# Neural plasticity and development in the first two years of life: Evidence from cognitive and socioemotional domains of research

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## Abstract:

Three models that can be used to investigate the effects of different environmental events on brain development and organization are explored. The insult model argues against brain plasticity, and the environmental model regards the brain as infinitely plastic. Our work is guided by the transactional model, which views brain development and organization as an interaction between (a) genetically coded programs for the formation and connectivity of brain structures and (b) environmental modifiers of these codes. Data are reported from our cognitive and socioemotional research studies that support the notion of plasticity during the first 2 years of life. From our work with normal developmental processes, we draw parallels to abnormal development and speculate how the transactional model can be used to explain abnormal brain organization and development.

## Article:

The question of whether there is neural plasticity in development is one that has taken many forms in the research literature. The high-risk infant literature has asked the question by examining the developmental consequences of injury to particular areas of the brain in very low-birthweight infants (e.g., intraventricular hemorrhage [IVH]; Sostek, Smith, Katz, & Grant, 1987). The more general question has been asked with regard to the role of experience on brain development. Here, the research literature has approached the problem from two opposing directions. There are studies that attempt to examine the effects of deprived environments on brain development both directly and indirectly, and to a lesser extent, there are studies that have examined the effects of enriched environments on brain development. Many of the studies on the role of either deprived or enriched environments have utilized animal models (e.g., Greenough & Volkmar, 1973; Rosenzweig, Bennett, & Diamond, 1972). These studies are able to document specific changes in neural development that occur as a function of environmental manipulation (e.g., synaptic growth, dendritic arborization or lack thereof). Studies with human infants or children have attempted through indirect methods to assess the effects of specific environments on brain growth and change. For example, studies of severe malnutrition or dietary supplement reveal the effects of altering the environment on intellectual or social development (e.g., Pollitt, Gorman, Engle, Martorell, & Rivera, 1993). Researchers assume that these documented effects are a function of changes in brain development, although the specific neural changes are left unspecified.

In part, the inability of researchers to specify the effects of environment on neural development has been a function of technology and the interpretive models that were associated with our knowledge about brain development. Although the recording of electrical activity off the scalp (the electroencephalogram [EEG]) of humans has been around since Berger first described it 65 years ago (Berger, 1929), this measure was, for a long period, relegated to use in clinical settings for the diagnosis or identification of epilepsy and tumor or as a measure of state. Due mainly to technical limitations on the ability to record multiple channels and to digitize, acquire, and store these data for complex signal analysis, EEGs were not utilized as a method for describing brain development. In addition, there have been, and continue to be, important questions regarding the localization of the EEG signals and the relation between these signals and brain function (e.g., to what degree do EEG measures reflect cortical vs. subcortical activation?; see Bell & Fox, 1994a, for a discussion of these and similar issues).

A number of changes have occurred over the past 20 years that enable a broader look into the effects of environmental manipulation on brain activity. First, computer technology has changed rapidly, allowing for the acquisition, storage, and manipulation of very large data sets. This has enabled complex analysis of signals acquired over time such as EEGs or evoked potentials. What was once relegated to analysis via paper strip chart can now be examined with the powerful tools of signal analysis to obtain new information about the signal.

Second, changes in technology have seen the advancement of multiple methods for imaging brain structure including computer automated tomography scan and magnetic resonance imaging (MRI). In addition, there are sophisticated means for assessing brain function with positron emission tomography (PET) scan and real-time MRI. A number of these methods involve the use of radioactive materials and all involve the need for a high degree of patient compli ance that have made these methods inaccessible to developmental researchers interested in studying infants and young children (but see Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987). However, the use of these technologies in combination with more traditional methods of measurement of brain electrical activity via EEGs and evoked potentials has illuminated both the positive aspects of the use of the EEG for the study of brain structure and function.

A third change in the utilization of measures of brain electrical activity involves the development of theoretical models to interpret the functional significance of certain parameters of both the ongoing EEG and evoked potentials. Among the more influential theorists in this area is Paul Nunez (1981), who has articulated a model for understanding dynamic changes in EEG activity. This model characterized the electrical activity recorded off the scalp in terms of its spatial properties. That is, EEG signals are thought of as waves propagating through cerebral space. The patterns of EEG activity reflect both cortico-cortical links and cortical-subcortical connections. While data on frequency and amplitude provide information on the excitability of neural networks, it is the interconnection between sites, the coherence, and phase relations in the EEG at a given frequency that are of most interest to Nunez (1981).

Thatcher (1991; Thatcher, Krause, & Hrybyk, 1986; Thatcher, Walker, & Giudice, 1987) has presented empirical support for Nunez's model. Thatcher utilized measures of the coherence of the EEG at specific frequencies between electrode sites. These measures of coherence reflect, in

part, the action of both long and short axonal connections. Thatcher predicted that, with development, coherence should decrease between sites that are topographically close. This decrease would reflect greater synaptic differentiation within a particular area. On the other hand, with development, coherence would increase between sites that are topographically distant. According to the Nunez model, this change would reflect increasing connectivity between anterior and posterior sites within and between hemispheres.

In sum, until recently, studies of the effects of environmental manipulation on brain organization or reorganization have been completed mainly via animal studies, or these effects have been understood via indirect measurement of intellectual or social behavior after severe environmental experience. Recent advances in technology and in the modeling of complex systems have allowed researchers to utilize sophisticated neuroimaging techniques as well as noninvasive measures that record brain electrical activity. These methods and approaches have opened the possibility of examining the effects of normal developmental events and extreme circumstances upon the course of brain development during the first years of life.

### *Models of Brain-Behavior Development*

The manner in which studies of neural plasticity are completed is obviously a function of the model of development and brain-behavior relations that is utilized. Three models come to mind as possible means for investigating the effects of different environmental events on brain development and organization. The first we call the insult model, the second the environmental model, and the third the transactional model of brain development.

#### The insult model

The insult model is one that argues against the notion of neural plasticity. Brain organization and development are fixed, and environmental input cannot change (except via damage) this organization and developmental course. There are a number of different ways that this model has been presented for studying neural development. The most obvious instantiation of this model is one that states that when environmental events produce changes or damage to brain structure, this damage (or insult) remains static and the functions that the damaged structure subsumed cannot be recovered. So, for example, IVH in premature infants may damage certain brain structures or particular regions of cortex. The functions subsumed by these structures or regions are lost and cannot be recovered.

Evidence against the strong "insult" position and for neural plasticity may be found in the work on infants who have undergone IVH. Sostek et al. (1987), for example, reported that an IVH insult may have limited predictive value for mental, motor, or neurologic functioning at 2 years of age. Such evidence might indicate that areas other than the one damaged have "taken over" the function lost through damage or that there has been reorganization at a systems level so that function is recovered via compensatory behaviors that do not precisely duplicate the original function. One might be able to differentiate between these two explanations by testing the specific competencies thought to underlie the damaged region or area. If function is present and cannot be discriminated from that of normal, nondamaged subjects, then it is possible that other areas have taken over for the damaged one. On the other hand, if there are subtle differences in function and performance, then one might infer that other compensatory mechanisms are involved in recovery.

