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Early Life Stress: Consequences for the Development of the Brain

N. A. Malinovskaya, A. V. Morgun, O. L. Lopatina, Yu. A. Panina, V. V. Volkova, E. L. Gasymly, T. E. Taranushenko, and A. B. Salmina

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This literature review demonstrates the importance and consequences of early life stress for the development of the brain and its role in the formation of neurological and mental illnesses (particularly depression). The most dangerous is chronic early life stress during the neonatal period of development in the first days after birth, when the effects on the development of the brain, neuro-, synapto-, and glio-, and angiogenesis are the most stable. Among all the neuropsychological effects of early life stress, the most common are apparent as depressive disorders in humans and animals, and this constitutes a widely used model of experimental depression in rodents.

Keywords: early life stress, animal models, depression, neurogenesis, angiogenesis.

Introduction. The early period is the most important factor in forming the individual and influences health in adulthood throughout life [Huang, 2014]. Child abuse and neglect are serious social problems: thus, the USA alone has about 1.2 million cases per year [Schmidt et al., 2011]. Unhappiness in childhood is seen in about 40% of children in the west [Harrison and Baume, 2014]. In Russia, data from 2008 indicate that among the 28 million children living in the Russian Federation, 161,000 suffer from violence, 1914 died at the hands of their parents or legal guardians, and 2300 suffered grievous harm to health [Migunova, 2014]. There is a tendency to a gradual reduction in the number of minors suffering criminal abuse, from 104,100 in 2000 to 175,000 in 2005, 100,200 in 2010, 93,200 in 2011, 89,200 in 2012, and 89,100 in 2013 [Rosstat, 2000–2013], which may be related to data collection methods (only data on child abuse reported as crimes committed were included; in Russia, as opposed to the USA, emotional and psychological violence, emotional and physical neglect of the child's interests and needs are not recorded) [Krivoruchenko 2012; Migunova, 2014].

Mental disorders such as anxiety, depressive disorders, schizophrenia, and autism spectrum disorders in all the cases addressed here were related to early life stress. The neurobiological and psychosocial sequelae of early life stress are also associated with the development of other socially important diseases, particularly cardiovascular diseases, type 2 diabetes mellitus, and obesity [Harrison and Baune, 2014].

Early life stress (ELS) consists of the actions of moderate/severe external factors on the body in childhood or adolescence [Cohen et al., 2006]. People experiencing early life stress have such complaints as depression, low self-esteem, increased feelings of guilt, sleep disorders, lack of social skills, anger and hostility, and problems with self-care and self-control. The symptoms of people who have suffered early life stress can be divided into "internal" (anxiety, depression, physiological arousal, feelings of fear and guilt, withdrawal, denial, avoidance, reexperiencing, somatic complaints) and "external" (aggression, physical hyperactivity and attention deficit, delinquency, abnormal sexual behavior, prostitution] [Carr et al., 2013].

On the one hand, the actions of stress factors, especially long-lasting factors, on children and adolescents lead to serious adverse sequelae throughout life [Carr et al., 2013]

Research Institute of Molecular Medicine and Pathobiochemistry, Department of Biochemistry with Teaching in Medical, Pharmaceutical, and Toxicological Chemistry, Krasnoyarsk State Medical University, Ministry of Health of the Russian Federation, Krasnoyarsk, Russia; e-mail: reg.kgmu@gmail.com.

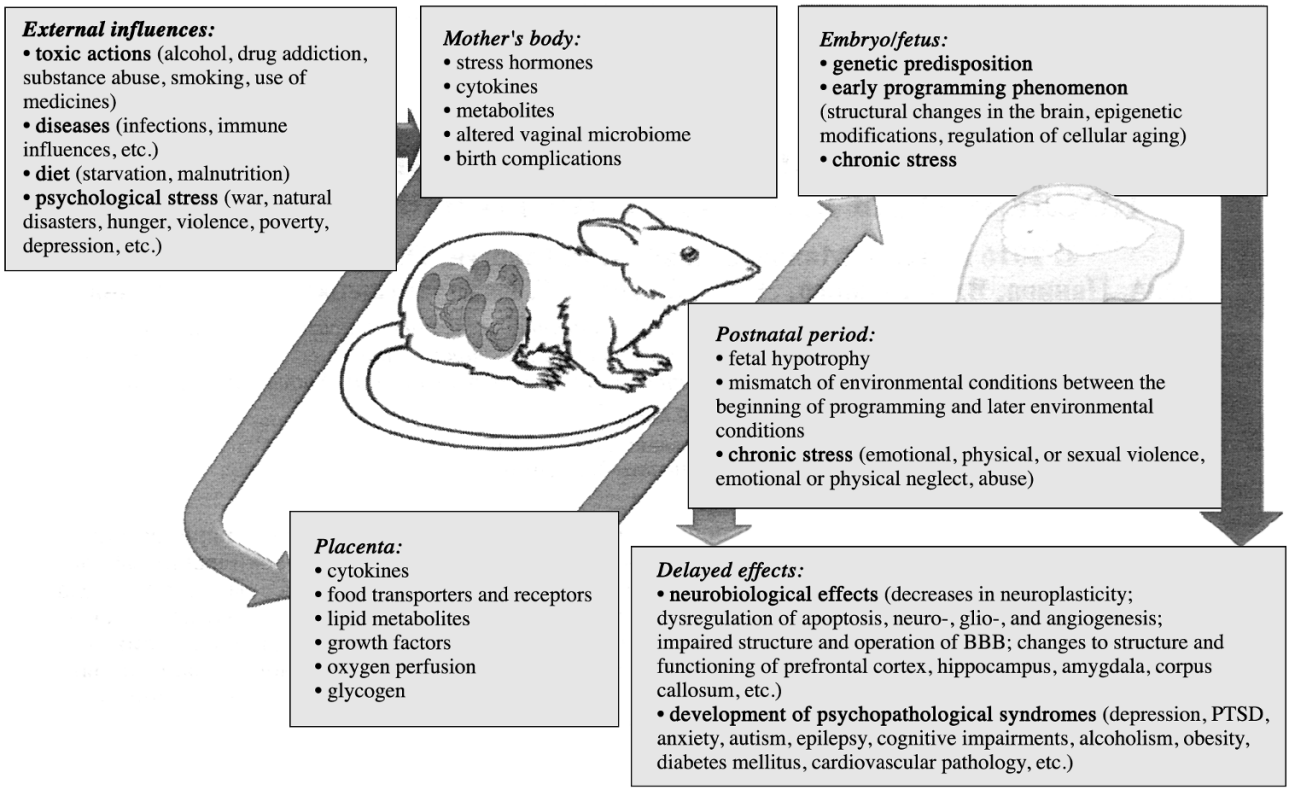

Fig. 1. Interaction between factors inducing perinatal early life stress and its main neurobiological effects (adapted from [Bale, 2015] with modifications).

(Fig. 1); for example, children subjected to ELS are at risk of developing such psychopathological syndromes as depression and depressive disorders and post-traumatic stress disorder [Nugent et al., 2011] and are at increased risk of developing obesity and cardiovascular disease [McEwen, 2008]. On the other hand, as demonstrated in model studies in monkeys, short-term discontinuous exposure to early life stress, conversely, can have positive effects, increasing the body's resistance to stress in adulthood [Lyons et al., 2010].

Factors Inducing the Development of Early Life Stress. ELS can be divided into prenatal, postnatal, and adolescent stress [Huang, 2014].

The actions of stress factors during the prenatal period can include toxic effects (drug addiction, substance abuse, alcoholism, or smoking in mothers, the actions of exogenous glucocorticoids, valproic acid, and other medications during pregnancy), maternal infection, and other maternal diseases, psychological stresses on the mother during pregnancy (war, natural disasters, violence, poverty, depression, etc.), and complications in childbirth [Huang, 2014]. Prenatal stress is regarded as a factor inducing premature childbirth or term birth with low birth weight. Low birth weight is a risk factor for the development of cardiovascular diseases, obesity, type 2 diabetes mellitus, and other diseases [McEwen, 2008].

Stress factors in the postnatal period of child development vary from external (natural disasters, war, violence, poverty, childhood illnesses) to family problems (family conflicts, loss of parents or one parent, rejection of the child, divorce, postnatal depression, lack of basic childcare, lack of food and shelter, lack of support or excessive criticism, etc.) [Carr et al., 2013; Cohen et al., 2006; Cohen et al., 2006; Molet et al., 2014], as well as toxic actions and medicines (e.g., exogenous glucocorticoids) on the child after birth [Huang, 2014].

