesocortical dopaminergic system, the authors conclude that the right cortex is at the top of a hierarchy for the processing of prolonged emotionally stressful inputs, and that endogenous dopaminergic modulation facilitates adaptive responses (Sullivan & Szechtman, 1995). Furthermore, they posit that under intense inputs, a left to right shift occurs in intrinsic neural activity. These ideas correspond with the assertion that this "nondominant" hemisphere plays a central role in the control of vital functions supporting survival and enabling the organism to cope with stressors

(Wittling & Schweiger, 1993). In line with the principle that the right cortex operates in conjunction with a frontal system that is involved in modulating the emotional valence of experience (Heller, 1993), I suggest that upon its maturation in the middle of the 2nd year, the orbitofrontal area of the right hemisphere acts as an "executive control system" for the entire right brain.

These findings bear upon an ongoing debate concerning hemispheric asymmetry and the regulation of emotions. There is now general agreement that right cortical posterior association regions are centrally involved in the perception of all emotional information. However, with regard to the production and experience and thereby the regulation of emotion, there is a controversy as to whether the right hemisphere regulates all emotions or the right is specialized for negative and the left for positive emotions. In general, studies examining hemispheric lateralization for emotional *non-verbal* stimuli (e.g., faces) have provided support for the right hemispheric model of emotional lateralization (Ali & Cimino, 1997), a finding that fits with the conception that the right hemisphere contains a "nonverbal affect lexicon," a vocabulary for nonverbal affective signals such as facial expressions, gestures, and prosody (Bowers, Bauer, & Heilman, 1993). Conditioned autonomic responses after subliminal presentations of facial expressions only occur when faces are presented to the right hemisphere (Johnsen & Hugdahl, 1991), clearly implying that future studies should use tachistoscopic facial stimuli. Furthermore, the majority of these studies have been done with adults, but recent infant studies (e.g., Nass & Koch, 1991) report that the right hemisphere plays a crucial role in mediating emotional expression from a very early point in development (note in earlier Figure 1, at point F, in the high arousal elated state, the infant turns the head to the left, indicating right hemispheric activation), and that infants with right posterior brain damage show a persistent deficit in the expression of *positive* affect (Reilly, Stiles, Larsen, & Trauner, 1995). These latter researchers conclude that the development of infant emotions represent "primitives" of affective communication.

It is important to note that emotions have, in addition to a valence (hedonic) dimension, an intensity or arousal (energetic) dimension. Many of the “primary” emotions are ergotropic-dominant, energy-expending high arousal, or trophotropic-dominant, energy-conserving low arousal affects, and these “primitive” affects appear early in development, arise automatically, are expressed in facial movements, and are correlated with differentiable ANS activity. Due to the lateralization of catecholaminergic systems in the right hemisphere, it is dominant in the regulation of arousal and is more closely associated with regulation of heart rate than the left. This hemisphere is specialized for processing the autonomic correlates of emotional arousal (Spence, Shapiro, & Zaidel, 1996), and activation of the right orbitofrontal area occurs during classical conditioning of an emotional response, the learning of the relationship between events that allows the organism to represent its environment (Hugdahl et al., 1995). The structural and functional qualities of the right cortex, which has a higher metabolic rate than the left, thus account for its essential role in highly arousing emotional processes.

The developmental approach presented here is compatible with a model in which the early maturing right hemisphere modulates all nonverbal “primary” emotions, regardless of valence, while the later maturing left (which does not begin its growth spurt until the last half of the 2nd year) modulates verbal “social” emotions and enhances positive and inhibits negative emotional behavior (Ross, Hohman, & Buck, 1994). It also supports the views that the right hemisphere mediates pleasure and pain and the more intrinsically primitive emotions, and that although the left cortex acts to inhibit emotional expression generated in the limbic areas of the right half of the brain, the right brain contains a circuit of emotion regulation that is involved in the modulation of “primary” emotions and “intense emotional-homeostatic processes” (Porges, 1995). Thus, the experience and regulation of affects mediated by extremes of arousal, both high, such as terror, excitement, and elation, or low, such as shame, would involve more right hemispheric activity, in contrast to their

left hemispheric-driven counterparts, anxiety, interest, enjoyment, and guilt.

The right cortex is also specialized for globally directed attention, holistic analysis, and the processing of novel information. As opposed to the left hemisphere’s “linear” consecutive analysis of information (Tucker, 1981), the processing style of the right hemisphere has been described as “nonlinear” based on multiple converging determinants rather than on a single causal chain (Galin, 1974). I conclude that the orbitofrontal cortex, especially in the right brain, is particularly suited to amplify appraisals of short-acting, small fluctuations of initial conditions into larger effects, and that it is primarily activated in “far-from-equilibrium” states of heightened ergotropic and/or trophotropic emotional arousal that create a potential for achieving novel states and a new stability.

#### **Critical Period Gene–Environment Interactions and the Development of a Vulnerability to Psychopathology**

The development, in the first 2 years of life, of a right hemispheric dynamic system that adaptively regulates psychobiological states is a product of the interaction of genetic systems and early experience. Recent transactional models view the organization of brain systems as an outcome of interaction between genetically coded programs for the formation of structures and connections among structures and environmental influence (Fox, Calkins, & Bell, 1994). The onset and offset of sensitive periods, “unique windows of organism–environment interaction,” are now attributed to the activation and expression of families of programmed genes which synchronously turn on and off during infancy, thereby controlling the transient enhanced expression of enzymes of biosynthetic pathways which allow for growth in particular brain regions. In light of the established principles that early postnatal development represents an experiential shaping of genetic potential (Kendler & Eaves, 1986) and that visual experience regulates gene expression in the developing cortex (Neve & Bear, 1989), I suggest that gene–environment

mechanisms are embedded within face-to-face visuo-affective interactions.

