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Review article

Mother-newborn separation at birth in hospitals: A possible risk for neurodevelopmental disorders?

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ABSTRACT

In the 20th century, mother-infant separation shortly after birth in hospitals became routine and unique to humans. However, this hospital birth practice is different from the practice in our evolutionary history, where newborn survival depended on close and essentially continuous maternal contact. This time shortly after birth represents a psychophysiologically sensitive or critical period for programming future physiology and behaviour. We hypothesize that early maternal separation as conducted in conventional hospital practice may induce similar epigenetic changes similar to those found in various mental diseases that may also be implicated in neurodevelopmental disorders.

1. Introduction

Traditionally, women used to give birth at home and the baby's crib was kept by the side of the mother's bed. The shift of giving birth at home to giving birth at the hospital − as well as the hospital practice of routine separation of mother and infant − was introduced with the turn-of-the-century development; in the same time as anaesthesia, asepsis, and surgery were started (Lindheim, 1981). In those days, women generally got general anaesthesia and could not care for their babies. The hospitals created nurseries to care for infants that were separated from their mothers for 24–48 h. The baby is brought to his/her mother mainly for breastfeeding, according to actual hospital protocol. In the 1920s, 80% of women gave birth at home in the UK, but in 2011, only 2.3% of births occurred at home (Office for National Statistics Births in England and Wales by Characteristics of Birth, 2012). In the US, the percentage of home births was 50% in 1938, but in 1955, it was less than 1% (MacDorman et al., 2014). In 1961, Brazelton's classic study (1961) revealed that general anaesthesia is harmful to newborns. As an outcome of this research, more people started to refuse to get general anaesthesia during birth, which made it possible to establish an interaction of the mother and infant immediately after birth. Later, works by Rubin (1967a, 1967b) and Klaus and Kennell (1976, 1983) about the importance of bonding between a mother and child became popularized that led to important changes in the hospital care of postpartum women, including the rooming-in policy.

However, during the 20th century, hospitals became the predominant sites of birth for human babies in the most developed countries. In this new practical situation, infants are kept in a separate nursery. While several hospitals have now started to keep the mother and baby in the same room (mainly since the advent of the WHO/UNICEF Baby Friendly Hospital Initiative in 1991, (WHO, 2017a)), this rooming-in practice (keeping mothers and babies together 24 h a day) is rare and used by mainly wealthier parents. Although the latest studies reported similar neonatal death rates and similar risk for planned home birth and planned hospital birth (Zielinski et al., 2015; Janssen et al., 2009; Bolten et al., 2016; de Jonge et al., 2015; Snowden et al., 2015; Kataoka et al., 2013), the debate about whether planned home birth is as safe as planned hospital birth continues (Wax et al., 2010; Grünebaum et al., 2015; Kennare et al., 2010) in practice, professional policy and the literature. We should also consider that maternal outcomes are better in the case of planned home birth in regard to reduced complication rates, less intervention, and increased satisfaction with the birth experience in the planned home birth surroundings (de Jonge et al., 2013; Merg and Carmoney, 2012; Hiraizumi and Suzuki, 2013; Cox et al., 2013).

We first overview of several harmful aspects of early mother-newborn separation and focuses exclusively on the effects of early maternal-infant separation, without consider any other environmental and social factors, differences in maternal nutrition and behaviour, or any gestational or perinatal complications. Next, we look over of several favorable aspects of early mother-newborn contact after birth. Finally, we present a hypothesis that early mother-infant separation, during

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conventional hospitalized birth, may have harmful effects on otherwise healthy newborn babies that may last throughout the entire life span of these children, influencing the maturation of their central nervous system and their behaviour, and it may put babies at risk for various mental and systemic diseases by means of stress-induced neuroepigenetic processes. Namely, early separation at the moment of birth and during the days that follow in-hospital birth may increase the risk of neurodevelopmental disorders.

2. Mother − newborn separation

2.1. Early maternal separation of neonatal rats

Neonatal maternal separation (MS) of rats (neonatal rats are removed from their mother for several hours daily during the first two weeks of life) has successfully been used as a neurodevelopmental model to mimic behavioural and neuroendocrine responsiveness to early-life stress in humans (Lippmann et al., 2007; Sanders and Anticevic, 2007; Caldiji et al., 2000).

In experiments by Kehoe and Bronzino (1999), rats were isolated from their dam for 1 h per day during postnatal days 2–9, which altered hippocampal neuroplasticity. This effect endured into adulthood. The isolation stress enhanced hippocampal long-term potentiation (LTP) induction and duration in both males and females. When Daniels et al. (2009) separated Sprague Dawley neonatal rats for 3 h per day from postnatal day 2–14, it induced hypothalamic-pituitary-adrenal (HPA) axis dysregulation and abnormal behaviours. Changes in the behaviour of pups were associated with increased plasma corticosterone release and increased nerve growth factor levels in the hippocampus. Monroy et al. (2010) studied maternal separation (MS) and found that substituted maternal handling disrupted the dendritic morphology of neurons in the prefrontal cortex (PFC), the ventral hippocampus (CA1), and the nucleus accumbens (NAcc) in male rat offspring. These brain areas are associated with affective disorders at pre-pubertal and post-pubertal ages in male rats. Colorado et al., (2006) investigated the effects of infant-mother separation in rat adolescence. During the first 2 weeks of life, pups were separated for 6 h per day and were subjected to early handling (EH) for 10 days. The authors compared MS and EH groups to standard facility reared (SFR) controls. MS induced a decreased orienting behaviour and an increased impulsive behaviour in adolescence. MS rats presented hyperactive behaviour in the novel environment, while EH rats were generally less active. Regarding the effects of mother-infant separation on regional metabolic capacity, Spivey et al. (2011) studied cytochrome oxidase (CO) activity (CO activity reflects long-term changes in the brain's metabolic capacity (Gonzalez-Lima and Cada, 1998)) in the brain of Holtzman rat pups. Prolonged mother-infant separation (6 h per day for 10 days) reduced the brain metabolic capacity in the deep layers of the medial prefrontal cortex, caudate putamen, and the shell of the nucleus accumbens. In contrast, early handling (EH) with brief separation (15 min per day for 10 days) increased CO activity in the lateral frontal and medial prefrontal cortex compared to prolonged mother-infant separation but decreased CO activity in the ventral tegmental region, subiculum, and posterior parietal cortex. These separations produced dysfunctions of the prefrontal and mesolimbic areas, which may promote behavioural changes later in life.

Aisa et al. (2007) have shown that Wistar rats exposed to 3-h separations per day from their mother during the first 3 weeks of life presented behavioural and neuroendocrine signs of increased stress reactivity as adults. The authors proposed that the behavioural and cognitive deficits were due to the elevated levels of glucocorticoids in the MS rats. The authors also suggested that the stress hyperresponsiveness observed in MS rats could be due to the disturbed feedback sensitivity mediated by hippocampal glucocorticoid receptors.

Early life separation stress (3-h long maternal separation or 15-min short maternal separation) could produce persistent perturbations in the serotonergic, noradrenergic and dopaminergic neurotransmitter systems in the rats' brains (Arborelius and Eklund, 2007). Three-hour separation per day for 2 weeks of Sprague-Dawley pups (Lee et al., 2007) decreased the 5-HT content in the hippocampus and the expression of 5-HTT mRNA in the raphe compared to controls. The persistent perturbation of these neurotransmitter systems can promote and participate in the development of depression- or anxiety-like behaviours in adulthood.

Neonatal maternal separation is also associated with the development of eating disorders. For example, Jahng (2011) exposed Sprague-Dawley pups to maternal separation for 3 h per day during the first 2 postnatal weeks, which produced binge-like eating disorders with increased activity of the HPA axis. Maternal separation can also create dysfunction of the brain-gut axis that is similar to irritable bowel syndrome (IBS), i.e., altered enteric microflora, alterations of intestinal barrier function, excessive stress response and visceral hypersensitivity (O'Mahony et al., 2011).

Early maternal separation can also perturb endogenous opioid systems. During the first few weeks of neonatal life, opioid systems are reorganized in many brain areas (Petrillo et al., 1987). The isolation of Long-Evans rats from their mothers for 3 h per day during postnatal days 2–14, or 15 min from the dam, produced changes in sensitivity to the effects of morphine that could reflect altered endogenous opioid systems (Kalinichev et al., 2002).