Overall, the factors inducing early life stress in the postnatal period of development can be divided into groups such as emotional and psychological violence (any behavior affecting the wellbeing or integrity of the child), physical violence (risk of developing physical trauma), sexual abuse (sexual behavior of any kind involving the child), and neglect of the child's interests and needs. This latter can be subdivided into emotional (refusal to meet the basic emotional and psychological needs of the child) and physical neglect (lack of the necessary child care). "Economic violence" is also identified (in spending family money the parents do not satisfy the child's basic needs and may use the children themselves as a means of "economic bargaining chip" in divorce) [Carr et al., 2013; Migunova, 2014]. Thus, childhood experiences in an emotionally cold climate in the family increase the probability of poor physical and mental development in the adult state, while substance abuse in childhood enhances proinflammatory responses (increased levels of C-reactive protein are detected decades later) and is a risk factor for the development of depression, post-traumatic stress disorder, idiopathic chronic pain syndrome, substance abuse, antisocial behavior, obesity,

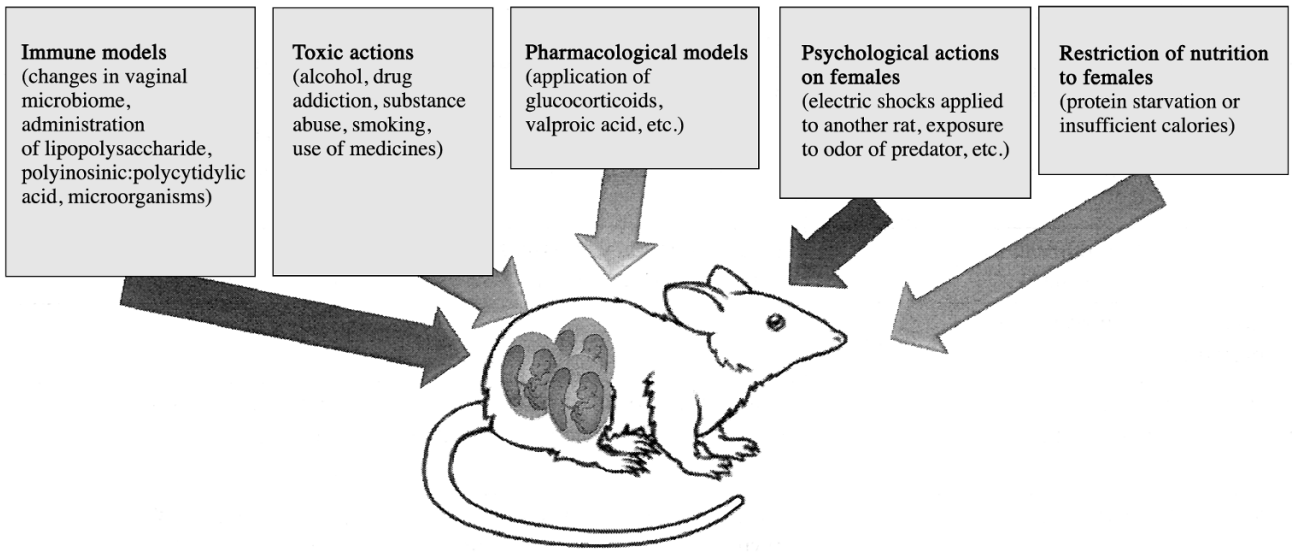

Fig. 2. Classification of models of prenatal early life stress in rodents.

diabetes mellitus, and cardiovascular diseases. Measures of the sequelae of low socioeconomic status in childhood include height and body weight and poor dental status. Chaos and poverty in home conditions constitute a key factor determining poor behavioral self-control, feelings of helplessness and psychological distress, obesity, and arterial hypertension, while social isolation in childhood increases the risk of cardiovascular diseases at later age [McEwen, 2008].

It is interesting that the nature and timing of outcomes on development of ELS are significantly dependent on the timing (the influences of adverse factors are most harmful during the critical periods of development of the brain periods of intense neurogenesis; data on the periods of brain development are shown in Table 1) and duration of action of traumatizing factors (short-term or long-term); they also depend on additional influences, in subsequent life, of factors modifying the course of ELS [Nugent et al., 2011].

Most of these stressors are reflected in models of early life stress in animals, mainly rodents (Tables 2, 3; Figs. 2, 3).

Animal Models of Early Life Stress. Despite the complexity of interpreting behavioral neurotesting data from rodents and extrapolating them to humans, animal models of early life stress are widely used: they provide the basis for our understanding of the mechanisms of development and physiological functioning of the brain in health and clarify how controlling actions during embryonic and postnatal development affect the subsequent functioning of the adult body; they also provide for identifying the characteristics and changes in physical and mental health in children subjected to ELS. At any stage of experiments in animal models, samples can be collected from both mothers and offspring. This type of study is absolutely impossible in humans because they are unethical [McEwen, 2008; Tarry-Adkins and Ozanne, 2011].

The term "early life stress" in rodents includes actions at the prebirth stage (the embryonic period of development), i.e., prenatal stress, at the onset of the postnatal period (from P0 to P21), at the beginning of the adolescent period (P21–P30), and postnatal stress [Schmidt, 2011].

The effects of early life stress in neurobiology depend on a multitude of factors: the nature of the stress, the period of development (for example, increases in brain plasticity during its rapid development at the beginning of the postnatal period, late childhood, and early youth make it more vulnerable to the actions of harmful factors), the duration of exposure to harmful factors, the age at which changes are assessed, and the species of rodent; these need to be borne in mind when designing experiments and interpreting study results [Harrision and Baune, 2014].

Models of prenatal stress (Table 2, Fig. 2) can include application of different toxic treatments to the female rodent during pregnancy (models using alcohol, narcotics, smoking, etc. have been used) [Hellemans et al., 2010; Loi et al., 2014], exposure of females to medicines at defined stages of pregnancy, pharmacological models (administration of valproic acid to female mice and rats at 12.5 days of embryonic development, which is not only a model of ELS, but also a widely accepted model of autism; administration of β-2-thienylalanine or glucocorticoids to female rats to provoke epileptogenesis in the offspring, etc.), models with changes to the immune system, (administration of lipopolysaccharide, polyinosinic:polycytidylic acid, borna disease virus, and others) [Bilbo and Schwarz, 2009], or vaginal microflora from pregnant females [Jasarevic et al., 2015], models of psychological actions on pregnant females in the last trimester of pregnancy (pregnant females were exposed to psychological stress three times daily for eight days in a row: rats were in social communication, with the

TABLE 1. Periods in Human and Rodent Development of Ontogeny and Extrapolation of Data on Age-Related Brain Development Scales in Rat Pups and Humans [Bayer et al., 1993; Clancy et al., 2007]

Period of development	Duration in humans	Duration in rodents (laboratory mice and rats)
Suckling age (neonatal)	Suckling period in humans (from birth to 1 year)	P1–P5
Suckling age (neonatal)		P6–P21
Puberty (infantile age)	Early childhood (1–3 years), preschool (3–7 years), school age (7–17 years)	Postnatal age P22–P50
Puberty (juvenile age)	End of puberty in girls by age 16–17 years, boys by age 17–18 years	Postnatal age P51–P120
Reproductive age (youth)	Reproductive period to age 55 years in women, to 60 years in men	Postnatal age 5–10 months
Reproductive age (adult)		11–18 months
Period of significant age-related changes (middle age)	Aging period: aged (60–76 years), elderly (75–89 years), and old (over 90 years)	Postnatal age 19–23 months
Period of significant age-related changes (aged)		Postnatal age 24–30 months
Period of significant age-related changes (old)		Postnatal age 31–40 months
Scale for extrapolation of data on brain development in experimental animals (rats) to humans, calibrated in terms of the intensity of neurogenesis in the limbic system and cortex:		
Differentiation of neuroepithelium and development of rudiments of forebrain, midbrain, and hindbrain. Further formation of telencephalon, diencephalon, midbrain, medulla oblongata, and hindbrain. Susceptibility is greatest during the period E12–E12.5 in rats, as compared with the period 4–5.2 weeks of intrauterine development	3.5–7 weeks (1–2 months) of intrauterine development in humans	Embryonic development days E11–E15
Intense development of the brain and its parts continues: the ventricles shrink, the basal ganglia form, there is intense development of the cortex and sensory organs, and motor and suckling reflexes form	7–15 weeks (2–4 months) of intrauterine development in humans	Embryonic development days E16–E20
Cortical development continues: the sleep-waking regime forms, the blink reflex appears, movement and facial expression coordination develop, there is intense neurogenesis in the limbic system and cortex	4–5 months of intrauterine development in humans	Embryonic development day E21 postnatal period P0
Cortical development continues but the intensity of neurogenesis in the limbic system and cortex gradually decreases	5–6 months of intrauterine development	Postnatal age P1
End of embryonic neurogenesis, beginning of postnatal neurogenesis	8–9 months of embryonic development and neonatal period	Postnatal age P7
Brain development continues, with "jumps" in neurogenesis with development of cognitive functions (in humans perception and awareness of the world; in rats, eye opening, development of olfactory discrimination, hearing)	3.5–7.2 months of postnatal development	Postnatal age P14
Brain development continues, gradual decrease in intensity of neurogenesis	16.5–24 months of postnatal development	Postnatal age P28
Completion of brain development	After 2 years	P72–P120

pregnant female separated from another rat, which received electric shocks, by a transparent partition) [Korosi et al.], and restriction of its nourishment, resulting in reduced fetal growth [Lajud and Torner, 2015].