These socioemotional interactions thus directly impact the growth of limbic regions. The right cerebral cortex, densely interconnected into limbic structures, is specifically impacted by early social experiences, is primarily involved in attachment experiences, and is more vulnerable to early negative environmental influences than the left. Bowlby (1969) points out that the development of a late-maturing control system associated with attachment is influenced by the particular environment in which development occurs. This implies that during sensitive periods of right hemispheric growth less than optimal early environments in interaction with genetic factors are important forces in compromised brain organization and the pathogenesis of disorders of affect regulation.

The brain growth spurt spans from the end of prenatal life through the end of infancy, a time period when the right hemisphere is rapidly expanding. During this exact interval the total amount of DNA in the cerebral cortex increases dramatically and then levels off (Winick, Rosso, & Waterlow, 1970). It is in this period that timed gene action systems which program the structural growth and connections of the higher structures of the limbic system are activated. Although it is established that these hereditary expressions require transactions with the environment, the question arises as to what mechanism embedded in the early caregiver–infant relationship could act to experientially shape genetic potential? Hofer's (1990) research shows that the mother acts as a "hidden" regulator of not only infant brain catecholamines, agents that activate the pentose phosphate pathway and ribonucleic acid synthesis (Cummins, Lorceck, & McCandless, 1985), but also of ornithine decarboxylase, a key enzyme in the control of nucleic acid synthesis in the developing brain (Morris, Seidler, & Slotkin, 1983). These events influence not only catecholaminergic-driven maturation of the amygdala, but later maturing paralimbic areas in the temporal pole and then orbitofrontal cortices.

There is now an increasing amount of evidence indicating that the underlying genetic

defect in psychiatric disorders is in the hereditary systems involved in the synthesis and catabolism of biogenic amines which trophically regulate maturation in subcortical and cortical information processing centers, and that such mutations lead to a disruption of normal synaptogenesis and circuit formation. The genes that encode the production of bioamines and their receptors continue to be activated postnatally, causing a dramatic expansion of these systems over the stages of human infancy. Aminergic neuromodulators regulate both the responsiveness of the developing cortex to environmental stimulation, and the organization of cortical circuitry, and because their activity is highly heritable (Clarke et al., 1995), altered genetic systems that program the key enzymes in their biosynthesis are now considered to represent potential contributors to high risk scenarios (Mallet, 1996). Indeed, the genes for tyrosine hydroxylase, the rate-limiting enzyme in both dopamine and noradrenaline production, are essential to both fetal development and postnatal survival (Zhou, Quaife, & Palmiter, 1995). Alterations in the genetic systems that program bioamines and their receptors, agents that directly influence morphogenesis, would thus negatively affect the critical period organization and functioning of ventral tegmental dopaminergic and lateral tegmental noradrenergic neurons that regulate the metabolic capacities of their corticolimbic terminal fields.

As previously mentioned, the construction of modular circuits in critical periods is associated with linkages between areas of high activity of the energy generating enzyme cytochrome oxidase. This implies that early mitochondrial pathology would underlie defective brain circuitry. Nuclear and mitochondrial genes that encode cytochrome oxidase (Hevner & Wong–Riley, 1993), especially in bioaminergic (and hypothalamic neuroendocrine) systems and their receptors, may turn out to be an important locus for the development of "faulty" circuit wirings that mediate a predisposition to later forming psychiatric disorders. In fact brain mitochondrial abnormalities are now implicated in the etiology of a childhood neurological disorder of the right frontal lobe (Rett Syndrome) that shows socialization deficits at 9 months and onset of

autistic-appearing regression of interpersonal interaction at 18 months (Cornford et al., 1994). Alterations of oxidative metabolism due to mutations of genes that encode isoforms of cytochrome oxidase are now being explored in the pathogenesis of the schizophrenic brain (Marchbanks, Mulcrone, & Whatley, 1995).

Mitochondrial gene expression is involved in “the mechanisms by which mammalian cells adapt to the changing energetic demands in response to functional, developmental and pathological factors” (Attardi, Chomyn, King, Kruse, Polosa, & Murdter, 1990, p. 509). The genetic system encoded in mitochondrial DNA is maternally inherited, is governed by non-Mendelian mechanisms, and has a mutagenicity rate 10 times that of nuclear DNA. A mutation of these genes may occur in utero, but the amplification of mitochondrial DNA (which occurs from infancy onward; Simonetti, Chen, DiMauro, & Schon, 1992) during a critical period of rapid mitochondrial proliferation in actively growing brain regions represents a mechanism by which the number of local genetic mutations could increase. It is now thought that once the mutant mitochondrial DNAs reach a critical level, cellular phenotype changes rapidly from normal to abnormal, and the resultant impairment of oxidative phosphorylation and ATP production leads to disease expression. Shoffner (1996) states “disease expression seems to be influenced by poorly understood genetic and environmental interactions” (p. 1284).

Current models of the genetic analysis of complex diseases prescribe an interaction between a susceptibility gene with a predisposing environmental agent. In these studies, “environmental” usually refers to factors in the physical environment, but I propose that in the case of the transmission of psychiatric diseases stressors in the social environment interact with genetic mechanisms to amplify a genetic predisposition and create a vulnerability to later forming mental illness. I further suggest that these interactions occur between the developing organism and the “nonshared” (Plomin, Rende, & Rutter, 1991) environment with which it interacts, responding first to the environmental signals provided by the internal body of the mother, and then after birth,

to the environmental signals provided by the external body of the mother. The brain growth spurt, from the last trimester of pregnancy through the 2nd year, spans both of these periods, emphasizing the principle that the genes that program its regional organization are expressed in two very different environments, first a totally anaerobic and then an increasingly aerobic cellular environment. Gene expression is regulated by oxygen levels in the cell as well as by neurohormones and biogenic aminergic neuromodulators.

