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Review

The mother–child interface: A neurobiological metamorphosis

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ABSTRACT

From the start of pregnancy, mother and child induce reciprocal neurobiological changes in the brain that will prove critical for neurodevelopment and survival of both. Molecular communication between mother and fetus is constantly active and persists even after the fetus starts to synthesize its hormones in late gestation. Intriguingly, some mother and fetus exchange cells remain in the other's brain and body with long-lasting effects and memories that do not follow the laws of classical genetics but involve complex epigenetic mechanisms. After childbirth, mother and child go through a transitional phase, a sort of *limbo* in which both will have a peculiar functioning profile, which is adaptive for contingencies but also renders them vulnerable. The interplay between these two "limbo" states allows for an easier transition to the subsequent phases of development.

In this review, we will trace mother's and child's path from pregnancy to the months following birth and, in particular, unravel i) the key features of pregnancy and brain development and the reciprocal influences; ii) how a transitory pattern of functioning characterize mother and child, moving them toward more flexible and evolved forms; and iii) how mother and fetus act during childbirth to promote neuroprotection, pain reduction, and neurophysiological changes. Therefore, this review covers a wide range of topics, integrating neuroanatomical, neurological, biochemical, neurophysiological, and psychological studies in a meaningful way, trying to integrate them in a holistic view of the mother–child interface that is usually neglected.

Introduction

The fetal brain's formation begins during the early phases of pregnancy. In this process, the mother is not only the agent that allows for repair and offers the fetus nutrition: although developmental processes are genetically determined, they are completely susceptible to maternal factors that can induce or inhibit them via *trans*-placental passage. The placenta serves throughout gestation as the primary communication organ for the exchange of nutrients, gases, waste, and hormones between mother and fetus. The placenta also produces neurotransmitters, including serotonin, dopamine, and norepinephrine/epinephrine, that may circulate and influence fetal brain development (Rosenfeld, 2021). The circulation of the fetus is separated from that of the mother; however, molecular communication is constantly active and persists even after the fetus starts to synthesize its hormones in late gestation. Therefore, the fetus is distinct from yet dependent on its mother.

Maternal molecules play a role in fetus growth and physiology, also probably informing the fetus about maternal conditions, such as stress (Wood and Keller-Wood, 2016). For this reason, maternal influence provides the ideal or deleterious conditions for several aspects of the fetus's physiology and neurodevelopment. The developmental origin of the adult disease hypothesis states that adverse influences early in development can result in permanent changes in physiology and metabolism, resulting in increased health risks in adulthood (Barker, 2004). Research has confirmed that exposure to intrauterine adversity or delivery complications places neonates at elevated risk for developing cognitive, social, emotional, and health problems (Cainelli et al., 2021a; Faa et al., 2014; Pluess and Belsky, 2011). These adversities could depend on a broad spectrum of maternal (depression, undernutrition, smoking, lifestyles, diabetes, etc.) and fetal (prematurity, hypoxic-ischemic encephalopathies, congenital cardiopathies, etc.) conditions (Faa et al., 2014).

Among the most studied hormones that could influence fetus development, thyroid hormones (THs) and glucocorticoids have been the most frequently studied (Moog et al., 2017; Olza-Fernández et al., 2014; Pathak et al., 2011); nevertheless, several other hormones seem to

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influence fetal neurodevelopment and have recently attracted researchers' attention, such as melatonin (Khazipov et al., 2008; Sagrillo-Fagundes et al., 2016). A very intriguing field of research, heretofore scarcely known, is microchimerism (Kinder et al., 2015). New evidence of this phenomenon shows that mother and fetus exchange cells that remain in the other's brain and body with long-lasting effects and persistent memories that do not follow the laws of classical genetics but involve complex epigenetic mechanisms (Boddy et al., 2015; Zeng et al., 2010).

At the end of pregnancy, childbirth is a hurricane that shuffles the cards on the table again. Maternal and fetal melatonin and oxytocin synergistically reduce pain, activate maternal physiological changes, and act as neuroprotective agents (Sharkey et al., 2010). Oxytocin is also crucial in the delicate neurochemical balance that modulates neonatal brain circuit formation, other than lactation and early attachment behaviors (Khazipov et al., 2008). Despite the hormonal support, the mother's role changes for the second time in nine months: it is different from before the pregnancy and from the time of the pregnancy (Orchard et al., 2023). Everything also changes for the newborn child: to use a computer metaphor, its brain's hardware is ready, but the software has to be put into operation. The main developmental processes have been completed, but postnatal experiences and stimulations will shape the emerging neural circuits. Just after childbirth and in the first postnatal months, mother and child go through a transitional phase, a sort of *limbo*, in which both dyad members will have a peculiar functioning profile. For the mother, the first postnatal months are crucial not only for the physiological changes that characterize her (i.e., breastfeeding) but also for entering a phase of brain plasticity that changes her brain, representing a new neurodevelopmental phase (Orchard et al., 2023). In this phase, a hyperactivated brain system sustains behavior focused on the child, guaranteeing their centrality in neuroplastic changes. The changes allow the mother to adapt to the child's developmental stages but also render her vulnerable to psychopathology. Meanwhile, the newborn exhibits transitory stereotypical and adaptive equipment endowed prenatally that allows them to adapt to life outside the uterus and move toward a more flexible form of functioning, perhaps to give the mother time to adapt. Birth represents the extension of the dependence period that begins in utero for the baby (Porges and Furman, 2011). However, this does not mean newborns are completely vulnerable and perceive a confusing world, as described in the past. Neonates are equipped for their new condition: they display organizational perceptual competencies, primitive reflexes, detection of relevant and *para*-verbal stimuli, and preferential attention toward faces and female voices (Cassia et al., 2004; George et al., 1996; Zafeiriou, 2004). They generally show transitory right hemispheric dominance, which supports abilities with a strong adaptive value (Geschwind and Galaburda, 1985). This specific equipment, which accompanies and guides the child through their first stages of interaction with the outside world, represents an ideal basis for developing experience-dependent neural networks but is transitory. It is likely a facilitative and "permissive" transitional pattern of functioning. The interplay between these two "limbo" states (maternal and fetal) allows for an easier transition to the subsequent phases of development.

Unfortunately, information about the reciprocal influences between mother and child in normal conditions is fragmentary. There is also a scarcity of established reference values for pregnancy or nonpregnant populations. Furthermore, the considerable crosstalk between hormonal axes is still poorly understood (Miranda and Sousa, 2018). Paradoxically, the literature on adverse prenatal conditions' effects on child neurodevelopment is richer whereas many aspects of the reciprocal influences in physiological conditions are poorly understood. For example, the literature on the fetus's effects of high levels of maternal glucocorticoids is dense (Fumagalli et al., 2007; Musillo et al., 2022). So is that of the long-lasting effects of maternal stress, undernutrition, smoking, and exposure to chemical substances (for a review see, Faa et al., 2014). These studies have enabled the scientific community to make enormous strides in understanding maternal-fetal mechanisms. Nevertheless, we believe that a better understanding of the mechanisms under normal conditions can provide the missing answers that studying pathological conditions alone cannot provide.

In this review, we will trace the mother's and child's path from pregnancy to the months following birth. More than parallel paths, they are a synergetic dance in which mother and child influence each other to create two new individuals. To identify key points, we unravel i) the key features of pregnancy and fetal brain development and the reciprocal influences; ii) how a transitory pattern of functioning characterizes mother and child, moving them toward more flexible and evolved forms; and iii) how mother and fetus act during childbirth to promote neuroprotection, pain reduction, and neurophysiological changes. Fig. 1 shows the various phases from 24 postconception weeks to 4 months postnatal life. The main fetal brain developmental phases and the reciprocal hormonal and microchimeric influences between the fetus and the mother are presented.