In studies by Diehl et al. (2014), Wistar rats endured long-term separation from their dam for 3 h per day during postnatal days 1–10. Offspring were also exposed to a contextual fear conditioning task at 60 days of age. Maternal separation stress induced increased amygdala activity (revealed by means of the activity of Na^+, K^+-ATPase) and affected the behaviours associated with fear in adulthood, and this outcome was task-specific.

In experiments by Wu et al. (2014), neonatal rats endured maternal isolation from postnatal days 1–9 that induced increased anxiety and depression, social deficits and excessive self-grooming, which are behavioural phenotypes with similar features to those of autism. The authors have also shown that the isolation of neonatal rats remarkably impaired adult neurogenesis.

Recently, Yang et al. demonstrated (2017) that the separation of neonatal rats from their mother for 3 h per day (during the first 3 postnatal weeks) modified myelination in the medial prefrontal cortex (mPFC) and impaired mPFC-dependent behaviours.

2.2. Early maternal separation of neonatal nonhuman primates

Regarding the effects of early maternal separation, most experiments have been performed on rats. However, while these studies are promising, we have to consider that there are large differences in the gene compositions of rats and humans. In addition, the primate brain is more mature at birth than the rodent brain, and rodents generally exhibit a stress hyporesponsive period (Lupien et al., 2009; Matsumoto et al., 2006) that is not present in primates. Therefore, a nonhuman primate is a more suitable model to examine early adversity in humans.

The first essential primate experiments (these studies were infamous for their cruelty) on maternal deprivation in rhesus monkeys were performed by Harlow in the 1950s, '60s, and '70s; later, Suomi conducted similar maternal deprivation experiments on infant monkeys (Harlow, 1953, 1958; Harlow and Zimmermann, 1959; Harlow and Suomi, 1971; Suomi, 2011). These studies revealed that permanently separating primate infants from their mothers and rearing them under conditions of total isolation produced devastating effects on their subsequent development and behaviour (Suomi, 1997). The strong and lasting social bond between mother and infant (Harlow, 1958) is basically homologous with Bowlby's (1958, 1977) model of human mother-infant early life attachment.

Large numbers of studies were conducted on primates regarding the effects of mother-infant separations (see the excellent reviews by Parker

and Maestripieri, 2011; Meyer and Hamel, 2014). However, our paper focuses on studies of early separation, during the first days and weeks of life that follow birth, which may mimic the separation common following human hospital birth.

Seiler et al. (1979) studied nocturnal cardiac arrhythmias in 9 infant pigtail monkeys (*M. nemestrina*). The cardiac arrhythmias (also known as *cardiac dysrhythmia* or irregular heartbeat) were examined during 3 normal nights, 3 nights after maternal separation, and 3 nights following the reunion with the mother. Maternal separation induced increases in arrhythmias and decreases in heart rate, and some infants presented prolonged separation-induced cardiac arrhythmias.

Laudenslager et al. (1995) determined the levels of plasma cortisol and growth hormone for brief maternal separations in bonnet (*Macaca radiata*) and pigtail monkeys (*Macaca nemestrina*). A 2-week maternal separation produced a rise in total and free cortisol immediately following maternal separation in both species. In addition, an increase in cortisol is positively related to distress behaviours, such as vocalization and postural slouch.

During the first weeks of life, the parent-infant relationship of marmoset infants, in contrast to the rat pups, is in continuous infant-mother body contact (24 h per day) (Pryce, 1996). Dettling et al. (2002) first successfully demonstrated that repeated early deprivation of parental care (ED) (used to examine the effects of early life stress in rats) can also be applied to marmoset monkeys. Seven pairs of marmoset monkey offspring (each provided control twins (CON)) were exposed to ED for 30–120 min/day on postnatal days (PND) 2–28. The ED procedure created a robust reduction in body weight by PND 28. Repeated ED induced acute increases of epinephrine and norepinephrine in the urinary samples, suggesting that ED activated the sympathetic autonomic nervous system (ANS) of infant monkeys. The ED infants also presented more distress vocalization, more time in the suckling position, and less social play than the control infant twins. In addition, repeated ED also induced increases in cortisol, although at PND 28, basal cortisol was reduced in the ED infants compared with that in the control monkey offspring. According to the authors (Dettling et al., 2002), these results are remarkable and parallel the human studies of neglected children with psychopathology, who present low peak basal cortisol levels, and children with post-traumatic stress disorder (PTSD) symptoms, who show enhanced dexamethasone suppression of cortisol (Heim and Nemeroff, 2001).

Pryce et al. (2004) continued their experiments with marmoset monkey regarding the repeated early deprivation of parental care (ED). Nine pairs of marmoset monkey offspring (each provided control twins (CON)) were exposed to ED for 30–120 min/day on postnatal days (PND) 2–28. They measured basal urinary norepinephrine (NE) and cardiophysiologic activity during the first year of life. The ED monkeys presented increased basal urinary NE and increased systolic blood pressure compared to the CON. After 1 year, with the help of neuropsychologic tests, the authors examined perseveration and the motivation to obtain reward in the ED monkeys compared to those in the CON. The ED monkeys required more sessions to reinstate stimulus-oriented behaviour following reversal and performed fewer PR operant responses (progressive ratio (PR) reinforcement schedule), indicating that reward was less of an incentive. The authors concluded that ED manipulations of marmoset monkey offspring could trigger chronic changes in the homeostatic systems of these monkeys that are similar to the changes seen in children exposed to early-life adversity and those associated with major depressive disorder (MDD) (Teicher et al., 2003) as well as responses to environmental stimuli that are similar to those characteristic of MDD.

Approximately 50% of patients with mood disorders present hypercortisolism. Cortisol takes affect through mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the central nervous system (CNS) (Medina et al., 2013). MR and GR are greatly expressed in the human hippocampus and a reduction in the levels of MR or GR may play a role in the development of major depressive disorder (MDD). Recently, Arabadzisz et al. (2010) exposed common marmoset infants (11 ED subjects and 9 CON subjects) to daily 30–120-min social isolation for 1 month and examined the long-term changes in homeostasis and emotional behaviour. Infants were separated from the parent and isolated in a neutral environment for 30–120 min/day on postnatal days 2–28. The control infants (CON) were handled by the parent. This study demonstrated that ED in primate infants generated moderate reductions in MR and GR gene expression in the hippocampus during adolescence, but did not generate reductions in the prefrontal cortex, other cortical areas, or the hypothalamus. The authors proposed that it is unlikely that chronic, moderate reductions in MR and GR gene expression in the hippocampus could be acute-mediators of the long-term emotional effects of ED; rather, these effects are likely due to the hippocampal neurodevelopmental processes that involve MR/GR.

The hippocampus belongs to the limbic system, which plays essential roles in the formation of memories and emotions about new events, places and stimuli (VanElzakker et al., 2008). Hippocampal dysfunction has been implicated in various diseases, such as post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), depression, anxiety, and autism, among others (Plessen et al., 2006; Campbell and MacQueen, 2004; Schumann et al., 2004; Shin et al., 2006). Law et al. (2009) examined the expression of eight hippocampal genes of deprived marmoset monkeys that are implicated in neural plasticity and the pathophysiology of various mood disorders. The monkeys were separated from their parents for 30–120 min each day with variable durations and times of day on post-natal days 2–28. The authors suggested that, ..“early deprivation in a nonhuman primate, in the absence of subsequent stressors, has a long-term effect on the hippocampal expression of genes implicated in synaptic function and plasticity.