During critical periods of regional maturation, prolonged perturbations in the social environment lead to dysregulated levels of stress-responsive catecholamines, thereby altering gene-environment interactions and providing for potential sites of pathomorphogenesis. Dopamine, acting at excitatory glutamatergic NMDA and D1 receptors, triggers *c-fos* immediate early genes (Berretta, Robertson, & Graybiel, 1992) that turn on other genes within the cell, ultimately leading to long-term structural changes associated with early imprinting experiences. But dopamine increases under stress (Bertolucci-D’Angio, Serrano, Driscoll, & Scatton, 1990), and can induce neurotoxic inhibition of mitochondrial respiration and defective energy metabolism (Ben-Shachar, Zuk, & Glinka, 1994) and DNA mutations in brain tissue (Spencer et al., 1994). An early stressful environment thus detrimentally and irreversibly impacts the genetic systems of catecholaminergic neurons and their receptors (including receptors on astroglial and endothelial cells, near dendritic spines) that trophically regulate the critical period growth and metabolism of widespread corticolimbic areas.

Indeed, animal studies show that early postnatal stress, such as maternal deprivation, produces permanent changes in dopamine receptor function (Lewis, Gluck, Beauchamp, Keresztury, & Mailman, 1990), especially in cortical areas, as well as a significant reduction in the number of dopaminergic neurons in the ventral tegmental area, long-lasting effects that result in “abnormalities of social and affective function” (Martin, Spicer, Lewis, Gluck, & Cork, 1991) and a reduced capacity to respond to aversive experiences in adulthood (Cabib, Puglisi-Allegra, &

D'Amato, 1993). It is now well established that postnatally maturing dopaminergic projections are potential sites of developmental defects. In light of the principle that "developing mesencephalic dopamine neurons may display varying subpopulation specific vulnerability to outside pathological influences over the course of postnatal ontogeny" (Wang & Pitts, 1994, p. 27), genetic systems, both nuclear and mitochondrial DNA, of the dopamine neurons within the ventral tegmental area, particularly the medial, rostral linear nucleus (as opposed to other mesencephalic dopaminergic subnuclei that innervate mesolimbic areas), would be particularly important, since these project collaterals to the cortex, including the ventral prefrontal areas (see Schore, 1994).

In addition, early social experiences also play a significant role in the development of the other catecholamine, noradrenaline. Attachment stress induces alterations in mammalian infant noradrenaline levels (Clarke, Hedecker, Ebert, Schmidt, McKinney, & Kraemer, 1996) that become permanent (Higley, Suomi, & Linnoila, 1991). The enduring changes in noradrenergic system function that result from disturbed mother–infant relations represent a biological substrate or "risk factor" for a vulnerability to despair in later life (Kraemer, 1992) and a susceptibility to affective and anxiety disorders (Rosenblum, Coplan, Friedman, Basoff, Gorman, & Andrews, 1994). In human studies, Rogness and McClure (1996) report lowered noradrenaline levels in children exposed to neglect, and suggest that this psychosocial stress modifies the genetic expression of the noradrenaline system. These authors conclude that early experience has long-lasting effects on neuro-modulator functioning, and that genetic–environmental factors, especially during early critical periods of development, are important in psychopathogenesis.

### **Excessive Developmental Parcellation and the Pathomorphogenesis of Frontolimbic Circuits**

As opposed to an adaptive stable dynamic system that can flexibly transition between

states, a pathological system lacks variability in the face of environmental challenge. What early factors could produce such an organization? According to the classical diathesis–stress model, psychiatric disorders are caused by the interaction of genetic–constitutional vulnerability *and* environmental psychosocial stressors. The interface of nature and nurture is now thought to occur in the psychobiological interaction between mother and infant, "the first encounter between heredity and the psychological environment" (Lehtonen, 1994, p. 28). In such transactions the primary caregiver is providing experiences which shape genetic potential by acting as a psychobiological regulator (or dysregulator) of hormones that directly influence gene transcription. This mechanism mediates a process by which psychoneuroendocrinological changes during critical periods initiate permanent effects at the genomic level. The final developmental outcome of early endocrine–gene interactions is expressed in the imprinting of evolving brain circuitry.

Of particular importance to the creation of a brain system which is "invulnerable" or "vulnerable" to future psychopathology are steroid hormones associated with stress responses. These bioagents regulate gene expression, and, depending upon the cell type, induce or repress sets of genes, and in this manner they act as an essential link between "nature and nurture." Levels of corticosteroids in the infant's brain are directly influenced by the mother–infant interaction. In beneficial experiences the infant's glucocorticoid stress response is modulated by the psychobiologically attuned mother, thereby inhibiting the infant's pituitary–adrenal response to stress. As a result of these experiences, the infant, in the face of a subsequent novel stimulus, shows a lesser corticoid output and a more rapid return of corticosterone to baseline levels, characteristics of a resilient coping mechanism. These critical period experiences also have long-term structural consequences—they permanently enhance glucocorticoid receptor concentrations in neurons in the frontal cortex that are involved in terminating the adrenocortical stress response.

On the other hand, stressful dyadic interac-

tions that generate enduring states of painful negative affect are associated with elevated levels of corticosteroids in the infant brain. Deprivation of early maternal stress modulation is known to trigger an exaggerated release of corticosteroids upon exposure to novel experiences which, in adulthood, persists for a longer period of time. Elevated levels of this stress hormone in prenatal and postnatal periods inhibit dendritic branching, reduce brain nucleic acid synthesis, and permanently decrease brain corticosteroid receptors. Critical periods are times of heightened energy production, and these neurohormones specifically inhibit brain energy metabolism (Bryan, 1990), a condition that enhances the toxicity of excitatory neurotransmitters (Novelli, Reilly, Lysko, & Henneberry, 1988) and produces alterations in mitochondrial structure and function (Kimberg, Loud, & Weiner, 1968). Glucocorticoids within the high physiological range impact both DNA and energy systems, and profoundly affect areas of the brain that are organizing in infancy.

