Abstract
This article describes research on the role of the environment in influencing the development of the nervous system, including synapse formation and capacity for autonomic regulation. Perspectives regarding the role of environmental factors in the development of physiological regulation contribute to our increasing understanding of the impact of gene-environment interactions in the origins of chronic illness such as type 1 diabetes. This excerpt emphasizes the role of the prenatal and perinatal time frame.

**NON-GENETIC FACTORS AFFECTING ANS FUNCTION**

**I. THE EXPERIENCE-DEPENDENT MATURATION OF THE NERVOUS SYSTEM**

Gene-environment interactions during development
The nervous system is immature at birth [1] and maturation takes place in early life during relatively defined periods of time. Pruning of synapses is genetically timed [2] and the number [3, 4] as well as strength [5, 6] of synapses is influenced by interactions with the environment [5, 7-9]. The contribution of environmental factors is referred to as experience-dependent maturation [4, 5, 9]. The process of experience-dependent maturation: 1) influences the density of synapses in different tissues as well as variations in density in the same tissues in different individuals [10], 2) can predispose to relative predominance of sympathetic or parasympathetic activity, and 3) fosters unique individual responses to different types of stress [8]. This process promotes plasticity of the nervous system and facilitates human organisms’
finely honed capacity for adaptation to their own unique environments [5, 9].

**Synapse development**

Cortical synaptogenesis begins prenatally, peaks by approximately 1 to 2 years of age, and appears to be activity-dependent [11]. Genetically timed apoptosis and elimination of synapses follows and is at least partly environmentally regulated [11]. Timing of cortical synapse elimination varies in different areas, is most dramatic from one year of age through mid-adolescence [11, 12], and continues at a slower rate in adulthood [4, 11]. Imaging studies used to evaluate growth rates of the developing nervous system have tracked patterns of glucose utilization as a measure of metabolism, synaptogenesis, and plasticity to demonstrate that growth is particularly active between 4 and 9 to 10 years of age, when glucose utilization is at its highest [13]. Levels of growth then decline to reach adult values by the ages of 16 to 18 [13].

During development, nerve pathways that are reinforced, such as through frequent utilization, are generally promoted through the stabilization and strengthening of synapses, while those that are underutilized are reduced through selective pruning [9]. Gene-environment interactions contribute to individuality, take place both in prenatal and postnatal life [9, 14, 15], and are believed to influence risk for pathology and disease [8, 10, 16, 17].

**Critical period programming**

The timing of environmental events most strongly influences developing structures [8, 15] and has the highest impact on organ systems undergoing periods of rapid growth [8, 18]. Critical period programming occurs primarily in prenatal and early life. Adverse events occurring during these times may have long-term and irreversible effects on the developing organism [4, 10].

**Influence of the prenatal environment**

*Maternal-infant bonding & psychobiological regulation*

The experience-dependent maturation of the nervous system is affected by interactions with the environment in general, and by the attachment bond between infant and primary caregiver(s) in particular [5, 8, 9, 19, 20]. The mother, who’s role has been the most frequently studied in the function of primary caregiver [8, 9], serves as a “psychobiological regulator” [8] for her dependent and essentially helpless infant [9]. In this capacity, she helps to modulate his or her levels of arousal to facilitate the establishment of self-regulation not only of behavioral rhythms, but also of physiological rhythms, including autonomic, neurochemical, and hormonal functions [8].

Many of the interactions that influence the ANS and the balance between parasympathetic and sympathetic activity occur at an unconscious nonverbal level [21] through a multitude of interactions inherent to parent-infant interactions, including holding, gazing, and soothing [8]. The mother’s ability to respond to and to stimulate her infant at optimal levels is influenced by the degree of attunement with her infant, and serves to buffer his or her physiological [9, 22] as well as emotional and behavioral responses to stress [8].

Attunement between mother and child is directly affected by the maternal-infant bond, which in turn is shaped by prenatal and perinatal events [8, 23].
Among the complex factors that influence bonding at birth are the mother’s attitude toward the pregnancy and her perception of available support systems [23, 24], her experience of procedures such as amniocentesis [25, 26], and her perception of stress during pregnancy [23, 27, 28].

The sensitive period
Among the most influential perinatal experiences affecting bonding are maternal-infant interactions in the hours and weeks following birth. Early contact during the first day in general, and the first hour postpartum in particular, appears to be of special importance [23, 29]. During the first hour the newborn exhibits qualities of alertness and exploratory behavior that do not occur again to the same extent for several weeks [23]. Contact during this first hour has been found to increase the number of mothers that breastfeed, the duration of breastfeeding [30], or both [23, 31-33]. In addition, early contact also appears to improve the quality of future behavioral interactions between mother and infant [29, 31, 34-36] and to reduce the frequency of early infections in the baby during the first months of life [23]. Measurable effects have been noted in the quality of maternal-infant interactions and infant development up to one [37] and three years [33] of age following early contact.

Bonding disruption
Separation in early life is associated with changes in hypothalamic-pituitary-adrenal (HPA) responses to stress [38], transient and long-term changes in immune competence in non-human primates [39], and reduced maternal-infant attunement [40]. The impact of maternal-infant separation during the sensitive period may permanently alter affectional ties [23], and may consequently influence developing organ systems, including the nervous system [8]. Events that affect the ability of the mother to attend to her infant shape the capacity of the newborn to tolerate stress, since the immature infant nervous system is unable to regulate states of high arousal. Events occurring during labor and delivery that may affect the mother or the infant’s ability to bond include early separation, pain in the mother or infant, the use of medication such as anesthesia, and anxiety, among others [23].

Whereas healthy newborns demonstrate more rapid returns to baseline cortisol following exposure to stress [41], babies born following mild obstetrical complications have less optimal HPA responses [42] as well as decreased habituation and sensitization to stressors [41]. Maternal-infant separation following cesarean sections is common and appears to negatively impact quality of maternal-infant interactions [43-46] as well as frequency of breastfeeding [46].

Prenatal stress
Early exposure to non-genetic factors such as stress in prenatal life stimulates the fetal HPA axis [47], can permanently affect the number and sensitivity of glucocorticoid receptors, and can program the HPA axis for life [18, 47]. Number of glucocorticoid receptors has been found to be proportional to the severity of symptoms of PTSD [48]. Maternal exposure to prenatal stress has also been found to predict birth size and gestational age independent of biomedical risk [49-51], and to influence physiological as well as psychological development postpartum [24]. Size at birth appears to be influenced by the timing [49] and quality [47, 49] of emotional stress experienced by the mother during
pregnancy, as well as by her perceived availability of social support [50].

References


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