

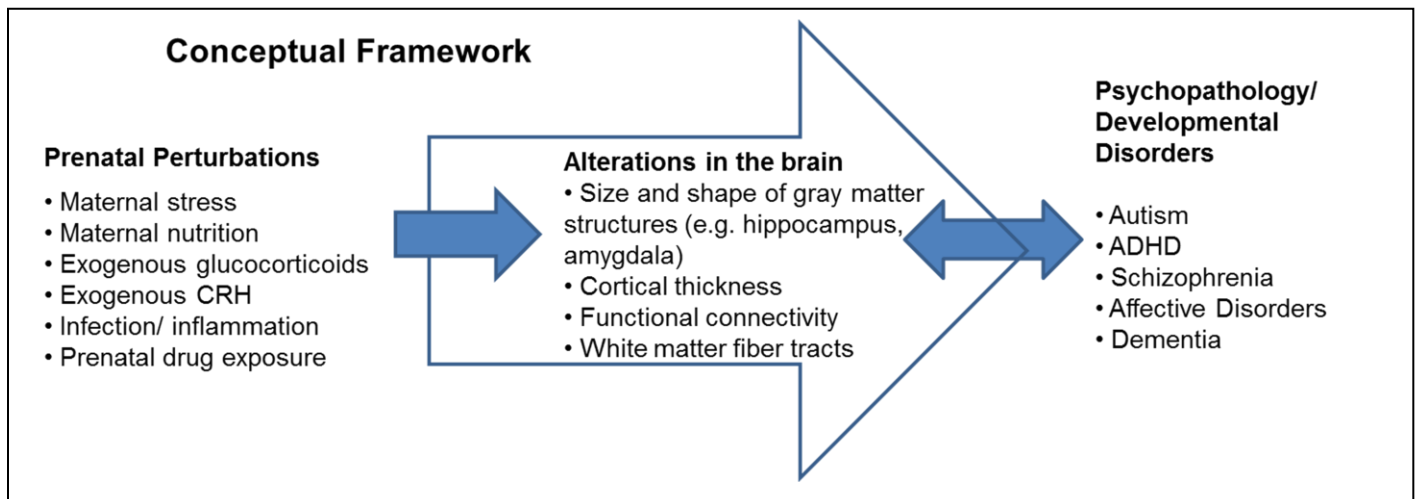
The Role of Stress in Brain Development:  
The Gestational Environment's Long-Term Effects on the Brain  
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*Editor's note: During gestation, the fetal brain develops dramatically as structures and connections form, providing the foundation for all future development. The fetal environment plays a critical role in these early neural processes, for better or for worse. Scientists now know that exposure to maternal stress can sometimes have deleterious effects on the fetus, depending on the cause, timing, duration, and intensity of stress. Fortunately, postnatal interventions, such as a secure parent-infant bond and an enriched environment, can buffer the potential negative consequences.*

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The gestational environment can impact fetal brain structure and function and increase long-term susceptibility to neurodevelopmental and neuropsychiatric disorders (see Figure 1).<sup>1-3</sup> This can occur independently or in conjunction with genetic or postnatal factors. For several reasons, environmental influences during fetal development are especially potent in the brain. First, gestation is when differentiation of major brain structures occurs, thus creating greater sensitivity to environmental conditions than at other times during the life span. Second, brain development involves a cascade of interactions with the environment, so that even small deviations from the normal developmental trajectory during fetal life can become progressively magnified over time, producing long-lasting or permanent consequences. And third, the immature fetal blood-brain barrier offers limited protection against neurological insults.<sup>4</sup> For these reasons, the brain's plasticity during gestation confers both increased vulnerability to environmental exposures and opportunities for therapeutic interventions.

