Early Life Programming and Neurodevelopmental Disorders

Tracy L. Bale, **Tallie Z. Baram**, **Alan S. Brown**, **Jill M. Goldstein**, **Thomas R. Insel**, **Margaret M. McCarthy**, **Charles B. Nemeroff**, **Teresa M. Reyes**, **Richard B. Simerly**, **Ezra S. Susser**, and **Eric J. Nestler**

Departments of Animal Biology (TLB), and Pharmacology (TMR), University of Pennsylvania, Philadelphia, Pennsylvania; Departments of-Pediatrics and Anatomy and Neurobiology (TZB), University of California, Irvine, California; College of Physicians and Surgeons of Columbia University (ASB, ESS), New York State Psychiatric Institute, New York, New York; Connors Center for Women's Health and Gender Biology (JMG), Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; National Institute of Mental Health (TRI), Bethesda, Maryland; Department of Physiology (MMM), University of Maryland School of Medicine, Baltimore, Maryland; Department of Psychiatry and Behavioral Sciences (CBN), University of Miami, Miller School of Medicine, Miami, Florida; Saban Research Institute (RBS), University of Southern California, Los Angeles, California; and Department of Neuroscience (EJN), Mount Sinai School of Medicine, New York, New York

Abstract

For more than a century, clinical investigators have focused on early life as a source of adult psychopathology. Early theories about psychic conflict and toxic parenting have been replaced by more recent formulations of complex interactions of genes and environment. Although the hypothesized mechanisms have evolved, a central notion remains: early life is a period of unique sensitivity during which experience confers enduring effects. The mechanisms for these effects remain almost as much a mystery today as they were a century ago. Recent studies suggest that maternal diet can program offspring growth and metabolic pathways, altering lifelong susceptibility to diabetes and obesity. If maternal psychosocial experience has similar programming effects on the developing offspring, one might expect a comparable contribution to neurodevelopmental disorders, including affective disorders, schizophrenia, autism, and eating disorders. Due to their early onset, prevalence, and chronicity, some of these disorders, such as depression and schizophrenia, are among the highest causes of disability worldwide according to the World Health Organization 2002 report. Consideration of the early life programming and transcriptional regulation in adult exposures supports a critical need to understand epigenetic mechanisms as a critical determinant in disease predisposition. Incorporating the latest insight gained from clinical and epidemiological studies with potential epigenetic mechanisms from basic research, the following review summarizes findings from a workshop on Early Life Programming and Neurodevelopmental Disorders held at the University of Pennsylvania in 2009.

Historically, the term epigenetics has referred to heritable traits that are not mediated by changes in DNA sequence. More recently, epigenetics has been used more broadly to refer to any change in gene function not associated with sequence variation (1,2) and has been embraced by the neuroscience community as a means by which we can integrate a role for

the environment to influence or "program" gene expression or patterns that may or may not be heritable (3–5). Epigenetic mechanisms typically involve DNA methylation, histone acetylation, and noncoding RNAs, including microRNAs. Increasing evidence shows that numerous types of chromatin modifications, referred to as chromatin remodeling, are widespread in the brain and undergo dynamic regulation in both the developing and adult nervous system (6). Incorporating the latest insight gained from clinical and epidemiological studies with potential epigenetic mechanisms from basic research, the following report summarizes findings discussed at a recent conference on Early Life Programming and Neurodevelopmental Disorders held at the University of Pennsylvania. The conference was thematically based on identifying common mechanisms that may underlie neurodevelopmental disease predisposition and included prenatal, postnatal, and early developmental determinants such as stress experience and maternal diet, behavior, and infection. The goal of the conference and this report is to disseminate the most recent findings across epidemiological, clinical, and basic science in early life programming to inform new directions and needs in the field. These findings are discussed below subdivided into areas of disease focus.

Fetal Antecedents and Programming in Neurodevelopmental Disorders

Schizophrenia

Prenatal and early life events have been associated with the development of schizophrenia. In support of a temporal specificity to the effects of stress on long-term outcome in neurodevelopmental disorders, a recent epidemiological study reported a significant association between maternal stress experienced during the first trimester of pregnancy with an increased risk of schizophrenia in male offspring (7). Prospective birth cohort studies have suggested that such stress exposures act by altering brain development and possibly influencing fetal brain growth through epigenetic modifications. Studies from large birth cohorts in which clinical, neurocognitive, and neuroimaging measures have been obtained have revealed associations between in utero exposure to infections, hypoxia, starvation, and other prenatal risk factors and risk for schizophrenia (8–14), including disturbances of executive function, working memory, verbal memory, and structural brain abnormalities among offspring with schizophrenia (11,15). Neuroimaging findings indicated that prenatal infection was related to enlargement of the cavum septum pellucidum and diminished intracranial volume in these cases (16). Sex also appears to be a strong determinant in schizophrenia risk where neurodevelopmental changes in the hypothalamus and arousal circuitry have been shown to be gender-specific (17,18).

