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The parental brain and behavior: a target for endocrine disruption

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Abstract

During pregnancy, the sequential release of progesterone, 17β-estradiol, prolactin, oxytocin and placental lactogens reorganize the female brain. Brain structures such as the medial preoptic area, the bed nucleus of the stria terminalis and the motivation network including the ventral tegmental area and the nucleus accumbens are reorganized by this specific hormonal schedule such that the future mother will be ready to provide appropriate care for her offspring right at parturition. Any disruption to this hormone pattern, notably by exposures to endocrine disrupting chemicals (EDC), is therefore likely to affect the maternal brain and result in maladaptive maternal behavior. Development effects of EDCs have been the focus of intense study, but relatively little is known about how the maternal brain and behavior are affected by EDCs. We encourage further research to better understand how the physiological hormone sequence prepares the mother's brain and how EDC exposure could disturb this reorganization.

Keywords

Progesterone; Estradiol; Prolactin; MPOA; Motivation; Endocrine disruptors; EDC; Maternal Behavior

1. Introduction

Brain function requires constant plasticity and remodeling. Neurogenesis and neuroplasticity have attracted attention because of the potential long term adverse consequences if these

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processes are impaired or disturbed by endogenous (hormones) or exogenous (social interaction) factors during development as well as during adulthood. Amongst the best studied examples in adulthood are hormonal-dependent physiological and behavioral changes linked to reproduction, including sexual behavior and parenting.

Parenting can be defined as behavioral interactions directed towards an immature conspecific to improve its survival after birth. In mammals, mothers are usually the most involved in parental care, in part due to the lactating ability of the female. In fact, for more than 90% of mammalian species, parental care is exclusively of maternal origin (Kleinman & Malcom, 1981). However, in the remaining species, parental care can be either paternal or biparental, this last case typically observed in monogamous species (Dulac *et al.*, 2014; Royle, 2014).

Like most behaviors, the performance of parenting behaviors occurs due to changes in the neural connections, number of neurons, activation of neurons, and expression of specific proteins within specific spatially-defined brain nuclei (Dragunow & Faull, 1989; Baez-Mendoza & Schultz, 2013; Galea *et al.*, 2014a; Luft *et al.*, 2014). As we will discuss below, the major drivers of these changes in the parental brain are endogenous hormones, including estrogens (such as 17β-estradiol), progesterone, oxytocin and prolactin. Although the major changes in hormone secretion will impact the whole brain, their main targets to modulate maternal behaviors are the medial preoptic area (MPOA) and ventral tegmental area (VTA) as confirmed by lesion studies, performed mostly in rodents species (Numan, 1974; Gaffori & Le Moal, 1979; Jacobson *et al.*, 1980; Numan & Smith, 1984; Numan *et al.*, 1988; Numan, 1990a). Indeed, experimental lesions of these brain regions in rodents abolishes the onset of maternal behaviors, disrupts nest building, and prevents nursing behaviors. Other brain regions including the bed nucleus of the stria terminalis, the nucleus accumbens, and the arcuate nucleus are also involved in maternal behaviors including lactation (Lonstein *et al.*, 2000; Numan & Insel, 2003; Crowley, 2015).

Because the establishment of parental behaviors and the associated changes in the brain are dependent on the action of specific hormones on hormone receptors, it has been proposed that they also have the potential to be affected by exposures to environmental chemicals that mimic or block the actions of endogenous hormones, i.e. endocrine disrupting chemicals (EDCs) (Walker & Gore, 2011; Catanese *et al.*, 2015; Gore *et al.*, 2015). Our review will describe the steroid-dependent mechanisms involved in the onset of parental brain and behavior and discuss, with the little data available from studies of EDCs, how activation or inhibition of specific hormone signaling pathways affect parental behavior and structures in the brain. Although there is a rich literature demonstrating that EDCs can affect numerous aspects of behaviors (e.g., anxiety-like behaviors, hyperactivity, social behaviors, sex behaviors), we focus our review on the effects of EDCs on maternal behaviors, particularly in females exposed *during pregnancy/lactation* or in females exposed *during perinatal development*. Similarly, there are many studies demonstrating that EDCs alter numerous aspects of specific brain regions and nuclei; here, we have focused on the much smaller subset of studies that examine maternally-relevant brain regions *during the display of maternal behaviors*, i.e. during the lactational period. Although these studies are relatively

limited, insights from this work on EDCs could provide new tools to probe the mechanisms by which maternal brain and behaviors are established.

2. Maternal behavior

2.1 The establishment of maternal behavior at parturition

Maternal behavior at birth presents very similar characteristics within many mammalian species (Numan, 2003). For most mammals, maternal behavior emerges at or close to parturition under the influence of changes in circulating hormonal levels (in particular, a drop in circulating levels of progesterone, a rise in circulating estradiol, and intracerebral release of oxytocin due to vagino-cervical stimulation; see (Brunton, 2008; 2010; Bridges, 2015) and section 3.4 of this review). Immediately following birth, the female shows a very rapid interest towards the newborn, and mothers start to lick the amniotic fluid and eat the extra-embryonic membranes covering the offspring. Females also often display placentophagia, i.e. consumption of the placenta. In many mammals, females begin to emit specific vocalizations in response to their young. Within the first hours following parturition, the offspring gets access to the udder or nipples to begin suckling. Nursing behavior is the most important and common pattern of maternal behavior in mammals, defined by obligatory contact with the mammary tissue. In addition, most mothers protect their young from predators or conspecifics by developing maternal aggression towards intruders. Finally, rodent mothers show various forms of retrieval, or carrying behaviors, to place their young in safe places like a nest.

Despite this common scheme, variations in the expression of maternal behaviors occur according to the degree of maturity of the young at birth. In altricial species, females usually have a large litter of young that are immature with regard to both sensory and motor development. In these species, parental behavior is organized around a nest that is used to isolate and protect the litter from the environment. Most rodent species fall into this category. Indeed, rodent pups are rather immobile with poor physiological maturity at birth; they are nude and unable to regulate their body temperature, and cannot defecate or urinate without the help of their mother.

By contrast, in precocial species, the litter is more limited (1–2 offspring) and the young are much more mature. In these species, the offspring can stand and suckle the mother shortly after birth; within a few hours, the young can follow the mother (Nowak, 2000). In this developmental state, maternal behavior is not typically organized around a nest and parental care usually requires a rapid attachment of the mother to its young, often leading to individual recognition of the offspring. Ungulates such as sheep and goats are good examples of this category (Lévy, 2008; Nowak, 2011). Indeed, lambs, once cleaned of fetal fluids by the mother, can regulate their body temperature on their own. They typically reach the mother's teat within one hour following birth and within a matter of hours can travel long distances. In addition, the mother develops an individual bond with the lamb that is formed within 4h of parturition and is based on the learning of the lamb's individual olfactory signature (Keller *et al.*, 2003; Keller, 2004). Once this has occurred, any alien lamb attempting to suckle will be rejected at the udder.

Finally, many species of primates, including humans, show an intermediate level of development at birth (semi-precocial), such that the young has relatively developed sensory abilities but is not yet mobile, resulting in a close contact of the mother with the infant when traveling. As the young develop, caregiving behaviors are shared with other conspecifics, especially in new world primates.

2.2. The sensory regulation of parental behavior

It has long been established that parental behavior is regulated by numerous sensory cues and that the sensing of infant cues is greatly enhanced at parturition. Among the various cues involved, olfaction plays a primary role in a very large number of mammalian species (Lévy, 2004; 2009). Indeed, olfaction mediates a shift from aversion to juvenile odors towards attraction to these odors. The typical response of virgin or non-pregnant/non-lactating female rats to pups is avoidance. This avoidance is due to the amniotic/placental fluids that cover the neonate at birth, which induce repellence (Kristal, 1976). Lesioning both the main and accessory olfactory systems eliminates the aversive response of nulliparous females to pups; these females then exhibit a rapid onset of maternal behavior (Fleming & Rosenblatt, 1974b; c; Carretero, 2003)(see also: Fleming et al., 1979). Such an inhibitory influence of olfaction on the onset of maternal behavior in virgin or non-pregnant females has been reported in many other mammalian species including hamsters and sheep (Marques, 1979; Lévy, 1983; Poindron, 1988).

