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A Role of Early Life Stress on Subsequent Brain and Behavioral Development

Damien A. Fair,* Alice M. Graham,** and Brian Mills***

ABSTRACT

The prevalence of pediatric neuropsychiatric disorders has risen dramatically during the past two decades. A study surveying the years 1997-2008 verified that one in six children have a developmental disability—a number on the rise. Along similar lines, studies show higher incidents of criminal activity, substance use disorders, and the emergence of psychopathologies in early adolescence and young adulthood, which are particularly sensitive periods of brain and behavioral maturation. While developmental trajectories that may lead to adverse outcomes in youth are the result of a mix of genetics and environmental exposure, it is becoming clearer that they do not start at the time of the diagnosis or problem behaviors; rather, these developmental trajectories start at the earliest periods of life. The ability of children to achieve their full physical, academic, and social potential is tightly related to early life events, some of which may occur even before birth. The science is now amassed with investigators and research targeting the role of Early Life Stress and its interaction with biological systems in impacting the development of the brain and complex behaviors across all stages development.

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I. A ROLE OF EARLY LIFE STRESS ON SUBSEQUENT BRAIN AND BEHAVIORAL DEVELOPMENT

Developmental neuropsychiatric disorders are a major public health concern that entails massive costs, leads to extensive hardship for children and families, contributes to serious negative long-term outcomes, and places substantial demands on the nation’s educational and health care systems.1 These consequences highlight the need for innovative approaches to understanding etiology, and ultimately improve treatment and preventative strategies for a range of disorders. Indeed, one in six children now have a developmental disability—a seventeen percent increase in children over the past decade, driven largely by increases in Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD).2

We note that typical development can put pressure on the health of our society. For example, even before the earliest conceptions of a juvenile justice system, adolescents and young adults have presented unique challenges to policy-makers.3 Studies reveal higher incidents of criminal activity, substance use disorders, and the emergence of psychopathologies during this sensitive time period amongst a range of potentially comorbid factors.4 In subsets of adolescents, the propensity for increased risky behaviors, higher degrees of sensation seeking and impulsivity, greater

4. See Bava & Tapert, supra note 3; and Cohen & Casey, supra note 3.
sensitivity to rewards, and heightened reactivity to threat and punishment are not uncommon.5 It is very likely that these types of developmental trajectories are the result of a mix of genetics and environmental exposure that do not start at the time of the diagnosis or problem behaviors; rather, they start at the earliest periods of life.6 Early life events, even those occurring before birth, correlate with the ability of children to achieve their full physical, academic and social potential.

II. CHILDHOOD, ADOLESCENT, AND LONG-TERM HEALTH OUTCOMES ARE INFLUENCED BY EARLY MATERNAL AND INFANT MARKERS OF NUTRITION, BIOLOGICAL, AND PSYCHOSOCIAL FACTORS

Maternal influences on neurobiological development during the prenatal period are thought to set the foundation for subsequent developmental processes.7 These early factors have a sizable impact on physical and mental health.8 The theory behind this concept, Developmental Origins of Health and Disease (DOHAD), provides a model for considering the effects of environment on brain/behavior outcomes later in life by integrating decades of research to examine the influence of the early environment on health outcomes.9 This model incorporates a programming perspective,

8. See Levitt, supra note 6; and see Rogers, supra note 7.
whereby salient cues in the early environment guide developmental processes to adapt to expected conditions. For example, work in this area has documented how a mismatch in the pre- versus post-natal environment, specifically with regard to nutritional availability and psychosocial stress, can lead to increased risk for diabetes, coronary heart disease, and changes in brain circuitry. What particularly distinguishes this model is that early exposures are neither “bad” nor “good” agents of development, but rather are cues to the developing brain on what environment to expect at birth. For example, early stress exposure may increase the likelihood that an organism becomes highly stress responsive to later exposures, with attendant consequences for behavioral and somatic health if there is a “mismatch” between the maternal cues and the expectant environments.

The concept of developmental programming represents a guiding theoretical principle in the study of Early Life Stress (ELS) on brain development. This concept suggests that during times of rapid growth, systems are more vulnerable to disorganizing influences. During the prenatal period, brain development proceeds from the basic foundational level of neural tube formation to the migration of neurons, and then to the initial myelination of axons and formation of synapses. Rapid brain development continues during infancy, with frontal and primary sensory

cortex showing seventy to eighty percent increases in synaptic density over the first eighteen months of life, and brain volume increasing four-fold from birth to four years of age, accompanied by a rapid decline in the ratio of gray to white matter volume (indicative of increasing myelination). During these periods of rapid change the brain is sensitive to environmental input, which is both necessary for healthy development and potentially harmful depending on factors such as the nature and timing of the input.

