Early brain development toward shaping of human mind: an integrative psychoneurodevelopmental model in prenatal and perinatal medicine

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Abstract

The article introduces an integrative psychoneurodevelopmental model of complex human brain and mind development based on the latest findings in prenatal and perinatal medicine in terms of integrative neuroscience. The human brain development is extraordinarily complex set of events and could be influenced by a lot of factors. It is supported by new insights into the early neuro-ontogenic processes with the help of structural 3D magnetic resonance imaging or diffusion tensor imaging of fetal human brain. Various factors and targets for neural development including birth weight variability, fetal and early-life programming, fetal neurobehavioral states and fetal behavioral responses to various stimuli and others are discussed. Molecular biology reveals increasing sets of genes families as well as transcription and neurotropic factors together with critical epigenetic mechanisms to be deeply employed in the crucial neurodevelopmental events. Another field of critical importance is psychoimmuno-neuroendocrinology. Various effects of glucocorticoids as well as other hormones, prenatal stress and fetal HPA axis modulation are thought to be of special importance for brain development. The early postnatal period is characterized by the next intense shaping of complex competences, induced mainly by the very unique mother – newborn´s interactions and bonding. All these mechanisms serve to shape individual human mind with complex abilities and neurobehavioral strategies. Continuous research elucidating these special competences of human fetus and newborn/child supports integrative neuroscientific approach to involve various scientific disciplines for the next progress in human brain and mind research, and opens new scientific challenges and philosophic attitudes. New findings and approaches in this field could establish new methods in science, in primary prevention and treatment strategies, and markedly contribute to the development of modern integrative and personalized medicine.

REVIEW ARTICLE

INTRODUCTION

Prenatal phase of human life is the most important and determining period from both, psychological and physiological points of view. It is the time of crucial development of all organs as well as the basic determination of the next complex personality. The prenatal child undergoes learning by different mechanisms and it experiences different ways of adaptation strategies, which are necessary to stay alive. All these unique processes serve as a preparation for postnatal life. Prenatal stress, maternal depression, maternal separation, hormonal deviations, immunology disorders, infections of various characters, and environmental influences have impact on the fetal brain and its differentiation in neurotransmitter level and/or neuro-endocrine development, disturbances and predispositions. It is generally accepted that experiences during critical periods of prenatal, perinatal and early childhood stages of life organize brain systems, and deeply influence the formation of complex human mind and behavior of individual (Fedor-Freybergh 1994; Fedor-Freybergh 1999; Fedor-Freybergh 2013). All these unique features and influences during crucial human brain development could be properly reflected by interdisciplinary and integrated scientific approaches, especially by those within the *prenatal and perinatal medicine.* The field includes all the aspects related to the development of whole organism as unique organization of all functions and structures during the critical prenatal and early postnatal periods (Fedor-Freybergh 1988; Fedor-Freybergh 1998; Fedor-Freybergh 2011; Fedor-Freybergh & Maas 2011; Hrubý & Fedor-Freybergh 2013). Rapidly increasing knowledge in this field also brings the very special emphasis on the human brain and human mind development since the critical neurodevelopmental processes have been recognized during these early life periods. Such progress is also reflected by *integrative neurosciences* approaches, including *prenatal and perinatal psychology.* It is aimed at the interdisciplinary study of early neurodevelopmental and psychological processes in human beeings and explores the psychological and physiological effects of individual experiences before birth (prenatal), as well as during and immediately after birth (perinatal) on mental and physical health and unique competences of the individual (Fedor-Freybergh 2002; Fedor-Freybergh 2013).

Prenatal period of human life represents a crucial phase in human life during which crucial developmental processes and regulations take place and these serve as adaptational strategies and physiological capabilities for the next postnatal life´s periods. This process of continuous tendency to maintain homeostasis as well as dynamics in all systems of individual following all the periods of life could be designated as *the concept of human life´s continuum.* According to this concept the human life has to be considered as an indivisible continuum, where each of the developmental stages is equally important (Fedor-Freybergh 1990; Fedor-Freybergh & Maas 2011). In this continuum, the individual represents an indivisible entity of all functions on both, physiological or physical psychological and social level. The physical, biochemical, endocrinological and psychological processes represent a whole that can not be divided. The continuum of life begins *in utero*. It is not possible to separate any stages of human development from the rest of an individual life's continuum (Figure 1). The life continuum is one of the basic needs in human life in order to maintain homeostasis and equilibrium (Fedor-Freybergh & Maas 2011).

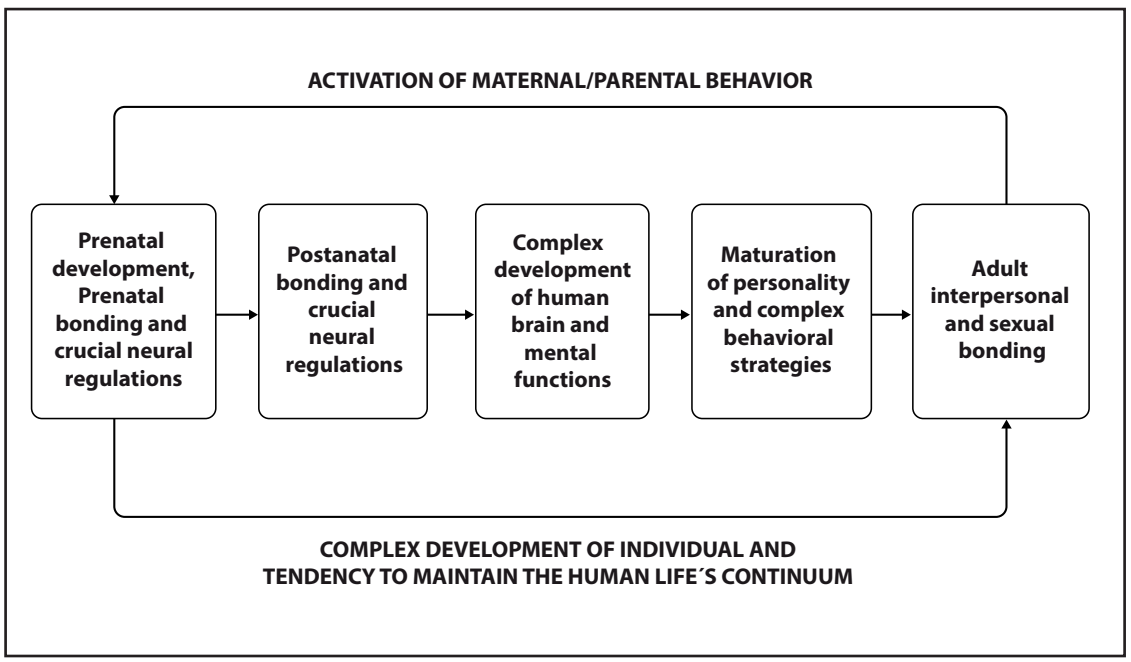

Fig. 1. The concept of complex human development and human life´s continuum.

Within all these regulations and processes, the human brain development is extraordinary eminent condition to maintain homeostasis, dynamic organization and integrity of human individual. Because of unique position of human mind in science, philosophy, medicine and other aspects of human existence, the research of human mind development is taking a very special role. There is a great evidence for extremely complex interactions and various factors to be involved in neurodevelopmental processes. All these important actions, including development *in utero,* exclusively determinate individual capacity and abilities to process a wide range of stimuli and to adapt to different conditions. Consequently, all these neurodevelopmental processes are of crucial importance in the "formation" of complex human mind. The article reviews scientific knowledge about these very unique features of human mind and behavior during early development in prenatal and early postnatal life periods from integrative neuroscientific perspective (Figure 2).

BRAIN DEVELOPMENT, BEHAVIORAL EMBRYOLOGY AND FETAL MIND

Prenatal life represents critical phase for *human brain development*. The development of human brain is extremely complex process which is potentially influenced by a lot of factors, including genetic predispositions, environmental events, neuroplastic responses to various stimuli modulating connectivity and communication between neurons. It involves a lot of unique and critical actions including early synapses and neural circuits formation. The development of the brain's circuitry requires the coordination of an extraordinarily complex set of neurodevelopmental events (Tau & Peterson 2010).

