

Stress In Utero: Prenatal Programming of Brain Plasticity and Cognition

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ABSTRACT

Animal studies confirm earlier anecdotal observations in humans to indicate that early life experience has a profound impact on adult behavior, years after the original experience has vanished. These studies also highlight the role of early life adversities in the shaping of a disordered brain. Evidence is accumulating to indicate that the epigenome, through which the environment regulates gene expression, is responsible for long-lasting effects of stress during pregnancy on brain and behavior. A possible differential effect of the environment on the epigenome may underlie the observation that only a small fraction of a population with similar genetic background deteriorates into mental disorders. Considerable progress has been made in the untangling of the epigenetic mechanisms that regulate emotional brain development. The present review focuses on the lasting effects of prenatal stress on brain plasticity and cognitive functions in human and rodent models. Although human studies stress the significance of early life experience in functional maturation, they lack the rigor inherent in controlled animal experiments. Furthermore, the analysis of molecular and cellular mechanisms affected by prenatal stress is possible only in experimental animals. The present review attempts to link human and animal studies while proposing molecular mechanisms that interfere with functional brain development.

Keywords: Cognitive impairments, Dendritic spines, Epigenetics, Prenatal stress, Synaptic plasticity

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Considerable evidence suggests a role of early life adversities in the shaping of the disordered brain. Prenatal stress (PS; including physical stress, infection, nutrition, hormonal, drug intake, and psychological stress) can have a lasting effect on the brain, depending on the timing and magnitude of exposure of the organism to the stressful stimulation (Figure 1). The diversity of early experiences may underlie the diversity of the responses to stress in adulthood, ranging from resilience to subsequent stressors to mental dysfunctions such as depression, post traumatic stress disorder, schizophrenia, and even neurodegenerative diseases.

Genetic predisposition, including animal strain, polymorphisms, and gender, are factors, which contribute to the vulnerability/resilience toward PS (1) (Figure 1). Behavioral, brain structural, and epigenetic consequences of PS may fluctuate across critical time windows of perinatal and peripubertal development. Thus, the time at which the behavioral and brain functions are analyzed is critical for detection of a PS effect. With respect to the mechanisms underlying vulnerability and resilience, that is, the capacity to withstand stress, there is a host of publications suggesting that vulnerability to develop a mental disorder or resilience is related to the presence of specific gene alleles (2). On the other hand, emerging evidence suggest that environmental factors also significantly contribute to vulnerability and/or resilience (Figure 2).

Recent reviews have addressed the impact of PS on endocrine functions and (re)programming of hypothalamic-

pituitary-adrenal (HPA) axis functions (3–6) in relation to emotional development and susceptibility to psychiatric disorders. The present review focuses on the lasting effects of PS on brain structure and physiology related to cognitive and executive functions in human and rodent models. Epigenetic and functional consequences of different types of stressors on different cognitive functions need to be compared in the juvenile and adult brain and in different brain areas, particularly in regions related to cognition, volition, and executive functions. Functional imaging of the human brain allows high resolution needed to correlate specific brain structures with cognitive functions (7). This system analysis should be complemented by well-controlled experimental studies in animal models which can zoom in to the cellular, molecular, and epigenetic levels.

Stress is not the only category of stimulus that has a prolonged impact on the adult brain. Early work by Wiesel and Hubel (8) indicated that some plastic functions of the brain are restricted to a specific period during development (critical period) and that the brain cannot maintain these plastic properties beyond this short period. One implication of these observations is that a restricted period during development determines its reactivity to the external world for the rest of its life. Recent studies attempt to prolong this critical period by drugs and behavioral manipulations (9–11). It is proposed that PS may use similar mechanisms, which modulate the on- or offset and duration of developmental critical periods, particularly with respect to limbic and prefrontal cortical regions (Figure 3).

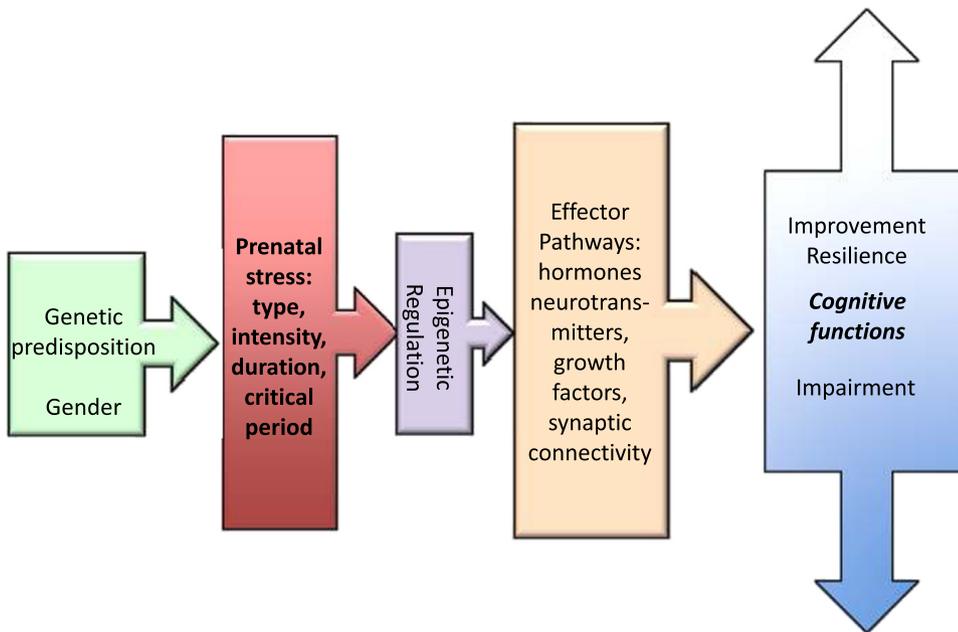


Figure 1. The overarching hypothesis outlined in this review. The nature and extent of epigenetic modifications and the neurostructural and cognitive outcome depend on the type, intensity, duration, and time windows (critical period) of the stressor.