**Figure 1**



A healthy, well-nourished mother is necessary but not sufficient for normal fetal development.<sup>5,6</sup> Stress-related biological processes can affect the ways in which nerve cells grow, survive, differentiate, and communicate with one another. Specifically, they can alter availability of protective neurotrophic growth factors, synapse (neuron junction) development, neurotransmitter (chemical signal) levels, myelination (sheathing of nerve fibers), and even adult neuron production. But the role of stress is not clear-cut. Scientists have found that the

consequences of maternal stress depend on the cause, timing, duration, and intensity of the stress, as well as maternal stress reactivity and the genetic susceptibility of the fetus.

### **Human Brain Development: A Brief Overview**

The immature brain can be considered under construction.<sup>7</sup> The development of the human central nervous system follows a protracted, orchestrated chain of events. Brain change and adaptation are part of a lifelong process, but the earliest phases of maturation are particularly important.<sup>8</sup> Understanding the timing of neurodevelopmental events is essential for determining how environmental disturbances can affect certain structures and functions.

The whole human organism develops from a single cell formed by the fusion of the ovum and sperm to form a fertilized egg (zygote). The processes of cell division and differentiation (specialization to distinct cell types) during early development produce all organs, including the brain. The brain has multiple cell types, and a vast number of connections between these cells specify eventual form and function. During fetal life, neurons proliferate, migrate, and aggregate, providing the hardware for the developing brain. Before birth, the brain produces about 250,000 cells per minute.<sup>9</sup> Between the 8th and 16th weeks of gestation, migrating neurons form the subplate zone, an area of the fetal brain that disappears after about 34 weeks, and await connections.<sup>10</sup> Once neurons reach their final destination at about the 16th fetal week, they branch out to establish connections among brain regions before migrating to their target locations.<sup>11</sup>

Little synapse formation occurs before the beginning of the third trimester, when it accelerates to approximately 40,000 synapses per minute.<sup>12</sup> Myelination, or the production of the fatty sheath that insulates the nerve fibers (axons) allowing for more efficient cell-to-cell communication, occurs alongside the proliferation and differentiation of oligodendrocytes, cells that assist with myelin development. Myelination of occipital white matter at the back of the brain begins one to two months before birth and extends gradually to the frontal lobe by the postnatal age of nine months.<sup>13, 14</sup> Genes associated with neurodevelopmental processes are robustly expressed starting in the embryonic period, and this expression continues at a very high rate during the fetal and infant life.<sup>15</sup>

Vast brain growth occurs during the first two years of postnatal life. Longitudinal studies conducted in normal, healthy newborns and infants by John Gilmore and his colleagues at the

University of North Carolina used magnetic resonance imaging (MRI) to document the rapid growth and organizational changes that take place during the first two postnatal years. In the first months there is enormous growth of regionally specific gray matter.<sup>16</sup> Overall brain size doubles during the first year of postnatal life; the brain is about 70 percent of adult size at one year of age, and 85 percent at two years of age.<sup>17</sup> Structural and functional connectivity emerge over the first two years of life.<sup>18, 19</sup> In infancy, the brain dramatically increases in size due to an overproduction of connections, synapses, and myelination. In later childhood and adolescence, pruning takes place as the brain eliminates unused axons, neurons, and synapses, thus reducing gray matter volume.<sup>20</sup> Thus, initially more connections develop than may be necessary which then get tuned down to those that are needed for efficient communication between neurons in an individual. This plasticity allows building brains for individual needs.

### **Stress Biology in Human Pregnancy**

Many of the endocrine (hormonal) and immune factors that play key roles in growth and development are also centrally involved in the stress response. This may be one reason why stress has the potential to impact intrauterine development. The role of stress and stress biology in development is common across all species and underlies evolutionary adaptations to external circumstances, such as food availability and challenges that threaten survival and reproduction. The development of a single fertilized egg into a fully formed individual represents a complex and breathtakingly elegant phenomenon. The endocrine and immune environments during gestation impact all aspects of embryonic and fetal development, starting with the implantation of the fertilized zygote in the mother's uterus; extending through growth and differentiation into specific cells, tissues, and organ systems; and culminating in birth. The placenta, a fetal organ that mediates exchanges and communication between mother and fetus, forms very early in gestation and produces key hormones, protein messengers, and growth factors.<sup>21</sup>