2.3. Early maternal separation of human infant

After birth, similar early separation experiments, such as in animals cannot be carried out ethically in human cases. A large number of studies in humans regarding the early maternal separation of infants (or preterm infant) mostly focus on the first 1–2 h (or early postpartum days) of the infants’ skin-to-skin interaction with their mother and its possible effects on breastfeeding, cortisol levels, infant’s crying, infant’s sleep, reduction of the pain, infants' physiological, emotional, and cognitive regulation, etc.) (Feldman et al., 2010; Mörelius et al., 2005; Bramson et al., 2010; Feldman et al., 2014; Mizuno et al., 2004; Christensson et al., 1992; Bystrova et al., 2003; Moore et al., 2016; Gray et al., 2000; Ahn et al., 2010; Widström et al., 2011). For example in a study of Bystrova et al. (2009) 176 mother-infant pairs were randomly assigned to four experimental groups, and one of the groups was assigned to a mother-infant separation for 2 h after birth. The study revealed that one-year old infants, who spent the first 1–2 h skin-to-skin (SSC) with their mother, displayed better self-regulation evaluated by means of a structured play session. They were less easily frustrated and better able to calm themselves. In contrast, mothers and infants who were separated for 2 h presented a higher risk of poor maternal-infant bonding one year later. This negative outcome of a 2-h separation after birth was not compensated by rooming in for the rest in the hospital stay. Morgan et al. (2011) examined the effect of maternal separation in 2-day-old, full-term human neonates. Neonates slept in skin-to-skin contact with their mothers and slept alone for 1 h in each place. They revealed a 176% increase in autonomic activity and an 86% reduction in quiet sleep in separated infants, and sleep cycling was almost abolished during maternal separation compared with that during skin-to-skin contact (also see an excellent sleep related paper by Russell et al., 2013). In Christensson et al. study (1995) newborn’s crying was registered during the first 90 min after birth. Human newborns who were separated from their mothers − compared to those who are skin to skin with their mothers − presented 10 times the number of cries and 40 times the duration of crying. The authors suggested that in human

infants this crying is not dependent on earlier social experience and may be a genetically encoded reaction to separation. Elverson et al. (2012) found higher cortisol levels in human infants who were not held by their mothers during the first 6 h after birth. Yamauchi and Yamanouchi (1990) revealed that the frequency of breastfeeding was considerably higher in infants rooming-in than in those not rooming-in.

3. Mother's odour, touch, voice, face, and microbiota

In this section we overview of several favorable aspects of early mother-newborn contact after birth.

3.1. Mother's odour

The olfactory system is one of the phylogenetically oldest sensory modalities and is a vitally important sense for animals. Olfaction can detect, discriminate and mediate the perception of an enormous number of chemicals (called odorants and pheromones) that convey information about the environment to the receiver in most mammals. The perception of odorants and pheromones is mediated by means of two major olfactory systems, the main olfactory system (or the main olfactory epithelium (MOE)) and the vomeronasal system (VNO or Jacobson's organ), as well as minor systems, such as the septal organ and the Grueneberg ganglion (Wackermannová et al., 2016). The two major olfactory systems by which most vertebrates can detect chemosensory cues mediate the neuroendocrine and behavioural processes important for social behaviour. The VNO accessory olfactory system mainly detects pheromone chemical cues that carry information between members of the same species. Although human embryonic VNO anlage exerts a developmental track, the existence and functionality of the VNO has been debated in adult human and pheromonal communication, and pheromones may be conveyed by means of the main olfactory system in humans (Frasnelli et al., 2011). It is possible that the main olfactory system and the VNO accessory olfactory system can detect, at least in part, overlapping social chemosignals (Spehr et al., 2006; Kelliher, 2007; Keller et al., 2009). Namely, the VNO is not the only pheromone detecting system (Martinez-Marcos, 2001). In addition, there is crosstalk between the main and accessory olfactory systems, and the neurons in the amygdala can receive inputs from both systems (Mucignat-Caretta et al., 2012). It has also been shown that steroids may act as sex pheromones in a sex-specific manner and that they can convey subconscious chemosensory biological cues in humans (Zhou and Chen, 2008; Zhou et al., 2014).

Newborn babies have a highly developed sense of smell and orient themselves by smell more than any other sense. Maternal odour can attenuate crying and enhance nipple acceptance and feeding in certain human infants (Sullivan and Toubas, 1998). Recently, Nishitani et al. (2009) examined the effects of odour from the mother's milk, another mother's milk and formula milk on infants' behavioural pain responses. They showed that crying, grimacing and motor activity were reduced by odour from the infants' own mother's milk. However, another mother's milk or formula milk did not produce these effects. Marin et al. (2015) demonstrated that 2-day-old infants who experienced skin-to-skin contact with their mothers could recognize their own mother's axillary odour. Studies revealed that mothers can discriminate the odors of their newborns from those of unfamiliar neonates (Porter, 1998; Vaglio, 2009). Thus, odour communication between a mother and her infant is a bidirectional process.

Vaglio et al. (2009) identified the volatile chemicals from sweat patch samples from the para-axillary and nipple-areola areas of women during pregnancy and after childbirth. They revealed that during pregnancy, women produced a distinctive pattern of five volatile compounds. The authors proposed that distinctive volatile compounds from the para-axillary region of pregnant women may help newborns recognize their own mother, and the specific volatile compounds of the nipple-areola area can serve as a guide to nourishment.

The latest study by Neshat et al. (2016) revealed that breast milk odour (compared to vanilla odour) could reduce the variability of preterm infants' heart rate and blood oxygen saturation during and after venipuncture.

The first postnatal hours may be a particularly sensitive period for olfactory learning by human neonates. In studies by Romantshik et al. (2007), newborns were subjected to an odorant for 30 min at a postnatal age of 4–37 min (early exposure, prior to being breast fed for the first time) or 12-h post-partum (late exposure). Early exposure led the infants to be oriented towards the familiar odour longer than a novel odour. This behaviour suggests that efficient olfactory learning and memory emerge only if the exposure occurs shortly after birth.

The major histocompatibility complex (MHC) molecules can bind peptide fragments derived from pathogens and present them on the cell surface for recognition by the appropriate T cells. MHC genes are linked to reproductive and social behaviours such as mate choice and kin selection (Penn and Potts, 1998; Janssen and Zavazava, 1999; Jacob et al., 2002). According to a Setchell et al. (2011) study on the Old World monkey, odour provides a cue of individual genetic quality as well as information against which the receiver can compare its own genotype to assess genetic similarity. The authors emphasized that odour signals take on a much greater role in communication in anthropoid primates, including humans, than previously believed.

It is well known that the dopaminergic system is the main regulator of reward-guided learning in humans in regions such as the caudate nucleus and putamen. Recently, Lundström et al. (2013), with the help of functional magnetic resonance imaging (fMRI), measured mothers' brain responses to infants' body odours. They did not find any significant activation in the primary olfactory cortex. In contrast, the body odors from 2-day-old newborns induced activation in the reward-related cerebral region (the dorsal caudate nucleus) in women, regardless of their maternal status (both in parent or non-parent females). The orbitofrontal and insular areas were also activated by the infants' body odours (However, the authors mentioned that there is a direct anatomical projection between the lateral orbitofrontal cortex and caudate nucleus and the ventral putamen (Seubert et al., 2012) and that a significant network can also exist between the insular cortex, medial putamen and medial caudate nucleus (Ongur and Price, 2000)). These results suggest that certain body odours may help mother-infant bonding processes via activation of the reward-related cerebral areas in women.

Recently, Nishitani et al. (2014) used near-infrared spectroscopy (NIRS) to study whether infant olfactory signals could also modulate PFC activity in mothers compared to nonmothers. They found an increased activation in the PFC during the detection task of infant odours in mothers but not in nonmothers; increased PFC activation was specific to motherhood. OFC participate in emotional reactions, social behaviours, reversal learning, associative memory, and adaptation to reward change (Constantinidis and Procyk, 2004). Since the PFC, mainly the OFC, is a secondary and tertiary olfactory cortical region, it suggests that infant cue–induced human maternal affection also involves the neural circuits of reward systems.

Studies showed that pleasant odours tend to induce positive moods, whereas unpleasant odours tend to induce negative moods (Chrea et al., 2009; Yeshurun et al., 2009; Herz, 2016). In addition, odours can induce changes in heart rate or skin conductance and produce effects on cognition and behaviour (Bensafi et al., 2002; Ludvigson and Rottman, 1989; Alaoui-Ismaïli et al., 1997; Pichon et al., 2015). In experiments by Matsunaga et al. (2013), pleasant odours evoked memories and decreased levels of interleukin 2 (IL-2) in plasma. IL-2 inflammatory cytokine is normally produced by T-lymphocytes during an immune response. Since the ventromedial prefrontal cortex (vmPFC) and the orbitofrontal cortex (the OFC is the secondary olfactory cortex) can regulate peripheral immune activities, this result suggests that odours may exert a direct influence on the immune system (Herz, 2016).

There is increasing evidence of an essential connection between

olfactory stimulation and emotional processing (Soudry et al., 2011). Odours are particularly powerful memory cues that induce the most vivid and emotional memories of all sensorial stimuli (Saive et al., 2014).