Affective Disorders

There is growing evidence supporting an association between fetal risk factors and affective disorders. Birth cohort studies have identified prenatal conditions, including maternal immune and stress responses, as significant risk factors for major depressive disorder (MDD) (19,20). Second trimester maternal exposure to type A_2/Singapore influenza significantly increased the risk for unipolar and bipolar disorders in Finnish and British cohorts of adults (21–23). Maternal exposure to famine during the second and third trimesters elevated risk for MDD, supporting again an important link between maternal nutrition and offspring neurodevelopment (24,25). Although maternal infection, stress, and undernutrition differentially impact the developing fetus, there may be shared underlying mechanisms contributing to an increased vulnerability to MDD, including effects on hypothalamic-pituitary-adrenal (HPA) axis programming (26).

As the brain continues to mature and develop well into adolescence, it is also critical to understand the influence of the postnatal environment on programming of disease risk. In

the past decade, remarkable progress has been made in studies of the long-term consequences of adverse early childhood experience. Analyses of an extensive database have unequivocally revealed that adults exposed to child abuse and/or neglect are at greater risk for the development of affective disorders (27). Therefore, investigators have sought to determine the neurobiological mechanisms that mediate these outcomes in clinical studies and in laboratory animal models. In nonhuman primates and clinical studies, there is clear evidence for long-term neurobiological, neuroendocrine, and immune alterations after exposure to early adverse events during critical periods in development (recent summaries are available [28,29]). Plasma adrenocorticotropic hormone and cortisol responses to relatively mild stressors are markedly increased in humans that have experienced childhood sexual or physical abuse. Evidence suggests that these effects are mediated by persistent hyperactivity of hypothalamic corticotropin-releasing factor (CRF)-containing neurons. However, these effects are not limited solely to hypothalamic CRF circuits but have also been observed in limbic areas including the amygdala (30), a brain region shown in imaging studies to be involved in the pathobiology of depression.

Similar to humans, in bonnet macaques and rhesus monkeys, hypersecretion of CRF, as evidenced by increased cerebrospinal fluid (CSF) concentration, has been detected years after the initial period of stress exposure to the mother-infant dyad (31). Similar findings have been reported in clinical studies where women with a history of child abuse and/or neglect exhibit hyperactivity of the HPA axis in the Trier Social Stress Test and increased CSF CRF concentrations. In addition, these patients exhibited decreased CSF concentrations of oxytocin, a peptide shown to be important in social biology and bonding, increased inflammatory markers such as interleukin-6 (IL-6), and reduced hippocampal volume as measured by structural magnetic resonance imaging (32). Genetic polymorphisms of the CRF receptor 1 and of FK506 binding protein 5, a gene that codes a glucocorticoid receptor (GR) co-chaperone protein, have recently been implicated in the child abuse-associated increase in vulnerability to major depression and posttraumatic stress disorder, respectively (33,34). Interestingly, there is emerging evidence that these genes can also be epigenetically regulated, thus building support for the long-term consequences of early life experience in programming disease risk, as recently reported for the promoter methylation of the neuronal specific GR in suicide victims with a history of childhood abuse, highlighting an effect of parental care on offspring long-term stress pathway regulation (35). Further supporting a gene × environment interaction for development of affective disorders is the growing evidence of a genetic predisposition that underlies a stress-sensitive phenotype, thereby increasing the likelihood for stress experience throughout life, elevating the risk for disease (as reviewed in [36]).

Animal Models

Focusing on outcomes from these epidemiological and clinical studies, animal models have aided in the examination of endophenotypes of neurodevelopmental disorders to identify the role of early life programming in the alterations of brain structure and function that may promote disease. The mechanisms by which early life experience, especially stress, inflammation/infection, and maternal care, are able to program the brain to confer vulnerability or resilience seem to involve epigenetic modulation of the expression of individual genes or large gene clusters. Historically, the term epigenetics referred to heritable traits that are not mediated by changes in DNA sequence. More recently, epigenetics has been used more broadly to refer to an alteration in gene function not associated with sequence variation (2). Epigenetic mechanisms involve DNA methylation; histone modifications, such as acetylation and methylation; and noncoding RNAs, including microRNAs (see recent reviews on this topic [3–5]). Increasing evidence shows that numerous types of chromatin modifications, referred to as chromatin remodeling, are