At parturition, the mother becomes highly responsive to olfactory cues from the young. This olfactory shift is important for the transition from a non-maternal state to a maternal one. In rats, rabbit and sheep, parturient females consume the placenta and amniotic fluid, and lick the offspring who are covered, while this behavior is not typically displayed by non-pregnant females (Kristal, 1980; Lévy, 1983; 2009). In addition, females begin to show a preference for bedding soiled by pups, over clean bedding, around the peripartum period (Kinsley, 1990). Various experiments aimed at disrupting the olfactory systems confirmed the importance of olfaction for the expression of maternal behavior.

Finally, neurobiological evidence supports the important role of olfactory cues in the onset and maintenance of maternal behavior. For example, in sheep, the mitral cells of the main olfactory bulb show a profound shift in response after parturition and become highly responsive to the lamb's odor (Kendrick *et al.*, 1992b). The importance of olfactory cues has been confirmed by studying the effects of lesions of the main olfactory neurons (zinc sulfate-induced lesion of the olfactory epithelium, including olfactory neurons); these lesions produce disturbances in the establishment of maternal behavior in primiparous mothers and affects lamb recognition regardless of maternal experience (Lévy, 1995).

Other sensory cues are also involved in maternal behavior depending on the species. Maternal behavior in sheep offers a model to understand multisensory interactions between the ewe and her lamb. While the ewe develops a selective olfactory bond with the lamb within a few hours of parturition (Keller, 2003), within one day the mother becomes able to recognize her offspring own's vocalizations (Sèbe, 2008). A recognition of the lamb face occurs within a few weeks following birth (Kendrick, 1994). In rodents, female searching behavior, to locate the pups, is facilitated by the playback of ultrasonic pup vocalizations

(Smotherman, 1974). Electrophysiological responses in the auditory cortex undergo significant plasticity in maternal females (Liu & Schreiner, 2007; Cohen, 2011).

Finally, somato-sensory cues coming from the vagina and the nipple are also important for the establishment of maternal behavior. First, the vagino-cervical stimulation caused by expulsion of the fetus triggers an intracerebral release of oxytocin (see section 3.4) that is responsible for a cascade of behavioral changes, including the interest towards amniotic fluid consumption and behaviors directed at the offspring at parturition, a mechanism especially well studied in sheep (Keverne *et al.*, 1983; Kendrick, 1987; Lévy, 1992). Interestingly, an artificial vagino-cervical stimulation performed during the early post-partum period allows for the establishment of a new olfactory recognition process for the lamb (Lévy, 2010). Second, the stimulation of the mammary gland through the pup's suckling activity induces an increase in the electrophysiological receptive field of the ventral skin surrounding the nipple area in the somatosensory cortex during lactation in rats (Xerri, 1994). More generally, teat or nipple stimulation induces a wide pattern of neuronal activity in the maternal brain, a result confirmed by the pattern of fMRI activation in post-partum female rats when suckled (Febo, 2011).

2.3 Hormones and maternal behavior

Work conducted in the 1930s (Wiesner & Sheard, 1933) showed that immediate maternal care and sensory responsiveness to pups cues are only present in parturient female rats whereas non-pregnant nulliparous or pregnant primiparous females during the first week of pregnancy do not show such behaviors. The initial response of nulliparous females is avoidance of the pups but infanticide can be observed in various strains (Fleming & Rosenblatt, 1974b; Jakubowski & Terkel, 1985; Mennella & Moltz, 1989). The classical work of Terkel and Rosenblatt (Terkel & Rosenblatt, 1968; 1972) showed that blood transfusion from a parturient female into virgin female significantly reduced latency to retrieve pups, suggesting the implication of humoral factor(s) to facilitate maternal behavior.

Consequently, additional studies have identified the changes in serum hormone concentrations that occur during pregnancy, at parturition, and to some extent during lactation, with focus on progesterone, 17β-estradiol, prolactin, oxytocin and placental lactogens (see figure 1). In rats (see figure 1A), estrogens (including 17β-estradiol, estrone and/or estriol) concentrations are relatively low during the first 10 days of pregnancy and then rapidly increase to reach a plateau 3–4 days before parturition; they then drop after parturition. In parallel, progesterone increases during the first part of pregnancy to reach a peak at around 15 days post-conception, before rapidly declining. The high level of progesterone and low level of estradiol is required for the maintenance of pregnancy, but interestingly, as will be discussed below, the shift in hormone concentration is the pre-requisite for the timely induction of maternal behaviors. A few days following parturition, circulating progesterone rises again, peaking on postpartum day 10–12 and waning again to reach basal levels 7 days later (Morishige *et al.*, 1973; Bridges, 1984). In addition, prolactin is secreted in daily surges during the first 10 days of pregnancy and then again after parturition while placental lactogens I and II are secreted the last 2 weeks of pregnancy and can also be found in the cerebrospinal fluid where they affect the central nervous system

(Robertson & Friesen, 1981; Peake *et al.*, 1983; Bridges *et al.*, 1996). Parturition itself is also associated with a high peak of oxytocin, important to stimulate contraction of the uterine wall. These hormonal variations during pregnancy and lactation occur in all species studied to date albeit there are variations in the sequential release pattern (see figure 1 B and C respectively for comparison with sheep and human). These changes not only suggest a role for hormones in sustaining pregnancy, but also in the modification of the brain network and resulting maternal behaviors. As we will discuss below, it is not any individual hormone that is able to facilitate a specific sequence of the maternal behavior but the precise and sequential exposure to this complex hormone mixture that allows for the parturient female to rapidly express maternal behavior.

The role of these hormones, or more precisely the tissues responsible for hormonal secretion, was first highlighted by the seminal work of Rosenblatt and his colleagues (Rosenblatt & Siegel, 1975; Siegel & Rosenblatt, 1975a; b). They developed a pregnancy termination model in rats to explore the endocrine basis of maternal behavior. Upon the presentation of foster pups to a primigravid female Sprague Dawley rat on day 17 of pregnancy (pregnancy lasts 20–22 days in rats), no maternal behavior was observed. However, hysterectomy (removal of the uterus, including placenta and pups) on day 15 of pregnancy, followed by presentation with foster pups 2 days later, induced the display of maternal behaviors 24 hours following pup exposure. Hysterectomy mimics parturition as it is associated with a rapid drop in progesterone, followed by an increase in estrogens and concomitant increase in prolactin. Interestingly, if the females were hysterectomized *and* ovariectomized on pregnancy day 15, followed by exposure to pups 48 hours later, the onset of maternal behavior was significantly delayed and did not appear for another 2 or 3 days, suggesting the importance of high estradiol after hysterectomy (Siegel & Rosenblatt, 1975b). The respective inhibitory role of progesterone and facilitative function of estradiol were confirmed by concurrent injection of hormones following surgical procedures (Moltz *et al.*, 1969; Bridges & Feder, 1978; Bridges *et al.*, 1978b; Numan, 1978) or just before pup exposure (Stolzenberg *et al.*, 2009). Similar observations were made with virgin females and males where a specific sequence of hormone exposure, with high prolactin (or placental lactogens) and high estradiol following progesterone withdrawal can stimulate maternal behavior and significantly reduce the onset of pup-directed aggressive behaviors (Moltz *et al.*, 1969).

It should be noted that both male and virgin female rats, even after ovariectomy and hysterectomy, will respond to pups and show maternal behavior following several days of pup exposure, a process called sensitization (usually taking 4 to 9 days, (Rosenblatt, 1967; Fleming & Rosenblatt, 1974a; Stern, 1983; Brown, 1986; Brown & Douglas, 1991)). This suggests that the maternal behavior itself is not hormone-dependent, but the precise onset is: hormonal exposure allows the parturient female to immediately respond to the pups to provide appropriate care. Any disruption in the timing of onset of the behavior will significantly reduce the chance of survival for the offspring.