In contrast to other sensory systems, mammalian olfactory pathways do not pass through the thalamus to reach the cortical regions. The olfactory input has direct connections via the olfactory bulb and the primary olfactory (piriform) cortex to the amygdala and hippocampus. From the amygdala and hippocampus, olfactory cues are conveyed to the secondary olfactory cortical areas, such as the orbitofrontal cortex (OFC) and the insular cortex (Kadohisa, 2013). It seems that the amygdala and hippocampus underwrite specific odour memories (Yeshurun et al., 2009; Herz, 2016).

Experiments have revealed that memories triggered by smells are more vivid and more emotional than those induced by pictures, sounds or words (Herz, 2004; Arshamian et al., 2013). Damage to the hippocampus or its nerve connections can produce amnesia. Odour-linked memories are the most resistant to being forgotten and can persist even after damage to the hippocampus (Gottfried et al., 2004). Patients with a damaged hippocampus can have amnesia stretching back many years but can still recall smells from their childhood.

3.2. Mother's touch

For a newborn, a mother's touch provides a feeling of safety, comfort and love. From rat pups to human infants, several studies have proven that touch is one of the earliest forms of mother-child interaction, promoting growth and development via the positive effects of supplemental mechanosensory stimulation (Ardiel and Rankin, 2010).

While previous models of interoception focused on visceral sensations, recent studies showed the essential importance of interoceptive mechanisms in emotion and self-recognition (Schleip and Jäger, 2012). In addition to proprioceptive nerve endings, human skin also contains interoceptive C-fibre endings (unmyelinated free nerve endings) that trigger a general sense of well-being. These slowly conducting interoceptive nerves (Löken et al., 2009) mainly project to the insular cortex rather than the primary somatosensory cortex, which is the main target of proprioceptive sensations (Berlucchi and Aglioti, 2010). Minor parts of these C-fibre endings perform multimodal functions or are chemoreceptors or thermoreceptors, but most of them work as mechanoreceptors. Craig (2009) suggested that the neural pathways associated with interoception may be correlates of consciousness.

The term 'social brain' refers to a set of brain regions, such as amygdala, orbital frontal cortex and temporal cortex that enable our dealings with the social world (Frith, 2007). Brauer et al. (2016) measured the frequency of maternal touch for 43 five-year-old children in a 10-min play session. Then, a resting-state functional magnetic resonance imaging (R-fMRI) was performed on all children. R-fMRI can evaluate regional interactions that occur when a subject is not performing any explicit task. The default mode network presented a positive relationship between the frequency of maternal touch and R-fMRI activity in the right posterior superior temporal sulcus (pSTS), which suggests that childhood tactile experiences can shape the development of a "social brain".

Early mother-infant skin-to-skin contact (SSC, also called Kangaroo Care) is a practice that involves, e.g., placing the naked newborn prone on the mother's bare chest immediately after birth. Several studies have proven the beneficial effects of SSC practice for preterm infants, e.g., it can improve infants' physiological, emotional, and cognitive regulatory processes. SSC decreases salivary cortisol and heart rate, organizes sleep-wake cycles, and improves mood (Feldman et al., 2002; Ludington-Hoe and Swinth, 1996; Mörelius et al., 2015). Meta-analysis (including 34 randomized studies involving 2177 mothers and their healthy babies) by Moore et al. (2012) also supports that SSC has positive outcomes on breastfeeding one to four months post birth, blood glucose, infant crying and infant temperature stability.

In the experiments by Mizuno et al. (2004), more than 50 min of SSC immediately after birth enhanced infants' recognition of their own mother's milk odour and produced longer breastfeeding sessions. Marin et al. (2015) provided evidence that newborns that experienced SSC with their mothers could recognize their mother by her axillary odour. SSC presented clinical benefits regarding breastfeeding, behaviour, infant crying, and physiology in mothers and their healthy newborns (Moore et al., 2012; Anderson et al., 2003).

Johnston et al. (2014) assessed (on 1594 infants) the effect of SSC alone on pain from medical or nursing procedures in neonates undergoing painful procedures and suggested that SSC can be effective (as measured by physiological and behavioural pain indicators) and safe for a single painful procedure.

Recently, Goksan et al. (2015) used fMRI investigation to find that 18 of the 20 brain areas involved in pain in adults are also activate in healthy full-term newborn infants. fMRI also revealed that babies' responses to a weak poke of the foot (a force of 128 mN) were the same as adults' responses a strong stimulus (512 mN). These results suggest that babies experience pain like adults but that they have a much lower pain threshold. In addition, noxious stimulation in infants did not induce activity in the amygdala or orbitofrontal cortex (OFC), unlike in adults. Goksan et al. (2015) proposed that infants experience the sensory and affective aspects of pain in ways similar to adults but that they may not experience all the emotions that adults do because infants are too immature and inexperienced to translate the nociceptive stimulus into a coordinated response. This notion may explain the lack of activity in these brain areas in babies. However, these results by Goksan et al. (2015) may also suggest that the newborn's skin is more sensitive to not only painful stimuli but also the mother's touch and caress.

SSC can be very useful in the case of healthy, low-birth-weight (LBW) infants (Ohgi et al., 2002; Feldman et al., 2002). For example, in studies by Ohgi et al. (2002), in the KC (SSC) LBW group, infants were visited by their mothers almost every day to perform KC (KC initially was started from 20 to 30 min that were later extended to 1–2 h.), but LBW infants in the control group got conventional medical nursing care without KC. KC (SSC) was started within postnatal 1–3 days and continued nearly every day in the KC group during hospital stay. KC presented favorable outcomes on the mental and psychomotor development that extended over the first year of life.

3.3. Mother's voice

Several studies indicated that newborns show a preference for (or recognize) the maternal voice and that in utero experience influences this preference. (DeCasper and Fiefer, 1980; Fernald, 1985; Purhonen et al., 2004). It was also revealed that in the uterus, foetuses present a preference for their mother's voices (Kisilevsky et al., 2003, 2009; Lee and Kisilevsky, 2014).

For the foetus, the voice of the mother and the sounds of her heartbeat are among the most important acoustic stimuli before birth. From the first days of life, newborns present a clear preference for their mother's voice (DeCasper and Fifer, 1980; Moon et al., 1993; Mills and Melhuish, 1974), which may be significant for initiating infant bonding to the mother. In the normal uterine milieu, the maternal voice is an exceptional source of sensory stimulation (auditory, vibratory, and vestibular) for the developing foetus.

A developing foetus starts hearing sound by the second trimester of pregnancy, and in the third trimester, can already recognize the mother's voice. Sound is conveyed mainly through bone conduction, from the amniotic fluid through the foetal skull and into the inner ear (Granier-Deferre et al., 2011). In a recent study by Moon et al. (2013), 40 neonates (M = 32.8 h postnatal age) were tested in hospitals in Tacoma, Washington, USA (N = 40), and Stockholm, Sweden (N = 40), while the babies listened to vowel sounds in their native tongue and in foreign languages. The authors found that newborns are able to distinguish between their mother's language and a foreign

tongue, i.e., exposure to ambient language in the womb alters their phonetic perception shortly after birth. It seems that experience in the womb affects the infants' perception of vowel sounds and that the foetus is able to partially learn language.

fMRI experiments revealed that maternal left PFC activations in response to infant auditory cues (crying and laughing) were higher than those of nonmothers (Seifritz et al., 2003). Benavides-Varela et al. (2011) studied 1- to 5-day-old human neonates by functional near-infrared spectroscopy (fNIRS) and revealed that infants are able to memorize words hours after birth.

Recently, Abrams et al. (2016) assessed the brain scans of children listening to their mothers' voices by means of fMRI. Twenty-four healthy children (mean age, 10.2 years old) were exposed to brief (< 1 s) nonsense words by their mother and two female control voices. Compare to the female control voices, the mother's voice induced greater activity in primary auditory areas in the midbrain and cortex; voice-selective superior temporal sulcus (STS); the amygdala; nucleus accumbens (NAc) and orbitofrontal cortex (OFC) of the reward circuit; anterior insula and cingulate of the salience network; and a subarea of the fusiform gyrus associated with visual face processing. The authors suggested that hearing the mother's voice indicates a critical source of emotional comfort and social learning in a child's life. It seems that the mother's voice performs a specialized representation and presents a rewarding nature for her children.

