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Review

Neonatal maltreatment and brain development

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Abstract

The early childhood years are a period of rapid change in the brain. During early childhood, the brain forms and refines a complex network of connections through synaptogenesis, pruning, and myelination. The development of the brain is regulated by genes, which interact profoundly with early experience. There are sensitive periods for development of certain capabilities. These refer to critical windows of time in the developmental process when certain parts of the brain may be most susceptible to particular experiences during its development. Most functions of the human brain result from a complex interplay between genetic potential and appropriately timed experiences. Early postnatal experiences play a major role in shaping the functional capacity of the neural systems responsible for mediating our cognitive, emotional, social and physiological functions. When the necessary experiences are not provided at the optimal times, these neural systems do not develop in optimal ways. Adverse environments and experiences during the neonatal period can dramatically affect the development of the hypothalamic-pituitary-adrenal axis (HPA axis) that underlies adaptive behavioral responses. Early life stress programs HPA axis development and exerts profound effects on neural plasticity, with resultant long-term influences on neurobehavior. Animal studies show that not only are these neurobiological changes long lasting, but that they too can be passed on to future generations via non-genetic transmission. Olfactory, auditory, visual and tactile stimulation may serve as an important cue for brain development exerting specific effects on neuroendocrine systems regulating social and emotional behavior which may have consequences for subsequent generations of offspring.

Keywords

Maternal care, early postnatal experiences, brain development, epigenetics.

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Introduction

Newborn infants are the weakest and most vulnerable individuals in society. They absolutely depend on adults for survival and care during this most rapid growth and development period in human life. They cannot recognize danger, cannot escape, or defend themselves. A newborn baby is not fully aware of the existence of the self, lacks self-consciousness, hence does not value itself. The value of a newborn baby is given by parents, other relatives, family friends and society [1]. Part of the value of the newborn infant is merely instrumental (subjective) and based on its use. At a materialistic, economic level, newborn is valuable as a human resource (e.g. workforce, armed force) for the society. It is a psycho-social and spiritual experience for the families, such as "fulfillment of several desires" or "a helping hand for the family in the future". On the other hand, each creature resulting from the inherent existence in itself has also an intrinsic (objective) value independent of its instrumental value [2].

Historically, many societies have regarded newborn babies as having less value than adults. Infanticide and abandonment of the unwanted, weak, malformed, sick newborn infants were common and accepted practice in ancient Greek and Roman societies for maintaining the quality of the citizens. Abandonment, leaving the infant to die of exposure (i.e. hypothermia, hunger, thirst, or animal attack), was used as a frequent method of infanticide in human history. Many ancient cultures considered newborn infants disposable and valued them to be reared if they had a potential to become future citizens contributing to society. Aristotle (384-322 BC) supported a law that advocated the compulsory exposure of all malformed babies: "As to exposing or rearing the children born let there be a law that no deformed child shall be reared" [2]. Soranus of Ephesus, a Roman physician of the first and second centuries AD, wrote a chapter for midwives in his treatise on gynecology called *How to Recognize the Newborn That is Worth Rearing*, giving detailed clinical signs by which a healthy newborn could be distinguished from a malformed or diseased baby [3].

The common attitude to newborn infants, as a being of potential value in the future (instrumental value) in the ancient Greece and Roman Empire, had a radical change by the teaching of the *Old Testament* saying: "So God created man in his own image …" (*Genesis*, 1:27). Every human being was created with an intrinsic value as a unique expression of God's image. Therefore the deliberate destruction of any human life, including that of a newborn baby, was an affront to the dignity of God. "Whoever sheds the blood of man, by man shall his blood be shed; for in the image of God has God made man" (*Genesis*, 9:6).The Old Testament law also put a strong emphasis on the duty of the strong to protect the weak and the defenseless from abuse.