III. EARLY LIFE STRESS COMES IN MANY FORMS TO AFFECT BRAIN DEVELOPMENT

ELS influences the development of neurobiological systems implicated in emotional functioning and mental health across the lifespan. Stress is posited to have a particularly pronounced impact during early periods of brain development, both pre- and postnatally, as development occurs rapidly in this window of time, exposing the ongoing formation of brain structural organization to vulnerability. However, as brain-imaging techniques have advanced, the importance of understanding these sensitive periods has become clearer.

studies examining the effects of ELS on the brain have predominantly focused on older children and adults, it is difficult to differentiate effects of stress during early developmental periods from the effects of subsequent ongoing adversity, the emergence of coping strategies, or symptoms of psychopathology. Moreover, ELS research has often focused on more extreme sources of adversity, such as institutional rearing, leaving a gap in our understanding of how more mild sources of prenatal and familial stress influence early development of brain systems linked to emotional and mental health.

Research into proximal effects of common forms of stress on brain structure and functioning is beginning to emerge, and has the potential to increase understanding of the vulnerability of the developing brain. For example, findings from a recent functional magnetic resonance imaging (fMRI) study indicate that something as simple as non-physical conflict between parents (interparental conflict) during the first year of life correlates with infants’ brain activity in regions thought to be important for processing and regulating stress and emotions. Infants’ exposure to higher levels of interparental conflict also correlates with heightened brain reactivity to a stressor-relevant stimulus (e.g., an angry tone of voice) in brain regions that are activated during neutral speech.

23. Refers to medial prefrontal cortex (MPFC; rostral anterior cingulate cortex [rACC]) and a subcortical region encompassing the hypothalamus and parts of the thalamus and caudate. Graham et al., supra note 22, at 782-89.
Maternal inflammation during pregnancy is believed to increase risk for offspring neuropsychiatric disorders and adverse physical health outcomes. Strong epidemiological evidence identifies connections between common conditions associated with heightened inflammation during pregnancy, including increased psychosocial stress, but also many other ‘stressors,’ such as infection, high maternal body mass index (BMI), maternal psychopathology, and more. Indeed, we now know that maternal inflammation, along with its correlate stressors, relates to elevated risk for offspring developing schizophrenia, ASD, ADHD, and other neurological and psychiatric disorders. Thus, maternal


30. Knuesel et al., supra note 26, at 643-60.
inflammation during pregnancy is a strong candidate for mediating effects of diverse conditions on offspring neurodevelopment with implications for long-term health.

One way to measure the inflammatory state during pregnancy is by measuring what are called cytokines in the blood. Cytokines are inflammatory signaling proteins, and can act as sensors, transducers, and effectors of environmental conditions on the developing embryonic and fetal brain. They can be pro-inflammatory, tending to increase the inflammation, or anti-inflammatory, tending to decrease the inflammatory state. Maternal pro-inflammatory cytokine levels are elevated across a range of diverse high-risk conditions (e.g. infection, high BMI, and psychosocial stress, all of which are sensors)\(^{31}\) with accompanying increases in pro-inflammatory cytokines in placental tissue, amniotic fluid, and the fetal brain (transducers).\(^{32}\) Cytokines are also expressed in the fetal brain as part of typical neurodevelopmental processes,\(^{33}\) and facilitate cellular survival, proliferation and differentiation, neuronal axonal growth and connectivity (i.e., synaptogenesis).\(^{34}\) Elevated cytokine levels in the

\[\text{31. John R. Challis et al., Inflammation and Pregnancy, 16(2) REPROD. SCI. 206, 206-15 (2009), https://doi.org/10.1177/1933791108329095; Coussons-Read et al., supra note 25, at 625-631; Juliette C. Madan et al., Maternal Obesity and Markers of Inflammation in Pregnancy, 47 CYTOKINE 61, 61-64 (2009), https://doi.org/10.1016/j.cyto.2009.05.004.}\]


\[\text{33. Ted M. Burns et al., Developmental Regulation of the Cytokine Expression in the Mouse Brain, 9 GROWTH FACTORS 253, 253-258 (1993).}\]

fetal brain (such as in response to maternal inflammation) trigger alterations in these aspects of neurodevelopment (effectors).  

Interleukin-6 (IL-6), a pro-inflammatory cytokine, exemplifies this tripartite role. Heightened IL-6 concentrations are evident across various maternal gestational conditions (e.g., obesity, psychosocial stress, depression and infection) that, in turn, have been shown to increase susceptibility for psychiatric disorders in offspring. Thus, a significant amount of work has targeted the role of maternal IL-6 concentrations in relation to human fetal brain development.