Despite research of human fetal brain development is limited, especially *in vivo* conditions, new promising possibilities are emerging especially with the development of new neuroimaging methods. The use of 3D magnetic resonance imaging (MRI) and dedicated postprocessing tools to measure brain tissue volumes (cerebral cortical gray matter, white matter), surface and sulcation index can elucidate phenotypes associated with early behavior development. The use of diffusion tensor imaging (DTI) can further help in assessing microstructural changes within the cerebral white matter and the establishment of brain connectivity. Finally, the use of functional MRI and resting-state functional MRI connectivity allows exploration of the impact of adverse conditions on functional brain connectivity *in vivo*. Results from studies using these methods have for the first time illustrated the structural impact of antenatal conditions on the functional brain

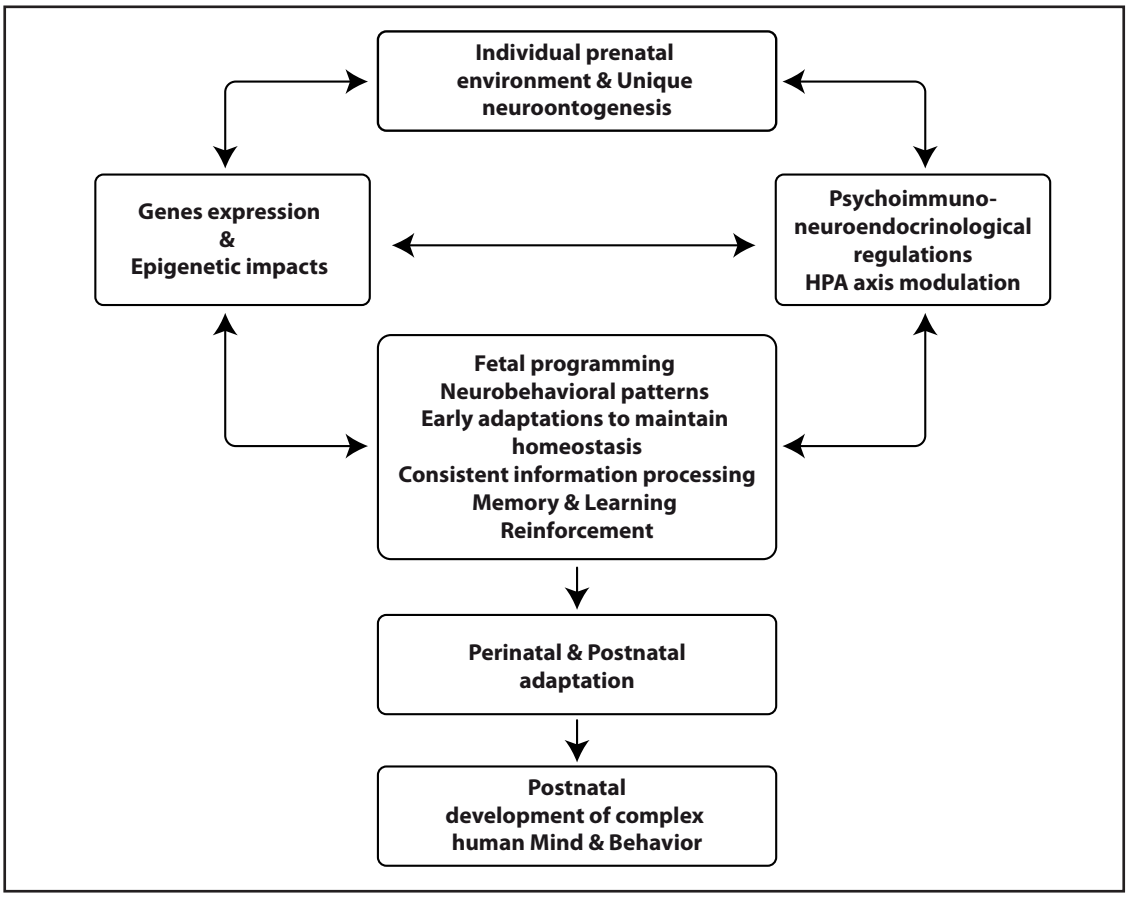

Fig. 2. Integrative psychoneurodevelopmental model in prenatal and perinatal medicine.

deficits (Lodygensky *et al.* 2010). The rapid advancement of MRI allows important progress in the understanding of normal and pathological human brain development. Structural MRI data from scanning *in vivo, in utero* and *post mortem*, combined with DTI, are allowing us to map development of the fetal human brain. The growth of axon pathways and the relative rates of growth of different regions of the cortex in terms of relative grey and white matter volumes, and the duration of transient structures such as the subventricular zone and subplate (see below), may now all be examined in this way (Marsh *et al.* 2008; Clowry *et al.* 2010; Huang 2010).

The *neuro-ontogenic process* in humans begins at gestational age weeks 2–3 with the folding and fusion of ectoderm to form the neural tube. At week 4 of gestation, the rostral portion of the neural tube forms three vesicles that are destined to give rise to the forebrain, the midbrain, and the hindbrain. The rostral-most prosencephalic (forebrain) vesicle then forms two vesicles that are destined to become the *telencephalon* (cerebral cortex) and the *diencephalon* (thalamus, hypothalamus, and other structures). By gestational age weeks 5–6, neuroblasts are proliferating rapidly within the ventricular zone that lines the cerebral ventricles. The laminar structure of the cerebral cortex is encoded early in development. By gestational age week 8, neuroblasts begin to differentiate into either specific neuronal cell types or macroglia, depending on their location in the ventricular zone layer. Postmitotic cells migrate out of this layer to form cortical laminae. *Migration* depends on a complex set of molecular interactions between neurons and the scaffolding glia. Another smaller group of neurons originates from the primordia of the basal ganglia nuclei and migrates tangentially to the developing cerebral cortex and thalamus. Neuronal migration peaks between gestational age weeks 12 and 20 and is largely complete by gestational age weeks 26–29. Since neurons complete their migration, they extend axons and dendrites to appropriate synaptic partners. Scaffolding cells and molecular gradients are important in the processes of their formation. The earliest synaptic connections are formed at approximately gestational age week 5 by neurons located in the first recognizable cortical layer known as the *preplate.* On their way to the preplate, and later to the *subplate,* axons of dorsal thalamic neurons are guided by molecular interactions with a population of tangentially migrating neurons, which, similar are a class of scaffolding cells. The neurons in the preplate serve as initial synaptic targets for neuronal projections from the developing thalamus and brainstem. The subplate is a *transient embryonic cortical layer* that forms within the preplate. The subplate is thicker than all other cortical layers between gestational age weeks 18 and 22, and rich with synapses and contains evidence of a laminar organization. The differential timing of developmental events across brain regions is evident in the subplate, in which somatosensory regions develop earlier than visual regions. Neurons in these portions of the subplate receive preliminary afferent inputs from the visual and somatosensory thalamus, cholinergic afferents from the basal forebrain, and monoaminergic afferents from the brainstem. After pausing in the subplate, subcortical afferents make more permanent connections within the cortical plate through a process of synaptic refinement that begins slowly around gestational age week 20, reaches its peak between gestational age weeks 24–28, and continues into the perinatal period. This refinement of synaptic connections causes the dissolution of the subplate, which can be observed in fetal MRI scans. After 28 weeks of gestation, the declining subplate largely contains neurons that are destined for association areas and commissural pathways, which are among the last of cortical regions and pathways to develop (reviewed by Tau & Peterson 2010).