In pre-Islamic Arabia, killing of female infants was very common and very often the moment a female was born she was buried alive. Islam prohibits infanticide or killing of female infants. This is considered a serious crime of murder in *Holy Quran*: "When the infant girl buried alive is asked for what crime she was killed" (*Surah Al-Takvir*, 81:8-9). Islam not only prohibits female infanticide, but it forbids all types of infanticide, irrespective of whether the infant is a male or female. "Kill not your children for fear of want: We shall provide sustenance for them as well as for you. Verily the killing of them is a great sin" (*Surah Al-Isra*, 17:31).

Infanticide was disturbingly common in Victorian Britain and defined as a social crisis (1837-1901). Social changes resulted a rise in illegitimate children. Most of these illegitimate babies killed (nearly always by mothers) because of poverty and shame (society has turned a blind eye to baby killings, many times no penalty) [4]. The Foundling Hospitals opened in 1756 and were able to take in some of the illegitimate children to reduce the problem of killing and abandonment of newborn infants. A fundamental change in public attitude to newborn infant loss occurred in the 19th century. In the United States, the death of a newborn baby became unbearable to mothers and

accepted as the most painful death in the society. The pain of the mother who lost her baby created a "Social Concern" in the community. Mourning leaflets were prepared to help mothers how to overcome this "Empty Cradle" tragedy. In 1860, to reduce high newborn and child mortality in the society, a group of physicians specialized in care and unique medical needs of infants and young children initiated "Pediatrics". The nursery hospitals (Foundling Hospitals) with charitable and religious motives to take care of unwanted children were established [5].

Today, every baby, however small or sick, has intrinsic value as a unique human person, deserves the very best care, and protection from harm, which is a founding principle of Neonatology. Infanticide, neonaticide, and abandonment still occur in today's societies. Neonaticide usually refers to the killing of an infant shortly after birth, usually on the first day of life [6]. Infanticide is generally considered to be the murder of a child aged 1 day to 1 year [7]. It is very difficult to get accurate figures on the incidence of neonaticide and infanticide, since many cases are never discovered; official figures are likely to be an underestimate. The risk of neonaticide is at least 10 times greater than the rate of homicide during any other time in life [8].

Neonaticides are committed simply because the child is not wanted. The major perpetrator is usually the mother. Newborns are vulnerable for neonaticide when bonding and maternal attachment has not yet established. The stigma and shame of having an illegitimate, unwanted child are the primary reason for neonaticide in unmarried women today as it has been through the centuries. Certain maternal characteristics and circumstances have been identified that are associated with neonaticide including young maternal age, being unmarried, still living at home with parents, keeping the pregnancy secret from family and associates, no or less prenatal care, denial of pregnancy and surprise by childbirth as a coping mechanism [9]. The most common causes of death were asphyxiation/strangulation and drowning [10]. Unlike neonaticide, mothers who commit infanticide are usually older, married or living with a partner and psychiatric morbidity is believed to be more common among these mothers [9]. Recent studies show that neonaticidal mothers do not present any specific socio-demographic or evident psychopathological profile. More than half of the mothers already had other children; more than half were living with a partner [11].

Nonfatal maltreatment

Nonfatal maltreatment to newborn infants receives less attention. Substantiated nonfatal maltreatment rate is the highest for children younger than 1 year in the US (23.2 per 1,000 population aged < 1 year). Among infant victims, 32.7% are aged < 1 week, and 30.6% are aged less than 4 days. Neglect is the most common type of maltreatment among these infants (experienced by 68.5% of victims), only about 13% of the newborn cases are physical abuse [12].

Neglect is frequently referred to as a failure of a parent or other caregiver who is responsible for providing for the needs of children to the degree that the child's health, safety and wellbeing are threatened with harm. Neglect frequently occurs behind the scenes and usually goes unrecognized. Recent clinical research and animal studies have emphasized that adverse caregiving environments and experiences (neglect, postnatal lack of maternal care, etc.) in the early days of life can dramatically affect brain development that would cause adverse consequences throughout the lifetime and even in the offspring [13].