widespread in the brain and undergo dynamic regulation in both the developing and adult nervous system (6). Determination of the long-term effect of such reprogramming on important biological phenomenon can be bidirectional. For instance, longitudinal studies of squirrel monkey development have shown that early life stress inoculation diminished subsequent indications of anxiety, increased exploration of novel situations, and decreased stress levels of cortisol compared with age-matched monkeys raised in undisturbed social groups (37). Stress inoculation also enhanced prefrontal-dependent cognitive control of behavior and increased ventromedial prefrontal cortical volumes (38). In rodent models, augmented maternal care promoted resilience to stress later in life, where rat pups that received enriched maternal care showed reduced excitatory drive to hypothalamic CRF neurons resulting from a reduced number of excitatory, glutamatergic synapses on these cells but without change in gamma-aminobutyric acid (GABA)-ergic innervation (39). Reduced excitation was associated with a long-term reduction in CRF expression and respective alterations in binding of the neuron-restrictive silencing factor and, hence, lowered activation of the HPA stress axis in response to future perturbations. In stark contrast with such models of stress-mediated resilience, chronic postnatal stress can promote cognitive decline via functional and structural programming of the hippocampus (40). Such studies suggest that the magnitude of stress may determine its long-lasting effects such that modest postnatal stress may promote resilience, whereas severe or chronic stress may set in motion mechanisms that contribute to stress-related neurodevelopmental disease.

Early life stresses have been broadly associated with disease susceptibility; however, it is important to recognize that the developing nervous system is likely to show a temporal specificity in programming of long-term effects. Recent studies in rodent models have focused on determining the timing of prenatal stress on offspring outcomes including anhedonia, emotionality, and cognitive deficits related to neurodevelopmental disorders. As supported by epidemiological findings, early prenatal stress in mice and guinea pigs has been shown to produce outcomes of increased stress sensitivity in physiological and behavioral measures in male animals (41,42). Such models have also demonstrated cognitive deficits in spatial learning and memory tasks, again supporting the specificity to the timing of the insult with the outcome.

As elevated physiological stress responsivity is a hallmark of many neuropsychiatric disorders (43), such models focusing on early gestation highlight a specific window in which genes may be epigenetically reprogrammed to produce long-term changes in stress pathway development. Adult male mice exposed to early prenatal stress show expression and DNA methylation changes in CRF and GR (42,44). The temporal specificity reported in these studies supports early pregnancy as a vulnerable period, and the sex specificity determined in these animal models may provide insight into male-biased neurodevelopmental disorders such as autism or schizophrenia. Mechanistically, maternal glucocorticoids are likely to be involved in transmitting the maternal stress signal to the developing embryo. Prenatal glucocorticoid overexposure produces long-term changes in offspring cardiometabolic, neuroendocrine, and behavioral outcomes via tissue-specific effects on gene promoter epigenetic changes (45). The importance of the endocrine placenta as the intermediary tissue joining the maternal milieu and the developing embryo must also be considered to mechanistically define genes and antecedents involved in programming of neurodevelopmental disorders (as reviewed in [46–48]. Studies have also begun to address transgenerational outcomes attributed to levels of maternal care, diet, stress, or infection to identify specific genes associated with disease endophenotypes, thereby supporting a true epigenetic mode of transmission (49).

Rodent models of maternal immune activation have substantiated a role for infections in offspring disease risk and changes in cognitive and affective behaviors (50–52). Increased

levels of cytokines such as IL-6 have been associated with deficits of several behaviors and neurophysiologic functions, including prepulse inhibition and latent inhibition (53). Mice treated with IL-6 antibodies and IL-6 knockout mice do not manifest these deficits following maternal infection, supporting a role for inflammation during neurodevelopment in programming of behavioral deficits that may be endophenotypes of schizophrenia. The linkage between prenatal immune challenge and behavioral deficits in the offspring related to schizophrenia may be due to a disruption of GABA and glutamate function in limbic structures including the prefrontal cortex and hippocampus (54). The temporal specificity noted in these studies supports an important mechanistic contribution of developmental timing in determination of the long-term programming effects.