Most models of postnatal stress (Table 2, Fig. 3) relate to the early period of development in rodents [Schmidt et al., 2011]. Models of ELS in animals are usually associated with deprivation of the mother-infant relationship (maternal deprivation models) or weaning of the infant from the mother for short periods (maternal separation models) [Harrison and Baune, 2014]. Short-term separation of animals from mothers (for 15–30 min) can occur in the wild, when the mother seeks food. Some females with low levels of care can spend even longer periods of time away from the offspring [Gutman and Nemeroff, 2002].

Models of discontinuous stress are the most widely used (otherwise, with excessively long-lasting separation of infants from mothers, they die from hypothermia and hunger) and are usually models reduced to separation of infants from mothers (separately or together) for 2–6 h per day from

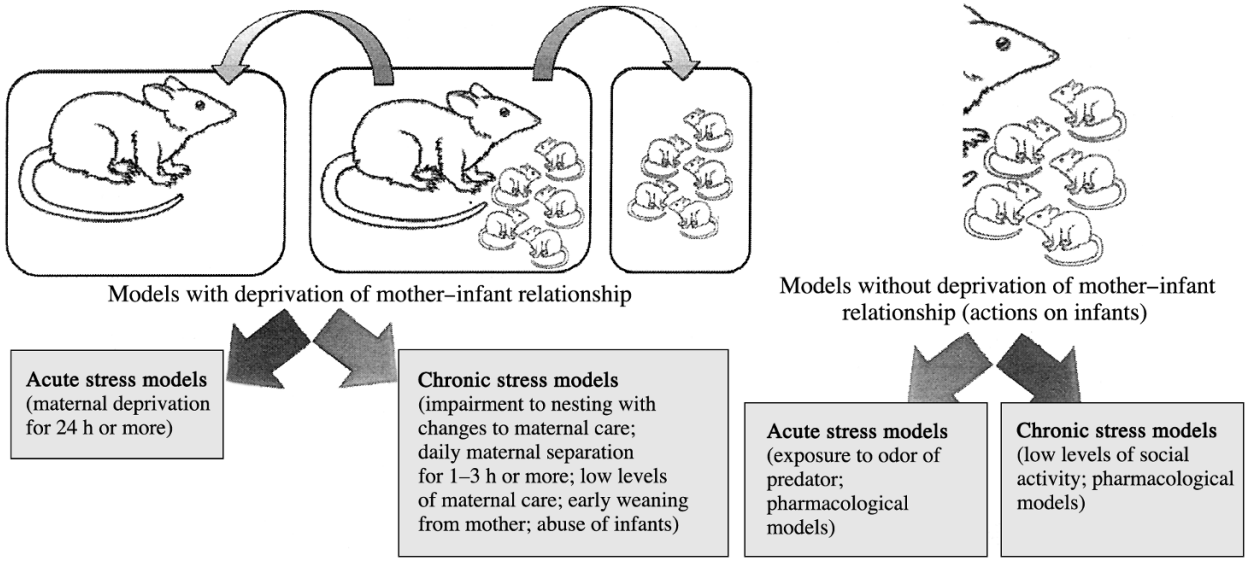

Fig. 3. Classification of models of postnatal early life stress in rodents.

postnatal day 14 or 21, though there are also models with other time periods. Maternal deprivation is the more severe form of early life stress and includes daily removal of infants from their mothers, starting from day 3 or day 9 of postnatal development or single separations for long periods of time 24 h. Another model of early life stress is that imposed by maternal aggression [Harrison and Baune, 2014].

As stress in humans is usually chronic, when babies and children grow in conditions of extreme poverty, hunger, war, or abuse, animal models of chronic stress have been developed, with restriction of litter and material for nest-building (modeling of poverty in humans). The original model was as follows: infant rodents of age P2–P9 from several litters were mixed together with females and transferred to a cage with a limited amount of litter and nest-building material: am aluminum mesh platform was positioned in the plastic cages 2.5 cm above the floor. Litter was added in a thin layer beneath the mesh floor and half a sheet of paper towel was provided as nest-building material. This volume of material is inadequate for constructing an adequate nest. Returning of infants aged P9 to the cage with sufficient material for a few hours led to normalization of the level of maternal care and a decreased level of stress hormones in the offspring [Molet et al., 2014].

The model using restriction of litter/nesting and fragmentary maternal care was initially developed for rats but was subsequently adapted for mice. The model demonstrated powerful predictable and reproducible effects in models in both types of rodent. Altered conditions in the cage lead to anomalous maternal care, when the sensory "information" provided to the infants by the mother and required for normal development of the nervous system is fragmentary and unstable (i.e., maternal care is fragmentary and chaotic), which creates a more chaotic than discontinuous "emotional" stress in the early period of life. Analysis of maternal behavior in this model demonstrated small or no changes in the total duration of maternal care or in the concrete aspects of care (care and licking,, care for sick infants, etc.). Nonetheless, maternal care in both rats and mice was discordant and unpredictable: each act of care was shorter and frequently interrupted and the sequence of "training" behavior was also unpredictable, which compares with parental neglect in humans [Molet et al., 2014].

In addition, some authors using this model (postnatal developmental days P1–P7, P3–P8, and P8–P12) have even noted mothers treating cubs roughly, which was used as a model of abuse and minimal maternal care [Molet et al., 2014]. Among the neurobiological changes demonstrated in this model are impairments to long-term potentiation and decreases in the number of dendritic spines in the hippocampus, the former correlating with learning and memory and the latter with synaptic plasticity; there were also increases in the basal plasma corticosterone level and a decrease in the expression of corticotropin-releasing hormone mRNA in the hypothalamus in adulthood [Harrison and Baune, 2014]. Signs are dominated by cognitive impairments induced by hippocampal dysfunction and emotional-behavioral disorders associated mainly with changes in the amygdala social inadequacy, depression, and anxiety [Molet et al., 2014].

A model of natural differences in maternal care of offspring as shown in Long Evans rats has been described during the postnatal period of development 0–8, in which females with high and low levels of care were identified. Prolonged, "high-quality" sensory "signals" from the mother are necessary for normal child development, as they influence the level of neural stem cells and the development of neurons and glial