Key maternal and fetal brain changes from pregnancy through the months following birth

The maternal journey

During pregnancy, the maternal immune system undergoes many important changes that begin at conception and continue through delivery (Sherer et al., 2017). The fetus is a semi-allogeneic presence inside the mother's body; however, unlike other allogeneic or "foreign" bodies, the mother does not reject the fetus during a successful pregnancy, thanks to significant immunomodulation. The entire pregnancy is supported by a delicate equilibrium between inflammatory and anti-inflammatory mechanisms (Kalagiri et al., 2016). This equilibrium is tightly controlled such that even minor disruptions in this process may affect the pregnancy's success (Gervasi et al., 2022). Abnormalities in maternal inflammatory responses have been implicated in abnormal neurodevelopment (Estes and McAllister, 2016; Gervasi et al., 2022; Harmon et al., 2016) through several mechanisms. For example, fetal microglia actions are directly influenced by maternal signals in normal development and following maternal immune activation (Lu-Culligan and Iwasaki, 2020). Microglia are the resident macrophages of the central nervous system; they are known to play a central role in developmental processes. Postnatally, they play a key role in pruning; prenatally, they eliminate the neural precursor cells and direct dopaminergic axonal outgrowth and interneuron positioning, among other functions (Paolicelli and Ferretti, 2017).

Immunological changes are not the only macroscopic changes the mother undergoes: hormones increase dramatically during pregnancy. The pregnant woman is exposed to sustained increases in hormones such as progesterone, estradiol, glucocorticoids, and prolactin (see the bottom part of Fig. 2).

These hormones are typically released for discrete periods during the menstrual cycle but, in pregnancy, are maintained at high levels for weeks (Grattan and Ladyman, 2020). The hormonal fluctuations associated with pregnancy drive a wide range of adaptive changes to maternal physiology to help the mother cope with these new physiological demands (Napso et al., 2018). The maternal brain is not the exception: the activity of several neuronal populations changes, and both transitory and persistent neural reductions in specific cerebral areas leading to fundamental changes in behavior have been documented (Pawluski et al., 2022). In particular, steroid hormones such as estradiol and progesterone readily access the brain and can influence specific receptors expressed in a wide range of neural centers. Peptide hormones are transported into the brain and, similarly, can act on receptors expressed in numerous brain regions. Among the targets, the hypothalamus is one of the most crucial, given its role in influencing many body targets through the autonomic nervous system (Grattan and Ladyman, 2020). In the next paragraph, the effects of hormones on the

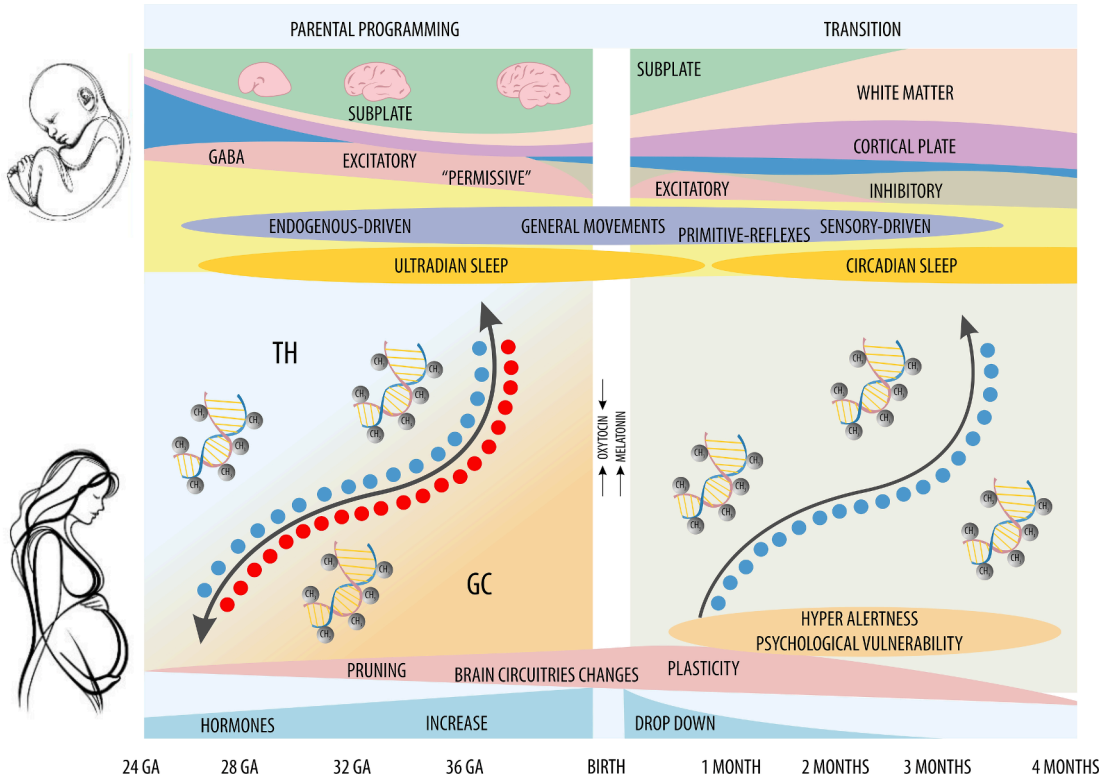

Fig. 1. The figure represents the developmental phases of mother and child from 24 postconception weeks to 4 months postnatal life and the reciprocal influence. In the top part of the figure, the crucial fetal phases of brain development are illustrated, in particular, the presence of the subplate cortex, which predominates the neuroanatomical scene; the neurochemical changes of GABA during pregnancy, birth, and postpartum; the parallel behavioral correlates have also been reported: first motor patterns and sleep architecture. In the bottom part, the changes are relative to the brain and hormonal changes in the mother. In the middle, the early increase of thyroid hormone (orange shadow), which triggers the early fetal brain development, and the near-birth increase of glucocorticoids (purple shadow), which prepares the fetus for birth. Again, the reciprocal influences of oxytocin, melatonin, and microchimerism (red points for maternal, blue for fetal). Legend: GA: gestational age; GC: glucocorticoids; Me: methylation; TH: thyroid hormone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

maternal brain will be discussed; further in the work, the effects on the fetal brain.

Changes in the maternal brain and behavior

Although the data about maternal brain changes during pregnancy are fragmentary, the interest in this topic has recently increased. The changes in the maternal brain involve brain systems that enhance maternal adaptation to the role of motherhood and the performance of caregiving behaviors, such as elaboration of emotional stimuli, reward, and motivation, constructs intimately associated with executive functions, empathy, and attention to the child (Hoekzema et al., 2020). In particular, the neural network regulating "theory of mind," the ability to decode mental states in ourselves and others, critical for sensitive maternal caregiving (Schaafsma et al., 2015), seems involved (Hoekzema et al., 2017). The other critical network is the mesolimbic reward system, which is associated with mothers' stronger ventral-striatal neural responses to their infants (Hoekzema et al., 2020). These motherhood-related modifications strongly overlap with the mothers' neural reactions to stimuli from their babies, and the observed structural and functional changes predicted measures of postpartum maternal attachment (Laurent and Ablow, 2012; Noriuchi et al., 2008). It has been suggested that the motivational system involved in maternal behavior uses dopamine and oxytocin-rich pathways (Numan and Woodside, 2010; Strathearn et al., 2009b). As confirmation, vaginal delivery provides critical sensory stimulation that increases oxytocin release and helps establish maternal behaviors (Morgan et al., 1992).

Interestingly, there are differences between pregnancy and the postpartum period. Pregnancy can generate neural reductions, transitory in overall brain size, and regional reductions exceeding and outlasting global changes (Pawluski et al., 2022). These decreases are not linked to deficits in cognitive abilities, as are those often associated with aging, but rather represent a "fine-tuning" of the maternal brain (Pawluski et al., 2022). This is similar to other developmental stages, such as early childhood and adolescence (another transitional life stage characterized by increased hormones): in these periods, a decrease in neurogenesis and synaptic pruning is necessary for healthy behavioral outcomes (Peper et al., 2011). Although grey matter reductions in some regions persist into the late postpartum period, other brain regions show increased structural and functional measures of brain plasticity after childbirth (Pawluski et al., 2022).

