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Serotonin and motherhood: From molecules to mood

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ABSTRACT

Emerging research points to a valuable role of the monoamine neurotransmitter, serotonin, in the display of maternal behaviors and reproduction-associated plasticity in the maternal brain. Serotonin is also implicated in the pathophysiology of numerous affective disorders and likely plays an important role in the pathophysiology of maternal mental illness. Therefore, the main goals of this review are to detail: (1) how the serotonin system of the female brain changes across pregnancy and postpartum; (2) the role of the central serotonergic system in maternal caregiving and maternal aggression; and (3) how the serotonin system and selective serotonin reuptake inhibitor medications (SSRIs) are involved in the treatment of maternal mental illness. Although there is much work to be done, studying the central serotonin system's multifaceted role in the maternal brain is vital to our understanding of the processes governing matrescence and the maintenance of motherhood.

1. Introduction

Becoming a mother is a time of significant physiological, neural, and behavioral plasticity that is necessary for females to produce and care for their newborns. The physiological changes underlying maternal neural and behavioral plasticity have been the focus of much research, with a particular emphasis on the roles of peptide and steroid hormones such as oxytocin, prolactin, estradiol, and progesterone (Agrati and Lonstein, 2016; Lonstein et al., 2015; Numan and Insel, 2003). However, much less is known about the function of classical neurotransmitter systems for the establishment of maternal behaviors at parturition or the behaviors' maintenance through lactation and beyond. The neurotransmitter system that has received the most attention for an involvement in maternal motivation and caregiving is, by far, dopamine (see Numan and Stolzenberg, 2009; Olazabal et al., 2013). However, there have also been a number of studies manipulating gamma-aminobutyric acid (GABA) (Arrati et al., 2006; Brown et al., 2017; Ferreira et al., 2000; Lee and Gammie, 2010; Numan et al., 2009; Salzberg et al., 2002; Yang et al., 2015; Febo et al., 2010) and norepinephrine (Bridges et al., 1982; Cox et al., 2011; Dickinson and Keverne, 1988; Levy et al., 1990; Scotti et al., 2011; Smith et al., 2012; Thomas and Palmiter, 1997).

It is surprising that the involvement of serotonin (5-HT) in the neural and behavioral plasticity of motherhood has historically been neglected. Serotonin is a phylogenetically ancient neurotransmitter that is distributed widely throughout key brain regions influencing affective state, impulsivity, learning and memory, attention, sleep, aggression, and neurovegetative control (Jacobs and Azmitia, 1992; Graeff et al., 1996; Cools et al., 2008). As such, it has the capacity to modulate many socially motivated behaviors and would be expected to play a significant role in matrescence (i.e., the transition to motherhood) and the regulation of caregiving thereafter. In addition, serotonin is implicated in the pathophysiology of numerous psychiatric disorders (Lucki, 1998; Lesch, 2007), and is the target of many pharmacologic therapies such as the selective serotonin reuptake inhibitor medications (SSRIs) that are broadly prescribed for depressive and anxiety disorders. Ten to twenty percent of women experience anxiety or depressive disorders during pregnancy and the postpartum period, with up to 10% of pregnant and postpartum women in the U.S., Canada, and a number of other countries being prescribed SSRIs (Gemmel et al., 2018a; Oberlander et al., 2006; Zoega et al., 2015; Charlton et al., 2015; Hayes et al., 2012; Lupattelli et al., 2014). Unfortunately, we know very little about how the serotonergic system is altered during female reproduction and how maternal mental illness can alter these normative changes (Lonstein, 2019). Therefore, the main aims of this review are to detail: (1) how the serotonin system of the female brain changes during pregnancy and postpartum; (2) the role of the central serotonergic system in maternal behaviors; (3) how the central serotonin system and SSRIs are involved

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in maternal mental illness. This is the first detailed review of the central serotonin system's role in maternal neurobehavioral outcomes, and we hope that consolidating this information herein leads to greater attention to serotonin's role in the many aspects of motherhood.

2. Brief overview of the central serotonin system

Serotonin-synthesizing cells in the brain are clustered in what was originally described as nine midbrain and hindbrain raphe nuclei (Dahlstroem and Fuxe, 1964; Steinbusch, 1981; Hornung, 2010). Of the raphe nuclei, the largest by far is the dorsal raphe nucleus (DR; B6 and B7 groups) lying just below the cerebral aqueduct, and which contains about one third of all serotonin cells in the brain (Lowry et al., 2008). The nearby and more ventrally situated median raphe nucleus (MR; B5 and B8 groups) contains one of the next largest clusters of serotonin cells. While the DR and MR are the most often studied because they have such dense clusters of serotonin cells, some of these cells co-synthesize an array of neuropeptides (e.g., substance P, dynorphin, enkephanlin, neurotensin, angiotensin) and others are not serotoninergic at all but instead produce neurotransmitters including GABA, glutamate, or dopamine (Lowry et al., 2008).

Serotonin synthesis is governed by tryptophan hydroxylase (TPH), a rate-limiting enzyme that converts the essential amino acid tryptophan into 5-hydroxytryptophan (5-HTP). 5-HTP is then converted to serotonin by aromatic l-amino acid decarboxylase (AADC). TPH has two isoforms, TPH1 that is found peripherally and TPH2 that is found centrally (Walther and Bader, 2003). Within the raphe serotonin neurons, serotonin is packaged into synaptic vesicles via vesicular monoamine transporters (VMAT, mainly VMAT2), and excess synaptic serotonin is returned back to serotonin cells by the serotonin transporter (SERT) (Mohammad-Zadeh et al., 2008). Degradation of serotonin within the presynaptic cell, an essential step of serotonin and other monoamine homeostasis, is primarily carried out by monoamine oxidase A (MAOA).

Almost all cells in the brain are in one way or another under the influence of serotonin, and the majority of serotonin terminals in the forebrain arise from somewhat overlapping projections from the DR and MR. The DR projects primarily to many subregions of the cerebral cortex, striatum, hippocampus, and amygdala (Descarries et al., 2010), while the MR has particularly dense projections to the septum, hypothalamus, midline thalamus, as well as the hippocampus and some areas of the cortex (Descarries et al., 2010). The cellular actions of serotonin are mediated by 14 genetically encoded subtypes of receptors, which are grouped into seven families (5-HT1 to 5-HT7) according to their structural and functional characteristics (Hannon and Hoyer, 2008). All but one of these receptors, the 5-HT3 receptor, are G-protein-coupled (GPCRs). The 5-HT3 receptor is instead a ligand-gated ion channel. In the present review, we will focus on three members of the 5-HT receptor family – the 5-HT1A, 5-HT2A, and 5-HT2C receptors – given the current available literature demonstrating that these 5-HT receptors influence maternal activities.

With regards to the densities these receptors in the brain, 5-HT1A receptor content is particularly high in the cerebral cortex (anterior cingulate, insular, orbitofrontal), hippocampus, amygdala, and septum where it acts as an inhibitory post-synaptic receptor (Burnet et al., 1995; Chalmers and Watson, 1991; Pompeiano et al., 1992; Stein et al., 2008). 5-HT1A receptor expression is also very high in the DR and MR (Burnet et al., 1995; Chalmers and Watson, 1991; Pompeiano et al., 1992; Stein et al., 2008; Pazos and Palacios, 1985), where it functions as an inhibitory autoreceptor that blunts serotonin cell firing (Hjorth and Magnusson, 1988; Bonvento et al., 1992). In general, activation of these presynaptic 5-HT1A autoreceptors hyperpolarizes the cell membrane and results in a reduction of the firing rate of serotonergic neurons in the raphe area, leading to suppressed serotonin synthesis, turnover, and release; activation of 5-HT1A receptors on postsynaptic cells decreases the firing rate of the postsynaptic cells (Barnes and Sharp, 1999; Lesch and Gutknecht, 2004).

5-HT2A receptors are found with high density in many forebrain sites including the frontal and cingulate cortices, main olfactory bulb, hippocampus, diagonal band of Broca, ventral pallidum, basolateral amygdala, a number of thalamic sites, and a few hypothalamic nuclei (Cornea-Hebert et al., 1999; Ettrup et al., 2016). 5-HT2C receptors are especially well represented in the olfactory bulb, cortex (frontal, parietal, cingulate parietal, piriform), hippocampus, caudate-putamen, shell of the nucleus accumbens, bed nucleus of the stria terminalis (BNST), dorsomedial amygdala, and a number of thalamic and hypothalamic nuclei (Pasqualetti et al., 1999; Clemett et al., 2000). While the 5-HT2A and 2C receptors clearly have overlapping central distributions, in laboratory rats, 5-HT2A expression appears to predominate in some areas of the cortex while 5-HT2C receptor expression is higher in the septum, hypothalamus, bed nucleus of the stria terminalis, amgydala, and thalamus (Pompeiano et al., 1994; Gundlah et al., 1999). In contrast to the inhibitory 5-HT1A receptor, activity of 5-HT2A and 2C receptors is most often excitatory (Hannon and Hoyer, 2008; Hoyer et al., 2002).

It is essential to note that almost all of the research on the distribution and relative densities of serotonin receptors across the brain summarized above had been conducted in male laboratory animals and men. This is despite the fact that a few studies have demonstrated sex differences in central serotonin receptor densities (Jovanovic et al., 2008; Moses-Kolko et al., 2011; Wooten et al., 2013; Zhang et al., 1999) and that the expression of these receptors is influenced by circulating ovarian hormones (Bethea et al., 2002).

3. Plasticity in the central serotonin system during pregnancy and postpartum

3.1. Neurochemical plasticity

Motherhood is a time of tremendous neuroplastic change, both chemically and structurally. While changes within the adult female serotonin system have not been particularly well studied, this system appears to be upregulated across the transition to motherhood and then shows a decline by the time of litter weaning. Research in humans demonstrates that pregnant and postpartum women have higher concentrations of serotonin or its metabolites in cerebral spinal fluid (CSF) and plasma compared to non-pregnant women (Spielman et al., 1985; Sekiyama et al., 2013), and while some late-pregnant and early postpartum women have lower serum levels of the serotonin precursor, tryptophan (Maes et al., 2002; Veen et al., 2016), levels of the biochemically free (rather than total) tryptophan are higher in reproducing women (Badawy, 2014). It is relevant in this context to mention that total tryptophan levels alone are not responsible for determining brain concentrations of serotonin (Fernstrom and Wurtman, 1972).

Studies of laboratory rodents mostly indicate elevated serotonergic activity during pregnancy and early motherhood. For instance, TPH2 expression, serotonin metabolism, and spontaneous cell firing in the DR are significantly higher in late pregnant or early postpartum rats compared to virgin females (Harding and Lonstein, 2016; Holschbach and Lonstein, 2017; Klink et al., 2002). However, serotonin levels in the DR, as detected by immunoreactivity, do not differ between postpartum and virgin laboratory rats (Holschbach and Lonstein, 2017) although are lower in postpartum versus virgin laboratory mice (Jury et al., 2015). In addition to serotonin measures in the rat midbrain DR changing with motherhood, cortical serotonin turnover has been reported to be either higher or lower during pregnancy compared to early postpartum (Desan et al., 1988; Glaser et al., 1990), and while hippocampal serotonin turnover is higher during mid-pregnancy than either before mating or during late pregnancy (Macbeth et al., 2008), hippocampal serotonin itself is especially low during the end of pregnancy (Desan et al., 1988). Elsewhere in the forebrain, serotonin turnover in the medial preoptic area (MPOA) and BNST, brains areas essential for the onset and

maintenance of active maternal caregiving behaviors (for reviews see Olazabal et al., 2013; Lonstein et al., 2014; Numan et al., 2008), is higher in postpartum rats compared to virgin females (Lonstein et al., 2003; Smith et al., 2013). There is no such elevation in MPOA serotonin turnover even late in pregnancy (Macbeth et al., 2008; Lonstein et al., 2003), so higher turnover in the MPOA may be more involved in the postpartum interactions with pups rather than preparing females for the rapid peripartum onset of motherhood.

Serotonin receptor binding and expression also are plastic across pregnancy and the postpartum period. Glaser et al. (1990) found relatively low cortical binding affinity for ketanserin (a 5-HT2A receptor antagonist) at four days postpartum compared to female rats in estrous or pregnancy, but there were no reproduction-related differences in the total binding concentration. Recent work from the Lonstein lab has revealed more than 50% less 5-HT2C receptor mRNA expression in the DR of early postpartum rats compared to females sacrificed during the estrus cycle or mid-pregnancy (Vitale et al., 2017). Because 5-HT2C receptors in the DR are mostly found on inhibitory GABAergic interneurons (Serrats et al., 2005), lower 5-HT2C expression may partly underlie (i.e., disinhibit) the elevated DR serotonergic activity during early motherhood discussed above.

3.2. Cellular plasticity

Not only are there changes in central serotonin neurochemistry and receptor expression across pregnancy and the postpartum period, but neuroplastic changes at a cellular level were recently found in the maternal DR. By now it is quite well known that the hormonal changes involved in female reproduction are accompanied by altered brain cell birth, survival, differentiation, and death (Pereira, 2016; Pawluski et al., 2016; Leuner and Sabihi, 2016; Leuner et al., 2010; Levy et al., 2011). Most studies on this topic have focused on how pregnancy and interactions with offspring affect cell proliferation in the subgranular zone (SGZ) of the hippocampus and the survival of new neurons in the granule cell layer (GCL) of the dentate gyrus (Pawluski et al., 2016, 2011, 2010; Leuner and Sabihi, 2016; Levy et al., 2017; Pawluski and Galea, 2007). Other work has focused on changes in the number of cells born in the maternal subventricular zone (SVZ) and their migration to the main olfactory bulb (Corona et al., 2018; Furuta and Bridges, 2005; Larsen and Grattan, 2010; Shingo et al., 2003).

