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Chapter

THE DEVELOPMENT OF THE FRONTAL LOBES IN INFANCY AND CHILDHOOD: ASYMMETRY AND THE NATURE OF TEMPERAMENT AND AFFECT

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ABSTRACT

The rapidity of growth of the entire brain, the frontal lobes and their connectivities, as well as lateralization evident in infancy that we know so little about can foretell so much about the cognitive and social-emotional capacities of the infant and developing child. This chapter outlines what happens to the frontal lobes at the outset of prenatal and postnatal life, as well as during early childhood. Specifically, the authors examine how early frontal brain development and its asymmetries and connectivities might affect temperament and social interaction, or *vice versa*.

Keywords: Frontal lobes; connectivity; development; lateralization; temperament; affect

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INTRODUCTION

At conception a zygote is roughly $1x10^{-7}$ of an inch in diameter (Schwoegler, 1991) and yet during the course of nine months of gestation the neonate reaches approximately 30 percent of his or her adult brain weight and approximately 85 percent by the age of two. The frontal lobes, as we all know painfully from our adolescent children, continue to develop through the remainder of the teenage years and early 20s depending upon sex and individual differences (Melillo and Leisman, 2009). Anatomic studies show that increases in absolute brain weight occur almost entirely before birth and in the first two years of life. Over 90 percent of human brain growth is completed by the age of 6 years (Blinkov and Glezer, 1968; Coppoletta and Wolbach, 1933) (see Table I). As indicated in Figure 1, while the brain and nervous system mature at an incredibly fast rate, Figure 2 indicates that certain areas take significantly longer to do so, especially the frontal and prefrontal areas, making the infant and child more vulnerable to environmental manipulation and experience. This is a good thing as long frontal lobe development that begins prenatally and that continues into early adulthood is altered by a wide range of positive and negative experiences that include: the development of short-term memory, associative learning, strategy formation, social/emotional behavior, response inhibition and behavioral spontaneity. Experiences that alter frontal lobe development will alter these functions too. A lot of what is guided by what we can call temperament, perhaps the basis of personality, has an affect on social interactions and it is based in part on cerebral asymmetry and lateralization.

The rapidity of growth of the entire brain, the frontal lobes and their connectivities, as well as lateralization evident in infancy that we know so little about can foretell so much about the cognitive and social-emotional capacities of the infant and developing child. It is what happens to the frontal lobes at the outset of prenatal and postnatal life as well as during early childhood that is the subject of this discussion. We are here examining how early frontal brain development and its asymmetries and connectivities might affect temperament and social interaction, or *vice versa*.

Table 1. Average brain weights of males and females developmentally ***(cf. Dekaban and Sadowsky , 1978)***

Age	Brain Weight-Male	Brain Weight Female

	(in grams)	(grams)
Newborn	380	360
1 Year	970	940
2 years	1,120	1,040
3 years	1,270	1,090
10-12 years	1,440	1,260
19-21 years	1,450	1,310
56-60 years	1,370	1,250
81-85 years	1,310	1,170

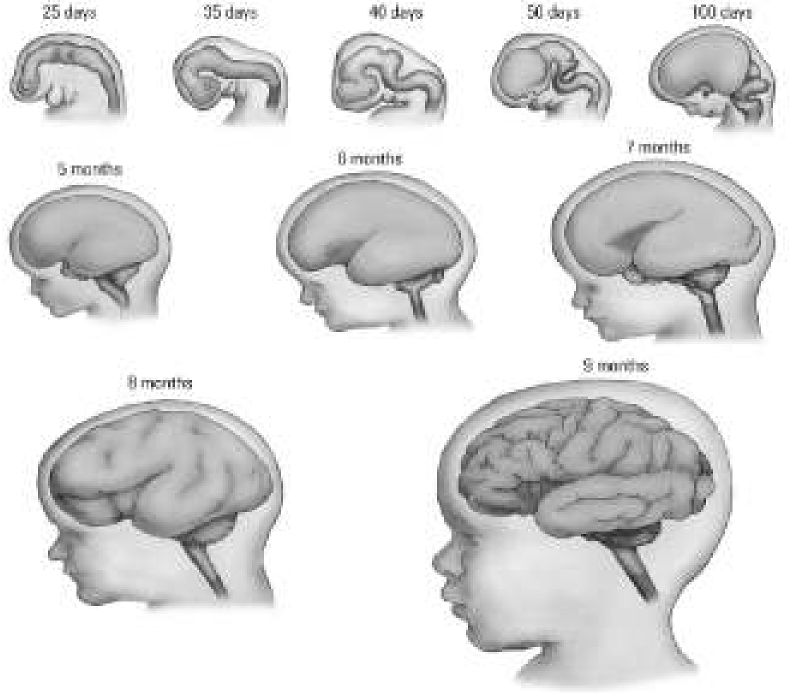


Figure 1. Development of brain from conception through the first nine post natal months. Frontal lobes do not fully develop until the early 20s on average.

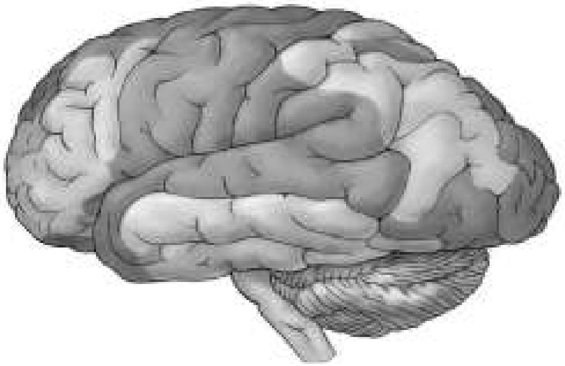


Figure 2. Some brain areas are slow to mature and thus vulnerable to change by experience which is especially true of lighter areas.

INDIVIDUAL DIFFERENCES IN TEMPERAMENT

While the old nature-nurture debate is today a non-starter, much from the earlier arguments has a singular value in understanding the nature and purpose of the development of the frontal lobes and brain asymmetry in infancy. It had for the longest time been thought by many that the infant was a *tabula rasa*. Systematic studies of the nature of the child's specific pattern of individuality and the presence of and contribution to the psychological development of the infant and child have been given much attention over the past decades, during which environmental approaches to the study of behavioral development has predominated, exemplified by early intervention programs, and even behavior modification programs for autistics as examples.

While these standards have served to identify the many aspects of parental attitude and practice, sibling and family relationships, social values, expectations, and cultural norms which appear to contribute significantly to a child's normal or deviant behavioral development, they do not address a principal component of infant development, namely, the infant as he himself is.

Earlier in the 20th century Gesell (1937) and Shirley (1933), reported significant individual differences in the behavioral characteristics of infants. However, over the succeeding years, scattered stands of theory were presented insufficient to provide the basis for systematic and comprehensive understanding of behavioral individuality and psychological development. A number of factors were responsible for this neglect. Important among these was the disrepute of the previously influential constitutionalist views which had ascribed personality structures and the elaborate psychopathological syndromes to heredity and constitution only. The alternatively held views in the past noted that purely environment explains most of child development. Unfortunately, the fact remains that a purely environmental approach does not adequately explain the great variability in responses of infants and children to similar childcare practices. Nor does it explain the absence of a one to one relationship between parental functioning in the presence of psychological abnormality in the child. Perhaps individual organismic behavioral differences important for development might exist in infants. Constitutionalist views had, of course, erred in discounting environmental influences. Was it not possible that the environmentalist positions might also be mistaken in ignoring significant organismic characteristics of the child?

The nature of the interactions of infant with his or her environment in the context of both the infant's specific characteristics of individuality and significant effects in his frontal lobe development in the context of cognition and emotionality speaks to the need for a fundamental understanding of the how differences in dynamic interactions between the brain and nervous systems of infants and children can create individual differences in the reactivity of these infants' to their environment and how the dynamic interplay between brain regions and their connectivities influences brain and nervous system development.

For infants' individuality to be seriously incorporated into the body of developmental theory, more substantial information on the nature of individual differences is required. The pertinent initial characteristics of individuality in infancy have to be identified along with the continuities and discontinuities over time and their relevance to various features of child psychological development determined. Such analyses require long-term longitudinal study of data on the behavioral characteristics of substantial sample of children analyzed from infancy onward. This in fact happened with the New York longitudinal study initiated in 1956 but with little follow up beyond its initial release. Observations of a number of normal and deviant children over periods of years revealed that the aspect of initial difference most likely to have pertinent for later development was behavioral style or temperament.

Temperament has been referred to as the "behavioral style" of a child and contains no inferences as to the genetic, somatalogic, endocrine or environmental etiologies. It was originally a phenomenological term used to describe the characteristics about, energy expenditure, focus, mood and rhythmicity that fire the behaviors of an individual child independently of their contents. Temperament refers only to the how, not the why, of behavior and implies neither immutability nor permanence (Rutter et al., 1964).