Interestingly, a mother's biological response to stress is dampened during gestation. Several investigators, including some in our group, have shown that pregnant compared to nonpregnant women experience a lower increase in heart rate in response to the same stressor, and cortisol increase in response to awakening is lower in pregnant women than in nonpregnant women.<sup>22-24</sup> The degree of reduction in biological stress responses over the course of pregnancy varies from one woman to another, and adverse birth outcomes are more likely in children of

women showing a lack of dampening (and thus greater biological stress responses) during pregnancy.<sup>38</sup> Also, a generalized reduction of maternal immune responsiveness occurs during pregnancy, presumably to tolerate the fetus, a foreign body, and not to the extent to suppress maternal immune responses that would increase maternal or fetal susceptibility to infection.<sup>25</sup>

Most studies of maternal stress rely exclusively on self-report questionnaires and interviews that ask pregnant women to state how they have been feeling psychologically or emotionally over a given period of time and then to estimate their average psychological or emotional state. This approach may be inaccurate and associated with retrospective-recall biases.<sup>22-24</sup> Also, it does not measure the individual's biological stress responsivity, which is necessary to complete the picture. We recently demonstrated a robust association between maternal psychosocial stress and the major stress hormone cortisol when we measured both repeatedly over the course of a day.<sup>26</sup> Since elevated cortisol is often the result of elevated inflammatory processes in the body, it is important to note that other studies have shown that elevated psychosocial stress in pregnant women is associated with higher circulating levels of C-reactive protein (CRP), a systemic marker of inflammation, and the proinflammatory cytokines IL-1b, IL-6 and TNF $\alpha$ , and with lower circulating levels of the anti-inflammatory cytokine IL-10.<sup>27, 28</sup> Imbalances in pro- and anti-inflammatory cytokines, along with elevated cortisol, can distort fetal brain and body development that results in life-long problems. This occurs in children who are abused and neglected early in life, as documented in the Adverse Childhood Experiences Study.<sup>29</sup> Gestational stress may have similar long-term effects.

Endocrine and immune markers may serve as signals of not only maternal stress but also of nutrient and oxygen availability, obstetric complications such as preeclampsia and infection, and other important environmental conditions, which can sculpt brain development and alter neural outcomes.<sup>30</sup> For these reasons, endocrine and immune biological measures indicate a range of adverse intrauterine conditions.<sup>24, 31</sup>

Our understanding of the potential mechanisms by which maternal stress may produce long-lasting changes in fetal brain structure and function comes primarily from animal studies. Several studies demonstrate that fetal exposure to inappropriate levels of biological stress mediators, which may occur during exposure to excess maternal stress or other adverse intrauterine conditions, can exert detrimental effects<sup>32</sup> and interfere with the long-term trajectory of gray and white matter development. In concordance with results in animals, in humans we and

others associated high placental corticotrophin-releasing hormone (CRH) and maternal cortisol with impaired fetal maturation, infant mental and motor development, and infant temperament.<sup>33-37</sup> Furthermore, researchers associated the administration of synthetic glucocorticoids during pregnancy (as a treatment for fetal lung maturation) with child neuroendocrine dysregulation, internalizing behavior, and social anxiety.<sup>38-41</sup> Researchers also linked elevated gestational levels of the inflammatory cytokine interleukin-8 with changes in the brain<sup>42</sup> that are associated with an increased risk of developing schizophrenia<sup>43</sup> in children and adult offspring.