A variant on this model would be one that was, for many years, a leading model for brain organization and language development. Lennenberg (1967) postulated that after a certain age brain development was set and injury to a particular area of the brain (that which involved language processes) would result in lasting impairment. Prior to the critical age at which brain organization was complete, there was some degree of plasticity so that other regions could subsume the function of the region or area that was damaged. Note, then, that the insult model is modified by the notion of a critical period. Prior to the critical period, after which organization is completed, neural plasticity is possible. After the critical period, the likelihood of plasticity is significantly diminished. The existence of a critical period for neural organization is evidence, in and of itself, of neural plasticity. The assumption of this model is that, prior to a certain developmental age, the brain is receptive to environmental input or at least to the possibility of reorganization. However, it is unclear whether specific structures have taken on the functions lost (via damage or loss of input) or whether, via system re-organization, compensatory mechanisms work to allow the function to operate.

A second variant of the insult model is the notion that particular individuals are born with certain patterns of brain structure, or differences in the excitability of certain structures, which forms the basis for certain unique qualities of behavior. For example, there is a great deal of discussion about inborn traits or temperament in infants and the "biological" basis of these patterns of behavior. There is evidence indicating that infants who display certain patterns of motor arousal and affect are likely to display behavioral inhibition as toddlers (Calkins, Fox, & Marshall, in press; Kagan & Snidman, 1991). And there are particular psychophysiological correlates of this infant temperamental pattern that suggest the involvement of particular subcortical structures. Specifically, Kagan and colleagues first reported that 4-month-old infants who exhibit extreme degrees of motor arousal and negative affect in response to novel stimuli are more likely to display behavioral inhibition in the 2nd year of life (Kagan & Snidman, 1991). Behaviorally inhibited toddlers are known to display high resting heart rates and high basal levels of cortisol (Kagan, Reznick, & Snidman, 1987). In our laboratory, we have found that infants who exhibit extreme degrees of motor arousal and negative affect in response to novelty display greater relative right frontal EEG activation and are likely to be fearful and inhibited as toddlers (Calkins et al., in press). Kagan has suggested that the pattern of motor arousal and negative affect expression is a function of greater excitability in areas of the limbic system thought to be involved in fear responses (Kagan & Snidman, 1991).

Animal work has shown that the central nucleus of the amygdala is an important structure in the conditioning and expression of fear in animals (e.g., Adamec & StarkAdamec, 1986). Given the structural connections between amygdala and frontal cortex, it is reasonable to assume that greater right frontal EEG activation, recorded in behaviorally inhibited infants, may reflect activity in those subcortical centers involved in fear responses. These physiological patterns may remain stable over time and reflect the underlying basis for certain temperamental dispositions.

Evidence for neural plasticity may be found if there are changes in the degree of arousal of these subcortical or cortical centers over the course of early development. There is evidence from Kagan's laboratory, for example, that a certain percentage of behaviorally inhibited infants become less inhibited over time due to certain types of rearing environments (Kagan, Snidman,

& Arcus, 1993). Is it the case that these phenotypic changes are accompanied by change in the activation of those subcortical or cortical patterns that earlier had been associated with the presence of behavioral inhibition (do these children, now no longer inhibited, present with EEG patterns similar to temperamentally noninhibited children) or does the original EEG pattern persist?

The first instance might be interpreted as evidence for neural plasticity because neural patterns associated with heightened fear are no longer present when the child ceases to display inhibited behavior. In the latter instance, the change in phenotypic behavior occurs as a result of activity in other brain regions that then serve to modulate the arousal of those centers involved in the fear response. However, infants with changed phenotypic behavior (those who were once inhibited and are no longer) continue to exhibit arousal of these fear centers, probably reflecting a lower threshold for the expression of negative affect similar to the pattern presented during the infancy period. They carry with them, according to the insult model, the original neural pattern. It is merely dampened by other processes. We will present data later in this paper that directly address this issue.

**The environmental model**

One possible position regarding neural plasticity is that the brain is infinitely plastic. Environmental input alters, at every turn, and, in some manner, neural organization. On some level, such a relation must exist, because neural changes occur when stimuli are sensed and when learning has taken place. On the other hand, the extreme position of this theory is that all regions or structures in the brain are somehow interchangeable, with each area having the potential to subsume multiple functions. This notion of equipotentiality was first articulated by Sherrington in the late 1800s with regard to the effects of brain injury particularly during development.

For the behavioral psychologist, this model may serve as a basis toward articulating a minimal role for genetic neural organization in the development and expression of behavior. Although behavior and psychological processes have their corresponding bases in neural organization, that organization is subject to constant change and modification when appropriate environmental stimuli are presented.

There are a number of reasons why this model fails to adequately describe neural plasticity. First and foremost, the literature on the effects of brain damage is overwhelming in finding that damage to certain regions of the brain affects function and that there is often little recovery of function (Milner, Petrides, & Smith, 1985; Shallice & Burgess, 1991; Wilkins, Shallice, & McCarthy, 1987). Second, there seems to be a clear genetic pattern to both the embryological and morphological development of brain structure that, if altered, significantly affects function (e.g., phenylketonuria [PKU]; (Diamond, Hurwitz, Lee, Grover, & Minarcik, 1994). Nevertheless, there are, in all probability, individual differences in the patterning of brain structure, and these differences are a function of differential environmental input. That is, within certain limits, it may be the case that different environments contribute to the pattern of inter-connections or other parameters of brain structure. Exactly what those limits are and how they correspond to structure is the subject of much debate.

**The transactional model**

A third possible model for understanding the role of plasticity in neural development is the transactional model. This model views development and organization of brain activity as a process of transaction between (a) genetically coded programs for the formation of structures and connections among structures and (b) environmental influence. This transaction regulates the initiation, speed, and success (or failure) of preprogrammed genetic codes. There is constant feedback between environment and genes and between genes and environment. Environment initiates the expression of certain genes while genetic tendencies create environments that in turn alter future biological expression (see Scarr & McCartney, 1983). Thus, for example, the source of the organization of the cortex with regard to interconnections among different regions may be a genetic program. But the rate and success of the program is under the influence of environmental input. This input may initiate, accelerate, and in some instances retard changes in neural organization or growth.

There are a number of examples from the area of behavioral neuroscience that support this model. For example, GoldmanRakic has reported in a series of studies, the effects of orbital prefrontal cortex lesions on monkeys' performance on a battery of prefrontal tasks (Goldman, 1971, 1976; Goldman & Mendelson, 1977). After receiving lesions as infants, the monkeys were tested at either age 1 or 2 years and could not perform the task; however, at a subsequent testing, 1 year later at either age 2 or age 3, the monkeys were successful. Goldman-Rakic speculated that experience interacted with neural development to improve performance.

Goldman-Rakic (Goldman & Mendelson, 1977) also looked at the more general effects of experience on brain organization. She reported that training orbital lesioned rhesus infants on a nonspatial task improved their performance on a spatial task as juveniles. Here, early training and experience acted nonspecifically to offset deficits. Early experience on one task generalized to other nonrelated tasks. General environmental experience produced new synaptic connections that aided the orbital monkeys to successfully solve the spatial task.