Programming Effects of Maternal Diet and Early Nutrition

Not surprisingly, maternal nutrition alone or in combination with other prenatal determinants has been identified as a likely factor involved in the programming of offspring disease risk (55). Recent epidemiological studies from the Dutch Hunger Winter and the 1959 to 1961 Chinese famines have provided convincing evidence that prenatal undernutrition increases the risk of schizophrenia twofold in adult life (56,57). A variety of scenarios may explain these outcomes, including epigenetic programming effects related to levels of nutrients and methyl donors such as choline or folic acid during development (58,59). Studies have begun to address the issue of epigenetic programming in schizophrenia risk by examining archived prenatal serum specimens for prospective biomarkers such as nutrient deficiency that might predict disease susceptibility. Examination of gene methylation changes associated with prenatal nutrition has revealed that individuals prenatally exposed to famine during the Dutch Hunger Winter showed reduced DNA methylation of the imprinted insulin-like growth factor 2 gene 6 decades later compared with unexposed same-sex siblings (60). This outcome was specific to a periconceptional exposure supporting the conclusion that very early development is a critical time point in programming of epigenetic marks that may determine disease risk.

Mechanistic studies using a variety of animal models have dissected the link between the perinatal nutritional state and the offspring's metabolic phenotype. As the organization of neural circuits controlling energy balance take shape during perinatal life, considerable attention has focused on the hypothalamus. The adipocyte hormone leptin plays a vital role in directing development of hypothalamic projections from the arcuate nucleus. Moreover, secretion of leptin during perinatal life changes in response to the nutritional environment and thus is poised to signal the developing brain regarding maternal overnutrition or undernutrition via distinct actions on two functionally divergent neuronal populations, the anorexigenic pro-opiomelanocortin and orexigenic neuropeptide Y neurons (61). Targets of these neurons, such as the paraventricular nucleus and lateral hypothalamus, contain several cell types that exert widespread regulatory actions on energy balance and are likely impacted by numerous hormonal and neurotrophic factors yet to be defined. Such studies have perhaps identified specific modes of neurodevelopmental programming whereby the wiring of the hypothalamus is determined through endocrine signals (62).

Equally intriguing is the possibility that perinatal nutritional cues influence growth, independent of adiposity, through central mechanisms that influence body length or height via epigenetic modifications of specific genes during early development (63). Maternal exposure to a high-fat diet in mice results in both significant body length increases and reduced insulin sensitivity that persist across at least two generations. The acquisition of this phenotype in the second generation is not attributable to altered intrauterine conditions or maternal feeding behavior, as both maternal and paternal lineages pass on the effect to the second generation, supporting a germline-based epigenetic manner of inheritance. Similarly,

a maternal low-protein diet affects offspring growth and food intake and recently was shown to disrupt the expression of dopamine-related molecules within the mesocorticolimbic circuitry and a number of dopamine-dependent reward-related behaviors (64,65). Epigenetic modification (DNA hypomethylation) and subsequent effects on target genes (overexpression) are potential mechanisms linking suboptimal prenatal environment and adverse behavioral outcome.

Epigenetic mechanisms that exert lasting effects on gene expression and can be heritable are a particularly intriguing target when examining links between the perinatal nutritional environment and offspring metabolic phenotype. For example, foods high in choline cause marked changes in DNA methylation, which, in turn, alter long-term gene expression. Choline deficiency induced during gestation produced alterations in histone methylation and subsequent changes in gene expression in mice (66). Pregnant dams fed choline-deficient diets during late gestation produced offspring with diminished progenitor cell proliferation and increased fetal hippocampus apoptosis, altered hippocampal angiogenesis, insensitivity to long-term potentiation as adults, and decremented visual-spatial and auditory memory. These changes in fetal brain development appeared to be mediated by epigenetic alterations such as maternal dietary choline-modulated DNA and histone methylation in the fetal hippocampus. Similarly, studies using changes in mouse coat color as a marker of dietary and nutrient influence on epigenetic regulation of the agouti locus document how relatively minor methylation changes can have a profound impact on gene expression (67).

Further mechanistic examination of maternal nutritional state effects on programming of offspring health has been modeled in paradigms including placental insufficiency and hypoxia. Using uterine artery ligation to model intrauterine growth retardation and examine offspring diabetes development, studies have highlighted specific alterations in histone acetylation, decreasing the expression of genes including pancreatic duodenal homeobox 1, a growth factor critical in pancreatic development (68–70). Recent observations suggesting that hormone receptor signaling pathways and genes that control expression of neurotrophic factors can be epigenetically regulated point to a promising avenue of future research.

What Does Sex Have to Do with It?