In addition to grey matter changes, in the peripartum, microglia levels decrease, suggesting that the maternal brain may assume a protective, inflammation-resistant state. These central immune changes parallel immune changes in the periphery necessary for sustaining a pregnancy and fetal development (Sherer et al., 2017). Given their timing, peripartum central immune changes may play a role in the motivational, cognitive, and mood-related changes found in new mothers (Pawluski et al., 2022).

Grey matter volume increased in mothers' widespread cortical and subcortical areas in the first weeks and months of the postpartum period (hippocampus, cerebellum, frontal, and occipital areas). The behavioral correlate of these structural and functional changes is not only associated with increased attention to the infant's needs and signals but with promoting mother-infant bonding (Laurent and Ablow, 2012; Pawluski et al., 2020); there is also an enhanced vigilance against various threats, such as those potentially associated with angry or fearful faces and sick-looking or out-group individuals. This information is very important

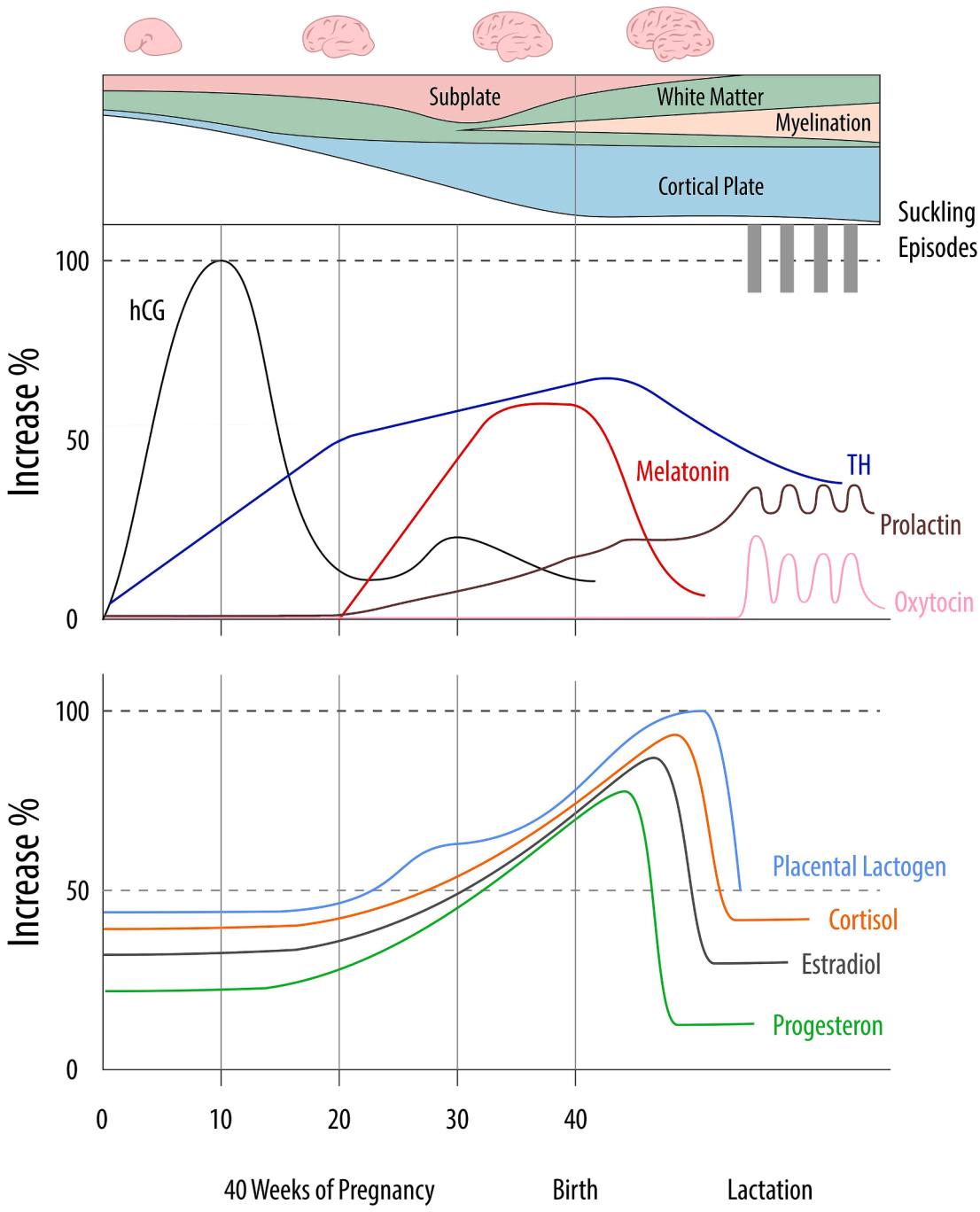

Fig. 2. The percentage increase in hormones during pregnancy and the first months of postnatal life of the child (bottom part). In the top part of the figure, the parallel brain development of the fetus and infant is shown. Legend: hCG: human chorionic gonadotropin; TH: thyroid hormone.

because it could be implicated in the maternal hyperactivation of the anxiety and worry circuit, which induces her to continue focusing on the newborn. The maternal anxiety levels peak immediately after childbirth and then begin to diminish during the first three to four months postpartum (Kim et al., 2016, Kim et al., 2013). Oxytocin receptors are also abundantly present in the amygdala (Viviani et al., 2011). This suggests the importance of maternal hormones in "checking and worrying" brain circuits, which include the basal ganglia and orbitofrontal cortex (Leckman et al., 2004). This condition can optimize the learning window the neuroevolutionary change creates in the maternal brain but can also predispose the mother to psychopathological vulnerability.

The fetal cerebral changes

Fetal life and infancy are the most rapid periods of brain growth in the life of one person, which provides the structural support for neurodevelopmental outcomes into childhood (Dubois et al., 2015; Herschkowitz et al., 1999, 1997; Peterson et al., 2003). The third trimester of pregnancy is particularly important for maturing the cerebral structures and establishing the cerebral organization; in the postpartum, the "brain system" is ready to be shaped by environmental experiences.

The germinative matrix starts in the mid-term, producing neurons that migrate to a transient structure, the cortical subplate. The subplate is now recognized as central to early circuitry formation. It has been shown that thalamocortical fibers approach their subplate target in

different cortical regions (Kostović et al., 2011), and then, about until 24–32 post-conception weeks, they start growing into the cortical plate (Kostovic and Goldman-Rakic, 1983; Krmpotić-Nemanić et al., 1983). This process determines a period of coexistence of transient endogenous and permanent thalamocortical circuitry, building the sensory-driven circuitry and allowing the development of the overlying cortical plate circuitry (Friauf and Shatz, 1991; Kostović, 2020).

Later in development, during the late preterm phase, the subplate zone starts to decline in parallel with the ingrowth of the callosal and long cortico-cortical pathways. The intracortical circuitry develops with the first evidence of intracortical differentiation (Penn and Shatz, 1999). Now, axonal arborization, dendrites, spines, and synapses within the cortical plate layers can start developing, and the retraction of exuberant axons can begin (pruning) (Kostović et al., 1995; Mrzljak et al., 1991).

Once an infant is born, the major challenge is the creation of short-term intracortical circuitry, which requires efficient inhibitory mechanisms. The development of the inhibitory mechanism is possible only with the transition of GABA from excitatory to inhibitory, which happens after birth. During fetal life, GABA is, in fact, excitatory: the excitatory activity generates primitive "giant" patterns of network activity, whose crucial role is to make neurons fire together to teach them to "wire together" (Ben-Ari et al., 2007). The maturation of intracortical interneuronal circuits is a necessary prerequisite of learning (Buzsáki and Draguhn, 2004a; Palva et al., 2005a; Steriade, 2006). Therefore, the neurochemical substrate underpins the transition from a primitive and limited reactivity in the fetus and neonate to a plastic and flexible pattern that allows the environment to shape the infant.