Partanen et al. (2013) studied the development and retention of the neural representations induced by melodies during the foetal period. At birth, newborns in the learning group presented larger brain event-related potentials (ERPs) in response to the melodies they heard as fetuses than the control group, for whom the melodies were unfamiliar. This difference was still significant at the age of 4 months. These results revealed that extensive prenatal exposure to a melody produces neural representations that could last for several months. The foetal brain can be shaped by the surrounding sounds, but it is also vulnerable to harmful environmental acoustic effects. When a foetus is exposed to noisy auditory environments, it may lead to incorrect auditory system organization, which may later influence speech perception and learning.

Regarding baby cries, it can be believed that a newborn just lies in a bed, where he/she cries or sleeps. However, babies cry because of the absence of maternal sensory regulators or because they are experiencing dysregulation (Hofer, 2005). Newborns communicate their needs and physiological states mainly through crying and facial expression. Thus, crying is the primary way for newborns to elicit parental care, mainly when their parents are out of sight (Piallini et al., 2015).

3.4. *Mother's face*

Infants possess poor visual acuity and their psychophysical sensitivity to light, colour, and contrast is far below that of adults (Brown and Lindsey, 2009; Dobson and Teller, 1978). Although, there has been much debate regarding the special nature of face processing by newborn infants, several studies suggest that neonates present a preference for the mother's face and for females, can discriminate and respond to different emotional facial expressions, and prefer to look at human and attractive faces.

Goren et al. (1975) found that forty neonates (averaged 9 min from birth), who had never seen a human face, turned their eyes and heads more to follow a two-dimensional schematic face-like pattern than to follow scrambled faces or blank stimuli. This finding indicated that there is a strong preference for a face pattern over the other stimuli. Experiments have demonstrated that human neonates can recognize their mother's face within the first hours after birth regardless of whether the presented face was live. In studies by Bushnell et al. (1989), neonates could recognize their mother on the basis of visual clues alone. Newborn infants (M age = 45 h) presented an initial preference for their mother's face than for the face of a stranger (Field et al., 1985). Neonates (from 12 to 36 h of age) displayed more sucking responses when they saw an image of their mother's face than when they saw an image of a stranger's face (Walton et al., 1992). Walton et al. (1998) found that neonates could learn to identify a face after seeing it for 8 s. Pascalis et al. (1995) revealed that female 4-day-olds showed a much greater preference for their mother's face than male 4-day-olds. The authors also revealed that 4-day-old infants looked at their mother's face longer than at a stranger's face, but newborns did not presented this reaction if both women were wearing headscarves (Pascalis et al., 1995). Pascalis and Bachevalier (1998), Pascalis et al. (1998) reported that adult humans, as well as monkeys (Macaca mulatta), presented a strong novelty preference for objects. In addition, human subjects could better recognize human faces than monkey faces, and vice versa for monkeys. Pascalis et al. (1999) suggested that face recognition requires an important adaptive function that has been conserved across species.

Different models were raised to account for human newborns' face preference in terms of both domain-specific and domain-general underlying mechanisms (Simion and Giorgio, 2015). Johnson and Morton (1991) and Morton and Johnson (1991) proposed a two-process theory on the development of face processing that suggested that human neonates can be born with some information about the structure of faces. According to their model, subcortical (low-spatial frequency) structural information guarantees the preference of newborns for face-like patterns (this structural information, termed CONSPEC, is responsible for face detection). This Conspec mechanism declines in the first 2 months of life and, during development, will be replaced by cortical circuits that are specialized for face processing (in this domain-specific mechanism, termed CONLEARN, the structures likely to be involved are the superior colliculus and the pulvinar, which are responsible for face recognition and learning and for maintaining foveal fixation on faces).

In addition, studies suggested that neonates prefer to look at physically attractive human faces compared to less physically attractive human faces (Van Duuren et al., 2003; Quinn et al., 2008; Slater et al., 2000; Hahn and Perrett, 2014), but this ability to discriminate and respond to different emotional facial expressions by newborns remains controversial (Farroni et al., 2007). fMRI experiments have shown that the orbitofrontal cortex (OFC), which is a prefrontal cortex (PFC) region, was activated when mothers viewed a picture of their own infants (Nitschke et al., 2004).

The sensory hypothesis model suggests that faces are not qualitatively different from other visual stimuli. Neonates present a preference for faces because the amplitude at different frequencies of these stimuli matches the sensitivity of the infant visual system (structural properties can induce a visual preference in newborns) (Kleiner, 1987). This sensory hypothesis could predict infants' preferences for various patterns but could not explain the experimental results concerning faces, such as stimuli. The binocular correlation model (Wilkinson et al., 2014) claims that neonatal face preference is due to the visual filtering processes related to the limited binocular integration possessed by infants. According to the alternative Conspec hypothesis by Quinn and Slater (2003), we have complex face processing abilities that are present from birth. Farah proposed that face recognition represents a face as a complex whole, while object recognition is performed by decomposition into its constituent elements (Farah et al., 1998; Farah et al., 1999).

Some studies have investigated the link between speech sounds and visual stimuli in face recognition in infancy, which supports the notion that the speech component may help with the memorization and recognition of the mother's face. Mehler et al. (1978) showed that a young infant prefers its own mother's voice. In the experiments by Sai (2005), mothers could speak to their baby from birth to the test session in the first group. In contrast, in the second group, mothers were asked not to talk to their infant. The average interval between birth and the test was 7 h. Neonates indicated preferences for their mother's face but

only when they were exposed to the mother's voice and face paired together (Sai, 2005). Recently, Coulon et al. (2011) extended Sai's (2005) findings to other faces using video films, and they showed that unfamiliar female faces were recognized by infants in the test phase but only when they were previously habituated with the speaking face and not if the face had been silent. Coulon et al. (2011) suggested that "the speech component could play a fundamental role in maternal face recognition."

Multisensory integration (also known as multimodal integration) refers to the process by which inputs (information) from two or more sensory modalities are combined by the nervous system to form a stable and coherent percept of the world (Yau et al., 2015). Increasing evidence suggests that the neural basis of multisensory integration begins in early sensory processing (Ghazanfar and Schroeder, 2006). During multimodal perception, input from one sensory modality can be modulated by information from a different modality. The mentioned studies support the fact that mothers' voices may help maternal face recognition by infants, highlighting the importance of early multimodal perception, more specifically audiovisual perception, which seems to play an important role in face processing at birth.

However, in a recently published study by Reid et al. (2017) the first evidence were presented that fetuses, during the third trimester, have enough light to see and have visual experiences in the womb. Namely, fetuses could distinguish between different shapes, preferring to track face-like compared to non-face-like shape. Reid et al. concluded that postnatal experience is not required for the emergence of a preferential visual system for face-like stimuli. This new result (Reid et al., 2017) may also support the importance of the mother's face for human neonates within the first hours after birth as it was suggested by previously studies (Bushnell et al., 1989; Walton et al., 1992, 1998; Pascalis et al., 1995).

3.5. Mother's microbiota

Recent studies have suggested that the gut microbiota plays several functions in human health and disease through the bidirectional brain-gut signaling system (Carabotti et al., 2015). The first days and weeks of newborn are vital for shaping the development of the gastrointestinal tract, immune system, and the adult microbiome. Several bacterial sources for the infant are derived from the maternal microbiota. In utero, the foetus is relatively microbe-free, but immediately after birth, microbes are passed from mother to their pups and are quickly colonized (Moon et al., 2015). The infant's gut microbiome can play a fundamental role in the development of the immune system, neurodevelopmental processes, and neurogenerative processes (Sharon et al., 2016; Gensollen et al., 2016). Post-birth 16S rRNA sequencing data demonstrated that infant gut microbiota is similar to the mother's vaginal or skin microbiota, depending on their mode of birth (Dominguez-Bello et al., 2010). By means of the brain-gut-microbiota signaling system, the intestinal microbiome may play a role in the regulation of stress and the early programming of the neuro-immune system (Dinan and Cryan, 2012). In newborn animals, maternal separation stress produced shifts in neonatal gut microbiota, i.e., it could significantly alter the normal balance of gut microbiota (Cong et al., 2015). In addition, interrupted skin-to-skin care for early bathing may raise the risk of neonatal hypothermia and remove the natural maternal bacteria and vernix, which is a possible risk for nosocomial infections.