TABLE 2. Neurobiological Effects of Prenatal Early Life Stress in Rodents

Model of ELS	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Immune models (administration of immune agents to pregnant females)					
Lipopolysaccharide	Mice	E8	Postnatal	Memory impairment impaired object recognition	Coyle et al., 2009
Polyinosinic:polycytidylic acid	Mice	E9	Postnatal	Impaired prepulse inhibition, latent inhibition, and spatial memory; changes in the expression of the GABA receptor A subunit; decreased density of D_1 receptors in prefrontal cortex	Meyer et al., 2005; Bilbo, Schwarz, 2009
Influenza or polyinosinic:polycytidylic acid	Mice	E9.5	Postnatal	Impaired latent inhibition and social behavior; impaired development of Purkinje cells	Shi et al., 2003
Polyinosinic:polycytidylic acid	Rats	E15	Postnatal	Impaired prepulse inhibition and latent inhibition	Wolff, Bilkey, 2008
Lipopolysaccharide	Rats	E15–E16	Postnatal	Decreased efficacy of neurogenesis in the dentate gyrus of the hippocampus at age P14; changes in synaptic transmission at age P20–25; decreased prepulse inhibition	Cui et al., 2009; Bilbo, Schwarz, 2009
Lipopolysaccharide	Rats	E15–E19	Postnatal	Decreased dopamine levels in the nucleus accumbens; impaired performance of open field test	Bakos et al., 2004
Polyinosinic:polycytidylic acid	Mice	E17	Postnatal	Potentiated motor activity and altered expression of NMDA receptor subunits	Meyer et al., 2009
Lipopolysaccharide	Rats	E17	Postnatal	Altered morphology of the hippocampus, decreased learning and memory	Golan et al., 2005
Lipopolysaccharide	Mice	E17	Postnatal	Increased anxiety and impaired social activity	Hava et al., 2006
Lipopolysaccharide	Rats	E18–19	Postnatal	Accelerated amphetamine-induced movement and increased acoustic startle	Fortier et al., 2004
Lipopolysaccharide	Rats	E1–21	Postnatal	Increased levels of serum cytokines and increased dopamine in the nucleus accumbens	Romero et al., 2007
Borna virus	Rats	P0	Postnatal	Locomotor hyperactivity, stereotypy, deficit of spatial memory and learning, hippocampal and cerebellar damage, cerebral atrophy; increases in cytokine levels in the brain, decreases in neurotrophic factor expression; glial activation	Hornig et al., 2001; Bilbo, Schwarz, 2009
Pharmacological models (drug treatment of pregnant females)					
β-2-thienylalanine	Mice	GD10–GD12	P23	Increases in seizure frequency (epileptogenesis)	Beck, Gavin, 1976
Dexamethasone (0.2 mg/kg/day) or betamethasone (0.2 mg/kg/day)	Rodents	GD15–GD18	P14–15	Prenatal administration of betamethasone increases the convulsion threshold in both models	Young et al., 2006; Huang, 2014
Hydrocortisone (2 × 10 mg/kg) or betamethasone (2 × 0.4 mg/kg)	Rodents	GD15	P15	Prenatal administration of betamethasone increases the convulsion threshold; hydrocortisone has no effect on susceptibility	Velíšek, 2011; Huang, 2014
Valproic acid (350 mg/kg)	Rats	E12.5	Postnatal	Decreased social interactions, appearance of stereotypical behavior, increased anxiety, impaired prepulse inhibition	Schneider et al., 2006; Kinast, 2013
Valproic acid (500 mg/kg)	Rats	E12.5	P1, P10, and P14	P1 and P14: decreased brain weight P10: anomalous nest-seeking behavior	Favre et al., 2013
	Mice	E12.5	P21	Males: decreased number of cells in the prefrontal and somatosensory cortex, deficit of social interactions	Hara et al., 2012

TABLE 2. Continued

Model of ELS	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Maternal restraint stress					
Stress due to maternal restraint, mid gestation (45 min, 3 times/day)	Rats	GD5–12	P14 and older	Prenatal stress, especially in the second half of pregnancy, increases sensitivity to impaired development in unborn offspring. Offspring are most vulnerable to impaired development during the infantile period, though some effects persist to adulthood, especially in males	Edwards et al., 2002; Huang, 2014
Stress due to maternal restraint, delayed (45 min, 3 times/day)	Rats	GD12–20			
Stress due to maternal restraint, mid gestation (45 min, 2 times/day)	Rats	GD15	P15	Prenatal stress significantly accelerates the onset and increase in number of NMDA-induced electrophysiological effects	Yem et al., 2012; Huang, 2014

cells. The offspring of rodents with increased maternal care showed improvements in cognitive functions and long-term resistance to developing stress and mental disorders. Decreases in maternal care can lead to adverse sequelae in the form of emotional and cognitive disorders [Molet et al., 2014]. While this model is widely used for studies of neuroendocrine regulation, hippocampal functions, and anxiety behavior, there are very few data of the development of the depressive phenotype [Schmidt et al., 2011].

There are also pharmacological models of ELS, which include the actions of various hormones, neurotransmitters/peptides, and inflammation mediators, the best studied of which are models based on postnatal administration of glucocorticoids and lipopolysaccharide [Schmidt et al., 2011] and models with low social activity in rodents (keeping infants in isolation), with early separation of infants from their mothers (at age P14–P15) or psychological stress (a model with exposure to the odor of a predator) [Lajud and Torner, 2015; Loi et al., 2014].

The actions of both prenatal and postnatal stress are known to involve a high risk of developing pathology in adulthood. However, pathology does not develop in all cases of early life stress either in humans or in animals, which may be associated with individual characteristics for example, different levels of glucocorticoid and/or cytokine release in the mother's body during pregnancy, species and strain differences in animals, the genetic characteristics of the developing fetus, retention and reprogramming of epigenetic profiles in offspring (not only in the first generation, but also in the second and third), and other differences which need to be considered in developing models of early life stress in animals [Boersma and Tamashiro, 2015].

The Early Programming Phenomenon. Many mental and neurological diseases are known to be inherited. At the same time, their development involves a role for environmental factors: thus, studies of monozygotic twins exposed to unfavorable factors in the uterus (particularly starvation) and use of animal models have shown that at the beginning of development, the environment, including the provision of nutrients during the embryonic period, plays an important role in disease development. The concept of the early programming of a life became widely accepted this holds that phenomena apparent at the very beginning of life can significantly influence its development many years later (by influencing cell function, as well as the metabolism of the body as a whole). The mechanisms of early reprogramming include: 1) long-term structural changes in the organs resulting from the actions of nonoptimum concentrations of the factors required in particular critical periods of development (for example, a consistent decrease in the mass of pancreatic β-cells in children with maternal protein starvation); 2) stable changes in epigenetic modifications (for example, methylation of DNA and modification of histone proteins), which lead to changes in gene expression (for example, some transcription factors undergo reprogrammed changes in gene expression via these mechanisms; 3) long-term actions on the regulation of cellular aging in children during development (for example, increases in oxidative stress can lead to damage to macromolecules, including DNA, especially in the telomere sequences, which significantly decreases the lifetime of the neonatal child [Tarry-Adkins and Ozanne, 2011].

According to the early programming concept, there are several models for the development of diseases in adults: the "fetal" model, proposed by Barker, suggests the existence of an interaction between fetal "malnutrition," low birth weight (less than 2500 g), and an increased risk of developing cardiovascular diseases, diabetes mellitus, and metabolic syndrome in later life. Low birth weight is regarded as the main indicator of altered fetal development in this model, though later studies showed that other factors are also relevant to the subsequent risk of developing diseases. Thus, the model was expanded to include events starting from conception and ending with the early postnatal period (the DOHaD model Developmental Origins of

TABLE 3. Neurobiological Effects of Postnatal Early Life Stress in Rodents

ELS model	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Models of acute stress					
Maternal deprivation 24 h	Rats, male and female	P3	P4, P21	P4: No changes in cell proliferation; P21 males show decreased cell proliferation but no effect on cell survival, increased cell differentiation; in females no effect on cell proliferation or survival, decreased cell differentiation	Oomen et al., 2009; Lajud, Torner, 2015
Maternal deprivation 24 h	Rodents, male	P3	10 weeks	Decreased cell proliferation, survival, and differentiation into neurons; decreased total number of cells in the caudal part of the dentate gyrus of the hippocampus; decreased learning ability but increased fear. Reduction of neurogenesis in the caudal but not rostral part of the dentate gyrus	Oomen et al., 2010; Lajud, Torner, 2015
Maternal deprivation 24 h	Rodents, female	P3	10 weeks	No significant differences between groups in cell proliferation, survival, or differentiation into neurons; however, decreased total number of cells and cell density	Oomen et al., 2011; Lajud, Torner, 2015
Maternal deprivation 24 h	Rats, male and female	P3	Juvenile, adult	24-h removal from mother accelerates neurogenesis to onset of puberty in males; decreased neurogenesis in females before puberty; effects drop off in adult rats	Loi et al., 2014
Maternal deprivation 24 h	Mice, male and female	P9	Adult	Decreased number of cells and cell proliferation in the dentate gyrus of the hippocampus; decreased anxiety	Fabricius et al., 2008; Lajud, Torner, 2015
Maternal deprivation 24 h	Rats, male and female	P4, P9, P18	Adult	Decreased number of synapses in hippocampal field CA1 and CA2; no differences between males and females	Karakas et al., 2009; Lajud, Torner, 2015
Acute exposure to odor of predator	Rats, male	P6	P7	Decreased cell proliferation in the dentate gyrus of the hippocampus	Tanapat et al., 1998; Lajud, Torner, 2015
Models of chronic stress					
Impaired nesting	Rats, Sprague–Dawley, males and females	P2–P9	P9	Disturbance of stress system: increased basal corticosterone, increased adrenal weight	Gilles et al., 1996; Molet et al., 2014
Impaired nesting	Rats, Long–Evans, males and females	P3–P8	P8	Disturbance of stress system: increased basal corticosterone; impaired cognitive and emotional functions (impaired social contact); accelerated neuronal activity in the amygdala	Raineki et al., 2010; Molet et al., 2014
Impaired nesting	Rats, Long–Evans, males and females	P8–P12	P20, P45	P20 and P45: deficit of social behavior P45: acceleration of neuron activity in the amygdala; depressive behavior	Raineki et al., 2012; Molet et al., 2014
Impaired nesting	Rats, Long–Evans, males and females	P1–P7	P7	Impaired cognitive and emotional functions (deficit of fixation of learning); impaired activity in the amygdala-locus ceruleus-olfactory bulb circuit	Moriceau et al., 2009; Molet et al., 2014
Impaired nesting	Rats, Wistar, males	P2–P9	P60	Impaired cognitive and emotional functions (anxiety behavior); increased plasma brain-derived neurotrophic factor (BDNF) level	Dalle Molle et al., 2012; Molet et al., 2014
Impaired nesting	Rats, Sprague–Dawley, males	P2–P9	10–12 months	Impaired cognitive and emotional functions (memory deficit but no anxiety); atrophy of dendrites of pyramidal cells in CA1 and increased dendrite branching in field CA3; defect of synaptic plasticity in CA3 and CA1 associated with physiological anomalies in CA3; increased corticotropin-releasing hormone in the hippocampus	Brunson et al., 2005; Molet et al., 2014