The work of Neville has important implications for examining how environmental experiences affect genetically programmed brain structure in humans. Neville (1988, 1990, 1991) has examined cortical functioning of hearing and deaf subjects by testing subjects on a task that requires visual sensory processing. Neville (1990) hypothesized that congenitally deaf subjects might utilize the area of the cortex normally used for auditory processing for other sensory processing. Utilizing a spatial visual attention task, Neville (1988, 1990, 1991) measured ERPs in hearing subjects, congenitally deaf subjects, and hearing subjects of deaf parents. The last two groups had learned American Sign Language from birth.

Neville found that both early sensory deprivation and early language experience with sign language had different and specific effects on specializations of cortical areas. Specifically, for spatial visual attention to peripheral stimuli, hearing subjects displayed right hemisphere parietal/temporal activation (typical for spatial tasks) while deaf subjects and hearing subjects of deaf parents displayed left hemisphere parietal/ temporal activation. This finding is significant because left hemisphere areas are usually involved in spoken language. Using a paradigm where hearing and deaf subjects saw a written word and then wrote it down and saw a signed word and then signed it back, Neville (1991) demonstrated that deaf subjects showed no left hemispheric specialization for the written word; however, deaf subjects did show left hemispheric special-

ization for the signed word. Neville hypothesized that initial brain growth and cortical organization is genetic, but that reorganization comes as a result of experience during a sensitive period of interconnections.

The transactional model considers multiple pathways in which environmental input affects brain organization. It includes the notion that, given a wide range of "nontoxic" environments, there are certain genetically programmed changes in brain organization that will occur. This unfolding of the genetic plan of neural development is what Greenough has written about as experience-expectant changes (Black & Greenough, 1986; Greenough & Black, 1992; Greenough, Black, & Wallace, 1987). For example, the development of the visual system involves the interaction of genetically programmed neural changes in visual cortex with a certain amount of visual stimulation. These genetically programmed changes "expect" a certain level of visual stimulation. Given this stimulation, neural organization of this system occurs across species in a highly deterministic manner. Obviously, in the absence of expected environmental input, these changes will not occur, but given the range of "normal" environments they are expected to happen across individuals. Neural plasticity occurs across environments that vary significantly in the degree of stimulus input that the organism receives. If animals are denied visual input during the period of experience-expectant growth, will growth occur after this period, and will function be similar to that which would have appeared had visual input not been denied?

Greenough (Greenough et al., 1987) interpreted the sensory deprivation literature as indicating that the complexity of the visual cortex is reduced in animals deprived of vision during the sensitive period of visual cortex development. Effects of visual deprivation can he reversed if the lack of stimulation is not prolonged. In cases of prolonged deprivation, however, morphological differences have been reported to persist in adult animals.

### *Research Evidence for the Transactional Model*

We have adopted the transactional model for our research on cognitive and socioemotional functioning during infancy. Our work is based on the two suppositions of this model. First, there are genetically coded programs for the formation of brain structures and for the connections among these structures. Second, environmental influence may be able to modify these preprogrammed genetic codes. Evidence from our cognitive and socioemotional research studies lend support to the notion of plasticity during infancy.

#### Neural plasticity and cognition

The transactional model is useful in describing the role of experience in the development of neural structures associated with certain developmental milestones. We (Bell & Fox, 1994b) examined the effects of a naturally occurring environmental event on neural development in infants during the second half of the 1st year of life. Infant performance on the classic Stage 4 object permanence task, Piaget's A-not-B, was observed and measured as a function of their self-produced locomotion. Three lines of evidence spurred our interest in attempting to link the onset and length of experience infants have had with locomotion to neural development and to A-not-B performance. First, there are a number of studies in the developmental literature that suggest that hands-and-knees crawling may be related to object permanence performance. It has been reported that infants who successfully recover the hidden object from Side B during the A-not-B task have longer locomotor experience than unsuccessful infants (Horobin & Acredolo, 1986).

And infants with 9 or more weeks of locomotor experience have been reported to perform at higher levels than either prelocomotor infants or infants with less than 4 weeks of crawling experience (Kermoian & Campos, 1988).

Second, Diamond et al. (1990, 1991; Diamond & Goldman-Rakic, 1983, 1986, 1989; Diamond, Zola-Morgan, & Squire, 1989) have proposed that the maturation or integrity of the dorsolateral prefrontal cortex is essential to successful search performance on the A-not-B task with delay. Thus, if early onset of hands-and-knees crawling affected the onset and performance success on the A-not-B task, it may also affect development of the dorsolateral prefrontal cortex or the connections between this area and other brain regions.

Third, the onset and length of time for naturally occurring, expected events such as locomotion should have a specific role on the development of neural connections. Greenough (Black & Greenough, 1986; Greenough & Black, 1992; Greenough et al., 1987) has proposed a model for the role of experience on the structure and function of the developing brain and on the further refinement of brain structure after maturation. Greenough's model predicts that the experience-expectant event of crawling will result in modifications in brain structure. Immediately prior to the onset of crawling, the brain should begin overproducing synapses in expectation of the event. Thus, the brain of an infant primed for crawling should be structurally different than the brain of an infant some time away from this developmental milestone. Likewise, the brain of a novice crawler should still be retaining extra synapses as this new skill is honed. With increasing experience from locomotion, these extra synapses will be pruned, so that the brain of the experienced crawler should have fewer synaptic connections associated with crawling than the brain of the novice crawler.

We therefore hypothesized relations among A-not-B performance, frontal lobe maturation (measured noninvasively via EEG), and locomotor experience. Specifically, we proposed that experience would affect performance on the A-not-B task and that frontal EEG recordings would differentiate between the infants with successful search skills and infants who were not successful. Successful infants would display greater power over the dorsolateral frontal cortex, and there would be changes in neural connectivity as a function of locomotor onset and duration of crawling.

Nunez (1981) has speculated that EEG power reflects the organization and excitability of a particular group of neurons. Across age, increases in EEG power have been proposed to reflect brain maturation (e.g., Bell & Fox, 1994a). Nunez (1981) further suggested that EEG coherence, the absolute value of the cross-correlation function between two electrode sites, reflects the level of axonal connectivity between two EEG recording sites. Thatcher (Thatcher et al., 1987) reported that periods of change in coherence between scalp locations during infancy and childhood are related to commonly accepted ages of major cognitive change during childhood. Thus, EEG power and coherence appear to be the most appropriate noninvasive electrocortical measures to use when investigating maturational change.

Eighty 8-month-old infants were recruited as the subjects for this study and were selected on the basis of the amount of experience with hands-and-knees crawling. One group of infants had 1-4 weeks of experience (n = 20), one group 5-8 weeks (n = 20), and one group 9 or more weeks (n =

20). The fourth group was prelocomotor (n = 20). For each infant, the EEG was recorded from frontal, parietal, and occipital scalp sites, using techniques described in previous papers (e.g., Bell & Fox, 1992, 1994b). After EEG recordings, performance on Piaget's A-not-B task was assessed.