HUMAN STUDIES

Human studies are important for the understanding of the lasting effects of PS on cognitive and executive functions and the comorbidity with the etiology of affective disorders. Still, human studies do not present a coherent picture of effects of PS and there is a surprising paucity of information on the predictability of the behavioral outcome. This may be due to inability to experimentally manipulate the timing, type,

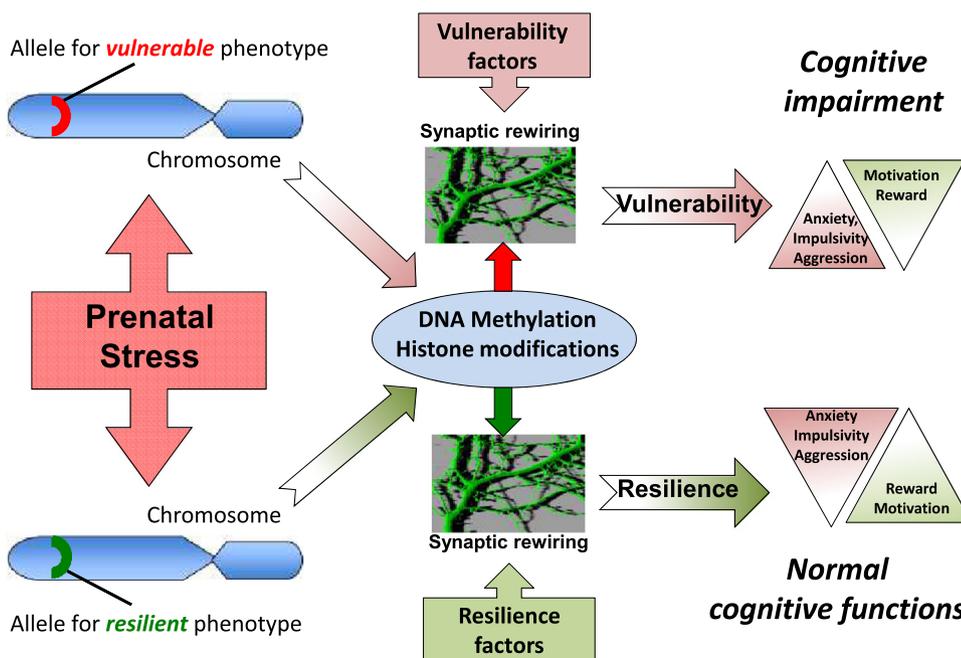
magnitude, and extent of the PS in humans (Table 1 and Supplement 1). Different studies used multiple definitions of stress and different assessment tools for PS, which may explain the differences in findings; for instance, some studies assessed major life events or anecdotal natural disaster (12–19), whereas others used daily hardship scores (20); some evaluated stress retrospectively (18,19) and others prospectively (17,21). Assessment of the magnitude of stress ranges

Genetic predisposition

Epigenetic changes

Behavioral outcome

Figure 2. An avalanche of events induced during prenatal stress and its impact on cognitive outcome. The genetic predisposition (gene alleles, gender) for stress vulnerability or stress resilience is enhanced or mitigated through prenatal stress-induced epigenetic modifications.



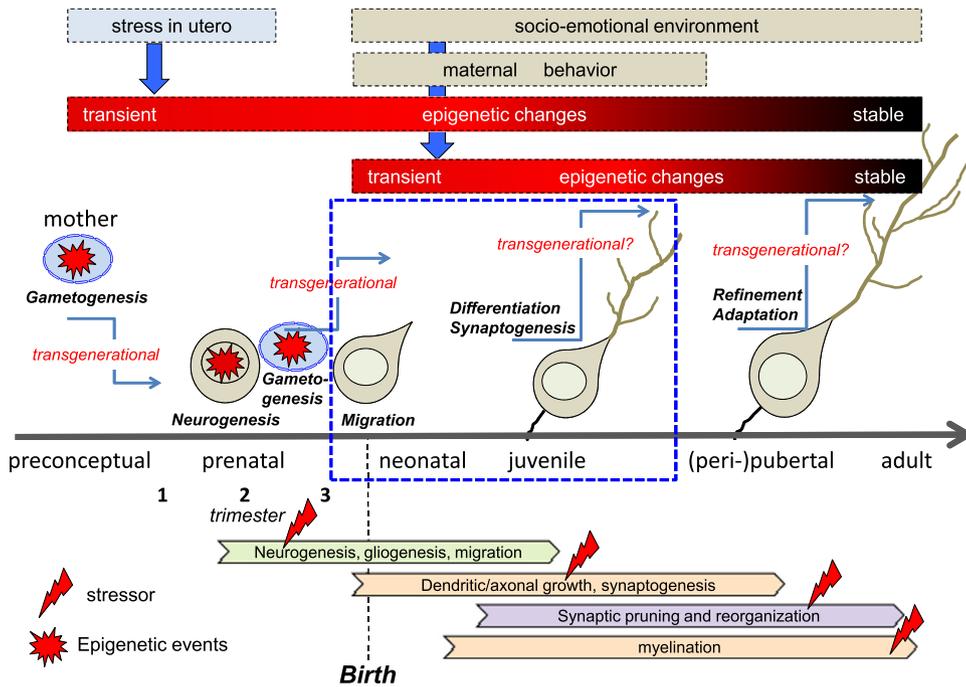


Figure 3. Transient and long-term prenatal stress-induced epigenetic and structural plasticity and potential mechanisms of transgenerational transmission. The center and bottom parts of the figure indicate that the brain is a shifting target for the exposure to environmental influences, including stress. Depending on the time window (“critical period”) in which the developing brain is exposed to stress, specific cellular events during brain development can be affected. The epigenetic changes (red bars, upper part of the figure) may occur only transiently (days/weeks) or may last for a lifetime. Even transient, relatively short epigenetic changes may have lasting effects on neuronal and synaptic development, depending on the critical time window during which they occur. In the upper part of the figure, two principal pathways for the transgenerational transmission of prenatal stress-induced structural and behavioral changes are shown, which are not mutually exclusive with respect to the long-term brain functional and behavioral outcome: On the one hand, stress in