As stated above, the development of human brain is influenced by an extraordinarily complex set of neurodevelopmental events. Thereby, there are a lot of potentially risk neurodevelopmental factors and these could have long term influences on the *structural and functional brain maturation*. Distinct sensitivity of the developing brain to prenatal environmental insults has been well established through experimental animal models. Rodent models are extremely valuable for the investigation of brain development, but cannot provide insight into aspects that are specifically human. Situation is much more complicated in humans, since the research of such factors is strongly limited. *The human brain*, and particularly the *cerebral cortex*, has some unique genetic, molecular, cellular and anatomical features that are significantly different in comparison to animals (Clowry *et al.* 2010). For example, cortical expansion in human is not just quantitative and some novel types of neurons and cytoarchitectonic areas were identified by their gene expression. Experimental data also show that human cortex exhibits connectivity and functions that do not exist in rodents. Recent research into human brain development has revealed more elaborated neurogenetic compartments, radial and tangential migration, transient cell layers in the subplate, and a greater diversity of early-generated neurons, including predecessor neurons. Experimental studies also showed that the earliest cortical structure, the preplate, has a more complex structure in humans than in rodents and the human subplate to be larger and more elaborate in comparison to other species. Recently it has been shown that during human fetal brain development in some of the prospective association areas, such as the prefrontal cortex, sets of genes are expressed that are not expressed in rodents. Moreover, there is increasing evidence for many neuropsychiatric disorders, including autism, schizophrenia or Alzheimer´s disease to have possible developmental origins in earliest stages of formation of the neocortex during pregnancy (Clowry *et al.* 2010). In humans, experimental approaches are not feasible, but numerous observational studies have linked frank

insults during prenatal life, abnormally low birth weight for gestational age and maternal exposure to radiation or starvation, to altered postnatal brain development. In humans, *birth weight variability* was recognized as one of suitable biological markers to assess the brain development (Raznahan *et al.* 2012). The evidence that subtle alterations of the prenatal environment may have meaningful consequences for postnatal development in humans can be found in large-scale epidemiological studies that use birth weight as a global proxy measure of uterine development. These studies find that lowered birth weight, even among people born full term and at weights considered appropriate for gestational age, is associated with an elevated risk for multiple common forms of mental illness (including schizophrenia and affective and anxiety disorders) (Abel *et al.* 2010) and reduced cognitive abilities (Shenkin *et al.* 2004). These data lead to the hypothesis that normative birth weight variation may be associated with detectable differences in postnatal human brain development that persist beyond childhood and could be connected with differences in cognitive abilities. Base on this hypothesis, Raznahan *et al.* (2012) studied relation of normative body weight in full-term pregnancies to postnatal measures of brain development and global cognitive functioning in twin-pairs (monozygotic and same-sex dizygotic) and unrelated singletons in age between 3 to 30 years. They considered global cognitive ability (cognitive functions tests) and performed structural magnetic resonance imaging to assess global brain volumes, total gray matter volume and total white matter volume. Finally, they focused on the relationship between birth weight and postnatal anatomy of the cerebral cortex because it represents a key biological substrate for many postnatal outcomes sensitive to birth weigh variation. *The cerebral cortex* undergoes rapid growth during *in utero* life with massive neurodevelopmental processes, which also play a pivotal role in formation of early neuronal circuits. To provide a detailed picture of the relationship between body weight variation and postnatal cortical development, they measured distinct morphometric cortical properties from structural MRI: cortical volume and its two sole determinants – mean cortical thickness and total cortical surface area. Final data showed that the influence of body weight on cerebral volume was driven more by surface area than cortical thickness. Greater body weight was associated with statistically significant and developmentally static increases in both surface area and cortical thickness, the effect-size estimate for body weight influences on surface area was almost twice that for cortical thickness. The main effect of body weight on cortical thickness became apparent in middle frontal sulcus, bilateral posterior superior temporal sulcus, left superior parietal lobule, and left middle temporal gyrus. Greater body weight was associated with developmentally fixed surface area increases within bilateral superior frontal gyrus, bilateral perisylvian cortices, and bilateral middle temporal gyrus. Their findings showed that subtle variations of the prenatal environment, as indexed by small body weight differences within healthy monozygotic twin-pairs born at full-term, are associated with statistically significant differences in postnatal cognition and robust alterations of brain anatomy that persist into early adulthood. The authors concluded that environmentally determined increases in body weight, within the normative body range, promoted increases in postnatal cognitive ability and developmentally stable increases in total brain volume, white matter volume, grey matter volume, and cortical volume. Body weight influences on cortical volume were largely driven by alterations of surface area rather than cortical thickness, and vulnerability of surface area to differences in the prenatal environment showed marked regional heterogeneity. As they suggest, the surface area is maximally sensitive to body weight variation within cortical regions implicated in the biology of several mental disorders, the risk for which is modified by normative body weight variation. Subtle in differences in prenatal growth could thereby lead to protracted surface area alterations that preferentially impact later-maturing associative cortices important for higher cognition (Raznahan *et al.* 2012). This is also supported by study of Dubois *et al.* (2008), in which they employed 3D MRI to measure brain tissue volumes, surface area and the sulcation index. Findings revealed cortical phenotypes associated with early behavioral development measured by neurobehavioral assessment at term and later development. Final data also showed there was a close relationship between the cortical surface at birth and neurobehavioral scores (Dubois *et al.* 2008). Other findings suggest that neurodevelopment could be influenced by different environmental factors, which produce abnormal patterns in developmental programming of cerebral laterality. It is well established that asymmetrical activation of the cerebral hemispheres is associated with altered affective states, including depression and with heightened stress-responsiveness. Based on this knowledge, Jones *et al.* (2011) tested the hypothesis that harmful events could promote the development of some brain regions over others and such regional specialization during fetal life might be reflected persistently in the relative activity of the cerebral hemispheres. The authors tested the hypothesis in healthy 8–9 years-old children, using tympanic membrane temperature to assess relative blood flow to the cerebral hemispheres at the rest and following psychosocial stress. They found that children who had a smaller weight at birth had evidence of greater blood flow to the right hemisphere than to the left hemisphere. This finding was strengthened if the children had a relatively low birth weight for their placental weight. Finally, they suggest that lateralization of cerebral activity is influenced persistently by early developmental experiences, with possible consequences for long-term neurocognitive function. It is known that

adverse fetal environments could be associated with serious neuropsychiatric disorders, including depression, reduced cognitive ability or increased stress responsiveness in later life, but underlying processes still remain unclear (Jones *et al.* 2011).

Another fruitful area to explore fetal human brain development is *behavioral embryology.* It comes out from knowledge about occurrence of both, spontaneous and coordinated behavior of the human fetus. There is an evidence for coordinated behavior of the human fetus as the reaction to various specific stimuli, including social and affective stimuli. Also it is very well established there is an increase of *spontaneous movement activity of the human fetus* in time with final spontaneous decrease close to the time of birth. The very beginning of spontaneous movements of the human fetus is observed approximately 8 weeks after fertilization. At the age of 10 weeks after fertilization the human fetus is able to change its position *in utero* and disposes of wide range of behavior, including independent movements of extremities, rotation, head movements, yawning, swallowing, breath movements and other at the age of 15 weeks after fertilization (Michel & Moore 1999). Assessment of motor development in the human fetus provides an opportunity to examine maturation of the central nervous system during gestation. During the third trimester, neuronal differentiation and synaptogenesis thrive in the cortical plate with afferent projections from the thalamus migrating deeper into the cortical layer increasing the probability that movement will be generated and modified in response to stimulation (Grant-Beuttler *et al.* 2011). Normal fetal motility is used to be characterized by specific movement patterns for the body part which actively participates in the movement including initiation and continuation of the movement with head, arm, leg, trunk or combination of all, and non-specific movement patterns like total body activity, gross movements and trunk movements. The fetal motility could be defined by the quantitative or qualitative analysis of the movement patterns recorded with ultrasound. Moreover, there are also *fetal behavioral states* which are defined as combination of specific movement pattern for eye movement, non-specific pattern for gross or body movement together with four classes of fetal heart rate patterns. Normal utterances of fetus motility in physiological pregnancy are characterized by a wide range of occurrence of each specific movement pattern and the ranking in the frequency of specific movement patterns is strongly age-related. The strongly age-related gradual changes in temporal patterning of, for instance, general movements, breathing movements and clustering of movements (behavioral states), suggest influence of the central nervous system, on which are superimposed the smaller influences of hormones (De Vries & Fong 2006). *Fetal neurobehavioral development* characterized by fetal heart rate variability, fetal movement, and coupling between fetal motor activity and heart rate patterning have also been associated with the optimality in newborn postnatal neurological maturation and general postnatal outcomes (DiPietro *et al.* 2010). Fetal movements recorded with continuous ultrasound suggest that some general movements, such as fetal breathing and mouth movements increase, whereas other movements, such as startles, decrease with advancing gestational age. Grant-Beuttler *et al.* (2011) applied vibro-acoustic stimulation over the maternal abdomen to detect when during gestation a fetus is capable of producing a motor response. The authors suggest that following vibro-acoustic stimulation, an immediate increase of large, jerky movements suggests instability in fetal capabilities. Fetal movement quality changes over gestation may reflect sensorimotor synaptogenesis in the central nervous system. Fetal ultrasound studies suggest higher is degree of fetal maturation the smoother and more complex fetal movements are observed. The development of more complex movements as the fetus ages is an important indicator of motor development and may signal neurological development and motor learning. However, during periods of intense stimulation, such as the vibro-acoustic stimulation, fetal movements are characterized by higher frequencies of more immature and uncoordinated movement patterns. The changes in fetal movement at different ages and following vibro-acoustic stimulation appear to be part of the normal maturational process (Grant-Beuttler *et al.* 2011).