As I have noted in other works, the developing brain of an infant who experiences frequent intense attachment disruptions is chronically exposed to states of impaired autonomic homeostasis which he/she shifts into to maintain basic metabolic processes for survival. These disturbances in limbic activity and hypothalamic dysfunction are accompanied by increased levels of "stress proteins" in the developing brain (see Schore, 1994). In addition to an extensive history of misattunement in the 1st year, stressful socialization experiences in the 2nd that elicit shame represent a traumatic interruption of interpersonal synchronizing processes, a rupture of attachment dynamics that triggers a state transition from energy-mobilizing sympathetic to energy-conserving parasympathetic dominant ANS activity, a sudden switch from ergotropic to trophotropic arousal that is accompanied by elevated levels of cortisol (see Schore, 1991, in press-b). Both catecholamines are released in response to stressful disruptions of the attachment bond. If the caregiver does not participate in reparative functions that reduce stress and reestablish psychobiological equilibrium, limbic connections in a critical stage

of growth are exposed for extended periods of time to heightened levels of circulating corticosteroids and catecholamines. This toxic brain chemistry induces synapse destruction and death in "affective centers" in the maturing limbic system and therefore permanent functional impairments of the directing of emotion into adaptive channels. More specifically, I suggest that the postnatal development of the affect regulating orbitofrontal cortex, the corticolimbic system which directly connects into the hypothalamus and influences corticosteroid levels (Hall & Marr, 1975), is specifically and permanently negatively impacted by high levels of circulating corticosteroids that accompany stressful socioemotional environmental interactions.

In support of this, there is evidence to show that that stress-induced increases of glucocorticoids in postnatal periods induce an abnormal intrinsic circuitry within the corticolimbic system. Benes (1994) suggests that the neurotoxic effects of glucocorticoids are associated with simultaneous hyperactivation of the excitotoxic NMDA-sensitive glutamate receptor, a critical site of synapse elimination and neurotoxicity during early development. It is now known that not only glucocorticoids (Wyllie, 1980) but also glutamate (Ankarcrona et al., 1995) and dopamine (Offen, Ziv, Sternia, Melamed, & Hochman, 1996) can induce apoptotic cell death. Dopamine activates NMDA receptors, and excessive NMDA receptor stimulation generates the superoxide free radicals associated with oxidative stress (Lafon-Cazal, Pietri, Culcas, & Bockaert, 1993). Both  $\text{Na}^+\text{K}^+\text{-ATPase}$  (Jamme, Petit, Divoux, Gerbi, Maixent, & Nouvelet, 1995) and mitochondria (Vercesi & Hoffmann, 1993) can sustain damage from the potentially toxic effects of the extremely reactive free radicals, especially hydroxyl radicals that destroy cell membranes and induce mutations in mitochondrial DNA (Giulivi, Boveris, & Cadenas, 1995). Defective mitochondrial biogenesis and energetic activity are early events in apoptosis (Vayssière, Petit, Risler, & Mignotte, 1994; Zamzimi et al., 1995). Impaired mitochondrial function would result in reduced ATP synthesis levels, which in turn is associated with synaptic transmission failure

(Lipton & Whittingham, 1982). These events, occurring during a critical period, could produce a permanently diminished local metabolic capacity and therefore reduced functional activity within and between particular brain regions, especially under challenging conditions that require sustained energy levels.

In fact, this same interaction between corticosteroids and excitatory transmitters is now thought to mediate programmed cell death and to represent a primary etiological mechanism for the pathophysiology of neuropsychiatric disorders (Margolis et al., 1994). Although the critical period overproduction of synapses is genetically driven, the pruning and maintenance of synaptic connections is environmentally driven. This clearly implies that the developmental overpruning of a corticolimbic system that contains a genetically encoded underproduction of synapses represents a scenario for high risk conditions. Carlson, Earls, and Todd (1988) emphasize the importance of “psychological” factors in the “pruning” or “sculpting” of neural networks in specifically the postnatal frontal, limbic, and temporal cortices. Excessive pruning is thought to be a primary mechanism in such “neurodevelopmental” disorders as autism and schizophrenia (Keshavan, Anderson, & Pettegrew, 1994), where large reductions in frontal connectivity are associated with the emergence of circuit pathology that mediates dysfunctional symptoms (Hoffman & Dobscha, 1989).

In most models of psychiatric disorders the concept of “pruning in parallel circuits” (Mender, 1994) has been applied to circuits within the cortex, but it is the pruning of hierarchical cortical–subcortical circuits that is central to the psychoneurodevelopmental origins of the corticolimbic defects that underlie a vulnerability to psychopathology. Of special importance to the emergence of adaptive affect regulation are the reciprocal connections between the orbitoinsular cortex and not only all sensory areas of the cortex, but with subcortical dopamine neurons in the ventral tegmental area, noradrenaline neurons in the medulla, and various neuroendocrine neurons in the hypothalamus. Critical period interactive experiences that lead to excessive pruning of catecholaminergic axonal terminals that innervate cortical areas or of cortical cholinergic

axons that project to different subcortical biogenic amine or hypothalamic nuclei, would have long-enduring negative effects.