utero may induce epigenetic changes in embryonic neural cells or their precursors (“epigenetic memory”), which interferes with ongoing developmental events such as neurogenesis, neuronal differentiation, and synaptic wiring patterns. On the other hand, stress exposure during pregnancy may alter maternal behavior of the mother (“behavioral memory”), which, together with the socioemotional environment during later critical developmental time windows (e.g., peripuberty), may induce postnatal neuronal epigenetic changes in the brain of her offspring (behavioral transmission). In addition, stress in utero may induce lasting epigenetic changes in embryonic gonadal (male and female) cells (blue cells), resulting in a genetic transmission of stress-induced changes. Finally, adult stress prior to pregnancy may induce epigenetic changes in the ova of the prospective mother, which after fertilization may be transmitted to the offspring and induce neuronal and behavioral changes (genetic transmission).

from questionnaires to measurement of cortisol in pregnant mothers. Nonetheless, most studies have demonstrated an association between PS and adverse pregnancy and birth outcomes, including effects on birth weight, length of gestation, and preterm birth (22–31). The outcome of PS is not always detrimental: Laplante *et al.* (32,33), for instance, found that after the ice storm in Canada, children of mothers with a moderate level of stress had actually better scores in language skills (Table 1).

A critical discussion of the most recent observations in the human studies is presented in Supplement 1 (17–52).

ANIMAL STUDIES

Systematic well-controlled experimental investigations using animal models, which mimic stress experiences during gestation in humans, are essential for understanding the epigenetic basis of long-term PS experience. In animals, PS is induced by the exposure of pregnant dams to repeated or single stressors during distinct gestational phases, with the intention of transferring this stress experience to the embryo in utero (48–52). One limitation in this research area, which makes direct comparisons between studies rather difficult, lies in the different PS paradigms used to stress animals. PS paradigms studied in animal models range from predictable stressor (same stressor across several days) to random

unpredictable variable stress. Stressors of different types (e.g., mental versus physical) and severity are applied, including restraint, exposure to a cold environment, food deprivation, prevention of sleep, swim stress, social stress (overcrowding), or exposure to loud noise (53).

Whereas most studies apply physical or psychological stressors, a few have assessed the impact of pharmacologically induced challenges during pregnancy (54). Immune challenge by using interleukin 1 β application during late pregnancy impaired cognitive performance in juvenile (postnatal day 28–30) male and female offspring (55). Dexamethasone injections during the last week of pregnancy impaired spatial memory in offspring (48,56), and prenatal corticosterone application impaired both the acquisition and recall of cue-conditioned fear extinction in males, which was paralleled by decreased glucocorticoid receptor (GR) protein levels in the medial prefrontal cortex (mPFC), hippocampus, and hypothalamus and decreased tyrosine hydroxylase levels in the locus coeruleus (57) (Table 2).

EFFECTS OF PRENATAL STRESS ON SYNAPTIC PLASTICITY

A U-shaped curve was originally proposed to illustrate the fact that moderate stress facilitates whereas severe stress impairs learning (58). In an attempt to extend this assertion to the

Table 1. Effects of Prenatal Stress on Cognitive Functions in Humans

Reference	Design	Independent/Dependent Variables (maternal and offspring assessments)	Sample Size (maternal-offspring dyads)	Main Findings
Lou <i>et al.</i> , 1994 (23)	Pro	Questionnaire at mid-pregnancy; newborn head circumference; Prechtl at 2W PN	120: 70 experienced moderate to severe stress, 50 control	Decreased head circumference and Prechtl score (126).
Maina, 2008 (26)	Pro	Mid gestation psychiatric evaluation. Fetal head size at 20 and 34EW	Psychiatric patients, 20, major stressful life event 20, control 40	No association between stress and fetal sonogram or head dimension
Sandman <i>et al.</i> , 1999 (25)	Pro	3 rd trimester placental CRH concentrations; fetal heart rate and uterine contractions in response to stimulation	33	Elevated placental CRH concentrations associated with responsiveness of the fetus to challenge
Buitelaar <i>et al.</i> , 2003 (27) Huiznik <i>et al.</i> , 2003 (28)	Pro	Daily turmoil and anxiety tests evaluate prenatal stress. Cortisol levels; Bayley scale evaluated infant development at ages 3 and 8 months	170 with no pregnancy or birth complications	Decreased attention, test-affectivity and goal-directedness. High cortisol in late pregnancy, lower Mental Developmental Index scores at 3M
Laplante <i>et al.</i> , 2004; 2008 (32,33)	Pro	PS questionnaire in reaction to an ice storm; perceived stress. Language development and intellect at age 2 and 5.5 Bayley Mental Scale	58 maternal-toddler pairs; 89 pairs in the later study	Objective PS associated with the intellect and language abilities. Timing of exposure had no effect In later moderate levels of stress enhance tests results
Gutteling <i>et al.</i> , 2006 (29)	Pro	Daily hassle and pregnancy-related anxiety tests salivary cortisol levels; cognitive function of children at the ages 5-8 using TOMAL test	112	Only life events measured during 15-17 gestational weeks was negatively associated with attention concentration
Bergman <i>et al.</i> , 2007 (34)	Retro	PS standardized questionnaires for anxiety, life events, social support and depression. Infants evaluated at 14-19 M using the Bayley scale	123	Negative association between number of prenatal maternal stressful life events and infants MDI, but not PDI score
Zhu <i>et al.</i> , 2014 (30)	Pro	Life events inventory at first trimester Infants evaluated at ages 15-19 months using the Bayley Mental Scale	152 women, 38 were exposed to severe life events during first trimester.	Lower MDI scores and impaired persistence and attention span
Schwabe <i>et al.</i> , 2012 (35)	Retro	Negative life events during pregnancy; memory performance, salivary cortisol and chronic stress were evaluated in adult offspring (mean age 24)	60 young adults were included: 19 were the prenatal stress group and 41 served as a comparison group	No association between maternal prenatal stress and learning performance, however there were differences in learning strategies between the groups
DiPietro <i>et al.</i> , 2006 (36)	Pro	Maternal stress, anxiety and depression-standardized questionnaire during prenatal and post partum period; infants at 2 years of age; Bayley scale	94	Prenatal anxiety and depression were associated with MDI and PDI score, however perceived stress was related to PDI only