TABLE 3. Continued

ELS model	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Impaired nesting	Rats, Sprague–Dawley, males and females	P2–P9	P9	Changes in the brain: decreased expression of corticotropin-releasing hormone mRNA in the paraventricular nucleus of the hypothalamus, expression of mRNA for its type 1 receptor in CA1 and the dentate gyrus of the hippocampus; decrease in its binding with receptors in the hypophysis and decreased expression of the gene encoding glucocorticoid receptors in the paraventricular nucleus of the hypothalamus and frontal cortex	Avishai-Eliner et al., 2001; Molet et al., 2014
Impaired nesting	Mice, C57BL/6J, males and females	P2–P9	P9 and 4–8 months	P9: decreased expression of corticotropin-releasing hormone mRNA in the paraventricular nucleus of the hypothalamus at 4–8 months, males: impaired cognitive and emotional functions (memory impairment, but no anxiety); decreased expression of corticotropin-releasing hormone mRNA in the paraventricular nucleus of the hypothalamus. All observation periods: disturbance of the stress system: increased basal corticosterone level	Rice et al., 2008; Molet et al., 2014
Impaired nesting	Mice, C57BL/6J, males and females	P2–P9	P21, P29, P63	Impaired cognitive and emotional functions: increased anxiety (males at P21, P29, P63, and females at P63)	Malter Cohen et al., 2013; Molet et al., 2014
Impaired nesting	Mice, C57BL/6Jx 129Sv-SvJ, males and females	P2–P9	P18–P26, 8 weeks	P18–P26: positive regulation of corticotropin-releasing hormone mRNA expression in the paraventricular nucleus of the hypothalamus; impaired glutamate reuptake by astrocytes and increased glutamatergic loading on dorsomedial neurons of the hypothalamus. 8 weeks: positive regulation of corticotropin-releasing hormone mRNA expression in the paraventricular nucleus of the hypothalamus	Gunn et al., 2013; Molet et al., 2014
Impaired nesting	Mice, 129S2/SvxC57BL/6J, males	P2–P9	3 months and 6 months	3 months: impaired cognitive and emotional functions (increased anxiety); no changes in the expression of corticotropin-releasing hormone and vasopressin genes in the paraventricular nucleus of the hypothalamus or mineralocorticoid or glucocorticoid receptors in the hippocampus and corticotropin-releasing hormone in the central amygdala. 6 months: impaired cognitive and emotional functions (memory impairment); deficit of long-term potentiation and decreased density of dendritic spines in field CA1; decreased density of inhibitory synapses in CA1 and excitatory synapses in CA1 and CA3; decreased expression of neurexin 1 mRNA in hippocampal field CA3 and neuroligin in field CA1	Wang et al., 2012; Molet et al., 2014
Impaired nesting	Mice, male and female	P2–P9	P9, adult	P9: increased cell proliferation and differentiation and number of immature cells in the dentate gyrus of the hippocampus; mature animals: males show decreased cell survival of "adult" neurons, no significant difference in females	Naninck et al., 2014; Lajud, Torner, 2015
Chronic maternal separation (3 h)	Rodents, male	P1–P14	P60–P70	Decreased cell proliferation and decreased production of mature neurons in the dentate gyrus of the hippocampus. Decreased neurogenesis or no effect	Mirescu et al., 2004; Lajud, Torner, 2015
Chronic maternal separation (3 h)	Rodents, male and female	P2–P14	P56, 11 weeks	P56: dysfunction of hippocampal pyramidal cell neurogenesis a mechanism increasing susceptibility to epileptogenesis. 11 weeks: no effect on neurogenesis	Kumar et al., 2011; Huang, 2014
Chronic maternal separation (3 h)	Rats, male	P1–P14	±P80	Decreased cell proliferation; cell survival, and ability to differentiate unaltered. Impaired cognitive functions with no effect on anxiety, exploratory behavior, or social interactions. Decreased neurogenesis in the ventral but not the dorsal hippocampus or no effect	Hulshof et al., 2011; Lajud, Torner, 2015
Chronic maternal separation (3 h)	Rodents, male	P2–P14	P21, 2 and 15 months	Decreased neurogenesis at ages P21 and 15 months, no effect at age 2 months	Suri et al., 2013
Chronic maternal separation (3 h)	Rats	P2–14	P56	Early life stress in female rats increases susceptibility to epileptogenesis, increasing amygdalar arousability	Salzberg et al., 2007; Huang, 2014

TABLE 3. Continued

ELS model	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Chronic maternal separation (3 h)	Rats, male	P2–P21	Adult	Decreased cell proliferation and synaptic markers of plasticity (synaptophysin, NCAM, BDNF mRNA)	Aisa et al., 2009; Lajud, Torner, 2015
Chronic maternal separation (3 h)	Mice, male and female	P1–P14	Adult	No changes in cell proliferation in the dentate gyrus of the hippocampus, though decreased survival and differentiation into neurons; decreased numbers of dendritic spines and dendrite branching	Lajud, Torner, 2015
Chronic maternal separation (3 h)	Rats	P2–P14	Amygdalar arousal	Early life stress induces stable changes in hippocampus neurons, which may underlie increased susceptibility to limbic epileptogenesis	Ali et al., 2013; Huang, 2014
Chronic maternal separation (3 h)	Rats, male	P1–P14 or P1–P21	P14, P21, P28	Decreased proliferation in the rostral migration pathway in all experimental groups	Racekova et al., 2009; Lajud, Torner, 2015
Chronic maternal separation (3 h)	Rats, male and female	P2–P14	P15	Males decreased cell survival and differentiation, decreased density of cells in the dentate gyrus of the hippocampus, decreased depression-like behavior, but no effect on anxiety; females decreased cell survival in the dentate gyrus of the hippocampus	Lajud et al., 2012; Lajud, Torner, 2015
Chronic maternal separation (1 h)	Rodents	P4–5	P14	No signs of altered hippocampus activity	Edwards et al., 2002; Huang, 2014
Chronic maternal separation for 15 (control) or 360 (experimental) min	Rats, male	P1–P21	P22	Decreased number of neurons and decreased cell density in the dentate gyrus of the hippocampus as compared with controls	Lajud, Torner, 2015
Chronic maternal separation for 15 (control) or 360 (experimental) min	Rats, male	P2–P14	Adult	Decreased density of fibers in the oriens part of the striatum but no changes in the volume of the dentate gyrus of the hippocampus	Huot et al., 2002; Lajud, Torner, 2015
Chronic maternal separation for 360 min (P1–P14) and earlier weaning from mother (P15)	Rats, male	P1–P15	P28	Decreased cell survival and differentiation, decreased cell density in the dentate gyrus	Baek et al., 2011; Lajud, Torner, 2015
Early weaning from mother at age P15	Mice, male and female	P15	Adult	Males show decreased BDNF levels in the hippocampus and prefrontal cortex, decreased cell survival in the dentate gyrus of the hippocampus	Kikusui, Mori, 2009; Lajud, Torner, 2015
Early weaning from mother at age P14 and subsequent isolation	Rats, male	P14	P35	Decreased cell proliferation in the dentate gyrus	Baek et al., 2012; Lajud, Torner, 2015
Low maternal care in genetic line E1	Mice, strain E1 (a model of epilepsy)	P2–21	P80–90	Early life stress increases the sensitivity of E1 mice to convulsions in adulthood	Orefice, Heinrichs, 2008; Huang, 2014
Natural maternal care (high or low)	Rats, male	Postnatal period	Adults	Decreased dendrite density in offspring from mothers with low maternal care	Bagot et al., 2009; Lajud, Torner, 2015
Pharmacological models					
Lipopolysaccharide	Rats	P3 and P5	Postnatal	Increased hypothalamo-hypophyseal-adrenal reactions to stress and exaggerated startle; decreased stress-induced production of antibodies and increased restlessness; decreased effects of corticosterone; decreased adjuvant-induced arthritis; increased behavioral sensitization to dopamine agonist	Shanks et al., 2000; Bilbo, Schwarz, 2009

