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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.

**Key words:** 5-HT; 5-hydroxytryptophan; maternal aggression; maternal brain; motherhood; neuroplasticity; parenting; postpartum depression; pregnancy; SSRI

## 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 [1; 2; 3]. However, much less is known about the function of classical neurotransmitter systems for the firm 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 behavior is, by far, dopamine (see [4; 5]). However, there have also been a number of studies manipulating gamma-aminobutyric acid (GABA)[6; 7; 8; 9; 10; 11; 12; 13] and norepinephrine [14; 15; 16; 17; 18; 19; 20].

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 [21; 22; 23]. 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 [24; 25] 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 [26; 27; 28; 29; 30; 31]. 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 [32]. 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 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 [33; 34; 35]. Of the raphe nuclei, the largest by far is the dorsal raphe nucleus (DR; B7 group) lying just below the cerebral aqueduct, and which contains about one third of all serotonin cells in the brain [36]. The nearby and more ventrally situated median raphe nucleus (MR; B8 group) 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, enkephalin, neurotensin, angiotensin) and others are not serotonergic at all but instead produce neurotransmitters including GABA, glutamate, or dopamine [36].

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 [37]. Within the raphe serotonin neurons, serotonin is packaged into synaptic vesicles via the vesicular monoamine transporter (VMAT, mainly VMAT2), and excess synaptic serotonin is returned back to serotonin cells by the serotonin transporter (SERT) [38]. 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 [39], while the MR has particularly dense projections to the septum, hypothalamus, midline thalamus, as well as the hippocampus and some areas of the cortex [39]. 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 [40]. 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 density 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 [41; 42; 43; 44]. 5-HT1A receptor expression is also very high in the DR and MR [41; 42; 43; 44; 45], where it functions as an inhibitory autoreceptor that blunts serotonin cell firing [46; 47]. In general,

activation of these presynaptic 5-HT<sub>1A</sub> 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-HT<sub>1A</sub> receptors on postsynaptic cells decreases the firing rate of the postsynaptic cells [48; 49].

5-HT<sub>2A</sub> 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 [50; 51]. 5-HT<sub>2C</sub> 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 [52; 53]. While the 5-HT<sub>2A</sub> and 2C receptors clearly have overlapping central distributions, in laboratory rats, 5-HT<sub>2A</sub> expression appears to predominate in some areas of the cortex while 5-HT<sub>2C</sub> receptor expression is higher in the septum, hypothalamus, bed nucleus of the stria terminalis, amygdala, and thalamus [54; 55]. In contrast to the inhibitory 5-HT<sub>1A</sub> receptor, activity of 5-HT<sub>2A</sub> and 2C receptors is most often excitatory [40; 56].

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 research animals and men. However, a few studies have demonstrated sex differences in central serotonin receptor densities [57; 58; 59; 60] and that these receptors are influenced by circulating ovarian hormones [61].

### **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 undergo an upregulation across the transition to motherhood and then 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 [62; 63], and while some late-pregnant and early postpartum women have lower serum levels of the serotonin precursor, tryptophan [64; 65], levels of the biochemically free (rather than total) tryptophan are higher in reproducing women [66]. It is relevant in this context to mention that total tryptophan levels alone are not responsible for determining brain concentrations of serotonin, though [67].

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 [68; 69; 70]. However, serotonin levels in the DR, as detected by immunoreactivity, do not differ between postpartum and virgin laboratory rats [69] or are lower in dams versus virgin laboratory mice [71]. 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 [72; 73], and hippocampal serotonin turnover is higher during mid-pregnancy than either before mating or during late pregnancy [74] although 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 [5; 75; 76], is higher in postpartum rats compared to virgin females [77; 78]. There is no such elevation in MPOA serotonin turnover even late in pregnancy [74; 77], 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-HT<sub>2A</sub> 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 revealed more than 50% less 5-HT<sub>2C</sub> receptor mRNA expression in the DR of early postpartum rats compared to females sacrificed during the estrus cycle or mid-pregnancy [79]. Because 5-HT<sub>2C</sub> receptors in the DR are mostly found on inhibitory GABAergic interneurons [80], lower 5-HT<sub>2C</sub> expression may in part underlie (i.e., disinhibit) the elevated DR serotonergic activity during 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 [81; 82; 83; 84; 85]. 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 survival of new neurons in the granule cell layer (GCL) of the dentate gyrus [82; 83; 86; 87; 88; 89]. 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 [90; 91; 92; 93].