2W, two weeks; 3M, three months of age; CRH, corticotropin-releasing hormone; EW, embryonic week; MDI, Mental Development Index of the Bayley scale; PDI, Psychomotor Developmental Index of the Bayley scale; PN, postnatal; Pro, prospective study; PS, prenatal stress; Retro, retrospective study; TOMAL, test of memory and learning.

functional brain network level, it was found that long-term potentiation (LTP) of reactivity to afferent stimulation is impaired by prior acute stress exposure (59). Interestingly, there is no indication for a U-shaped curve relating the magnitude of stress to an opposite effect on LTP (60,61). Because corticosterone is the main hormone released during stress, it was not surprising to find that corticosterone by itself reduced the ability to generate LTP, in brain slices (61). Subsequent studies proposed that corticosterone affects glutamate receptor distribution and kinetics (62,63). Corticosterone and stress affect other neurotransmitter systems, including GABA, as well as the expression of several peptides and growth factors (64,65).

Early studies of the effects of PS on LTP did not present a coherent picture. Setiawan *et al.* (66) could not find an effect of prenatal maternal exposure to glucocorticoids on LTP in hippocampal slices, whereas Yang *et al.* (67) and Yaka *et al.* (68) did find detrimental effects of PS on LTP and perhaps also on long-term depression in offspring rats. More recently Grigoryan and Segal (69) did not report an effect of PS on LTP but on the ability of isoproterenol to convert short-term potentiation into LTP.

In the search for mechanisms underlying PS-induced changes in synaptic circuitry, it is important to emphasize the fact that, depending on the brain region, the neurons whose further development is affected by PS are exposed to the stressor during different stages of neurodevelopment such as neurogenesis, migration, or differentiation (Figures 3 and 4A). This implies that stressed immature neurons generate a long-term "memory," which interferes with ongoing brain development for a much longer duration than that of the stressor. Thus, even a short stress experience can trigger an avalanche of molecular cascades (Figure 4) and thereby can dramatically affect brain development even after termination of the stressor.

PS causes elevation of corticosteroids, and most studies assume that corticosterone is the main trigger for long-term neuronal changes following stress. However, the contribution of other stress mediators such as monoamines should not be underestimated. Stress releases norepinephrine (NE) from fibers originating in the locus coeruleus (70), and long-term changes in monoaminergic neurotransmission have been reported following stress (71). Findings in primates indicate that chronic unpredictable stress during pregnancy has long-lasting effects on noradrenergic and dopaminergic activity and

Table 2. Brain Structural Changes After Prenatal Stress: Animal Models

Reference Study Year (ref)	Species (Strain)	Paradigm	Assessment/Gender/ Analyzed Brain Structure	Main Findings
Bock <i>et al.</i> , 2011 (77)	Rat (SD)	Variable stress: restraint 45 min E15+18; crowding (social stress) E16+19; forced swim E17+20	PND 23/♂, ♀/ hippocampus (CA1, CA3, DG)	CA1: ↑ spines only ♂ DG: ↑ spines, length, complexity ♂, ↓ spines, length, complexity ♀; CA3: ↓ length, complexity ♂, ♀
Murmu <i>et al.</i> , 2006 (82)	Rat (SD)	Variable Stress: Restraint E15+18; crowding (social stress) E16+19; forced swim E17+20	PND 23/♂, ♀/ mPFC, OFC	Sex-specific effects: mPFC + OFC ↓ spines ♂, ♀; mPFC + OFC ↓ length, complexity ♂
Muhammad <i>et al.</i> , 2011 (84)	Rat (LE)	Elevated platform 2 × 10 min/day E12-16	Adult/♂, ♀/ mPFC, OFC	↓ spines mPFC, no change OFC
Mychasiuk <i>et al.</i> , 2012 (83)	Rat (LE)	Elevated platform 2 × 10 min/day E12-16	weaning/♂, ♀/ mPFC, OFC	↑ spines mPFC + OFC
Xu 2013 (94)	Rat (SD)	Restraint, 3 × 45 min/day 2 groups: ML E8-21, L E15-21	PND 22/♂, ♀/ hippocampus	abnormal neurons and myelin sheets in ML and L; ↓ synaptophysin; ML more affected than L; ♂ greater impairments than ♀
Mychasiuk <i>et al.</i> , 2011 (83)	Rat (LE)	Mild: EP, 2 × 10 min/day E12-16 High: EP, 2 × 30 min/day E12-16	PND 21/♂, ♀/ hippocampus, frontal cortex	brain weight: ↓ mild ↓ high ♂ ↓ Mild ↑ high ♀
Suenaga <i>et al.</i> , 2012 (74)	Rat (SD)	Restraint, 3 × 45 min/day E13-19	10 weeks/♂, ♀/ hippocampus, mPFC	CA3, DG: ↓ length, complexity ♂ PL: ↓ complexity ♂ no effects in ♀
Jia <i>et al.</i> , 2010 (75)	Rat (SD)	Restraint, 3 × 45 min/day E14-20	PND 30/♀/hippocampus	CA3: ↓ length, complexity
Gutierrez-Rojas <i>et al.</i> , 2013 (85)	Mouse (CF-1)	Restraint, 3 × 45 min/day E15-21	PND 14, 21/♂/OFC PND23/♂/parietal Cx	↓ dendritic growth reduced by maternal exercise ↓ PND 14 apical length ↑ PND 21 apical length
Behan <i>et al.</i> , 2011 (89)	Mouse (Bl6)	Restraint, 3 × 45 min/day E13-17	PND 25/♂, ♀/hippocampus	↓ glia cell density ♀