After birth, breastfeeding is one of the most important determinants of infant gut colonization. Maternal breast milk contains numbers of various microbial strains, oligosaccharides, immunoglobulins, cytokines, and other substances, which are essential for host–microbe interactions as well as for healthy intestinal and immunological development in early life (Gomez-Gallego et al., 2016; Rautava et al., 2012). It was recently suggested that maternal gut bacteria reach breast milk through an entero- mammary path to influence infant gut colonization and maturation of the immune system (Jost et al., 2014). Thus, early maternal separation at hospital could impair infants' microbiome composition.

4. The inner ear vestibular system

We should mention Prescott, who evaluated data from approximately 49 primitive cultures and could predict which cultures were peaceful or violent (Prescott, 1974). Cultures in which babies were carried on mothers' bodies throughout the first year after birth were more peaceful cultures. He also found an association between a longer duration of breastfeeding and lower suicide rates in 26 primitive cultures. Prescott suggested that there can be a sensitive period during infant brain development when touch and movement are required and touch and movement are protective against depression and violence. Prescott (1975) first identified that touch and motion were critical for normal neurointegration of the cerebellum–limbic–prefrontal cortex.

The inner ear vestibular system contributes to the visuospatial ability (coordinating eye and head movements), attention, executive function, cognitive and memory processes, language development and a sense of self and self-consciousness (Bigelow and Agrawal, 2015; Besnard et al., 2015). Vestibular deficits are related to sensations such as vertigo, disorientation, etc., and these sensations are associated with psychiatric problems, such as agoraphobia, depression and anxiety (Wiener-Vacher et al., 2013). The vestibular system is very important to a child's early development. The level of prenatal motion is especially high since the foetus constantly changes position in the amniotic fluid. After birth, the baby does not experience the same degree of vestibular stimulation until he/she starts independently walking.

If a child's vestibular system did not develop properly, he/she is constantly fidgeting and cannot sit still or listen to the teacher. Vestibular disorders can produce a high level of alertness and vigilance and problems with maintaining focus and paying selective attention, as well as alterations in precision and attention to stimuli (Wang et al., 2003). There is a possible correlation between vestibular deficit and ADHD (Haghshenas et al., 2014). It is hardly a coincidence that individuals from cultures in which babies are carried on mothers' bodies during the first year after birth were more emotionally balanced and peaceful. Similarly, at home, when a cradle was placed near the mother's bed, it made it possible to rock the cradle in the first days after birth, which promoted the optimal development of the vestibular system in the baby.

5. Early maternal separation of premature babies

Without going into detail, if we consider the potential adverse effects of conventional hospital birth (as presented in this paper), these effects may be especially manifest in premature babies who are separated from their mothers in an incubator for a long time. The physical and emotional closeness between the preterm infant and parent is particularly important in the neonatal intensive care unit (Conde-Agudelo and Díaz-Rossello, 2016; Kristoffersen et al., 2016; Scher et al., 2009). In a study of Mehler et al. (2011) it was demonstrated that a 'sensitive period' also exists for preterm infants within the first hours after birth. Those infants who had been seen by their mothers shortly after birth presented more secure attachment patterns at the age of 12–18 months of life. According to Mehler et al. (2011), "The authors postulate that this 'sensitive period', which is characterized by a special neuroendocrine situation leads, via conditioning or imprinting effects, to a subconscious learning process shaping the interaction of mother and child. This process forms the behavioural basis of mother and child in the first year, which ideally leads to a secure attachment pattern. On the basis of these observations, it was concluded that for full-term infants, an early contact of mother and child should be allowed whenever possible". In 2015, preterm birth affected about one out of 10 infants born in the United States (WHO, 2017b). We should seriously consider the effect of this preterm birth rate.

6. Early maternal separation may be associated with epigenetic regulation

Epigenetics refers to changes in the genome that can be transmitted through mitosis and meiosis by stable mechanisms without altering the DNA sequence. Major epigenetic mechanisms include DNA methylation, histone post-translational modifications (such as methylation, acetylation, ubiquitination and phosphorylation), and regulatory noncoding RNAs, such as micro-RNA, PIWI-interacting RNA and long noncoding RNAs, and chromatin organization (Clark et al., 2016; Imani et al., 2015; Peschansky and Wahlestedt, 2014). The term epigenome refers to all the potentially heritable chemical modifications in DNA and histone proteins throughout the genome that modulate gene activity without actually changing the genetic sequence of a given cell type. Phenotype refers to the observable properties of an organism that are produced by the interactions between the genotype and the environment. Since diverse exogenous environmental factors and endogenous factors (for example, pre- and perinatal effects (maternal care and interaction, maternal health and social environment, mother's diet and stress, etc.), nutrition, drugs, exercise, alcohol, smoking, environmental chemicals, ageing, etc.) continuously influence the epigenome, epigenetic modulations occur during the entire lifespan, from conception to death (Kanherkar et al., 2014). We should also mention that fMRI signals correlated with the expression of genes that are tightly linked to synaptic function (Richiardi et al., 2015).

Several studies have reported that epigenetic regulations are fundamental contributors in neuronal gene expression, synaptic plasticity, formation and stabilization of long-term memory, cognitive functions, and neural stem cell self-renewal, as well as in numerous neurodevelopmental and neurodegenerative diseases and psychiatric disorders (Grigorenko et al., 2016; Podobinska et al., 2017; Guan et al., 2015; Woldemichael et al., 2014; Gräff et al., 2011).

The critical brain areas for emotional regulation, such as the prefrontal cortex, hippocampus and amygdala (Izquierdo et al., 2016), may play essential roles in cognitive deficits and aberrant emotional behaviours due to early-life adversity in humans, which may increase the risk of developing stress-induced psychopathology later in life (Teicher and Samson, 2016; Teicher et al., 2016).

There is increasing evidence that the epigenetic molecular processes underlying the lifelong or transgenerational perpetuation of changes in gene expression and behaviour are induced by early-life adversity, such as stress, abuse and neglect (Weder et al., 2014; Mitchell et al., 2016). Namely, epigenetic mechanisms can make key contributions to stress responses in an intergenerational (parent-infant) and transgenerational manner (Nestler, 2016; Jensen, 2013).

The glucocorticoid receptor gene (NR3C1) is one of the most studied genes in the literature regarding childhood maltreatment and neglect (Turecki and Meaney, 2016; McGowan et al., 2009) NR3C1 presented changes in methylation that were associated with maternal care and later behaviours (Weaver et al., 2004a).

Of course, early-life-adversity-induced epigenetic changes are not restricted to NR3C1. Several other genes, including brain-derived neurotrophic factor (BDNF), serotonin transporter (SLC6A4), gamma-aminobutyric acid A receptor ($GABA_A$ receptor complex), estrogen receptor-α (ERα), oxytocin receptor (OTR), and glutamate receptor (mGluR), are also implicated in early life stress (for example, maternal separation or the quality and quantity of maternal care, etc.) that may contribute to increased malfunctions in behaviour and cognitive mechanisms and are also important risk factors of later mental illness (Jawahar et al., 2015; Cunliffe, 2016; Opendak et al., 2017)

In the above mentioned study, (Law et al., 2009), the expression of eight genes implicated in neural plasticity and mood disorders in the hippocampus of early deprived infant marmoset monkeys. Early parental deprivation produced a long-term effect on the hippocampal expression of genes, i.e., reductions in hippocampal growth-associated protein-b43 (GAP-43) and serotonin 1A receptor (5-HT1AR), decreased hippocampal volume and expression of brain-derived neurotrophic factor (BDNF), and increased expression of vesicular GABA transporter (VGAT, also called VIAAT). According to authors (Law et al., 2009), "The reductions in GAP-43 and serotonin 1A receptor expressions are comparable with findings in mood disorder, supporting the possibility that the latter reflect an early developmental contribution to disease vulnerability."

In studies by Franklin et al. (2010), dams and pups were exposed to unpredictable maternal separation combined with unpredictable maternal stress (MSUS, 20-min restraint in a Plexiglas tube or 5-min forced swim in cold water) for 3 h daily from postnatal day 1–14 (PND 1–14), which produced depressive-like behaviours and altered the behavioural response to aversive environments in the separated mice; this effect persisted through adulthood. These behavioural alterations could be transmitted to offspring across two generations. The authors also revealed that the transmission of social anxiety to F2 and F3 MSUS mice was sex-specific (social anxiety was not observed in F1) and occurred by means of males that did not have any contact with their pups. In addition, Franklin et al. (2010, 2011) suggested an association between reduced serotonin receptor 5HT1A expression in the dorsal raphe and increased serotonin release in the frontal cortex and abnormal social behaviours in MSUS offspring (although other noradrenergic or dopaminergic processes may also be involved in abnormal social behaviours).