Childbirth and behavioral changes

Like other mammals, birth for humans is not a transition into independence but an extension of the dependence period that begins in utero (Porges and Furman, 2011). However, this does not mean newborns are completely vulnerable and perceive a confusing world: they are competent and equipped for their new condition. Newborns display organizational perceptual competencies by which they organize and structure the world. Several experiments have shown that just a few hours from birth, a newborn's attention is preferentially attracted to faces and human voices (Cassia et al., 2004), an ability with a strong adaptive value.

This specific equipment, which accompanies and guides the child through the first stages of interaction with the outside world, represents an ideal basis for developing experience-dependent neural networks but is transitory. Probably, it is a facilitative and "permissive" transitional pattern of functioning. This is reflected in the transitory neonatal right hemispheric dominance, which sustains essential functions: emotional processes, recognition of faces and expressions, mental rotation, detection of relevant stimuli, and *para*-verbal stimuli (George et al., 1996; Geschwind and Galaburda, 1985). Additionally, neonatal sleep-state cycling is transitory and more similar to prenatal life. After birth, prenatal EEG phenomena persist for about 1–2 months (André et al., 2010). In neonates, ultradian rhythms and brainstem regulation mostly drive sleep-state cycling in fetuses and preterms: circadian rhythms only develop during the first few months after childbirth (Bueno and Menna-Barreto, 2016).

However, this transitory pattern of functioning is mainly rigid and stereotypical. When a child is born, he expresses emotions, shares feelings, and exhibits a simple form of awareness of his own self and others. However, the development of integrated sensations and consciousness is a progressive functional evolution of multiple intricate components (Padilla and Lagercrantz, 2020). This makes the neonatal period challenging (some authors call it the "neonatal gap"), given the qualitative shift characterizing multiple levels of brain functions (Stjerna et al., 2015). However, functional brain networks are rapidly adapted to the postnatal environment (Tokariev et al., 2016). This shift is developmentally timed to the parallel transition from endogenously guided (experience-independent maturation) brain activity in utero to a more environmentally influenced (with increasingly greater experience dependence) brain function in the postnatal period (Espinosa and Stryker, 2012; Feller and Scanziani, 2005).

The mother–child interface: A transition

We think that this transitory pattern of functioning has several functions. Human evolution and attaining the upright position have resulted in the need to give birth to smaller, immature fetuses. These fetuses would have needed to complete their fetal maturation process postnatally, on the one hand, but on the other hand, possessing a certain functional autonomy may have ensured greater chances of survival. This transient and stereotypical functioning pattern may safely carry the infant toward more flexible forms of functioning, in which external stimulation and brain plasticity acquire a crucial role and allow the mother a period of optimal adaptation to her new condition and hormonal changes. Indeed, the mother, too, would seem to face a peculiar transition period in the first postnatal months. After birth, the mother's brain and body undergo dynamic changes to support the establishment and maintenance of maternal caregiving behaviors. On a physiological level, the body has to cope with important changes (such as lactation and the abrupt drop of hormones); on a neurobiological level, the mother faces a real neuroevolutionary phase, as only during prenatal or adolescence. The interplay between pregnancy hormones and peripheral stimulation leads to multiple structural and functional adaptations in the mother's brain that are necessary for the onset, maintenance, and regulation of maternal behavior (Numan, 2007). The immune, endocrine, and nervous systems constantly communicate and are closely interconnected. Once this circuit is primed by the endocrine events associated with pregnancy and parturition, maternal behavior is maintained by environmental cues derived from the interaction with offspring (Numan, 2007).

During this period, not only does she have to adapt to the enormous changes in her body, but she also has to learn to understand her child's needs, so radical changes occur in certain brain circuits that will allow her to take care of her child but also make her more vulnerable to psychopathology.

Therefore, in the same postnatal months, mother and child go through a period of transitional functioning, which allows them to become new individuals. Meanwhile, the exchanges between mother and child continue to enable this transition.

Potential mechanisms of fetal brain development influenced by maternal factors

Abnormal conditions during pregnancy are renowned factors impacting fetal brain development and, as a consequence, neurodevelopment. Paradoxically, the physiological mechanisms implicated in normal development are less known. The next section will describe some pivotal mechanisms, although this description can only partially account for a much broader and more complex process (see Table 1 for a summary).

Hormonal influences

Hormones increase dramatically during pregnancy. Some of these hormones are directly implicated in fetal brain development: They act as signaling or activating molecules that could start or interrupt developmental processes. Interestingly, when the fetal nervous system starts to produce its own hormones, maternal hormones continue modulating the fetal processes.

In the following paragraphs, we will focus on the TH and cortisol, hormones with more complete evidence, and melatonin, which has attracted increasing research interest. As a complement to this paragraph, Fig. 2 shows a complete framework of the hormonal changes

Table 1
Maternal factors influence the fetus's brain development and, as a consequence, neurodevelopment.

Maternal factors	Way of action	Action
Thyroid hormones	**Placenta**	**Prenatal**: neuronal proliferation, migration, and differentiation. Neurite outgrowth and guidance. Synaptogenesis and myelination switch from proliferation to differentiation. Contribute to the number of mature GABAergic neurons **Postnatal:** contributes to the switching of the GABA from depolarizing (excitatory) to hyperpolarizing (inhibitory)
Glucocorticoids	**Placenta**	**Prenatal:** switch from proliferation to differentiation to coordinate fetal readiness for extrauterine life and the timing of parturition.
Melatonin/ tryptophan	**Placenta**	**Prenatal:** modulates differentiation, neurogenesis, and myelination **Childbirth:** synchronizes and facilitates parturition. Analgesic to the associated pain.
Oxytocin	**Placenta Lactation Touch**	**Postnatal:** Contributes to early mother–child attachment behaviors. Promotes epigenetic modifications and influences the timing of myelination processes and cortical thickness.
Microchimerism	**Placenta Lactation**	**Prenatal:** fetal immunity **Postnatal**: infant immunity
Gut Microbiota	**Delivery Lactation Touch**	**Postnatal:** colonization of the infant's intestine and consequent epigenetic modifications
Epigenetic gene regulation	**Placenta Lactation Behavior**	**Prenatal:** accelerates the rate of DNA synthesis, DNA methylation patterns, and chromatin, which heightened the vulnerability to environmental influences. **Postnatal:** alters the DNA structure at glucocorticoid receptor gene promoter in the hippocampus. DNA methylation patterns

during pregnancy, birth, and postpartum and their influences on the fetal brain.

Thyroid hormone (TH)

The TH has a widespread evolutionary history (THs and their metabolites are widely distributed in the animal and plant kingdoms) and is involved in the maturation of various tissues and organs during the transition to extrauterine life (Buchholz, 2015). During pregnancy, several changes occur in the mother that are connected with TH production: iodine clearance and serum levels of thyroxin-binding globulin increase. Moreover, the deiodination of triiodothyronine (T3) and thyroxine (T4) by the placenta is upregulated (Springer et al., 2017). Total T4 concentration increases in the first trimester due to the increased thyroxin-binding globulin levels, and it decreases relatively during the second and third trimesters (Medici et al., 2015).

In the fetus, there are two sources of TH: the developing fetal thyroid gland and the maternal thyroid gland. Maternal T4 is especially important in the first half of pregnancy – before the fetal thyroid matures and starts producing, where the fetus completely depends on the maternal TH supply. Maturation of the fetal thyroid gland happens by week 11–12, whereas TH is secreted around week 16 (Obregón et al., 1991). However, even after the onset of fetal thyroid secretion, human data show that maternal transfer still represents about 30 %–60 % of fetal serum thyroxine and maintains an important protective role in fetal neurodevelopment until birth (De Escobar et al., 2004). For this reason, maternal TH levels must be maintained within strict levels to ensure normal fetal brain development.

In the fetal brain, TH is critical for neuron proliferation, neuronal migration and differentiation, neurite outgrowth and guidance, synaptogenesis, and myelination (Moog et al., 2017; Pathak et al., 2011; Shimokawa et al., 2014). Furthermore, maternal THs have been identified as a critical factor for the switch from proliferation to differentiation of embryonic stem cells, thereby contributing to the neurogenesis in the telencephalon during early brain development (Chen et al., 2012). THs regulate the differentiation of neurons, oligodendrocytes, astrocytes, and microglia (Rodriguez-Pena et al., 1993). Alterations in these processes affect the maturation of interhemispheric connections, with a specific effect on myelinization (Berbel et al., 1994).