The birth of new cells occurs in numerous other areas of the brain, though (Levy et al., 2017; Ming and Song, 2005). Through postmortem visualization of bromodeoxyuridine (BrdU), a thymidine analogue that can be systemically injected at specific timepoints of pregnancy and postpartum to identify differences in the number of mitotic cells in the brain, Holschbach and Lonstein (2017) found for the first time that newborn cells exist in the adult DR. This was somewhat expected because the lining of the cerebral aqueduct above the DR is a major proliferative niche for the midbrain during other times of the lifespan (Arenas et al., 2015). They found in rats that the number of BrdU-containing cells born in the DR during the first week postpartum were less likely to survive almost two weeks later into late lactation compared to cells born during late pregnancy (Holschbach and Lonstein, 2017). This pattern of results was paralleled by the pattern of DR immunoreactivity for NeuroD, a cellular differentiation factor, and many of the surviving newborn DR cells were immunoreactive for neuronal nuclei antigen (NeuN) thus suggesting that the cells had a neuronal phenotype (Holschbach and Lonstein, 2017). Like many changes in the maternal brain, removing the litter soon after parturition prevented the effects of motherhood on DR newborn cell survival (i.e., litter removal increased cell survival), as well as reduced DR apoptosis (Holschbach and Lonstein, 2017). Interestingly, late pregnancy and early motherhood is also associated with reduced cytogenesis and new neuron survival (particularly in first-time mothers) in the dentate gyrus, with the postpartum effects on neurogenesis being a consequence, in part, of elevated maternal glucocorticoids (Pawluski and Galea, 2007; Pawluski et al., 2009; Leuner et al., 2007; Darnaudery et al., 2007). Adrenal secretion of corticosterone was not responsible, however, for the relatively low postpartum cell survival in the DR (Holschbach and Lonstein, 2017). While regressive events such as lower cell genesis and higher cell death help refine neural circuits and optimize their function (Chechik et al., 1999; Fricker et al., 2018), it remains to be determined if the changes in cell genesis and cell death in the adult female rat DR underlie the behavioral changes females display across the peripartum period and beyond.

4. Serotonergic mechanisms underlying maternal behavior in rodents

4.1. Broad serotonin system influences on maternal behavior

Given the discussion above indicating that the transition to motherhood is often associated with an upregulation of the serotonin system, it seems reasonable to hypothesize that naturally occurring or experimental events producing less central serotonin signaling would generally impair maternal caregiving. As will be detailed in the following sections, this is not necessarily the case, as relatively high or relatively low serotonin signaling in particular brain areas can derail aspects of maternal behavior.

Early studies involving midbrain raphe lesions via the serotonin neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) revealed that prepartum lesions of the most caudal aspects of the female rat MR produced a host of negative effects including transient impairment in retrieving scattered pups, a few animals that did not nurse after being separated from their litters, and a few cases of infanticide (Barofsky et al., 1983a). 5,7-DHT lesions of the caudal DR only produced minor negative effects on maternal behaviors, but still resulted in pup mortality, possibly by impairing suckling-induced pituitary prolactin release (Barofsky et al., 1983b). Interpreting the results of this early study is difficult because the maternal behavior observations by Barofsky and colleagues were limited; the lesions were focused on the caudal midbrain raphe so would have missed many raphe serotonin cells; and 5,7-DHT is taken up not only by serotonin cell bodies but also the terminals of serotonin cells that project to the infusion site (limiting site-specificity). Therefore, a reanalysis of the effects of DR serotonin-specific lesions on maternal behaviors was recently undertaken using an antiserum to the serotonin transporter that was conjugated to the neurotoxin, saporin (Holschbach et al., 2018). This study in rats involved very detailed behavior observations and found that cell-body specific serotonergic lesions focused on the dorsomedial DR at mid rostrocaudal levels significantly reduced pup licking and generated aberrant patterns of nursing behavior (Holschbach et al., 2018). More specifically, the total time that dams nursed their pups was unaffected by the lesions but serotonin-lesioned dams did not display the expected decline in crouched nursing (i.e., kyphosis) across days of testing that was seen in the controls. This indicates that serotonin may affect how mothers perceive or behaviorally readjust to changes in the sensory cues emitted by their offspring as they age. The DR serotonin-lesioned mothers studied by Holschbach and colleagues were also much less maternally aggressive, which was concomitant with reduced serotonin-immunoreactive fiber density in the anterior hypothalamus, a brain site previously implicated in serotonin's influence on aggressive behaviors in male animals (Melloni and Ricci, 2010; Terranova et al., 2017).

Other evidence from studies using mutant mice demonstrates that broad serotonin deficiency can be associated with impaired maternal care. In a study by Lerch-Haner et al. (2008) involving mice with a mutation of the *Pet-1* gene (a E26 transformation-specific transcription factor critical for serotonin neuron development) (Hendricks et al., 1999), severe restriction of the central serotonin cell population was associated with impaired pup retrieval, nursing, and nest building (Lerch-Haner et al., 2008). Similarly, Alenina et al. (2009) reported that mutation of *TPH2* produced dams that failed to retrieve their pups into

the nest site and nurse them (Alenina et al., 2009). Other mouse mutants with impaired serotonin metabolism also showed reduced reproductive fitness and abnormal maternal behaviors (Girirajan and Elsea, 2009; Angoa-Perez et al., 2014). Because these serotonin-related genes are critical for natural brain maturation and homeostatic modulation of neural circuits, lack of these genes throughout the lifetime may disrupt the development of the neural circuits governing maternal behavior. Thus, whether the maternal deficits seen in these mutant dams are caused by altered serotonin neurotransmission during adulthood (a primary effect) or by altered brain connectivity and structure (a secondary effect) remains unclear.

Studies of lactating female rhesus monkeys with prior maternal experience found that those with relatively low cerebrospinal fluid (CSF) levels of the serotonin metabolite 5-HIAA (5-hydroxyindoleacetic acid), reflecting low brain serotonin metabolism, are more protective and less rejecting of infants compared to mothers with relatively high 5-HIAA (Maestripieri et al., 2009). The opposite relationship between CSF serotonin metabolites and maternal rejection is found in first-time rhesus mothers indicating a complex interplay among serotonin neurochemistry, caregiving experience, and current mothering (Maestripieri et al., 2007). In human mothers, those with polymorphisms in the serotonin transporter gene (*5HTT*) that lead to relatively low transcriptional activity (s allele) have been reported to have less (Bakermans-Kranenburg and van Ijzendoorn, 2008) or more (Mileva-Seitz et al., 2011; Cents et al., 2014) sensitive mothering styles compared to mothers with high-transcription *5HTT* polymorphisms (l allele). Work by Sturge-Apple et al. (2012) further indicates that the influence of these *5HTT* alleles on mothering is not simple. They found no significant main effect of the *5HTT* polymorphisms on maternal parenting, but instead an interaction between *5HTT* alleles and interparental conflict: mothers with *s* alleles were highly sensitive and unlikely to use harsh parenting when partner conflict was low, but were relatively insensitive mothers and more likely to likely use harsh parenting when conflict was high (Sturge-Apple et al., 2012). They interpreted these findings to indicate that the s alleles of *5HTT* do not necessarily convey risk, but instead convey greater maternal susceptibility or sensitivity to both the positive and negative aspects of the environment (Belsky et al., 2009).

Many steroids and neuropeptides associated with motherhood have the capacity to influence midbrain raphe cell function. Interactions between the oxytocin system and DR cells has recently been revealed by studies manipulating DR oxytocin receptors (OTRs). While oxytocin and OTRs are not absolutely necessary for the onset or maintenance of motherhood in rats or mice, oxytocin system signaling is often found to facilitate or improve the quality of caregiving (for critical review see Yoshihara et al., 2018). Almost all experimental work on the role of OTRs in caregiving behavior has focused on forebrain sites such as the MPOA and nucleus accumbens (e.g., D'Cunha et al., 2011; Olazabal and Young, 2006; Pedersen et al., 1994). OTRs are also expressed in numerous midbrain sites, however, and their peripartum activity in the ventral tegmental area (VTA) for instance promotes the onset of mothering in rats by modulating the mesolimbic dopamine system (Pedersen et al., 1994; Shahrokh et al., 2010). OTRs are expressed in the DR, but not MR (Grieb and Lonstein, 2015; Yoshimura et al., 1993), and it was recently found that OTR autoradiographic binding in the DR is higher on the day of parturition compared to during pregnancy or 7 days postpartum (Grieb and Lonstein, 2015; Grieb et al., in preparation). This suggests that enhanced DR sensitivity to oxytocin may be involved in the peripartum onset of maternal behavior. Dual-label *in situ* hybridization revealed that OTR expression at parturition increased specifically on serotonin cells of the DR, but instead decreased on DR GABAergic cells (Grieb et al., in preparation). Because many GABA-synthesizing cells within the DR are inhibitory interneurons that tonically suppress serotonin cell firing (Hernandez-Vazquez et al., in press), these results collectively suggest that the peripartum period involves enhanced direct OT stimulation of DR serotoninergic cells as well as reduced inhibition of them by OT-sensitive local GABAegic inputs.

The importance of OTR signaling in the DR for maternal caregiving behaviors was determined in study involving local, permanent short hairpin RNA (shRNA)-induced knockdown of OTRs beginning during mid-pregnancy. Dams with suppressed OTR gene expression in the DR (which in some cases extending into the adjacent ventral periaqueductal gray) were more likely to commit infanticide in the first few days after parturition when compared to control dams receiving a scrambled shRNA into the DR. OTR-knockdown dams also spent less time licking and nursing pups, but showed completely normal retrieval. OTR-knockdown dams were less maternally aggressive to a male intruder to the home cage, and showed less anxiety-related behavior in an elevated plus maze (Grieb et al., in preparation). Another recent study involving OTR gene knockout only from 5-HT cells of the DR of postpartum mice also found no effects on retrieval, but also no effects on pup licking or general mother-litter contact during the 10 min after retrieval (Pagani et al., 2015). These latter results could suggest that the OTRs on GABA or some other phenotype of DR cells are more important for any effects on maternal behavior, and/or there is a species difference in the need for OTR activity in the DR for maternal caregiving.

4.2. Role of serotonin 5-HT1A receptors in maternal behavior

The inhibitory 5-HT1A receptor is one of the most studied serotonin receptors in neurobiological and psychopharmacological research due to its involvement in anxiety, emotion, and motivation (Carhart-Harris and Nutt, 2017). The 5-HT1A receptor is implicated in many motivated behaviors, such as eating, drinking, sexual behavior, aggression, and drug abuse (Graeff et al., 1996; Cools et al., 2008; Bendotti and Samanin, 1986; McBride et al., 1991; Cassaday et al., 2000; Clissold et al., 2013; Burton et al., 2013; Albert et al., 2014; Snoeren et al., 2014), yet still unclear how it is involved in regulating maternal behaviors. Several early pharmacological studies reported a role of 5-HT1A receptors in maternal aggression (Ferreira et al., 2000), but not in other maternal responses such as retrieval or nursing (Ferreira et al., 2000; Yoshimura and Ogawa, 1991; De Almeida and Lucion, 1994; Veiga et al., 2007). More specifically, acute or chronic stimulation of 5-HT1A receptors by peripheral injection of agonist drugs suppressed maternal aggression in postpartum female rats (Olivier et al., 1995). Where in the brain the targeted 5-HT1A receptors are located matters for the outcome - agonizing 5-HT1A receptors in the MR, dorsal periaqueductal gray, or corticomedial amygdala nucleus reduced maternal aggression (De Almeida and Lucion, 1997), whereas agonizing 5-HT1A receptors in the medial septum or DR increased maternal attacks (De Almeida and Lucion, 1997; da Veiga et al., 2011). Therefore, the inhibitory effect of 5-HT1A receptor agonism on maternal aggression involves a complex neural network, and is likely mediated by both presynaptic and post-synaptic 5-HT1A receptors in different brain sites.

Given that maternal aggression is an integral part of the maternal behavior repertoire, it seems puzzling that activating 5-HT1A receptors affects maternal aggression but not other maternal responses such as caregiving. Li et al. (2018) recently reexamined this issue by treating postpartum lactating rats with either 8-OH-DPAT, a 5-HT1A receptor full agonist, or WAY-101405, a 5-HT1A receptor antagonist, and tested their maternal responses in the home cage. They found that acutely activating 5-HT1A receptors with 8-OH-DPAT dose-dependently disrupted various maternal responses (Li et al., 2018). Dams treated with 8-OH-DPAT took longer to retrieve pups, retrieved fewer pups, spent less time licking and hovering over pups, and spent less time nest building. In contrast, the 5-HT1A receptor antagonist WAY-101405 had no effect on these maternal behaviors. Importantly, 5-HT1A receptor activation did not affect maternal interest, as mother rats treated with 8-OH-DPAT still preferred to interact with pups over a novel object. 5-HT1A receptor activation also did not affect maternal motivation or motoric function as increasing maternal motivation by a 4-h pup separation technique did not attenuate 8-OH-DPAT's disruptive effects,

Table 1
Summary of rodent studies investigating central serotonergic effects on maternal behavior. 5-HT = serotonin, CeA = central amygdala, DG = dente gyrus, DR = dorsal raphe, GD = gestation day, LSv = ventrolateral septum, MPOA = medial preoptic area, MR = median raphe, NAc = nucleus accumbens, PAG = periaqueductal grey, PD = postpartum day, mPFC = medial prefrontal cortex.