Experience dependent brain development

The development of human brain begins within the first few weeks after the conception and continues throughout lifespan. Starting from prenatal period brain development involves a scheduled and programmed process of neural proliferation, cell differentiation, and migration to the final location, axonal growth, apoptosis (cell death), myelination, and synaptic formation. Organization and regulation of brain development are influenced and orchestrated by chemical stimuli, hormones (thyroid, growth, steroid, sex hormones), neurotrophins, growth factors, and neurotransmitters (acetylcholine, norepinephrine, dopamine, serotonin, gamma-amino butyric acid, glutamate, aspartate), as the location and density of their receptors being developed timely during the developmental process. Accelerated growth and functional differentiation phases of the brain development create critical, sensitive periods that have greater susceptibility to environmental influences such as nutrients, exposure to toxic chemicals (including endocrine disrupting chemicals), radiation, infection, as well as love and care in interaction with genetic and epigenetic factors.

Majority of brain growth and development takes place after birth. The newborn brain at 2-4 weeks of age is approximately 36% the size of an adult brain. The brain grows to about 70% of its adult size by 1 year of age and to about 80% of adult size by age 2 years [14, 15]. Neuronal proliferation and migration to form various parts of the brain largely occurs during the prenatal period. Beginning at 6 weeks gestation, there is an ongoing and systematic neuronal proliferation, with extensive axonal migration and synapse formation [16]. Newborn infants have more than 100 billion neurons at birth ready to aid the growth and development of the newborn child, guaranteeing that the young brain will be capable of adapting to virtually any environment [17].

Neurons become differentiated as they migrate. When they reach their residence, they extend axon and dendrites to send and receive (respectively) information from other neurons forming numerous synaptic connections and neuronal networks. A single cell can have thousands of synapses on it: there are up to 60,000 synaptic points on a large cortical neuron and these neurons can connect with up to a hundred thousand other cells [18]. The brain processes information by forming networks of neurons. These neuronal connections and circuits appear as the infants try to identify what they see, process spoken language, or assess whether there is a threat or danger around, through sending messages to each other across synapses using electrical and chemical signals. These messages are the physical basis of learning and memory [19].

Newborn's brain requires environmental sensory stimuli for brain development

Whenever the infant sees an object, hears a voice or smells the breast milk, millions of neurons in the infant's brain interconnect through synapses that together serve for a specific function. When trillions of nerves and synapses get stronger through repeated experiences, structural links and pathways of neurons make up the "wiring" of the brain to allow all of the various brain areas to communicate and function together in a coordinated way. Unused or unconnected neurons undergo selective apoptosis later during postnatal life and die resulting in a loss of up to 50% of cortical neurons. The newborn brain seeks stimulation of particular kinds that will facilitate developing circuitry in the brain. Environmental stimulation (vision, hearing, smell, taste, touch) builds neuronal connections to form various synaptic formations. The synapses can change and adapt over time in response to experience, a characteristic called "synaptic plasticity". Therefore, newborn infants should receive necessary positive stimuli and have "expected experiences" during this critical time of brain organization [20].

Typical, expected, postnatal experience is necessary for the emergence of normal patterns of neocortical organization. When that input is lacking, brain areas will develop differently. Mother-infant attachment is a special form of emotional bond, and unique with respect to provide optimal stimulus for the normal brain development in newborn infants. Secure infant attachment is thought to be dependent on physical contact between the mother and infant. The main function of attachment is to maintain contact between the infant and the primary care provider to ensure infant survival, optimal growth and development. Mother-infant attachment is bidirectional and involves both maternal and offspring's neurobehavioral and chemosensory systems [21].