In the original New York longitudinal study of infants' individual differences, the authors (Chess et al., 1959) found through inductive content analyses of the infant behavior protocols that it was possible to characterize the individual behavior style of each child the study in terms of nine categories of reactivity. These qualities were defined when the child was only two months of age were also identified at all subsequent age periods, in infancy and in childhood. Nine categories of reactivity in which temperamental attributes were subsumed were:

1 Activity level: motor components present in a given child's functioning and the diurnal proportion of active and interactive periods. Protocol data on the child's motility when he is being bathed, fed dressed, and handled, as well as information concerning his sleep-wake cycle and is reaching, crawling, walking, and his play patterns.
2 Rhythmicity (biological regularity): the predictability and rhythmicity and/or the unpredictability and arhythmicity in time of any function, analyzed in relation to the child's sleep-wake cycle, his hunger or feeding patterns and his elimination schedule.
3 Approach-withdrawal (positive-negative initial responses): the nature of the child's initial response to a new or altered in numerous, being new food, a new toy, or a new person.
4 Adaptability: the nature of the child's responses to new or altered situations with respect to the ease with which they are modified in the desired direction, irrespective of the initial response.
5 Intensity of reaction: the energy level or vigor of a child's response, independent of direction. (Either a negative or a positive response could be mild or intense.) Responses to stimuli, to pre-elimination tension, to hunger, to repletion, to new foods, to attempts at control, to restraint, to dressing and to diapering.
6 Threshold of responsiveness: the intensity level of stimulation necessary to evoke a discernible response without regard to the specific form that the response may take or the sensory modality affected. The behaviors used are responses to a) sensory stimuli b) environmental objects, and c) social contacts.
7 Quality of mood: the amount of pleased, joyful, and friendly versus the amount of displeased, crying, and unfriendly behavior. (Does the

infant show more smiling and laughing for more fussing and crying behavior?

8 Distractibility: the ease with which a child can be diverted from an ongoing activity by extraneous peripheral stimulus.

9 Attention span and persistence: attention span is the length of time to nuclear activity is pursued by the end persistence refers to the continuation of an activity by the infant in the face of the obstacles to the maintenance of the activity direction.

In attempting to understand the systems physiology basis of temperament thusly described, it has been postulated for a significant period of time already (Grey Walter, 1953) that patterns of electroencephalographic activity might be correlated with various types of temperament. Although there has been a long history in seeking indications of biochemical individuality that might offer clues to initial sources of individuality in infants, in recent times (Fox et al., 2005, 2007) gene x environment interactions have been noted involving child temperament and maternal social support. Investigators have found heightened behavioral inhibition in children homozygous or heterozygous for the serotonin transporter (5HTTLPR) gene short allele whose mothers reported low social support. Fox and colleagues had proposed how with plasticity for affective neuro-circuitry, genetic dispositions could be described that allow for interaction with environmental circumstances. Children with persistently fearful temperament (and the 5HTTLPR short allele) would be are more likely to experience care-giving environments in which threat is highlighted. This in turn will exacerbate an attention bias that alters critical affective neuro-circuitry to threat and enhances and would maintain anxious behavior in the child. In contradistinction to the descriptions above, temperament in the context of frontal lobe development refers to individual differences in motor and emotional reactivity and self-regulation according to Rothbart and Bates (1998). The temperamental variable related to the development of executive attention is termed effortful control, representing the infant's ability to inhibit a dominant response in order to perform a sub-dominant response. The construct of effortful control is extremely important in understanding the influence of temperament on behavior.

Most of the more behaviorally based definitions of temperament have focused on temperament's more reactive aspects related to positive and negative affect, reward, punishment, and arousal to stimulation. Brain-based systems of effortful control are understood in the context of immediate cues and avoidance. The program of effortful control is critical to socialization.

Kochanska (1995) has indicated that conscience is related to temperamental individual differences in effortful control. Although the literature on temperament had originally believed that temperament systems would be in place very early in development and change little over time (Buss and Plomin, 1975; Rowe and Plomin, 1977) we have since learned that temperament systems follow a developmental course. Children's reactive tendencies to experience and their emotional expressivity and response to events in their environment can be observed very early in life. Children's self-regulatory executive attention develops relatively late and coincidently with the development of their frontal and prefrontal cortices throughout the early school years.

Self-regulation, a direct manifestation of temperament, involves complex questions about the nature of volition and its relation to one's genetic endowment and social experiences. Much of the work on self-regulation has been purely behavioral. The lack of appropriate methods to study the physiology of the developing human brain has led to understandable hesitation in thinking about these processes at the neuro systems level. Kandel (1999) however, has argued persuasively that new concepts in the neurosciences make it possible to relate higher level cognitive concepts to underlying brain systems.

Control of distress is a major task for the infant and the caregiver in the early months of life and of course the tasks involved in distress control in turn require external or self-regulatory processes. In the first few months, caregivers help control distress mainly by holding and rocking. Increasingly in the early months, visual orienting is also used. Caregivers then attempt to involve the child in activities that will occupy their attention and reduce their distress. These interactions between infant and caregiver may train the infant in the control of distress and lead to the development of the mid-frontal area as a control system for negative emotion. Later when similar cognitive challenges arise, a system for regulating remote brain areas may already be prepared.

Evidence exists for a physiological basis of individual differences in the self-regulation of distress and its resultant system of emotional control (inhibition) in human infants. Differences among infants in negative and positive emotionality are often assumed to reflect differences in temperament that are expected to have a constitutional basis (Goldsmith et al., 1987; Porges and Furman, 2011). According to Rothbart (1989), the constitutional basis of temperament should be reflected in endocrine processes that may, in turn, be related to genetic differences among individuals (Buss and Plomin, 1986, Pluess and Belsky, 2011).

Studies using vagal tone, a measure of parasympathetic input to the heart, have shown that by the end of the first year of life, high vagal tone is associated with greater emotional expressivity (both positive and negative), while low vagal tone is associated with inhibition of approach to strange objects and people (Porges, 1991; Graham, 2010). Kagan and Snidman (1991) have also shown that a variety of measurements of sympathetic tone are associated with behavioral inhibition among preschoolers. Higher cortisol concentrations have also been reported for behaviorally inhibited children compared to uninhibited children (Kagan et al., 1987). In a series of studies with nine-month olds, Gunnar and Associates (1991) found that infants who are more distressed had higher cortisol concentrations following separation. Evidence consistent with this notion has been presented in several studies. Significant heritability components of temperament have also been reported in the Louisville twin study (Goldsmith and Campos, 1986; Finkel and Metheny Jr, 2000).

In a detailed and fascinating study by Gunnar and Nelson (1994), event-related potentials (ERPs) were recorded from year-old infants with sets of familiar faces presented frequently and sets of novel faces presented infrequently. The normative response of infants in this sample was a late positive slow wave to the infrequent familiar faces, and a return to baseline for the frequent familiar and infrequent novel faces. A factor score based on data from frontal and central leads that reflected this normative pattern was significantly associated with infant emotional behavior and cortisol level. Infants scoring higher on the normative ERP factor and distressed during separation, as reported by their parents, smiled and laughed more and had lower cortisol concentrations during ERP testing. These data were interpreted as reflecting the coordination of adaptive responding among different physiological and behavioral systems and reflective of individual differences in infant responsivity. These data are reflected in Table II and clearly indicate that there are relationships between ERP's and emotional stimuli in year-old infants.

FRONTAL LOBES, TEMPERAMENT AND AFFECT REGULATION

A number of neuropsychological studies have linked the frontal lobes to affect expression and regulation (e.g. Luria, 1973; Pribram, 1973).

Anatomically, the frontal lobe has extensive connections with various limbic structures directly implicated in control of emotion.

Table 2. Correlations between event-related potentials and separation distress, IBQ temperament, and cortisol

	ERP Summary Factor	Event-Related Potentials		
		FF	IF	IN
Separation distress (df=17)	$.73^{**}$	-.23	$.72^{**}$	.34
IBQ: Positive Affect (df=21)	$.49^{*}$	.02	$.54^{*}$	.06
IBQ: Difficultness (df=21)	.31	.18	.31	$.40^{*}$
IBQ: Fearfulness (df=21)	.01	-.26	-.03	-.02
ERP cortisol (df=17)	$-.57^{*}$	.29	$-.50^{*}$	-.01
Pre-SEP cortisol (df=16)	-.07	.11	.13	$-.45^{*}$
Post-SEP cortisol (df=15)	-.31	.12	-.33	.13

Note: FF= Frequent Familiar, IF=Infrequent Familiar, and IN=Infrequent Novel.

$^{*}p<.05$.

$^{**}p<.01$.

Findings in both normal (Tucker, 1981) and brain damaged adults (Pessoa, 2008) indicate that left and right frontal regions are differentially specialized for specific emotions. The data suggests that the left frontal region is specialized for the expression of emotions associated with approach, such as joy and interest, whereas the right frontal region is specialized for emotions associated with withdrawal such as disgust or distress (Davidson et al., 1990). Several early EEG studies of infants (Fox a and Davidson, 1988; Kim and Bell 2006) suggest that these functional brain asymmetries are present at least very early in life and possibly even at birth if not before.

Davidson and Fox (1989) noted that individual difference in resting infant EEG asymmetries were highly predictive of that infant's emotional response to stress. They showed that infants with greater right rather than left frontal EEG activity during a resting state were significantly more likely to cry when later separated from their mothers compared with infants who exhibited significantly greater left frontal activity.

The few revealing studies of EEG in infancy assist us in understanding the nature and purpose of frontal activation asymmetries in infancy, and whether extremes in these patterns of hemispheric asymmetry relate to temperamental differences in infants and/or risk for psychopathology. Some investigators have reported that the pattern of the resting frontal EEG reflects individual differences in the predisposition of the infant to experience positive or negative affect and is associated with individual differences in affective style in healthy infants, children, and adults, as well as in some clinical populations (Davidson, 2000; Coan and Allen, 2004).

We can see in the patterns of resting frontal EEG of neonates and infants significant individual differences of asymmetry that tend to remain in a stable fashion across the development of the child and adolescent. These EEG patterns also tend to correlate with temperament and can predict developmental outcome (Henderson et al., 2001).

Davidson and Fox (1989) examined whether certain features of infant temperament might be related to individual differences in the asymmetry of resting frontal activation. EEG was recorded from the left and right frontal and parietal scalp regions of 13 normal 10-month-old infants. Infant behavior was then observed during a brief period of maternal separation. Those infants who cried in response to maternal separation showed greater right frontal activation during the preceding baseline period, as exemplified in Figure 3 below, compared with infants who did not cry. Frontal activation asymmetry may be a state-independent marker of individual differences in threshold of reactivity to stressful events and vulnerability to particular emotions.