This table provides a selective overview illustrating the variability of methods used for induction of prenatal stress and the different time points of assessment of the impact on the newborn (53). Bl6, C57BL/6 mouse strain; CF-1, CF-1 mouse strain; Cx, cortex; DG, dentate gyrus; E15+18, embryonic days 15 + 18; L, late period of pregnancy; LE, Long-Evans rats; ML, mid-to-late period of pregnancy; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PND, postnatal day; SD, Sprague Dawley rat.

on behavior in the offspring. Prenatally stressed monkeys had higher concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3,4-dihydroxyphenylacetic acid (a degradation product/metabolite of NE and dopamine, respectively) in cerebrospinal fluid, which was paralleled by behavioral changes including more time clinging to their surrogates and reduced locomotion and social play (46). Likewise, the modulating action of beta adrenergic receptors on the ability to generate LTP has been reported to change after PS (69). Because NE, 5-hydroxytryptamine (5-HT), and dopamine have been linked to neuronal maturation and functions in the brain, it is only logical to assume that even mild changes in monoamine regulation and functions may exert a lasting impact on neuronal development. To disentangle the contribution of every neurotransmitter/hormone requires the individual pharmacological manipulation of each system. This is especially important since some of the proposed drugs for dealing with PS are actually aimed at monoamines (62).

REGION-SPECIFIC STRUCTURAL ALTERATIONS

Increasing evidence reveals that the physiological and structural changes resulting from PS exposure do not affect brain development in a global manner. PS-induced neuronal and synaptic changes are highly region-specific, which may be related to the different maturity of sensory, prefrontal, and

limbic areas during stress exposure (Figure 3). On the structural level, the most dramatic changes are found in limbic and prefrontal cortical areas (i.e., those regions which are involved in cognitive and emotional functions). Studies in adult males revealed that repeated restrained stress during the second half or last trimester of pregnancy resulted in decreased dendritic length and complexity in the hippocampal CA1, CA3, and dentate gyrus (72–74). A number of studies using similar stress paradigms revealed that these structural changes are already detectable in neonatal offspring (75,76). Also, it was demonstrated that repeated variable stress during the last gestational trimester resulted in a sex-specific pattern of structural changes in the hippocampal formation of prepubertal rat offspring (6,77).

Structural plasticity in the hippocampus in response to PS is also revealed by a number of studies in rats and non-human primates showing a reduction in hippocampal neurogenesis (78–80). In this context, it is of particular interest that the effects on neurogenesis appear to depend on the genetic background of the stressed mother, because PS applied between days 5 and 20 of pregnancy resulted in reduced postnatal neurogenesis only in high anxiety but not in low anxiety rat strains (81). The importance of the genetic background has also been revealed in a comparative study of three rat strains, which differed in stress sensitivity. In that study, strain-specific changes in the expression of specific genes