These interactive experiences are embedded in different types of dyadic attachment transactions, and if they are less than optimal they can induce an excessive apoptotic parcelation (e.g., elimination of long axon collaterals, cell death, dendritic regression) of the components of either one or both of the dual limbic circuits (Schore, 1994, 1996). Frontolimbic parcelation is mediated by the same mechanism described above—excitotoxins have been shown to destroy orbitofrontal neurons (Dias et al., 1996), and this would produce modifications in the microstructural organization and thereby metabolic limitations of areas that hierarchically dominate the two limbic circuits. Different amounts and types of connectional degenerations of the maturing orbitofrontal cortex, an area intimately involved in attachment dynamics, would account for the different patterns in biobehavioral organizations of securely and insecurely attached infants (Spangler & Grossmann, 1993).

More specifically, infants with a history of “disorganized–disoriented” insecure attachments show a high rate of exposure to abuse experiences (Main & Solomon, 1986). Perry, Pollard, Blakley, Baker, and Vigilante (1995) assert that the abused infant responds to this threatening interpersonal environment with both states of hyperarousal that induce long-lasting elevations of sympathetic catecholaminergic activity, and of parasympathetic vagal-associated dissociation associated with hypoarousal and increased cortisol production, and that these states are internalized as a sensitized neurobiology. The latter effect is revealed in the finding that this group of toddlers exhibits higher cortisol levels than all other attachment classifications (Hertsgaard, Gunnar, Erickson, Farrell, & Nachmias, 1995). These dysregulating environmental events trigger extreme and rapid alterations of ergotropic and trophotropic arousal that create chaotic biochemical alterations in the infant brain, a condition conducive to extensive oxidative stress and apoptotic destruction of developing synaptic connections within both limbic circuits. This psychoneurobiological

mechanism may mediate the effects by which exposure of an infant to emotional trauma results in a sensory-affecto-motor “emotional–instinctual recordings” of the experience that are inscribed in the neurotransmitter patterns in the limbic system (Weil, 1992).

Early abuse experiences of neglect and/or trauma thus create abnormal critical period microenvironments for the development of corticolimbic areas. Critical period cell death of orbitofrontal and/or temporal cortical neurons that respond to emotional facial displays would lead to permanent deficits in reading the facially expressed emotional states of others. Deficits in emotion decoding ability are seen in abused children (Camras, Grow, & Ribordy, 1983). Since the orbitofrontal areas are tied into both limbic circuits and both branches of the autonomic nervous system, an extensive developmental parcellation of both circuits would result in a poorly evolved fronto-limbic cortex, one in which sympathetic and parasympathetic components could not operate reciprocally (Berntson, Cacioppo, & Quigley, 1991). This organization of autonomic control prevents the integration of lower more primitive autonomic states that allows for the elaboration of new higher states. Because of its fragile regulatory capacities, under even moderate stress, it is vulnerable to disorganization and to affect shifts that are extremely discontinuous and labile.

It is now established that structural alterations of the developing hypothalamic–pituitary–adrenal system are responsible for a vulnerability to pathology in later life and that chronically elevated levels of corticosteroids are associated with psychiatric disturbance. Exposure of the right hemisphere to extensive and long-enduring traumatic alterations of arousal during its critical period of organization may predispose the disorganized–disoriented infant to a vulnerability to posttraumatic stress disorders (Rauch et al., 1996). This hemisphere is dominant for the regulation of the secretion of cortisol (Wittling & Pfluger, 1990) and shows heightened activity in overwhelming and uncontrollable panic states marked by terror and intense somatic symptoms (Heller, Etienne, & Miller, 1995) and during recall of traumatic memories (Schiffer, Teicher, & Papanicolaou, 1995).

In contrast, different attachment histories indelibly influence the dual limbic components of the “organized” forms of insecure attachments. An insecure–resistant (ambivalent) attachment organization reflects an experience-dependent expansion of the excitatory ventral tegmental circuit and an extensive parcellation of the inhibitory lateral tegmental circuit. The final wiring of this type of orbitofrontal system is sympathetically biased towards states of ergotropic high arousal and heightened emotionality, but it lacks in “vagal restraint” and therefore has a reduced functional capacity of, under stress, stimulating the parasympathetic and inhibiting the sympathetic components of limbic function. This system manifests a susceptibility to the underregulation disturbances that underlie externalizing psychopathologies. Such personalities show difficulty in repressing negative affects and easy access to negative memories, and an inability to inhibit emotional spreading (Mikulincer & Orbach, 1995). On the other hand, insecure–avoidant attachment histories experientially shape an expansion of the inhibitory lateral tegmental and excessive parcellation of the excitatory ventral tegmental limbic circuits. In the middle of the 2nd year, a point of orbitofrontal maturation, insecure–avoidant infants of depressed mothers, during separation stress, exhibit reduced right frontal EEG activity (Dawson, 1994). This type of fronto-limbic system is biased towards parasympathetic states of trophotropic low arousal and reduced overt emotionality, but under stress it is inefficient in regulating high arousal states, and is vulnerable to overregulation disturbances and internalizing psychopathologies. These personalities show defensiveness and low accessibility to negative memories, as well as high levels of “deactivating strategies” (Dozier & Kobak, 1992). A recent finding of gender differences in orbital functions that are established in the 2nd year but thought to persist across the life span (Overman, Bachevalier, Schuhmann, & Ryan, 1996) suggests differences in wiring of the limbic system between the sexes, and may be relevant to the well-known susceptibility of males to externalizing and females to internalizing disorders.