Consistent with the work of Kermoian and Campos (1988) and Horobin and Acredolo (1986), the four locomotor groups performed differentially on the object permanence task, $F(3, 75) = 8.74$, $p < .001$. The three groups of crawling infants had similar performances on the task, while the prelocomotor infants performed less well (by Newman-Keuls). Specifically, 35% of the prelocomotor infants showed successful performance on the task, while 85% of the infants with 1-4 weeks of crawling experience, 60% of the infants with 5-8 weeks of experience, and 80% with 9 or more weeks of experience were successful in retrieving the hidden object. Thus, even limited crawling experience enhanced performance on the task. In addition, we found that infants who were successful on the A-not-B task displayed greater EEG power compared to those who were unable to do the task.

In confirmation of Greenough's model, we found differences among the locomotor groups on measures of EEG coherence. Infants with 1-4 weeks of crawling experience displayed greater overall coherence than either prelocomotor infants or long-term crawlers (see Figure 1). This suggests that the onset of crawling was associated with changes in cortical organization. At the onset of locomotion, there was an overproduction of cortico-cortical connections between frontal/occipital and parietal/ occipital sites. With increased locomotor experience, there was pruning of these connections. As seen in Figure 1, the particular pattern of pruning depended on the specific cortical connections. Frontal/occipital connections (see Figure 1, top) showed a sharp increase with locomotion and a gradual decline. Parietal/occipital connections (see Figure 1, bottom) also showed a sharp increase but also an earlier decline. These differential changes in EEG coherence may reflect changes in axonal connection. The pattern may be specific to the type of developmental change we investigate. The parietal lobes are intimately related to spatial skills (Andersen, 1988). Their interconnection with other regions may be critical for the rapid onset of crawling. As crawling became more automatic and length of time of crawling increased, the overabundance of the connections was no longer necessary.

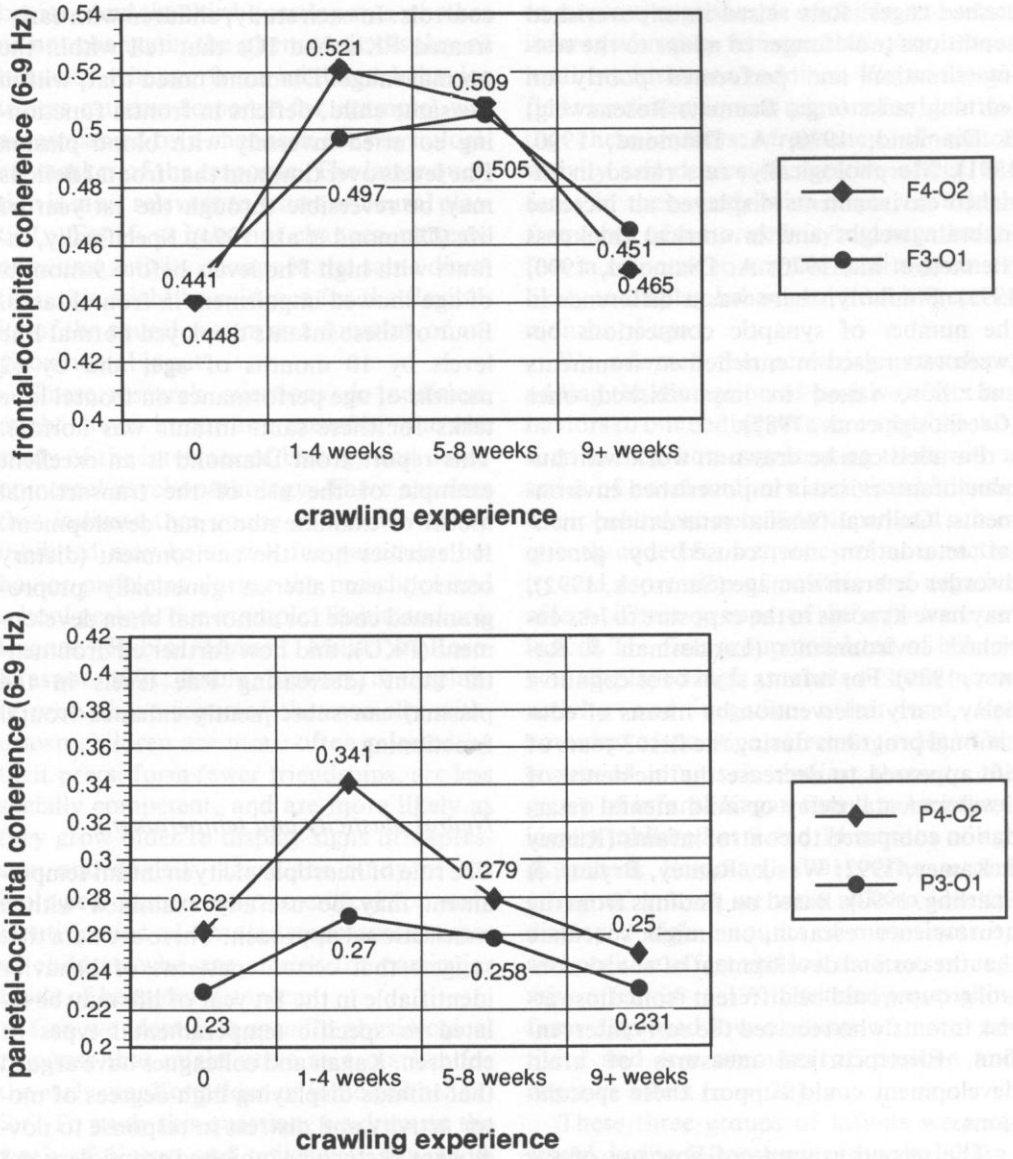


**Figure 1.** Left and right hemisphere frontal/occipital coherence (top) and parietal/occipital coherence (bottom) for hands-and-knees crawling experience at 8 months of age. From "Individual Differences in Object Search Performance at Eight Months of Age: The Relations Among Locomotor Experience, Sustained Attention, and Brain Electrical Activity" by M. A. Bell and N. A. Fox, 1994, manuscript submitted for publication.

We have used the transactional model to investigate normal cognitive development. This type of research also has ramifications concerning abnormal cognitive development. Two examples highlight this notion. First, neuroscientists using a classic enrichment paradigm have reported that brain structure and chemistry of rats were altered by experience (e.g., Greenough & Volkmar, 1973; Rosenzweig et al., 1972). Environmentally, the rats were raised in either complex (i.e., enriched) environments or impoverished cages. Rats raised in impoverished conditions took longer to adapt to the testing situation and performed poorly on learning tasks (e.g., Bennett, Rosenzweig, & Diamond, 1970; A. Diamond, 1990, 1991). Morphologically, rats raised

in enriched environments displayed an increase in brain weight and in cortical thickness (Bennett et al., 1970; A. Diamond, 1990, 1991). Similarly, there was a difference in the number of synaptic connections between rats raised in enriched environments and those raised in impoverished ones (Greenough et al., 1987).