Moreover, human fetus also responds to sensory stimuli like chemical (taste and smell), touch, pain and sound. It is established well that all of human sensory organs are already developed and functional before the birth. It is suggested that higher degree of development in these special fetal capabilities could represent early development of ecological self (recognized as a one of domains of human personality), which already emerges *in utero* (Fedor-Freybergh 2013; Koukolík 2008; Michel & Moore 1999). Kachewar and Gandage (2012) in their study considered the *fetal mind* as a collection of brain functions and a reflection of functions of its organs of sense and of its inner self. They hypothesized that fetal brain reactivity could be objectively demonstrated by Colour Doppler ultrasound evaluation of waveform patterns of the Middle Cerebral Artery of the fetal brain. The fetal Middle Cerebral Artery supplies almost 80% of the blood to the fetal brain and can give abundant information about fetal heart and fetal stress. They observed the normal waveform pattern with regular systolic and diastolic components in states of complete fetal health. But when the fetal inner self was traumatized by cardiac ectopics or arrhythmias, bizarre and aberrant patterns were observed to replace normal waveform. In the conditions the entire fetus was under stress, as in cases of intra uterine growth retardation, changes were again manifested in the fetal Middle Cerebral Artery velocity waveform patterns and were designated as the fetal Brain Sparing Effect. The authors concluded that imaging evaluation of the vessel could

reflect various effects of sense organs and brain contact as the function and information processing of the fetal brain. Thereby, it could be the unique non-invasive opportunity to observe the fetal inner self expressions.

Based on the animal studies, it is hypothesized the crucial developmental processes involved in a formation of neural structures responsible for memory capacities already take place in prenatal period. Thus, there is a suggestion for *fetal origins of memory* as indicated by data supporting importance of choline for optimal memory circuits formation in rodent studies (Zeisel 2006). Choline is the precursor for many important compounds, including phospholipids, acetylcholine, and the methyl donor betaine. Dietary intake of choline by the pregnant mother and later by the infant directly affects brain development and results in permanent changes in brain function. High choline concentrations in the brain and spinal cord are important for neural tube closure and brain development. In rodent models, maternal dietary choline intake influenced brain development (specifically development of the hippocampus, the brain's memory center). In rats and mice, embryonic days 11 to 18 are the critical period for development of the hippocampus and septum. More choline during days 11 to 18 of gestation resulted in increased cell proliferation and decreased apoptosis in rodent fetal hippocampal progenitor cells. Morphological alterations occurred in the brain after choline supplementation during fetal life, including larger soma and increased numbers of primary and secondary basal dendritic branches. The brief exposure to extra choline *in utero* and subsequent changes in hippocampal structure resulted in enhanced long-term potentiation, and enhanced visuospatial and auditory memory throughout the lifespan. Moreover, perinatal supplementation of choline enhances memory and learning functions, which persist across the lifespan. Conversely, choline deficiency during these sensitive periods results in memory and cognitive deficits that also persist. Furthermore, recent studies suggest that perinatal choline supplementation can reduce the behavioral effects of prenatal stress and the cognitive effects of prenatal alcohol exposure in offspring. In humans, the architecture of the *hippocampus* continues to develop after birth, and it closely resembles the adult structure by age 4 years. The hippocampus is one of the few areas of the brain in which nerve cells continue to multiply slowly in adults. Extrapolating from the rodent data, human sensitivity to the developmental effects of choline would occur *in utero* through perhaps up to age 4 years (Zeisel 2006).

It is hypothesized that all the special capabilities and responsiveness to various stimuli enable the human fetus to process a wide range of prenatal experiences, which induce learning and patterns playing a role also in postnatal period. Sensory stimulation could induce important neuro-motoric development. For example, it is hypothesized that side differences in vestibular stimulation and perceptions could co-explain functional specializations of human brain hemispheres. The hypothesis is that human fetus prefers such *in utero* position, in which the left side vestibular apparatus exhibits higher stimulation in comparison to that on the right side. Consequently, the left side stimuli are processed in the right brain hemisphere, which undergoes higher degree of stimuli processing. This could be one of the explanations why fetuses as well as newborns exert higher degree of functional development of the right brain hemisphere (Michel & Moore 1999). The human fetus faces very specific environment and stimuli *in utero*, including movements of mother, movements of fetus itself (stimulation of vestibular apparatus), chemical properties of amniotic fluid, a lot of sounds from mother's body like intestinal sounds, heart rhythm, movements of diaphragm etc. There is also evidence for human fetus abilities to perceive and process mother's voice and speech, including prosody and those are thought to be prominent to induce special human fetuses reactions and learning, which could consequently serve as a pre-condition of high sensitivity to the mother's speech (melody and rhythm), the phenomena very well known in newborns, together with unique imitating and face emotional expression abilities. In this way, prenatal sound background could be very important experience for later postnatal cognitive, social and emotional capabilities. The human fetus undergoes *in utero* different ways of learning and various patterns of adaptational – behavioral strategies, which are probably of special importance for postnatal survival and the next adequate development (Michel & Moore 1999; Fedor-Freybergh 2013).

NEURODEVELOPMENTAL GENETICS AND EPIGENETICS

It is suggested that human brain development could be influenced by approximately 2/3 of all human genes. Despite such complex genetic determination there is still a great body of knowledge that requires to be elucidated in terms of special neurodevelopmental processes. There are only several genes recognized to be clearly associated with the human brain development. For example, intense development of the human cortex is also co-regulated by *HAR-1 gene*, which is very active in the Cajal-Retzius cells. These cells produce the *reelin*, peptide, which serves as a „guide" to create a typical architecture of the human cortex. Another gene *FOXP 2* influences development of brain areas, which are involved in the human language development. *Microcephalin* and *ASPM-1* genes also influence human brain development (Koukolík 2008). Mutations or other inappropriate changes in these genes expression could result in very serious consequences in brain development, perturbances in brain maturation and mental and behavioral disturbances. For example, *contactins* are the neural cell-adhesion molecules and belong to

the immunoglobulin superfamily of neural cell-adhesion molecules. They represent major molecules for neuronal development and formation of synaptic contacts and also play role in neuritogenesis, fasciculation of neurons, axonal and dendritic targeting, synapse formation and synaptic plasticity. Disruptions in contactin genes may increase the risk for autism spectrum disorders. The neural cell-adhesion molecules contactin 4, contactin 5 and contactin 6 may differ in binding properties as well as in effects on neurite outgrowth (Mercati *et al.* 2013). Also the molecules known to be members of the SRY box-containing *(Sox)* family of transcription factors exhibit activity as important transcriptional regulators for the development and differentiation of multiple organ systems. Twenty *Sox genes* have been identified in the mouse and human genomes. Several Sox genes are expressed in the developing central and peripheral nervous system and appear to regulate differentiation. For example, studies showed central role for Sox11 in regulating the processes of neurite growth and neuron survival. Special cell culture model showed that Sox11 knockdown increased expression of the pro-apoptotic gene *BNIP3* (Bcl2 interacting protein 1 NIP3) and decreased expression of the anti-apoptotic gene *TANK* (TRAF family member-associated NFκB activator) (Jankowski *et al.* 2006). Another transcription factors involved in the brain development are the *Pax factors* determined by related *Pax family genes* with similar domain binding specifity (Carbe *et al.* 2013). *Brain-derived neurotrophic factor* (BDNF) is a member of the neurotrophin family of secreted signaling molecules. BDNF is a potent regulator of neuronal development and synaptic plasticity that is fundamental to neural circuit formation and cognition. It is also involved in the control of energy homeostasis. Its dysfunctions with mutations in the genes for BDNF and its receptor, TrkB, could result in serious pathological conditions like Alzheimer´s disease, schizophrenia, depression and severe obesity in humans and mice (Vanevski & Xu 2013). Gleason *et al.* (2011) found that genetic inactivation of the *serotonin 1A receptor* (5-HT1AR) and the *fmr1* gene in mouse females resulted in psychiatric disease-like phenotypes in their genetically unaffected offsprings. 5-HT1AR deficiency in mouse females resulted in anxiety and increased stress responsiveness in their offsprings. Offsprings of 5-HT1AR deficient mouse females displayed altered development of the hippocampus, which could be linked to their anxiety-like phenotype. Maternal inactivation of *fmr1* resulted in a hyperactivity-like condition and was associated with receptor alterations in the striatum. These data indicate a high sensitivity of the offspring to maternal mutations and suggest that maternal genotype effects can increase the impact of genetic risk factors in a population by increasing the risk of the genetically normal offspring. Another interesting finding comes from research of *mitochondria DNA*. It is well known that all the mitochondria DNA is only maternally inherited and it means all DNA from the moment of fertilization during whole life of the individual comes exclusively from the mother. And this finding is even more impressive since mitochondria are very well know to be extremely important for a lot of essential biochemical processes as well as for neuronal morphogenesis and differentiation (Hroudová & Fišar 2011; Koukolík 2008). On the other hand, pathophysiology of mitochondria is involved in the pathogenesis of many psychiatric disorders, behavioral disturbances, learning dysfunctions, circadian rhythms disturbances, eating and sleep disorders (Fišar & Hroudová 2010; Hroudová & Fišar 2011; Sharpley *et al.* 2012; Lane 2012) and aging (Camus *et al.* 2012).