### **Sculpting Development: Stress and the Fetal Brain**

Exposure to neurotoxins like alcohol, lead, and pesticides, particularly during sensitive periods of early fetal development, often produces long-term deficits in brain structure and function. Exposure to psychosocial stressors, on the other hand, has more nuanced effects on the developing brain. Overgeneralized assertions, such as “Stress is bad for you and your baby,” may inadvertently contribute to anxiety and worry among pregnant women. In fact, some researchers reported a beneficial effect of moderate psychosocial stress during pregnancy on certain child neurodevelopmental outcomes, noting that such stress may have different consequences depending on factors including its duration, intensity, context, as well as the social support systems available to the mother.<sup>44</sup> This is consistent with the stress-inoculation theory, which posits that early-life stressors may provide a challenge that, when successfully overcome, can induce advantageous adaptations.<sup>45</sup> Thus, issues critical to determining whether prenatal stress exposure has beneficial or deleterious consequences relate to the nature, magnitude, chronicity, and timing of stress, the pregnant mother’s biological and psychological responses to stress as well as to her sense of control over the stressor. As discussed above, several hormones and cytokines that feature prominently in stress-response pathways play an essential role in normal brain development. However, as noted earlier, exposure to excessive or deficient levels of stress hormones or cytokines at inappropriate times of gestation may increase vulnerability to neurodevelopmental disorders and psychopathology.<sup>3</sup>

Maternal exposure to excessive psychosocial stressors during pregnancy, such as domestic violence or the death or serious illness of a loved one, may have negative effects on fetal and infant neurodevelopment, including delayed mental and motor development, difficult temperament, and impaired cognitive performance.<sup>46,47</sup> The underlying reasons for these effects

are assumed to be stress-related alterations in brain structure and connectivity. We recently uncovered evidence of a direct link between the maternal emotional state during pregnancy and changes in the offspring's brain structure. Children born to mothers who experienced high levels of anxiety in the early second trimester of pregnancy had region-specific reductions in gray matter volume<sup>48</sup> and impaired executive function<sup>49</sup> in middle childhood.

Alterations in brain structure and function as a consequence of the gestational environment may have an adaptive value in some contexts but be disadvantageous in others.<sup>5, 50, 51</sup> For example, one function of neuroendocrine stress responses may be the enhancement of predator detection and avoidance mechanisms.<sup>5</sup> Such changes may be useful for coping with the demands of adverse social environments, such as an unstable family or a dangerous neighborhood. However, these same changes may confer increased susceptibility for post-traumatic stress disorder (PTSD) and depression. Thus, adaptation can be difficult to distinguish from insult, and the beneficial effects may be context specific.<sup>52</sup>

### **Interaction of the Postnatal Environment with Prenatal Stress**

Although the first year of postnatal life represents a period of heightened developmental vulnerability, it also may be a time when therapeutic interventions may have the greatest benefit. Interventions that provide a child with an enriched environment, along with age-appropriate psychomotor, attention, and other cognitive training, may be most beneficial during infancy and toddlerhood, when the brain is still highly plastic. Research suggests a substantial potential for the reversal of prenatal stress' negative effects, with evidence suggesting postnatal compensation for prenatal adversity.<sup>53</sup> We found an association between lower birth weight (a marker of intrauterine adversity) and a smaller hippocampus, a brain structure important for learning and memory processes, in young adults who reported low parental bonding during childhood. However, we found no such association among those who reported high parental bonding.<sup>54</sup>

Recent longitudinal data provide further evidence for the quality of mother-infant attachment as a modifier of both the effects of prenatal maternal stress on infant temperament<sup>55</sup> and the effects of prenatal maternal cortisol on infant cognitive development.<sup>37</sup> The detrimental consequences of elevated maternal stress are reduced in securely attached infants. Programs like nurse-family partnerships may provide women with additional support to offer the developing infant a more favorable environment. But not all children are equally sensitive to environmental

cues, and the degree of postnatal plasticity may result from both an individual's genetic makeup and the intrauterine environment.<sup>50, 51</sup> Thus, identifying at-risk children based on their prenatal and perinatal risk factors would improve the success of interventions. Researchers observed impressive treatment results when interventions focused on particularly vulnerable populations.<sup>56</sup>

### **Directions for the Future**

Some questions that need to be addressed in a critical evaluation of this vulnerability hypothesis include the following: Alterations in which specific brain regions increase fetal vulnerability? What conditions produce changes in these brain regions? What is the trajectory of these brain changes from their initial occurrence to the overt manifestation of the disorders of interest? During which critical periods do these conditions exert their greatest impact? When can these brain alterations first be detected reliably?