Andersen and Teicher (2004) separated rat pups from their mother for 4 h per day between postnatal days 2 and 20. They examined the immunoreactivity of synaptophysin (a glycoprotein that is an integral part of the neuroendocrine secretory granule membrane in humans and is encoded by the SYP gene) in the hippocampus CA1 and CA3, amygdala, and prefrontal cortex. The authors observed that early maternal separation reduced the overall synaptophysin levels in the hippocampus compared to those of the control groups and prevented the normal overproduction of synapses in hippocampus but not in the amygdala or prefrontal cortex. Andersen and Teicher (2004) suggested that stress-induced alterations in human hippocampal size caused by early separation may not emerge until at least early adulthood. In other words, early maternal separation induced a regionally specific delayed effect on the structure of the hippocampus. Enduring and delayed alterations in hippocampal synapse formation may explain the vulnerability of individuals who endured childhood abuse to develop depression or post-traumatic stress later in life.

McGowan et al. (2011) examined the DNA methylation, histone acetylation and gene expression in a 7 million base pair region of chromosome 18 that contains the NR3C1 gene (also known as GR or GCR, NR3C1 is a glucocorticoid receptor to which cortisol and other glucocorticoids bind) in the hippocampus of adult rats. The hippocampal samples originated from the adult offspring of rat mothers that differed in the frequency of pup licking/grooming in the first week of life (i.e., high vs low LG adult offspring). Adult offspring that received low levels of maternal care (low LG) presented several hypermethylated and hyperacetylated regions in NR3C1 exon variants and intronic regions. The chromosomal area that contains the protocadherin-α, −β, and -γ (Pcdh) gene families implicated in synaptogenesis displayed the highest differential response to maternal care. More importantly, the authors revealed that the epigenetic response to maternal care induced dramatic changes in not only a single gene or a few genes; it produced coordinate changes in gene-networks with increased and decreased peaks of histone acetylation and DNA methylation throughout the observed region.

Champagne et al. (2003) studied the expression of estrogen receptor-α (ERα) in response to variations in maternal care. They revealed a significant elevation of ERα mRNA expression in the medial preoptic area (MPOA of the hypothalamus) of high LG-ABN (licking/grooming and arched back-nursing) dams compared to low LG-ABN, and this effect could be transmitted to the female offspring of the high LG-ABN dams. However, ERα can modulate HPA axis activity and

oxytocin receptor (OTR) transcription (oxytocin, OT is important in homeostatic processes, such as food intake, thermoregulation, and mating and has an important function in maternal behaviour) (Acevedo-Rodriguez et al., 2015).

Bagot et al. (2012) measured metabotropic glutamate receptor (mGluR1) mRNA as well as proteins in hippocampal tissues from the adult offspring of high- or low-LG (LG, licking/grooming) mothers. They found that maternal care produced epigenetic changes via increased expression of the Grm1 gene in the offspring of high-LG mothers compared with those of low-LG mothers. Bagot et al. suggested that maternal care firmly influences the epigenetic condition of genes that encode proteins that regulate hippocampal synaptic function and cognitive performance.

Emerging evidence shows that the epigenetic programming of gene expression is particularly sensitive to the early-life environment, in terms of both the chemical and social environment, and that epigenetic alterations early in life can induce a life-long impact on gene expression and thus on phenotypes, including susceptibility to disease (Szyf, 2009).

Several studies support the fact that the development of epigenetic imprinting during the pre- and early post-natal periods has a fundamental effect on neurodevelopmental processes and the emergence of neurodevelopmental diseases later in life (Skinner, 2014; LaSalle et al., 2013). Prosperous early postnatal maternal care can shape epigenetic programming in the brain, creating an adult female with good maternal care characteristics that can be passed on to subsequent generations (Skinner, 2014). In contrast, disadvantageous early postnatal maternal care (as in environmental stress) produces bad maternal characteristics later in life via epigenetic programming of the brain, propagating disadvantageous maternal care generationally (Suderman et al., 2012).

Tactile stimuli from mother to neonate have a great impact on infant brain development. Rat pups that received expressive tactile stimulation from their mother, such as licking and grooming, presented lower stress responses during adulthood (Meaney, 2001). This tactile stimulation could induce 5 HT release in the hippocampus of pups, which epigenetically modulated the CpG islands of glucocorticoid receptors (Weaver et al., 2004a, 2004b). After birth, tactile stimulation can have particularly strong effects on the epigenetic changes of DNA methylation (Nagasawa et al., 2012). In experiments by Barrett et al. (2015), PND 6–7 prairie voles neonates were brushed for 5-min. This tactile stimulation could induce significant expression of the immediate-early gene product EGR1 in oxytocin neurones in the PVN (paraventricular nucleus of hypothalamus). The authors suggested that parental tactile stimulation could positively influence the development of neural systems involved in adult social attachment via neonatal oxytocin receptor (OTR) signaling.

Recent studies pointed out that nutrition may be influenced by the genome (Mutch et al., 2005) and nutrients may regulate gene expression (Ho and Zempleni, 2009). Breastfeeding may also be associated with epigenetic regulation that may produce significant changes in phenotype (Verduci et al., 2014). Many studies recommended the possible role of microRNA in the epigenetic control of normal and aberrant mammary development, and mainly lactation performance (Alsaweed et al., 2015). NF-kappaB (NF-kB) protein complex comprise a family of eukaryotic transcription factors that are involved in the control of numerous normal cellular processes, such as immune and inflammatory responses, developmental processes, cellular growth, and apoptosis, etc. (Perkins, 2007). Minekawa et al. (2004) demonstrated *in vitro* that human breast milk could suppress the interleukine (IL) 1-β-induced activation of the IL-8 gene promoter in human intestinal cells by means of inhibiting the activation of NF-κB. They proposed that human breast milk could be protective in newborns with neonatal necrotizing enterocolitis through inhibiting the activation pathway of NF-κB. Lactoferrin (LF) is an iron-binding glycoprotein of the transferrin (TF) family that is a major protein of breast milk. Thus the breastfeeding infants have high concentrations of intact LF in the intestinal epithelium. Mulligan et al. (2006) investigated the immunomodulatory role of human breast milk through regulation of gene expression lead to LF properties. They reported that LF could bind proinflammatory bacterial DNA sequences (CpG motifs, unmethylated CpG motifs are prevalent in bacterial but not vertebrate genomic DNAs) in extracellular compartments and this binding inhibited the CpG-motif DNA-induced activation of NF-κB-regulated genes, such as IL-8 and IL-12 in B cells. Human milk (HM) is species-specific and an optimal source of various bioactive components and also contains microRNAs and small non-coding RNAs. HM is one of the richest sources of microRNAs (Kosaka et al., 2010). Baier et al. (2014) studied bovine milk-derived microRNAs (miR-29b and miR-200c) in human adults after consuming cow's milk and revealed that both microRNAs were increased 2-fold in human peripheral blood mononuclear cells (PBMCs) that could potentially alter gene expression. Pauwels et al. (2017) recently demonstrated that maternal dietary and breastfeeding can influence infant DNA methylation levels in the early postnatal period.

7. Summary and conclusions

A mother and her foetus basically form a single organism. It was suggested that the process of birth can be a large trauma with the physical and psychic separations that we suffer at birth, affecting us throughout our life (Bion, 1962; Rank, 1924). After birth, noradrenalin wakes up the brain, and its concentration is 10 times higher at birth than at any other point (Lagercrantz and Bistoletti, 1977). High concentrations of noradrenalin activate the lungs and ensure early bonding with the mother (Ross and Young, 2009). At birth, a newborn arrives in a cold world, perceiving alien sounds and smells. The mother's smells, touch and voice may naturally reduce and control birth stress.

If we consider the numbers of studies (see Section 2) regarding early maternal separation and its possible harmful effects, we may draw the conclusion that standard hospitalized birth (not the rooming-in practice) where infants are kept in a separate nursery and the neonates are brought to their mother principally for breastfeeding according to hospital practice, may be similar to animal separation experiments. According to Morgan et al. (2011), "Maternal-neonate separation (MNS) in mammals is a model for studying the effects of stress on the development and function of physiological systems. In contrast, for humans, MNS is a Western norm and standard medical practice".