The very intense research during last decades gives evidence for a very special role of epigenetic mechanisms also to be markedly involved in the processes of development and organization of human brain functions. *Epigenetic mechanisms* play an important role in the regulation of gene expression in response to environmental signals and drugs and represent the interface of the genome and the environment without gene´s mutation. There is an evidence for interplay between sensory experience and innate genetic programs leading to the formation of neuronal circuits during early brain development. Recent evidence suggests that the dynamic regulation of gene expression through epigenetic mechanisms is at the interface between environmental stimuli and long-lasting molecular, cellular and complex behavioral phenotypes acquired during periods of developmental plasticity. Moreover, there is also evidence for important functions of epigenetic factors for embryonic neurogenesis (Fagiolini *et al.* 2009; Jakovljevic *et al.* 2010; Jobe *et al.* 2012). There are 3 main basic epigenetic molecular mechanisms, including *DNA methylation, histone modification* and *microRNA dysregulation* (Fagiolini *et al.* 2009; Hsieh & Eisch 2010). All these epigenetic changes could be involved in pathophysiology of many disorders and pathological conditions, including psychiatric disorders. Various stressors can operate through the epigenetic mechanisms, especially during rapid fetal development or early-life episode. For example, human infants of mothers with high levels of depression and anxiety during the third trimester have been showed to have *increased methylation* of the *Nr3c1 gene* promoter in cord blood cells. Infants delivered by C-section exhibited higher levels of *global DNA methylation* in leucocytes compared to those delivered vaginally. Remarkably, these findings indicate that the epigenome of a prenatally developing infant is sensitive to the mother's experiences, the prenatal environment, and even the experience of birth (Roth & Sweatt 2011). It is also suggested that epigenetic regulation mechanisms are seriously employed in the development and prolonged maturation of the human cerebral cortex. Development of prefrontal and other higher-order association cortices is associated with widespread changes in the cortical transcriptome, particularly during the transitions from

prenatal to postnatal development, and from early infancy to later stages of childhood and early adulthood (Shulha *et al.* 2013). This is supported by identification of 1,157 genomic loci in neuronal cells from the prefrontal cortex that show developmental changes in a chromatin mark, histone H3 trimethylated at lysine 4 (H3K4me3), which has been associated with regulation of gene expression. Majority of developmentally regulated H3K4me3 peaks were defined by rapid gain or loss of *histone methylation* during the late prenatal period and the first year after birth, followed by slower changes during early and later childhood and minimal changes thereafter. These findings suggest that there is highly regulated, pre-programmed remodeling of neuronal histone methylation landscapes in the human brain that begins before birth and continues into adolescence (Shulha *et al.* 2013). Moreover, *transgenerational epigenetic effects* have been associated also with pathological conditions such as schizophrenia, depression, drug abuse, and social dysfunction in animals and humans (Murgatroyd *et al.* 2010; Peter & Akbarian 2011; Welnhold 2012). Very interesting data brought study of transgenerational transmission of trauma by Yehuda *et al.* (2008), (also reviewed by Yehuda 2011). The authors found offsprings of the Jewish parents who underwent an extreme psychic trauma during second world war (extremely stressful, life-threatening conditions including Holocaust), recognized as posttraumatic stress disorder (PTSD), to have a lower plasma cortisol and higher risk to develop PTSD, especially in the case of maternal PTSD, and depression and anxiety in comparison to healthy controls (offsprings of parents without PTSD). Finally, multiple data analyses supported suggestion that the main pathophysiological mechanism could be explained by epigenetic changes of glucocorticoid receptor´s gene. Stress during gestation has been recognized as a powerful factor influencing both, maternal mental health and offspring brain plasticity and development. Pregnant rats exposed to stress exhibited disrupted parturient maternal behavior and changes of *microRNA profiles.* Moreover, these microRNA profiles changes were observed also in their offsprings. In the offsprings brains, prenatal stress induced changes of those microRNAs, which influence genes related to development, axonal guidance and neuropathology, including those known as putative markers of schizophrenia and bipolar affective disorder in humans (Zucchi *et al.* 2013). The role of epigenetic modification has also been demonstrated in the postnatal mother-infant interactions in animal studies. Individual variations in maternal care during the immediate postpartum period in rats are associated with changes in offspring hypothalamic-pituitary-adrenal (HPA) activity, neuroendocrine systems involved in reproduction and hippocampal plasticity (Meaney 2001). Studies also show that variations in maternal care influence the development of neuromediattor systems through epigenetic mechanisms and could be linked to the pathophysiology of neuropsychiatric diseases (Zhang *et al.* 2010).

PSYCHOIMMUNONEURO-ENDOCRINOLOGY IN PRENATAL AND PERINATAL MEDICINE

The evolution has selected tightly regulated processes aimed at maintaining stability among internal parameters despite external changes, a process termed homeostasis. This internal equilibrium is based on the interplay of three interrelated physiological systems: the nervous, immune, and endocrine systems. Their functions work as a permanently activated watching network, which communicates by the mean of specialized molecules. It could be characterized as the *immuno-endocrine-neurotransmitters-behavioral integration* with multi-level interactions and influence of neuromediattors, neuropeptides, cytokines, hormones, neurohormones and other molecules within unified interplay and integration, where each of the systems could influence other in physiological or pathophysiological way (Fedor-Freybergh 1994; Fedor-Freybergh 1999; Song & Leonard 2002; Viltart & Vanbesien-Mailliot 2007). During critical developmental periods of the neuro-endocrine-immune system, neurotransmitters, hormones and cytokines, when occurring in unphysiological concentrations, and various toxic agents, can be effective as endogenous malorganizers and result in life-long functional disturbances and diseases (Fedor-Freybergh 1994; Fedor-Freybergh 1999; Fedor-Freybergh & Maas 2011). Potential threats to homeostasis might occur as early as during *in utero* life, potentially leaving these lasting effects on the developing organism. Various environmental factors exert potentially early-life influences on the structural and functional development of individuals. This organizational phenomenon, encompassing prenatal environmental events, altered fetal growth, and development of long-term pathophysiology, has been named *early-life programming* (Viltart & Vanbesien-Mailliot 2007).