The birth of new cells occurs in numerous other areas of the brain, though [88; 94]. 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 [95]. They found 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 [69]. 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 [69]. 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., increased cell survival), as well as reduced DR apoptosis [69]. While regressive events such as reduced cell genesis and increased cell death help refine neural circuits and optimize their function [96; 97], it remains to be determined if the changes in cell genesis and cell death in the female DR underlie the behavioral changes females display across the peripartum period and beyond. 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 [89; 98; 99; 100]. Adrenal secretion of

corticosterone was not responsible, however, for the relatively low postpartum cell survival in the DR [69].

#### **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 resulting in 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 low serotonin signaling in particular brain areas can derail specific 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 MR produced a 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 [101]. 5,7-DHT lesions of the caudal DR only produced minor negative effects on maternal behaviors, but still resulted in pup mortality, possibly through impaired suckling-induced pituitary prolactin release [102]. 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 by serotonin cell bodies as well as terminals of 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 conjugated to

the neurotoxin, saporin [103]. This study, using very detailed behavior observations, 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 [103]. 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 were 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 dams studied by Holschbach and colleagues were also much less maternally aggressive, which was concomitant with lower serotonin-immunoreactive fiber density in the anterior hypothalamus, a brain site previously implicated in how serotonin influences aggressive behaviors in male animals [104; 105].

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 and colleagues (2008) involving mice with a mutation of the *Pet-1* gene (a E26 transformation-specific transcription factor critical for serotonin neuron development) [106], severe restriction of the central serotonin cell population was associated with impaired pup retrieval, nursing, and nest building [107]. 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 [108]. Other mouse mutants with impaired serotonin metabolism also showed reduced reproductive fitness and abnormal maternal behaviors [109; 110]. 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 structures (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 [111]. 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 [112]. 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 [113] or more [114; 115] sensitive mothering styles compared to mothers with high-transcription *5HTT* polymorphisms (*l* allele). Work by Sturge-Apple and colleagues (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 relatively insensitive mothers and more likely to likely use harsh parenting when conflict was high [116]. 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 [117].

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 involving manipulation of 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 [118]). Almost all experimental work on the role of OTRs in caregiving behavior have focused on forebrain sites such as the MPOA and nucleus accumbens (e.g., [119; 120; 121]). 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 [121; 122]. OTRs are expressed in the DR, but not MR [123; 124], 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 [123](Grieb, Manfredsson and Lonstein, in preparation). This suggests that enhanced DR sensitivity to oxytocin is 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 also decreased on DR GABAergic cells (Grieb, Manfredsson and Lonstein, in preparation). Because many GABA-synthesizing cells within the DR are inhibitory interneurons that tonically suppress serotonin cell firing [125], these results collectively suggest that the peripartum period involves enhanced direct OT stimulation of DR serotonergic cells as well as reduced inhibition of them by OT-sensitive local GABAergic inputs.