Cues from the infant for the attachment

Attachment starts in utero during the development of the fetal brain's sensory systems. The fetus is able to detect, learn, and retrieve the information from intrauterine environment and use it to adjust for the transition to postnatal life. At birth, the full-term infant is attracted to the mother's voice and smell, including the scent of amniotic fluid. This attraction to the mother's sensory stimuli is the first sign of the infant's attachment and bonding to the mother. This attachment begins during the last trimester of pregnancy, when auditory and olfactory systems become functional, allowing the fetus to learn about the mother's voice (filtered through tissues, bones), and odors through synaptic formations [22].

In the womb the fetus is suspended in amniotic fluid, causing the olfactory mucosa and its receptors to be bathed in waves of this fluid during infant swallowing and thumb sucking. Both amniotic fluid and milk originate in the mother's blood system, resulting in a chemically similar "aromatic signature" for the fetus and then the newborn. A mother's milk, sweat, and saliva contain some of the same odors as her amniotic fluid. Newborns can recognize the smell of their own amniotic fluid, their own mothers' distinctive scents based on earlier fetal exposure. If left quietly on the mother's abdomen immediate after birth, the newborn infant

makes motor movements (crawling) toward the odor of the mother's breast and nipple to latch on and suckle. Evidence of a "sensitive period" for olfactory sensory development has been defined to occur within the first hours after birth. Exposure to amniotic fluid and the mother's breast milk during this sensitive period later influences mother-infant relationships and breastfeeding outcomes. The infant can memorize the mother's individual odors associated with suckling. This type of odor memory is regulated by oxytocin. Oxytocin is released in the infant brain while suckling, and it acts on the olfactory bulb. In the olfactory bulb, oxytocin can enhance memory-related neural activation through long-term potentiation [23].

Infant's responses (such as suckling) to maternal multisensory stimuli elicit care giving behavior from the mother. Breastfeeding increases oxytocin in both the infant's brain and the mother's brain. Suckling stimulates the nerve endings in the nipple and areola, which signal pituitary gland in the mother's brain to release oxytocin hormone. Maternal oxytocin levels correlated with affectionate parenting behavior. Early pregnancy and postpartum maternal oxytocin levels are related to set of maternal bonding behaviors, including attachment-related thoughts, proximity seeking, tenderly look, "motherese" vocalizations, positive feelings towards the baby, and affectionate touch, frequent checking of the infant and adaptation to cues expressed by the infant. Oxytocin plays a fundamental role in establishing mother-infant bonding, and suckling in the first hours of life may contribute to reduced abandonment. Knowing the inverse associations between oxytocin and cortisol, high maternal cortisol level is also associated with a reduction in these maternal behaviors [24, 25].

Mother-infant bonding strongly influences offspring sociality later in life. Infant's central oxytocin pathways have important role in the development of social affiliation. Monkeys removed from their mother shortly after birth and raised in standard nursery conditions develop a syndrome characterized by decreased affiliation, increased aggression, and increased self-directed, repetitive behavior. Cerebrospinal fluid oxytocin in these nursery reared monkeys was significantly reduced compared to mother reared monkeys measured at 18, 24, and 36 months of age. Mother reared monkeys showed an increase in social contact, a reduction in abnormal repetitive behaviors, and a reduced cortisol response in the presence of a familiar companion [26]. A recent study also showed that social vocalization from the mother to the daughter stimulates oxytocin release and reduces stress responses in humans [27].

Basic attachment behaviors of the infant further improve as the infant learns more about maternal features through suckling, such as her face, her voice, her smell, taste of breast-milk, sense of her skin (skin-to-skin contact). During this early learning process, synaptic development occurs at an astounding rate. Synaptic density increases markedly and reaches far above adult levels during early postnatal period. An 8 months of age baby may have 1,000 trillion synapses in his brain. New synapses between cells are constantly being formed, while others are broken or pruned away. Pruning allows the brain to keep the connections that have a purpose, while eliminating those that are not working [28]. Neurons that are unable to adequately "connect" into an active neural network will die [29].