Frontal functions have long been known to

be associated with personality functioning. An important emphasis of the chaotic systems approach is a shift away from the study of traditional group-oriented procedures toward a new emphasis on individual differences of personality. In the latest neuroscience literature, authors are proclaiming that rather than concentrating on a singular "average" neuro-anatomic design, attention should now be focused on the large range of variation that "normal" structures can exhibit, and that the variability in the morphology of the frontal lobe may underlie individual differences in functional capacities. These principles equally apply to the ontogenesis of "abnormal" organizations, and particularly to the experience-dependent evolution of frontal and limbic microarchitectures and metabolic limitations that are associated with emotional dysfunction and a vulnerability to psychiatric disorders. According to Rutter (1995) environmental stresses impinge most on those who have already exhibited psychological vulnerability and accentuate preexisting psychological characteristics.

The question is, which specific structural systems exhibit this vulnerability? I am suggesting that the orbital frontolimbic system, the "executive control system" for the entire right cortex, the primary cortical hemisphere involved in attachment functions, the processing of socioemotional information, and the regulation of psychobiological states, is sensitive to prolonged aversive experiences during its critical period of growth, and that different types of alterations of its organization account for its adaptive limitations and dysfunctional operations. This formulation is congruent with Main's (1996) assertion that "disorganized" and "organized" forms of insecure attachment are primary risk factors for the development of mental disorders.

### **Early Forming Structural Pathology of Nonlinear Right Hemisphere and Origins of Predisposition to Psychiatric Disorders**

At the beginning of this work, I presented a general model of self-organization, one that emphasizes the central role of synchronized energy exchanges between a developing liv-

ing system and its environment. These patterned energy fluctuations, associated with nonlinear changes in state, allow for more complex interconnections between the system's components, and therefore constitute a salutary primordial matrix for self-organization and the emergence of a hierarchical structural system that is capable of dynamically transitioning between a range of possible states and exploring new states. This allows for the operation of a stable and resilient system, one that can adaptively change in response to environmental perturbations yet retain continuity. I then applied this general model to the developmental organization of the orbitofrontal cortex and its subcortical and cortical connections, a homeostatic system that dynamically regulates organismic energy balance and transitions between psychobiological states in response to internal and external alterations. This hierarchical regulatory structure acts as an executive control system for the nonlinear right brain.

As opposed to growth-promoting environments, growth-inhibiting environments negatively influence the ontogeny of homeostatic self-regulatory and attachment systems. Non-optimal environments do not supply sufficient quantities of nutritive matter and modulated levels of energy to the growing brain, and these circumstances, especially in interaction with a genetically encoded lowered limbic threshold and hyperreactivity to novel environmental events, give rise to a developing system that is poorly equipped to enter into a dyadic open homeostatic system with the human environment. This precludes exposure to a variety of socioemotional experiences that are required for experience-dependent brain maturation, and therefore negatively influences the stabilization of interconnections within subcortical and cortical areas of the infant's brain that are in a critical period of growth. Furthermore, the infant's transactions with an emotionally unresponsive or misattuned environment that provides poor interactive repair are stored in the infant's developing corticolimbic circuitries as imagistic, visceral, and nonverbal procedural memories. As opposed to a secure interactive representation of an regulated-self-in-interaction-with-

an-attuning-other, these “pathological” working models of attachment encode an enduring prototypical cognitive–affective schema of a dysregulated-self-in-interaction-with-a-misattuning-other (see Schore, 1994, 1997).

Early attachment experiences represent psychobiological transactions between the mother’s and infant’s right hemispheres. The child’s growing brain imprints the output of the mother’s right cortex which contains the mechanism for the maternal capacity to comfort the infant (Horton, 1995). Structural limitations in the mother’s emotion processing right brain are reflected in a poor ability to comfort and regulate the infant’s negative affective states, and these experiences are stamped into the infant’s right orbitofrontal system and its cortical and subcortical connections. Exposure to such conditions throughout a critical period of corticolimbic maturation results in inefficient coping systems that cannot adaptively switch internal states in response to stressful external environmental challenges. The functional indicators of this intergenerationally transmitted adaptive limitation are specifically manifest in recovery deficits of internal reparative coping mechanisms, a poor capacity for the state regulation involved in self-comforting in times of stress.

Such deficits are most obvious under highly emotional and challenging conditions that call for behavioral flexibility and affect regulation. The adaptive limitation of all psychopathologies is manifest in more intense and longer lasting emotional responses and the amplification of negative states. This characterization describes the dysfunction of a structurally impaired frontal ventromedial system that results in “emotional response perseveration” (Morgan & LeDoux, 1995), that is, an inefficiency in the temporal organization of behavior (Fuster, 1985) and in the adjustment and correction of emotional states (Rolls, 1986). Recent neurobiological studies indicate that due to its unique neurobiological characteristics, the orbital cortex shows a “preferential vulnerability” to a spectrum of psychiatric disorders (Barbas, 1995). In previous work I have begun to chronicle a growing number of studies that implicate orbitofrontal metabolic dysfunction in autism, schizophre-

nia, bipolar disorder, unipolar depression, posttraumatic stress disorder, drug addiction, alcoholism, and psychopathic, borderline, and narcissistic personality disorders (see Schore, 1994, 1996 for references).

A fundamental postulate of clinical psychiatry holds that the major source of stress precipitating psychiatric disorders involves the affective response to a rupture or loss of a significant relationship. It is now thought that an environmental event, appraised to be emotionally meaningful, may be the direct cause of a neurochemical change that then becomes the psychopathogenic mechanism of the illness (Gabbard, 1994). Because of the “patterning of the nervous system” psychiatric patients show an inability to adapt internally to stress, and this is symptomatically expressed in a continuing activation or inhibition of organ systems in a manner inappropriate to the immediate environmental situation. In updated neuropsychiatric models, defective modulators are viewed as causal agents for mental abnormalities that are characterized by a disturbance in the continuity of successive stable memory states (Mender, 1994). According to dynamic systems theory a stable yet resilient dynamic open system can return to a previous stationary state within an appropriate time period (Thelen, 1989), but a dysfunctional system shows poor capacity to recover after stressful departures from homeostatic equilibrium. Systems that exhibit good primitive organization become more complex (Schwalbe, 1991), but those with a compromised early ontogeny are inefficient at state regulation and therefore exhibit an abnormality in the dimensionality of state transitions, specifically an overreliance on an oversimplified set of transition paths among attractors which constrains the individual’s flexibility to adapt to challenging situations with new strategies.