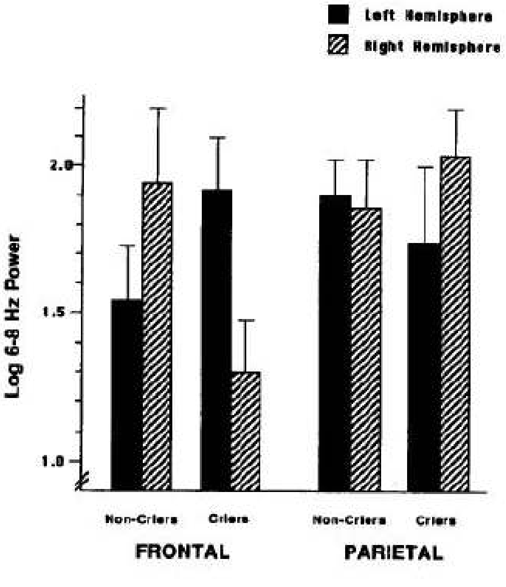


Figure 3. Mean log 6-8-Hz power for the resting baseline period in the left and right frontal and parietal regions for criers (N = 6) and non-criers (N = 7). (Decreases in 6-8-

Hz power are indicative of increases in activation. Error bars indicate standard errors of the mean.) [From Davidson and Fox, 1989].

Davidson (2000) had reported that left frontal EEG asymmetry at rest is associated with individual differences of the neonate and infant to regulate affect and behavior. Fox and colleagues have indicated that infants displaying elevated left frontal EEG asymmetry at rest have been reported to have “easy” temperaments, manifested by reports of these infants being easily soothed and calmed.

In contrast, Davidson and Fox (1989) noted that negative affect and a lowered ability by the infant to regulate his or her affect and behavior is highly associated with lower right frontal EEG asymmetry at rest. Infants, when crying had demonstrated elevated right frontal activity during the baseline conditions preceding crying. This is highly associated with what we have reported elsewhere in asymmetric activation patterns in ADHD and autistic spectrum children (Leisman and Melillo, 2006; Melillo and Leisman, 2009a; 2009b). Fox reports that the infants who exhibited this pattern of right frontal EEG asymmetry in resting state-at rest have been characterized as having ‘‘negative reactive’’ temperaments (Fox et al., 2001). These infants are easily distressed, are difficult to soothe, certainly do not generally self-soothe, and have problems switching and focusing attention.

Since the demand for higher level integrative behavior placed upon the infant in the investigation of his reflexes by standard clinical methods and his muscle tonus are normally quite minimal, such indicators are frequently insensitive to even marked neurological deficiencies. Although the examination of neuroelectrical activity is promising with respect to identifying individual infants with immature or defective neuro-integration or organization, the examination is limited by our imperfect understanding of the relationship between such neuroelectrical activity and behavior at the present time.

In children with inadequately developing frontal lobe function, hyperactivity, depression, poor sustained attention, language difficulties, and impulsive or impetuous behavior are common. We normally see this in later childhood as abnormal but we are in fact describing the typical behavior of the neonate likely because of the status of his or her frontal lobes. Motor activity in the infant will grow his or her motor skills but coincidentally if not causally increasing the growth of the frontal lobes.

We also have to consider that since the cerebellum and thalamus may both be important to the anatomical and functional development of the frontal cortex, that if a child does not have normal or proper motor development, we would expect that the higher frontal lobe functions of cognition and behavior would be delayed in their development. Likewise, helping an infant to develop his or her motor skills should also help develop their non-motor skills.

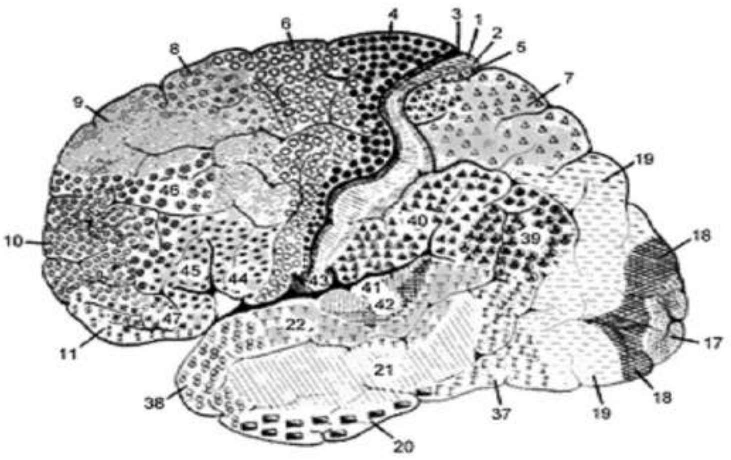
So from this we see that we have inadequate measuring tools, to examine the nature and function of the frontal lobes in infancy along with numerous confounding variables that impede our understanding of the relationship between motor function and cognition, asymmetry and lateralization and how all impact on the cognitive and affective development of the infant and child.

DEVELOPMENT OF NEUROLOGICAL SYSTEMS ARTICULATING WITH THE FRONTAL LOBES AND ASSOCIATED STRUCTURES IN THE DEVELOPMENT OF TEMPERAMENT

The Frontal and Prefrontal Cortices

Major developmental events in the first year include the cortical inhibition of the brainstem, the improvement in recognition and working memory, and the appearance of separation anxiety. From around the age of 3 months, the neonatal palmar grasp reflex begins to disappear. This event is related in time to the differentiation of the pyramidal neurons in the supplementary motor cortex (Kennard et al., 1934). Stimuli are transmitted by the cortico-bulbar tract to the interneurons in the brainstem. These inhibit the motor neurons by means of the neurotransmitter GABA, leading to an inhibition of the reflex action of the muscles of the hand. At this age, the cortico-bulbar tract shows intensive myelination, accelerating nerve conduction speed. In the brainstem, synaptic contacts of interneurons to motor neurons are intensified, and GABA synthesis is increased. These processes increase the cortical inhibition of brainstem reflex activity. If brainstem mechanisms controlling respiration are immature or compromised, then the increased cortical inhibition could place infants at risk for sudden infant death syndrome, which can occur around that age (Touwen, 1971). Conversely, persisting primitive brainstem reflex activity may be associated with a lack of cortical inhibition.

The frontal lobe (Figure 4) plays a major role in motor activities like planning and in the execution of movements. The primary motor area proximal to the precentral gyrus is known as the motor strip (Brodmann’s area 4). This is located just anterior to the central sulcus. The primary motor area is also referred to as motor area 1 or MI. Anterior to this area are two additional primary motor areas (Brodmann’s 4, 5, and 6). This supplementary motor cortex lies anterior to the motor strip and extends around to the hemisphere’s medial surface. The premotor cortex lies anterior to the supplementary motor cortex and on the lateral surface of the hemispheres. These motor areas contain motor neurons whose axons extend to the spinal cord and brainstem and synapse on motor neurons in the spinal cord. The motor neurons are located in layer 5, the output layer of the motor cortex. This layer contains large pyramidal cells; they are the largest neurons in the cerebral cortex. The most anterior region of the frontal lobe, the prefrontal cortex is responsible for higher aspects of motor control and planning and in the execution of behavior, tasks requiring integration of information over time. The prefrontal cortex has two main areas, the dorsolateral prefrontal cortex, which is found on the lateral surface of the frontal lobe anterior to the premotor regions, and the orbito-frontal cortex. The orbito-frontal cortex is located on the frontal lobe’s anterior-ventral surface and is more medial. The orbito-frontal cortex includes limbic lobe structures and is connected to them. The frontal lobe is the largest lobe in humans (Figure 4) and the prefrontal cortex constitutes approximately 50 percent of the size of the frontal lobes. The prefrontal cortex is included in a neuronal system that includes the basal ganglia, the thalamus, and the cerebellum.