The human brain at birth has an overproduction of neurons, but most of the cells will go through apoptosis when the cells are about one week of age, unless infant receive stimuli and have expected experience for learning. If learning does occur, the new cells become incorporated into brain circuits used for learning [30]. The extreme lack of stimulation may result in fewer neuronal pathways available for learning. As the brain operates on the "use it or lose it" rule, when the child does not have expected stimuli in early life as it happens in neglect, an "over-pruning" of synaptic connections and apoptosis of unused neuronal cells can occur. Maternal neglect or stimulus deprivation lead lack of development in multiple brain regions such as language, tactile sensation and communication and the effect is not temporary: it can be observed much later in life. One survey found that youngsters who were adopted from Romanian orphanages in the early 1990s (with little contact with caregivers and little to no stimulation from their environment) had significantly smaller brains than the normal children, suggesting decreased brain development [31].

Maltreated but medically healthy children with the diagnosis of posttraumatic stress disorder (PTSD) also had smaller intracranial and cerebral volumes and larger ventricles, and cortical and prefrontal cortical cerebrospinal fluid volumes than matched controls [32]. These children excreted significantly greater amounts of urinary free cortisol and catecholamine concentrations than non-abused children [33]. Children and adolescents with PTSD had smaller total mid-

sagittal area of corpus callosum and the middle and posterior regions [32].

Early handling had significant effects on corpus callosum size in rats. Corpus callosum size was larger in adult male rats when maternal handling stimulation was provided immediate after birth than non-handled male controls [34]. Maternal care and handling resulted in larger and more regulated shaped corpus callosum in male but not female rats. Similar to animal studies, early traumatic experience also associated with decrease in corpus callosum size in abused/neglected children. Total corpus callosum area of the abused/neglected patients was 17% smaller than in control subjects and 11% smaller than in psychiatric children who had not been abused or neglected. Neglect had less effect on corpus callosum size in girls. Male children are more vulnerable to neglect and require more maternal stimulation for normal brain development [35].

Maternal behavior and programming of the hypothalamic-pituitary-adrenal axis during early life

Infant's neuronal pathways depend upon not only the presence but the nature of the total sensory experience of the child. Infants' brains grow and develop as they interact with their environment and learn how to function within it. When infants' cries bring food or comfort, they are strengthening the neuronal pathways that help them learn how to get their demands met, both physically and emotionally. But newborn infants who do not get responses to their cries, and babies whose cries are met with abuse, learn different lessons. Mothers with a history of child neglect typically show low sensitivity to the child's demands, and provide insufficient, inadequate or inappropriate care to fulfil the child's cognitive, emotional, educational, and physical protection needs. The mother does not recognize the clues expressed by the infant, does not respond to infant needs adequately, or shows unpredictable response, or inconsistent care, and prevents physical contact. When the infant lives in such threatening, chaotic, hostile environment, the child's brain activates the neuronal pathways for the fear response, the brain may be hyperalert for danger, because survival may depend on it. Chronic stimulation of the brain's fear response means that the regions of the brain involved in this response are frequently activated [36]. If this environment persists, the child's brain is focused on developing and strengthening its strategies meeting the child's day-today needs for survival, and other strategies and other parts of the brain such as the hippocampus, which is involved in cognition and memory, may not develop as fully. Chronic activation of the neuronal pathways involved in the fear response can also create permanent memories that shape the child's perception of the environment and automatically trigger that response without conscious thought [37].

Stress response pathways primarily involve the hypothalamic-pituitary-adrenal axis (HPA axis). Within the HPA pathways, external stressor leads to neuronal activation within the hypothalamus, which triggers the release of corticotrophin releasing factor (CRF) and vasopressin. CRF and vasopressin then stimulate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then stimulates the release of glucocorticoids (cortisol in humans and corticosterone in rodents) from the cortex of the adrenal gland. Cortisol released into the blood stream prime the body for "fight or flight" condition, and starts signaling cascades in several cell types, resulting in an increase in blood pressure, heart rate, and increase in blood sugar levels. Although these short-term effects of cortisol are often adaptive, exposure of the developing brain to severe and/or prolonged fear or stress can result in enduring hyperactivation of the HPA axis and results in excess glucocorticoids [38].