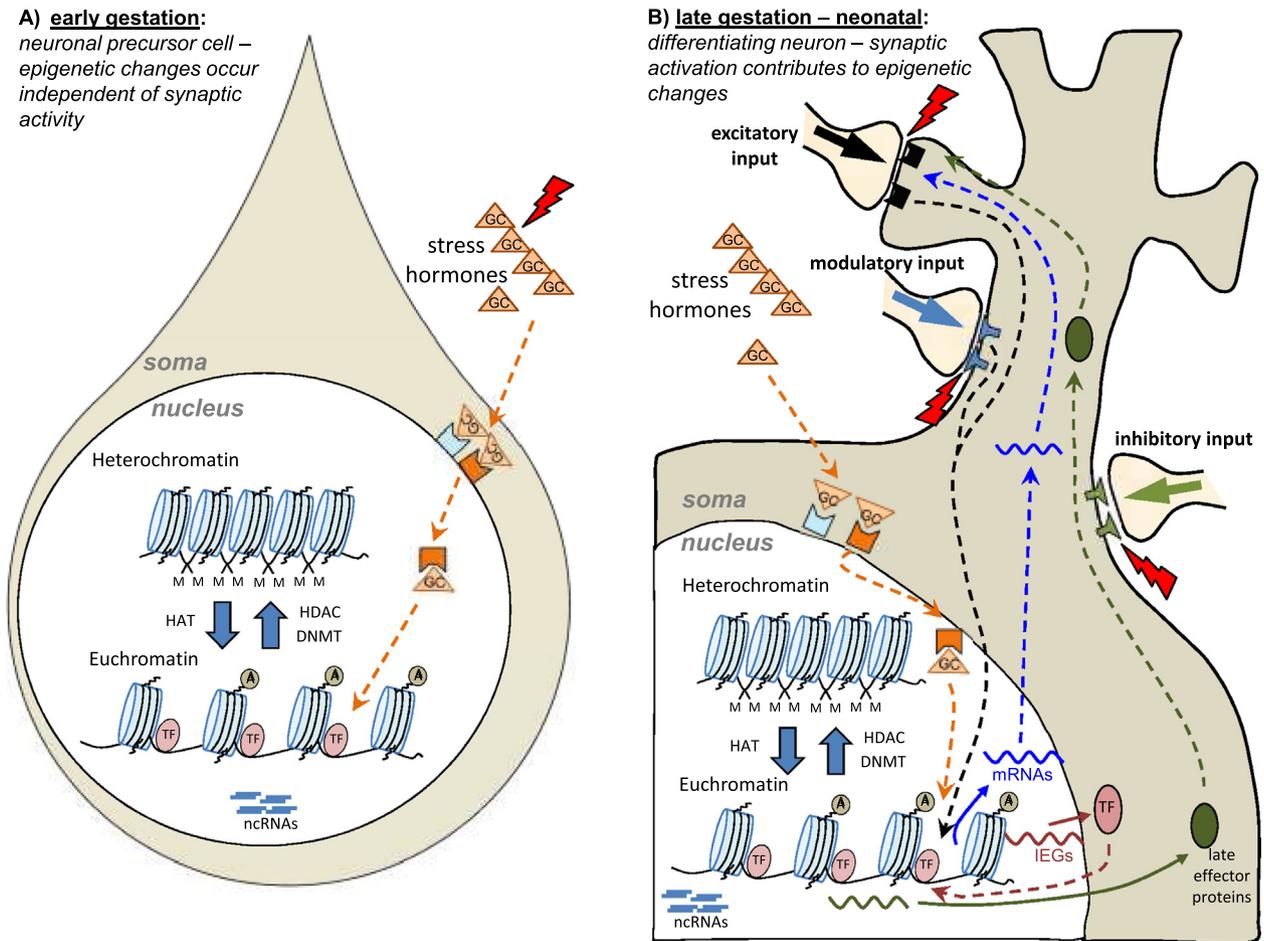


Figure 4. Events are shown in a magnified view within the blue hatched area outlined in Figure 3 to display the intracellular cascades induced by prenatal stress (red lightning symbol). **(A)** During early gestation, prenatal stress (PS)-induced epigenetic changes in neuronal precursor cells are predominantly mediated by hormonal mechanisms (i.e., stress hormones from the maternal organism), which in part can be transmitted via placental pathways. During this developmental time window, synaptic activity plays no or only a minor role because at this stage no or only few synaptic connections have been established in the prefrontal cortex, hypothalamus, and limbic system (i.e., the brain pathways which are most sensitive to stress). PS may induce stable epigenetic marks that, even if transient, can continuously interfere with the functional development of the affected neuron later in life. In addition, PS may interfere with preprogrammed epigenetic events (DNA methylation, histone acetylation/methylation) that are involved in the regulation (controlled silencing and activation) of developmental genes during differentiation of neuronal precursor cells. **(B)** During later gestational stages, the mechanisms underlying PS-induced epigenetic changes become more complex, because now, in addition to endocrine activation, PS-induced activation of excitatory (e.g., glutamate, acetylcholine, corticotropin-releasing factor), inhibitory (e.g., GABA), and modulatory (dopamine, serotonin, noradrenaline) systems within prefrontolimbic circuits also contribute to the induction of epigenetic changes. In turn, these epigenetic changes may interfere with stress-induced synaptic reorganization (Figure 3) and thereby mediate the structural and physiological adaptation of these neurons to future stressors. We speculate that, in the case of positive cognitive outcome, PS induces transient and/or long-lasting epigenetic modifications triggering adaptive processes that lead to resilience. In contrast, negative outcomes may be the result of epigenetic alterations mediating maladaptive processes (e.g., limited synaptic plasticity and thereby result in neuronal, synaptic, and mental retardation). We also propose that similar or the same cellular mechanisms can also be induced by therapeutic interventions to overcome or “rescue” the genetic predisposition for stress vulnerability. It is essential to gain a more detailed understanding of these events and the underlying mechanisms to create novel individually tailored protective and therapeutic interventions. A, acetyl groups; DNMT, DNA methyltransferase; GC, glucocorticoids; HAT, histone acetyltransferase; HDAC, histone deacetylase; IEGs, immediate early genes; M, methyl groups; ncRNAs, noncoding RNAs; TF, transcription factor.

were observed in response to prenatal repeated variable stressors (81).

Besides the stress-induced region-specific changes in the hippocampus, PS during the last gestational trimester has been shown to induce dendritic atrophy and decreased dendritic spine density in pyramidal neurons of the mPFC anterior cingulate and orbitofrontal cortex (OFC) (82). A “milder” form of PS at embryonic days 12-16 resulted in

increased spine densities in the mPFC and the OFC at weaning age (83,84), whereas stress in adulthood resulted in decreased spine densities in the mPFC and no changes in the OFC. A study in mice demonstrated decreased dendritic length in the OFC of 14-day-old offspring but an increase in dendritic length in the OFC of 21-day-old offspring of mothers exposed to restrained stress during the last gestational trimester (85).