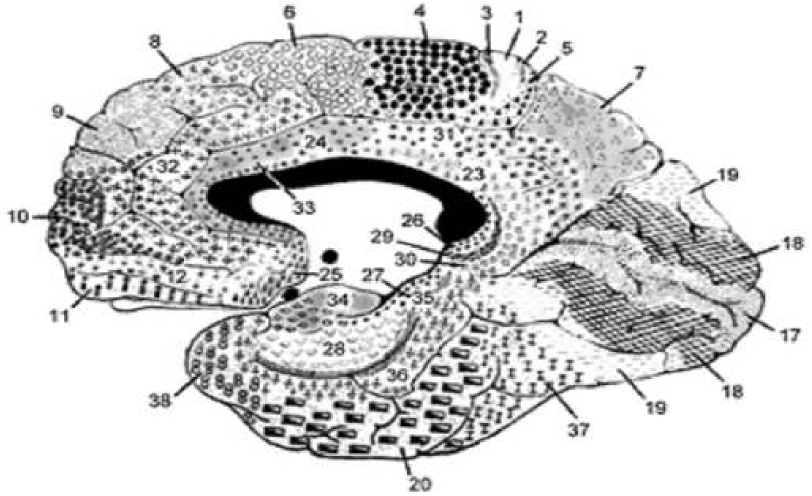


Figure 4. Cytoarchitecture of the cortex with reference to the frontal lobes according to Broadmann. Areas 1, 2 and 3 - Primary Somatosensory Cortex, Area 4 - Primary Motor Cortex, Area 5 - Somatosensory Association Cortex, Area 6 - Pre-Motor and Supplementary Motor Cortex (Secondary Motor Cortex), Area 7 - Somatosensory Association Cortex, Area 8 - Includes Frontal eye fields, Area 9 - Dorsolateral prefrontal cortex, Area 10 – Fronto-polar area (most rostral part of superior and middle frontal gyri), Area 11 – Orbito-frontal area (orbital and rectus gyri, plus part of the rostral part of the superior frontal gyrus) Area 12 – Orbito-frontal area (used to be part of BA11, refers to the area between the superior frontal gyrus and the inferior rostral sulcus), Area 13 and Area 14* - Insular cortex, Area 15* - Anterior Temporal Lobe, Area 17 - Primary Visual Cortex (V1), Area 18 - Visual Association Cortex (V2), Area 19 – (V3), Area 20 - Inferior Temporal gyrus Area 21 - Middle Temporal gyrus, Area 22 - Superior Temporal Gyrus, of which the rostral part participates to Wernicke's area, Area 23 - Ventral Posterior cingulate cortex, Area 24 - Ventral Anterior cingulate cortex, Area 25 – Sub-genual cortex, Area 26 – Ecto-splenial area, Area 28 - Posterior Entorhinal Cortex, Area 29 – Retro-splenial cingular cortex, Area 30 - Part of cingular cortex, Area 31 - Dorsal Posterior cingular cortex, Area 32 - Dorsal anterior cingulate cortex, Area 34 - Anterior Entorhinal Cortex (on the Para-hippocampal gyrus), Area 35 – Peri-rhinal cortex (on the Para-hippocampal gyrus), Area 36 – Para-hippocampal cortex (on the Para-hippocampal gyrus), Area 37 - Fusiform gyrus, Area 38 – Temporo-polar area (most rostral part of the superior and middle temporal gyri, Area 39 - Angular gyrus, part of Wernicke's area, Area 40 – Supra-marginal gyrus part of Wernicke's area, Areas 41 and 42 - Primary and Auditory Association Cortex, Area 43 – Sub-central area (between insula and post/pre-central gyrus), Area 44 - pars opercularis, part of Broca's area, Area 45 - pars triangularis Broca's area, Area 46 - Dorsolateral prefrontal cortex, Area 47 - Inferior prefrontal gyrus, Area 48 – Retro-subicular area (a small part of the medial surface of the temporal lobe), Area 52 – Para-insular area (at the junction of the temporal lobe and the insula).

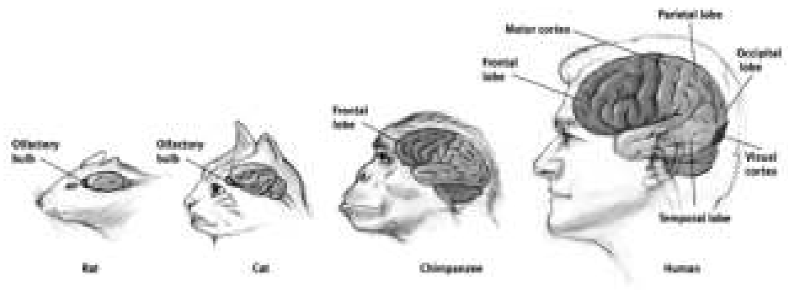


Figure 5. Compared to other parts of the brain, frontal lobe development is on a delayed timetable. As frontal lobes mature throughout childhood and adolescence, the ability to think through, inhibit, and plan actions as well as executive functions of governing emotions, judgment, planning, organization, problem solving, impulse inhibition, abstraction, analysis/synthesis, self-awareness and self-concept, and identity gradually develops.

Most of the higher and more complex motor, cognitive, and emotional behavioral functions are thought to be found primarily in the frontal lobes. This area of the neocortex has expanded evolutionarily more than any other in the human brain.

The frontal lobes comprise one-third of the neocortex and the prefrontal cortex constitutes 50 percent of the frontal lobes. The prefrontal cortex is unique to humans; the reference to highbrow, for example, is a reference to the structural changes of one forehead that humans underwent to provide more space for our prefrontal cortices. It is thought that most of the unique qualities that humans possess are found or connected in some way with the expansion of the prefrontal cortex. This brain region is also important because the frontal lobes include areas of motor control as well.

Proceeding anteriorly in the frontal lobes from the motor strip to the supplementary motor areas and the premotor cortices, we see the control of motor activity becoming more sophisticated (Figure 5). We also see that as the brain expanded and evolved anteriorly, the frontal lobes became more concerned with the cognitive control, timing, and duration of movement whereas the motor strip was an evolutionary advance giving humans greater gross voluntary motor control. The newer areas of the frontal lobe provide more precision and direction to the movement. Eventually we see that the prefrontal cortex has little to do with the movement per se, but has become largely concerned with the control of direction of the movement and the behavior that drives that movement.

It is well established that humans need normal frontal lobes to accomplish goals, make decisions, express creatively and navigate through complex social situations (Chatterjee, 1998). The frontal lobes regulate goal directed behavior, a hierarchy of reflexive movements, cross-temporal contingencies, approach and avoidance behavior, response inhibition, and perseveration. As we will see, all of the activities that the prefrontal cortex controls revolve around improvement of goal directed behavior.

We hypothesize that the development of the human prefrontal cortices was a natural expansion of the evolutionarily earlier developed areas of the frontal lobe and that goal directed movements and behavior provided for an expansion of those areas. The same regions of the human central nervous system that were already employed for better control, coordination, and timing of movements, expanded in parallel with the frontal cortex. The lateral portions of the cerebellum, for example, are more involved with the cognitive coordination and control of motor activity than with the control of the actual movement of muscles. The ventral lateral thalamus, linking the lateral cerebellum to the prefrontal cortex, is witness to the fact that these two areas evolved together.

There must have developed a partnership between the cerebellum and the prefrontal cortex. The initial focus of the frontal lobes was the control of motor activity as it was for the cerebellum, but as the movements became more goal-directed, greater cognitive control over movement was necessitated.

The prefrontal cortex was required in higher organisms and in humans not just for more speed, precision, and coordination, but also for the provision of a control mechanism for memory of previous motor actions, projection of future movements, facilitation and inhibition of movement and the reaction or inhibition of reaction to stimuli; to know when to move toward prey or away from a predator. All of these involve higher cognitive control that all link to the emotion controlling limbic system which provides motivation, emotion in general and aggression/temperament in particular, and autonomic regulation, the subject of this paper.

The links of frontal and prefrontal regions of the cortex to the limbic system had as its main function the provision of a mechanism to either allow the organism to catch the prey, to run from a predator, or to seek a mate. The frontal lobes then in coordination with the cerebellum and basal ganglia have expanded beyond their control of movements and have evolved to control the behaviors that guide goal directed movement and most of our basic actions, but driven in large measure by emotionality and its regulation, based upon approach and avoidance behavior.

Frontal Lobes in Infancy

Many developmentalists agree with Denkla (1996) when she stated that, “the difference between the child and the adult resides in the unfolding of executive functions.” Luria (1973) and Rothbart and Bates, (1998) both concurred that the development of a frontal lobe and the resultant higher level social attention system as well as well as the development of more volitional attentional mechanisms and individual differences in executive function have important implications for the early development of behavioral and emotional control.

Infants and their developing frontal lobes demonstrate exaggerated approach and avoidance behavior. Exaggerated approach activities can be as simple as their grasp reflex, or complex like using whatever implements that are within view. Avoidance behavior can be simple or complex such as extension of finger to touch, spatial neglect of an area of space in a way characteristic of the behaviors described by Piaget and other Developmental Psychologists, and certainly reminiscent of post-stroke adults.

Also controlled by the frontal lobes are movements over time and, therefore perseveration, a characteristic of the dysfunctioning adult, is appropriate to the developing neonate and infant over the first year of life, and is the result of the status of the frontal lobes. We can see the repeated sounds or facial expressions made by an adult that causes the infant to laugh again and again in a perseverative fashion.

It had been previously thought that the functions of the prefrontal cortex and its role in cognitive or emotional activities were separate from other motor areas of the frontal lobe (Luria, 1966). Therefore, motor functions of the frontal lobe did not necessarily relate to non-motor function of the frontal lobe. However, it can be alternatively viewed that goal directed behaviors are merely evolutionary expansions of goal directed movements, and that all of the activities of the frontal lobe are variations and refinements of the same function. Achieving a goal is provided by the stimulation of the limbic system and therefore of emotionality. Therefore temperament and frontal lobe development are associated.

The Maturation of Prefrontal Cortex in Human and Nonhuman Primates

Like other primates, humans are born with an immature brain. After birth, the cerebral cortex experiences a massive proliferation of synapses (synaptogenesis), followed by an extended pruning period (synaptic elimination). In the Rhesus Macaque—an old-world monkey whose brain development has been studied extensively—these developmental processes occur at the same rate in all cortical areas (Rakic et al., 1986).

In contrast, analyses of human cortex across the life span (using autopsy tissue samples) reveal a different pattern. In humans, synaptogenesis reaches its peak in visual and auditory cortex within a few months after birth, but the increase in the number of synaptic junctions occurs much more slowly in the PFC (Huttenlocher and Dabholkar, 1997) (Figure 6).

In the evolution of the human brain, there has thus been a shift from concurrent to heterochronous cortical development. The synaptic density of the human PFC does not “catch up” with the auditory cortex until the fourth year of life. Heterochronicity in human cortical development is also observed in measurements of dendritic arborization (the development of treelike terminal branching of nerve fibers), regional metabolism (the extent of anabolic and catabolic processes within a brain region), and myelination; for example, positron emission tomography (PET) data indicate a lag of up to eight months in glucose metabolism in human PFC as compared to occipital, temporal, and parietal cortices (Chugani and Phelps, 1986).

As a result of this long period of prefrontal development, human children exhibit impaired behavioral and cognitive control—akin to adult patients with neurological PFC damage, and they do so for a long time.