The importance of OTR signaling in the DR for maternal caregiving behaviors was recently 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 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 (Greib, Manfredsson, and Lonstein, in preparation). Another recent study involving OTR gene knockout only from 5-HT cells of the DR of postpartum mice instead found no effects on retrieval, and no effects on pup licking and general mother-litter contact during the 10 minutes after retrieval [126]. This 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 here 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 [127]. The 5-HT1A receptor is implicated in many motivated behaviors, such as eating, drinking, sexual behavior, aggression, and drug abuse [22; 23; 128; 129; 130; 131; 132; 133; 134], 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 [135], but not in other maternal responses such as retrieval or nursing [135; 136; 137; 138]. More specifically, acute or chronic stimulation of 5-HT1A receptors by peripheral injection of agonist drugs suppressed maternal aggression in postpartum female rats [139]. 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 corticomедial amygdala nucleus reduced maternal



aggression [140], whereas agonizing 5-HT1A receptors in the medial septum or DR increased maternal attacks [140; 141]. Therefore, the inhibitory effect of 5-HT1A receptor agonism on maternal aggression involves a complex neural network, and is likely mediated by both pre-synaptic 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 and colleagues (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 [142]. 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, and mother rats under the 8-OH-DPAT treatment traveled a similar distance in their cage with similar speed as the controls [143; 144; 145]. Li and colleagues did find that activating 5-HT1A receptors disrupted prepulse inhibition (PPI, a measure of sensorimotor gating) [146; 147; 148] and enhanced basal startle response (a putative measure of stress sensitivity) [142]. 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-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in maternal behavior*

The 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors are involved in many behaviors involving sensorimotor, attentional, emotional, learning, memory, and executive functions [22; 23]. The first studies on how 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors affect maternal behavior showed that infusing a 5-HT<sub>2A/2C</sub> agonist (DOI, 2,5-dimethoxy-4-iodo-amphetamine) into the lateral ventricles of postpartum rats decreased maternal attacks toward a male rat [137]. 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-HT<sub>2A/2C</sub> receptors found disruption in the active components of maternal behavior such as pup approach, pup retrieval and nest building [149; 150]. Interestingly, the 5-HT<sub>2A/2C</sub> agonist DOI (1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) also disrupts maternal behavior [151] by causing less pup licking, less activity and fewer frequencies of rearing and self-grooming, which often interrupted the normal sequence of pup-directed responses (e.g. pup retrieval and pup licking fragmentation), indicating disrupted organization of microregulatory maternal responses [151]. Because both the 5-HT<sub>2A/2C</sub> receptor antagonist clozapine/olanzapine and agonist DOI disrupted maternal behavior, these early studies suggest that balanced 5-HT<sub>2</sub> 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-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors help 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 discussed 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 [152]. Blockade of 5-HT2A receptors with a highly selective 5-HT2A antagonist, MDL 100907, had no effect [153]. 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 [152]. Similarly, selectively activating 5-HT2C receptors with the agonist MK 212 also disrupted pup retrieval, pup licking, pup nursing, and nest building [153], whereas blocking 5-HT2C receptors with the selective antagonist SB242084 had no effect [145]. 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 MK212-induced maternal disruption [145]. These results demonstrate that

only activation, not blockade, of 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub> 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 [75; 154; 155; 156]. Activating 5-HT<sub>2A</sub> receptors by TCB-2 and activating 5-HT<sub>2C</sub> receptors by MK 212 could potentially disrupt any of these processes to affect caregiving behavior. Given the prominent roles of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in motivation, affect, and executive function [23], activating 5-HT<sub>2A</sub> receptors may particularly disrupt executive control of maternal activities (behavioral organization) whereas activating 5-HT<sub>2C</sub> receptors may especially decrease maternal motivation. To examine whether activation of 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub> receptors suppress maternal motivation [144; 145], Wu and colleagues employed a pup separation paradigm to increase maternal motivation [157]. If pup separation could ameliorate the disruption induced by 5-HT<sub>2A</sub> 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-HT<sub>2A</sub> agonist TCB-2 or the 5HT<sub>2C</sub> agonist MK 212, or vehicle, and tested after either a 4-h pup-separation or no-pup-separation [144; 145]. 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-HT<sub>2A</sub> agonist-induced maternal disruption [144]. In contrast, pup separation significantly attenuated the 5-HT<sub>2C</sub> agonist-induced decrease in retrieval [145]. Thus, activating the 5-HT<sub>2C</sub>, but not the 5-HT<sub>2A</sub>, receptor disrupts maternal behavior by suppressing mothers' motivation to interact with pups. Because pup