One area of emphasis that has not been well examined or discussed in early life programming is that of the role or involvement of sex in disease vulnerability, presentation, and outcome. Why do some neurodevelopmental disorders predominate in male subjects and others in female subjects? Numerous neurodevelopmental diseases exhibit such a sex bias: for example, women present with affective disorders at two to three times the rate of men, autism affects four times as many boys as girls, and the onset of schizophrenia and depression rises dramatically during adolescence when major sex differences in brain maturation occur (19). Therefore, elucidation of the mechanisms by which sex-specific susceptibility arises is likely to provide critical insight into disease etiology, leading to the identification of novel targets for therapeutic development across disease areas that are affected by a gene × environment influence. Although there are many factors that likely contribute to sex differences in disease predisposition, sex-specific responses to fetal antecedents occurring during sensitive windows of development may promote long-term programming effects that underlie such disease biases (71). Along these lines, structural brain volume analyses using magnetic resonance imaging in male and female patients with schizophrenia have confirmed a disruption of the normal sexual dimorphism of the brain (72), including the dimorphic ratio of orbitofrontal cortex to amygdala where male schizophrenic patients showed a feminization of these brain regions (73). Interestingly, the neurodevelopmental disorders schizophrenia and autism have been categorized as hypomasculinized and hypermasculinized, respectively, supporting potential involvement of

perturbations in the normal trajectory and maturation of the sexually dimorphic brain in disease etiology.

The developing brain is characterized by the combined and opposing forces of resiliency and vulnerability. The central factors important in resilience, ongoing neurogenesis, migration, myelination, differentiation, and synaptogenesis are the same processes subject to derailment, which can have enduring and devastating consequences. The complex interplay of genetics, early experience, and later environment underlies the weak but consistent heritability of numerous neurodevelopmental disorders. The developing brain is organized by developmental hormone exposure, with male subjects experiencing elevated androgens that drive masculinization, an active process affecting cell differentiation and connectivity. Estrogenic involvement in cell death and cell birth in the developing nervous system is a critical component in programming the sexually dimorphic brain (74,75). Recent evidence implicates epigenetic changes in the estrogen receptor gene promoter as a component of the lasting effects of developmental estradiol action (76). The variety of mechanisms evoked by estradiol provides numerous avenues for disruption of the active process of masculinization, which may contribute to the sex bias found in many neurodevelopmental disorders. Programming of important regulatory brain regions such as the hypothalamus via steroid hormone effects on cell migration patterns during early development may also contribute to sex differences in disease susceptibility (77).

Epigenetic Mechanisms for Stable Behavioral Modification

Studies in adult animal models have used molecular and pharmacological methodologies to identify potential genes and mechanisms involved in disease programming. For example, histone deacetylase (HDAC) inhibitors, which are thought to promote gene transcription, produce antidepressant-like effects in rodent models of chronic stress such as social defeat (78). Chronic exposure of inbred mice to social defeat stress induces long-lasting behavioral abnormalities that are reminiscent of depression and posttraumatic stress disorder and can be treated effectively with standard antidepressant medications. Interestingly, roughly one third of the inbred mice exposed to chronic social defeat stress are resilient to its deleterious consequences. Insight into the molecular basis of vulnerability versus resiliency and the reversal of symptoms in vulnerable animals with antidepressants has come from gene expression microarrays and chromatin immunoprecipitation-on-chip arrays, which respectively permit genome wide assessments of alterations in messenger RNAs and in chromatin modifications within brain regions of interest (78,79). These data illustrate that resilience is an active process, mediated by changes in gene expression and chromatin modifications unique to the resilient state. Moreover, they have revealed important overlap between the mechanisms of resilience and of antidepressant action, suggesting that antidepressants may work, in part, by inducing changes in gene expression that occur naturally in more resilient individuals. Such findings provide new avenues for the development of more effective antidepressant treatments.

In addition to being potential targets as antidepressants, HDACs have recently been identified as important regulators of the developmental switch controlling synapse maturation. Both histone deacetylase 1 and histone deacetylase 2 function during early synaptic development causing a robust facilitation of excitatory synapses with a modest increase in synapse numbers (80). Interestingly, these studies found that in adults, a decrease in histone deacetylase 2 levels alone was sufficient to decrease basal excitatory neurotransmission. These findings provide important information on an underlying intrinsic developmentally specific pathway and suggest that HDAC inhibitors as therapeutics may have vastly different outcomes during development than they would in the adult.

Conclusions

At the crossroads of the developing brain and the perturbations poised to promote any deviation from this norm may lay the programming events contributing to disease susceptibility or resistance. Studies aimed at this level afford us a great opportunity to define disease mechanisms and identify novel targets in therapy and prevention. The interaction of the clinical, epidemiological, and basic science communities is essential in evaluation of study outcomes and in defining future directions and needs. New mechanisms and models developed at the bench will inform clinicians as to potential markers and targets to be examined at the bedside, with novel clinical observations then characterized for underlying mechanisms in animal models. Highly innovative tools and techniques are continuously being developed with greater and greater depths of analyses that will, no doubt, in the near future identify an array of novel genes and epigenetic mechanisms involved in the development of neuropsychiatric diseases. It is crucial that as this fast-moving field progresses, conversations at all levels and across disease areas continue and forums for such dialogue continue to be encouraged and supported.