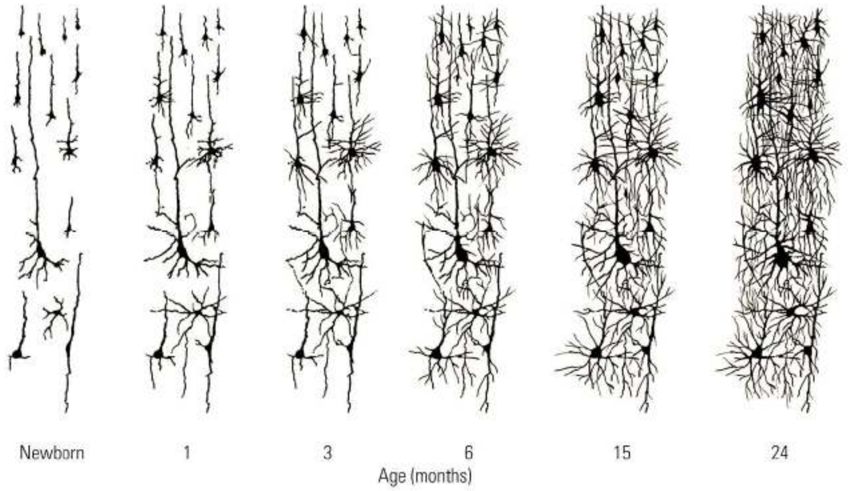


Figure 6. Brain Cells develop connections over the first two years of the infant's life. These connectivities are formed, altered, and actively sculpted over the first twenty years of life.

Changes in both working memory capacity and the ability to produce behaviors that conflict with prepotent responses—two canonical frontal lobe functions—are linked to the maturation of the PFC (e.g., Diamond and Doar, 1989). Furthermore, the extended immaturity of the PFC may carry the cost of a longer period of vulnerability than that which occurs in more rapidly-developing cortical systems. Prefrontal sensitivity to environmental factors has been described in children with phenylketonuria (PKU) (Diamond, 1996) and may contribute to specific cognitive deficits associated with poverty (Farah et al., 2006). The accumulation of evidence for the prolonged period of prefrontal immaturity—and the behavioral consequences thereof—has spurred the scientific community to develop programs to facilitate the development of cognitive control abilities. While these efforts might be instrumental in vulnerable populations, some caution might be warranted in a more widespread effort to hasten PFC development, as we had earlier indicated.

Late prefrontal development seemingly has some negative consequences for childhood behavior. Yet despite this, there are many examples of learning tasks (e.g., language acquisition) at which children do better than adults. We propose that these differences may reflect the costs and benefits of hypofrontality that arise from the inherent tradeoffs between learning and performance. That is, a system optimized for performance may not be optimal for learning, and vice versa.

In the domain of emotion, crucial early experiences must occur for behavioral development to proceed on a normal track and for the brain systems underlying these behaviors to develop normally. This is achieved by neural plasticity. Some of neuronal systems remain open only so long to environmental inputs and if such input fails to occur, or if the input is abnormal, the window of opportunity closes and development goes astray – the concept of critical period.

Greenough and colleagues have taken that concept and referred to part of this process as experience-expectant (Markham and Greenough, 2004), by which they mean a process by which synapses form after some minimal experience and is common to all members of the species thereby saving the genome from the trouble of orchestrating and regulating all aspects of development. It is for this reason that the frontal lobes and asymmetry speak very well to the issue of the dynamics of change in early infant development.

In general, Greenough has proposed that the structural substrate of expectation is the a pattern of temporary overproduction of synapses distributed within a relatively wide area during early development, followed by a subsequent retraction of synapses that had not formed connections at all or that had formed abnormal connections. The nature of neuronal connectivity is illustrated in Figure 7 below. The expected experience produces patterns of neuronal activity, targeting those synapses that will be selected for preservation. The assumption is that synaptic contacts are initially transient and require some type of confirmation for their continued survival. If such confirmation is not obtained, synapses will be retracted according to a developmental schedule or due to competition from confirmed synaptic connectivities (Black, 1998).

Experience-expectant neurogenesis stands in marked contrast to the other type of plasticity that Greenough then calls *experience-dependent*. This is the process that optimizes the individual's adaptation to specific and possibly unique features of the environment e.g. learning.

Thus, for any given instance, diverse information will be obtained and stored for use at a later time, giving rise to individual differences in a variety of cognitive domains, including temperament and emotionality. The fundamental difference between experience-expectant and experience-dependent development is that the former applies in a similar fashion to all members of the species, whereas the latter applies to individual members, seen in normal emotional development in infancy.

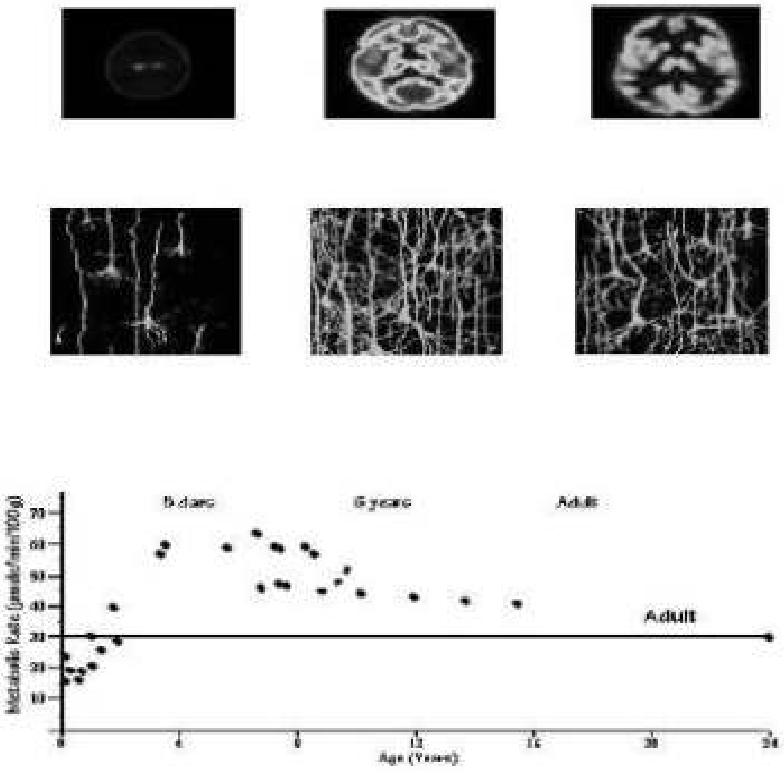


Figure 7. Cerebral metabolic rate as a function of age. Elevated CMRGlc during 3-10 yrs. corresponds to era of exuberant connectivity needed for energy needs of neuronal processes which is greater by a factor of 2 in childhood as compared to adults. PET shows relative glucose metabolic rate. We see the complexity of dendritic structures of cortical neurons consistent with expansion of synaptic connectivities and increases in capillary density in frontal cortex.

The massive overproduction of synapses by the brain early in life followed postnatally by selective elimination of these exuberant connections has as its likely purpose the preparation of the nervous system for experience by the proliferation of connections on a sensory system-wide basis. Experience-related neuronal activity can then select functionally appropriate subsets of the abundant synaptic connections (represented in Figure 7). This period of excessive synaptogenesis is also correlated with a burst of brain metabolism and, at least in the monkey, with the onset of social interactions (Jacobs et al., 1995).

Infancy is a critical period of development, in which rapidly growing structures are more sensitive to damage (Leisman, 2011; Melillo and Leisman, 2009a). For example, disturbances such as disease, metabolic disturbances, malnutrition, sensory impairment, and trauma produce both structural and functional impairment in the development of the cerebral cortex if they occur during periods of synaptogenesis (Taylor and Alden, 1997). These same global conditions, when occurring in the older child or adult, do not seem to produce the same degree of impairment in both structure and function.

In addition, many children with brain insults, including those who sustain traumatic brain injury, are susceptible to both immediate and long-term neurobehavioral impairments (Vargha-Khadem et al., 1997). In some cases, there is little evidence that sequelae resolve with age. In contrast, the infant brain also demonstrates greater ability to recover from some types of injury than seen later in development. The best examples of neuronal system reorganization to environmental inputs come from studies of adult animals in enriched environments (Leisman, 2011) and infants deprived of sensory input (Bowering, et al., 1997).

The slow development of the frontal lobe allows the infant the slow journey through circuit developments necessary for response inhibition, socialization, and emotional control.

To thrive as social animals, we need to master a myriad of cultural and linguistic conventions. We need to be able to do and say and understand the right thing in the right context, and we must agree with one another on what these right things are. This is a formidable task. We suggest that in convention-learning, the ability to think unconventionally (i.e., flexibly) is a disadvantage. The consequences of conventional versus flexible thinking have been computationally demonstrated for the acquisition of irregular plurals (e.g., mice), a set of linguistic conventions adults find particularly difficult to master. The trajectory of learning of these exceptions is non-monotonic in children, marked by a brief period in which over-regularization errors (e.g., “mouses”) replace previously correct plural forms. An associative learning model that simply practices and reinforces the most frequent forms it “hears” easily simulates this U-shaped pattern (Ramscar and Yarlett, 2007).

Our account explains the developmental trajectories and sensitive periods in language acquisition in terms of the gradual development of the PFC (and its associated control mechanisms) rather than a change to some putative language-specific device. Consider the case of Simon, a deaf child who learned ASL from parents who were late learners of ASL; by age 7, Simon had acquired an orderly morphological-rule system that far surpassed the imperfect input, from his parents, from whom he learned ASL (Singleton and Newport, 2004).

From the perspective we propose here, adults' ability to control their responses allows them to mix and match correct and incorrect signs for the same things at different times, such that staying true to their probabilistic understanding leads them to produce noisy patterns of input. Absent these control abilities, young children will practice (and hence learn) only the most frequent of any alternate patterns they hear (Ramscar and Yarlett, 2007). This allows children to learn conventions from the output of parents who, because of their ability to monitor and control their responses, may never master them themselves.