Serotonin manipulation	When	Species	Findings	Reference
MR lesion	PD1	Rat	↓pup retrieval and nursing	Barofsky et al. (1983a)
DR lesion	PD1	Rat	↑pup mortality (impaired lactation)	Barofsky et al. (1983b)
5-HT2A/2C agonist to lateral ventricle	PD7	Rat	↓maternal aggression	De Almeida and Lucion (1994)
5-HT1A agonist 5-HT2A/2C agonist	Postpartum	Rat	↓maternal aggression	Olivier et al. (1995)
5-HT1A agonist in MR, dPAG, amygdala 5-HT1A agonist to DR and septum	PD7	Rat	↓maternal aggression ↑maternal aggression	De Almeida and Lucion (1997)
Pet1-/-	–	Mouse	↓pup retrieval, ↓nursing, ↓nest building	Lerch-Haner et al. (2008)
TPH2-/-	–	Mouse	↓pup retrieval, ↓nursing	Alenina et al. (2009)/Angoa-Perez et al. (2014)
5-HT2C agonist 5-HT2A antagonist	PD5, 7, 9	Rat	↓pup retrieval, ↓pup licking, ↓nursing, ↓nest building No effect of antagonist	Chen et al. (2014)
5-HT2C agonist 5-HT2C antagonist 5-HT2C agonist to NAc, mPFC, MPOA	PD4-7	Rat	↓maternal behaviors due to ↓maternal motivation No effect of antagonist No effects on maternal behaviors of microinjections	Wu et al. (2016)
5-HT1A agonist 5-HT1A antagonist	PD3, 5, 7	Rat	↓pup retrieval, ↓pup licking, ↓nest building No effect of antagonist	Li et al. (2018)
5-HT2A agonist 5-HT2A antagonist 5-HT2A agonist to mPFC or MPOA	PD8	Rat	↓pup retrieval, ↓nest building, ↓hovering No effect of antagonist Microinjection to mPFC, not MPOA, disrupted maternal behavior	Gao et al. (2018)
5-HT2A agonist	PD4-6/12	Rat	↓pup retrieval, ↓pup licking, ↓nursing, ↓nest building ↑ pup preference	Wu et al. (2018)
5-HT cell-body specific lesions of DR	GD15 or PD2	Rat	GD15: ↑pup licking after retrieval only, ↑hovering over after retrieval only, ↓maternal aggression PD2: ↓pup licking, ↑kyphosis, ↓supine nursing ↓maternal aggression	Holschbach et al. (2018)

and mother rats under the 8-OH-DPAT treatment traveled a similar distance in their cage with similar speed as the controls (Zhao and Li, 2009; Wu et al., 2018, 2016). Li and colleagues did find that activating 5-HT1A receptors disrupted prepulse inhibition (PPI, a measure of sensorimotor gating) (Svensson and Ahlenius, 1983; Nanry and Tilson, 1989; Conti, 2012) and enhanced basal startle response (a putative measure of stress sensitivity) (Li et al., 2018). These findings suggest that 5-HT1A receptors are not only important for maternal aggression, but play an important role in other maternal behaviors, possibly by affecting a host of maternal psychological responses. For a summary of the effects of central 5-HT system manipulations on maternal behaviors see Table 1.

4.3. Role of serotonin 5-HT2A and 5-HT2C receptors in maternal behavior

The 5-HT2A and 5-HT2C receptors are involved in many behaviors involving sensorimotor, attentional, emotional, learning, memory, and executive functions (Graeff et al., 1996; Cools et al., 2008). The first studies on how 5-HT2A and 5-HT2C receptors affect maternal behavior showed that infusing a 5-HT2A/2C agonist (DOI, 2,5-dimethoxy-4-iodo-amphetamine) into the lateral ventricles of postpartum rats decreased maternal attacks toward a male rat (De Almeida and Lucion, 1994). Other maternal behaviors and non-aggressive social interaction with the intruder were unaffected. Later studies using atypical antipsychotic drugs - such as clozapine, olanzapine, risperidone, and quetiapine – that antagonize 5-HT2A/2C receptors found disruption in the active components of maternal behavior including pup approach, pup retrieval and nest building (Li et al., 2004, 2005). Interestingly, the 5-HT2A/2C agonist DOI (1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) also disrupts maternal behavior (Zhao and Li, 2010) by causing less pup licking, less activity, and fewer frequencies of rearing and self-grooming that often interrupted the normal sequence of pup-directed responses (e.g. pup retrieval and pup licking fragmentation), indicating disrupted organization of microregulatory maternal responses (Zhao and Li, 2010). Because both the 5-HT2A/2C receptor antagonist clozapine/olanzapine and agonist DOI disrupted maternal behavior, these early studies suggest that balanced 5-HT2 receptor neurotransmission is critical for the normal expression of maternal behaviors. As discussed immediately below, more recent studies using highly selective agonists and antagonists for the 5-HT2A and 5-HT2C receptors helped clarify the role of these receptors in maternal caregiving behaviors.

4.4. Specific effects of 5-HT2A and 5-HT2C receptors on maternal behaviors

Although the studies summarized above using non-selective 5-HT2A/2C receptor antagonists and agonists indicated that 5-HT2A/2C receptors are important for normal maternal behavior, several issues remained. First, it was unclear which receptor was specifically involved in altering maternal behaviors because the agonist/antagonists used are nonselective for 5-HT2A vs. 5-HT2C receptors. Second, the 5-HT2A and 5-HT2C receptors are involved in many behavioral functions and the exact psychological processes affected by 5HT2A and/or 5-HT2C receptors that contributed to their effects on maternal behavior were unclear. Using highly selective agonists and antagonists against 5-HT2A and 5-HT2C receptors, Li and colleagues demonstrated that selective activation of 5-HT2A receptors by peripheral injection of the selective agonist TCB-2 dose-dependently disrupted maternal behavior, particularly pup-retrieval, hovering over pups and nest building (Gao et al., 2018). Blockade of 5-HT2A receptors with a highly selective 5-HT2A antagonist, MDL 100907, had no effect (Chen et al., 2014). They also found that the disruptive effect on maternal behavior induced by 5-HT2A receptors could be attenuated by pretreatment with a selective 5-

HT2A receptor antagonist, indicating that the effects of TCB-2 was specific to the 5-HT2A receptor (Gao et al., 2018). Similarly, selectively activating 5-HT2C receptors with the agonist MK 212 also disrupted pup retrieval, pup licking, pup nursing, and nest building (Chen et al., 2014), whereas blocking 5-HT2C receptors with the selective antagonist SB242084 had no effect (Wu et al., 2016). The receptor specificity of MK 212's disruptive effect on maternal behavior was confirmed by the finding that pretreatment with the selective 5-HT2C receptor antagonist SB242084 alleviated the MK212-induced disruptions (Wu et al., 2016). These results demonstrate that activation, but not blockade, of 5-HT2A or 5-HT2C receptors impairs maternal caregiving behaviors.

The display of maternal caregiving behavior involves many processes, from detecting and processing offspring cues, regulating maternal motivation according to the individual's internal and external environments, to the motoric display of specific behaviors such as retrieving, grooming, nest building, and huddling with infants (Lonstein et al., 2014; Kohl et al., 2017; Barrett and Fleming, 2011; Lonstein and Fleming, 2002). Activating 5-HT2A receptors by TCB-2 and activating 5-HT2C receptors by MK 212 could potentially disrupt any of these processes to affect caregiving behavior. Given the prominent roles of 5-HT2A and 5-HT2C receptors in motivation, affect, and executive function (Cools et al., 2008), activating 5-HT2A receptors may particularly disrupt executive control of maternal activities (behavioral organization) whereas activating 5-HT2C receptors may especially decrease maternal motivation. To examine whether activation of 5-HT2A or 5-HT2C receptors suppress maternal motivation (Wu et al., 2018, 2016), Wu and colleagues employed a pup separation paradigm to increase maternal motivation (Hansen, 1994). If pup separation could ameliorate the disruption induced by 5-HT2A and 2C agonists, it would suggest that at least one of the behavioral mechanisms by which these agonists disrupt maternal behavior is via suppressed maternal motivation. To test this, postpartum females were treated subcutaneously with the 5-HT2A agonist TCB-2 or the 5HT2C agonist MK 212, or vehicle, and tested after either a 4-h pup-separation or no-pup-separation (Wu et al., 2018, 2016). Although the 4-h pup separation before maternal behavior tests increased maternal performance (e.g., increased time spent nursing and licking pups), it did not reduce the 5-HT2A agonist-induced maternal disruption (Wu et al., 2018). In contrast, pup separation significantly attenuated the 5-HT2C agonist-induced decrease in retrieval (Wu et al., 2016). Thus, activating the 5-HT2C, but not the 5-HT2A, receptor disrupts maternal behavior by suppressing mothers' motivation to interact with pups. Because pup separation did not completely reverse the effects of 5-HT2C agonism, other behavioral effects of 5-HT2C activity may also contribute to its impairment of caregiving, and may be mediated by distinct 5-HT2C receptor-sensitive brain networks (e.g., prefrontal cortex (PFC), nucleus accumbens, and VTA, etc.).

To examine whether activating 5-HT2A or 5-HT2C receptors alters the detection and emotional processing of pup cues, Wu and colleagues then used a pup preference test. The pup preference test is similar to the partner preference test commonly used in the study of pair bonding in monogamous prairie voles (Curtis and Wang, 2005; Ahern et al., 2009). It measures perceptual, emotional, and motivational responses toward pups that do not involve consummatory responses and learning (different from conditioned place preference) (Lonstein and Fleming, 2002). Dams treated with the 5-HT2A agonist TCB-2, or the 5-HT2C agonist MK 212, showed significantly less pup preference (Wu et al., unpublished data). The disruptive effect of activating the 5-HT2C receptors on pup preference is consistent with the pup separation data, indicating a motivational action, while the effect of activating the 5-HT2A receptors is not. To further examine this issue, Wu et al. (2018) tested TCB-2-treated dams in a pup-male preference test to determine whether 5-HT2A receptors activity reduced pup preference when dams were faced with two socially rewarding stimuli (Agrati et al., 2008, 2016). Activating the 5-HT2A receptor increased pup preference in this test (Wu et al., 2018) such that dams treated with the 5-HT2A agonist, TCB-2, spent more time exploring the pups than the male, and showed a greater percentage of exploration time with pups compared to controls. This finding, together with the results from the maternal motivation study, further suggest that the 5-HT2A agonist TCB-2 disrupts maternal behavior by suppressing maternal motivation. It is unknown how it does so, but perhaps agonism of the 5-HT2A receptor disrupts a dam's ability to exert executive control of various maternal activities by either diverting her focused attention on pups towards other environmental cues, or by increasing behavioral fragmentation and premature responding.

4.5. 5-HT2A and 5-HT2C receptors affect distinct neural networks in the maternal brain

If activating 5-HT2A receptors by TCB-2 impairs the executive control or behavioral organization of maternal activities (Wu et al., 2018), it would likely do so by acting on the medial PFC (mPFC). The mPFC plays a central role in top-down control of many higher-order functions, such as working memory, attention, emotion regulation, inhibitory control, and cognitive flexibility (Moghaddam and Homayoun, 2008; Puig and Gulledge, 2011; Puig et al., 2015; Anastasio et al., 2015). The mPFC is also densely interconnected with numerous cortical and subcortical structures, including the serotonergic neurons in the raphe nuclei (Vazquez-Borsetti et al., 2009). In return, the mPFC sends projections back to the raphe nuclei for the feedback control of cortical serotonin release (Celada et al., 2001, 2002). However, 5-HT2A receptor agonism with TCB-2 did not affect Fos expression in the maternal mPFC, although other areas did show increases (ventral BNST, central amygdala, and DR) (Gao et al., 2017). Acute subcutaneous injection of the 5-HT2C agonist MK 212 (2.0 mg/kg) also did not affect Fos in the mPFC, but decreased it in the VTA, ventrolateral septum, MPOA, and DR, and increased it in the central amygdala (Wu et al., 2016; Gao et al., 2018). The different patterns of drug-induced Fos expression clearly indicate that the 5-HT2A and 5-HT2C receptor activation involves distinct neural networks, despite their similar disruptive effects on maternal behaviors. Neither the precise neural networks involved, nor why 5-HT2A and 5-HT2C receptor activation has different effects on the Fos expression in certain brain regions (e.g., DR), is clear.

By injecting serotonin receptor agonists site-specifically into the brain, it was possible to determine what brain regions were involved in their disruptive effects on maternal caregiving behaviors. Gao et al. (2018) found that 5-HT2A agonist TCB-2 into the mPFC suppressed pup retrieval, whereas intra-MPOA infusion had no effect (Gao et al., 2018). With regards to the 5-HT2C receptors, Wu et al. (2016) targeted three brain regions by microinjecting the 5-HT2C agonist MK 212 into the nucleus accumbens shell, mPFC, or MPOA but found no effects on any maternal caregiving behaviors (Wu et al., 2016). Recently, Li and colleagues examined the VTA due to its involvement in motivation and reward processing (Morales and Margolis, 2017). The 5-HT2C agonist MK 212 microinjected into the VTA disrupted pup retrieval and pup preference, supporting the hypothesis that 5-HT2C receptors in the VTA are involved in maternal motivation. Based on these findings a general hypothesis can be proposed suggesting that 5-HT2A receptors in the mPFC are involved in mediating maternal behavior through an executive control mechanism, whereas the 5-HT2C receptors in the VTA are involved in maternal motivation. Future work is needed to delineate the precise functional role of 5-HT2A-containing or 5-HT2C-containing neural substrates within each brain region and pinpoint the neural circuitry through which these 5-HT2 receptors influence maternal behavior.

5. Maternal mental illness, serotonin and SSRI effects on the maternal brain and behavior

Much of the work above has documented how the serotonin system is involved in maternal brain plasticity and behavior in healthy dams.