TABLE 3. Continued

ELS model	Rodent species, strain, gender	Stress period	Observation period	Neurobiological effects	Authors describing models
Lipopolysaccharide	Mice	P4–P5	Postnatal	Impaired active avoidance; decreased LPS-induced central level of IL-1β mRNA	Kohman et al., 2008; Bilbo, Schwarz, 2009
Lipopolysaccharide	Rats	P14	Postnatal	Decreased hypothalamic cyclooxygenase type 2 and LPS fever; altered expression of NMDA receptor subunits	Boisse et al., 2005; Bilbo, Schwarz, 2009
Models with combined pre- and postnatal stress					
Prenatal exposure to nicotine (GD7–GD21) + chronic maternal separation (P2–P21)	Rats, male and female	GD7–GD21 and P2–P21	P14	Increased numbers of pyramidal neurons in hippocampal field CA1, decreased number of granule neurons in thank you dentate gyrus of the hippocampus, inhibition of neurogenesis	Wang et al., 2013; Lajud, Torner, 2015

Health and Disease) for example, epigenetic programming, the distribution and metabolic activity of cells, and the development of the endocrine system vary depending on the time, type, dose, and duration of action of various factors in the process of early human development (in the first 1000 days of life). This was the period with the greatest level of developmental plasticity, suggesting the ability to mount adaptive reactions to future environmental conditions, increasing the chances of survival and abandonment of the offspring. Development is a process during which the body is not only able to undergo changes in response to ongoing environmental conditions, but can also receive information relating to potential future environmental conditions and adapt to them. The early periods of fetal development and early childhood (with that highest level of plasticity in the development of the body) give some notion of the most likely deviations in the future. Thus, the role of hormonal imprinting (the role of hormonal signals acting during pregnancy or the beginning of postnatal development which can alter the sensitivity of particular target tissues, via changes in the expression of receptors for these hormones in further development) has been demonstrated. For humans, an additional period of biological programming is present at the beginning of the period of reproductive maturity [Lewis et al., 2014].

The DOHaD model proposes a novel hypothesis for the predisposition to mental disorders the noncorrespondence of the environmental conditions between the beginning of programming and the later environmental conditions (thus, "adaptive" changes in the intrauterine environment may constitute the basis of diseases for the actions of the postnatal environment). In the context of this model, mental and other disorders should be regarded not as pathological deviations from normality, but as mismatch between the developmental conditions during the early programming period and later attempts to adapt to the prevailing environmental conditions [Lewis et al., 2014].

Neurodevelopmental programming is the realization of genetic and epigenetic programs directing and coordinating the normal development of the brain. The so-called phenomenon of the early programming of the development of the nervous system consists of a mechanism forming rapid and delayed effects of changes in the functional activity of the brain in response to endogenous and exogenous factors acting on the body during the perinatal period of development. There is also the concept that reprogramming of neurodevelopment constitutes changes to the original plan of brain development in response to external factors and changes in the homeostasis of the environment in which the body develops (stress, infections, eating difficulties, etc.) [Salmina et al., 2012; Bale, 2015].

Early life stress plays an adverse role in the development of the nervous system, particularly the brain, as has been demonstrated in animal models: a long-term effect of its "programming" on the establishment of brain functions and behavior in the future has been demonstrated. Early life stress has been shown to have adverse consequences, with impairments to the regulation of the hypothalamo-hypophyseal-adrenal system and increases in anxiety and cognitive dysfunction. Neuroactive steroids modulate neuron activity and play a key role in the nervous system but can decrease the functions of the hypothalamo-hypophyseal-adrenal system, have anxiolytic effects, and influence cognitive functions [Brunton, 2015]. A further unfavorable factor affecting the development of the fetal nervous system is the maternal microflora (in particular the vaginal microflora): thus,

dysbacteriosis of the mother's vaginal microflora can affect the microbial community in the neonate's intestine, which leads to dysfunction of immunity and impairments to the development of the nervous system, and derangement of the operation of the hypothalamo-hypophyseal-adrenal system, the development of which coincides with the beginning of intestinal colonization [Jasarevic et al., 2015].

As noted quite recently, the immune system plays critical roles not only in protecting the host, but also in physiological "homeostatic" processes (sleep, metabolism, memory) and the development of pathology in immune system dysregulation. Microglial cells and astrocytes, the primary immunocompetent cells of the CNS, and the cytokines produced by them (tumor necrosis factor α, interleukins 1β and 6), are involved in such important aspects of the development and functioning of the brain as synaptogenesis, neurogenesis, angiogenesis, axonal growth, and apoptosis. Infectious processes during the perinatal period of life operate as a susceptibility factor for the developing nervous system [Bilbo and Schwarz, 2009].

Apart from the environmental factors described above, whose actions lead to the development of pathology only when there is a genetic predisposition, polymorphisms of "candidate" genes with roles in the development of mental disorders in early life stress have been found: the gene encoding the serotonin transporter (SLC6A4), genes encoding tryptophan hydroxylase (TPG1, TPH2), serotonin receptors (5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}), the corticotropin-releasing hormone receptor type 1 (CRHR1), glucocorticoid receptors, the cochaperone FKBP5, neurotrophins (BDNF and others), and genes for the dopaminergic system, the neurotransmitters GABA (GABRA2), and others [Nugent et al., 2011]. The development of the nervous system also shows genetically determined gender-related differences behavioral problems and hyperactivity are twice as common in prepubertal boys as in girls, while during puberty three times as many girls as boys experience symptoms of depression [Lewis et al., 2014].

Epigenetic processes which do not alter DNA nucleotide sequences but do provide for responses to genetic signals and environmental signals also play an important role in the process of early programming. Epigenetic programming of the fetus and the development of the child are extremely complex, though a number of events (DNA methylation and modification of histone proteins) have been seen to play fundamental roles in cell differentiation during embryogenesis. New data provide evidence that epigenetic programs operate with significant changes in the early postnatal period (thus, from birth to 18 months of development, about a third of DNA methylation sites are methylated) [Lewis et al., 2014].

Thus, impairment to the normal process of programming of the nervous system plays an important role in the development of neurological and mental diseases associated with early life stress.

Biological Effects of Early Life Stress in Humans. The biological effects of early life stress include impaired brain development, dysfunction of neuro-, synapto-, and gliogenesis, and impairments to the development of the blood-brain barrier as a whole and angiogenesis in particular.

At the beginning of life, stress can affect the development of the hypothalamo-hypophyseal-adrenal system and can induce cellular and molecular cages in the developing hippocampus, which can lead to neurobehavioral changes in future life [Huang et al., 2014]. At the macroscopic level, early life stress affects various parts of the brain: higher-level parts of the brain (for example the prefrontal cortex and the corpus callosum) may be the most affected, with impairments to emotional regulation and the development of depression. Other parts of the brain, also associated with emotional regulation (for example the amygdala) are more resistant to the development of repeated stress [Pechtel and Pizzagalli, 2011].

Children experiencing abuse, children living in poverty, orphaned children, and children separated from their parents show decreases in the size of the hippocampus in adulthood. At the same time, no differences were seen in the hippocampus in primates separated from their parents, in orphan children subsequently reared by adoptive parents in a normal environment, or in children with diagnoses of post-traumatic stress disorder. This is probably related to the stress-associated glucocorticoid cascade, which can reduce hippocampus size over time [Hanson et al., 2015].

Structural neuroimaging data in studies of the volume of the amygdala in humans were unconvincing: children subject to early neglect could show increases in amygdalar size or the absence of any difference. Children living in poverty showed both increases and decreases in amygdalar size. Adolescents suffering from abuse had reductions in amygdalar size or there were no differences. It should be noted that many of these studies of humans covered quite wide age ranges (5–15 years). This is particularly important, as the development of the amygdala in nature is a nonlinear process. Long-term stress has also been shown to induce apoptosis of amygdalar cells. The initial actions of stress factors probably lead to increases in amygdalar volume and activity. With time, the excess functional activity may lead to neuron loss. People subject to especially powerful or long-lasting stress and having more severe sequelae have smaller amygdalar volume due to hypotrophy [Hanson et al., 2015]. It is interesting that subjects with more than two types of trauma in childhood showed decreases in the size of the anterior cingulate cortex and the caudate nucleus, but no changes were seen in the hippocampus or amygdala [Cohen et al., 2006].