THE DEVELOPMENT OF CORTICAL-LIMBIC INTERACTIONS IN AFFECTIVE DEVELOPMENT

We can now explore in more detail the cortical and limbic interactions that are involved (represented in Figure 8). The most basic division of cortico-limbic structures is not left/right, but rather dorsal/ventral. It is thought that evolution of the neocortex from para-limbic cortices occurred by two paths of network differentiation: the first, the dorsal archi-cortical network, concentrated on the hippocampus; the second, the ventral paleo-cortical network, focused on the olfactory cortex with important interconnections with the amygdala (Pandya et al., 1988). Studies have been conducted to explore the cognitive and perceptual differences between these two systems. These studies suggest that the dorsal pathways are specialized for spatial memory and that the ventral pathways are specialized for object memory (Ungerleider and Mishkin, 1982).

It is also thought that the functional differences between these two networks are significant in the motivational realm as they are in the cognitive realm. It is also thought that there has not been an equal distribution of dorsal and ventral networks within the left and right hemisphere. It is thought that the left hemisphere has specialized to express the so-called “cybernetic” characteristics of the dorsal cortical network. It is further thought that asymmetries of dorsal and ventral expansion lead to hemispheric asymmetries in the limbic control of cognition (Liotti and Tucker, 1992).

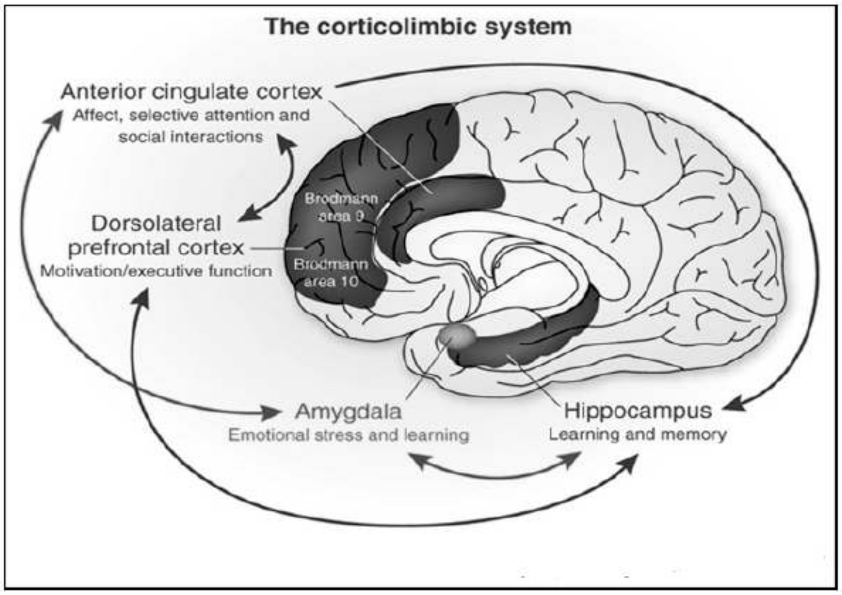


Figure 8. The cortico-limbic system consists of several brain regions that include the rostral anterior cingulate cortex, hippocampal formation, and baso-lateral amygdala. The anterior cingulate cortex has a central role in processing emotional experiences at the conscious level and selective attentional responses. Emotionally related learning is mediated through the interactions of the basolateral amygdala and hippocampal formation and motivational responses are processed through the dorsolateral prefrontal cortex (from Benes, 2010).

Some of the research has shown that lesions in the dominant (right-handers) or the left hemisphere typically result in what has been termed “catastrophic reaction,” for example, tears, despair, and anger. Damage to the right hemisphere, which in most people is the minor hemisphere, is accompanied by indifference reactions such as unawareness, euphoria, or lack of concern (Goldstein, 1952; Gainotti, 1970; 1972). Therefore, the left and right hemispheres, based on this early research, were thought to result in opposite emotional tone with the left normally being more oriented towards a positive mood, whereas the right was oriented towards a more negative mood. Other studies have confirmed that pathologic crying occurs with left hemispheric lesions (Poeck, 1969; Rinn, 1984). It has been reported by Sackheim and associates (1982) that changes in affect following unilateral injury is due to disinhibition of contralateral cortical regions and not because of release of ipsilateral subcortical areas. A significant finding has been the relation between arousal and hemisphericity. Right hemisphere lesioned patients have been described as “hypo-aroused” (Heilman et al., 1978) and show reduced cortical and autonomic responsivity, in skin conductance or heart rate, especially when exposed to emotionally charged stimuli (Morrow et al., 1981; Zoccolotti et al., 1982).

Anterior and posterior cortical regions appear to express different levels of control over the vertical hierarchy of subcortical centers (Robinson et al., 1984; Starkstein et al., 1988). It is further thought that the right hemisphere global conceptual skills may be critical to combining external and internal environmental information to achieve the integration of emotional experience (Safer and Leventhal, 1977). In other words, it is thought that the right hemisphere is able to access internal feelings that monitor and individuals internal state (Buck, 1985). It appears that the right hemisphere has greater interconnectivities between areas of the right hemisphere than the left hemisphere (Leisman and Ashkenazi, 1980; Iturria-Medina et al., 2011). This suggests that the specialized psychological abilities are due to its more diffuse interconnections, which provide it with a more dynamic and holistic integration across different sensory modalities (Semmes, 1968).

EEG studies appear to confirm this belief, showing in both children (Thatcher et al., 1986) and adults (Tucker et al., 1986) with greater coherence among right hemisphere regions than left (Leisman and Ashkenazi, 1980; Leisman, 2002). Dense interconnections between regions are characteristic of the paralimbic cortex. In fact, the greatest density of interregional connections is achieved by the paralimbic cortex (Pandya et al., 1988). If connection density reflects the level of functional integration, it is thought that the brain’s functional integration would be more likely to occur in the denser paralimbic areas than in higher “association” areas (Tucker, 1991). It is also thought that greater connection density in the right hemisphere would indicate that its representation would be formed with greater interaction with paralimbic influences.

It is fairly well documented that subcortical structures like the basal ganglia are associated with the development of affective disorder. A possibility is that lateralized cerebral changes may result from the release or disinhibition of ipsilateral subcortical centers that may have a vertical hierarchy of emotional control (Tucker, 1981; Tucker and Frederick, 1989). Poeck (1969) and Rinn (1984) in their research noted involvement of subcortical structures mainly the basal ganglia and the internal capsule in practically all the cases they studied of patients who suffered from pathologic emotional outbursts in the absence of brainstem lesions. Subcortical centers may be able to affect emotional expressions independent of the cerebrum; an example of this may be seen in anencephalic newborns that show normal facial expression of emotion (Buck, 1988).

It has been postulated that with lesions that exclude the frontal convexity, both dorso-lateral and dorso-medial prefrontal cortices are associated with slowness, indifference, apathy, and lack of initiative. On the other hand, lesions of the orbito-frontal cortex appear to lead to disinhibition, lack of social constraint, hyperactivity, grandiose thinking, and euphoria (Smith et al., 2006, Volkow et al, 2011).

Others have shown a relationship between secondary mania being associated with orbito-frontal and basal-temporal lesions, especially in the right hemisphere. In addition, mania is more frequent in right subcortical lesions of the thalamus and basal ganglia as opposed to left (Starkstein et al., 1988; Starkstein and Robinson, 1988).

There are five functional parallel cortico-striatal-thalamic loops; two of them are purely motor (Alexander et al., 1986). The three non-motor loops have different levels of limbic connections. It is thought that each loop represents a functional unit, which includes as the primary target, the prefrontal region. One of these non-motor loops, a dorso-lateral prefrontal network is thought to support temporary storage in working memory of spatial locations (Goldman-Rakic, 1987a;1987b).

There is also a lateral orbito-frontal circuit, projecting from the orbito-frontal cortex and connecting to different parts of the caudate and globus pallidus, which project to the thalamus and back to the orbito-frontal cortex. This circuit is thought to be involved in the control of inhibitory responses during learning and recognition tasks requiring frequent shifts of set developing during infancy. This may explain perseveration or repetitive compulsive behavior seen with damage to the orbito-frontal cortex and the perseveration seen in infancy.

Another circuit, the anterior cingulate circuit, includes the ventral striatum, nucleus accumbens, and medio-dorsal nucleus of the thalamus. The hippocampus and entorhinal cortex is thought to send inputs in this circuit, which integrates information from the para-limbic association cortex.

ONTOGENY OF HUMAN LATERALIZATION AND ITS SIGNIFICANCE IN COGNITIVE AND AFFECTIVE DEVELOPMENT

When Does Lateralization Occur Developmentally?

To understand fully the function of the adult human brain we need to examine not only its phylogenetic, but also its embryologic and childhood development. There are specific lateralized functions that have ontogenetic significance. Neuroanatomic asymmetries have been noted in infants (Chi et al., 1977; Wada et al., 1975; Weinberger et al., 1982; Witelson and Pallie, 1973) that seem similar to those seen in adults (Geschwind and Levitsky, 1968; Lemay and Culebras, 1972; Wada et al., 1975). Asymmetries in normal children's brains have been studied and provide even greater support for early lateralization of language. In regard to non-verbal function, it has been shown that left lateralized lesions result in more mathematical difficulties than do right-sided lesions (Ashcraft et al., 1992) as well as temperamental problems, involving mood and rhythmicity all being noted after right and not left hemispherectomy (Nass and Koch, 1987). These findings all argue for early lateralization of hemispheric specialization of mood and temperament.