Stress (including psychological) promotes immune dysregulation, inflammation, impairs antibody responses to vaccination, slows wound healing, and suppresses cell-mediated immune function. Importantly, the immune system changes substantially support healthy pregnancy, with attenuation of inflammatory responses and impairment of cell-mediated immunity. This adaptation is postulated to protect the fetus from rejection by the maternal immune system. Thus, stress-induced immune dysregulation during pregnancy has unique implications for both maternal and fetal health (Christian 2012). For example, *prenatal stress* and inflammatory processes during pregnancy have implications for fetal development. In non-human primates, repeated exposure to stress during pregnancy affected the transfer of antibodies across the placenta. *Maternal stress* can also indirectly alter offspring

immune function through effects on preterm birth and fetal weight. In part because maternal antibodies are transferred to the fetus primarily in the final weeks of pregnancy, infants born prematurely are likely to have significantly impaired immune function. Furthermore, low birth weight has been associated with poorer antibody response to vaccination in adolescence, higher cortisol responses to acute psychosocial stress in adulthood, and increased risk of cardiovascular and metabolic disorders including diabetes later in life. Maternal immune activation could lead to strong gene expression changes (for example in crystalline gene family), which are associated with disrupted neuronal differentiation and axonal growth. Such insults could contribute to the risk of neurodevelopmental disorders such as schizophrenia and autism (Christian 2012; Garbett *et al.* 2012; Shi *et al.* 2009). Animal research also shows that antenatal maternal stress could alter functional brain responses to the fear conditioned cue in adult offspring. Rats with prior maternal stress exposure compared to those without, demonstrated heightened fear responsivity, exaggerated and prolonged corticosterone release, increased functional cerebral activation of limbic and paralimbic regions, the locus coeruleus, and white matter, and deactivation of medial prefrontal cortical regions. Dysregulation of corticolimbic circuits may represent risk factors in the future development of anxiety disorders and associated alterations in emotional regulation (Sadler *et al.* 2011). Stress and its influences on the human fetus during pregnancy are studied intensely and studies bring interesting findings. Primary and very important pathway of the effect of stress on the human fetus is the *HPA stress axis* (Sandman *et al.* 2003; Sandman *et al.* 2006). Different stress inducing stimuli result in activation of the maternal HPA axis and may alter essential developmental processes of the fetus. Depending on the duration of the gestational stress, stress-induced maternal hormonal secretions might program short- and/or long-term consequences for the health of the offspring. A lot of experimental studies support a causal role of perinatal stress on the developing organism in the occurrence of long-term physiological and psychological disturbances. For instance, malnutrition, psychological stress, or hypoxia during gestation, have been shown to impair the physiological development of the offspring. In addition, adverse effects of prenatal stress can not only alter the brain morphology of the offspring, the time course of normal aging, and the longevity of individual, but it can also affect neuroendocrine systems, thus leading to a reduced growth rate, an altered sexual differentiation, an inappropriate stress response, and immune dysfunctions. It is now widely accepted that prenatal influences on the offspring are mediated by the maternal response to stress, and more especially through maternal stress hormones secreted by the pituitary gland and adrenals. Glucocorticoids are known to act on different organs *via* mineralocorticoid or glucocorticoid receptors, therefore exerting a crucial effect on their development and function. Thus, a disturbed gestation can modify the setup and the organizational patterns of the developing individual's physiological circuits (Viltart & Vanbesien-Mailliot 2007).

Human fetal nervous system undergoes enormous development, including migration, proliferation and differentiation of the brain cells. By week 20 of gestation, axons form synapses with the cortical plate. This process continues so that by 24 weeks cortical circuits are organized. The enormous growth of the human fetal nervous system is characterized by the proliferation of neurons estimated to increase at a rate of 250,000 per minute. These unique processes are so intense that by 24 weeks after fertilization the cortical circuits are organized well (Cowan 1979). Because of the dynamics and intensity of these changes, the human fetus is particularly vulnerable to both, organizing and disorganizing influences, the phenomenon known as *"fetal programming"*. Programming is a process by which a stimulus or insult during a critical developmental period has a long-lasting or permanent influence (Sandman & Glynn 2009). Regarding stress to be an important factor influencing neural development, knowledge that the placenta expresses gene for CRH is taking a special importance. The key point elucidating its stress-related effects is that placental CRH increases maternal cortisol, but on the other hand it activates the promoter region of placental CRH gene (Sandman & Glynn 2009). In such condition the consequences of stressful events during pregnancy might exert massive effects. For example, intense social or other kind of stress in pregnant woman leads to increased maternal cortisol in plasma, which pathologically enhances the next production of cortisol since it is induced by the production of placental CRH. In such situation are both, mother and fetus exposed to increased levels of cortisol with potentially harmful effects.

The various and important effects of *natural glucocorticoids* on the central nervous system are known. Steroid hormones are considered as powerful mediators of the fetal organization since they readily cross the placental barrier. Optimal levels of glucocorticoids are required for neuronal growth, differentiation, and survival, and they positively modulate synaptic plasticity and physiologically modulate early life programming of stress reactivity. On the other hand, both animal and human studies showed that prenatal exposure to glucocorticoids excess, due to maternal endogenous overproduction or exogenous administration, may cause permanent behavioral changes in offspring and induce neuroendocrine and cardiometabolic lifelong disorders (Fietta *et al.* 2009; Viltart & Vanbesien-Mailliot 2007). Studies in animals suggest limbic regions in the developing brain are particularly sensitive to exposure to the stress hormone cortisol. However, the nature and time course of these effects have not yet been adequately characterized in humans. A prospective, longitudinal

study was conducted in healthy mother–child dyads to examine the association of maternal cortisol in early, mid-, and late gestation with subsequent measures at approximately 7 years age of child amygdala and hippocampus volume and affective problems. The data analysis revealed higher maternal cortisol levels in earlier but not later gestation was associated with a larger right amygdala volume in girls, but not in boys. Moreover, higher maternal cortisol levels in early gestation were associated with more affective problems in girls, and this association was mediated, in part, by amygdala volume. No association between maternal cortisol in pregnancy and child hippocampus volume was observed in either sex. Based on the results, the authors suggest the possible origins of neuropsychiatric disorders in early-life periods (Buss *et al.* 2012). Animal studies also showed the juveniles exposed to experimentally increased maternal corticosterone during embryonic phase had a protracted decline in corticosterone during the recovery phase of the stress response. In addition, embryonic exposure to corticosterone resulted in higher levels of reactive oxygen metabolites and an over-representation of short telomeres. In many species, individuals with higher levels of oxidative stress and shorter telomeres have the poorest survival prospects. Thus, long-term costs of glucocorticoid-induced phenotypes may include accelerated ageing and increased mortality (Haussmann *et al.* 2012). The study of Sandman and Glynn (2009) showed fetuses exposed to optimal placental CRH to exert an enhanced maturity, while fetuses exposed to higher levels exerted lower reactivity to stimulation. The authors suggest an important role of the placental CRH for fetal programming. Animal studies also demonstrated decreased DNA methylation of the corticotrophin-releasing-factor gene promotor and increased methylation of the glucocorticoid receptor exon 17 promotor region in hypothalamic tissue of adult male mice born to gestationally stressed females. These epigenetic modifications are associated with exposure to stress during the early stages of prenatal development and may involve dysregulation of placental gene expression (Fagiolini *et al.* 2009). As mentioned above, animal studies consistently show an important role for *stress pathway dysregulation* during prenatal or early life stress experiences, including prenatal stress, malnutrition, hypoxia, glucocorticoids exposure, smoking and drug abuse which increase sex – dependent risk for development neuropsychiatric disorders including major depressive disorder or schizophrenia. It is suggested that the main role in these early life periods is played by intense interaction between genes expression and environmental influences and lead to increased developmental vulnerability. In some of these studies analyses of expression and epigenetic patterns revealed changes in CRH and glucocorticoid receptor genes. Stress early in pregnancy produced a significant sex-dependent effect on placental gene expression supportive of altered fetal transport of key growth factors and nutrients (Goel & Bale 2009; Chan & Zhang 2011). Experiences of the mother during gestation play a powerful role in determining the developmental programming of the central nervous system. In particular, stress during gestation alters developmental programming of the offspring resulting in susceptibility to sex-typical and stress-sensitive neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. It is hypothesized that allopregnanolone, during gestation, could play a particularly vital role in mitigating effects of stress on the developing fetus. Prenatal stress may alter these responses and dysregulate allopregnanolone and its normative effects on stress axis function. Specifically, altered balance between glucocorticoids and progestogens during critical periods of development may permanently influence behavior, brain morphology, and/or neuroendocrine-sensitive processes (Frye *et al.* 2011).