Mice are somewhat different from rats as they can show spontaneous maternal behavior such as pup retrieving, grooming and licking (Gandelman *et al.*, 1970; Gandelman, 1973; Rosenson, 1975). The idea that maternal behavior is independent of hormones is further

reinforced by studies in genetically modified mouse models. ERα knockout mice from a mixed background of C57BL/6J and 129 strains showed only mild impairment in maternal behaviors (Ogawa *et al.*, 1998) although potential compensatory effects from ERβ activation was not investigated. In addition, C57BL/6J mice lacking aromatase, the key enzyme for synthesis of 17β-estradiol, still show maternal behavior (Stolzenberg & Rissman, 2011). It should however be noted that, even if maternal behavior is spontaneously shown by mice and can be triggered only by sensory input from pups, the quality of the behavior is usually inferior to parturient females, with slower pup retrieval and reduced amount of time crouching over pups (Stolzenberg & Rissman, 2011).

The results obtained from transgenic mice should be interpreted with caution due to the differences existing between strains (Numan, 2003). Indeed, strain differences were first documented more than 60 years ago (Thompson, 1953). For example, the widely used C57BL/6J strain is known to exhibit very poor maternal behavior, especially when primiparous, with a high level of infanticide at parturition, limited time spent on nest building or crouching over pups, contributing to a high mortality rate in pups (Broida & Svare, 1982; Brown et al., 1999). However, this same strain exhibits very short latency to pup retrieval in comparison to strains such as Balb/C or DBA/2 (Carlier et al., 1982). On the other side, DBA/2 exhibits a higher level of maternal care behavior, spending more time crouching over pups and nursing them (Brown et al., 1999).

In addition to the timing and quality of maternal behaviors, steroid hormones seem to play an important role for maternal motivation, at least in rats and mice. Indeed, the motivation of the parturient female rat or mouse to retrieve the pups is significantly higher than virgin females when placed in a novel or complex environment. For example, virgin rats and mice will show a significantly lower or absent maternal motivation when tested in a T-maze or when they have to press on a lever to obtain the pup (Gandelman *et al.*, 1970; Hauser, 1985; Lee *et al.*, 1999;Bridges *et al.*, 1972). However, some maternal motivation can be induced in certain conditions, following extended pup exposure, even in animals devoid of circulating ovarian hormones (Scanlan *et al.*, 2006; Seip & Morrell, 2008; Stolzenberg & Rissman, 2011).

Altogether, it is clear that hormones are required for the proper onset of maternal behavior in rodents. This hormonal shift during pregnancy, parturition and lactation is obviously vital to the survival of the offspring, but also insures that the mother will behave appropriately to sustain her own health to reproduce again. Interestingly, once maternal behavior has been established, the dependence on steroid hormones seems to be significantly reduced, if not absent. Indeed, circulating progesterone and estradiol level are basal and postpartum ovariectomy and hysterectomy do not affect maternal behavior. Furthermore, the presence of hormones that were required around parturition can become inhibitory during lactation. For example, some studies suggest that injection of estradiol in postpartum mice actually reduces maternal behavior (Kasper & Telegdy, 1975; Svare & Gandelman, 1975). Similarly, progesterone exposure just before parturition or during lactation significantly affects maternal displays, albeit differently depending on the timing of exposure (Moltz *et al.*, 1969; Bridges & Feder, 1978; Bridges *et al.*, 1978a; Numan, 1978; Grieb *et al.*, 2017). The timing of hormone exposure is therefore fundamental to allow for adequate care of the offspring;

potential disruption of this pattern is likely to result in adversity for the offspring, but also to the mother herself as we will discuss below. These hormones are essential to reset the neuronal network, allowing the female to mother.

While the effects of sex steroid hormones are, by far, the most investigated, stress hormones are also important in the display of parenting behaviors. The basal level of corticosterone is significantly elevated during the postpartum period compared to virgin females and corticosteroid binding globulin concentration is significantly reduced following parturition, probably due to a reduction in estradiol levels (Koch, 1969; Stern *et al.*, 1973; Garland *et al.*, 1987; Fischer *et al.*, 1995; Pawluski *et al.*, 2009b). However, the responsiveness of the hypothalamic-pituitary-adrenal axis is attenuated postpartum in the majority of species studied so far. Large numbers of studies, using various stressors, highlight the attenuation of ACTH secretion and corticosterone synthesis compared to control virgin animals (restraint: (da Costa *et al.*, 2001); Noise: (Windle *et al.*, 1997); Swimming: (Walker *et al.*, 1995; Toufexis *et al.*, 1998); Foot shock: (Stern *et al.*, 1973); Ether evaporation: (Banky *et al.*, 1994); LPS: (Shanks *et al.*, 1999); Interleukin (Brunton *et al.*, 2005)). Importantly, it should be noted that the presence of pups and relevance of the stressor for the safety of the pups modulates the maternal stress response (Deschamps *et al.*, 2003). The hyporesponsiveness is linked to blunted activity of the opioidergic and noradrenergic systems during late pregnancy and lactation, via a modulation of steroid receptors (Douglas *et al.*, 2003; Douglas *et al.*, 2005; Slattery & Neumann, 2008; Brunton & Russell, 2011).

2.4.1. Direct exposure to EDCs in the adult female—As discussed above, the onset of maternal behaviors upon the birth of the pups requires very specific coordination of levels, ratios, and timing of several hormones. Disrupting the action of any one of these hormones during pregnancy and/or parturition is therefore likely to prevent the mother from appropriately responding to the pups to provide appropriate care. Endocrine disrupting chemicals (EDC) are one way that hormone action can be modified.

To date, most EDC studies that have examined the effects of compounds administered during pregnancy and/or lactation (e.g., directly to the adult female) have focused on chemicals that mimic estrogens, typically as estrogen receptor agonists. Ethinyl estradiol (EE2), a prototypical estrogen used in oral contraceptives, has produced conflicting effects on several aspects of maternal behavior. In the first study of EE2, exposure only during pregnancy limited the number of pups that were retrieved by treated rat dams, although other overt signs of toxicity due to the high dosage were also observed (Dugard *et al.*, 2001). Yet a second study by the same group found exactly the opposite effect, where high dose EE2 exposures only during pregnancy to rats improved pup retrieval behaviors (Arabo *et al.*, 2005). To address these inconsistent findings, another study examining lower, non-toxic doses of EE2 administered throughout pregnancy and the lactational period to mice found no significant changes to maternal behavior, but increased display of stereotypy behaviors (Catanese & Vandenberg, 2017b). This study might suggest that exposures to estrogen receptor agonists during pregnancy or lactation do not affect maternal behaviors, yet numerous studies of other xenoestrogens suggest otherwise. For example, exposures from the beginning of pregnancy through the entire lactational period to bisphenol A (BPA), a complex EDC with estrogen receptor agonist and androgen receptor antagonist activities

among others (Vandenberg *et al.*, 2009; Vandenberg *et al.*, 2013), reduced licking and grooming of pups in rats (Della Seta *et al.*, 2005); in mice, exposures during pregnancy also decreased licking and grooming of pups as well as the display of arched-back nursing, the posture associated with the greatest milk let-down (Kundakovic *et al.*, 2013b) and decreased the time mothers spent on the nest (Palanza *et al.*, 2002a). BPA was also shown to disrupt maternal behaviors in cynomolgus monkeys, with effects that were particularly pronounced in females with male offspring (Nakagami *et al.*, 2009). Follow-up studies of bisphenol S (BPS), a BPA analogue often used in BPA-free consumer products, found that exposures during pregnancy and lactation increased the time mouse dams spent on the nest during the mid-to-late lactational period, and increased the latency to touch pups during retrieval assays (Catanese & Vandenberg, 2017a).

It is important to note that most of these compounds are known to modulate steroid receptor activity but little focus was paid to potential interactions of endocrine disrupter with steroid binding globulins. The concentration of sex hormone binding globulin (SHBG), a plasma protein secreted by the liver with a strong affinity for androgens and to a lesser extent to estrogens, increases significantly in women during gestation (Hammond, 2016). the precise function of this protein is not fully understood but its present would limit the amount of free, active, steroid. This protein is able to bind numerous well known endocrine disrupters such as bisphenol A, phthalate and nonyphenol, albeit in the micromolar range (Danzo, 1997; Déchaud *et al.*, 1999; Hodgert Jury *et al.*, 2000). The same low interaction between anthropogenic molecules and SHBG was observed in zebra fish, using QSAR modeling and in vitro competition assay (Thorsteinson *et al.*, 2009; Miguel-Queralt and Hammond, 2008). To our knowledge, the physiological impact of this interaction is not known during pregnancy as the classical rodent models (rats and mice) do not express SHBG in adulthood (Sullivan *et al.*, 1991). It should be noted that a humanized transgenic mouse line expressing human SHBG was developed and the potential impact of endocrine disrupter in the presence of plasma binding globulin could be investigated in a more physiologically relevant model (Jänne *et al.*, 1998; Jänne *et al.*, 1999).