Recent research in biological psychiatry is focusing on the relationships between the disturbed emotions and cognitions of psychopathological states and neurotransmitter dysfunctions (Maas & Katz, 1992) and is emphasizing the functional role of monoaminergic neuromodulators in psychiatric disorders (Dolan & Grasby, 1994). Indeed, the lim-

bic receptors of these bioamines are the primary target of the psychopharmacological agents that are currently being used by clinical psychiatry. Contemporary psychiatry is also now delving more deeply into the role of right hemispheric dysfunction in psychiatric disorders (Cutting, 1992), such as schizophrenia (Cutting, 1994), autism (Ozonoff & Miller, 1996), depression (Liotti & Tucker, 1992), mania (Starkstein, Federoff, Berthier, & Robinson, 1991), and posttraumatic stress disorder (Rauch et al., 1996). This hemisphere is deeply connected into the two forebrain-midbrain limbic circuits, the noradrenergic vagal brain circuit of emotion regulation and the mesocortical dopaminergic system that processes emotionally stressful inputs. The dysfunction of these limbic circuits is central to the affect regulatory deficits of all psychiatric disorders.

A major contribution of the discipline of developmental psychopathology to the study of psychiatric disorders is its emphasis on the elucidation of the early ontogenetic factors that predispose high risk individuals to later psychopathologies. In consonance with dynamic systems theory, this developmental perspective underscores the fact that a more detailed knowledge of the self-organization of the developing brain is essential to a deeper understanding of specifically how genetic and environmental factors interact to generate an enduring vulnerability to stress-induced disorganizations of adaptive functions. Developmental neurobiological studies indicate that the right brain system, which more than the left is deeply interconnected into the limbic system and is fundamentally involved in responding to and coping with stress, is in a growth spurt in early infancy. The limbic areas of the cortex are in an intense state of myelination from the middle of the first through the middle of the 2nd year (Kinney, Brody, Kloman, & Gilles, 1988) and show an anatomical maturation at the end of this period. Most importantly, the biogenic aminergic systems that regulate the growth and activity of the limbic system are in an active state of experience-dependent growth in these same stages of human infancy.

This clearly implies that various patterns of alterations of right brain bioamine activity should be exhibited in the high risk infant. Indeed, there is now current interest in identifying the critical involvement of dopamine in development, before signs and symptoms are expressed (Winn, 1994). Psychobiological research indicates that prenatally stressed developing systems show, soon after birth, an alteration of dopamine levels in the right hemisphere and alterations of emotionality (Friede & Weinstock, 1988). Children diagnosed as high risk for schizophrenia exhibit early neurointegrative deficits, reflecting dysregulation of hypothalamic and reticular activating systems (Fish, Marcus, Hans, Auerbach, & Perdue, 1992). Under challenge, these infants show left-sided postural and movement abnormalities, reflecting overactivity of ascending dopaminergic systems in the right hemisphere (Walker, 1994). This developmental syndrome may reflect an early inefficient orbitocortical modulation of ascending excitatory influences which results in an overactivity of right brain ascending dopaminergic systems and enhanced responsiveness of subcortical mesolimbic dopaminergic systems to stress (Deutch, 1992). High risk offspring of schizophrenic parents show EEG abnormalities in the right rather than left hemisphere (Itil, Hsu, Saletu, & Mednick, 1974), and disturbances in facial expressions of emotion are seen in preschizophrenic infants in the first year of life (Walker, Grimes, Davis, & Smith, 1993). These early events may play a critical role in the "developmental disconnection of temporolimbic prefrontal cortices" seen in the hypometabolic prefrontal areas of the schizophrenic brain (Weinberger & Lipska, 1995) and in the genesis of the negative symptoms of the disorder.

This model of early right brain deficits is also supported in another high risk population. Three- to 6-month-old infants of depressed mothers show a right frontal EEG asymmetry (Field, Fox, Pickens, & Nawrocki, 1995) which has been interpreted as reflecting a subcortical asymmetry in the amygdala (Calkins & Fox, 1994). At 10 months, infants who express more intense distress to maternal

separation display a greater right than left frontal activation (Davidson & Fox, 1989), and this asymmetry has been related to emotional reactivity and vulnerability to psychopathology in both infants and adults (Davidson, Ekman, Saron, Senulis, & Friesen, 1990). Individuals with extreme right frontal activation are thought to exhibit a negative affective response to a very low intensity negative affect elicitor, and to be impaired in the ability to terminate a negative emotion once it has begun (Wheeler, Davidson, & Tomarken, 1993). In very recent work, Fox, Schmidt, Calkins, Rubin, and Coplan (1996) report that young children with internalizing *and* externalizing problems show greater right than left frontal EEG activation, and suggest that this pattern reflects difficulties with affect regulation, whether the affect arousal is extremely negative or positive. These findings fit nicely with the model of right hemispheric regulation of intense emotional states presented earlier.