There is also increasing knowledge of very important *roles of placenta in the fetal brain development.* For example, studies are consistently showing hormonal signals of maternal status, including glucocorticoids, insulin-like growth factors, insulin, and leptin, are sensed by the placenta and transmitted to the fetus predominantly through effects on placental function. In animal experiments was demonstrated that the placenta can convert maternal tryptophan into the neurotransmitter serotonin, providing the primary source of serotonin for the developing forebrain. Animal studies also suggest placenta has mechanism for placental adaptations to adverse maternal environments that protect the developing hypothalamus at midgestation (embryonic days 11–13), an important period of neuronal proliferation and differentiation (Zeltser & Leibel 2011). Human studies also showed maternal exposure to stress during pregnancy is associated with significant alterations in offspring neurodevelopment and elevated maternal glucocorticoids likely play a central role in mediating these effects. Placental 11b-hydroxysteroid dehydrogenase type 2 (HSD11B2) buffers the impact of maternal glucocorticoid exposure by converting cortisol/corticosterone into inactive metabolites and targeted gene deletion and pharmacological studies suggest a functional consequence of 11b-hydroxysteroid dehydrogenase for the development of the hypothalamic-pituitary response to stress. Animal molecular studies indicate regulation changes and epigenetic effects of prenatal stress in both, placenta and fetal brain. For example, prenatal stress was associated with a significant decrease in HSD11B2 mRNA, and increased DNA methylation at specific CpG sites within the HSD11B2 gene promoter in the placenta. Within the fetal hypothalamus, prenatal stress induced decreased CpG methylation within the HSD11B2 promoter and increased methylation at sites within exon 1. All these findings implicate DNA methylation as a mechanism by which prenatal stress alters HSD11B2 gene expression (Jensen Peña *et al.* 2012). Very important steroid hormones are

progesterone and estradiol during human pregnancy. It is generally accepted that maternal LDL-cholesterol is a single substrate for placental synthesis of maternal progesterone. Despite this fact, it is not clear why the levels of progesterone are substantially higher in fetal as opposed to maternal blood. The fetal zone of fetal adrenal is suggested to have a role in the synthesis of progesterone precursors as sulfates of dehydroepiandrosterone (DHEAS) and pregnenolone (PregS). While the significance of C19 3β-hydroxy-5-ene steroid sulfates originating in fetal zone of fetal adrenal for placental estrogen formation is mostly recognized, it is still not clear if maternal or fetal functions are more determining for excessive production of PregS in the in fetal zone of fetal adrenal. Thus, it may be more convenient to utilize the fetal PregS than synthesis of progesterone *de novo*. It is hypothesized that possible explanation could be the function of 17β-hydroxysteroid dehydrogenase type 2, which is expressed in placental endothelial cells lining the fetal compartment and oxidizes estradiol to estrone and 20α-dihydroprogesterone to progesterone. This action could potentially serve to provide substances which may influence the placental production of progesterone and synthesis of neuroprotective steroids in the fetus, and also to create hormonal milieu enabling control of the onset of labor (Hill *et al.* 2010). Moreover, progesterone and its isomers are suggested to have pregnancy-stabilizing effect and estradiol to have stimulating effect on the onset of parturition (Pařízek *et al.* 2005; Hill *et al.* 2007). As stated above, the gestation from the moment of fertilization is a critical "time window" during which a very intense interplay between hormones, neuromediators, cytokines, other substances and genes takes place. All these actions represent the unique interaction between maternal and fetal factors and various functions, but also determining interaction between genome and environment with possible long-lasting or ultimate consequences.

Postnatal brain development is also strongly determined by various hormones effects and interactions. Prenatal neurodevelopmental processes are of the critical importance, but subsequent postnatal regulations and interactions are necessary for adequate affective, social and cognitive development. This early postnatal life period is known as the attachment period (see below). It is characterized by very intense and unique interactions (bonding) between mother and child. Among all these unique neurobehavioral regulations are hormones influences of special importance. *Oxytocin* is also known as a *hormone of attachment* with important effects in the central nervous system, including its special role in setting of positive social and affective interactions. After birth, oxytocin is released by stimulation of the mother's nipples and besides smooth muscle relaxation it induces positive maternal emotions. During feeding oxytocin is released to the brain in both, mother and child and is probably a special co-element to induce mutual mother-infant affection, interaction and calmness. Animal and human studies indicate that other hormones, including antidiuretic hormone and prolactin are also markedly involved in the determination of parental behavior (reviewed by Hrubý *et al.* 2011).

PRENATAL CHILD, INTEGRATIVE NEUROSCIENCE OF BONDING AND COMPLEX HUMAN BEHAVIOR

All the mammalians begin to live already from the moment of fertilization as a part of the system which is represented by very close bonding between the fetus and the mother. Also the newborn consistently preserves this special kind of bonding. While during prenatal and early postnatal period is the bonding mostly physiological, postnatal period is characterized by the qualitative shift from the bio-social to psycho-social level (Michel & Moore 1999). There is a great body of evidence and knowledge that degree of the development *in utero* enables the human fetus to perceive and process a lot of sensory and even emotional and social stimuli, and that the fetus disposes of critical neurobehavioral regulations to be considered not „only the fetus", but the *prenatal child* (Fedor-Freybergh 2013). The prenatal period is the most important, critical phase for the brain development, which enables, if going well, to continue in the next very important postnatal development – the attachment period. It is characterized by unique interactions between mother and her child – *postnatal bonding*, which are necessary for complex human development. This very important life-time period is very intensely studied and described by *Bowlby´s attachment theory.* The theory reflects the importance of early close mother-infant relationships and psychosocial factors for mental health and personality organization; functional interactions and essential neurobiological processes, including emotional, cognitive, social and other interactions (Shaver & Mikulincer 2009; Hrubý *et al.* 2011). According to the theory, *attachment* is a strong offspring´s tendency of proximity-seeking to significant others. Attachment behavior has developed during evolution to assure proximity and create special bonds to these significant others (caregivers). The child's proximity-seeking behavior is organized by the behavioral system and this complex behavioral strategy emerged in evolution to increase the likelihood of survival and reproduction (Hašto 2006; Shaver & Mikulincer 2009). The attachment emerges from special interactions between child and mother and is exclusively enabled by specific neural coordination of essential quality during the critical early life period. These special bonding interactions have types of unique patterns, which are of significant importance to create essential neurobehavioral regulations for individual survival. Postnatal bonding between mother and child begins as fast as early after the birth, arising from spontaneous activation of maternal and newborn´s

behavior. The very *early "skin to skin" contact* between mother and newborn is of essential importance for postpartum adaptation and cardiorespiratory stability in newborn. Approximately 15 minutes after the birth newborn exhibits spontaneously generated movements on the mother´s chest with the breast/nipple seeking behavior. Finally, adequately postpartum adapted newborn is able to find breast/nipple of mother and breast crawl within 55 minutes after the birth. There is also an evidence how important is support of early and continuous contact between mother and child, at least for 2 hours after the birth. It is suggested that these early interactions play an important role in reinforcement of maternal behavior and mutual bonding, and establishment of mental and physical health in newborn (Mrowetz & Peremská 2013).

Interdisciplinary research and clinical data have affirmed the concept that in infancy and beyond, the *regulation of affect is a central organizing principle* of human development and specific motivation systems (Figure 3). Affect regulations are crucial to coordinate other behavioral characteristics and emotional reactions to novelty and stress. Socio-emotional learning during the attachment period is internalized consequently and leads to an individual capacity to regulate, generate and maintain emotional security during life (Schore 2001). There are several types of attachment, but generally it is useful to distinguish between secure and insecure attachment. The secure type is the physiological one and it is characterized by accessibility of the mother whom the child uses as a "safe base" as well as by the correct maternal evaluation of the child's signals to fulfill its needs. The complex developmental psycho-neurobiological model of attachment suggests that *secure attachment* is a protective factor for psychosocial development. The secure type of attachment is crucial for mental health because of its facilitating effect on adaptivity, stress copying abilities and social functioning as well as for somatic health because of its affective, neuroendocrine and psycho-somatic regulations and influence on immunity. The established attachment relationships represent a fixed pattern of strategies (reviewed by Hrubý *et al.* 2011). *The insecure attachment* occurs significantly more often in patients with mental disorders (Agrawai & Gunderson 2004; Hašto 2006). Many studies have shown that insecure attachment is inversely related to well-being and positively associated with depression, anxiety, eating disorders, substance abuse, conduct disorder and personality disorders (Shaver & Mikulincer 2009). The progress of modern neuroscience enables interpretation of neurobiological aspects of the theory as multilevel neural interactions and functional development of important neural structures, effects of neuromediattors, hormones and essential neurobiological processes including emotional, cognitive, social interactions and the special key role of mentalizing (Hrubý *et al.* 2011). *Mentalizing* or *Theory of Mind* could be explained as a

