Biological Psychiatry: Celebrating 50 Years

Prenatal Programming of Neuropsychiatric Disorders: An Epigenetic Perspective Across the Lifespan

Bruce S. McEwen

This issue of *Biological Psychiatry* examines emerging aspects of prenatal influences on psychiatric disorders, including transgenerational influences that result from experiences affecting the parent's physiology and that can begin even before conception. The reviews included in this special issue illustrate the important notion that each stage of life depends on what has come before in a unidirectional trajectory that can be redirected but never reversed (1). Moreover, it is now evident that the immune, metabolic, autonomic, and neuroendocrine systems not only are regulated by neural activity, but they also "talk to" and influence each other's activity nonlinearly and "talk back" to the brain to influence its structure and function (2). The brain is sensitive to stress, sex, and metabolic hormones, which, in turn, influence their structure and function (2).

This continuous reciprocal interaction between systemic physiology and the brain and behavior is the basis of the concepts of allostasis and allostatic load/overload, whereby the mediators of the autonomic, immune, metabolic, and endocrine systems and brain interact with each other nonlinearly to either promote normal adaptation or facilitate pathophysiology when these mediators are overused or dysregulated among themselves (3). Efficient allostasis involves turning on a response, e.g., cortisol or heart rate, or release of the glutamate neurotransmitter when needed and turning it off efficiently when the "stressor" is over. When the response is not turned on when needed or is not turned off, this contributes to long-term changes in the body and brain referred to as "allostatic load or overload." That these interacting mediator systems simultaneously affect the brain as well as systemic organs is the basis for "multimorbidity" of systemic, neurological, and mental health disorders and their progression over the life course where early life experiences have disproportionate and lasting epigenetic effects (1).

Two reviews in this issue examine the influence on later neuropsychiatric outcomes of inflammation in the mother and fetus during gestation. Hantsoo *et al.* (4) summarize the clinical evidence that specific kinds of stressors cause an inflammatory load during pregnancy that affects the programming of the fetal brain, increasing the likelihood of neuropsychiatric disorders. Gumusoglu and Stevens (5) review the strengths and limitations of preclinical models of prenatal inflammation that examine how fetal brain development is affected. In particular, maternal immune activation in a variety of animal models has demonstrated convergent outcomes, including shifts/disruptions in the normal developmental trajectory of molecular and cellular processes in the offspring brain. Indeed, the brain contains microglia that can produce inflammation, including dendritic-like cells that are capable of presenting antigen for immune responses and continue to be present throughout the life course (6). Moreover, animal models have shown that interleukin-6 enters the brain after social defeat stress, indicating the adult brain's vulnerability to systemic inflammation (7).

Regarding metabolism, three reviews in this issue focus on the negative and positive effects of nutrition during pregnancy on brain development and risk for neuropsychiatric disorders. One review discusses emerging knowledge about the contribution of the microbiome to metabolic regulation and brain health. DeCapo *et al.* (8) examine preclinical studies on how the maternal consumption of protein, fats, and carbohydrates, as well as overall dietary patterns, influences behaviors relevant to neuropsychiatric disorders in their offspring. Lindsay *et al.* (9) examine the bidirectional nutrition–stress interplay in pregnancy on fetal programming of brain development in animal and human studies; they conclude that the effects of prenatal stress on brain development may be mitigated by higher fat diets or increased intake/status of specific dietary fats as well as higher dietary intake or supplementation by targeted nutrients. Codagnone *et al.* (10) summarize the evidence showing that gut microbiota interact both prenatally and postnatally with diet, drugs, and stress, and that these exogenous factors also affect the dynamic changes in the microbiota composition occurring during pregnancy. Animal models have shown how the microbiota affect brain development, the neuroimmune systems, and the hypothalamic-pituitary-adrenal axis, which predisposes the offspring to behaviors mimicking the aspects of psychiatric disorders in a manner that differs between the sexes.

Among the most important brain–body interactions affected by stress, diet, and the composition of the microbiota are the actions of insulin, leptin, and ghrelin [see McEwen (11) for review]. Metabolically, the healthy brain has receptors for and responds procognitively to these three metabolic hormones and is subject to insulin and leptin resistance as a precursor to cognitive impairment and depression, with further risk for dementia later in life (12). The long-term consequences of maternal obesity are illustrated by the finding of hippocampal insulin resistance and impairment of neuroplasticity and cognitive function without any signs of systemic obesity in the offspring of obese mother rats (13).