There is now convincing evidence that the deficits of an early compromised right cortex persist as the individual passes into early childhood. A loss of interconnections (extensive parcellation) within the infant's early developing right hemisphere is associated with an impairment of social perception (i.e., difficulty in evaluating facial expression, gestures, or prosody). These children are at high risk for the nonverbal learning disabilities (Semrud-Clikeman & Hynd, 1990) associated with a "developmental right hemisphere syndrome" (Gross-Tsur et al., 1995). The latter authors enumerate specific emotional and interpersonal problems that are present early in development but frequently not recognized until the child begins school. These include maladaptation to new situations, difficulties in maintaining friendships, withdrawn and excessively shy behaviors, and avoidance of eye contact. A "developmental social-emotional processing disorder" associated with electrophysiological abnormalities of the right hemisphere has been reported by Manoach, Sandson, Mesulam, Price, and Weintraub (1993). In a previous study these authors concluded that early right hemisphere dysfunction is expressed in later life as introversion, poor so-

cial perception, chronic emotional difficulties, inability to display affect, and impairment in visuospatial representation (Weintraub & Mesulam, 1983).

These deficits endure into adulthood, since longitudinal studies are now showing that undercontrolled and inhibited disturbances in early childhood predict adult psychiatric disorders (Caspi, Moffitt, Newman, & Silva, 1996). In adults "greater right hemisphericity" is associated with a history of more frequent negative affect and lower self-esteem (Persinger & Makarec, 1991), that is, chronic difficulties in affect regulation. Functional limitations of affect regulation reflect structural and metabolic impairments in right frontolimbic distributed systems that contain connections between cortical and subcortical areas, and these prefrontal organizations represent primary sites of psychopathogenesis. This is because early relational environments that inhibit the organization of this control system generate an unstable right cortical capacity to evaluate and guide behavior, a metabolically inefficient one that under stress is easily displaced by an inflexible subcortical mechanism. The uncoupling of the two right brain limbic circuits would occur in response to high levels of interactive stress in episodes of "expressed emotion," intense levels of humiliation, criticism, hostility, and emotional overinvolvement within a close relationship (Vaughn & Leff, 1976). This uniquely potent psychobiological stressor for the induction of all classes of psychiatric disorders triggers extremely high levels of sympathetic ergotropic and parasympathetic trophotropic arousal that are beyond the individual's regulatory capacities. The resultant "transient frontolimbic imbalance" elicits subcortical limbic kindling, subjectively experienced as a sudden transition into rapidly shifting and intensely affective states, that is, "emotional chaos" (Grostein, 1990).

The right hemisphere, which is preferentially activated in stress, is specialized to process intensely negative states (Otto, Yeo, & Dougher, 1987). PET imaging studies that measure energy metabolism are now revealing the preeminent role of right hemispheric

paralimbic activity as traumatic emotional memories are activated (Rauch et al., 1996), and are documenting the changes in orbitofrontal metabolic activity during the evocation of a phobic state (Frederikson, Wik, Annas, Ericson, & Stone–Elander, 1995). The importance of these studies is that they can do more than simply “localize” psychiatric impairments in the brain. Rather, they offer information regarding the temporal organization of dysregulated dynamic systems, and can therefore elucidate a deeper understanding of the state changes that underlie the various forms of emotional dysregulation manifest in different classes of psychiatric disorders. The fact that a broad spectrum of psychiatric disorders show disturbances of the right hemisphere, the hemisphere that is centrally influenced by attachment experiences, accounts for the principle that all early forming psychopathology constitutes disorders of attachment and manifests itself as failures of interactional and/or self-regulation.

### **Dynamic Systems Theory and Ongoing Right Hemispheric Development**

Attachment is “the apex of dyadic emotional regulation, a culmination of all development in the first year and a harbinger of the self-regulation that is to come” (Sroufe, 1996, p. 172). The attachment dynamic continues throughout the life span as an unconscious mechanism that mediates the interpersonal and intrapsychic events of all relationships, especially intimate relationships. By the 2nd year, the infant can construct accurate representations of events that endure and are accessible over time (Bauer, 1996), and these experiences are imprinted into right hemispheric networks that store autobiographical memory (Fink et al., 1996). In this manner, “dispositional characteristics that appear to be linked to right hemisphere activity are a product of a developmental process involving cognitive and memory structures” (Heller, 1993, p. 484). The ability to access an internal working model of relationships that encodes strategies of affect regulation and expectations of future interactions, to interact with a meaningful other to share positive affect and reduce

negative affective states, to develop a theory of mind of the intentions of others, and to be psychobiologically attuned and thereby empathic to the internal states of an other self are fundamental prerequisites of an adaptive capacity to enter into satisfying interactions with other humans. Affect regulating interactions are essential to the development of the infant’s coping skills, but at later points in the life span they continue to be necessary for the continued growth of the brain and the expanding capacity to experience more complex psychobiological states.

The nonlinear right hemisphere, the substrate of early attachment processes, ends its growth phase in the 2nd year, when the linear left hemisphere begins one, but it cycles back into growth phases at later periods of the life cycle (Thatcher, 1994). This allows for the continuity of attachment mechanisms in subsequent functioning, and yet also for the potential continuing reorganization of the emotion-processing right brain throughout life. The orbitofrontal regions, centrally involved in the regulation of psychobiological state and energy balance, are unique in that they retain the neuroanatomic and biochemical features of early development, and for this reason they are the most plastic areas of the cortex (Barbas, 1995). If, however, an infant, especially one born with a genetically encoded altered neurophysiologic reactivity, does not have adequate experiences of being part of an open dynamic system with an emotionally responsive adult human, its corticolimbic organization will be poorly capable of coping with the stressful chaotic dynamics that are inherent in all human relationships. Such a system tends to become static and closed, and invested in defensive structures to guard against anticipated interactive assaults that potentially trigger disorganizing and emotionally painful psychobiological states. Because of its avoidance of novel situations and diminished capacity to cope with challenging situations, it does not expose itself to new socioemotional learning experiences that are required for the continuing experience-dependent growth of the right brain. This structural limitation, in turn, negatively impacts the future trajectory of self-organization.

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