Biological Effects of Early Life Stress in Animals (rodents). Studies of the amygdala revealed an increase in its volume due to branching of dendrites in the nuclei in adult rodents subjected to stress [Hanson et al., 2015]. Other data indicate that in mice of both genders at age P150, early

life stress leads primarily to a decrease in the size of the dentate gyrus of the hippocampus, which has critical roles in learning and memory processes and in controlling the response to stress and is a niche for neurogenesis in the development of mammals after birth [Naninck et al., 2015].

The dentate gyrus of the hippocampus in mammals is one of the few parts of the brain in which neurogenesis occurs in the adult state, this being termed hippocampal neurogenesis. The hippocampus is the site of embryonic, fetal, postnatal, and "adult" neurogenesis, depending on the period of development. In rodents, the peak of "postnatal" neurogenesis in the dental gyrus of the hippocampus is seen on day 8 of development, and the concept of "adult" neurogenesis applies to animals from age P15. The intensity of adult neurogenesis then starts to decrease in normal animals, after sexual development. Adult neurogenesis is a multistep process of proliferation of neural progenitor cells with subsequent selection of the unrequired products ("sprouts") by apoptosis, migration, and differentiation into fully functional neurons which join existing networks of hippocampal neurons. Adult neurogenesis is one of the mechanisms mediating neuroplasticity, which is important for the development of the brain overall and for establishing cognitive and emotional functions [Korosi et al., 2012].

Dysregulation of hippocampal neurogenesis may be an important component of impairments to cognitive functions and behavioral disorders in early life stress. It is important to note that hippocampal neurogenesis undergoes significant modulation at various levels: thus, education and training significantly enhance it, while aging, acute and chronic stress, conversely, suppress it, affecting one or several phases of the neurogenic process. The actions of stress at adult age on neurogenesis are reversible (when exposure to the harmful factor ends or after use of medication), while decreases in neurogenesis associated with early life stress are stable throughout life. One reason for such persistent changes may consist of structural transformations in the development of the hippocampus associated with the fact that the period of action of stress factors (the first two weeks of the postnatal period of development) coincide in time with the development of the dentate gyrus of the hippocampus in rodents [Korosi et al., 2012].

At the early stages of life, there is also a dynamic process of synaptogenesis, which makes this period extremely vulnerable to harmful influences [Girardi et al., 2014].

Overall, short-lived acute early life stress has useful effects because of increases in neurogenesis, synaptogenesis, and neuroplasticity, while chronic stress, conversely, has negative effects on hippocampal neurogenesis and synaptogenesis, decreasing neuroplasticity [Kuipers et al., 2014]. However, studies in various models have described different effects on the stages of neurogenesis mainly impairment to the proliferation of neural progenitor cells and increases in apoptosis at the selection stage, or impairments to neuron differentiation.

Thus, studies in a model based on repeated separation of infants from their mothers produced behavioral and neuroendocrine signs of elevated reactivity, along with cognitive defects in adulthood. Offspring initially (at age 21 days) showed mainly an increase in cell proliferation, leading to decreases in cell proliferation in rats aged 2–7 months, without any change in cell survival or differentiation. Studies in a 24-h maternal deprivation model at age P3 demonstrated transient increases in neurogenesis in three-week-old males, with a subsequent reduction in cell proliferation along the rostrocaudal axis of the dentate gyrus of the hippocampus in two-month-old rats and a decrease in precursor cell survival and differentiation in the caudal part of the dentate gyrus in three-week-old rats. Apart from these changes in neurogenesis, there were also changes in dendrite morphology in granule cells, decreases in the numbers of neurons and glial cells in the hippocampus, and a decrease in the density of fibers in the hippocampus. These structural changes coincided with impairments to spatial memory. Prenatal exposure to alcohol decreased neuron survival without affecting cell proliferation in male rats at age two months, and this was accompanied by cognitive deficit. Additional involvement of chronic stress in the adult state did not significantly decrease cell survival, which could potentially point to a reduction in hippocampal plasticity and the adaptability of the nervous system in subsequent life. The offspring of pregnant rats subjected to psychological stress in the last trimester of pregnancy demonstrated decreased cell proliferation and cell survival in the dorsal hippocampus at age one month and increased emotionality at age two months [Korosi et al., 2012].

Chronic unpredictable stress in adult animals leads to decreases in the intensity of hippocampal neurogenesis. The weak actions of predictable stressors, conversely, lead to increased neurogenesis in the hippocampus. Animals subjected to early life stress during the postnatal (P21) and juvenile (two months) periods of development showed increased hippocampal neurogenesis, though at intermediate age (15 months) there was a decrease in neurogenesis in the hippocampus [Suri et al., 2013].

Vasculogenesis of the neural tube in rats starts from 10–11 days of embryogenesis (E10–E11); gap junctions in endotheliocytes become visible on day 16 of embryogenesis; angiogenesis continues to day 20 of postnatal development. Astrocytes start to condense around vessels at the E16 period, and perivascular processes occur most actively during the second and third weeks of postnatal development. Maturation of the basal membrane also occurs during the postnatal period, and its development ends in the fourth week after birth. Thus, the blood-brain barrier (BBB) during the prenatal and early postnatal periods is characterized by functional and structural immaturity. Any unfavorable action during the perinatal period of development can impair the process of the normal development of the BBB. A delay or impairment to BBB maturation may threaten the normal functional develop-

ment of the nervous system due to mismatch between the capacity to supply neurons with blood (in restricted vasculo- and angiogenesis and their constantly increasing metabolic needs [Gomez-Gonzalez and Escobar, 2009].

Chronic prenatal stress impairs the functioning of the blood-brain barrier due to increases in the caveolae-mediated transport in cerebral vessel endotheliocytes and in adulthood induces reductions in vessel area in the hippocampus and increases in the amygdala [Neigh et al., 2010]. Toxic agents circulating in the blood can impair the functional activity of neurons and glial cells, with subsequent damage to the brain structures required for learning, forming memories, and movement activity [Gomez-Gonzalez and Escobar, 2009].

Overall, the actions of stress in adulthood, in contrast to prenatal and some types of postnatal stress, lead to stable changes in neurogenesis, showing the presence of learning plasticity and the ability to adapt to the surrounding environment [Korosi et al., 2012]. The neurobiological effects of early life stress in different animal models are shown in Tables 2 and 3.

Data have been obtained indicating that some of the neurobiological effects of early life stress can be affected, minimizing or even preventing the sequelae of stress: simulation of maternal care in rats by daily stroking the backs of offspring; physical exercises and training tasks play an important role in the prophylaxis and treatment of mental disorders in ELS and can play an important role in the prophylaxis of age-related cognitive dysfunction, increasing neuroplasticity. Increases in dendrite branching, neurogenesis, synaptogenesis, and long-term potentiation have been recorded in response to an enriched environment in animal models. A positive effect was also demonstrated with pharmacological treatment with cannabinoid receptor agonists, which improved cell proliferation, migration, and differentiation, axon growth, and synaptogenesis, while use of anti-inflammatory preparations, particularly type 2 cyclooxygenase inhibitors, the anti-inflammatory cytokine interleukin 10, and antidepressants also produced positive effects on early changes in ELS [Harrison and Baune, 2014].

Early Life Stress in the Development of Depression in Humans. The sequelae of early life stress at the body level consist of developmental impairments in multiple domains in the child physical, emotional, behavioral, cognitive, and social, predisposing to the development of neuromental diseases at all periods of life neurocognitive diseases (impairments to spatial memory and learning), mental illnesses, behavioral disorders (development of anxiety and depression), and others [Carr et al., 2013; Cohen et al., 2006; Harrison and Baune, 2014].

Thus, one hypothesis for the development of schizophrenia is that of early life stress, which suggests that the neurochemical impairments of adverse events in early life can influence brain functions, producing anomalies underlying the occurrence of schizophrenia [Girardi et al., 2014]. However, the most frequent and important consequence of early life stress in humans and animals is the development of depression [Cohen et al., 2006; Harrison and Baune, 2014].

Depression is a multifactorial disease with a genetic predisposition. The heritability of depression varied from 30 to 50% depending on gender and severity. On the other hand, environmental factors also affect the development of depression, increasing or decreasing the individual risk of developing it. Some of the best studied factors predisposing to depression are those associated with early life stress: large-scale studies have shown significant increases in the risk of depression in nearly life stress, particular in women [Schmidt et al., 2011].