Parallels can be drawn to work with human infants raised in impoverished environments. Cultural-familial retardation, mental retardation not caused by genetic disorder or brain damage (Santrock, 1992), may have its roots in the exposure to less enriched environments (Landesman & Ramey, 1989). For infants at risk for cognitive delay, early intervention by means of educational programs during the first 3 years of life appeared to decrease the incidence of developmental delay or mild mental retardation compared to control infants (Ramey & Ramey, 1992; Wasik, Ramey, Bryant, & Sparling, 1990). Based on findings from the neuroscience research, one might speculate that the cortical development of at-risk control group would be different from those at-risk infants who received the early intervention. Electrocortical measures of brain development could support these speculations.

The second example of how use of the transactional model has ramifications for abnormal cognition involves recent research on infants and young children with PKU, a genetic disorder causing an elevated Phe amino acid level in the blood. PKU causes mental retardation if not treated with dietary restrictions soon after birth. Diamond and colleagues (Diamond et al., 1994) and Welsh and Pennington and colleagues (Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990) have reported that infants and preschoolers with early-treated PKU were impaired on age-appropriate frontal lobe tasks compared to matched controls. In each study, children with early-treated PKU had IQs that fell within the normal range. Diamond noted that, within the same child, deficits in frontal functioning covaried inversely with blood plasma Phe levels over time and that frontal deficits may be reversible through the 1st year of life (Diamond et al., 1994). Specifically, infants with high Phe levels before 9 months of age showed impairment in frontal tasks. Four of these infants displayed normal Phe levels by 10 months of age, and by 12 months of age performance on frontal lobe tasks for these same infants was normal. This report from Diamond is an excellent example of the use of the transactional model to examine abnormal development. It describes how the environment (dietary control) can alter a genetically preprogrammed code for abnormal brain development (PKU), and how further environmental input (decreasing Phe levels in the plasma) can subsequently enhance frontal functioning.

**Neural plasticity and temperament**

The role of neuroplasticity in infant temperament may be usefully examined with a transactional approach. There are data that suggest that certain patterns of behavior identifiable in the 1st year of life may be related to specific temperamental types of children. Kagan and colleagues have argued that infants displaying high degrees of motor activity and distress in response to novelty are likely to be inhibited as toddlers and young children. We have focused our efforts on the study of the neural correlates of this behavior/temperament pattern. In doing so, we hoped to answer a number of questions directly related to the issue of neural plasticity and environmental influence on infant temperament. The first question was whether we could identify a specific physiological response or measure that could serve as a marker for the early manifestations of behavioral inhibition. The second question of interest was whether this physiological measure remained stable over time and adequately predicted inhibited behavior. And the third question

was whether or not change in the phenotypic display of behavior (change from inhibited behavior to less extreme response for example) was accompanied by a change in the physiological marker of the response. The latter question is most relevant to issues of neural plasticity. For if, as behavior changes, patterns of neural activity change in the same direction, this might be evidence for the flexibility of the neural system as a function of environmental input.

These research questions, in addition, might have important meaning for the study of the interface of biology and developmental psychopathology. There are data that indicate that young children who are inhibited may be at risk for particular behavior problems during the preschool and school period. For example, Rubin and colleagues (Rubin, Hymel, Mills, & RoseKrasnor, 1991; Rubin, Stewart, & Coplan, in press) have reported that socially withdrawn children are more often rejected by their peers, form fewer friendships, are less socially competent, and are more likely as they grow older to display signs of depression and anxiety. Thus, the study of the biological factors may be critical for early identification of certain temperament types of children who are at risk for particular kinds of behavior disorders.

Can we identify a specific physiological response that might serve as a marker for the early manifestations of inhibited behavior? To study this question, we drew on the work of Kagan and colleagues (Kagan & Snidman, 1991) and our own research with an unselected random sample of infants (Calkins & Fox, 1992) in order to identify specific behaviors in early infancy that might be predictive of later fearful and anxious behavior in children. In previous studies (Calkins & Fox, 1992), we reported that infants who responded with negative affect and distress to a series of novel elicitors were more likely to display fear and anxiety as toddlers. Kagan and colleagues (Kagan & Snidman, 1991) developed a battery of tasks, including presentation of novel auditory and visual events, which they utilized to screen a large sample of children to select infants who they felt would display behavioral inhibition as toddlers. Kagan identified two dimensions as relevant for identifying these infants: frequency of motor activity and degree of negative affect. Infants in their study who displayed a high frequency of motor activity and negative affect in response to novel stimuli were more likely to display behavioral inhibition at 14 months of age.

We adopted this screening procedure, adding the dimension of positive affect behaviors to our coding. We screened 200 children in their homes presenting them with a series of novel auditory and visual stimuli. Their behaviors were videotaped and subsequently coded for frequency of motor activity and expression of positive and negative affect. Three groups of infants were selected. The first group consisted of infants who displayed high amounts of both motor activity and negative affect and low amounts of positive affect ($n = 30$). This group of infants is similar, then, to the group of infants Kagan found to be behaviorally inhibited at 9 and 14 months of age (Kagan & Snidman, 1991). The second group of infants we were able to identify displayed high amounts of motor activity and positive affect and low amounts of negative affect ($n = 19$). The third group of infants displayed low amounts of motor activity and low amounts of positive and negative affect ($n = 32$).

These three groups of infants were assessed during follow-up visits to the laboratory at 9, 14, and 24 months of age. At 9 months of age, infants came to the laboratory at which time the EEG was

recorded. At 14 months of age, infants and mothers were observed in a procedure designed to elicit inhibited versus uninhibited behavior, and the EEG was again recorded. At 24 months of age, infants and mothers were observed in a series of procedures designed to elicit inhibition, compliance, frustration tolerance, and impulsivity, and, again, the EEG was recorded. EEG data were available for 66 of the 81 subjects seen at 9 months of age and for 61 of 71 subjects seen at 24 months of age. Artifact-free data were available on less than 50 of the 14-monthold subjects. Data loss at this age was likely due to the fact that these children, having recently attained upright mobility, were difficult to keep still during the procedure.

At 14 months of age, 67 infants (30 males and 37 females) were observed in a playroom for three brief episodes: (a) novel room (5 min of free play with mother in playroom); (b) novel person (stranger enters playroom and presents truck while keeping head down for 1 min, stranger plays with truck for 1 min, stranger invites child to play for 1 min); and (c) novel object (stranger presents electronic robot for 2 min). The primary measure of interest to us from these laboratory procedures was an index of inhibited behavior. Inhibition was scored using procedures similar to those used by Calkins and Fox (1992) and by Kagan and colleagues (Kagan et al., 1987; Reznick, Gibbons, Johnson, & McDonough, 1989). A single summary index of inhibition was computed using the sum of standardized scores representing latency to touch the first toy, latency to vocalize, and time spent in proximity to the mother during free play; latency to vocalize to and approach the stranger and robot, and time spent in proximity to mother during the stranger, truck, and robot sequences; and frequencies of displays of negative affect during all episodes.