V. THE AMYGDALA IS A KEY BRAIN/LIMBIC STRUCTURE INVOLVED IN MOOD REGULATION AND ANXIETY THAT IS PARTICULARLY VULNERABLE TO EARLY LIFE STRESS

The amygdala is a key limbic structure of the brain nestled in the medial aspect of the temporal lobes and is involved in mood regulation and anxiety. Amygdala structure and function is altered in patients with anxiety and depression. Further, children with ASD show atypical

https://doi.org/10.1002/(SICI)1097-4547(19980401)52:1<7::AID-JNR2>3.0.CO;2-I.
37. Coussons-Read, supra note 25, at 625-631; Sina Haeri et al., Do Pregnant Women with Depression Have a Pro-Inflammatory Profile? 204(1) AM. J. OBSTETRICS AND GYNECOLOGY S322 (Supplement, Jan. 2011), https://doi.org/10.1111/j.1520-059X.2011.03915.x; Meyer et al., supra note 26, at 26R-33R.
patterns of functional connectivity, and abnormal amygdala growth trajectories have been documented in the disorder. The amygdala is rich in receptors for cortisol, a hormone involved in the neurobiological response to both physiological and psychological stress, and it appears to be particularly vulnerable to the effects of stress exposure during infancy and childhood. Recently, studies also have emerged relating stress in the prenatal environment to amygdala structure and functional connectivity during infancy. Together these studies point to a potential role for alterations in the amygdala as an important pathway through which ELS, beginning prenatally, may influence long term risk for psychiatric disorders. However, this large body of research has not examined the role of inflammation in this pathway.

VI. RECENT EVIDENCE SUGGESTS THAT THE AMYGDALA IS SENSITIVE TO PRENATAL EXPOSURE TO INFLAMMATION

The recent findings of greater right amygdala volume and atypical bilateral amygdala connectivity in the brain have potential implications for offspring susceptibility for psychiatric disorders, either independently, or through altering vulnerability to postnatal environmental influences. Consistent with this interpretation, the newborn amygdala phenotypes associated with higher maternal IL-6 concentrations during pregnancy are associated with lower impulse control at twenty-four months of age, a


44. See Buss et al., supra note 13.
behavioral phenotype repeatedly linked to difficulties regulating emotions and behaviors at later developmental stages. Furthermore, the newborn amygdala phenotypes mediate an association between higher maternal IL-6 concentrations during pregnancy and lower impulse control at two years of age. These data provide support for a pathway from heightened maternal IL-6 concentrations during pregnancy to an altered balance between offspring impulsivity and regulatory capacity through alterations in the developing amygdala.

Previous research has identified associations between adversity in early childhood and increased amygdala volume in children. Extending this work to the prenatal environment, Buss and colleagues found an association between higher maternal cortisol concentrations (a stress related hormone) during pregnancy and increased right amygdala volume in school-aged girls, which partially mediated an association between maternal cortisol and child psychiatric symptoms. These most recent findings indicate a potential interaction between the immune system and stress hormones in shaping the developing fetal amygdala. This is consistent with previous findings linking maternal inflammation during pregnancy with increased risk for offspring psychiatric disorders in


47. Buss et al., supra note 13, at E1312–E1319.
humans, and amplified stress reactivity and social deficits in animal models, phenotypes that larger amygdala volumes have been shown to underlie. Variation in maternal IL-6 concentrations during pregnancy explained approximately six percent of the variance in right amygdala volume. While this effect may seem modest, it may be clinically meaningful, as suggested by the association between larger right amygdala volume and lower impulse control at age two. Overall, findings are in line with the conceptualization of larger amygdala volume and increased connectivity as indicative of increased risk for subsequent difficulties regulating emotions and behaviors across various stages of development.

CONCLUSION

There continues to be a growing need to understand and combat the impacts of developmental mental health disorders and problem behaviors that occur in childhood, adolescents, and young adulthood. The ability of children to achieve their full physical, academic and social potential is tightly related to early life events. As such, a growing realization that the trajectories that lead to negative outcomes begin at the earliest stages of development—even prior to birth—is transforming the field. The science is now amassed with investigators and research targeting these issues, and recent work highlights the role of ELS (which comes in many forms) and its interaction with biological systems, such as the immune system, in impacting the development of the brain and complex behaviors. Brain regions particularly important for mood regulation, anxiety, and fear, such as the amygdala, appear to be particularly sensitive. However, the brain is

a complex system with billions of neurons and anywhere from 100-1000 trillion connections. Hence, while the work goes on, a complete understanding of the interactions between ELS, environment, brain, and behavior will continue to be a significant challenge in years to come.