When the elevation of glucocorticoids remains for a prolonged period, it threatens neuronal viability and increases the risk of stress-related disorders. Early adverse life experiences, such as abuse, neglect, or loss of a parent, have an impact on cardio-metabolic risk profile and increase the risk of developing mental health disorders, including attention deficit/hyperactivity disorder, conduct disorders, anxiety, depression, suicide, drug abuse, and posttraumatic stress disorder [39].

The elevation of glucocorticoids is thought to be the main factor for programming of the fetal HPA axis during early life experience. To prevent the long-term exposure to glucocorticoids, there is a negative feedback loop that acts on the HPA axis involving glucocorticoid receptors (GRs) in the hippocampus [39]. The hippocampus is a region rich in GRs, detects high levels of cortisol and suppresses hypothalamus activation (self-limiting) to prevent excess cortisol production. Glucocorticoid stimulation of these receptors triggers an inhibition of hypothalamic and pituitary

release of CRF and ACTH, leading to reduced stimulation of glucocorticoid output from the adrenal gland. Activation of the HPA axis to psychological stressors involves the amygdala, whereas inhibition of the HPA response involves the hippocampus and medial prefrontal cortex [38].

Maintenance of low and stable levels of glucocorticoids is necessary during early life for normal growth and development of the central nervous system. Prolonged, severe, or unpredictable stress in early life can cause long term changes in brain areas that regulate stress, cognition, and emotion [36]. Animal research demonstrated the significant effects of maternal postpartum behavior on brain morphology and physiology, lifelong susceptibility for stress responsiveness, and the offspring's ultimate capacity for social affiliation [40]. The most intriguing question is how maternal care or early life stress affects long-term HPA responses to stress. Animal and human researches indicate epigenetic programming of the genes that are involved in the stress regulation cognition and emotion may play an important role in the long term effects of early life stress.

Epigenetic effects of early experiences

Studies have suggested a causal relationship between the quality of the caregiving environment and DNA methylation patterns of the brain. DNA methylation is a process that leads to gene silencing and prevents gene expression. Altered DNA methylation patterns acquired during development can seemingly be maintained throughout life. Quality of maternal care influences hypothalamic-pituitary-adrenal function (HPA axis) through epigenetic programming of GRs. Low levels of maternal care in rats were associated with increased methylation of the promoter region of the GR gene that is involved in the production of GRs in the hippocampus, contributing less receptor production and disrupted negative feedback of the HPA axis. Rat pups that received intensive tactile stimulation from their mother, such as licking and grooming (LG, a stimulation that can be mimicked by stroking with a soft paintbrush), show lower stress responses during their adulthood. Pups raised by higher LG mothers have decreased GR methylation corresponding to a higher level of GR expression in the hippocampus, and showed an enhanced negative feedback ability along the HPA axis of stress responses. Increased LG level is associated with increased hippocampal GR level in adulthood. Consistent with this finding, offspring of high LG dams seem to have enhanced negative feedback of the HPA response to stress and have reduced corticosterone and ACTH levels after a stressor [41]. GR gene regulation is also effected by prenatal stress. Prenatal stress is known to induce abnormal regulation of the HPA axis in offspring, resulting in higher basal levels of corticosteroids and differences in the activation of the HPA axis between prenatally stressed and control offspring after exposure to stress [42].

Depression during pregnancy is associated with increased maternal cortisol level [43]. Analysis of cord blood samples from infants born to mothers with elevated ratings of depression (using the Hamilton Depression Scale) during the third trimester of pregnancy indicates elevated levels of DNA methylation within the GR promoter region [44]. The degree of DNA methylation within the neonatal GR promoter was found to predict increased salivary cortisol levels in infants at 3 months of age. Prenatal effects on GR gene methylation may persist through adolescence. Children and adolescents (aged 10-19 years) born to women who had experienced stress in the form of intimate partner violence during pregnancy were found to have elevated GR gene methylation levels in whole blood samples [45].