Furthermore, triiodothyronine (T3) directly regulates reelin expression during development (Alvarez-Dolado et al., 1999; Pathak et al., 2011). In particular, Cajal-Retzius cells in rodents are under T3 control (Alvarez-Dolado et al., 1999; Bernal, 2017). These cells secrete the extracellular matrix protein reelin, which acts as a barrier for the newly arriving neurons from the ventricular layer during the formation of the cortical layers, thus becoming critical in controlling neuronal positioning (Rakic and Caviness, 1995).

Last but not least, TH has a role in the proliferation and maturation of the precursors of cerebellar gamma-aminobutyric acid (GABA) interneurons, influencing the number of mature GABAergic neurons and GABAergic terminals (Manzano et al., 2007). As above described (paragraph 2.3), early in development, primitive patterns of network activity, notably the giant depolarizing potentials, guide neurons and networks from a silent ensemble of newly differentiating neurons to an ensemble of coactive neurons that generate many patterns and oscillations (Ben-Ari et al., 2007). To "wire together," neurons have to fire together. This happens largely through the action of the GABA, which, at this stage, is excitatory and synergistically interacts with glutamate signaling (Ben-Ari et al., 2007). Unlike mature neurons, where GABA is the main inhibitory transmitter that hyperpolarizes its target neurons (Kaila, 1994), immature neurons have a higher intracellular chloride concentration, leading to chloride efflux and depolarizing postsynaptic responses (Rivera et al., 1999). This renders the GABAergic transmission excitatory and consequently facilitatory or "permissive" in generating endogenous events (Sipilä et al., 2005). The subsequent neurochemical maturational change in inhibitory is crucial in mediating network shaping but also in exerting potential vulnerabilities and damages.

GABA interneurons have been demonstrated to be strongly affected by TH in the neocortex, hippocampus, and cerebellum. Hypothyroidism, in the early phases, affects GABAergic neurons and their axonal and dendritic processes (Gilbert et al., 2007; Sawano et al., 2013) and leads to a 50 % reduction of glutamic acid decarboxylase 65, the enzyme responsible for converting glutamate to GABA (Sawano et al., 2013). Furthermore, transient maternal TH deficiency alters the tangential migration of neurons derived from the medial ganglionic eminence, which includes GABAergic interneurons (Cuevas et al., 2005).

Furthermore, tangentially migrating GABAergic neurons form a subpopulation of subplate neurons, the transient structure with the role of guiding ingrowing thalamocortical axons and the maturation of intra- and extracortical circuits in the third trimester of pregnancy (Hoerder-Suabedissen and Molnár, 2015). These processes play a critical role in the functional maturation of developing neural circuits and extend well into the postnatal period when external stimulation will act crucially in shaping them. Subplate abnormalities have been shown in rats with maternal hypothyroidism (Navarro et al., 2014); in particular, developmental hypothyroidism has been associated with a substantial reduction in thalamocortical axonal arborization, potentially due to asynchrony in the maturation of thalamocortical afferents and their

cortical targets (Berbel et al., 2014).

The molecular mechanisms by which TH induces the above-mentioned changes are still not fully understood. In neural cells, it is estimated that around 5 % of all expressed genes are under T3 control, mostly by direct regulation at the transcriptional level (Gil-Ibáñez et al., 2014). Nevertheless, TH's influence on gene regulation can also be accomplished at the posttranscriptional level by affecting proteins involved in RNA stability and splicing (Aniello et al., 1991). In fact, TH has been shown to modify the expression of genes associated with cell cycle and intracellular signaling, cytoskeleton organization, and extracellular matrix contents, which are involved in neurogenesis and neuronal migration (Bernal, 2017; Lin et al., 2004; Miranda and Sousa, 2018).

Recent studies have focused on genes specific to the subplate neurons to understand the molecular basis of this structure. Interestingly, T3 regulates most of the genes identified (Gil-Ibañez et al., 2017), pointing to an important regulatory effect of TH in subplate development and function. As confirmation, hypothyroidism has been shown to interfere with the proper development of cortical circuitry (Lucio et al., 1997). It also could be of particular relevance for the etiology of autism, a neurodevelopmental disorder in which an alteration of the neural circuitries and connectivity has been demonstrated (Berbel et al., 2014).

Finally, TH may also alter other the brain's neurotransmitters. Widespread decreases in monoamines (norepinephrine, epinephrine, dopamine, and serotonin) and acetylcholinesterase have been documented in hypothyroid rats (Ahmed et al., 2010).

In conclusion, TH functions are important throughout fetal brain development, particularly in the early stages, where the brain exhibits maximal vulnerability to an imbalance of TH supply (Moog et al., 2017). Studies on hypothyroidism in rats have demonstrated less defined cortical layering, neuronal migration and differentiation defects, and abnormal cerebral circuitry (Berbel et al., 2014).

Cortisol

Glucocorticoids act with TH in mediating several brain maturational processes. In particular, they synergistically induce the cell cycle's switch from proliferation to differentiation (Bernal, 2017). Glucocorticoids are implicated in circuitry formation, as shown by altered neonatal amygdala connectivity patterns, sensory processing and integration, and subsequent internalizing symptoms in pregnancy characterized by abnormal levels of these hormones (Graham et al., 2019; Krontira et al., 2020; Monk et al., 2019).

However, cortisol is mainly known for its role in coordinating fetal readiness for extrauterine life and the timing of parturition (Miranda and Sousa, 2018; Wood and Keller-Wood, 2016). It is arguably the most important hormone for organizing maturation in late gestation, not only of the brain but of the entire body. Corticosteroids suppress cell proliferation and DNA replication and stimulate terminal differentiation (Liggins, 1976), a process of the utmost importance for the maturation of fetal organ systems, such as the lung, liver, skeletal muscle, kidney, and central nervous systems (Liggins, 1976; Wood and Keller-Wood, 2016).

The fetal adrenal gland is active from very early gestation, but adrenal cortisol is only produced in appreciable quantities 22 weeks after conception (Weinstock et al., 1992); therefore, most of the cortisol circulating in the fetal blood derives from the maternal adrenal glands, even if also placenta has a role (Hennessy et al., 1982). As confirmation, a reduction in maternal cortisol concentration alters blood pressure, fluid balance, and uterine blood flow and slows fetal growth (Wood and Keller-Wood, 2016). Untreated maternal adrenal insufficiency causes premature labor and neonatal morbidity (Björnsdottir et al., 2010; Fux Otta et al., 2008).

Melatonin

Melatonin has become an object of interest for its neuroprotective function in recent years. Its role is related to its antioxidant properties, activation of intracellular protection pathways via specific receptors, and epigenetic modulation. In rats, melatonin has been shown to protect the brain from oxidative stress, lipid peroxidation, and DNA damage caused by ischemia and reperfusion during gestation (Okatani et al., 1999).

Melatonin's protective effects are closely related to fetal brain programming, and a reduction in melatonin might have long-term consequences (Irmak et al., 2005). Tryptophan derivatives, such as serotonin and melatonin, have been described as modulators of brain differentiation and neurogenesis (Bonnin et al., 2011; Luchetti et al., 2010). Other tryptophan-derivative molecules, such as serotonin, the direct melatonin precursor, are involved in forebrain maturation in mice and have a long-term effect on neurodevelopment (Bonnin et al., 2011). In particular, serotonin has been recently discovered to be related to the lack of myelination during the third trimester, a condition that could determine several neurocognitive abnormalities in later life (Fan et al., 2015).

Furthermore, together with oxytocin, placental melatonin might be involved in the parturition process. Oxytocin and melatonin share the same signaling pathway to induce myometrium contractility (Sharkey et al., 2010). Indeed, melatonin has been suggested to synchronize and facilitate parturition while alleviating the associated pain.