Numerous findings in infants strongly suggest that the human brain is functionally asymmetric long before language and other higher cognitive skills have developed. It has been proposed that these asymmetries are not indicative of the lateralized neural processors that manifest later in development, but instead indicate precursors of these lateralized processors, especially given the immaturity of the newborns cerebrum (Dobbing and Sands 1973). These precursors are thought to be at the level of the basal ganglia and thalamus, structures that are now known to share in the complementary specialization that is familiar in the case of cerebral hemispheres. The concept of precursors, which is an important explanation for early behavior (Kinsbourne and Hiscock, 1977), allows us to appreciate that lateralization of behavior or the lateralization of certain early developing components of a behavior may preclude the expression of the behavior itself. Therefore, development of the cortical areas that direct behaviors is dependent on the proper development of subcortical structures. If these precursory structures do not develop appropriately, then the subsequent cortical areas would resultantly not develop appropriately. In addition, the behavior for which these inadequately developed cortical areas are responsible will likewise not develop adequately.

The asymmetries that are seen at the neonatal level are to some degree regarded as precursory to a more mature form of hemispheric specialization for perpetual, motor, and cognitive functions (Kinsbourne and Hiscock, 1977). As lateralized precursors develop and the degree of asymmetry increases

(Moscovitch, 1977) these precursors evolve to become the controllers of increasingly mature behaviors.

The Planum temporale asymmetry is already present in the fetal brain (Chi et al., 1977 Wada et al., 1975). Increased size of right anterior and left posterior brain is also seen in the fetus (Lemay, 1984). Therefore, we see that precursors of adult asymmetries are present at a very early stage of development.

There is adaptive significance of asymmetric lateralization of the brain. Corballis (1983) indicates that bilateral symmetry is itself an evolutionary adaptation and that, “for bilateral symmetry to have emerged in so precise and comprehensive a fashion there must have been adaptive advantages associated with symmetry sufficiently strong to overcome a natural predisposition to asymmetry.” One advantage may have come from the neural network characteristic of the forebrain and from the hemispheric representation of contralateral turning. The activation of each vertebrate half-brain, occasions contralateral turning (Kinsbourne, 1974). The processing of information relative to a target is best accomplished in the hemisphere opposite its location because that is where processing and orienting functions are congruent. Processing information ipsilateral to the target would incur cross-talk interference between hemispheres (Kinsbourne, 1970). It is thought that mental operations not targeted to specific points in space (e.g. language, emotions, problem solving) do not need to be bilaterally represented and therefore the relaxation of the need for bisymmetry may be a sufficient condition for lateralization to evolve (Kinsbourne, 1978).

Specialization can also occur in orientations other than along a lateral left-right plane. There is also evidence for a dorsal-ventral specialization of the brain. It has been postulated that there may be a phylogenetic shift from dorsal-ventral to right-left complimentarity in a hominid ancestor (Kinsbourne and Duffy, 1990).

Directional responses to spatially distributed stimuli are among the earliest organized patterns of behavior to emerge in ontogeny. The early emergence of such patterns is evidenced by their appearance in the embryo, fetus and neonate of such diverse vertebrate forms as salamanders (Coghill, 1929), rats (Angulo y Gonzales, 1933) and man (Minkowski, 1921). In view of their prevalence and early appearance, directionalized behaviors appear to represent sensitive indicators of neurointegrative organization. It is known that in normal infants between 24 and 72 hours of age, the head response to laterally applied somesthetic stimulation of the perioral region is not equivalently manifested when the stimulus is applied to the infant’s left side compared to when it is applied to his right (Turkewitz et al., 1965) (Figure 9). Although the response typically elicited on stimulation of either side is, in turn, in the direction of stimulation (Prechtl, 1958), ipsilateral responses seem to be more readily elicited by stimulation of the infant's right than by stimulation of his left side.

In summary, we can see that structural and functional asymmetries are seen in non-human vertebrates. Therefore, we cannot say that brain lateralization is an exclusively human characteristic. It appears that natural selection favors bisymmetry in motile organisms. Only when selection pressures are relaxed do asymmetries appear in species. Human brain asymmetries exist much earlier in development than previously thought. The fact that asymmetries appear so early implies that a subcortical mechanism is the foundation of infantile lateralization. The more commonly recognized cortical asymmetries might therefore be an expression of the corresponding subcortical asymmetries.

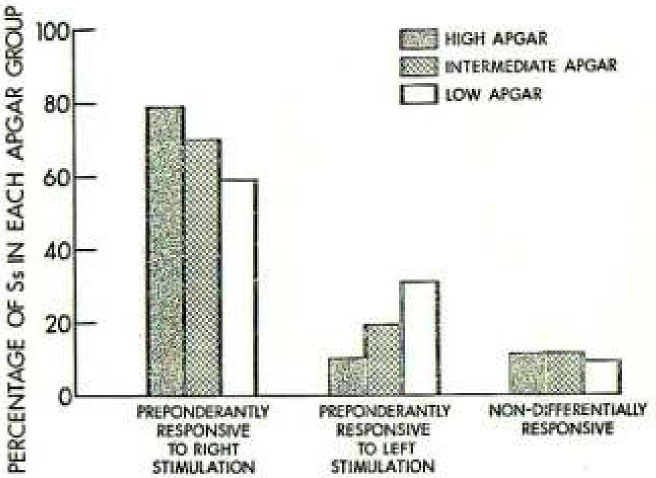


Figure 9. Preponderant responses of infants responding to right v. left visual stimulation as a function of Apgar score (after Turkewitz et al.,1971).

FRONTAL LOBES, ASYMMETRIES, EMOTIONALITY AND TEMPERAMENT IN INFANCY: APPROACH-WITHDRAWAL BEHAVIOR AS A BASIS FOR TEMPERAMENT

How Adult Models of Asymmetry Inform Emotional Development in the Infant and Child Brain

It is clear that in complex organisms, and especially in humans, the cerebral cortex plays an important role in aspects of emotional behavior and experience (Kolb and Taylor, 1990), especially anterior or frontal cortical regions, which have extensive anatomic reciprocity with both subcortical centers and with posterior control circuits, all extremely important in emotional behavior. The frontal lobes or anterior cortical zones are the brain areas, which have shown the most dramatic growth in relative size over the course of phylogeny in comparison to other brain regions (Luria, 1973; Leisman and Melillo, 2006; Melillo and Leisman, 2009a). Asymmetries of frontal lobe function have been implicated in different forms of emotional behavior. Some of the first observations of asymmetries and their role in emotional behavior were with patients with unilateral cortical lesions (Jackson, 1878). Most of these reports seemed to show that injury to the left hemisphere was more likely to result in what has been called catastrophic-depressive reaction. This was seen with similar injury to the right hemisphere (Goldstein, 1939). More recent studies show that damage specifically to the left frontal lobe results in depression.

In addition, the closer the injury is to the frontal pole, the more severe the depression. However, patients with right frontal lobe injury are more likely to develop mania (Robinson et al., 1984). It has been stated that a fundamental asymmetry in the control of functions related to emotion should not be surprising based on speculation in regard to the evolutionary advantage of cerebral asymmetry (Melillo and Leisman, 2009).

Most researchers agree that approach and withdrawal are fundamental motivational behaviors, which are found at all levels of phylogeny. It has been postulated that the frontal lobes or anterior regions of the left and right hemispheres are specialized for approach and withdrawal behavior respectively (Davidson, 1984; 1987; 1988; Davidson et al., 1990; Davidson and Towarken, 1989). This is thought partly because the left frontal region has been noted as an important center for intention, self-regulation, and planning (Luria, 1973). This area is thought to be the region that produces behaviors that have been described as the "will."

Also, during development, the child will approach and reach out to objects that it is drawn to using the right hand more than the left, which would involve the left frontal motor areas more than the right (Young et al., 1983). Right-handed reaching and positive behavior or affect are thought together to be an expression of a brain circuit controlling approach behavior, and the left frontal region is thought to act as a "convergence zone" for this current circuit (Samasion, 1989; Davidson, 1992a;1992b).

It has also been noted that injury to the left frontal region results in a deficit in approach behavior. Adult patients with damage in this area of the brain are reported to present with apathetic behavior, experience a loss of interest and pleasure in objects and people, and have difficulty initiating voluntary action. Therefore, it is thought that hypoactivation in this brain region would be expected to be associated with a lowered threshold for sadness and depression (Davidson, 1995).

On the other hand, it is thought that the right anterior region is specialized for withdrawal behavior. Some of the most informative studies have been those on normal human subjects that involve measurement of regional hemispheric activation based on electrophysiologic measurement. These studies show that activation of withdrawal-related emotional states (e.g. fear and disgust) occur when the right frontal and anterior temporal regions are specifically stimulated; also, baseline tonic activation on these same areas show greater likelihood of response with increased withdrawal-related negative behavior to emotional stimuli. In addition, individuals with chronically increased baseline activation of these areas are reported to have greater negative disposition in general (Davidson, 1995).

Morris and associates studied a patient with right temporal lobectomy exposed to positive and negative emotional stimuli (Morris et al., 1991). Surgical ablation included the right temporal lobe including the anterior part and the complete right amygdala. The investigators recorded skin conductance responses to stimuli. They found that skin response to positive stimuli was normal whereas skin conductive response to negative stimuli was markedly decreased. Interestingly, PET studies have reported increased activation of a resting baseline activity in a right hemisphere subcortical area which projects to the amygdala in panic prone patients (Reiman et al., 1984). These results are thought to suggest anterior cortical and subcortical right hemisphere regions for specializing in the control of withdrawal-related negative affect (Davidson, 1995). Therefore, it can be stated that activation of the left anterior region of the cerebral cortex is associated with approach-related emotions. Decreased activation in this same area is associated with approach-related deficit behaviors, such as sadness, apathy, and depression. Conversely, activation in the right anterior region is associated with withdrawal-related emotions such as fear and disgust, and withdrawal-related psychopathology like anxiety or mania. However, it is important to understand that the areas of the hemisphere that perceive emotional information are thought to be different from those that experience the actual emotion (Davidson, 1995). Research appears to suggest that the right posterior cortical region is specialized for the perception of emotional information not depending on the type of emotion.