separation did not completely reverse the effects of 5-HT<sub>2C</sub> agonism, other behavioral effects of 5-HT<sub>2C</sub> activity may also contribute to its impairment of caregiving, and may be mediated by distinct 5-HT<sub>2C</sub> receptor-sensitive brain networks (e.g., prefrontal cortex (PFC), nucleus accumbens, and VTA, etc.).

To examine whether activating 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub> 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 [158; 159]. It measures perceptual, emotional, and motivational responses toward pups that do not involve consummatory responses and learning (different from conditioned place preference) [156]. Dams treated with the 5-HT<sub>2A</sub> agonist TCB-2, or the 5-HT<sub>2C</sub> agonist MK 212, showed significantly less pup preference (Wu et al., unpublished data). The disruptive effect of activating the 5-HT<sub>2C</sub> receptors on pup preference is consistent with the pup separation data, indicating a motivational action, while the effect of activating the 5-HT<sub>2A</sub> receptors is not. To further examine this issue, Wu and colleagues (2018) tested TCB-2-treated dams in a pup-male preference test to determine whether 5-HT<sub>2A</sub> receptors activity reduced pup preference when dams were faced with two socially rewarding stimuli [160; 161]. Activating the 5-HT<sub>2A</sub> receptor increased pup preference in this test [144] such that dams treated with the 5-HT<sub>2A</sub> 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-HT<sub>2A</sub> agonist TCB-2 disrupts maternal behavior by suppressing maternal motivation. It is unknown how it does so, but perhaps agonism of the 5-HT<sub>2A</sub> 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-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors affect distinct neural networks in the maternal brain*

If activating 5-HT<sub>2A</sub> receptors by TCB-2 impairs the executive control or behavioral organization of maternal activities [144], 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 [162; 163; 164; 165]. The mPFC is also densely interconnected with numerous cortical and subcortical structures, including the serotonergic neurons in the raphe nuclei [166]. In return, the mPFC sends projections back to the raphe nuclei for the feedback control of cortical serotonin release [167; 168]. However, 5-HT<sub>2A</sub> 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) [169]. Acute subcutaneous injection of the 5-HT<sub>2C</sub> 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 [145; 152]. The different patterns of drug-induced Fos expression clearly indicate that the 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptor activation involves distinct neural networks, despite their similar disruptive effects on maternal behaviors. Neither the precise neural networks involved, nor why 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> 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 and colleagues (2018) found that 5-HT<sub>2A</sub> agonist TCB-2 into the mPFC

suppressed pup retrieval, whereas intra-MPOA infusion had no effect [152]. With regards to the 5-HT<sub>2C</sub> receptors, Wu and colleagues (2016) targeted three brain regions by microinjecting the 5-HT<sub>2C</sub> agonist MK 212 into the nucleus accumbens shell, mPFC, or MPOA but found no effects on any maternal caregiving behaviors [145]. Recently, Li and colleagues examined the VTA due to its involvement in motivation and reward processing [170]. The 5-HT<sub>2C</sub> agonist MK 212 microinjected into the VTA disrupted pup retrieval and pup preference, supporting the hypothesis that 5-HT<sub>2C</sub> receptors in the VTA are involved in maternal motivation. Based on these findings a general hypothesis can be proposed suggesting that 5-HT<sub>2A</sub> receptors in the mPFC are involved in mediating maternal behavior through an executive control mechanism, whereas the 5-HT<sub>2C</sub> receptors in the VTA are involved in maternal motivation. Future work is needed to delineate the precise functional role of 5-HT<sub>2A</sub>-containing or 5-HT<sub>2C</sub>-containing neural substrates within each brain region and pinpoint the neural circuitry through which these 5-HT<sub>2</sub> 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%)[171]. These disorders can have detrimental effects on the mother, child and family [171; 172; 173; 174]. Mothers with depression, anxiety, and frequent stress often show changes in their offspring caregiving behaviors [171; 175; 176]. For example, depressed and anxious mothers respond less sensitively, and more negatively, to their infants compared with non-depressed mothers [177; 178; 179]. Depressed mother-infant dyads also have reduced