These changes in early life stress may be associated with the neurogenic hypothesis of immune programming of development [Kuipers et al., 2014], which is supported by such impairments to the functioning of the brain at the cellular level as changes in neuroendocrine activity, immune functions, and neurotransmission (primary changes have been described in the hippocampus and prefrontal cortex, with secondary changes in the amygdala) [Harrison and Baune, 2014].

Impairments to neurogenesis have been seen in the pathogenesis of depression: some authors have reported suppression, while others have found that decreases in hippocampus size are associated not with decreased neurogenesis but with increased apoptosis in the entorhinal cortex, the base of the hippocampus, and its fields CA1 and CA4 and the dentate gyrus [Boldrini et al., 2012].

Early Life Stress in the Development of Depression in Animals (rodents). The changes seen in early life stress in humans (impairments to the immune functions of the brain, changes in neurogenesis and angiogenesis) are also seen in animals. Thus, studies in primates and rodents have demonstrated impairments to the cell-mediated immune functions of the brain, along with increased basal proinflammatory activity. Decreases in the expression of serotonin receptors were seen in the prefrontal cortex, hippocampus, and raphe nuclei of the medulla oblongata, leading to deterioration of serotoninergic signaling. Changes in dopaminergic signaling have also been described, i.e., decreases in the activity of the mesolimbic dopaminergic system leading to the development of depression. A number of studies have also linked the development of depression, anxiety, and social deficit with changes in monoaminergic neurotransmission. Decreases in the expression of parvalbumin (a GABAergic marker) in the prefrontal cortex have been described in relation to separation of infants from their mothers, correlating with the development of depressive behavior [Harrison and Baune, 2014].

An interaction between ELS and the risk of alcohol abuse in adulthood was identified, as demonstrated in rodents [Comasco et al., 2015].

The infants of "uncaring" mothers show lower levels of expression of estrogen receptors in the medial preoptic field, decreased expression of glucocorticoid receptors in the hippocampus, and a tendency to anxiety and depression,

in contrast to infants receiving good care. A relationship was also found between the expression of the associated mechanism oxytocin receptors in the medial preoptic field in that their expression in offspring increased in conditions of good maternal care. In animal models, oxytocin plays an important role in the neuroendocrine modulation of stress, anxiety, social behavior, and the perception of pain. Impairments to the expression of oxytocin receptors in this case may be a secondary effect [Harrison and Baune, 2014].

Models based on animals subjected to early life stress show impairments to stages of neurogenesis, neuronal differentiation and synaptogenesis in the hippocampus, amygdala, and cerebral cortex by day 90 of development, along with intensification of apoptosis and the development of depressive disorder, which is consistent with the hypothesis of Eisch et al. of the double role of dysfunction of neurogenesis in the pathogenesis of depression: on the one hand, an increase in the number of actively interacting neurons is required to overcome the consequences of stress (the "buffer" function of newly formed neurons in relation to the action of the stress factor), which is seen on application of acute stress; on the other hand, on further application of the stress factor, newly formed neurons die, and longer-lasting stress factors also decrease all phases of neurogenesis (starting with cell proliferation and ending with survival and differentiation) [Yauzina et al., 2013b; Eisch and Petrik, 2012; Kuipers et al., 2014].

Most studies of the role of early life stress in the development of depression have been performed using rodents, though there is another feature: modeling of depression in rodents produces the difficulty of interpreting the results for example, such symptoms of depression in humans as low self-esteem, feelings of guilt, and suicidal behavior have no analogs in rodents. At the same time, some of the symptoms of depression in rodents have quite clear correlates: loss of satisfaction in humans correlates with anhedonia in rodents (loss of activity in achieving satisfaction); loss of motivation in humans is similar to the passive task-solving strategy and low motor activity in rodents; sleep impairments in people correlate with sleep impairments and stereotypical activity in animals; anxiety/anxious behavior and cognitive deficit are also apparent in humans; signs of hypercorticism in humans and animals are expressed as hyperactivity of the stress system. In addition, some models are not very specific for depression and show "side" symptoms not characteristic of depression. Nonetheless, such nonspecific symptoms are characteristic of the whole complexity of depressive syndrome, which in humans may be due to multiple illnesses [Pryce and Seifritz, 2011; Schmidt et al., 2011].

In general, rodent models show quite rough approximations to depression in humans, though some aspects of depression can be reproduced in these models: for example, animal models are required for studies of the role of genetic and environmental factors in the development of depression in humans, for studies of its epidemiology, pathophysiology, psycho- and neuropathology, semiotics, and diagnosis, as well as for translational studies (on the basis of emotional-cognitive endophenotypes and markers of depression, socially significant endophenotypes and markers for states in humans can be identified in rodents) [Pryce and Seifritz, 2011; Schmidt et al., 2011].

Data on the use of early life stress models as models of depression are also ambiguous: on the one hand, one type of model of depression consists of a model of early life stress: for example, a model of separation of the infant from its mother from day 2 to day 15 of the postnatal period for 3 h in an incubator [Yauzina et al., 2013a; Marmendal et al., 2004; McKinney, 2001]. On the other hand, even this model, which produces a quite clear simulation of the development of the depressive phenotype, has the drawback of variability in the expression of depressive symptoms in different mouse and rat strains [Schmidt et al., 2011].

Historically, one of the first experimental models of ELS in rodents was the model based on daily transient (maximum 15 min) separation of infants from mothers in the first 2–3 weeks of life, which stimulates maternal care behavior and induces an acute neuroendocrine response in the infants. Unfortunately, animals rarely develop the depressive phenotype in this model [Schmidt et al., 2011].

Longer-lasting separation of mothers and litters leads to quantitative decreases in the duration of maternal care, thus modeling both emotional and physical neglect. The models used vary strongly not only in terms of the beginning of separation and its duration, but also in terms of the ambient temperature used for the litter (warm or cold), and the type of separation (mother or litter removed from the cage) or isolation (infant removed from mother to another cage or dispersed on the litter in the same cage). Single-session deprivation (removal of the mother) for 24 h at different points in postnatal development of rodents is widely used for studies of the neuroendocrine functions of the developing rat or mouse pup and for studies of a number of neuroendocrine effects in adult animals, though this model provides few data on the formation of depressive behavior [Schmidt et al., 2011].

A model of natural differences in maternal care is also widely used for studies of neuroendocrine regulation and anxiety behavior in rodents, though there are very few data on the development of the depressive phenotype in these animals. Models of environmental poverty and impairments to social contacts have received more study from the point of view of the development of anxiety and cognitive dysfunction in rodents than the formation of the depressive phenotype. A pharmacological mode of ELS using synthetic glucocorticoids (dexamethasone) is not particularly suitable for creating models of depression [Schmidt et al., 2011].

Another pharmacological model of early life stress and depression may consist of a model of postnatal treatment with LPS in rodents, which simulates infection with Gram-negative bacteria in children. The immune system plays an

important role in the development of mental diseases, including depression. A model based on chronic exposure to lipopolysaccharide (LPS) in adult animals simulates many aspects of depression. The action of endotoxins in the early period of life is a serious problem in view of the fragility of the immune system in neonates. Application of LPS during the early postnatal period leads to impairment of the development of the stress response system, which is apparent in adulthood as altered neuroendocrine and neuroimmune responses. Behavioral changes include social behavior, cognitive capacity, and anxiety. Changes in cognitive capacity and anxiety are relevant to depression, though they are not its main signs. However, the combination of this action with additional risk factors can be regarded as a model of depression [Schmidt et al., 2011].

Overall, of all early life stress models inducing depressive manifestations and operating as models of depression, the closest are models using long-term daily removal of infants from mothers and postnatal treatment with lipopolysaccharide combined with other factors. In the near future, the most reliable models of depression in rodents may be those models considering both genetic factors and environmental conditions (mainly early life stress) [Schmidt et al., 2011].

Conclusions. Thus, from the point of view of the neurobiological effects, the most dangerous factor is early life stress in the prenatal and postnatal periods of development in the first days after birth (the early nervous system developmental programming phenomenon), when effects on the development of the brain, neuro-, synapto-, glio-, and angiogenesis and actions on the immune functions of the brain are the most stable. These lead not only to functional impairments, but also to organic rearrangements in the limbic system (mainly the hippocampus, but to a lesser extent the amygdala), corpus callosum, and cerebral cortex. The neuropsychological signs of early life stress in humans are the development of depression, anxiety, schizophrenia, and neurocognitive diseases. Among these neuropsychological signs, ELS is most commonly apparent in the form of depressive disorders in humans and depression-like behavior in animals (which is probably linked with lesions primarily to the prefrontal cortex and corpus callosum) and is one of the standard models of experimental depression in rodents.

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