However, we know that a considerable number of women suffer from clinical levels of anxiety and depression during the peripartum period (up to 20%) (Pawluski et al., 2017). These disorders can have detrimental effects on the mother, child and family (Pawluski et al., 2017; Almond, 2009; Leung and Kaplan, 2009; Marcus, 2009). Mothers with depression, anxiety, and frequent stress often show changes in their offspring caregiving behaviors (Pawluski et al., 2017; Hillerer et al., 2012; Talge et al., 2007). For example, depressed and anxious mothers respond less sensitively, and more negatively, to their infants compared with non-depressed mothers (Field, 1995; Field et al., 1990; Fleming et al., 1988). Depressed mother-infant dyads also have reduced synchrony – involving less mutual attention, vocal and visual communications, touching, and smiling - compared to healthy controls (Field, 1995; Field et al., 1990). In rodent models, repeatedly stressed dams show abnormalities in their maternal caregiving behaviors including their nursing, time on the nest, and time licking the offspring (Hillerer et al., 2012; Champagne and Meaney, 2006; Leuner et al., 2014; Smith et al., 2004; O'Mahony et al., 2006). Little is known about the role of the central serotonin system on the maternal brain and behavior in cases of mental illness but recent research is beginning to show that, as with major depression (Blier and El Mansari, 2012; Hamon and Blier, 2013), serotonin may be an important player in both the etiology and treatment.

5.1. Maternal mental illness and the central serotonin system

In women with postpartum depression (PPD), platelet serotonin levels are 50% lower than normal levels (Maurer-Spurej et al., 2007), and there is a significant positive association between postpartum depressive symptoms and expression of *5-HTT* genotypes (Sanjuan et al., 2008), specifically that short allele carriers of *5-HTT* have an increased risk of developing PPD, particularly in women with low socioeconomic status (Binder et al., 2010; Mitchell et al., 2011). When investigating serotonin in the maternal brain in humans, Moses-Kolko et al. (2008) show that 5-HT1A receptor binding potential in women diagnosed with PPD is reduced 20–28% relative to healthy postpartum women (Moses-Kolko et al., 2008). Of the brain areas investigated, the most significant reductions in 5-HT1A binding are in the anterior cingulate and mesiotemporal cortices.

Although limited, studies of maternal stress applied to laboratory rodents in order to model maternal depression show that gestational and postpartum stressors affect the central serotonin system of the maternal brain. Research by Gemmel et al. (2016) report that repeated restraint stress during the last week of pregnancy increases serotonin turnover in the PFC, but not the hippocampus, when measured three weeks after dams give birth (Gemmel et al., 2016). Other work in postpartum rat dams shows that repeated separation from pups, which may be a psychological stressor for the dams, reduces 5-HT1A receptor levels in a number of brain areas including the hippocampus, PFC, MPOA, and central amygdala (Stamatakis et al., 2015). Five months after gestational stress, 5-HT1A receptor mRNA levels remain reduced in the PFC and hippocampus of rat dams (Szewczyk et al., 2014). Although this research points to widespread effects of stress on the central serotonin system in the mother, further work is needed to clearly delineate the relationship between maternal mental illness and the maternal serotonin system.

5.2. SSRI effects on maternal brain and behavior

The first-line pharmacological treatment for maternal affective disorders are the SSRIs (Kimmel et al., 2018). This is despite the fact that we have limited knowledge of how maternal mental illness interacts with the serotonin system of the maternal brain. SSRIs act by preventing the reuptake of serotonin at the synaptic cleft and thus initially increase serotoninergic signaling. These medications, such as fluoxetine, sertraline, and escitalopram, are prescribed to a growing number of pregnant women suffering from mental illness in developed countries (Oberlander et al., 2006; Zoega et al., 2015; Charlton et al., 2015; Hayes et al., 2012; Lupattelli et al., 2014; Cooper et al., 2007). SSRIs are used with the expectation that they promote maternal mental health and, by extension, confer a health benefit to the fetus and child.

SSRIs and their metabolites cross the placenta and can be found in breast milk (Kristensen et al., 1999), raising questions about the safety for the child of using these medications to treat maternal mental illnesses (Oberlander et al., 2009; Hutchison et al., 2018; Olivier et al., 2013; Homberg et al., 2010). However, untreated maternal mental illness can also affect the maternal and fetal serotonergic system (Gemmel et al., 2016, 2017; Huang et al., 2012) and SSRI effects cannot be completely disentangled from the effect of maternal mental illness on the mother and child (Kyriacou and Lewis, 2016; Oberlander and Zwaigenbaum, 2017). While it is beyond the scope of this review to cover the impact of these factors on the mother *and* offspring (Gemmel et al., 2018a; Kimmel et al., 2018; Oberlander et al., 2009; Hutchison et al., 2018; Olivier et al., 2013; Brummelte et al., 2017; Pawluski and Gemmel, 2018), below we will review how SSRIs affect the maternal brain and behavior.

5.2.1. SSRIs and maternal caregiving behaviors

Clinical work, and a growing body of animal research, shows that SSRIs alter maternal caregiving behaviors. Reebye et al. (2002) report that during feeding and free-play, mothers treated with SSRIs do not differ in positive or negative interactions with their infants compared to non-treated mothers. However, mothers treated with an SSRI and Rivotal (a benzodiazepine derivative) show more inconsistent positive and negative affective messages towards their infants (Reebye et al., 2002). More recent work that controlled for maternal mood symptoms report that mothers treated with an SSRI during pregnancy have more interruptive and forcing behaviors with their three-month-old infants during play (Weikum et al., 2013). This study also showed that maternal depression is related to infant readiness to play in both control and SSRI-treated dyads (Weikum et al., 2013), pointing to the complex interaction between SSRIs and maternal mood on interactions within the mother-infant dyad.

In laboratory rodents, treating healthy pregnant rats with fluoxetine during gestation increases later offspring touching, increases the duration of crouching over offspring (low doses only), decreases nest-building and increases maternal aggression (Johns et al., 2005) (for a summary of findings see Table 2). On the other hand, treatment with sertraline during pregnancy and not postpartum decreases the time that rat dams spend nursing postpartum (Kott et al., 2018). SSRI effects on maternal behaviors are also evident with postpartum SSRI treatment, with treated rat dams showing less passive nursing (Workman et al., 2016), more kyphotic nursing (Pawluski et al., 2012), and less nest building (Workman et al., 2016; Pawluski et al., 2012; Mitra et al., 2017). Others have found that peripartum SSRI treatment (SSRIs during gestation *and* postpartum) can also increase nursing in rat dams (Gemmel et al., 2018b). These same effects of peripartum SSRIs on maternal behavior are not evident in mouse dams (Kiryanova et al., 2016). When examining acute effects of fluoxetine on pup retrieval in an elevated plus maze, fluoxetine-treated rat dams showed impaired pup retrieval, but this may have been due to the decreased percentage of time dams spent on the open arms (Yang et al., 2015).

In the few studies that have investigated SSRI effects on maternal behavior in rodent models of maternal depression and anxiety, SSRIs prevent the effect of maternal exogenous corticosterone on kyphotic nursing (Workman et al., 2016) and alter the amount of time spent off the nest (Kott et al., 2018; Pawluski et al., 2012; Gobinath et al., 2018). An additional study using peripartum administration of venlafaxine, a serotonin norepinerphrine reuptake inhibitor medication, showed that treated dams spend more nursing and less pup licking, regardless of maternal stress exposure (Belovicova et al., 2017). Thus, clinical research and work with laboratory rodent models report that maternal

Table 2
Summary of rodent studies investigating effects of SSRIs on maternal brain and behavior. 5-HIAA = 5-hydroxyindoleacetic acid, 5-HT = serotonin, BLA = basolateral amygdala, DG = dentate gyrus of the hippocampus, Dnmt3a = DNA (cytosine-5)-methyltransferase 3A, HPC = hippocampus, i.p. = intraperitoneal, NAc = nucleus accumbens, PD = postpartum day, mPFC = medial prefrontal cortex, s.c. = subcutaneous.

SSRI administration	Treatment	Species	Findings	Reference
Fluoxetine (2–8 mg/kg/day; water)	GD1-GD20	Rat	↑ touch/sniff of pups, ↑ hovering over pups (low dose only), ↓ nest building, ↑ maternal aggression	Johns et al. (2005)
Fluoxetine (5 mg/kg/day; minipump)	PD 1–28	Rat	↑kyphosis, ↓nest building No effects on DG cell proliferation ↑ DG immature neurons*, no effect on cell proliferation	Pawluski et al. (2012)
Fluoxetine (5 or 10 mg/kg;i.p.)	PD4, 6, 8	Rat	↓ pup retrieval	Yang et al. (2015)
Fluoxetine (10 mg/kg/day;i.p.)	PD2-23	Rat	↑ kyphosis*, ↓ passive nursing, ↓nest building ↓ intermediate, ↑ postmitotic immature neurons in DG	Workman et al., 2016
Fluoxetine (5 mg/kg/day; minipump)	PD 1–21	Rat	↓5-HIAA/5-HT in HPC, ↓Dnmt3a in HPC Prevents gestational stress effects on 5-HIAA/5-HT and synaptophysin in PFC No effects on DG immature neurons	Gemmel et al. (2016)
Fluoxetine (25 mg/kg/day; water)	GD4-GD18	Mouse	no effects on maternal behavior	Kiryanova et al. (2016)
Citalopram (10 mg/kg/day;minipump)	PD1-PD23	Rat	Prevents gestational stress-induced structural alterations of neurons in the NAc shell and mPFC No effect on NAc core or BLA	Haim et al. (2016)
Fluoxetine (10 mg/kg/day; s.c.)	GD1-GD21[a]	Rat	↓pup retrieval in female offspring as mothers	Svirsky et al. (2016)
Fluoxetine (50 mg/kg/day;water)	Postpartum	Mouse	↓nest building in compulsive-like lactating mice	Mitra et al. (2017)
Sertraline (20 mg/kg/day; i.p.)	PreGD– GD21	Rat	↓ time nursing, ↑time off the nest*	Kott et al. (2018)
Fluoxetine (10 mg/kg/day;i.p.)	PD2-PD25	Rat	↑ time nursing, ↓time off the nest* ↓ DG immature neurons	Gobinath et al. (2018)
Fluoxetine (1 0 mg/kg/day; biscuit)	GD10-PD28	Rat	↑ nursing only on PD4-6 ↑ DG immature neurons	Gemmel et al. (2018b)

* Only in group also treated with high levels of corticosterone or restraint stressed.
[a] Mothers in the study exposed *in utero*.

SSRI administration alters maternal caregiving behaviors, but that these effects depend on the type of SSRI, dose, and timing of administration.

More recently research has investigated the maternal behaviors of female offspring exposed to SSRIs *in utero*. During initial pup retrieval tests, mothers that were exposed to fluoxetine during development took longer to retrieve offspring compared to controls (Svirsky et al., 2016). Thus, maternal SSRI treatment may not only affect aspects of maternal behaviors (direct effect) but can have enduring effects on maternal, and possibly paternal, behaviors of offspring exposed to SSRIs during early development.

5.2.2. SSRIs affect maternal neuroplasticity

To date, direct effects of antepartum and/or postpartum SSRI treatment on the maternal brain exists only in animal models. However, recent work in women shows that SSRIs significantly increase serum brain derived neurotrophic factor (BDNF) levels in late pregnancy and that serum S100 calcium binding protein B (S100B), but not BDNF, is associated with depressive symptoms in SSRI-treated women (Pawluski et al., 2019). When specifically looking at the central serotonin system in rodent models, Gemmel et al. (2016) show that postpartum fluoxetine treatment decreases serotonin turnover in the hippocampus and prevents the effect of gestational stress on serotonin turnover in the PFC (Gemmel et al., 2016). Further research in this area has predominantly focused on the effects of SSRIs in the maternal hippocampus, in part due to the role of the hippocampal neuroplasticity in mental illness and the actions of SSRIs, via effects on the hippocampus, in alleviating depressive-like behaviors (Bremner et al., 2000; Djavadian, 2004; Dranovsky and Hen, 2006). As mentioned above, previous research also shows that the hippocampus has a high degree of plasticity during pregnancy and the postpartum period (Pawluski et al., 2016; Leuner and Sabihi, 2016; Levy et al., 2011; Medina and Workman, 2018; Galea et al., 2014), making it a likely region for the actions of these medications on the maternal brain. Indeed, postpartum SSRI treatment affects the maternal hippocampus by decreasing intermediate and increasing post-mitotic immature neurons in the SGZ and GCL of the dentate gyrus three weeks after giving birth (Workman et al., 2016) as well as a decrease in the density of immature neurons around the same period (Gobinath et al., 2018). There appears to be a time course with regards to SSRI effects on neurogenesis in the maternal hippocampus, as others report that at weaning and one week after weaning postpartum SSRI treatment has no effect on the rates of cell proliferation (Pawluski et al., 2012) or the number of immature neurons in the dentate gyrus (Gemmel et al., 2016; Workman et al., 2016; Pawluski et al., 2012). When administered perinatally from gestation day 10 to postpartum day 28, and thus for a longer period of time, fluoxetine (Gemmel et al., 2018b), and venlafaxine (Belovicova et al., 2017), increase the number of immature neurons in the hippocampus of both control and dams stressed prior to pregnancy. Interestingly, when postpartum SSRI treatment occurs after pregnancy stress, an increased number of immature neurons in the hippocampus is evident one week after weaning (Pawluski et al., 2012), pointing to a complex relationship between the timing of stress and SSRI treatment on plasticity in the maternal hippocampus.

In addition to work on the hippocampus, research in rats reveals effects of postpartum SSRI treatment on other areas of the maternal circuit including the nucleus accumbens and PFC. Using a model of gestational stress, postpartum fluoxetine prevents the effect of gestational stress on synaptophysin density in the cingulate cortex, a region of the mPFC (Gemmel et al., 2016). Furthermore, postpartum citalopram treatment prevents the effects of gestational stress-induced structural changes of neurons in the nucleus accumbens shell and mPFC, but not the nucleus accumbens core or basolateral amygdala (Haim et al., 2016). These findings show that activating serotonin-related mechanisms can alter plasticity in the maternal neural circuit, particularly in the presence of stress. Whether or not changes in the maternal brain with SSRI treatment relate to decreased depressive-like behavior in the animal models of maternal depression is unclear. In the studies mentioned above that did investigate SSRI effects on maternal depressive-like behavior (primarily tested with the forced swim test (Porsolt et al., 2001) in models of maternal depression (Workman et al., 2016; Pawluski et al., 2012; Gobinath et al., 2018; Haim et al., 2016), only one found that postpartum SSRI treatment clearly prevented the effects of maternal stress on depressive-like behaviors (Haim et al., 2016). Differences between studies may be due to the type, timing, and dose of SSRI administration as well as the methods used to induce maternal depression-like behaviors (i.e., repeated restraint vs

exogenous corticosterone administration) (Perani and Slattery, 2014).