Additional examples of disrupted maternal behaviors have been observed in female rodents exposed during pregnancy for a range of estrogenic EDCs including the phytoestrogen genistein (rat: Ball *et al.*, 2010), industrial chemicals such as polychlorinated biphenyls (rat: Simmons *et al.*, 2005; Krishnan *et al.*, 2019), and the pesticides methoxychlor (mouse: Palanza *et al.*, 2002b) and glyphosate (Dechartes *et al.*, 2019). The anti-androgenic chemical chlorpyrifos, an organophosphate insecticide, increased pup grooming in female mice exposed during pregnancy (Venerosi *et al.*, 2009). Finally, other known reproductive toxicants including the herbicides sulentrazone (rat: de Castro *et al.*, 2007) and glyphosate (Dechartres *et al.* 2019), the insecticides carbaryl (meadow jumping mouse: Punzo, 2003) and fipronil (rat: Udo *et al.*, 2014), and the herbicide 2,4-dichlorophenoxyacetic acid (rat: Sturtz *et al.*, 2008) altered numerous aspects of maternal behavior including retrieval behaviors, infanticide, nest quality, and pup licking in adult females exposed during pregnancy. Albeit these last molecules seem to act as endocrine disrupter, their precise target(s) to alter maternal behavior is, to our knowledge, not defined.

Collectively, these studies of EDCs have shed light on the neuroendocrine mechanisms that play a role in the establishment and maintenance of maternal behaviors. Yet, these studies also offer the potential to evaluate the effects of dose, period of exposure and species/strain. For example, several studies revealed different effects of low doses than high doses; mouse dams exposed to a low dose of methoxychlor during pregnancy spent less time nursing and more time off the nest compared to controls, whereas higher doses had no effect on these outcomes (Palanza *et al.*, 2002b). These kinds of non-monotonic dose responses are common for EDCs, and there are well-established mechanisms by which low doses can have effects that are not predicted by studies at higher doses (Vandenberg *et al.*, 2012). The endocrine mechanisms for non-monotonic responses of maternal behaviors have not yet been elucidated, nor have they been explored for many other physiological and behavioral responses. It is however likely that the multiple molecular targets for EDCs, as confirmed for BPA (Rubin, 2011; Acconcia *et al.*, 2015; MacKay & Abizaid, 2018), are one cause for non-linear responses.

To our knowledge, there is also no information available on the potential disrupting activity of compounds affecting progesterone, oxytocin, glucocorticoid or prolactin-sensitive pathways linked to maternal behavior. It should be mentioned that a number of pharmacological treatments, such as fluoxetine (Prozac®, (Gemmel *et al.*, 2018) see Pawluski et al. this issue), haloperidol (Stern & Keer, 1999), diazepam (Yang *et al.*, 2015), and bromocriptine (Bridges & Ronsheim, 1990; Price & Bridges, 2014), will also affect the neuro-endocrine system underlying maternal behavior; we will not discuss these examples in depth here, as these molecules were specifically developed to target the neuronal network and are used to alleviate mental health disorders, including those associated with maternal behavior.

It is also important to note that the few EDC studies described above were dedicated to species that are mostly mono-parental (or at least rendered as such by the experimental paradigm). Only a handful of studies have investigated parental behavior in biparental species, including California mice (Peromyscus californicus) and to some extent avian species. These studies are important because an alteration of behavior of even one parent could lead to altered offspring outcomes (in addition to the chemical exposure experienced *in ovo*) but also could produce compensatory behaviors in the other parent. For example, work from Rosenfeld lab (Johnson *et al.*, 2015) suggest that early exposure to BPA or ethynylestradiol of the male only will affect the maternal behavior of his partner non-exposed female. The parental behavior of the male himself was not affected by the exposure to these molecules and it was suggested that females were somehow able realize that the male partner was exposed to compound and, as a consequence, reduced their own parental investment in offspring. On the other hand, limited studies in birds suggest that males could be more sensitive to chemical exposures than females, likely due to the partial elimination of contaminants in the female by deposition into the eggs (Fisher *et al.*, 2001; Verboven *et al.*, 2009). These males were less likely to participate in the care of the nest, albeit survival of the offspring was not affected. It is however suggested that effects on offspring survival are likely to be masked by the short term behavioral adaptation of the compensating parent; in the long term, the extra energy burden required for this compensation is likely to result in reduced reproductive outcome during the next reproduction bout (see (Carere *et al.*, 2010).

These handful of studies clearly call for more comparative studies to understand the consequence of EDC exposure in biparental species.

2.4.2. Co-exposure to EDCs in the Mother and the offspring—As noted above, EDC exposures to the pregnant or lactating female are also likely to lead to exposures to the offspring, depending on the toxicokinetic properties of the compound being studied. Therefore, the effects of EDC exposures on the mother should be studied in light of maternal-pup interactions during the display of parental behaviors; abnormal maternal behaviors could be due to the mother's response to abnormal pup development or behavior. For example, rat dams treated during pregnancy with one polychlorinated biphenyl, PCB77, spent more time on the nest and more time grooming their pups compared to untreated dams (Simmons *et al.*, 2005). When a subsequent study used a cross-fostering design, it was determined that PCB77 exposure of *both* the offspring and the mother was required to disrupt nesting and grooming behaviors, highlighting the impact of EDC on the maternal-neonate dyad, but not on a single individual (Cummings *et al.*, 2005).

In addition, it is important to note that rat mothers may discriminate the sex of their offspring and maternal behavior toward individual pups varies according to the sex of the pup, such that males usually receive more attention from their mother than females (licking and grooming, latency to retrieve (Moore & Morelli, 1979; Richmond & Sachs, 1984;; Deviterne & Desor, 1990). It should be noted that skewed litter composition (male only) in mice also lead to higher licking and grooming behaviors from the mother (Alleva *et al.*, 1989; Musi *et al.*, 1993). More importantly, hormone injections to the newborn, using progestins (Birke & Sadler, 1985) or androgens (Moore, 1982), modify maternal behaviors. These studies suggest that manipulations to the endocrine systems of pups are likely to affect maternal responsiveness and the pup-mother social interaction. To our knowledge, this aspect has not received the attention it deserves in studies of EDCs.

2.4.3. Effects of perinatal exposure on early organization of maternal behavior—As discussed above (section 2.4), EDC exposures in adulthood, during pregnancy and/or the lactational period, can disrupt the display of different aspects of maternal behavior. In this study design, not only is the mother exposed to the compound of interest, but the offspring are likely exposed via blood (*in utero*) or milk (during lactation). Other studies have examined whether developmental EDC exposures (typically during gestation, or gestation plus the perinatal period) can alter the display of maternal behaviors when the females reach adulthood. This work has mostly focused on evaluating the endocrine disrupting activities of estrogenic compounds including ethinyl estradiol (EE2), Bisphenol A and S (BPA, BPS), chlorpyrifos and lindane, an insecticide with both estrogenic and anti-estrogenic properties (Catanese *et al.*, 2015). Low dose EE2 exposure only during perinatal development increased the time mice spent on self-care and nest building in adulthood, during the early postpartum period (Catanese & Vandenberg, 2018). Developmental BPA (Palanza *et al.*, 2002a) and BPS exposure (Catanese & Vandenberg, 2017a) both decreased time spent on the nest once females reached adulthood; developmental BPS exposure also induced severe disruptions to maternal behavior including infanticide. Neonatal exposure of mice to chlorpyrifos increased the latency to build nests,

decreased their latency to lick pups, and altered pup retrievals in adulthood (Venerosi *et al.*, 2008). Finally, mice exposed to lindane during early development and throughout adulthood were less likely to retrieve their pups to the nest (Matsuura *et al.*, 2005). Additional studies were performed in California mice and similarly to the common laboratory mice, exposure to BPA or EE2 during gestation and lactation affected the maternal behavior of the adult offspring, including a reduction of time spent in the nest and time nursing the pups (Johnson *et al.*, 2015). Although the total number of studies examining the effects of *early life* EDC exposures on *later-life* display of maternal behaviors remains small, these studies collectively suggest that activation of estrogen signaling pathways during early development can have long lasting effects on pup-directed behaviors after parturition (see Johnson *et al.*, 2018).