Volitional self-regulatory behavior is a significant part of the notion of temperament consistent with the view of most theorists on the topic. Ziaie (Rothbart et al., 1992) performed a longitudinal study (at 3, 6.5, 10 and 13.5 months) in which the development of behaviors that serve to regulate distress were observed. The study was part of a larger longitudinal study of temperament, in which infants were presented with auditory, visual and tactile stimuli varying in novelty, intensity and complexity, and their reactions videotaped. Because these episodes were designed to evoke emotional reactions, they proved to elicit a number of self-regulatory strategies as well. Behaviors that had been identified as self-regulatory in the literature were grouped together into larger functional categories of forms of self-regulation (Rothbart and Derryberry, 1981).

The larger categories included Active Avoidance (including specific behaviors of Arch Back, Arm Retraction, Leave Chair, Lean Away, Push Back and Withdraw Hand), Orientation Toward Mother (Look Toward Mother, Lean Toward Mother and Leave Chair Toward Mother), Disengagement of Attention (Gaze Aversion, Look Down, Look Away, Turn Head and Look Toward Experimenter), Approach (Lean Forward, Reach, Point-Reach, and Inhibited Reach), Attack (Bang Toy, Pounding and Push Toy Away), Body Self-Stimulation (Arm Movement, Banging, Body Movement, Kicking and Repeated Hand Movement), Tactile Self-Soothing including Hand-Mouth Activity (Hand-Mouth, Mouthing), Touch Ear-Head, Clasp Hands, and Respiration (Heavy Breathing, Sigh and Yawn).

They related self-regulatory behaviors to infant temperament by investigating relationships between 13.5 month self-regulation and infant emotionality as reported by the mother and observed in the laboratory. They found that by 13 months, the negative emotions of Fear and Distress to Limitations were differentially related to patterns of self-regulation, with Fear related to less active forms of coping, and Distress to Limitations to active attack.

Associated with approach-withdrawal developments is its relation to the development of attentional disengagement and temperament. The marked development occurs between two and six months of infants' orienting of attention in space and approach-withdrawal undergoes marked development between two and six months of life, with changes related to infants' preferences for novel locations (Clohessy et al., 2001), their ability to disengage gaze from an external stimulus (Johnson et al., 2007) and their ability to anticipate the location of upcoming visual events (Haith et al., 1988). The development of infants' ability to disengage attention from one location so as to be able to move it to another and their ability to anticipate the location of future events is particularly important for the early self-regulation of emotion.

Johnson and colleagues studied both contingency learning and disengagement in infant stimulation (Johnson et al., 2007). Using a disengagement measure, these investigators found that four-month-old infants disengaged more readily than the younger infants. The four-month-olds disengaged on an average close to 90% of the trials, in comparison with 36% and 46% disengagement for two- and three-month olds. In our measure of contingency learning, only the four-month olds showed a significant preference for the predicted side above chance (61% vs. 56% for the other two ages). Thus, a developmental shift appears to be occurring between three and four months on both of these capacities.

In examining whether infants’ ability to disengage was found to be related to their susceptibility to the negative emotions and to their soothability, mothers filled out an Infant Behavior Questionnaire, a caregiver-report measure of infant temperament that assesses the child's tendency to express the negative affects of Fear and Distress to Limitations (frustration) as well as their soothability (Rothbart, 1981). They found that the four-month-old infants who were better able to disengage tended to be less susceptible to negative affect (Fear and Distress to Limitations) and more soothable as described by their mothers.

The development of these attentional abilities is in turn related to brain development (Johnson, 1990). Evidence from neuroanatomy indicates that only the deeper layers of primary visual cortex are supportive of organized activity in the newborn. During the first weeks of life, development of middle level lamina comes to support an inhibitory pathway to the superior colliculus. For a period of several weeks, this control system may inhibit disengagement when the infant is engaged at a visual location.

It is likely that this development is also responsible for the phenomenon of "obligatory attention" observed in young infants, where infants may look at a single location for extended periods, sometimes appearing to try to move their gaze but not being able to, and become distressed after a period of intent looking (Rothbart and Posner, 1985). By 4 months, development of both the parietal cortex (Posner and Peterson, 1990) and/or frontal eye field connections (Johnson, 1990) allows for more flexible disengagement of attention and greater self-regulation for the infant.

These early developments in attentional control are of interest to those who study social-emotional development because early changes in social interaction are related to these changing patterns of self-regulation. When caregiver and infant are observed interacting with one another in the *vis a vis* position (face-to-face), periods of extended visual orienting of the infant toward the mother seen at 6 and 13 weeks are followed by decreased orienting toward her by 6.5 months (Kaye and Fogel, 1980).

In other studies, a shift of infant visual orienting to foci other than the mother has been observed by about 4 months of age (Cohn and Tronick, 1987; Kaye and Fogel, 1980). This change in infant orienting is often associated with the mother turning the infant away from the *vis a vis* position so that the child can more easily look around.

What we know then is that in self-regulation infants at three months infants already demonstrate ability to stimulate or soothe themselves, but engage in few approach behaviors. In comparison to three-month-old infants, six-month-old infants are more active stimulus seekers. They demonstrate greater use of organized patterns of motor behavior such as reaching, which showing further increases to thirteen months of age. In comparison with their behavior at six months, ten-month-olds appear generally inhibited, showing less active self-stimulating behavior and more self-soothing. Increases in inhibitory capacity, self-soothing, and social communication thus appear to be hallmarks of development of self-regulation at ten months. Thirteen-month-old infants, in comparison to ten-month-old infants, are more active at seeking stimulation, showed less self-soothing, more approach, fewer avoidance behaviors, and more self-stimulating behaviors than ten-month-old infants.

In their attentional regulation, they further increased their visual regard toward human beings as opposed to inanimate aspects of the environment. They also showed greater gestural communication in pointing and an increased ability to move objects away from themselves rather than moving themselves away from the objects.

In general, a change from more palliative methods of self-regulation (e.g., clasping, mouthing) to more active coping, and a decrease over time in near receptor activity is seen. Overall, there were no changes in frequency of attentional disengagement from stimuli after six months, but older infants were more likely to redirect their attention toward their mothers. Major changes in disengagement occur between three and four months. The summary of the literature indicates that 3 to 13 months is a period of rapid development in self-regulatory behaviors, with little individual stability in their use other than in oral self-soothing, and with disengagement of attention continuing to be related to lower susceptibility to distress and consistent with the development of inhibitory systems.

Child Brain Asymmetry in Affective Behavior

In attempting to integrate our understanding of asymmetry frontal lobe development in temperament development and emotionality in infancy and childhood we had noted previously that Davidson and Fox (1989) reported that measures of cerebral asymmetry in prefrontal regions predicts negative emotionality during infancy. Specifically, infants with moral rights/left as measured under baseline conditions are more likely to fuss and cry during maternal separation than our infants with more or less lateralized activity. Davis (1992) further reported that Kagan's measures of behavioral inhibition in preschool children were correlated with greater right lateralization. These data on children are similar to reports of adults showing that right frontal cerebral asymmetry is associated with predispositions to negative emotional response Davidson (1988).

Results of baseline asymmetry and affective style in adults have proven to be the same as in children. It has been noted that among ten-month-old infants, there can be extreme differences in response to maternal separation. Some infants become distressed right away and cry as soon as their mother leaves. Other infants show a much different pattern of response and show almost no negative emotions when separated from their mothers.

In a study of ten-month-old infants separated into groups based on whether they cried or not after being separated from their mother for approximately 60 seconds (Davidson and Fox, 1989), it was found that about half the group cried and half did not. Baseline measures of frontal and parietal activation from both hemispheres were taken 30 minutes prior to separating the infants from their mothers. It was found that there was a large difference in frontal asymmetry that could predict which infants would cry and which would not. The infants that cried had greater right-sided and less left-sided frontal activation during the baseline period as compared to those who did not cry. There did not appear to be the same asymmetry in the parietal lobes. This is thought to be the first study that demonstrated that in infant's individual differences in frontal asymmetry can predict emotional reactivity. In addition, this relationship is the same as seen with adults.

Another study examining behavior and frontal asymmetry in children specifically examined behavioral inhibition (Kagan et al., 1987). Behavioral inhibition is a young child's tendency to withdraw or freeze in novel or unfamiliar situations. In these new or unfamiliar situations, behaviorally inhibited children will stay close to their mothers without playing or interacting with other children. Three hundred and eighty six children aged 31 months were tested in a peer play session. Brain electrical activity was taken at rest and in response to several tasks.

Results showed that inhibited children show right frontal activation whereas uninhibited children show left frontal activation. The question raised after examining the results was whether the behavioral inhibition is due to a decreased left-sided approach behavior, or due to increased right-sided withdrawal activity.

Further information confirmed that in these children, the reason for inhibited behavior appeared to be due to a decrease in left frontal activation rather than due to an increase in right frontal activation. The pattern of decreased left frontal activation found in inhibited children was practically the same that has been reported in depressed adults. It would be expected with these children, that they should be more likely to experience sadness and depression-like reactions to emotionally stressful situations.

However, it has been speculated that although only a small percentage of the vulnerable children would be expected to actually develop an affective disorder, more of them would be expected to have sub-clinical characteristics like dysthymic mood, shyness, and decreased dispositional affect (Davidson, 1995). It is possible that children with the opposite finding of decreased right-sided withdrawal behavior would show the same results. Nevertheless, it would be expected that these uninhibited children would display impulsive behavior and show an overreaction to reward. We see that these asymmetries can be acute or chronic over time and can predict the affective behavior or threshold to appropriate stressors.

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