Acknowledgments

References

1. Insel TR, Cuthbert BN. Endophenotypes: Bridging genomic complexity and disorder heterogeneity. Biol Psychiatry. 2009; 66:988–989. [PubMed: 19900610]

2. Bird A. Perceptions of epigenetics. Nature. 2007; 447:396–398. [PubMed: 17522671]

3. Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P. Decoding the epigenetic language of neuronal plasticity. Neuron. 2008; 60:961–974. [PubMed: 19109904]

4. Franklin TB, Mansuy IM. Epigenetic inheritance in mammals: Evidence for the impact of adverse environmental effects. Neurobiol Dis. 2009; 39:61–65. [PubMed: 19931614]

5. Sweatt JD. Experience-dependent epigenetic modifications in the central nervous system. Biol Psychiatry. 2009; 65:191–197. [PubMed: 19006788]

6. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci. 2007; 8:355–367. [PubMed: 17453016]

7. Khashan AS, Abel KM, McNamee R, Pedersen MG, Webb RT, Baker PN, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry. 2008; 65:146–152. [PubMed: 18250252]

8. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatry. 2001; 58:1032–1037. [PubMed: 11695949]

9. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun. 2001; 15:411–420. [PubMed: 11782107]

10. Cannon TD, Rosso IM, Hollister JM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. Schizophr Bull. 2000; 26:351–366. [PubMed: 10885636]

11. Cannon TD, van Erp TG, Rosso IM, Huttunen M, Lonnqvist J, Pirkola T, et al. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry. 2002; 59:35–41. [PubMed: 11779280]

12. Hoek HW, Brown AS, Susser E. The Dutch famine and schizophrenia spectrum disorders. Soc Psychiatry Psychiatr Epidemiol. 1998; 33:373–379. [PubMed: 9708024]

13. Susser E, St Clair D, He L. Latent effects of prenatal malnutrition on adult health: The example of schizophrenia. Ann N Y Acad Sci. 2008; 1136:185–192. [PubMed: 18579882]

14. Zornberg GL, Buka SL, Tsuang MT. Hypoxic-ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: A 19-year longitudinal study. Am J Psychiatry. 2000; 157:196–202. [PubMed: 10671387]

15. Brown AS, Vinogradov S, Kremen WS, Poole JH, Deicken RF, Penner JD, et al. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. Am J Psychiatry. 2009; 166:683–690. [PubMed: 19369317]

16. Brown AS, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Penner JD, et al. Prenatal infection and cavum septum pellucidum in adult schizophrenia. Schizophr Res. 2009; 108:285–287. [PubMed: 19135339]

17. Goldstein JM. Sex, hormones and affective arousal circuitry dysfunction in schizophrenia. Horm Behav. 2006; 50:612–622. [PubMed: 16876167]

18. Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS Jr, et al. Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. Biol Psychiatry. 2007; 61:935–945. [PubMed: 17046727]

19. Bale TL. Neuroendocrine and immune influences on the CNS: It's a matter of sex. Neuron. 2009; 64:13–16. [PubMed: 19840541]

20. Goel N, Bale TL. Examining the intersection of sex and stress in modelling neuropsychiatric disorders. J Neuroendocrinol. 2009; 21:415–420. [PubMed: 19187468]

21. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. Arch Gen Psychiatry. 1997; 54:625–631. [PubMed: 9236546]

22. Van Os J, Jones PB. Early risk factors and adult person—environment relationships in affective disorder. Psychol Med. 1999; 29:1055–1067. [PubMed: 10576298]

23. Machon RA, Mednick SA, Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. Arch Gen Psychiatry. 1997; 54:322–328. [PubMed: 9107148]

24. Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM. Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944–45. Br J Psychiatry. 1995; 166:601–606. [PubMed: 7620744]

25. Brown AS, van Os J, Driessens C, Hoek HW, Susser ES. Further evidence of relation between prenatal famine and major affective disorder. Am J Psychiatry. 2000; 157:190–195. [PubMed: 10671386]

26. Goldstein JM, Jerram M, Abbs B, Whitfield-Gabrieli S, Makris N. Sex differences in stress response circuitry activation dependent on female hormonal cycle. J Neurosci. 2010; 30:431–438. [PubMed: 20071507]

27. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998; 14:245–258. [PubMed: 9635069]

28. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: Insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008; 33:693–710. [PubMed: 18602762]