Activational effects of hormones during pregnancy, parturition and/or lactation are likely to be superimposed on organizational effects of sex steroid hormones from fetal, perinatal and pubertal periods of development. For example, females exposed to testosterone during the perinatal period have significantly reduced aspects of maternal behavior including less time spent grooming pups and poorer pup retrieval behaviors (Quadagno & Rockwell, 1972; Quadagno *et al.*, 1973; Rosenberg & Herrenkohl, 1976). Bridges and colleagues (Bridges *et al.*, 1973) found that perinatal treatment with androgens reduced maternal motivation to retrieve pups in a T maze while not affecting the onset of maternal behavior displays or the response in a simple environment such as the home cage. These studies suggest that, similar to what is known for the organization of the neurocircuitry underlying sexual behavior and the ovarian cycle, early modulation of hormone exposure around the time of birth is likely to affect later maternal behaviors. To our knowledge, little is known about the neuroendocrine changes occurring around birth that are necessary for appropriate maternal behavior later in life. However, the effects of early exposure to EDC on later parental behavior tend to confirm the existence of organizational effects of steroid on parental brain and behavior, albeit via unknown mechanisms.

3. Maternal brain

3.1 The core neurobiological circuit driving the expression of maternal behavior

A neurobiological network model for the control of maternal behavior has been proposed in female rats (see figure 2). In this model, two opposite and competing pathways mediate the activation or inhibition of maternal behavior respectively (Sheehan, 2001). First, an aversive circuit, innervated by the vomeronasal organ, suppresses maternal behavior through amygdale (AMY)-dependent mechanisms. Indeed, experimental evidence demonstrates that the corticomedial amygdala exerts an inhibitory effect on the expression of maternal behavior. Lesions of this structure induce a facilitation of maternal behavior when tested in a sensitization paradigm in female rats (Fleming *et al.*, 1980; Numan, 1993). In contrast, stimulation of the corticomedial amygdala delayed the sensitization response (Morgan, 1999). In addition to results showing that the corticomedial amygdala is involved in fear and anxiety processes (Luiten, 1985; Adamec, 1993) and the fact that anosmia facilitates maternal behavior in virgin female rats, the general view is that novel olfactory cues from the pups inhibit maternal responsiveness through fear arousing mechanisms in this structure.

By contrast, the medial preoptic area (MPOA) and the adjacent ventral part of the bed nucleus of the stria terminalis (vBST) have been shown to play a key role not only in the stimulation of the expression of maternal behavior at parturition but also for its maintenance throughout the lactational period (Numan, 2006; Numan & Stolzenberg, 2009; Olazabal *et al.*, 2013). As a result of hormonal and sensory stimulation at the end of pregnancy and at parturition, this system becomes dominant over the aversion system, thus resulting in approach behavior and the expression of maternally responsive behaviors. Indeed, experiments have shown that disruption of the MPOA's function, in a variety of species, produces a disturbance in maternal behavior. In rodents, electrical or excitotoxic lesions of the MPOA disrupt the onset of maternal behavior at parturition (Lee *et al.*, 1999) or the sensitization of virgin females (Numan, 1977; Lee *et al.*, 1999). A similar result was obtained when the dorsolateral efferent projections of the MPOA were disconnected (Numan, 1990b). Importantly, those lesions produced mainly deficits in the appetitive aspects of maternal behavior, as some nursing responses may remain in females. Finally, the MPOA is involved not only in the establishment of maternal behavior but also in its maintenance since lesion of this structure disrupts established maternal behaviors in lactating females (Numan, 1988).

The vBST is also involved in the onset of maternal behavior because lesion of this structure produces similar effects in lactating female rats (Numan, 1996). In other species such as sheep, the stimulatory role of the MPOA and BST has also been explored. Inactivation of the MPOA in primiparous mothers at parturition using the reversible anesthetic lidocaine severely disrupts the establishment of maternal behavior in ewes (Perrin *et al.*, 2007). The same procedure was less effective when targeting the BST, but still produces deficits in maternal motivation to join the lamb (Perrin *et al.*, 2007).

It is clear that these core structures act through a more extended neural circuit to ensure proper expression of maternal behaviors. Within this broader neural circuit, the projections from the MPOA to the ventral tegmental area (VTA) are posed to stimulate the mesolimbic dopaminergic projections to centers regulating reward such as the nucleus accumbens (NAcc, see below). Other MPOA/vBST projections to the periaqueductal gray (PAG) are involved in the reduction of pup avoidance. Finally, the paraventricular nucleus of the hypothalamus (PVN), which plays a key role in oxytocinergic signaling, is clearly involved in the establishment of maternal behavior.

Importantly, the brain regions described above are not only dedicated to maternal behavior but are also implicated in male and female sexual behavior and aggression. It is the specific hormone exposure pattern described above, during pregnancy as well as during the lactation period, that accurately rewires the brain circuitry and allow the female dams to respond appropriately to pup cues.

3.2 Motivation circuitry

While maternal behavior is primarily under hormonal control around the time of parturition, this control moves mainly to sensory control once the endocrine events of parturition have waned. The observation that the hormone sequence during pregnancy and at parturition promotes immediate maternal responsiveness toward pups, even in primiparous mother, has

strong motivational implications. It suggests that hormonal action on the brain alters the function of defined neural circuits so that avoidance, rejection, and defensive circuits that would respond to novel stimuli in naïve virgins are inhibited, while neural circuits regulating approach, acceptance, and maternal responses are upregulated to respond strongly to newborn-related sensory cues.

In this context, it is not surprising that several studies showed that a higher estradiol/progesterone ratio at the end of pregnancy is linked to an increase in maternal motivation in a range of mammalian species (Poindron, 1980; Pryce, 1993; Gonzalez Mariscal, 1996; Numan, 2006). This role of gonadal hormones on maternal motivation is reflected in operant conditioning devices, for example through the amount of work mothers are willing to do to gain access to pup stimuli (Lee *et al.*, 1999), as well as when using conditioned place preference (Fleming *et al.*, 1994). Thus, the concomitant actions of the estradiol increase and progesterone withdrawal induces more pup-reinforced lever presses in parturient or hormonally treated female rodents, than in ovariectomized or virgins females (Hauser, 1985; Lee *et al.*, 1999).

Then, as maternal motivation is less dependent on gonadal hormones during the postpartum period, the same neural systems that were modified by hormones at the end of pregnancy continue to be activated and strengthened by newborns during the postpartum period independent of hormone release. In this perspective, the dopaminergic (DA) system appears one of the main systems regulating maternal motivation. Injections of DA antagonists induce deficits in retrieval behavior in maternal rats or voles (Fleming *et al.*, 1994; Lonstein & Fleming, 2002) (Stern & Keer, 1999; Pereira & Ferreira, 2006; Zhao & Li, 2010). When injected in this structure, DA antagonists of the D1 receptor induced a deficit in retrieval behavior, while D1 agonists reduced the latency to induce maternal behavior (Stolzenberg, 2007).

In conclusion, it is clear that DA in the nucleus NAcc is necessary for the proactive components of maternal motivation. It is important to note however, that exogenous steroid exposures (progesterone) during different stages of the postpartum period will affect maternal behavior (see for example (Herrenkohl, 1974; Herrenkohl & Reece, 1974; Grieb *et al.*, 2017)), but this has not received much attention.

3.3 Hormone receptor expression in maternal brain regions

The brain regions described above are directly targeted by endogenous steroids as well as exogenous EDCs. For example, the MPOA is central for both the onset and maintenance of maternal behavior in rodents. Importantly, numerous studies have now shown that hormones can specifically modulate the dam's behavior toward pups via direct action on this brain region. Different receptors, including both estrogen receptor alpha and beta (Giordano *et al.*, 1989; Giordano *et al.*, 1990; Simerly *et al.*, 1990; Yuan *et al.*, 1995; Shughrue *et al.*, 1997), progesterone receptor (Lauber *et al.*, 1991; Guerra-Araiza *et al.*, 2002; Guerra-Araiza *et al.*, 2003; Maerkel *et al.*, 2005; Quadros & Wagner, 2008) and prolactin receptors (Brown *et al.*, 2010; Brown *et al.*, 2017) are present within the MPOA. Other brain regions, directly or indirectly implicated in the control of maternal behavior, also strongly express these receptors, including the BnST, the septum, the VTA and the medial amygdala.