synchrony – involving less mutual attention, vocal and visual communications, touching, and smiling - compared to healthy controls [177; 178]. 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 [175; 180; 181; 182; 183]. 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 [184; 185], 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 [186], and there is a significant positive association between postpartum depressive symptoms and expression of *5-HTT* genotypes [187], specifically that short allele carriers of *5-HTT* have an increased risk of developing PPD, particularly in women with low socioeconomic status [188; 189]. When investigating serotonin in the maternal brain in humans, Moses-Kolko and colleagues (2008) show that 5-HT<sub>1A</sub> receptor binding potential in women diagnosed with PPD is reduced 20%–28% relative to healthy postpartum women [190]. Of the brain areas investigated, the most significant reductions in 5-HT<sub>1A</sub> 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 and colleagues (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 [191]. Other



work in postpartum rat dams shows that repeated separation from pups, which may be a psychological stressor for the dams, reduces 5-HT<sub>1A</sub> receptor levels in a number of brain areas including the hippocampus, PFC, MPOA, and central amygdala [192]. Five months after gestational stress, 5-HT<sub>1A</sub> receptor mRNA levels remain reduced in the PFC and hippocampus of rat dams [193]. 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 [194]. 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 serotonergic 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 [27; 28; 29; 30; 31; 195]. 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 [196], raising questions about the safety for the child of using these medications to treat maternal mental illnesses [197; 198; 199; 200]. However, untreated maternal mental illness can also affect the maternal and fetal serotonergic system [191; 201; 202] and SSRI effects cannot be completely disentangled from the effect of maternal mental illness on the mother and child [203; 204]. While it is beyond the scope of this review to cover the impact of these factors on the

mother *and* offspring [26; 194; 197; 198; 199; 205; 206], 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 and colleagues (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 [207]. 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 [208]. This study also showed that maternal depression is related to infant readiness to play in both control and SSRI-treated dyads [208], 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 [209] (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 [210]. SSRI effects on maternal behaviors are also evident with postpartum SSRI treatment, with treated rat dams showing less passive nursing [211], more kyphotic nursing [212; 213], and less nest building [211; 213; 214]. Others have found that peripartum SSRI treatment (SSRIs during gestation *and*

postpartum) can also increase nursing in rat dams [215]. These same effects of peripartum SSRIs on maternal behavior are not evident in mouse dams [216]. 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 [12].

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 [211] and alter the amount of time spent off the nest [210; 213; 217]. An additional study using peripartum administration of venlafaxine, a serotonin norepinephrine reuptake inhibitor medication, showed that treated dams spend more nursing and less pup licking, regardless of maternal stress exposure [218]. Thus, clinical research and work with laboratory rodent models report that maternal 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 [219]. 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 [220]. When specifically looking at the central serotonin system in rodent models, Gemmel and colleagues (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 [191]. 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 [221; 222; 223]. As mentioned above, previous research also shows that the hippocampus has a high degree of plasticity during pregnancy and the postpartum period [82; 83; 85; 224; 225], 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 [211] as well as a decrease in the density of immature neurons around the same period [217]. 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 [213] or the number of immature neurons in the dentate gyrus [191; 211; 213]. When administered perinatally from gestation day 10 to postpartum day 28, and thus for a longer period of time, fluoxetine [215], and venlafaxine [218], 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 [213], 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 [191]. 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 [226]. 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 [227]) in models of maternal depression [211; 213; 217; 226], only one found that postpartum SSRI treatment clearly prevented the effects of maternal stress on depressive-like behaviors [226]. 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) [228].