In a standard hospitalized birth, neonates endure repeated separation from their mother's smells, voices and touch. In contrast, a planned home birth or rooming-in practice can guarantee constant smell, voice and touch cues from the mother to the infant. We may also consider the fact that infants in a separated nursery may induce harmful emotional effects on each other through crying and diverse odour cues.

7.1. Early maternal separation and neurodevelopmental disorders

Increasing evidence suggests that neurodevelopmental disorders, such as autism spectrum disorders (ASDs), attention deficit (hyperactivity) disorder (ADHD), depressive illness, schizophrenia and addiction, are due to the interaction between epigenetic and environmental factors (van Loo and Martens, 2007; Kubota et al., 2013; Jakovcevski and Akbarian, 2012; Rangasamy et al., 2013). In addition, the prevalence of ASDs, ADHD, depressive illness and addiction has been increasing in recent decades, and these neurodevelopmental disorders can be heritable (Baio, 2014; Turgay and Ansari, 2006; Loke et al., 2015; Bron et al., 2016; Li et al., 2014; Sullivan et al., 2000). Bron et al. (2016) suggested that ADHD may be due to comorbid conditions, such as depression and anxiety, since ADHD is approximately 7.5 times more prevalent in chronic major depressive disorders (MDD) than in the general population.

In Section 2, we presented several experiments on early deprivation. Some of these studies are summarized here. Early neonatal maternal separation in rats can mimic the behavioural and neuroendocrine

responsiveness to early life stress in humans (Lippmann et al., 2007; Sanders and Anticevic, 2007; Caldji et al., 2000; Aisa et al., 2007). ED produces impaired adult neurogenesis and increases anxiety, depression, social deficits and excessive self-grooming, which are behavioural phenotypes with similar features to those of autism (Wu et al., 2014). ED modifies myelination in mPFC (Yang et al., 2017) and produces persistent perturbation in serotonergic, noradrenergic and dopaminergic neurotransmitters (Arborelius and Eklund, 2007). Repeated ED in monkeys increases basal urinary NE and systolic blood pressure and makes reward less of an incentive (Pryce et al., 2004). ED can trigger chronic changes in homeostatic systems that are similar to those in children who are exposed to early-life adversity and to major depressive disorder (MDD) (Pryce et al., 2004). ED in monkeys has a long-term effect on the hippocampal gene expression implicated in synaptic function and plasticity (Law et al., 2009). Repeated ED in monkeys reduces body weight, induces acute increases of epinephrine and norepinephrine in the urinary samples, and increases cortisol levels and the infants present more distress vocalizations and less social play (Dettling et al., 2002). Following 30 years of studies on the effects of early handling and maternal separation in rats, Thierry et al. (1984) proposed that mother-infant separation may be considered an evolutionary model for human depression. According to Wang et al. (2014), "Repeated postnatal maternal separation is one of the most potent stressors to which neonates can be exposed, and may permanently modify neurobiological and behavioural parameters in the adulthood (Neigh et al., 2013)".

7.2. Early maternal deprivation/separation may induce similar epigenetic changes and features similar to those of various mental diseases

In Section 6, we mentioned a number of experiments on early maternal deprivation/separation, the quality and quantity of maternal care, early-life adversity, breastfeeding, as well as odour- and tactile-stimulation-induced neuroepigenetic gene expression changes. These induced gene expression changes play essential roles in neuronal gene expression, synaptic plasticity, the formation and stabilization of long-term memory, and cognitive functions as well as in neurodevelopmental and neurodegenerative diseases (Grigorenko et al., 2016; Podobinska et al., 2017; Guan et al., 2015; Woldemichael et al., 2014; Gräff et al., 2011).

According to Skinner (2014), good early postnatal maternal care can shape epigenetic programming within the brain that supports the development of an adult female with good maternal care characteristics (and vice versa (Suderman et al., 2012)), and this feature can be transmitted to the following generations (Skinner, 2014).

Many authors argued that the separation of a newborn infant from his/her mother is not harmless and should be carefully considered (Crenshaw, 2014; Bergman, 2014; Dageville et al., 2011; Bergman and Bergman, 2013; Phillips, 2013; Conde-Agudelo and Díaz-Rossello, 2014; Russell et al., 2013). Here, we propose that both a rooming-in practice (keeping mothers and babies together 24 h a day) and a planned home birth are adequate and good practices, as a planned home birth can be as safe as a planned hospital birth (Zielinski et al., 2015; Janssen et al., 2009; Bolten et al., 2016; de Jonge et al., 2015; Snowden et al., 2015; Kataoka et al., 2013). The studies mentioned in this paper may also support the practice of zero separation, not only for the first day of a newborn's life (Bergman, 2014) but for the newborn's first days of life.

7.3. Hypothesis on early mother − infant separation

One might argue that the main limitation of this review is that the large part of presented studies was conducted on animals and that human epigenetic results have been described after childhood abuse but not after newborns stress.

According to Suderman et al. (2012) "Considering the parallel behavioural and epigenetic responses in humans and rats to early life environments described above, it is reasonable to assume that at least part of the broad epigenetic responses observed in rats to early life experiences may be evolutionarily conserved in humans"…"These results provide support for an analogous cross-species epigenetic regulatory response at the level of the genomic region to early life experience. (Suderman et al., 2012). Morgan et al. (2011) claim that: "Maternal-neonate separation (MNS) in mammals is a model for studying the effects of stress on the development and function of physiological systems. In contrast, for humans, MNS is a Western norm and standard medical practice".

In addition, according to the American Psychiatric Association (2013 5th ed.; DSM-5) PTSD is no longer classified as an anxiety disorder but is categorised in disorders relating to traumatic and stressful events (Friedman, 2013). DSM-5 contains PTSD subtypes such as the dissociative subtype or the preschool subtype that incorporates important developmental factors affecting the expression of PTSD in young children (Friedman, 2013).

Furthermore, it was proposed that the process of birth can be a large trauma with the physical and psychic separations, affecting us throughout our life (Bion, 1962; Rank, 1924). After birth, noradrenalin (also called Norepinephrine (NE) or noradrenaline (NA)) wakes up the brain, and its concentration is 10 times higher at birth than at any other point (Lagercrantz and Bistoletti, 1977). In addition, PTSD is associated with increased cortisol and norepinephrine responses and the stress response include the amygdala, hippocampus, and prefrontal cortex (Bremner, 2006; Kosten et al., 1987; Ronzoni et al., 2016; Rasmusson et al., 2000). Moreover, stress (PTSD) is one of the major environmental factors that trigger epigenetic changes (Rampp et al., 2014; Auxéméry, 2012; Sipahi et al., 2014; Uddin et al., 2011, 2010; Smith et al., 2011). As a consequence of the above mentioned, birth as well as early mother-infants separation may also be considered as a subtype of PTSD for infants.

Here we hypothesize that early maternal deprivation/separation in conventional hospitals may induce similar epigenetic changes and features similar to those of various mental diseases that may also be implicated in neurodevelopmental disorders. We do not claim that early separation alone causes neurodevelopmental disorders; however, it is one of the possible risk factors that also promote the formation of neurodevelopmental disorders (Skinner, 2014; LaSalle et al., 2013).

Finally, we speculate that stressful birth itself, which is extreme sensitive period, may be similar event to a post-traumatic event with sustained epigenetic responses. We have previously described several experimental results suggesting that unconscious processes precede voluntary actions and decisions (Bókkon et al., 2014; Libet, 1985; Bode et al., 2011; Soon et al., 2013). We also discussed how obtained and inherited epigenetic information in pre-, peri-, and early postnatal periods plays essential roles in unconscious processes and numerous brain functions of the mature organism (Bókkon et al., 2014). According to Blandin et al. (1994), ".separation anxiety must be understood as resulting from the unconscious internal conflicts inherent in the individuation process and gradual attainment of autonomy."… "Freud considers the primary experience of separation from protecting mother as the prototype situation of anxiety and compares the situations generating fear to separation experiences". Therefore, it may also be possible that early separation induced stress may remain latent and unconscious by means of neuroepigenetic regulations but it can be activated later in life.

However, in the future, more research is necessary to further understand the human newborn response to early separation in hospitals, including whether it is sustained response and whether it has any long-term neurodevelopmental effects.

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