6. Future directions and conclusion

Research on central serotonergic control of maternal behavior is still in its infancy, leaving many unanswered questions. First, most studies examining the role of particular serotonin receptors rely on pharmacological tools, which are limited by the degree of selectivity of the drugs available. It is imperative to employ other approaches (e.g., transgenic models, viral vectors, etc.) to further delineate the specific roles of the various serotonin receptors in maternal caregiving. Second, although we have gained some understanding of the specific behavioral mechanisms underlying how the various serotonin receptors affect maternal behavior, this issue is far from settled, especially for 5-HT1A and 5-HT2A receptors. Third, we do not know much about the molecular mechanisms of action of serotonin and its receptors. Given the well-known modulation of 5-HT2A and 5-HT2C on the mesolimbic and mesocortical dopamine activity, and ample expression of both receptors in the mPFC, nucleus accumbens, and VTA (Howell and Cunningham, 2015), it is very likely that 5-HT2A and 5-HT2C receptors may influence maternal behavior by affecting dopamine. Thus, the potential interactions among the 5-HT2A and 5-HT2C receptors and dopamine receptors need to be elucidated in order to fully understand monoaminergic involvement in maternal behavior. Fourth, given the importance of reproductive hormones such as estrogen, progesterone, oxytocin, prolactin, and glucocorticoids in the mediation of maternal behavior (Lonstein et al., 2014; Barrett and Fleming, 2011; Bridges, 2015) and their demonstrated regulation of serotonin activity and function (cf. Bethea et al., 2002, 1998; Hernandez-Hernandez et al., 2018), it would be valuable to study how serotonin's effects on the maternal brain and behavior are impacted by these hormones. Future research should also focus on dissecting the precise neurocircuits that support the maternal regulatory effects of serotonin receptors (Barnes et al., 2017; Haim et al., 2017).

In terms of the use of SSRIs to treat maternal mental illness, much more work is needed to understand how these medications act in the brain specifically during both the postpartum period *and* during pregnancy (there is no published work to date), mechanistically how SSRIs improve maternal mental health, why they improve mental health in only some mothers, and how they affect maternal caregiving behaviors. Perhaps of greater importance when trying to understand how SSRIs affects the maternal brain and behavior is to investigate the reverse relationship - how maternal mental illness affects the central serotonin system. Mothers are prescribed medications that act on a neurochemical system that has not yet been well described in either healthy or unhealthy maternal states. With increased knowledge about the central serotonin system during the transition to, and maintenance of, motherhood we will be able to more accurately understand how this system contributes to maternal and infant behavioral and affective well-being - moving from molecules to mood.

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References

Agrati, D., Ferreno, M., Marin, G., Uriarte, N., Zuluaga, M.J., Fernandez-Guasti, A., Ferreira, A., 2016. Previous and recent maternal experiences modulate pups' incentive value relative to a male without affecting maternal behavior in postpartum estrous rats. J. Physiol. Paris.

Agrati, D., Lonstein, J.S., 2016. Affective changes during the postpartum period: influences of genetic and experiential factors. Horm. Behav. 77, 141–152.

Agrati, D., Fernandez-Guasti, A., Ferreira, A., 2008. The reproductive stage and experience of sexually receptive mothers alter their preference for pups or males. Behav. Neurosci. 122, 998–1004.

Ahern, T.H., Modi, M.E., Burkett, J.P., Young, L.J., 2009. Evaluation of two automated metrics for analyzing partner preference tests. J. Neurosci. Methods 182, 180–188.

Albert, P.R., Vahid-Ansari, F., Luckhart, C., 2014. Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre- and post-synaptic 5-HT1A receptor expression. Front. Behav. Neurosci. 8, 199.

Alenina, N., Kikic, D., Todiras, M., Mosienko, V., Qadri, F., Plehm, R., Boye, P., Vilianovitch, L., Sohr, R., Tenner, K., Hortnagl, H., Bader, M., 2009. Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc. Natl. Acad. Sci. USA 106, 10332–10337.

Almond, P., 2009. Postnatal depression: a global public health perspective. Perspect. Public Health 129, 221–227.

Anastasio, N.C., Stutz, S.J., Fink, L.H., Swinford-Jackson, S.E., Sears, R.M., DiLeone, R.J., Rice, K.C., Moeller, F.G., Cunningham, K.A., 2015. Serotonin (5-HT) 5-HT2A receptor (5-HT2AR):5-HT2CR imbalance in medial prefrontal cortex associates with motor impulsivity. ACS Chem. Neurosci. 6, 1248–1258.

Angoa-Perez, M., Kane, M.J., Sykes, C.E., Perrine, S.A., Church, M.W., Kuhn, D.M., 2014. Brain serotonin determines maternal behavior and offspring survival. Genes Brain Behav. 13, 579–591.

Arenas, E., Denham, M., Villaescusa, J.C., 2015. How to make a midbrain dopaminergic neuron. Development 142, 1918–1936.

Arrati, P.G., Carmona, C., Dominguez, G., Beyer, C., Rosenblatt, J.S., 2006. GABA receptor agonists in the medial preoptic area and maternal behavior in lactating rats. Physiol. Behav. 87, 51–65.

Badawy, A.A., 2014. The tryptophan utilization concept in pregnancy. Obstet. Gynecol. Sci. 57, 249–259.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2008. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Soc. Cogn. Affect Neurosci. 3, 128–134.

Barnes, J., Mondelli, V., Pariante, C.M., 2017. Genetic contributions of inflammation to depression. Neuropsychopharmacology 42, 81–98.

Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.

Barofsky, A.L., Taylor, J., Massari, V.J., 1983a. Dorsal raphe-hypothalamic projections provide the stimulatory serotonergic input to suckling-induced prolactin release. Endocrinology 113, 1894–1903.

Barofsky, A.L., Taylor, J., Tizabi, Y., Kumar, R., Jones-Quartey, K., 1983b. Specific neurotoxin lesions of median raphe serotonergic neurons disrupt maternal behavior in the lactating rat. Endocrinology 113, 1884–1893.

Barrett, J., Fleming, A.S., 2011. Annual Research Review: all mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. J. Child Psychol. Psych. 52, 368–397.

Belovicova, K., Bogi, E., Koprdova, R., Ujhazy, E., Mach, M., Dubovicky, M., 2017. Effects of venlafaxine and chronic unpredictable stress on behavior and hippocampal neurogenesis of rat dams. Neuro Endocrinol. Lett. 38, 19–26.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes? Mol. Psych. 14, 746–754.

Bendotti, C., Samanin, R., 1986. 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) elicits eating in free-feeding rats by acting on central serotonin neurons. Eur. J. Pharmacol. 121, 147–150.

Bethea, C.L., Pecins-Thompson, M., Schutzer, W.E., Gundlah, C., Lu, Z.N., 1998. Ovarian steroids and serotonin neural function. Mol. Neurobiol. 18, 87–123.

Bethea, C.L., Lu, N.Z., Gundlah, C., Streicher, J.M., 2002. Diverse actions of ovarian steroids in the serotonin neural system. Front. Neuroendocrinol. 23, 41–100.

Binder, E.B., Newport, D.J., Zach, E.B., Smith, A.K., Deveau, T.C., Altshuler, L.L., Cohen, L.S., Stowe, Z.N., Cubells, J.F., 2010. A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort. J. Psychiatr. Res. 44, 640–646.

Blier, P., El Mansari, M., 2012. Serotonin and beyond: therapeutics for major depression. Philos. Trans. R. Soc. Lond. Series B Biol. Sci. 368, 20120536.

Bonvento, G., Scatton, B., Claustre, Y., Rouquier, L., 1992. Effect of local injection of 8-OH-DPAT into the dorsal or median raphe nuclei on extracellular levels of serotonin in serotonergic projection areas in the rat brain. Neurosci. Lett. 137, 101–104.

Bremner, J.D., Narayan, M., Anderson, E.R., Staib, L.H., Miller, H.L., Charney, D.S., 2000. Hippocampal volume reduction in major depression. Am. J. Psych. 157, 115–118.

Bridges, R.S., 2015. Neuroendocrine regulation of maternal behavior. Front. Neuroendocrinol. 36, 178–196.

Bridges, R.S., Clifton, D.K., Sawyer, C.H., 1982. Postpartum luteinizing hormone release and maternal behavior in the rat after late-gestational depletion of hypothalamic norepinephrine. Neuroendocrinology 34, 286–291.

Brown, R.S.E., Aoki, M., Ladyman, S.R., Phillipps, H.R., Wyatt, A., Boehm, U., Grattan, D.R., 2017. Prolactin action in the medial preoptic area is necessary for postpartum maternal nursing behavior. Proc. Natl. Acad. Sci. USA 114, 10779–10784.

Brummelte, S., Mc Glanaghy, E., Bonnin, A., Oberlander, T.F., 2017. Developmental changes in serotonin signaling: implications for early brain function, behavior and adaptation. Neuroscience 342, 212–231.

Burnet, P.W., Eastwood, S.L., Lacey, K., Harrison, P.J., 1995. The distribution of 5-HT1A and 5-HT2A receptor mRNA in human brain. Brain Res. 676, 157–168.

Burton, C.L., Rizos, Z., Diwan, M., Nobrega, J.N., Fletcher, P.J., 2013. Antagonizing 5-HT(2)A receptors with M100907 and stimulating 5-HT(2)C receptors with Ro60-0175 blocks cocaine-induced locomotion and zif268 mRNA expression in Sprague-Dawley rats. Behav. Brain Res. 240, 171–181.

Carhart-Harris, R.L., Nutt, D.J., 2017. Serotonin and brain function: a tale of two receptors. J. Psychopharmacol. 31, 1091–1120.

Cassaday, H.J., Simpson, E.L., Gaffan, E.A., 2000. Rapid visual learning in the rat: effects at the 5-HT1a receptor subtype. Q. J. Exp. Psychol. B 53, 225–238.