29. Neigh GN, Gillespie CF, Nemeroff CB. The neurobiological toll of child abuse and neglect. Trauma Violence Abuse. 2009; 10:389–410. [PubMed: 19661133]

30. Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology. 2005; 30:2192–2204. [PubMed: 15920504]

31. Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, Nemeroff CB. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci U S A. 1996; 93:1619–1623. [PubMed: 8643680]

32. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. Mol Psychiatry. 2009; 14:954–958. [PubMed: 18957940]

33. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008; 299:1291–1305. [PubMed: 18349090]

34. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, et al. Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry. 2008; 65:190–200. [PubMed: 18250257]

35. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009; 12:342–348. [PubMed: 19234457]

36. Kendler KS. Anna-Monika-Prize paper. Major depression and the environment: A psychiatric genetic perspective. Pharmacopsychiatry. 1998; 31:5–9. [PubMed: 9524977]

37. Parker KJ, Buckmaster CL, Justus KR, Schatzberg AF, Lyons DM. Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. Biol Psychiatry. 2005; 57:848–855. [PubMed: 15820705]

38. Katz M, Liu C, Schaer M, Parker KJ, Ottet MC, Epps A, et al. Prefrontal plasticity and stress inoculation-induced resilience. Dev Neurosci. 2009; 31:293–299. [PubMed: 19546566]

39. Korosi A, Shanabrough M, McClelland S, Liu ZW, Borok E, Gao XB, et al. Early-life experience reduces excitation to stress-responsive hypothalamic neurons and reprograms the expression of corticotropin-releasing hormone. J Neurosci. 2010; 30:703–713. [PubMed: 20071535]

40. Brunson KL, Kramar E, Lin B, Chen Y, Colgin LL, Yanagihara TK, et al. Mechanisms of late-onset cognitive decline after early-life stress. J Neurosci. 2005; 25:9328–9338. [PubMed: 16221841]

41. Kapoor A, Leen J, Matthews SG. Molecular regulation of the hypothalamic-pituitary-adrenal axis in adult male guinea pigs after prenatal stress at different stages of gestation. J Physiol. 2008; 586:4317–4326. [PubMed: 18635650]

42. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci. 2008; 28:9055–9065. [PubMed: 18768700]

43. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002; 34:13–25. [PubMed: 11931738]

44. Nemeroff CB. New vistas in neuropeptide research in neuropsychiatry: Focus on corticotropin-releasing factor. Neuropsychopharmacology. 1992; 6:69–75. [PubMed: 1610487]

45. Seckl JR, Holmes MC. Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. Nat Clin Pract Endocrinol Metab. 2007; 3:479–488. [PubMed: 17515892]

46. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: Focus on the HPA axis and role of the placenta. Dev Neurosci. 2009; 31:285–292. [PubMed: 19546565]

47. Gheorghe CP, Goyal R, Mittal A, Longo LD. Gene expression in the placenta: Maternal stress and epigenetic responses. Int J Dev Biol. 2010; 54:507–523. [PubMed: 19876832]

48. Maltepe E, Bakardjiev AI, Fisher SJ. The placenta: Transcriptional, epigenetic, and physiological integration during development. J Clin Invest. 2010; 120:1016–1025. [PubMed: 20364099]

49. Fagiolini M, Jensen CL, Champagne FA. Epigenetic influences on brain development and plasticity. Curr Opin Neurobiol. 2009; 19:207–212. [PubMed: 19545993]

50. Bilbo SD, Newsum NJ, Sprunger DB, Watkins LR, Rudy JW, Maier SF. Differential effects of neonatal handling on early life infection-induced alterations in cognition in adulthood. Brain Behav Immun. 2007; 21:332–342. [PubMed: 17126527]

51. Bilbo SD, Rudy JW, Watkins LR, Maier SF. A behavioural characterization of neonatal infection-facilitated memory impairment in adult rats. Behav Brain Res. 2006; 169:39–47. [PubMed: 16413067]

52. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: A critical role for the immune system. Front Behav Neurosci. 2009; 3:14. [PubMed: 19738918]

53. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci. 2007; 27:10695–10702. [PubMed: 17913903]

54. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr Bull. 2009; 35:959–972. [PubMed: 18408229]

55. Gillman MW, Rifas-Shiman SL, Kleinman K, Oken E, Rich-Edwards JW, Taveras EM. Developmental origins of childhood overweight: Potential public health impact. Obesity. 2008; 16:1651–1656. [PubMed: 18451768]

56. Brown AS, Susser ES. Prenatal nutritional deficiency and risk of adult schizophrenia. Schizophr Bull. 2008; 34:1054–1063. [PubMed: 18682377]