As for TH and glucocorticoids, circulating melatonin is mainly of maternal origin. Interestingly, lifestyle, nutrition, and exposure to chemical endocrine disruptors can modulate maternal levels. Of all modulators of fetal brain development, melatonin is among the most susceptible to environmental variations (e.g., season, luminosity, maternal nutrition, sleep-wake cycle, and geographic location) (Carrillo-Vico et al., 2005; Valenzuela et al., 2015).

Childbirth: GABA and oxytocin

Once an infant is born, the major challenge is now the creation of short-term intracortical circuitry. The formation of intracortical circuits requires efficient inhibitory mechanisms, which can emerge with the transition of GABA from excitatory to inhibitory after birth. To make this happen, the expression patterns of chloride-regulating molecules undergo a profound change (Rivera et al., 1999), allowing GABA to become gradually more hyperpolarizing.

The maturation of intracortical interneuronal circuits and inhibitory neurotransmission—processes that span from birth into infancy—are required before cortical networks can generate the robust, highly synchronized activity believed to be essential for many cognitive functions (Buzsáki and Draguhn, 2004; Palva et al., 2005; Steriade, 2006). Therefore, the neurochemical substrate underpins the transition from a primitive and limited reactivity in the fetus and neonate to plastic and flexible cerebral networks shaped by the interplay of the child with their caregiver first and the environment subsequently. In the process of switching the GABA actions from depolarizing (excitatory) to hyperpolarizing (inhibitory), the maternal TH seems implicated. The rise in K+/Cl cotransporter, a postsynaptic component essential for the switching of GABAergic neurotransmission from excitatory to inhibitory (Ben-Ari, 2002), is absent in hypothyroid animals, inducing a significant delay in the timing of the switch (Sawano et al., 2013).

The mother has another crucial influence in this process. The GABA's maturation process from excitatory to inhibitory is not linear. GABA is expected to be depolarizing in utero and a few days after delivery, but shortly before, during, and after delivery, there is a dramatic transient fall of the concentration of chloride and a depolarizing-hyperpolarizing shift (Tyzio et al., 2006). Cell-attached recordings confirmed that GABA transiently loses its excitatory action during this narrow window due to the maternal hormone oxytocin the mother releases to trigger labor (Ben-Ari et al., 2007). Oxytocin supports the critical transition from excitatory to inhibitory functioning, which is critical for the infant's survival because the oxytocin-dependent GABA transition protects the fetal brain from hypoxic conditions, which are common during parturition. In addition, the oxytocin-induced GABA transition also acts as an analgesic, reducing the polarization of GABA on nociceptive neurons.

Therefore, oxytocin not only initiates labor through uterine

contractions but also changes the infant's GABA neuromodulators from inhibitory to excitatory, with neuroprotective and analgesic effects on the newborn (Tarsha and Narvaez, 2023).

Oxytocin and Breastfeeding: Effects on the fetus

Oxytocin is also implicated in the milk ejection reflex, and during breastfeeding, it is released into the brains of both mother and infant, inducing a great variety of functional responses. Several studies have shown that breastfeeding is associated with improved neurodevelopmental outcomes (Koh, 2017; Lewallen, 2012; Wallenborn et al., 2021) and higher intelligence quotients (Horta et al., 2015a; Kramer et al., 2008).

Breastfeeding exerts its effects, probably influencing the timing of myelination processes in the developing infant brain by prolonging the peak of myelination to a later age (Deoni et al., 2018, 2013; Isaacs et al., 2010; Kafouri et al., 2013), with effects on whole-brain volume, cortical thickness, and white matter volume and consequently on cognitive and neuropsychological functioning (Krol and Grossmann, 2018).

The mechanism underlying the breastfeeding effects on the fetal brain is not completely clear, but it is hypothesized that it can promote epigenetic modifications via its bioactive components, including growth factors, microbiota, stem cells, micro-RNAs, and long non-coding RNAs (Camacho-Morales et al., 2021; Melnik et al., 2021), thus influencing the fetal health intergenerationally (Chutipongtanate et al., 2022; Gialeli et al., 2023; Ozkan et al., 2020).

Researchers are also exploring new intriguing hypotheses. For example, researchers have recently explored the role of maternal microchimerism, elucidating its postnatal manifestations in relation to lactational transmission (Kinder et al., 2017). Colostrum is dense with a diverse assortment of immune cells and progenitor cells, potentially serving as a vector for the transference of maternal cells to the offspring, thereby facilitating the maturation of the neonatal and infantile immune systems as well as tissue repair mechanisms (Molès et al., 2018). Moreover, empirical evidence has demonstrated a quantifiable relationship between microchimerism and cross-generational reproductive fitness (Burlingham et al., 1998).

Furthermore, the role of breastmilk microbiota has also been investigated. The microbiome of breast milk shares common characteristics with the gut microbiome. After the establishment of bacterial colonization in infants, the composition of intestinal microbes becomes distinct and individualized (Rutayisire et al., 2016). The colonization of the infant's intestine after birth, influenced by several factors, such as maternal flora, delivery mode, early maternal contacts, and neonatal diet, results in specific epigenetic patterns that can influence the protective function of the gut mucosa against future insults (Indrio et al., 2017) and is also associated with brain development and neurodevelopment (Lu et al., 2023; Vuong, 2022).

In this process, the mother has a crucial role: breastfeeding can be associated with different sensations that vary dramatically between women, inducing in some women physical discomforts or even anxiety and depression (Isbister, 1954). Furthermore, maternal conditions such as diabetes mellitus, overweight or obesity, diet, psychosocial factors, and stress can influence the composition of human milk (Kupsco et al., 2021; Mirza et al., 2019; Shah et al., 2022).

However, there are also contradictory data that do not support the role of breastfeeding in neurodevelopment (Tozzi et al., 2012).

Mood of delivery and perinatal interventions

The mood of the delivery can influence the fetus, too. In particular, the delivery process has an important physiological effect on the fetal immune system and stress level. In infants born by vaginal delivery, oxytocin levels in umbilical arterial blood were higher than in infants born by cesarean section. In addition, oxytocin levels recorded postpartum in infants born vaginally correlate inversely with fetal arterial pH and also with the duration of labor (Marchini et al., 1988). It has also been shown that infants delivered by cesarean section exhibit lower total microbiota diversity (Jakobsson et al., 2014), an increased risk of immune disorders (Cho and Norman, 2013), and some studies found an association with an increased risk of autism spectrum disorder and other developmental disabilities (Curran et al., 2015). However, not all find differences in the children's long-term development (Zavez et al., 2021), and there is no evidence from randomized controlled trials upon which to base any practice recommendations regarding planned cesarean section for non-medical reasons at term (Lavender et al., 2012).

Other factors could influence the oxytocin system. Epidural analgesia may be linked to reduced oxytocin release as the Ferguson reflex is partly blocked, and infusions of oxytocin may influence spontaneous oxytocin release via a feedback inhibitory mechanism (Jonas et al., 2009; Nissen et al., 1998). Routine health practices promoting skin-to-skin contact early after the delivery and the days after contribute to early mother-infant bonding, given that the first few hours after delivery are considered critical for establishing a healthy mother-infant interaction and breastfeeding (Anderson et al., 2003; Gomes-pedro et al., 1995; Klaus and Kennell, 2001). Such practices are much easier to be implemented after vaginal delivery (Buhimschi and Buhimschi, 2006).

Epigenetics

In addition to normal genetic effects handed down via genetic material from parent to offspring, mothers may influence their offspring by affecting gene regulation through epigenetic mechanisms (Breed, 2017). The epigenome is especially prone to dysregulation during critical life stages, including gestation, neonatal development, puberty, and senescence. Of particular note is its heightened vulnerability to environmental influences during embryogenesis. This susceptibility arises from the accelerated rate of DNA synthesis and the concurrent establishment of intricate DNA methylation patterns and chromatin modifications, which are integral for normal tissue development at this early stage (Nafee et al., 2008). For example, maternal gestational diabetes was associated with lower cord blood methylation levels in two regions, the promoter of OR2L13, a gene associated with autism spectrum disorder, and the gene body of CYP2E1, which is upregulated in type 1 and type 2 diabetes (Howe et al., 2020). However, DNA methylation patterns are not fixed in postnatal life.