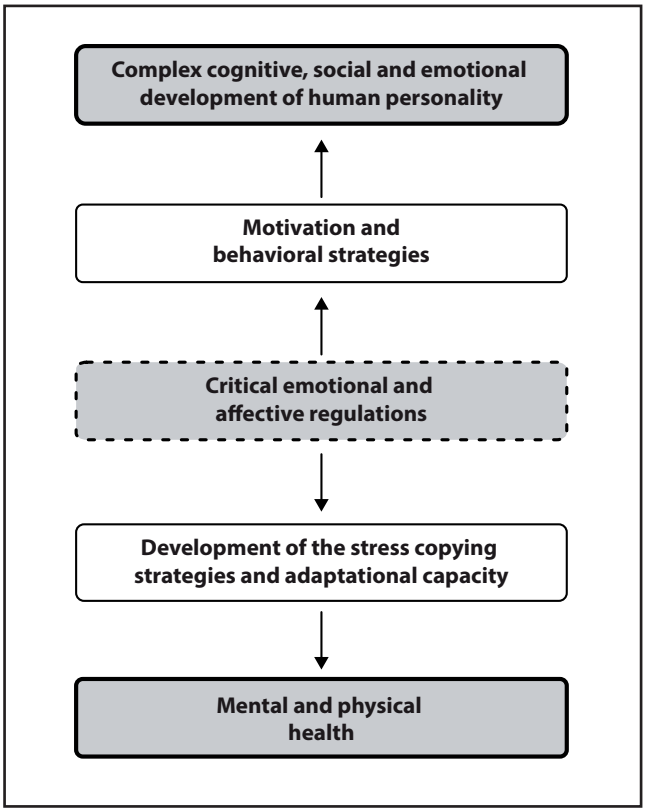

Fig. 3. Central role of emotional and affective regulations in human development.

man's ability to read other people's gestures and faces within identification of their underlying emotions and mental states (Frith & Frith 2005; Blakemore 2010). Mentalizing is closely related to the function of neural mirror mechanism. In humans, the mirror mechanism is organized into two main cortical networks, the first being formed by the parietal lobe and premotor cortices, and the second by the insula and anterior cingulate cortex. Its role is to provide a direct understanding of the actions and emotions of others without higher order cognitive mediation (Rizzolatti *et al.* 2009). Such function and organization enable early identifications and emotional reactions and have an enormous importance for early mother-child interaction. It is supposed that it is just the brain mirror system, which is fundamentally involved in the neural processes allowing us to share emotions, intentions and actions of others. The human brain has the unique ability to represent the mental states of the self and others and the relationship between these mental states, making possible the communication of ideas (Frith & Frith 2006). Such neural processes underlying social interactions are already active in infants, exhibiting gradual enhancement during development. A large body of research indicates that theory of mind typically develops in children during the first few years of life (Dumontheil *et al.* 2009). Mentalizing involves important emotional, cognitive and interpersonal processes and is suggested

to be a pivotal factor in the evolution of attachment (Allen *et al.* 2008). The studies which used mentalizing tasks and neuroimaging methods showed activation of a network of regions including the superior temporal sulcus at the temporo-parietal junction, the temporal poles and the dorsal medial prefrontal cortex (Burnett & Blakemore 2009; Blakemore 2010). This network is considered to be *the social brain* and mentalizing is one of the wide range of actions within its unique capacity. Having theory of mind in attachment relationships creates the human capacity for rapid development of the social brain and consequently cultural learning (Frith & Frith 2005; Allen *et al.* 2008). Thus, the attachment relationship between infant and mother with its unique interactions and neurobehavioral regulations is critical for *complex human development*, including optimal social, emotional, and cognitive development (Strathearn *et al.* 2009). As mentioned above, the period of prenatal and early postnatal bonding represents very important life time phase during which crucial neurodevelopmental processes and basic coordinations are enforced in order to develop and maintain the complex human capabilities necessary for complex human functioning (Figures 1 and 2).

CONCLUSIONS

The progress in science and medicine has brought an enormous knowledge about unique importance of processes involved in the physiology and pathophysiology of human pregnancy, fetal development, perinatal and early life periods. There is a great evidence for life span or long-lasting effects of complex multifactorial interplay during these periods, which are recognized from many points of view as a "critical time window" to promote health or induce predisposition to pathological conditions. It is the time of crucial regulations and interactions on all levels of developing individual organism. New research approaches and scientific findings elucidate also the unique processes of very early fetal brain and human mind development. New findings indicate that human fetus is able to recognize and process a lot of stimuli, including social and affective stimuli, and it also exhibits behavioral patterns and cognitive processing (Hrubý & Fedor-Freybergh 2013). Consistent scientific data continuously point at development *in utero* as a crucial period for human brain development. Prenatal and early life periods represent the crucial developmental gap which gives arise of necessary neural regulations for development of complex human behavior and establishment of mental and physical health. Prenatal brain development is extraordinarily complex set of events and because of this fact it could by influenced by an extreme range of factors in many different ways. Increasing knowledge in many scientific areas like developmental neuroscience, behavioral embryology, neurodevelopmental genetics and epigenetics, molecular biology, psychoimmunoneuroendocrinology, and others, and emerging findings with the help of new neuroimaging methods (DTI, MRI, fMRI etc.) enable to identify crucial processes and factors employed in accurate or abnormal brain development. For example, there is a great evidence for prenatal maternal stress to be one of major pathophysiological factors influencing *in utero* development with life-long consequences. Animals studies show early embryonic exposure to maternal glucocorticoids can broadly impact physiology and behavior in offsprings with long-lasting effects in adulthood (Haussmann *et al.* 2012). In humans, maternal exposure to stress during pregnancy is associated with significant alterations in offspring neurodevelopment and elevated maternal glucocorticoids likely play a central role in mediating these effects, especially through epigenetic mechanisms (Jensen Peňa *et al.* 2012). On the other hand, results of recent studies imply that there is a degree of plasticity that remains in the adult for alterations in gene expression by epigenetic modification, which could promote the reversibility of induced phenotypic effects. Those findings suggest that aberrant phenotypes induced *in utero* or during early development can be potentially rescued. In this way, epigenetics provides a probable target for promising development in diagnostics and treatment in future (Chen & Zhang 2011). Based on this knowledge, the prenatal stages of life could represent a unique opportunity for the primary prevention of psychological, emotional and physical disorders in later life and better recognition of the pathophysiology of many serious neuropsychiatric and other disorders or potentially harmful conditions (Fedor-Freybergh 1993; Fedor-Freybergh & Maas 2011). Among all these special actions and interplays, arise of human mind is taking a unique position. Scientific data support human fetus ability to process a wide range of stimuli as well as exhibition of adaptation and memory capacities, and even well defined neurobehavioral states. All these unique findings suggest the very early beginning of the processes that probably underlie the formation of unique human mind capacities. This is also supported by identification of extraordinary newborn´s capabilities to generate spontaneous behavioral strategies in order to develop very unique type of bonding between mother and child. These crucial prenatal and early postnatal life periods involve special neural coordinations and regulations of absolutely critical importance for an adequate development of complex human mind and behavior, including affective, social and cognitive capabilities, and stress copying strategies (Figures 2 and 3). In such settings is human tendency to maintain the life´s continuum transformed into typically human strategies to create long-time partnerships, alliances, bonding and activations of parental behavior, which are necessary for adequate upbringing and complex development of human youngsters (Figure 1). Consequently, all these unique human capacities are critical for individual functioning in very complex human soci-

ety, which requires extraordinarily developed system of complex communication abilities, various interactions, well established adaptation capacity, moral liability, and highly coordinated level of social interactions. Moreover, all these critical capacities are directly interconnected with individual mental and physical health. A lot of findings in many neuroscientific areas indicate that integrative neuroscientific approaches could be very benefitial to study extraordinary complex functioning of human mind and behavior. It gives us opportunity to assess the human mind as a dynamic organization of unique mental processes and continuous mutual interplay between various domains of human capabilities. Such integrative approaches could establish new methods in science, in primary and secondary prevention, in treatment strategies, and markedly contribute to the development of modern integrative and personalized medicine.

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