Advances in neuroimaging technologies and analytic methods offer unprecedented opportunities to answer some of these questions. MRI techniques are attractive because of the lack of ionizing radiation. There is no evidence that the magnetic field used by the scanner has any harmful effects; thus this method is considered safe and can be used in infants. Newborns and infants can be scanned without sedation during natural sleep, and head movements can be minimized with special stabilizing cushions. Conventional structural MRI scans assess size and growth of specific brain regions and cortical folding. Diffusion-weighted imaging provides valuable insight into white matter development and structural connectivity. Recently, researchers have begun studying brain function under resting conditions, which allows assessment of functional connectivity (resting-state functional MRI, or fMRI). The underlying principle is that brain networks that wire together fire together, and therefore simultaneous activity of brain regions is indicative of their connectivity. Therefore, resting-state fMRI provides information regarding the emergence of brain networks. Furthermore, researchers can use techniques like fMRI to measure brain activity in response to a stimulus, and proton magnetic resonance spectroscopy (MRS) to assess brain metabolic function. Through the use of these methods, researchers have obtained important and novel insights about normal brain development from birth through infancy<sup>17, 19, 57, 58</sup> and the consequences of fetal exposure to drugs including nicotine.<sup>59, 60</sup>



Ultrasound imaging is still the primary fetal monitoring modality, but MRI provides greater anatomical detail. Increasingly, clinicians are using MRI to look at anatomical regions and structures that are difficult to see on a sonogram. Recent impressive methodological advances are addressing limitations, such as dependency upon motion-free scans, tedious manual segmentation, and spatial inaccuracy due to thick slice scans,<sup>61</sup> which have increased application of fetal MRI both for clinical and research purposes. Repeated scans during fetal and early postnatal life allow investigators to assess brain development as it happens, including examination of gray and white matter changes and myelination.

Acquiring neuroimaging data at the time of birth in children whose mothers have been studied over the course of pregnancy would provide an important baseline against which to compare outcomes in subsequent assessments to quantify developmental trajectories. A second critical time point is at 12 months of age, as the first year of postnatal life is characterized by larger increases in brain size than any other time during the life span.<sup>16, 62</sup> Serial assessments at least at these two times could characterize changes during the most dynamic stages of brain development, as well as distinguish prenatal effects from early postnatal conditions and study their interactions. Further follow-up of these children with MRI scans and behavioral assessments (including assessments of neurocognitive function, temperament, and, at later ages, psychiatric diagnostic interviews) at the critical periods when neurodevelopmental and other mental disorder symptoms typically emerge (two to three and five to six years, as well as before and after puberty) would be very informative.

Research has demonstrated that the quality of both prenatal and postnatal environments can influence fetal and infant brain development, with consequences for lifelong mental health. Healthy brain development can be promoted by supporting maternal health and well-being not only during pregnancy but also in the period prior to conception. This includes maintaining a healthy diet and lifestyle. Furthermore, infant growth trajectories and milestones should be monitored to allow early detection of developmental delays, thereby providing the opportunity for early interventions when they are most effective. While all children should be provided a warm and enriched environment, this is particularly important in the case of at-risk children—like children born after the occurrence of prenatal complications or children born prematurely—who may benefit the most from such a favorable postnatal environment.<sup>54, 55, 56</sup> Such an environment may exert compensatory effects on the potential negative consequences of prenatal

and perinatal risk conditions. Additional research into preconception, prenatal, and postnatal neuroprotection is warranted in order to specifically harness these processes through behavioral and, potentially, pharmacological strategies.

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