Bariatric surgery before conception reduces the incidence of obesity in offspring of an obese woman, while bariatric surgery on morbidly obese men alters the epigenetic methylation profile of sperm DNA, suggesting a reduced propensity

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to transmit obesity to offspring (12). In their review, Morgan *et al.* (14) discuss germline transfer of nongenetic information from sire to offspring via extracellular vesicles that carry a microRNA signal from the paternal compartment to the maternal reproductive tract and future embryo. The "memory" encoded by the paternal experience is carried by the molecular signal, which then enacts downstream responses whereby a target cell or tissue receives the signal and converts it into an effect on embryonic development. Morgan *et al.* (14) speculate that paternal extracellular vesicles could themselves serve as vectors, delivering signals not only to gametes or the zygote but also to tissues of the maternal reproductive tract to influence fetal development. A similar study revealed that traumatic stress in early life altered mouse microRNA expression and behavioral and metabolic responses in the progeny. Moreover, injection of sperm RNAs from traumatized males into fertilized wild-type oocytes reproduced the behavioral and metabolic alterations in the resulting offspring (15).

Another animal model shows transgenerational transfer that involves DNA methylation in germ cells and enhances olfactory-based fear conditioning (16). However, we should be reminded that there are multiple ways of transmitting to the next generation that can operate during mating and during embryonic and postnatal life in mammals (17). Besides signals in seminal fluid and during gestation, there is also transgenerational behavioral transmission from the mother based on amount and consistency of maternal care, which can also be demonstrated using cross-fostering (18).

Epigenetics emphasizes a trajectory over the life course where there is no such thing as "reversal" but rather a one-way direction, where changing trajectory negatively or positively through compensatory mechanisms that may be different at each life stage can hurt or improve the course of health and alter the "health span" (1). Postnatally, a child may come into a home with poverty, including chaos or abuse, and show altered brain development and an increased risk of mental and physical health problems throughout life (19). For example, children living for 10 years with a depressed mother developed an enlarged amygdala and elevated cortisol levels (20). Graham *et al.* (21) relate normative variation in maternal cortisol during pregnancy to the coordinated functioning of the amygdala in a sex-specific manner, leading to an association of elevated maternal cortisol to higher internalizing symptoms in females via alterations in neonatal amygdala connectivity.

Thus, along with other mediators (2), cortisol is a biomarker for and a participant in how brain development is shaped by both adverse and positive experiences, where an early life of uncertainty and chaos may predispose an individual to greater reactivity, chronic vigilance, anxiety, and depression as well as diabetes and coronary artery disease. At the same time, those adverse experiences help the individual adapt to the immediate environment, much as the prenatal experience of starvation programs the offspring to expect sparse food supply (22). For example, we can contrast danger versus safety and how the prefrontal cortex and amygdala differentially respond. A prefrontal cortex that has developed during early life adversity is prepared to expect threat and danger and is less able to control moods and impulses and less able to engage in decision making and proactive planning, and, in a dangerous environment, the orbitofrontal part of the prefrontal cortex promotes vigilance for possible threat and danger (23). In a safe environment, a normal prefrontal cortex regulates impulses and moods via downstream control of amygdala and nucleus accumbens and facilitates decision making and proactive planning.

The challenge for the prenatal and postnatal effects discussed in these reviews is to promote adaptation when conditions change. While prevention of adversity is important through the promotion of better parenting and family/child health during pregnancy (e.g., the Nurse-Family Partnership), there are other windows of opportunity for intervention—e.g., adolescence is a time when change is possible because the adolescent's brain and body are in a time of flux—including the Strong African American Families program (24). Other programs are focused on promoting emotional well-being via mindfulness and empathy sensitizing programs, as well as promoting physical activity, social integration to counteract loneliness, better sleep, and healthier diets (25–27).

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Article Information

From the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, New York.

Address correspondence to Bruce S. McEwen, Ph.D., Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Ave, New York, NY 10065; E-mail: mcewen@mail.rockefeller.edu.

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