## 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 vector, 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 of various central serotonin receptors in maternal behavior, this issue is far from settled, especially for 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> 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-HT<sub>2A</sub> and 5-HT<sub>2C</sub> on the mesolimbic and mesocortical dopamine activity, and ample expression of both receptors in the mPFC, nucleus accumbens and VTA [229], it is highly likely that 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors may mediate maternal behavior by affecting dopamine. The potential interactions among the 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> 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 [75; 155; 230] and their demonstrated regulation of serotonin activity and function (cf. [61; 231; 232], it would be valuable to study how serotonin's effects on the maternal brain and behavior are impacted by these factors. Future research should also focus on dissecting the precise neurocircuits that support the maternal regulatory effects of serotonin receptors [233; 234].

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), how they 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 diseased maternal states. With increased understanding of 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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**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 et al. 1994
5-HT1A agonist	Postpartum	Rat	↓maternal aggression	Olivier et al. 1995
5-HT2A/2C agonist				
5-HT1A agonist in MR, dPAG, amygdala	PD7	Rat	↓maternal aggression	De Almeida & Lucien 1997
5-HT1A agonist to DR and septum			↑maternal aggression	
Pet1 <sup>-/-</sup>	-	Mouse	↓pup retrieval, ↓nursing, ↓nest building	Lerch-Haner et al. 2008
TPH2 <sup>-/-</sup>	-	Mouse	↓pup retrieval, ↓nursing	Alenina et al. 2009/Angoa-Perez et

				al. 2014
5-HT2C agonist	PD5, 7, 9	Rat	↓pup retrieval, ↓pup licking, ↓nursing, ↓nest building	Chen et al. 2014
5-HT2A antagonist			No effect of antagonist	
5-HT2C agonist	PD4-7	Rat	↓maternal behaviors due to ↓maternal motivation	Wu et al. 2016
5-HT2C antagonist			No effect of antagonist	
5-HT2C agonist to NAc, mPFC, MPOA			No effects on maternal behaviors of microinjections	
5-HT1A agonist	PD3, 5, 7	Rat	↓pup retrieval, ↓pup licking, ↓nest building	Li et al. 2018
5-HT1A antagonist			-no effect of antagonist	
5-HT2A agonist	PD8	Rat	↓pup retrieval, ↓nest building, ↓hovering	Gao et al. 2018
5-HT2A antagonist			No effect of antagonist	
5-HT2A agonist to mPFC or MPOA			Microinjection to mPFC, not MPOA, disrupted maternal behavior	
5-HT2A agonist	PD4-6/12	Rat	↓pup retrieval, ↓pup licking, ↓nursing, ↓nest building	Wu et al. 2018

↑ pup preference

5-HT cell-body specific lesions of DR	GD15 or PD2	Rat	GD15: ↑ pup licking, ↑ hovering over, ↓ maternal aggression PD2: ↓ pup licking, ↑ kyphosis, ↓ supine nursing ↓ maternal aggression	Holschbach et al. 2018
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**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-	Gemmel et al., 2016

			HT and synaptophysin in PFC -no effects on DG immature neurons	
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 <sup>a</sup>	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 (10 mg/kg/day; biscuit)	GD10-PD28	Rat	↑ nursing only on PD4-6 ↑ DG immature neurons	Gemmel et al., 2018

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\*only in group also treated with high levels of corticosterone or restraint stressed

<sup>a</sup> mothers in the study exposed *in utero*

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### Highlights

- Serotonin is involved motherhood and neuroplasticity in the maternal brain
- Effects of serotonin on maternal behaviors are brain site-specific
- 5-HT1A, 5-HT2A and 5-HT2C receptors are involved in maternal behaviors
- Maternal mood and SSRIs affect the serotonin system and maternal behavior
- More research is needed on serotonin in maternal mental health

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