57. Xu MQ, Sun WS, Liu BX, Feng GY, Yu L, Yang L, et al. Prenatal malnutrition and adult schizophrenia: Further evidence from the 1959–1961 Chinese famine. Schizophr Bull. 2009; 35:568–576. [PubMed: 19155344]

58. Zeisel SH. Genetic polymorphisms in methyl-group metabolism and epigenetics: Lessons from humans and mouse models. Brain Res. 2008; 1237:5–11. [PubMed: 18789905]

59. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, Lindemans J, Siebel C, Steegers EA, et al. Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. PLoS One. 2009; 4:e7845. [PubMed: 19924280]

60. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105:17046–17049. [PubMed: 18955703]

61. Simerly RB. Hypothalamic substrates of metabolic imprinting. Physiol Behav. 2008; 94:79–89. [PubMed: 18262209]

62. Tobet SA, Fox TO. Sex- and hormone-dependent antigen immunoreactivity in developing rat hypothalamus. Proc Natl Acad Sci U S A. 1989; 86:382–386. [PubMed: 2911582]

63. Dunn GA, Bale TL. Maternal high-fat diet promotes body length increases and insulin insensitivity in second-generation mice. Endocrinology. 2009; 150:4999–5009. [PubMed: 19819967]

64. Palmer AA, Brown AS, Keegan D, Siska LD, Susser E, Rotrosen J, Butler PD. Prenatal protein deprivation alters dopamine-mediated behaviors and dopaminergic and glutamatergic receptor binding. Brain Res. 2008; 1237:62–74. [PubMed: 18703024]

65. Zambrano E, Bautista CJ, Deas M, Martinez-Samayoa PM, Gonzalez-Zamorano M, Ledesma H, et al. A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. J Physiol. 2006; 571:221–230. [PubMed: 16339179]

66. Mehedint MG, Niculescu MD, Craciunescu CN, Zeisel SH. Choline deficiency alters global histone methylation and epigenetic marking at the Re1 site of the calbindin 1 gene. FASEB J. 2010; 24:184–195. [PubMed: 19752176]

67. Waterland RA, Jirtle RL. Transposable elements: Targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol. 2003; 23:5293–5300. [PubMed: 12861015]

68. Reid GJ, Flozak AS, Simmons RA. Placental expression of insulin-like growth factor receptor-1 and insulin receptor in the growth-restricted fetal rat. J Soc Gynecol Investig. 2002; 9:210–214.

69. Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. Diabetes. 2001; 50:2279–2286. [PubMed: 11574409]

70. Pinney SE, Simmons RA. Epigenetic mechanisms in the development of type 2 diabetes. Trends Endocrinol Metab. 2010; 21:223–229. [PubMed: 19864158]

71. Weinstock M. Gender differences in the effects of prenatal stress on brain development and behaviour. Neurochem Res. 2007; 32:1730–1740. [PubMed: 17406975]

72. Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia

assessed by magnetic resonance imaging. Arch Gen Psychiatry. 2002; 59:154–164. [PubMed: 11825137]

73. Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, et al. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol Psychiatry. 2004; 55:512–517. [PubMed: 15023579]

74. Zhang JM, Konkle AT, Zup SL, McCarthy MM. Impact of sex and hormones on new cells in the developing rat hippocampus: A novel source of sex dimorphism? Eur J Neurosci. 2008; 27:791–800. [PubMed: 18333959]

75. McCarthy MM. Estradiol and the developing brain. Physiol Rev. 2008; 88:91–134. [PubMed: 18195084]

76. McCarthy MM, Auger AP, Bale TL, De Vries GJ, Dunn GA, Forger NG, et al. The epigenetics of sex differences in the brain. J Neurosci. 2009; 29:12815–12823. [PubMed: 19828794]

77. Tobet S, Knoll JG, Hartshorn C, Aurand E, Stratton M, Kumar P, et al. Brain sex differences and hormone influences: A moving experience? J Neuroendocrinol. 2009; 21:387–392. [PubMed: 19207813]

78. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell. 2007; 131:391–404. [PubMed: 17956738]

79. Wilkinson MB, Xiao G, Kumar A, LaPlant Q, Renthal W, Sikder D, et al. Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. J Neurosci. 2009; 29:7820–7832. [PubMed: 19535594]

80. Akhtar MW, Raingo J, Nelson ED, Montgomery RL, Olson EN, Kavalali ET, Monteggia LM. Histone deacetylases 1 and 2 form a developmental switch that controls excitatory synapse maturation and function. J Neurosci. 2009; 29:8288–8297. [PubMed: 19553468]