SEX-SPECIFIC EFFECTS

A growing number of studies highlight sex-specific effects of PS. However, sex-bias is not consistent in terms of the direction and predictability of the outcome in the offspring. On the behavioral level, some studies report changes in offspring emotionality predominantly in males (87). In contrast, other studies report opposite findings, such as increased anxiety and depressive-like behavior predominantly in prenatally stressed females (52,87–89). It appears that the time-point of stress exposure during specific gestational periods provides a critical factor for the sex-specific behavioral outcomes, but this view requires further systematic investigations. It has been shown that stress experience during early gestational periods affects predominantly behavioral development of male offspring, whereas stress experience during late gestation appears to have stronger effects on female offspring behavior (86,90).

Further studies in rodents show that PS induces sex-specific alterations of neuronal structure and synaptic connectivity in a region-specific pattern (82,89,91–93). Repeated variable stress during the last gestational trimester resulted in a reduction of dendritic spine density in the mPFC and OFC in both males and females, whereas reduction of dendritic length and complexity was restricted to male offspring (82). Similarly, a decrease of dendritic complexity in the prelimbic cortex induced by repeated restrained stress during the last gestational trimester was found only in adult male offspring (74).

A somewhat different pattern was found for hippocampal neurons: Whereas, pyramidal dendritic length and complexity in CA1 and CA3 were reduced in both sexes, an increase of dendritic spine in the CA1 region was restricted to male offspring of mothers exposed to variable stressors during the last gestational trimester (87). The same study revealed that neurons in the dentate gyrus appeared to be affected in opposite directions in males and females. Although male offspring of PS rats ended up with larger and more complex dendrites and higher dendritic spine densities, their sisters displayed dendritic atrophy and lower spine density (91). The analysis of neurogenesis revealed a similar sex-specific impact of PS. Prenatal restrained stress during the second half or last week of pregnancy has been shown to increase cell death and reduce the survival rate of newborn cells in the offspring, effects that were predominant in male animals and mainly in the ventral hippocampus (92,93). A recent study reported a more pronounced rate of degenerating neurons in male offspring following prenatal restrained stress, an effect that was paralleled by abnormal ultrastructural appearance of hippocampal neurons and myelin sheaths (94). Sex-specific effects have also been described for glia, which were reduced only in female offspring of mouse mothers exposed to prenatal restrained stress (89).

PS INDUCES EPIGENETIC (RE-) PROGRAMMING

Epigenetic mechanisms represent a form of molecular memory that may modify brain function over extended periods of time. Perinatal stress experience can induce transient and permanent alterations in gene functions that result in long-term alterations of emotional and cognitive behaviors. A growing body of evidence indicates that epigenetic mechanisms

represent a crucial interface between early environmental influences and genetically programmed developmental processes in the brain leading to long-term behavioral and neuronal alterations later in life (6,95–103) (Figures 3 and 4).

Epigenetic mechanisms are defined as processes responsible for alterations in gene functions, which are heritable through both, mitosis and meiosis, but that cannot be explained by changes in the DNA sequence itself (104,105). At the molecular level, epigenetic mechanisms are biochemical modifications of the DNA and histone proteins, the major constituents of chromatin. They include direct modifications of the DNA (i.e., through DNA-methylation at CpG islands in promoter or coding regions and specific modifications of histone proteins such as acetylation, phosphorylation, and methylation around distinct gene loci). Overall, these mechanisms induce alterations in the accessibility of specific genes to transcription factors and, depending on the type of modification, this results in actively transcribed or silenced genes (105,106).

Evidence for epigenetic programming induced by PS was provided by a study in mice showing that stress experienced during early gestation induced alterations of DNA-methylation at corticotropin-releasing factor and GR gene promoters. These epigenetic changes resulted in long-term alterations in central corticotropin-releasing factor and GR expression related to elevated HPA axis responsiveness (86). Recent studies examined the effects of prenatal glucocorticoid treatment during late gestation in guinea pigs. These studies indicated organ-specific developmental trajectories of DNA-methylation in the fetus and newborn and alterations of these trajectories by intrauterine glucocorticoid exposure during pregnancy (107). These glucocorticoid-induced changes in DNA methylation have been shown to remain into adulthood and are even transmitted to the next generation. It was also shown that glucocorticoid treatment during pregnancy can modify the transcriptional and epigenetic machinery of the developing fetal hippocampus particularly associated with modified GR DNA-binding and DNA-methylation (107). A study in rats, applying mild or strong stress during mid-gestation demonstrated showed that PS induced region-specific changes of global DNA-methylation in male and female offspring. Whereas mild PS increased global DNA-methylation levels in the frontal cortex and hippocampus, the opposite, that is, a dramatic decrease was observed after strong PS (83). Distinct sex-dependent changes of gene expression in the hippocampus and frontal cortex were also reported in the offspring of rat mothers that were exposed to restraint stress during the last trimester of gestation (108). This study indicates once again that epigenetic regulation is affected differentially in male and female PS offspring. For example, the expression of HDAC4 was upregulated in the hippocampus of PS male offspring but downregulated in the frontal cortex of female offspring. Similarly, specific proteins that are involved in epigenetic regulation were downregulated in the frontal cortex only in PS female offspring (108).

In a recent study, a genome-wide DNA-methylation screening was performed in offspring of 5-HT (serotonin), transporter (HTT)-deficient mice subjected to prenatal restrained stress. The 5HTT gene (*5-HTT/SLC6A4*)-linked polymorphic region has been suggested to have a modulatory role in mediating

effects of early-life stress exposure on psychopathology. It was found that 5-HTT genotype, PS, and their interaction differentially affected the DNA-methylation signature of numerous genes (109).