The involvement of these receptors in defined brain regions was investigated using hormone receptor agonists or antagonists implanted directly in the region of interest. For example, early studies with bilateral progesterone canula implanted in the MPOA, VMH, or VTA in hysterectomized-ovariectomized females treated peripherally with estradiol benzoate helped to decipher the mode of action and target of progesterone. Rather surprisingly, the implants failed to delay the onset of maternal care towards foster pups (Numan, 1978). It was hypothesized that progesterone might act at other sites or multiple sites concurrently to inhibit the rapid expression of maternal behavior in the rat. Similar methods were used to define the neural target of estradiol: direct bilateral implants of estradiol into the MPOA of either pregnancy-terminated primigravid rats (Numan, 1977), ovariectomized, virgin rats (Fahrbach & Pfaff, 1986) or progesterone- and estradiol-primed male rats (Rosenblatt & Ceus, 1998) produced shorter latencies to show maternal behaviors. Conversely, injection of the estrogen receptor antagonist tamoxifen into the MPOA reduced maternal behavior, while leaving intact female sexual behavior, demonstrating the specificity of action within this brain region in female (Ahdieh *et al.*, 1987). Despite recent progress, hormone receptor expression in specific MPOA cell types and in other brain areas involved in parenting behavior remains incompletely described (See however (McHenry *et al.*, 2017; Tsuneoka *et al.*, 2017).

3.4 Neurobiological consequences of hormonal changes

Late pregnancy or pregnancy-mimicking exposures to estradiol were shown to have important effects on dopaminergic circuits. Indeed, a recent study indicates that estrogen receptor-positive neurons in the MPOA are necessary and sufficient to activate maternal behavior via an indirect activation of dopaminergic neurons in the VTA (Fang *et al.*, 2018). A large number of estrogen receptor-positive cells are also GABAergic and project to non-dopaminergic cells that tonically inhibit surrounding dopaminergic cells. This disinhibition of dopaminergic cells following the activation of estrogen receptor-positive cells in the MPOA induces maternal behavior rapidly in mice. This confirms previous work of Numan and collaborators that the action of MPOA by estrogens leads to the release of dopamine in the NAcc to suppress inhibitory input to the ventral pallidum. The estrogen-sensitive release of dopamine not only affects the NAcc, but also the MPOA itself, likely to further modulate the ongoing behavioral pattern as well as the medial prefrontal cortex, the dorsal striatum, the septum, amygdala and hippocampus (Kalivas & Volkow, 2005; Numan *et al.*, 2005). Interestingly, while estradiol activates dopamine release in the VTA to promote maternal behavior, it also exerts a direct inhibitory effect on tuberoinfundibular dopaminergic neurons (TIDA neurons, (Cramer *et al.*, 1979; Blum *et al.*, 1987; Morrell *et al.*, 1989; Pasqualini *et al.*, 1993). The role of this inhibition is to facilitate prolactin secretion by the pituitary gland, as prolactin release is repressed by the dopamine presence in the portal system (Jones & Naftolin, 1990; Arbogast & Voogt, 1993; 1994; DeMaria *et al.*, 2000).

Changes in estrogens and/or progesterone during pregnancy and around parturition are also linked to major changes in various signalization pathways, including the oxytocinergic (OXT) system. The expression levels of estrogen receptors and oxytocin receptors in the MPOA and other regions such as the amygdala, are positively correlated with natural variations in maternal care (Champagne *et al.*, 2001). It is well known that exposures to

estrogens significantly increase oxytocin receptor expression in various brain regions directly involved in maternal behavior (Bale *et al.*, 1995; Pedersen, 1997) but cortical regions are also impacted; oxytocin activity via oxytocin receptor expressing neurons in the auditory cortex and in the somatosensory cortex of mouse dams increases the salience of pup calls, facilitating pup retrieval (Sabihi *et al.*, 2014; Marlin *et al.*, 2015; Valtcheva & Froemke, 2018). While the OXT system is mostly activated by the social interaction with the pups, the onset of activation and fine tuning with early offspring-mother communication is modulated by steroid release during pregnancy. The release and action of numerous neuropeptides and neurotransmitters are also strongly modulated by estrogens and progesterone, in addition to the feedback received from the pups (see for example Prolactin (Tate-Ostroff & Bridges, 1985; Tate-Ostroff & Bridges, 1987; Grattan & Averill, 1990), GABA (Akbari *et al.*, 2013; Gomora-Arrati *et al.*, 2016), Neurotensin (Scotti *et al.*, 2011; Tsuneoka *et al.*, 2013), CRF (Keverne & Kendrick, 1991; Broad *et al.*, 1995), and serotonin (Kendrick *et al.*, 1992a; de Moura *et al.*, 2015; Stamatakis *et al.*, 2015)).

In addition to the major rewiring of existing cell groups, pregnancy is also associated with significant changes in neurogenesis. Neurogenesis is no longer thought to be limited to the fetal and neonatal brain, but is now understood to occur in mammals throughout life (Zhao *et al.*, 2008; Ming & Song, 2011). Two brain regions, the sub-ventricular zone of the lateral ventricles and the sub-granular zone in the dentate gyrus of the hippocampus are known to produce new neurons throughout adulthood (Zhao *et al.*, 2008; Migaud *et al.*, 2010; Ming & Song, 2011; Lim & Alvarez-Buylla, 2014). Hippocampal cell proliferation is significantly altered throughout pregnancy and the postpartum period in rodents (Darnaudery *et al.*, 2007; Leuner *et al.*, 2007; Pawluski & Galea, 2007; Galea *et al.*, 2014b; Hillerer *et al.*, 2014; Pawluski *et al.*, 2016) suggesting that the hormones of pregnancy can induce neurogenesis in this structure. Specific studies of estrogens revealed that these hormones induce neurogenesis in immature granule neurons in the adult female rat dentate gyrus (Galea, 2008).

Additional studies have shown a reduction in cell proliferation during late pregnancy and parturition (Galea, 2008; Pawluski *et al.*, 2009a; Galea *et al.*, 2013; Galea *et al.*, 2014a), including in sheep (Brus *et al.*, 2010; Brus *et al.*, 2013). This decrease is transient and associated with maternal behavior; by weaning, cell proliferation is restored to the level observed in nulliparous rats and mice. The total number and density of immature neurons is significantly reduced in the dorsal and ventral rat hippocampus (Leuner *et al.*, 2007; Pawluski & Galea, 2007; Workman *et al.*, 2015) although see (Hillerer *et al.*, 2014). On the other hand, it is interesting to note that neurogenesis is upregulated in the subventricular zone during these same periods. It should be mentioned that neurogenesis is also observed in the hypothalamus in numerous species, including mouse (Kokoeva *et al.*, 2005), rat (Pencea *et al.*, 2001; Xu *et al.*, 2005; Matsuzaki *et al.*, 2009; Perez-Martin *et al.*, 2010), hamster (Huang *et al.*, 1998), sheep (Hazlerigg *et al.*, 2013; Migaud *et al.*, 2015) and human (Pellegrino *et al.*, 2018). A very few studies suggest that the newly generated hypothalamic neurons may be involved in metabolism, energy balance, and weight regulation (Bolborea & Dale, 2013; Lee & Blackshaw, 2014) but to our knowledge, no study has really investigated the involvement of these new neurons in maternal behavior. It is however important to note that gestation and lactation is linked to major metabolic changes (Newbern & Freemark,

2011; Mouzon & Lassance, 2015). The changes that have been reported include alterations in dendritic architecture, as well as the number and density of spines in different brain regions within the maternal network including the hippocampus, the olfactory bulb, the medial prefrontal cortex, the NAcc and the medial amygdala in addition to what is observed in the hypothalamus (Langle *et al.*, 2002; Theodosis *et al.*, 2006; Oliet & Bonfardin, 2010; Hillerer *et al.*, 2014).