In another study hippocampal expression of the GR gene *NR3C1* in the brains of 12 suicide cases, severely abused or neglected during their childhood, was significantly lower in postmortem studies and had increased methylation of the GR gene's promoter region, compared with other 12 suicide cases without such histories, and 12 controls who died accidentally and did not have such histories [46]. Furthermore in a group of 99 patients with bipolar disorder, those reporting different types of childhood maltreatment were more likely to have a high percentage of methylation in the promoter region of the GR gene (*NR3C1*) in blood lymphocytes, than those reporting no childhood trauma [47].

Besides hippocampus, mother-infant relations also cause epigenetic regulation of genes in the prefrontal cortex. The *BDNF* (brain-derived neurotrophic factor) gene codes for a protein that is essential in development and synaptic plasticity which is important for learning and memory and has been linked to several psychiatric disorders. *BDNF* promotes the survival of neurons by playing a role in the growth, maturation, and maintenance of these cells. Postnatal maltreatment predicts reduced

expression of *BDNF* in the prefrontal cortex in adulthood. Among non-abused offspring, there are very low levels of DNA methylation within the *BDNF* gene promoter, whereas abused offspring during the first 7 days of life have elevated levels of methylation of the *BDNF* gene in the prefrontal cortex. Epigenetic silencing of *BDNF* gene may account for the profound effect of childhood maltreatment and lead to heightened risk of psychopathology among abused children [48].

Non-genomic behavioral transmission

Studies also suggest that the consequences of early adverse experiences may not be limited to the individual experiencing adversity but may also be observed in the non-exposed offspring of these individuals. Pups that received higher levels and more intensive care from their mother in turn showed higher LG behavior toward their own offspring after delivery. The female rats that received higher LG behavior from the mother showed higher estrogen receptor (ER) expression in the same cells that also express oxytocin receptor. ER activation acts to induce oxytocin receptor expression; therefore, higher ER expression results in higher oxytocin receptor expression. The oxytocin system in the medial preoptic area of the hypothalamus (MPOA) is associated with the induction of maternal behavior. Therefore, these epigenetic modulations are plausible candidates to cause the individual differences in maternal behavior. Low levels of LG in female rat pups during the postnatal period have been found to be associated with decreased transcription of ER alpha (ERα) in the MPOA and elevated DNA methylation within the promoter region of this gene [49, 50].

Maternal effects on ERα DNA methylation and transcription may explain the effects of maternal care on maternal behavior of female offspring [51]. Cross-fostering studies confirm that these epigenetic effects on gene expression are associated with the quality of the care received in infancy. Offspring born to low LG dams then cross-fostered at birth to high LG dams have elevated levels of ERα in the MPOA whereas offspring born to high LG dams that are cross-fostered at birth to low LG dams have decreased levels of ERα [52]. Taken together, these findings indicate that variations in maternal care can serve as the basis for a non-genomic behavioral transmission of individual differences in stress reactivity across generations.

Conclusions

Healthy development of the neural systems which allows optimal social and emotional functioning depends upon attentive, nurturing caregiving in early life. Greater attention must be given to preventing maltreatment. Increasing maternal sensitivity to infant cues and promoting increased maternal contact with infants may also be an effective strategy for intervention. Skin-to-skin contact should be facilitated, supported, and encouraged as early and often as possible to initiate attachment relationship for appropriate synaptic formation and brain development and to prevent maltreatment. Especially for the hospitalized newborn infants, painful and unpredictable procedures, inconsistency with pain alleviating and soothing interventions, and separation from the regulating processes of the mother may contribute to early changes in brain with potential epigenetic consequences.

Declaration of interest

The Author declares that there is no conflict of interest.

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