At 24 months of age, 71 infants and mothers returned to the laboratory and were observed during several brief episodes designed to elicit the child's ability to cope with novelty, frustration, impulsivity, and compliance. To assess the child's response to novelty, the child was observed in the following episodes: (a) novel room (5 min of free play with mother in playroom); (b) novel person (stranger enters playroom and presents truck while keeping head down for 1 min, stranger plays with truck for 1 min, stranger invites child to play for 1 min); (c) novel object (stranger presents electronic robot for 2 min); (d) tunnel (stranger presents play tunnel and invites child to enter for 2 min); and (e) clown (research assistant dressed as clown enters room, stands si lently for 30 s, and then invites child to play for 1 min). To assess compliance, the experimenter entered the room after an initial 5-min free play and asked the child to clean up the toys. Mothers were instructed to handle the situation as they would at home and were free to assist the child in cleaning up. The child was given 5 min to clean up the toys. To assess impulsivity, the child was seated at a small table, with a box of crayons and several sheets of paper placed in front of him or her. The experimenter told the child not to touch the crayons until he or she had returned to the room. The child waited for up to 2 min. To assess frustration tolerance, the child was given a closed plastic container that contained an attractive toy. The child was asked to open the container to retrieve the toy and was given 2 min to do so.

From these episodes, several behavioral summary scores were computed. A single summary index of inhibition was computed using the sum of standardized scores representing latency to touch the first toy, latency to vocalize, and time spent in proximity to the mother during free play; latency to vocalize to and approach the stranger, robot, clown, and tunnel, and time spent in proximity to the mother during the stranger, robot, tunnel, and clown sequences; and frequencies of displays of negative affect during el episodes. A single summary index of compliance was

computed by using the standardized summary score representing the amount of time it took the child to clean up, the number of refusals of maternal requests, and a negative affect score. Impulsivity was scored as the standardized summary score of latency to touch the crayons and latency to color with the crayons. Frustration tolerance was scored as the standardized summary score of the amount of time the child spent opening the container minus the number of refusals to open the container and a rating of affect.

Is EEG asymmetry related to early infant temperament? The EEG asymmetry score is a measure applied when examining differences in hemispheric functioning within an individual subject. Asymmetry scores (right power-left power) are computed for each region, and this difference score is used to express the magnitude and direction of asymmetry. A positive number reflects left hemisphere activation, while a negative number reflects right hemisphere activation. Our previous work has shown that right frontal asymmetry is associated with negative reactivity to maternal separation and to novelty (e.g., Calkins et al., in press; Fox, Bell, & Jones, 1992). (As we have demonstrated in this paper and elsewhere, the EEG asymmetry score is a measure of underlying brain organization that may be predictive of later temperament. Unlike the EEG power and coherence measures, which fluctuate with age, EEG asymmetry scores are not reflective of maturation. Rather, we propose that EEG asymmetry reflects an inborn temperamental disposition.)

To answer this question, we examined differences in EEG activity as a function of temperamental group (Calkins et al., in press). We found that infants who were high motor/high negative at 4 months of age exhibited a pattern of right frontal EEG asymmetry at 9 months of age and were inhibited at 14 months of age. Infants who were high motor/high positive at 4 months of age were showing a pattern of left frontal EEG asymmetry at 9 months of age and were uninhibited at 14 months of age. Thus, there seemed to be a significant relation between the infant's temperament and the pattern of frontal brain electrical activity.

Is the EEG pattern stable over time, and what are the implications of stability for temperamental behaviors? To answer these questions, we created three groups of infants based on the pattern of their frontal EEG activity across the 15-month period of the study. One group of infants whose pattern of EEG was characterized by greater right frontal activation at both 9 and 24 months of age was placed together: These represented the stable right group. A second group of infants who displayed left frontal asymmetry at both ages were grouped together: These represented the stable left group. A third group of infants whose EEG asymmetry changed from left to right or from right to left over the 15-month period comprised the change group.

Analysis of variance and post-hoc analyses indicated that the stable right group differed significantly from the stable left group in right hemisphere power at 9 months of age ($F(2, 40) = '7.28$, $p = .002$, Newman-Keuls, $p = .05$), and the stable right group differed significantly from the stable left group in both right and left hemisphere power at 24 months of age ($F(2, 40) = 11.08$, $p = .001$, Newman-Keuls, $p = .05$). That is, stable right infants were more right activated in the frontal scalp region across the 15-month period compared to the other groups of infants. The stable right infants were also more likely to have been selected at 4 months of age as high motor/ high negative affect infants. A chi-square analysis comparing the 4-month temperament groups and the EEG stability groups indicated a significant relation between these two groups,

$X^2 = 9.87$, $p = .04$. Of the 11 infants classified as stable right, 7 were in the high motor/high negative group.

We next investigated the relation between the stability of EEG and behavior at 14 and then at 24 months of age. An analysis of variance (ANOVA) comparing the three EEG asymmetry groups on the index of inhibition at 14 months of age indicated a significant group difference. A priori planned comparisons of the stable right and stable left groups indicated that the stable right group was significantly more inhibited at 14 months of age than the stable left group, $t(32) = 2.15$, $p = .04$. ANOVAs comparing the three asymmetry groups on several 24-month behaviors indicated a number of significant group differences. A priori comparisons of the stable right and stable left groups revealed that the stable right group was more compliant ($t(40) = 1.98$, $p = .05$), less impulsive ($t(40) = -2.01$, $p = .05$), and more tolerant of frustration ($t(39) = 2.12$, $p = .04$) than the stable left group (see Figure 2).

Finally, an ANOVA examining 24-month inhibition as a function of EEG asymmetry group and inhibition at 14