Plasticity in the maternal brain is obviously not limited to neurons, and gestation and motherhood were shown to be associated with major remodeling of astrocytes (Featherstone *et al.*, 2000; Salmaso *et al.*, 2005; Salmaso and Woodside, 2006; Salmaso *et al.*, 2011), oligodendrocytes (Gregg *et al.*, 2007; Maheu *et al.*, 2009) and microglial cells (Haim *et al.*, 2017; Eid *et al.*, 2019). More specifically, astrocytes within the supraoptic and paraventricular nuclei of the hypothalamus show significant morphological changes correlated with the release of oxytocin that occurs during lactation (Theodosis and Poulain, 1984a; Theodosis and Poulain 1984b; Theodosis *et al.*, 1986; Montagnese *et al.*, 1988). Also in the MPOA, the number of astrocytes of multiparous rats recently exposed to pups was significantly higher compared to non-pup exposed multiparous females (Featherstone *et al.*, 2000). These changes were observed not only in the hypothalamus but also in various brain regions, including the cingulate cortex (Salmaso and Woodside, 2006; Salmaso *et al.*, 2011). In addition, the total number of microglia in the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens was found to be significantly decreased during late pregnancy and early postpartum period (Haim *et al.,* 2017) and the morphology of these cells and more specifically the size of the process was also altered in the hippocampus, during the early postpartum period (Eid *et al.*, 2019).

It should also be noted that several studies have highlighted the modulatory role of reproductive experience as multiparity significantly affects hormone release and hormone sensitivity, the neurocircuitry and maternal behavior (Lévy, 1995; Fleming & Korsmit, 1996; Pawluski *et al.*, 2006; Pawluski & Galea, 2007; Pawluski *et al.*, 2009b).

3.5 Disruptions to the maternal brain: lessons from EDCs

There is a large literature describing the effects of EDCs on various brain regions and/or behaviors in mice and rats: for example, perinatal exposure to estrogenic chemicals are known to alter expression of hormone receptors and hormone-sensitive proteins in brain regions such as the hypothalamus and the midbrain [see for example (Maerkel *et al.*, 2007; Rebuli *et al.*, 2014; Walker *et al.*, 2014; Arambula *et al.*, 2016; Johnson *et al.*, 2017)]. However, the vast majority of these studies were conducted in non-pregnant and non-lactating females, making it difficult to extrapolate these findings to the maternal brain and maternal behavior.

Only a small number of studies have examined the effects of estrogenic EDCs on the MPOA during the actual display of maternal behaviors (e.g., during the lactational period), either in females exposed during adulthood (pregnancy and lactation) or in females exposed during perinatal development. In a study that evaluated the effects of adult BPA exposure in rats, administered during pregnancy and lactation, estrogen receptor expression was examined in the MPOA, arcuate nucleus, and ventromedial nucleus (Aloisi *et al.*, 2001). High dose BPA

(mg/kg) decreased estrogen receptor expression in the arcuate nucleus but not the MPOA. Interestingly, studies of adult mouse dams exposed to low doses of BPS (μg/kg) during pregnancy and lactation found increased expression of estrogen receptor in the MPOA during lactation (Catanese & Vandenberg, 2017a). In contrast to these findings, low doses of EE2 during pregnancy and lactation did not alter estrogen receptor expression in the MPOA (Catanese & Vandenberg, 2017b), emphasizing the need for more studies to understand the mechanisms by which estrogenic EDCs disrupt sensitive brain regions in the maternal brain.

Along the same lines, EDCs such as BPA are also known to affect motivational and reward systems, but this work has been conducted in non-maternal models. For example, in rats, gestational and/or juvenile exposure to BPA led to an alteration of dopamine related genes, involved in dopamine metabolism and transport in the prefrontal cortex (Castro *et al.*, 2015a,b) as well as in the hippocampus, amygdale and several midbrain nuclei including the ventral tegmental area (Matsuda *et al.*, 2010; 2012; Tanida *et al.*, 2009). To our knowledge, only one study investigated monoamine concentrations in BPA-exposed dams and found that 4 or 40 mg/kg/day treatment from pregnancy day 6 to lactational day 20 did not lead to change in dopamine in the hypothalamus, medulla oblongata nor in the cerebellum when investigated 3 weeks after delivery (Honma *et al.*, 2006). To our knowledge, there is no other study investigating the direct impact of EDCs on the motivation system in pregnant or lactating models but current recognition that dopamine as well as neurotransmitters/ neuromodulator systems can be affected by environmental chemicals strongly suggest that maternal motivation might also be altered, warranting more detail investigations.

A small number of studies suggest that the estrogenic EDC BPA and its analogue BPS can interfere with neurogenesis, although no studies have examined neurogenesis specifically during pregnancy, parturition, or the lactational period. BPA exposure *in utero* disrupts neurogenesis in the fetal mouse neocortex (Komada *et al.*, 2012) and prepubertal BPA exposure alters neurogenesis in the hippocampus (Kim *et al.*, 2011). A recent study in developing zebrafish revealed that exposure to low doses of either BPA or BPS increased neurogenesis in the hypothalamus (Kinch *et al.*, 2015), although the relevance of these findings to maternal behavior is unclear. Future studies examining the effects of EDCs on neuronal cell proliferation in known neurogenic zones such as hippocampus, the subventricular zone and the hypothalamus, as well as other regions known to be responsible for maternal behaviors, in species that display maternal behaviors, are needed.

Additional studies are also needed to examine a greater number of EDCs, including compounds with broader mechanisms of action. EDC studies should benefit from the rich literature evaluating the effects of steroid hormones on the maternal brain, including numerous studies that have evaluated the effects of hormones administered to the adult female including exposures during pregnancy (Sheehan & Numan, 2002; Numan & Stolzenberg, 2009).

4. EDCs: What is next for maternal studies?

The number of studies investigating the potential endocrine disrupting activities in offspring following EDC exposure during the perinatal period (gestation, or gestation + lactation) is

rapidly increasing. These experimental paradigms involve, in a large number of cases, the direct exposure of the dam and indirect (via placenta and/or milk) exposure of the offspring. Unfortunately, the mothers are often considered only as a way to treat the offspring, and it is the offspring who are typically the target of toxicological studies; thus, potential effects on the dam's brain and behavior are rarely investigated, ignoring the importance of the mother-offspring dyad for offspring development. Equally important, few studies have evaluated the long term consequences of EDC exposures for the well-being of the mother, and her potential to reproduce again and perform appropriate maternal behaviors. The investigation of potential disrupting activities of chemicals in mothers is rendered difficult by several parameters that we would like to highlight here:

A. As stated above, the fundamental understanding of the maternal brain and its remodeling by the endocrine system, both at the spatial and temporal level, is far from being complete. Without this basic knowledge, it is currently impossible to fully grasp the potential impact of environmental chemicals such as EDCs.

B. There are strain-specific responses and phenotypic differences in response to EDC exposures. Numerous factors including the administered dose, timing and duration of exposure (perinatal vs. adult, during gestation) are likely to affect the responses observed (Spearow *et al.*, 2001; Kendziorski *et al.*, 2012) as has already been shown in studies investigating the perinatal effects of EDCs. In addition, differences in animal husbandry (composition of the cages, including material used for bedding and water bottles, phytoestrogen free diet, etc.) are likely to cause differences in response to exposure. Normalized experimental conditions should be defined and used to provide better foundations to explore the effects of EDCs.

C. The offspring influences, through direct tactile contact, olfactory cues, and ultrasonic vocalizations, the amount of parental care given by the mother. In rodents, the male is more likely to initiate contact with the mother and in turn, licking and grooming from the dam toward their male offspring is usually more important and fundamental for the male for develop appropriate socio-sexual interaction later in life (Moore, 1984; Della Seta *et al.*, 2005; Porrini *et al.*, 2005). Early EDC exposures that disrupt these features may alter the offspring's ability to stimulate maternal care, yet few studies have examined the effects of EDCs on olfaction or ultrasonic vocalizations (see however Johnson *et al.*, 2018; Harris et al., 2018; Krishnan et al., 2019). Cross fostering studies seem to confirm this hypothesis as the behavioral outcome (social response and anxiety) of juvenile male and female mice was not only affected by BPA exposure but also by early interaction with the biological or foster non exposed dam (Cox *et al.,* 2010). This remains an important research need.