Celada, P., Puig, M.V., Casanovas, J.M., Guillazo, G., Artigas, F., 2001. Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: involvement of serotonin-1A, GABA(A), and glutamate receptors. J. Neurosci. 21, 9917–9929.
Celada, P., Puig, M.V., Martin-Ruiz, R., Casanovas, J.M., Artigas, F., 2002. Control of the serotonergic system by the medial prefrontal cortex: potential role in the etiology of PTSD and depressive disorders. Neurotox. Res. 4, 409–419.
Cents, R.A., Kok, R., Tiemeier, H., Lucassen, N., Szekely, E., Bakermans-Kranenburg, M.J., Hofman, A., Jaddoe, V.W., van, I.M.H., Verhulst, F.C., Lambregtse-van den Berg, M.P., 2014. Variations in maternal 5-HTTLPR affect observed sensitive parenting. J. Child Psychol. Psych. 55, 1025–1032.
Chalmers, D.T., Watson, S.J., 1991. Comparative anatomical distribution of 5-HT1A receptor mRNA and 5-HT1A binding in rat brain–a combined in situ hybridisation/in vitro receptor autoradiographic study. Brain Res. 561, 51–60.
Champagne, F.A., Meaney, M.J., 2006. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. Biol. Psych. 59, 1227–1235.
Charlton, R.A., Jordan, S., Pierini, A., Garne, E., Neville, A.J., Hansen, A.V., Gini, R., Thayer, D., Tingay, K., Puccini, A., Bos, H.J., Nybo Andersen, A.M., Sinclair, M., Dolk, H., de Jong-van den Berg, L.T., 2015. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG 122, 1010–1020.
Chechik, G., Meilijson, I., Ruppin, E., 1999. Neuronal regulation: a mechanism for synaptic pruning during brain maturation. Neural Comput. 11, 2061–2080.
Chen, W., Zhang, Q., Su, W., Zhang, H., Yang, Y., Qiao, J., Sui, N., Li, M., 2014. Effects of 5-hydroxytryptamine 2C receptor agonist MK212 and 2A receptor antagonist MDL100907 on maternal behavior in postpartum female rats. Pharmacol. Biochem. Behav. 117, 25–33.
Clemett, D.A., Punhani, T., Duxon, M.S., Blackburn, T.P., Fone, K.C., 2000. Immunohistochemical localisation of the 5-HT2C receptor protein in the rat CNS. Neuropharmacology 39, 123–132.
Clissold, K.A., Choi, E., Pratt, W.E., 2013. Serotonin 1A, 1B, and 7 receptors of the rat medial nucleus accumbens differentially regulate feeding, water intake, and locomotor activity. Pharmacol. Biochem. Behav. 112, 96–103.
Conti, L.H., 2012. Interactions between corticotropin-releasing factor and the serotonin 1A receptor system on acoustic startle amplitude and prepulse inhibition of the startle response in two rat strains. Neuropharmacology 62, 256–263.
Cools, R., Roberts, A.C., Robbins, T.W., 2008. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn. Sci. 12, 31–40.
Cooper, W.O., Willy, M.E., Pont, S.J., Ray, W.A., 2007. Increasing use of antidepressants in pregnancy. Am. J. Obstet. Gynecol. 196 (544), e1–e5.
Cornea-Hebert, V., Riad, M., Wu, C., Singh, S.K., Descarries, L., 1999. Cellular and subcellular distribution of the serotonin 5-HT2A receptor in the central nervous system of adult rat. J. Comp. Neurol. 409, 187–209.
Corona, R., Meurisse, M., Cornilleau, F., Moussu, C., Keller, M., Levy, F., 2018. Disruption of adult olfactory neurogenesis induces deficits in maternal behavior in sheep. Behav. Brain Res. 347, 124–131.
Cox, E.T., Jarrett, T.M., McMurray, M.S., Greenhill, K., Hofler, V.E., Williams, S.K., Joyner, P.W., Middleton, C.L., Walker, C.H., Johns, J.M., 2011. Combined norepinephrine/serotonergic reuptake inhibition: effects on maternal behavior, aggression, and oxytocin in the rat. Front. Psych. 2, 34.
Curtis, J.T., Wang, Z., 2005. Ventral tegmental area involvement in pair bonding in male prairie voles. Physiol. Behav. 86, 338–346.
da Veiga, C.P., Miczek, K.A., Lucion, A.B., de Almeida, R.M., 2011. Social instigation and aggression in postpartum female rats: role of 5-Ht1A and 5-Ht1B receptors in the dorsal raphe nucleus and prefrontal cortex. Psychopharmacology (Berl) 213, 475–487.
Dahlstroem, A., Fuxe, K., 1964. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand. (Suppl 232), 1–55.
Darnaudery, M., Perez-Martin, M., Del Favero, F., Gomez-Roldan, C., Garcia-Segura, L.M., Maccari, S., 2007. Early motherhood in rats is associated with a modification of hippocampal function. Psychoneuroendocrinology 32, 803–812.
D'Cunha, T.M., King, S.J., Fleming, A.S., Levy, F., 2011. Oxytocin receptors in the nucleus accumbens shell are involved in the consolidation of maternal memory in postpartum rats. Horm. Behav. 59, 14–21.
De Almeida, R.M., Lucion, A.B., 1994. Effects of intracerebroventricular administration of 5-HT receptor agonists on the maternal aggression of rats. Eur. J. Pharmacol. 264, 445–448.
De Almeida, R.M., Lucion, A.B., 1997. 8-OH-DPAT in the median raphe, dorsal periaqueductal gray and corticomedial amygdala nucleus decreases, but in the medial septal area it can increase maternal aggressive behavior in rats. Psychopharmacology (Berl) 134, 392–400.
Desan, P.H., Woodmansee, W.W., Ryan, S.M., Smock, T.K., Maier, S.F., 1988. Monoamine neurotransmitters and metabolites during the estrous cycle, pregnancy, and the postpartum period. Pharmacol. Biochem. Behav. 30, 563–568.
Descarries, L., Riad, M., Parent, M., 2010. Ultrastructure of the serotonin innervation of the mammalian central nervous system, Handbook of Behavioral Neuroscience. Elsevier, pp. 61–101.
Dickinson, C., Keverne, E.B., 1988. Importance of noradrenergic mechanisms in the olfactory bulbs for the maternal behaviour of mice. Physiol. Behav. 43, 313–316.
Djavadian, R.L., 2004. Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals. Acta Neurobiol. Exp. (Wars) 64, 189–200.
Dranovsky, A., Hen, R., 2006. Hippocampal neurogenesis: regulation by stress and antidepressants. Biol. Psych. 59, 1136–1143.
Ettrup, A., Svarer, C., McMahon, B., da Cunha-Bang, S., Lehel, S., Moller, K., Dyssegaard, A., Ganz, M., Beliveau, V., Jorgensen, L.M., Gillings, N., Knudsen, G.M., 2016. Serotonin 2A receptor agonist binding in the human brain with [(11)C]Cimbi-36: Test-retest reproducibility and head-to-head comparison with the antagonist [(18)F] altanserin. Neuroimage 130, 167–174.
Febo, M., Felix-Ortiz, A.C., Johnson, T.R., 2010. Inactivation or inhibition of neuronal activity in the medial prefrontal cortex largely reduces pup retrieval and grouping in maternal rats. Brain Res. 1325, 77–88.
Fernstrom, J.D., Wurtman, R.J., 1972. Brain serotonin content: physiological regulation by plasma neutral amino acids. Science 178, 414–416.
Ferreira, A., Picazo, O., Uriarte, N., Pereira, M., Fernandez-Guasti, A., 2000. Inhibitory effect of buspirone and diazepam, but not of 8-OH-DPAT, on maternal behavior and aggression. Pharmacol. Biochem. Behav. 66, 389–396.
Field, T., 1995. Psychologically depressed parents. In: Bornstein, M. (Ed.), Handbook of Parenting. L. Erlbaum Associates, New Jersey.
Field, T., Healy, B., Goldstein, M., Guthertz, M., 1990. Behavior-state matching and synchrony in mother-infant interactions of nondepressed versus depressed dyads. Dev. Psychobiol. 26, 7–14.
Fleming, A.S., Ruble, D.N., Flett, G.L., Shaul, D., 1988. Postpartum adjustment in first-time mothers: relations between mood, maternal attitudes and mother-infant interactions'. Dev. Psychobiol. 24, 71–81.
Fricker, M., Tolkovsky, A.M., Borutaite, V., Coleman, M., Brown, G.C., 2018. Neuronal cell death. Physiol. Rev. 98, 813–880.
Furuta, M., Bridges, R.S., 2005. Gestation-induced cell proliferation in the rat brain. Brain Res. Dev. Brain Res. 156, 61–66.
Galea, L.A., Leuner, B., Slattery, D.A., 2014. Hippocampal plasticity during the peripartum period: influence of sex steroids, stress and ageing. J. Neuroendocrinol. 26, 641–648.
Gao, J., Wu, R., Davis, C., Li, M., 2017. Activation of 5-HT2A receptor disrupts rat maternal behavior. Neuropharmacology.
Gao, J., Wu, R., Davis, C., Li, M., 2018. Activation of 5-HT2A receptor disrupts rat maternal behavior. Neuropharmacology 128, 96–105.
Gemmel, M., Rayen, I., van Donkelaar, E., Loftus, T., Steinbusch, H.W., Kokras, N., Dalla, C., Pawluski, J.L., 2016. Gestational stress and fluoxetine treatment differentially affect plasticity, methylation and serotonin levels in the PFC and hippocampus of rat dams. Neuroscience 327, 32–43.
Gemmel, M., Hazlett, M., Bogi, E., De Lacalle, S., Hill, L.A., Kokras, N., Hammond, G.L., Dalla, C., Charlier, T.D., Pawluski, J.L., 2017. Perinatal fluoxetine effects on social play, the HPA system, and hippocampal plasticity in pre-adolescent male and female rats: interactions with pre-gestational maternal stress. Psychoneuroendocrinology 84, 159–171.
Gemmel, M., Bogi, E., Ragan, C., Hazlett, M., Dubovicky, M., van den Hove, D.L., Oberlander, T.F., Charlier, T.D., Pawluski, J.L., 2018a. Perinatal selective serotonin reuptake inhibitor medication (SSRI) effects on social behaviors, neurodevelopment and the epigenome. Neurosci. Biobehav. Rev. 85, 102–116.
Gemmel, M., Harmeyer, D., Bogi, E., Fillet, M., Hill, L.A., Hammond, G.L., Charlier, T.D., Pawluski, J.L., 2018b. Perinatal fluoxetine increases hippocampal neurogenesis and reverses the lasting effects of pre-gestational stress on serum corticosterone, but not on maternal behavior, in the rat dam. Behav. Brain Res. 339, 222–231.
Girirajan, S., Elsea, S.H., 2009. Abnormal maternal behavior, altered sociability, and impaired serotonin metabolism in Rai1-transgenic mice. Mammalian Genome: Off. J. Int. Mammal. Genome Soc. 20, 247–255.
Glaser, J., Russell, V.A., de Villiers, A.S., Searson, J.A., Taljaard, J.J., 1990. Rat brain monoamine and Serotonin S2 receptor changes during pregnancy. Neurochem. Res. 15, 949–956.
Gobinath, A.R., Richardson, R.J., Chow, C., Workman, J.L., Lieblich, S.E., Barr, A.M., Galea, L.A.M., 2018. Voluntary running influences the efficacy of fluoxetine in a model of postpartum depression. Neuropharmacology 128, 106–118.
Graeff, F.G., Guimaraes, F.S., De Andrade, T.G., Deakin, J.F., 1996. Role of 5-HT in stress, anxiety, and depression. Pharmacol. Biochem. Behav. 54, 129–141.
Grieb, Z.A., Lonstein, J.S., 2015. Effects of Reproductive State on the Expression of Oxytocin Receptor mRNA and Protein in the Midbrain Raphe Nuclei of Female Rats. Society for Neuroscience, Chicago, IL.
Gundlah, C., Pecins-Thompson, M., Schutzer, W.E., Bethea, C.L., 1999. Ovarian steroid effects on serotonin 1A, 2A and 2C receptor mRNA in macaque hypothalamus. Brain Res. Mol. Brain Res. 63, 325–339.
Haim, A., Albin-Brooks, C., Sherer, M., Mills, E., Leuner, B., 2016. The effects of gestational stress and Selective Serotonin reuptake inhibitor antidepressant treatment on structural plasticity in the postpartum brain–a translational model for postpartum depression. Horm. Behav. 77, 124–131.
Haim, A., Julian, D., Albin-Brooks, C., Brothers, H.M., Lenz, K.M., Leuner, B., 2017. A survey of neuroimmune changes in pregnant and postpartum female rats. Brain Behav. Immun. 59, 67–78.
Hamon, M., Blier, P., 2013. Monoamine neurocircuitry in depression and strategies for new treatments. Prog. Neuropsychopharmacol. Biol. Psych. 45, 54–63.
Hannon, J., Hoyer, D., 2008. Molecular biology of 5-HT receptors. Behav. Brain Res. 195, 198–213.
Hansen, S., 1994. Maternal behavior of female rats with 6-OHDA lesions in the ventral striatum: characterization of the pup retrieval deficit. Physiol. Behav. 55, 615–620.
Harding, K.M., Lonstein, J.S., 2016. Extensive juvenile “babysitting” facilitates later adult maternal responsiveness, decreases anxiety, and increases dorsal raphe tryptophan hydroxylase-2 expression in female laboratory rats. Dev. Psychobiol. 58, 492–508.
Hayes, R.M., Wu, P., Shelton, R.C., Cooper, W.O., Dupont, W.D., Mitchel, E., Hartert, T.V., 2012. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am. J. Obstet. Gynecol. 207 (49), e1–e9.
Hendricks, T., Francis, N., Fyodorov, D., Deneris, E.S., 1999. The ETS domain factor Pet-1 is an early and precise marker of central serotonin neurons and interacts with a conserved element in serotonergic genes. J. Neurosci. 19, 10348–10356.