Regarding the brain, it was demonstrated in animals and humans that the mother's attention alters the DNA structure at a childhood glucocorticoid receptor gene promoter in the offspring's hippocampus, which could underlie the associations between adversity, alterations in stress reactivity, and the risk for psychopathology (McGowan et al., 2009). Moreover, breastfeeding for more than three months or more than six months was associated with different DNA methylation patterns in children at age 10. Still, these associations did not persist at 18 or 26 years (Sherwood et al., 2020).

Potential mechanisms of maternal brain development influenced by offspring factors

The influences of the fetus on the maternal brain and physiology are much less known. The reduced knowledge in the field is probably the legacy of years of research in which the neonate was considered a passive creature with no active role in its environment. From a clinical point of view, this conception has been scaled down since Brazelton's work (Brazelton and Nugent, 1973), but from a research point of view, we are still far behind. We will outline below what is known from various scientific fields (see Table 2 for a summary).

The placenta action

Perhaps the more conspicuous and hidden fetal influence on the mother relies on the placenta. As we previously showed, women undergo a dramatic hormonal increase. The hormones of maternal origin are complemented by additional pregnancy-specific hormones produced by the placenta, such as human chorionic gonadotropin and chorionic

Table 2
Fetal factors influencing the maternal brain and behavior.

Fetal factors	Way of action	Action
Placental corticotrophin-releasing hormone (CRH)	**Placenta**	**Prenatal**: not being inhibited by cortisol, overrides the maternal neuroendocrine mechanisms by stimulating the maternal pituitary gland to release adrenocorticotrophic hormone and thus contributing to stress-protective hypercortisolism
Placental lactogen	**Placenta**	**Prenatal:** not under inhibitory regulation and short-loop feedback, it chronically activates prolactin receptors, thus contributing to maternal behavioral adaptions
Fetal microchimerism	**Placenta**	**Prenatal with long-term implications:** immunity. Brain plasticity
Oxytocin	**Breastfeeding Touch**	**Postnatal:** induces the production of oxytocin, which contributes to early mother–child attachment behaviors. Reduction of HPA activating, thus acting on the stress system

somatomammotropin (Grattan and Ladyman, 2020). These placental hormones are secreted at specific stages during pregnancy and contribute significantly to driving adaptive change in the mother. However, the placenta is essentially fetal tissue: throughout it, the fetus overrides the mother's normal endocrine processes and drives changes to promote its development (also at a cost to the mother).

Particularly interesting to our discussion is the role of the placenta in glucocorticoid production. Pregnancy is a period of relative hypercortisolism (Valsamakis et al., 2019). This high production is partly due to the corticotrophin-releasing hormone (CRH), uniquely expressed by the placenta in primates (Power and Schulkin, 2006; Thomson, 2013). Placental CRH stimulates the fetal adrenal and acts on the maternal pituitary gland to release adrenocorticotrophic hormone, subsequently stimulating cortisol from the adrenal cortex. Hypothalamic CRH is inhibited by cortisol, but placental CRH is not; by contrast, it is stimulated by cortisol, providing a positive feedback mechanism that increases cortisol secretion as gestation proceeds (Power and Schulkin, 2006). The free levels of these steroids are high, and they cross the blood–brain barrier, bonding with their receptors expressed in numerous brain regions, particularly the hypothalamus and hippocampus (Joëls, 2018; Pryce, 2008).

Similarly, a protein hormone, the human placental lactogen, the placental analog of prolactin, which progressively increases throughout pregnancy and becomes in the third trimester extremely high (Aghaeepour et al., 2018), reach the brain. Placental lactogen is very interesting because, together with estradiol, progesterone, and prolactin, it determines the neuroendocrine changes underlying the maternal behavior, as shown by animal models (Terkel et al., 1972).

How placental lactogen acts in the maternal brain is a prototypical example of neuroplasticity. The placental lactogen is not under inhibitory regulation and short-loop feedback, and it of the prolactin receptors in tuberoinfundibular dopamine (TIDA) neurons. This appears to be critical for the induction of enkephalin in those neurons, as the knockout of prolactin receptors in these neurons prevents this adaptive change (Yip et al., 2019).

After childbirth, all placentally-derived hormones are abruptly lost from the maternal circulation, providing a significant change in signaling to the brain that may have important consequences for postpartum brain function. A precipitous drop in estrogen and progesterone after delivery of the placenta has also been prosed as the origin of the psychopathological vulnerability of the mother in the postpartum (Pawluski et al., 2017).

Fetomaternal microchimerism

In the prenatal period, the physiological linkage between the mother and fetus facilitates a bidirectional transfer of cells via the placenta. These enduring cells, which remain long-term (decades, at least) in the recipient, are genetically distinct, exemplifying the concept of microchimerism. Naturally occurring microchimerism is characterized by its asymmetric nature, with more fetal cells migrating to the mother (fetal microchimerism) than maternal cells to the fetus (maternal microchimerism) (Lo et al., 2000). However, chimeric cells' impact appears more pronounced in the fetus, attributable to its underdeveloped immune response (Gammill and Nelson, 2010). It is involved in immune adaptation during pregnancy and priming of tolerogenic responses in the progeny (Lo et al., 2000). Interestingly, microchimerism can be cross-generational, with cells from siblings and grandmothers transferred from the mother to the fetus (Kinder et al., 2015).

Fetal microchimerism has been identified as potentially beneficial in various conditions for the mother (Khosrotehrani and Bianchi, 2005). Because chimeric cells show stem-like behavior, their presence in maternal tissues could contribute to tissue repair and regeneration. For instance, microchimeric fetal cells have been found in the maternal brain, suggesting they may participate in neural regeneration and plasticity (Zeng et al., 2010). The integration of these cells into the maternal brain raises the possibility of their involvement in cognitive functions and emotional regulation during and after pregnancy (Boddy et al., 2015; Tan et al., 2005). Additionally, these cells might help modulate the maternal immune system, promoting tolerance during gestation and potentially influencing maternal health postpartum (Kinder et al., 2017).

It has been demonstrated that fetal progenitor cells (FPCs) are integrated into various regions of the maternal brain, persisting until the 7th month after birth and, in many cases, becoming permanent structures (Zeng et al., 2010). The expression of mature neuron markers in these FPCs indicates their adoption of a neuronal fate akin to that observed in regular adult neurogenesis. The neuronal maturation of FPCs, characterized by the increased complexity of axonal dendritic architecture, underlines a molecular and morphological maturation program resembling that of adult neurogenesis. This similarity between FPCs' maturation and adult neurogenesis opens up new avenues of understanding microchimerism's long-term impacts on maternal neurobiology. The integration and maturation of FPCs in the maternal brain may have various physiological and psychological implications. It is hypothesized that this mechanism might influence maternal behavior and cognitive functions and may also have potential implications for neurological diseases (Boddy et al., 2015; Tan et al., 2005).

On the other hand, fetal microchimerism can have less favorable implications (Nelson, 2012). Although fetal cells can differentiate into various cell types within the maternal brain, they might also contribute to neurological disorders if they elicit immune responses or disrupt normal neural function. Some studies have suggested associations between microchimerism and autoimmune neurological diseases, such as multiple sclerosis and Alzheimer's disease, although the mechanisms remain unclear (Boddy et al., 2015; Tan et al., 2005). The presence of genetically distinct cells in the maternal brain could potentially trigger immune-mediated damage or alter neural networks, highlighting the need for further research into their long-term effects on maternal brain health (Boddy et al., 2015; Shrivastava et al., 2019).