D. While most studies assume that changes in behavior are a consequence of the direct alteration of the central nervous system physiology by anthropogenic molecules, several studies showed that some molecules could also affect the periphery, such as the nipple and mammary gland, resulting in the modulation of nursing behavior, as observed for BPS (LaPlante *et al.,* 2017). Numerous

compounds are known to affect mammary gland development (for example Ventura *et al.*, 2016; Perrot-Applanat *et al.,* 2018; Mandrup *et al.*, 2015; LaPlante *et al.*, 2018) but the outcome on maternal behavior was, to our knowledge not investigated. In the same line of idea, some EDC seem to act on the maternal brain and behavior partly by modulating the dam's microbiota, as suggested for BPA (Javurek *et al.*, 2016) and for glyphosate (Dechartres *et al.*, 2019). This point to the importance of looking at maternal behavior, like any other behavior, as an output from a whole organism/individual and not only as a consequence of a few changes in neuronal activation.

E. The comparative perspective is currently missing and does not allow one to draw general conclusions on the impact of EDC exposure, especially because most of the experimental studies performed so far have concentrated on altricial rodents. Even though there are many benefits to using rodents (ease of manipulation of rodents, short duration of gestation, well-established genetic mutants, etc.), our investigation of EDCs disrupting activities is non-existent in species with alternative maternal strategies.

In conclusion, EDCs can induce adverse consequences for progeny, even if disruptions to maternal behavior are mild. Although childhood abuse is associated with increased vulnerability to several psychopathologies (Kaffman & Meaney, 2007; Gilbert *et al.*, 2009) and other diseases including cancer and heart disease (Felitti *et al.*, 1998), even modest alterations to parental behavior can affect the development and health of the offspring.

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Highlights

1. Hormone secretion organizes the adult female brain to trigger maternal behaviors
2. Alterations to these precise patterns of hormone release affect maternal behavior
3. Exposures to EDCs during vulnerable periods can alter maternal behaviors
4. Although EDCs are known to affect the brain, the maternal brain remains poorly studied
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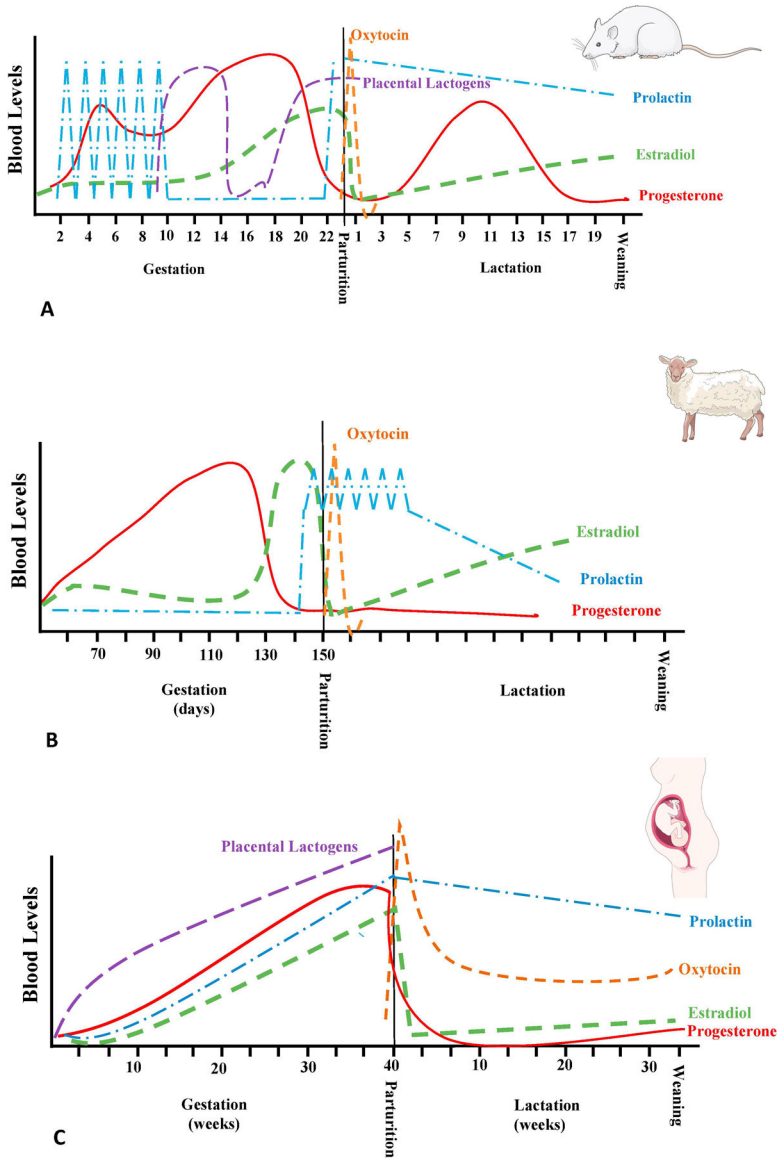

Figure 1.

Schematic representation of relative variation of Estradiol (----), Progesterone (—), prolactin (–.–.), oxytocine (……) and placental lactogens (----) during gestation, parturition and lactation. These variations are presented for rats (**A**), sheep (**B**) and human (**C**) for comparison. Images of rat, sheep and human were obtained from Servier Medical Art (https://smart.servier.com/)

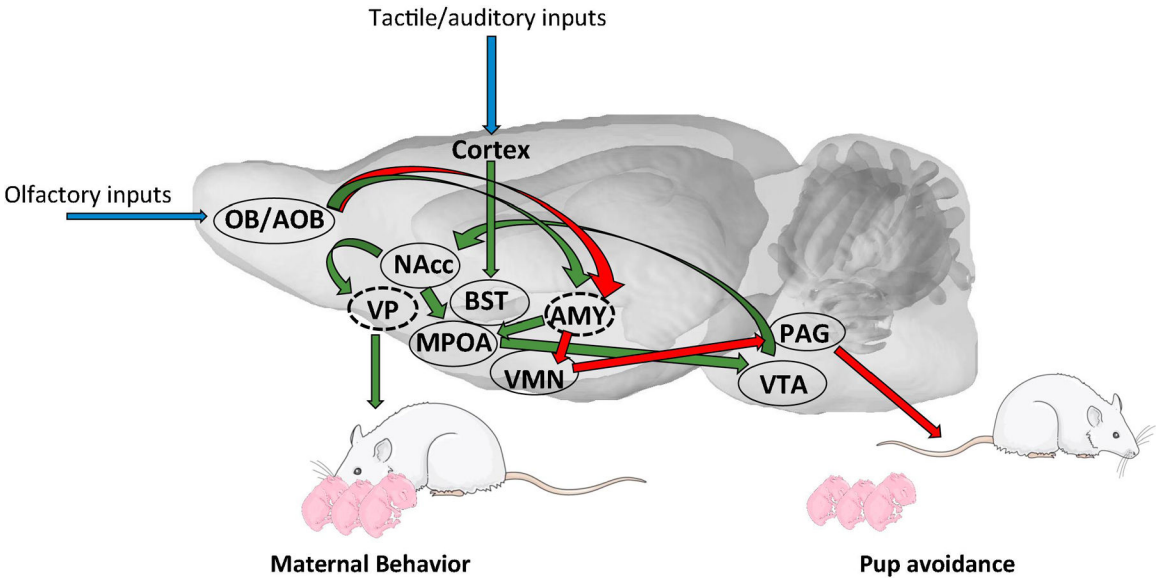

Figure 2.

Schematic representation of the neural network in rat. Blue arrows indicate sensory inputs, green arrows represent the maternal network and red arrows represent neural network in non-maternal male and female rat to trigger pup avoidance. Nuclei in dashed lines are located more laterally. **AMY**: Amygdala; **BST**: Bed nucleus of the stria terminalis; **MPOA**: Medial preoptic area; **NAcc**: Nucleus Accumbens; **OB/AOB**: Olfactory bulb/Accessory olfactory bulb; **PAG**: Periaqueductal Gray; **VP**: Ventral pallidum; **VMN**: Ventromedian nucleus of the hypothalamus; **VTA**: Ventral Tegmental Area. Images of pups and adult rats were obtained from Servier Medical Art (https://smart.servier.com/)