Hernandez-Hernandez, O.T., Martinez-Mota, L., Herrera-Perez, J.J., Jimenez-Rubio, G., 2018. Role of estradiol in the expression of genes involved in serotonin neurotransmission: implications for female depression. Curr. Neuropharmacol.
Hernandez-Vazquez, F., Garduno, J., Hernandez-Lopez, S., 2018;al., in press. GABAergic modulation of serotonergic neurons in the dorsal raphe nucleus. Rev. Neurosci. https://doi.org/10.1515/revneuro-2018-0014. (in press).
Hillerer, K.M., Neumann, I.D., Slattery, D.A., 2012. From stress to postpartum mood and anxiety disorders: how chronic peripartum stress can impair maternal adaptations. Neuroendocrinology 95, 22–38.
Hjorth, S., Magnusson, T., 1988. The 5-HT 1A receptor agonist, 8-OH-DPAT, preferentially activates cell body 5-HT autoreceptors in rat brain in vivo. Naunyn Schmiedebergs Arch. Pharmacol. 338, 463–471.
Holschbach, M.A., Lonstein, J.S., 2017. Motherhood and infant contact regulate neuroplasticity in the serotonergic midbrain dorsal raphe. Psychoneuroendocrinology 76, 97–106.
Holschbach, M.A., Vitale, E.M., Lonstein, J.S., 2018. Serotonin-specific lesions of the dorsal raphe disrupt maternal aggression and caregiving in postpartum rats. Behav. Brain Res. 348, 53–64.
Homberg, J.R., Schubert, D., Gaspar, P., 2010. New perspectives on the neurodevelopmental effects of SSRIs. Trends Pharmacol. Sci. 31, 60–65.
Hornung, J.P., 2010. The neuroanatomy of the serotonergic system, Handbook of Behavioral Neuroscience, vol. 21, 51–64.
Howell, L.L., Cunningham, K.A., 2015. Serotonin 5-HT2 receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder. Pharmacol. Rev. 67, 176–197.
Hoyer, D., Hannon, J.P., Martin, G.R., 2002. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol. Biochem. Behav. 71, 533–554.
Huang, Y., Xu, H., Li, H., Yang, H., Chen, Y., Shi, X., 2012. Pre-gestational stress reduces the ratio of 5-HIAA to 5-HT and the expression of 5-HT1A receptor and serotonin transporter in the brain of foetal rat. BMC Neurosci. 13, 22.
Hutchison, S.M., Masse, L.C., Pawluski, J.L., Oberlander, T.F., 2018. Perinatal selective serotonin reuptake inhibitor (SSRI) effects on body weight at birth and beyond: a review of animal and human studies. Reprod. Toxicol. 77, 109–121.
Jacobs, B.L., Azmitia, E.C., 1992. Structure and function of the brain serotonin system. Physiol. Rev. 72, 165–229.
Johns, J.M., Joyner, P.W., McMurray, M.S., Elliott, D.L., Hofler, V.E., Middleton, C.L., Knupp, K., Greenhill, K.W., Lomas, L.M., Walker, C.H., 2005. The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. Pharmacol. Biochem. Behav. 81, 769–785.
Jovanovic, H., Lundberg, J., Karlsson, P., Cerin, A., Saijo, T., Varrone, A., Halldin, C., Nordstrom, A.L., 2008. Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. Neuroimage 39, 1408–1419.
Jury, N.J., McCormick, B.A., Horseman, N.D., Benoit, S.C., Gregerson, K.A., 2015. Enhanced responsiveness to selective serotonin reuptake inhibitors during lactation. PLoS One 10, e0117339.
Kimmel, M.C., Cox, E., Schiller, C., Gettes, E., Meltzer-Brody, S., 2018. Pharmacologic treatment of perinatal depression. Obstet. Gynecol. Clin. North Am 45, 419–440.
Kiryanova, V., Meunier, S.J., Vecchiarelli, H.A., Hill, M.N., Dyck, R.H., 2016. Effects of maternal stress and perinatal fluoxetine exposure on behavioral outcomes of adult male offspring. Neuroscience 320, 281–296.
Klink, R., Robichaud, M., Debonnel, G., 2002. Gender and gonadal status modulation of dorsal raphe nucleus serotonergic neurons. Part I: effects of gender and pregnancy. Neuropharmacology 43, 1119–1128.
Kohl, J., Autry, A.E., Dulac, C., 2017. The neurobiology of parenting: a neural circuit perspective. Bioessays 39, 1–11.
Kott, J.M., Mooney-Leber, S.M., Li, J., Brummelte, S., 2018. Elevated stress hormone levels and antidepressant treatment starting before pregnancy affect maternal care and litter characteristics in an animal model of depression. Behav. Brain Res. 348, 101–114.
Kristensen, J.H., Ilett, K.F., Hackett, L.P., Yapp, P., Paech, M., Begg, E.J., 1999. Distribution and excretion of fluoxetine and norfluoxetine in human milk. Br. J. Clin. Pharmacol. 48, 521–527.
Kyriacou, D.N., Lewis, R.J., 2016. Confounding by indication in clinical research. JAMA 316, 1818–1819.
Larsen, C.M., Grattan, D.R., 2010. Prolactin-induced mitogenesis in the subventricular zone of the maternal brain during early pregnancy is essential for normal postpartum behavioral responses in the mother. Endocrinology 151, 3805–3814.
Lee, G., Gammie, S.C., 2010. GABAA receptor signaling in caudal periaqueductal gray regulates maternal aggression and maternal care in mice. Behav. Brain Res. 213, 230–237.
Lerch-Haner, J.K., Frierson, D., Crawford, L.K., Beck, S.G., Deneris, E.S., 2008. Serotonergic transcriptional programming determines maternal behavior and offspring survival. Nat. Neurosci.
Lesch, K.P., Gutknecht, L., 2004. Focus on The 5-HT1A receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. Int. J. Neuropsychopharmacol. 7, 381–385.
Lesch, K.P., 2007. Linking emotion to the social brain. The role of the serotonin transporter in human social behaviour. EMBO reports 8 Spec No, S24–9.
Leuner, B., Fredericks, P.J., Nealer, C., Albin-Brooks, C., 2014. Chronic gestational stress leads to depressive-like behavior and compromises medial prefrontal cortex structure and function during the postpartum period. PLoS One 9, e89912.
Leuner, B., Sabihi, S., 2016. The birth of new neurons in the maternal brain: hormonal regulation and functional implications. Front. Neuroendocrinol. 41, 99–113.
Leuner, B., Glasper, E.R., Gould, E., 2010. Parenting and plasticity. Trends Neurosci. 33, 465–473.
Leuner, B., Mirescu, C., Noiman, L., Gould, E., 2007. Maternal experience inhibits the production of immature neurons in the hippocampus during the postpartum period through elevations in adrenal steroids. Hippocampus 17, 434–442.
Leung, B.M., Kaplan, B.J., 2009. Perinatal depression: prevalence, risks, and the nutrition link–a review of the literature. J. Am. Diet Assoc. 109, 1566–1575.
Levy, F., Gervais, R., Kindermann, U., Orgeur, P., Piketty, V., 1990. Importance of beta-noradrenergic receptors in the olfactory bulb of sheep for recognition of lambs. Behav. Neurosci. 104, 464–469.
Levy, F., Gheusi, G., Keller, M., 2011. Plasticity of the parental brain: a case for neurogenesis. J. Neuroendocrinol. 23, 984–993.
Levy, F., Batailler, M., Meurisse, M., Migaud, M., 2017. Adult neurogenesis in sheep: characterization and contribution to reproduction and behavior. Front. Neurosci. 11, 570.
Li, M., Davidson, P., Budin, R., Kapur, S., Fleming, A.S., 2004. Effects of typical and atypical antipsychotic drugs on maternal behavior in postpartum female rats. Schizophr. Res. 70, 69–80.
Li, M., Budin, R., Fleming, A.S., Kapur, S., 2005. Effects of chronic typical and atypical antipsychotic drug treatment on maternal behavior in rats. Schizophr. Res. 75, 325–336.
Li, X., Ding, X., Wu, R., Chen, L., Gao, J., Hu, G., Li, M., 2018. A behavioral mechanistic investigation of the role of 5-HT1A receptors in the mediation of rat maternal behavior. Pharmacol. Biochem. Behav. 169, 16–26.
Lonstein, J.S., 2019. The dynamic serotonin system of the maternal brain. Arch. Womens Ment. Health (in press).
Lonstein, J.S., Dominguez, J.M., Putnam, S.K., De Vries, G.J., Hull, E.M., 2003. Intracellular preoptic and striatal monoamines in pregnant and lactating rats: possible role in maternal behavior. Brain Res. 970, 149–158.
Lonstein, J.S., Fleming, A.S., 2002. Parental behaviors in rats and mice. Curr. Protoc. Neurosci. Chapter 8 Unit 8 15.
Lonstein, J.S., Pereira, M., Morrell, J.I., Marler, C.A., 2014. Parental behavior. In: Plant, T.M., Zeleznik, A.J. (Eds.), Knobil and Neill's Physiology of Reproduction, fourth ed. Elsevier, pp. 2371–2438.
Lonstein, J.S., Levy, F., Fleming, A.S., 2015. Common and divergent psychobiological mechanisms underlying maternal behaviors in non-human and human mammals. Horm. Behav. 73, 156–185.
Lowry, C.A., Evans, A.K., Gasser, P.J., Hale, M.W., Staub, D.R., Shekhar, A., 2008. Topographic organization and chemoarchitecture of the dorsal raphe nucleus and the median raphe nucleus, Serotonin and Sleep: Molecular, Functional and Clinical Aspects, Birkhauser, Basel, pp. 25–67.
Lucki, I., 1998. The spectrum of behaviors influenced by serotonin. Biol. Psychiatry 44, 151–162.
Lupattelli, A., Spigset, O., Twigg, M.J., Zagorodnikova, K., Mardby, A.C., Moretti, M.E., Drozd, M., Panchaud, A., Hameen-Anttila, K., Rieutord, A., Gjergja Juraski, R., Odalovic, M., Kennedy, D., Rudolf, G., Juch, H., Passier, A., Bjornsdottir, I., Nordeng, H., 2014. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open 4, e004365.
Macbeth, A.H., Gautreaux, C., Luine, V.N., 2008. Pregnant rats show enhanced spatial memory, decreased anxiety, and altered levels of monoaminergic neurotransmitters. Brain Res. 1241, 136–147.
Maes, M., Verkerk, R., Bonaccorso, S., Ombelet, W., Bosmans, E., Scharpe, S., 2002. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci. 71, 1837–1848.
Maestripieri, D., Lindell, S.G., Higley, J.D., 2007. Intergenerational transmission of maternal behavior in rhesus macaques and its underlying mechanisms. Dev. Psychobiol. 49, 165–171.
Maestripieri, D., Hoffman, C.L., Anderson, G.M., Carter, C.S., Higley, J.D., 2009. Mother-infant interactions in free-ranging rhesus macaques: relationships between physiological and behavioral variables. Physiol. Behav. 96, 613–619.
Marcus, S.M., 2009. Depression during pregnancy: rates, risks and consequences–Motherisk Update 2008. Can. J. Clin. Pharmacol. 16, e15–e22.
Maurer-Spurej, E., Pittendreigh, C., Misri, S., 2007. Platelet serotonin levels support depression scores for women with postpartum depression. J. Psych. Neurosci. 32, 23–29.
McBride, W.J., Murphy, J.M., Gatto, G.J., Levy, A.D., Lumeng, L., Li, T.K., 1991. Serotonin and dopamine systems regulating alcohol intake. Alcohol Alcohol (Suppl 1), 411–416.
Medina, J., Workman, J.L., 2018. Maternal experience and adult neurogenesis in mammals: implications for maternal care, cognition, and mental health. J. Neurosci. Res.
Melloni Jr., R.H., Ricci, L.A., 2010. Adolescent exposure to anabolic/androgenic steroids and the neurobiology of offensive aggression: a hypothalamic neural model based on findings in pubertal Syrian hamsters. Horm. Behav. 58, 177–191.
Mileva-Seitz, V., Kennedy, J., Atkinson, L., Steiner, M., Levitan, R., Matthews, S.G., Meaney, M.J., Sokolowski, M.B., Fleming, A.S., 2011. Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants. Genes Brain Behav. 10, 325–333.
Ming, G.L., Song, H., 2005. Adult neurogenesis in the mammalian central nervous system. Annu. Rev. Neurosci. 28, 223–250.
Mitchell, C., Notterman, D., Brooks-Gunn, J., Hobcraft, J., Garfinkel, I., Jaeger, K., Kotenko, I., McLanahan, S., 2011. Role of mother's genes and environment in postpartum depression. Proc. Natl. Acad. Sci. USA 108, 8189–8193.
Mitra, S., Mucha, M., Owen, S., Bult-Ito, A., 2017. Postpartum lactation-mediated behavioral outcomes and drug responses in a spontaneous mouse model of obsessive-compulsive disorder. ACS Chem. Neurosci. 8, 2683–2697.
Moghaddam, B., Homayoun, H., 2008. Divergent plasticity of prefrontal cortex networks. Neuropsychopharmacology 33, 42–55.