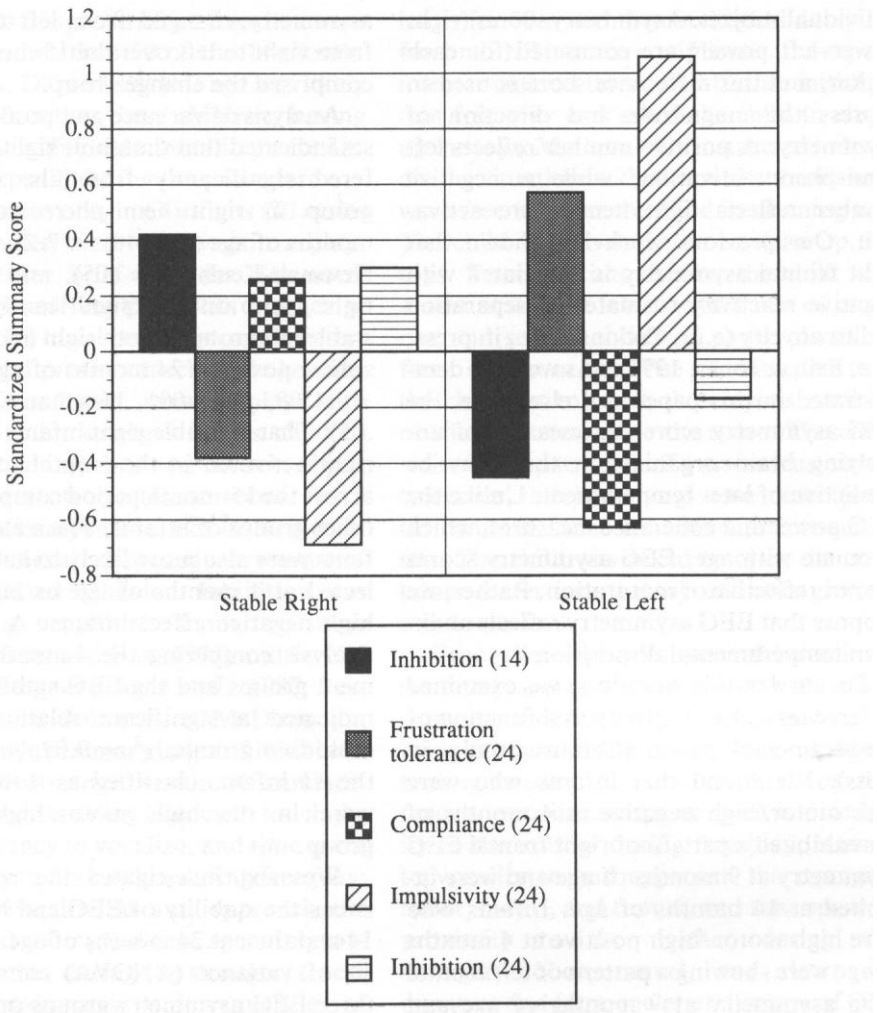


**Figure 2.** Standardized summary scores reflecting inhibition at 14 months of age and frustration tolerance, compliance, and impulsivity inhibition at 24 months of age for the stable left and stable right infants.

months of age revealed a significant main effect for 14-month inhibition ($F(1, 30) = 10.92$, $p = .002$). In addition a significant interaction between inhibition at 14 months of age and EEG group was found ($F(1, 30) = 3.99$, $p = .05$). The interaction indicates that infants who had been stable right in their pattern of EEG asymmetry and who had been inhibited at 14 months of age were more inhibited than those infants who had been stable right but had not been inhibited at 14 months of age. None of the stable left infants were inhibited at 14 months of age. These findings indicate that there may be a small group of infants who exhibit a stable pattern of right frontal EEG asymmetry across the infant and toddler age period and that this pattern of asymmetry may be predictive of later temperament and social behavior.

Does the EEG pattern change when behavior changes? To examine whether or not a change in behavior across the 24-month age period would be reflected in a change in EEG pattern, several exploratory analyses were conducted. First, we examined infants selected at 4 months of age for high motor/

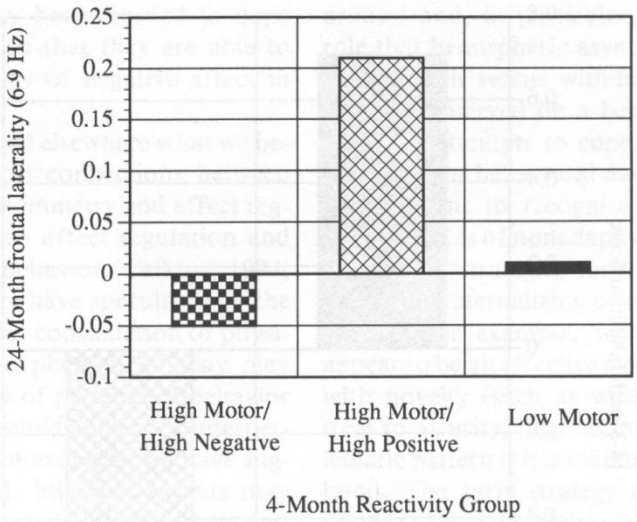


**Figure 3.** Laterality difference scores for the three 4-month temperament groups. Negative laterality difference scores reflect greater relative right frontal activation, and positive laterality difference scores reflect greater relative left frontal activation.

high negative affect in terms of their 24-month behavior and their 24-month EEG asymmetry. We were interested to see how many of this temperamental type were still inhibited in their response to novelty and still displayed a pattern of right frontal asymmetry. As Figure 3 indicates, at 24 months of age, infants who had been selected at 4 months of age as high motor/high negative still displayed right frontal EEG activation, $F(2, 57) = 4.37$, $p = .02$. However, some of the infants no longer tended to be inhibited. Even though a number of high motor/high negative infants did not display behavioral inhibition at 24 months of age, they continued to exhibit greater relative right frontal activation.

In a second exploratory analysis, we compared those infants who were selected at 4 months of age for high motor/high negative affect and who also displayed right frontal EEG asymmetry at 9 months of age to those infants selected at 4 months of age for the opposite temperamental pattern (high motor/high positive affect) who also displayed left frontal EEG asymmetry at 9 months of age. These two groups of infants displayed, then, both the behavioral and physiological profile thought to be predictive of inhibited behavior. These two groups of infants differed significantly in terms of inhibited behavior at 14 months of age, $t(14) = 2.27$, $p = .04$. As Figure 4 indicates, infants displaying the negative temperament and EEG right frontal pattern were more likely to be inhibited at 14 months of age compared to those displaying the positive temperament and EEG left pattern. However, by 24 months of age, a number of the negative temperament and EEG right infants had changed their behavior and were no longer inhibited. All but one of the positive temperament and EEG left infants retained their uninhibited style of behavior. An examination of behavior and EEG at 24 months of age indicated that, despite the fact that several of the negative temperament and EEG right infants were no longer inhibited at 24 months of age, they retained the physiological profile of right frontal asymmetry. Among the infants whose behavioral pattern changed from inhibited at 14 months of age to no longer inhibited at 24 months of age, only one child displayed a change in EEG pattern (from right frontal asymmetry to left frontal asymmetry). These findings indicate that the early behavioral and physiological profile of negative reactivity and right frontal

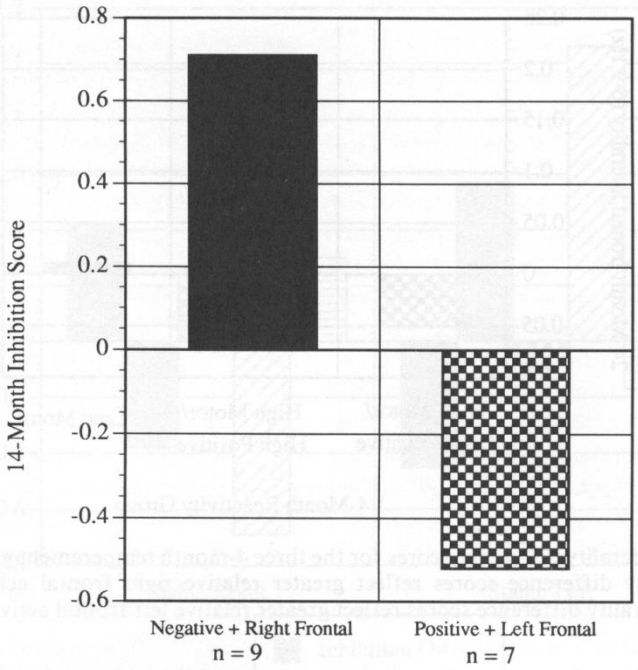


**Figure 4.** Fourteen-month inhibition score for infants displaying high motor/high negative profile at 4 months of age and right frontal laterality at 9 months of age and infants displaying high motor/high positive profile at 4 months of age and left frontal laterality at 9 months of age.