Immunological brain changes

Given their timing, peripartum central immune changes may play a role in the motivational, cognitive, and mood-related changes found in new mothers (Pawluski et al., 2022). Hormones are most likely responsible because microglia express receptors for many hormones that are altered across the peripartum period and that affect neuroinflammatory signaling, including glucocorticoids, estrogens,

progestins, and oxytocin (Sierra et al., 2008; Vegeto et al., 2001). However, the functional significance of peripartum immune changes is an open question. It does not preclude the possibility that the fetus could play a role. As studies investigating how fetal sex differences could influence pregnancy have shown, fetus-derived signals can alter maternal metabolism. Signal molecules, such as hormones, cytokines, and growth factors, modulate maternal metabolism in pregnancy through the placenta, with the fetal organ exhibiting massive endocrine activity at the interface between mother and fetus (Stern et al., 2021).

Furthermore, a possible trigger of changes in the maternal brain plasticity and immune function could be a phenomenon of fetal microchimerism. Fetal microchimerism appears to play a role in autoimmune diseases (Lambert et al., 2001; Nelson, 2002), a fact that renders these cells a possible, if not likely, candidate for triggering maternal immune changes. A possibility that supports this hypothesis is that fetal microchimerism may trigger graft-versus-host disease, activate and regulate maternal immune responses, and even induce the immune tolerance necessary to maintain the pregnancy (Cómitre-Mariano et al., 2022). Fetal cells could differentiate into active T lymphocytes, developing an autoimmune response against the maternal tissues (graft-versus-host reaction). However, the exact mechanisms are unknown (Ando et al., 2002; Fugazzola et al., 2011), but this phenomenon may have a broader scope from early gestation well into several decays after childbirth.

Oxytocin and Breastfeeding: Effects for the mother

We have previously shown how the oxytocin system and breastfeeding influence the fetus; in this paragraph, the focus is on the effects on the mother.

Maternal oxytocin increases throughout pregnancy to facilitate calmness and preparedness for childbearing. During birth, maternal oxytocin is released centrally and is induced through the activation of afferent sensory nerve fibers in the mother's pelvis (Moberg et al., 2020). When the infant's head exerts pressure on the cervix and vaginal wall, oxytocin is released into the mother, an effect known as the Fergusson reflex. Maternal pulses of oxytocin in the brain released during the childbearing process activate her reward system, decreasing pain, fear, and stress and increasing bonding with the newborn (Buckley, 2015). In addition, the childbirth process increases maternal oxytocin receptor expression (Broad et al., 1999), which is though < ht to promote breastfeeding and healthy attachment. Interestingly, there is a significant functional difference between vaginal and cesarean-delivering mothers' brains in response to the baby's cry, lasting three to four months postpartum (Swain, 2011).

After childbirth, as earlier shown, oxytocin is crucial for breastfeeding, and the suckling during breastfeeding releases itself oxytocin. Suckling is detected by mechanoreceptors of sensory nerve terminals in the nipple, which send afferent cholinergic impulses to the paraventricular nuclei and supraoptic nuclei in the hypothalamus that, in turn, stimulate the pulsatile release of oxytocin from the posterior pituitary (Newton and Newton, 1948; Truchet and Honvo-Houéto, 2017). It seems that neural reflexes induced from the oral mucosa by the touching of the nipple are involved in the creation of the primitive "attachment" behavior (Moberg and Prime, n.d.).

The neonate is not a passive actor; rather, the baby is crucial in the breastfeeding interaction. In fact, the suckling frequency and the baby's characteristics influence breastfeeding.

Not only suckling: thanks to conditioned reflex, with time, oxytocin release also occurs in response to such stimuli as the sight or sound of the baby that actively catches and attracts the attention of the mother (Jonas and Woodside, 2016). If posed on the mother's chest immediately after birth, the fetus induces a release of oxytocin into the maternal circulation. The effect has been associated, in part, with the massage of the breasts by the infant (Matthiesen et al., 2001). The oxytocin release that is induced by this skin-to-skin contact occurs in a few protracted pulses, different from the short pulses induced by sucking, with a probable function of "prime" the starting breastfeeding and mother–child interaction (Matthiesen et al., 2001).

At the brain level, oxytocin acts in the central nervous system to facilitate the psychological integration of the interactions between the mother and the suckling neonate. Breastfeeding has been shown to facilitate maternal sensitivity and secure attachment (Brandt et al., 1998; Kennell and McGrath, 2005), and is associated with reduced levels of child neglect and increased maternal neural responses to the child's cry (Britton et al., 2006; Strathearn et al., 2009a).

Furthermore, breastfeeding is protective for the mother from several pathologies (do Carmo França-Botelho, 2012; Horta et al., 2015b), and from stress (Altemus et al., 1995), thanks to an inhibitory action on the HPA axis (Neumann, 2002). This oxytocin-linked, anti-stress pattern is facilitated in certain situations, such as when the skin is exposed to touch, warmth, and light pressure. This explains why mothers and newborn infants experiencing skin-to-skin contact exhibit a marked anti-stress pattern. Finally, given the critical role of oxytocin in peripartum and postpartum maternal functions and behavior, it seems a prime candidate to explain possible changes in postpartum mood and behavior (Pawluski et al., 2017).

Implications for the future

The intriguing thing about the process described above is that in such a short period, the foundations of cognitive functioning and the health status of all future offspring's life can be established. A lot is now known about the long-term effects of adverse pre-perinatal factors (Cainelli et al., 2021b; Faa et al., 2014; Musillo et al., 2022),and about how, during pregnancy, the foundations can be laid not only for neurodevelopment but also for psychopathology in adulthood (Bacchin et al., 2023) and even in the elderly and in the next generation (Barlow et al., 2007)!

The critical period of brain development of the fetus and infants makes it relatively easy to imagine how even small differences during the gestational period and early months of life can translate into huge differences in adult life following the different life experiences that can amplify and/or mitigate certain developmental trajectories. By contrast, much less is known about the long-term implications of pregnancy for the mother. Only a few studies have investigated the question, particularly how pregnancy can change the mother's brain in the long term (Hoekzema et al., 2020; Orchard et al., 2023; Pawluski et al., 2022). Newer fields, such as microchimerism, may offer intriguing insight into this phase of life's long-term and intergenerational implications.

Pregnancy is a wondrous period in which the mother and fetus program and prepare for their new lives. In this path, mother and child do not run parallel and independently, but both parties' development results from synergy. During pregnancy, the dyad constantly exchanges cells, and this exchange influences their transformation. In the first months after birth, the child and the mother face a very important task: to adapt to a new and revolutionary life. Just after birth, the child enters a transitory state of functioning that helps them face an external environment that will gradually shape their behavior and perhaps survive until maternal adaptation to the new situation. Apparently, the mother also goes through a similar transitional period, which helps her face one of the most sensitive neuroplastic periods of her life. Rather than a purely hormone-driven process, the observed changes likely reflect an interplay among various biological and social factors. These changes' adaptive function is to allow the mother to acquire experience-dependent skills and knowledge readily. This renders the first months postpartum a critical moment for women because it could heighten their vulnerability to psychopathology. In this period, a transient and stereotyped pattern in the infant's functioning, aimed at continually attracting maternal attention on the one hand and presenting stereotyped and predictable behavior on the other, can accompany the mother on her path to acquiring new skills, which will allow her to grow close to the growing child in the various developmental stages. In the mother,

the anxiety and worry circuit is hyperactivated, causing her to continue to focus on the newborn. The anxiety begins to diminish during the first three to four months postpartum, paralleled by the resolution of the transitory pattern of the child's functioning. This condition can optimize the learning window the neuroevolutionary change in their brain provides.

Unfortunately, many aspects of the reciprocal mother–child influences in physiological conditions are poorly understood. Paradoxically, the literature studying adverse prenatal conditions on child neurodevelopment is richer. A better understanding of the mechanisms under normal conditions can provide the missing answers that studying pathological conditions alone cannot provide.

In this review, we traced the mother's and child's path from pregnancy to the months following birth: their synergetic dance, where reciprocal influences create two new individuals.

Ethical statement

I have read and have abided by the statement of ethical standards for manuscripts submitted to Neuroscience.

CRediT authorship contribution statement

Elisa Cainelli: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Luca Vedovelli:** Writing – review & editing, Methodology, Conceptualization. **Patrizia Bisiacchi:** Writing – review & editing, Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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