Mohammad-Zadeh, L.F., Moses, L., Gwaltney-Brant, S.M., 2008. Serotonin: a review. J. Veterin. Pharmacol. Therap. 31, 187–199.
Morales, M., Margolis, E.B., 2017. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat. Rev. Neurosci. 18, 73–85.
Moses-Kolko, E.L., Wisner, K.L., Price, J.C., Berga, S.L., Drevets, W.C., Hanusa, B.H., Loucks, T.L., Meltzer, C.C., 2008. Serotonin 1A receptor reductions in postpartum depression: a positron emission tomography study. Fertility Sterility 89, 685–692.
Moses-Kolko, E.L., Price, J.C., Shah, N., Berga, S., Sereika, S.M., Fisher, P.M., Coleman, R., Becker, C., Mason, N.S., Loucks, T., Meltzer, C.C., 2011. Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. Neuropsychopharmacology 36, 2729–2740.
Nanry, K.P., Tilson, H.A., 1989. The role of 5HT1A receptors in the modulation of the acoustic startle reflex in rats. Psychopharmacology (Berl) 97, 507–513.
Numan, M., Insel, T.R., 2003. The Neurobiology of Parental Behavior. Springer, New York.
Numan, M., Stolzenberg, D.S., 2008. Hypothalamic interaction with the mesolimbic dopamine system and the regulation of maternal responsiveness. In: Bridges, R.S. (Ed.), Neurobiology of the Parental Brain. Elsevier, New York.
Numan, M., Stolzenberg, D.S., Dellevigne, A.A., Correnti, C.M., Numan, M.J., 2009. Temporary inactivation of ventral tegmental area neurons with either muscimol or baclofen reversibly disrupts maternal behavior in rats through different underlying mechanisms. Behav. Neurosci. 123, 740–751.
Numan, M., Stolzenberg, D.S., 2009. Medial preoptic area interactions with dopamine neural systems in the control of the onset and maintenance of maternal behavior in rats. Front. Neuroendocrinol. 30, 46–64.
Oberlander, T.F., Warburton, W., Misri, S., Aghajanian, J., Hertzman, C., 2006. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch. Gen. Psych. 63, 898–906.
Oberlander, T.F., Gingrich, J.A., Ansorge, M.S., 2009. Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. Clin. Pharmacol. Ther. 86, 672–677.
Oberlander, T.F., Zwaigenbaum, L., 2017. Disentangling maternal depression and antidepressant use during pregnancy as risks for autism in children. JAMA 317, 1533–1534.
Olazabal, D.E., Pereira, M., Agrati, D., Ferreira, A., Fleming, A.S., Gonzalez-Mariscal, G., Levy, F., Lucion, A.B., Morrell, J.I., Numan, M., Uriarte, N., 2013. New theoretical and experimental approaches on maternal motivation in mammals. Neurosci. Biobehav. Rev. 37, 1860–1874.
Olazabal, D.E., Young, L.J., 2006. Oxytocin receptors in the nucleus accumbens facilitate “spontaneous” maternal behavior in adult female prairie voles. Neuroscience 141, 559–568.
Olivier, J.D., Akerud, H., Kaihola, H., Pawluski, J.L., Skalkidou, A., Hogberg, U., Sundstrom-Poromaa, I., 2013. The effects of maternal depression and maternal selective serotonin reuptake inhibitor exposure on offspring. Front. Cell. Neurosci. 7, 73.
Olivier, B., Mos, J., van Oorschot, R., Hen, R., 1995. Serotonin receptors and animal models of aggressive behavior. Pharmacopsychiatry 28 (Suppl 2), 80–90.
O'Mahony, S.M., Myint, A.M., van den Hove, D., Desbonnet, L., Steinbusch, H., Leonard, B.E., 2006. Gestational stress leads to depressive-like behavioural and immunological changes in the rat. Neuroimmunomodulation 13, 82–88.
Pagani, J.H., Williams Avram, S.K., Cui, Z., Song, J., Mezey, E., Senerth, J.M., Baumann, M.H., Young, W.S., 2015. Raphe serotonin neuron-specific oxytocin receptor knockout reduces aggression without affecting anxiety-like behavior in male mice only. Genes Brain Behav. 14, 167–176.
Pasqualetti, M., Ori, M., Castagna, M., Marazziti, D., Cassano, G.B., Nardi, I., 1999. Distribution and cellular localization of the serotonin type 2C receptor messenger RNA in human brain. Neuroscience 92, 601–611.
Pawluski, J.L., Brain, U., Hammond, G.L., Oberlander, T.F., 2019. Selective serotonin reuptake inhibitor effects on neural biomarkers of perinatal depression. Arch. Womens Ment. Health.
Pawluski, J.L., Barakauskas, V.E., Galea, L.A., 2010. Pregnancy decreases oestrogen receptor alpha expression and pyknosis, but not cell proliferation or survival, in the hippocampus. J. Neuroendocrinol. 22, 248–257.
Pawluski, J.L., Charlier, T.D., Fillet, M., Houbart, V., Crispin, H.T., Steinbusch, H.W., van den Hove, D.L., 2012. Chronic fluoxetine treatment and maternal adversity differentially alter neurobehavioral outcomes in the rat dam. Behav. Brain Res. 228, 159–168.
Pawluski, J.L., Galea, L.A., 2007. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. Neuroscience 149, 53–67.
Pawluski, J.L., Gemmel, M., 2018. Perinatal SSRI medications and offspring hippocampal plasticity: interaction with maternal stress and sex. Hormones (Athens) 17, 15–24.
Pawluski, J.L., Brummelte, S., Barha, C.K., Crozier, T.M., Galea, L.A., 2009. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. Front. Neuroendocrinol. 30, 343–357.
Pawluski, J.L., van den Hove, D.L., Rayen, I., Prickaerts, J., Steinbusch, H.W., 2011. Stress and the pregnant female: Impact on hippocampal cell proliferation, but not affective-like behaviors. Horm. Behav. 59, 572–580.
Pawluski, J.L., Lambert, K.G., Kinsley, C.H., 2016. Neuroplasticity in the maternal hippocampus: relation to cognition and effects of repeated stress. Horm. Behav. 77, 86–97.
Pawluski, J.L., Lonstein, J.S., Fleming, A.S., 2017. The neurobiology of postpartum anxiety and depression. Trends Neurosci. 40, 106–120.
Pazos, A., Palacios, J.M., 1985. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res. 346, 205–230.
Pedersen, C.A., Caldwell, J.D., Walker, C., Ayers, G., Mason, G.A., 1994. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. Behav. Neurosci. 108, 1163–1171.
Perani, C.V., Slattery, D.A., 2014. Using animal models to study post-partum psychiatric disorders. Br. J. Pharmacol. 171, 4539–4555.
Pereira, M., 2016. Structural and functional plasticity in the maternal brain circuitry. New Dir. Child Adolesc. Dev. 2016, 23–46.
Pompeiano, M., Palacios, J.M., Mengod, G., 1992. Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. J. Neurosci. 12, 440–453.
Pompeiano, M., Palacios, J.M., Mengod, G., 1994. Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. Brain Res. Mol. Brain Res. 23, 163–178.
Porsolt, R.D., Brossard, G., Hautbois, C., Roux, S., 2001. Rodent models of depression: forced swimming and tail suspension behavioral despair tests in rats and mice. Curr. Protoc. Neurosci. Chapter 8 Unit 8 10A.
Puig, M.V., Gulledge, A.T., 2011. Serotonin and prefrontal cortex function: neurons, networks, and circuits. Mol. Neurobiol. 44, 449–464.
Puig, M.V., Gulledge, A.T., Lambe, E.K., Gonzalez-Burgos, G., 2015. Editorial: Neuromodulation of executive circuits. Front. Neural Circuits 9, 58.
Reebye, P.N., Morison, S.J., Panikkar, H., Misri, S., Grunau, R.E., 2002. Affect expression in prenatally psychotropic exposed and nonexposedmother–infant dyads. Infant Mental Health Journal 23, 403–416.
Salzberg, H.C., Lonstein, J.S., Stern, J.M., 2002. GABA(A) receptor regulation of kyphotic nursing and female sexual behavior in the caudal ventrolateral periaqueductal gray of postpartum rats. Neuroscience 114, 675–687.
Sanjuan, J., Martin-Santos, R., Garcia-Esteve, L., Carot, J.M., Guillamat, R., Gutierrez-Zotes, A., Gornemann, I., Canellas, F., Baca-Garcia, E., Jover, M., Navines, R., Valles, V., Vilella, E., de Diego, Y., Castro, J.A., Ivorra, J.L., Gelabert, E., Guitart, M., Labad, A., Mayoral, F., Roca, M., Gratacos, M., Costas, J., van Os, J., de Frutos, R., 2008. Mood changes after delivery: role of the serotonin transporter gene. Br. J. Psych. 193, 383–388.
Scotti, M.A., Lee, G., Gammie, S.C., 2011. Maternal defense is modulated by beta adrenergic receptors in lateral septum in mice. Behav. Neurosci. 125, 434–445.
Sekiyama, T., Nakatani, Y., Yu, X., Seki, Y., Sato-Suzuki, I., Arita, H., 2013. Increased blood serotonin concentrations are correlated with reduced tension/anxiety in healthy postpartum lactating women. Psych. Res. 209, 560–565.
Serrats, J., Mengod, G., Cortes, R., 2005. Expression of serotonin 5-HT2C receptors in GABAergic cells of the anterior raphe nuclei. J. Chem. Neuroanat. 29, 83–91.
Shahrokh, D.K., Zhang, T.Y., Diorio, J., Gratton, A., Meaney, M.J., 2010. Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology 151, 2276–2286.
Shingo, T., Gregg, C., Enwere, E., Fujikawa, H., Hassam, R., Geary, C., Cross, J.C., Weiss, S., 2003. Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. Science 299, 117–120.
Smith, C.D., Holschbach, M.A., Olsewicz, J., Lonstein, J.S., 2012. Effects of noradrenergic alpha-2 receptor antagonism or noradrenergic lesions in the ventral bed nucleus of the stria terminalis and medial preoptic area on maternal care in female rats. Psychopharmacology (Berl) 224, 263–276.
Smith, C.D., Piasecki, C.C., Weera, M., Olszewicz, J., Lonstein, J.S., 2013. Noradrenergic alpha-2 receptor modulators in the ventral bed nucleus of the stria terminalis: effects on anxiety behavior in postpartum and virgin female rats. Behav. Neurosci. 127, 582–597.
Smith, J.W., Seckl, J.R., Evans, A.T., Costall, B., Smythe, J.W., 2004. Gestational stress induces post-partum depression-like behaviour and alters maternal care in rats. Psychoneuroendocrinology 29, 227–244.
Snoeren, E.M., Veening, J.G., Olivier, B., Oosting, R.S., 2014. Serotonin 1A receptors and sexual behavior in female rats: a review. Pharmacol. Biochem. Behav. 121, 43–52.
Spielman, F.J., Mueller, R.A., Corke, B.C., 1985. Cerebrospinal fluid concentration of 5-hydroxyindoleactic acid in pregnancy. Anesthesiology 62, 193–195.
Stamatakis, A., Kalpachidou, T., Raftogianni, A., Zografou, E., Tzanou, A., Pondiki, S., Stylianopoulou, F., 2015. Rat dams exposed repeatedly to a daily brief separation from the pups exhibit increased maternal behavior, decreased anxiety and altered levels of receptors for estrogens (ERalpha, ERbeta), oxytocin and serotonin (5-HT1A) in their brain. Psychoneuroendocrinology 52, 212–228.
Stein, P., Savli, M., Wadsak, W., Mitterhauser, M., Fink, M., Spindelegger, C., Mien, L.K., Moser, U., Dudczak, R., Kletter, K., Kasper, S., Lanzenberger, R., 2008. The serotonin-1A receptor distribution in healthy men and women measured by PET and [carbonyl-11C]WAY-100635. Eur. J. Nucl. Med. Mol. Imaging 35, 2159–2168.
Steinbusch, H.W., 1981. Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. Neuroscience 6, 557–618.
Sturge-Apple, M.L., Cicchetti, D., Davies, P.T., Suor, J.H., 2012. Differential susceptibility in spillover between interparental conflict and maternal parenting practices: evidence for OXTR and 5-HTT genes. J. Fam. Psychol. 26, 431–442.
Svensson, L., Ahlenius, S., 1983. Enhancement by the putative 5-HT receptor agonist 8-OH-2-(di-n-propylamino)tetralin of the acoustic startle response in the rat. Psychopharmacology (Berl) 79, 104–107.
Svirsky, N., Levy, S., Avitsur, R., 2016. Prenatal exposure to selective serotonin reuptake inhibitors (SSRI) increases aggression and modulates maternal behavior in offspring mice. Dev. Psychobiol. 58, 71–82.
Szewczyk, B., Kotarska, K., Daigle, M., Misztak, P., Sowa-Kucma, M., Rafalo, A., Curzytek, K., Kubera, M., Basta-Kaim, A., Nowak, G., Albert, P.R., 2014. Stress-induced alterations in 5-HT1A receptor transcriptional modulators NUDR and Freud-1. Int. J. Neuropsychopharmacol. 17, 1763–1775.
Talge, N.M., Neal, C., Glover, V., 2007. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J. Child Psychol. Psych. 48, 245–261.

Terranova, J.I., Ferris, C.F., Albers, H.E., 2017. Sex differences in the regulation of offensive aggression and dominance by arginine-vasopressin. Front. Endocrinol. 8, 308.
Thomas, S.A., Palmiter, R.D., 1997. Impaired maternal behavior in mice lacking norepinephrine and epinephrine. Cell 91, 583–592.
Vazquez-Borsetti, P., Cortes, R., Artigas, F., 2009. Pyramidal neurons in rat prefrontal cortex projecting to ventral tegmental area and dorsal raphe nucleus express 5-HT2A receptors. Cereb. Cortex 19, 1678–1686.
Veen, C., Myint, A.M., Burgerhout, K.M., Schwarz, M.J., Schutze, G., Kushner, S.A., Hoogendijk, W.J., Drexhage, H.A., Bergink, V., 2016. Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression. J. Affect. Disord. 189, 298–305.
Veiga, C.P., Miczek, K.A., Lucion, A.B., Almeida, R.M., 2007. Effect of 5-HT1B receptor agonists injected into the prefrontal cortex on maternal aggression in rats. Braz. J. Med. Biol. Res. 40, 825–830.
Vitale, E.M., Washington, C.L., Lonstein, J.S., 2017. Female Reproduction State Influences Raphe and Forebrain Serotonin 1A, 2A and 2C Receptor Expression. Society for Neuroscience, Washington, D.C.
Walther, D.J., Bader, M., 2003. A unique central tryptophan hydroxylase isoform. Biochem. Pharmacol. 66, 1673–1680.
Weikum, W.M., Mayes, L.C., Grunau, R.E., Brain, U., Oberlander, T.F., 2013. The impact of prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and maternal mood on mother-infant interactions at 3 months of age. Infant Behav. Dev. 36, 485–493.
Wooten, D.W., Hillmer, A.T., Moirano, J.M., Tudorascu, D.L., Ahlers, E.O., Slesarev, M.S., Barnhart, T.E., Mukherjee, J., Schneider, M.L., Christian, B.T., 2013. 5-HT1A sex based differences in Bmax, in vivo KD, and BPND in the nonhuman primate. Neuroimage 77, 125–132.
Workman, J.L., Gobinath, A.R., Kitay, N.F., Chow, C., Brummelte, S., Galea, L.A.M., 2016. Parity modifies the effects of fluoxetine and corticosterone on behavior, stress reactivity, and hippocampal neurogenesis. Neuropharmacology 105, 443–453.
Wu, R., Gao, J., Chou, S., Davis, C., Li, M., 2016. Behavioral, pharmacological and neuroanatomical analysis of serotonin 2C receptor agonism on maternal behavior in rats. Psychoneuroendocrinology 73, 252–262.
Wu, R., Davis, C., Li, M., 2018. Behavioral mechanisms underlying the maternal disruptive effect of serotonin 5-HT2A receptor activation in Sprague-Dawley rats. J. Neural Transm. (Vienna).
Yang, Y., Qin, J., Chen, W., Sui, N., Chen, H., Li, M., 2015. Behavioral and pharmacological investigation of anxiety and maternal responsiveness of postpartum female rats in a pup elevated plus maze. Behav. Brain Res. 292, 414–427.
Yoshihara, C., Numan, M., Kuroda, K.O., 2018. Oxytocin and parental behaviors. Curr. Topics Behav. Neurosci. 35, 119–153.
Yoshimura, R., Kiyama, H., Kimura, T., Araki, T., Maeno, H., Tanizawa, O., Tohyama, M., 1993. Localization of oxytocin receptor messenger ribonucleic acid in the rat brain. Endocrinology 133, 1239–1246.
Yoshimura, H., Ogawa, N., 1991. Ethopharmacology of maternal aggression in mice: effects of diazepam and SM-3997. Eur. J. Pharmacol. 200, 147–153.
Zhang, L., Ma, W., Barker, J.L., Rubinow, D.R., 1999. Sex differences in expression of serotonin receptors (subtypes 1A and 2A) in rat brain: a possible role of testosterone. Neuroscience 94, 251–259.
Zhao, C., Li, M., 2009. Sedation and disruption of maternal motivation underlie the disruptive effects of antipsychotic treatment on rat maternal behavior. Pharmacol. Biochem. Behav. 92, 147–156.
Zhao, C., Li, M., 2010. c-Fos identification of neuroanatomical sites associated with haloperidol and clozapine disruption of maternal behavior in the rat. Neuroscience 166, 1043–1055.
Zoega, H., Kieler, H., Norgaard, M., Furu, K., Valdimarsdottir, U., Brandt, L., Haglund, B., 2015. Use of SSRI and SNRI antidepressants during pregnancy: a population-based study from Denmark, Iceland, Norway and Sweden. PLoS One 10, e0144474.