EEG asymmetry is a strong predictor of inhibited behavior at 14 months of age. And, although some infants may show a change in this behavioral pattern from 14 to 24 months of age, this behavioral change does not appear to be accompanied by a change in the underlying physiology.

In answering the questions regarding the behavioral outcomes that may be related to physiological stability and the physiological changes that may accompany behavioral changes, several conclusions may be drawn. First, our assumption that physiology seems to drive behavior appears to have support in the data from our selected longitudinal sample. The physiological profiles of stable right frontal asymmetry and stable left frontal asymmetry were strongly related to a number of behavioral outcomes at 14 and 24 months of age. Second, although we have clearly observed behavioral change among our selected sample of infants, this change is not reflected in a change in the underlying physiology of the infant. Infants who, in the 1st year of life, displayed a behavioral pattern of negative reactivity and a physiological pattern of right frontal EEG asymmetry, did show some behavioral change by the 2nd year of life. This behavioral change, however, was not reflected in their pattern of EEG.

Our assumption regarding the behavioral display of inhibition is that it represents the child's attempt to cope with high levels of arousal. Children who are particularly aroused by novelty and stress may develop regulatory mechanisms that remove them from threatening situations but that may, over time, involve internalizing their anxiety, stifling their impulsivity, and, in general, making them timid and compliant. Moreover, one interpretation regarding behavioral change is that some infants have learned to regulate their reactivity to novelty such that they no longer

appear as inhibited as they once did. They may still experience a high degree of arousal to novelty, but through interactions with parents, for example, they may have learned to cope with that arousal so that they are able to control their display of negative affect in novel situations.

We have discussed elsewhere what we believe are the critical connections between patterns of brain asymmetry and affect regulation and between affect regulation and developing social behavior (Calkins, 1994; Fox, 1994). And we have speculated on the role that a particular constellation of physiological/behavioral phenomena may play in the development of patterns of behavior that may place the child at risk for interpersonal problems. For example, we have suggested that fearful, inhibited infants may develop a particular behavioral pattern that reflects inadequate regulation of affective arousal: They rarely exhibit autonomous behavior, they fail to approach novelty, and they lack exploratory skills. Using data from a previous longitudinal study with unselected infants, we found that these inhibited children, when faced with interactions with unfamiliar peers were reticent, withdrawn, and anxious. These children were also rated by their mothers as being shy and they scored higher on the internalizing scale of the Child Behavior Checklist than their uninhibited counterparts (Calkins, Fox, Rubin, & Coplan, 1994). These findings suggest that negotiating interactions with peers may be difficult for inhibited children, because they are unable to begin that interaction with the necessary approach behaviors: The strategy they have chosen to help them cope with the arousal evoked by novelty has precluded them from acquiring skills necessary to initiate social interaction. The result is that these children tend to exist on the periphery of activity and become isolated from the play of their peers.

The data that we have collected over the last several years, from both selected and unselected longitudinal samples of children, highlight the utility of an emotion regulation framework for interpreting both behavioral and physiological data. Our physiological data suggest links between hemispheric activation and emotional arousal and, in particular, emphasize the role that hemispheric asymmetry may play in approach versus withdrawal tendencies that are observed on a behavioral level as the child attempts to cope with emotional arousal. Our behavioral data suggest that it is important to recognize that long-term consequences of nonadaptive or dysregulating coping strategies may, over time, develop into internalizing or externalizing disorders. For example, what may initially appear to be an effective strategy for coping with novelty (such as withdrawal and retreat to security) may become a more problematic pattern if it is maintained into childhood. The early strategy may establish a pattern of social withdrawal that, while perhaps not a severe behavior problem of itself, may become so if the child's missed opportunities for peer interaction result in depression and low self-esteem. The dysregulation that caused the child to withdraw from social novelty may not of itself have been psychopathological in nature, but its consequences could nevertheless enhance the risk of developing internalizing disorders at a later point in childhood or adolescence (Rubin et al., in press). Indeed, the question of long-term implications of this tendency to be inhibited has recently been explored from the perspective of developmental psychopathology (Hirshfeld et al., 1992). This follow-up of children studied from infancy to age 7 found that, among children who had consistently displayed inhibition across the 7-year span, there were significantly higher rates of anxiety disorder than among a group of children who were consistently uninhibited.

Although the observations we have made regarding physiological stability and its relation to behavioral change seem to argue against a transactional approach, we remain somewhat cautious

regarding their conclusions. First, the number of subjects who change behavior over the brief period of study is small. The general pattern we have observed in our data is, at least among the most extreme children, one of behavioral and physiological stability. Second, we have only followed these infants through 2 years of age. It is possible that as social behavior becomes more complex and inhibitory systems mature there will be a change in the organization of brain activity that will follow that found for behavior. Future longitudinal work will hopefully allow us to answer these issues.

## *Conclusions*

The issues of neural plasticity are critical to our understanding of the relation between biology and experience in the development of complex behavior patterns. In this paper, we have presented evidence from two different domains on the role of maturation and experience in developing brain organization. From our work with normal infants and children, we have shown how our use of the transactional model of brain plasticity has implications for abnormal cognitive development and emotional regulation.

Our work has demonstrated the utility of the ongoing EEG as a means of assessing neural organization in the awake, intact, alert infant and young child. Using measures of EEG power and coherence, we have illustrated how different rates of maturation of an expected locomotor event affect neural organization and cognitive performance at a specific point in time. We found EEG coherence differences among 8month-old infants with varying amounts of crawling experience and speculated that changes in axonal connections between brain regions are modified with this kind of environmental input. We also reported that the infants who were locomotor performed at a higher level on the A-not-B task than prelocomotor infants and that infants exhibiting successful A-not-B performance also displayed greater EEG power values at frontal, but not other, recording sites. These performance data, along with the coherence and power data, point to an interaction among experience, brain development, and object permanence performance in normal infant cognition. We noted that the association between environment and brain development also has ramifications concerning abnormal cognitive development and cited recent work on environmental influences on cognitive performance in support of this idea.

We have also used EEG to explore the relations between physiology and temperament and have applied a model of the relation between innate dispositions that have at their core a particular pattern of brain asymmetry and the development of particular styles of emotion regulation. In investigating this model, we have found (a) that there is a pattern of right frontal EEG asymmetry that maps onto an early predisposition to be irritable; (b) that for some infants, this predisposition is highly stable and predictive of fear and anxiety in early childhood; and (c) that there is a tendency for the underlying biological predisposition to remain, even when the behavior itself does not. Moreover, we have used this model of the relations between EEG asymmetry and temperament to speculate on the development of more extreme forms of child behavior that may in fact fall within the realm of developmental psychopathology.

Through use of the transactional model of brain development, we investigate the crucial interaction between environmental input and neural plasticity during infancy. Each of the EEG methods we use to assess brain activity (i.e., power, coherence, and asymmetry) provide different aspects to the complex picture of the role of the environment on neural organization. The

ultimate end product, normal or abnormal brain development and behavior, depends on this intricate interaction.

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