A number of studies searched for epigenetic biomarkers of PS in the placenta. The placenta represents a critical barrier between and modulator of maternal and fetal physiology, and specifically also for the effects of maternal stress hormones. Studies in rats revealed that there were changes in the placental glucocorticoid barrier during pregnancy (110) and that PS interfered with the endocrine function of the fetoplacental unit (111). The barrier function of the placenta, which prevents the fetus from excess exposure to maternal glucocorticoids, is achieved through expression of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), an enzyme that converts glucocorticoids into inactive metabolites. PS has been shown to reduce expression and activity of 11 β -HSD2 (111,112), which may enhance the exposure of the fetus to maternal stress hormones and thereby promote developmental dysregulations. On the epigenetic level, PS-induced reduction of the 11 β -HSD2 gene expression was paralleled by increased DNA-methylation at specific CpG sites within the 11 β -HSD2 promoter (113). Another promising placental biomarker of maternal stress is represented by *O-linked-N-acetylglucosamine (O-GlcNAc) transferase (OGT)*, a gene linked to the X-chromosome and an important regulator for proteins involved in chromatin remodeling (114). Levels of OGT activity were lower in males and were further reduced by PS. The importance of placental OGT for developmental processes was further demonstrated in placenta-specific hemizygous OGT mice that displayed altered hypothalamic gene expression and epigenetic microRNA environment (114).

IMPACT OF PRENATAL STRESS ON COGNITIVE FUNCTIONS

Analysis of the behavioral consequences of PS is challenging because all the parameters listed above, including PS timing, duration, type, and severity, contribute to the behavioral outcome. In view of this heterogeneity, it is important to note that there is consensus that PS has detrimental effects on behavior in a sex-specific manner. Nevertheless, the question why males or females are more vulnerable or resilient and the contribution of hormonally mediated mechanisms remains open (115). Most studies analyze male individuals and report impaired spatial memory and territory discrimination after PS. Several studies indicate that learning deficits appear to be more prevalent in prenatally stressed males, whereas PS females display increased anxiety (51). A more pronounced impact of repeated variable PS on memory functions was found in males than in females (116); Males showed impaired memory for novel objects and spatial locations, whereas facilitated memory was observed for novel object/context pairing task. A more pronounced impact of repeated variable PS on memory functions was found in males than in females. Males showed impaired memory for novel objects and spatial locations, whereas facilitated memory was observed for novel object/context pairing task (117). Other studies reported that cognitive deficits are more pronounced in prenatally stressed females. PS (repeated restraint stress during the last third of

pregnancy) induced impaired object recognition and fear conditioning in females (89,118), which was paralleled by reduced hippocampal glial cells (90), that is, histological changes reminiscent of findings in the brain of depressed patients (89,119). Finally, there are studies with no clear sex-specific effects of PS exposure. PS (restraint stress) impaired both the young (postnatal day 30/31) male and female rats' memory retention in a passive avoidance test (120).

Only few studies addressed the concept of critical periods of PS exposure and the relevance for cognitive outcome. Comparing the cognitive consequences of PS during the first or second half of gestation in rats revealed that spatial learning was impaired only in offspring that were stressed during the first half of gestation (121).

A seminal question with respect to PS is: does stress during pregnancy alter the dam's maternal behavior (Figure 3), and, if so, does it have an additional impact on the behavioral outcome of her offspring? As the mother provides both, the genetic predisposition and the pre- and neonatal environment, associations between prenatal risk factors and offspring disorders may be attributable to confounding effects of genetic disposition that are shared by mother and offspring. This aspect is addressed in "adoption" and in vitro fertilization experiments following PS induction, but the picture emerging is far from clear. Some studies report that PS newborns raised by a nonstressed foster mother still develop the behavioral/electrophysiological symptoms. Repeated variable PS followed by cross-fostering to an unstressed dam resulted in impaired object recognition in both, males and females, paralleled by reduced spine density in the dorsal hippocampus (55). On the other hand, there is evidence that PS exposure and altered maternal care affects the brain and behavioral development of the offspring (122). PS pups elicited less maternal licking from unstressed foster dams than controls, and previously stressed dams licked unstressed foster pups less than controls (123). Cross-fostering experiments in rats exposed to pharmacological PS (124) revealed impaired working memory and reference spatial memory in unstressed and PS males and females when reared by a PS dam. Prenatal cross-fostering by in vitro fertilization revealed that the association between PS and offspring anxiety in related and unrelated dam-offspring groups appeared to be due to maternal anxiety/depression rather than PS, whereas the link between PS and offspring attention deficit hyperactivity disorder was observed only in related mother-offspring pairs and therefore was attributable to inherited factors (125). These findings indicate that stress exposure during pregnancy affects maternal behavior and emphasizes the importance of maternal care. Further experiments are needed to disentangle maternally inherited and environmental influences and their contribution to the transgenerational transmission of stress-related neuronal and behavioral traits.

CONCLUSIONS AND FUTURE DIRECTIONS

Much progress has been achieved in the understanding of the role of prenatal environment in the development of cognitive and emotional brain functions, but numerous questions remain to be addressed: for example, is there a dose-response relationship for PS; is mild stress during pregnancy beneficial

and can it induce resilience; at what point does PS become “toxic”; how do “good” and “bad” stressors reprogram brain and behavior; and, finally, in which way do males and females differ in their vulnerability/resilience toward PS? What are the epigenetic mechanisms through which PS exerts its lasting impact on brain and behavioral development? The mechanisms underlying the longevity and selectivity of the impact of PS need to be explored further, and more detailed research on sex-specific epigenetic brain structural and behavioral changes is the prerequisite for developing more efficient, individually tailored protective and therapeutic interventions for the treatment of stress-induced mental disorders. Finally, understanding the mechanisms mediating transgenerational programming of stress responses and pathologies will in the future help to explain the generational persistence of human behaviors in families and populations exposed to long-term adversity.

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