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Several other studies addressing cord blood methylation made use of a candidate-based approach. For example, Oberlander and colleagues (2008) studied the degree of methylation at the *NR3C1* locus in both maternal and neonatal blood samples and found that children of women with mid-to-third trimester depressed mood displayed increased levels of DNA methylation at various CpG sites within exon 1F of *NR3C1* in the umbilical cord blood. They also found that maternal depressed mood during the second trimester was associated with increased methylation levels at one of those same CpG sites in the newborn. However, they found no association between use of SSRIs during pregnancy and the degree of methylation in the cord blood of the newborn (Oberlander et al., 2008b). In a similar study, Non et al. (2014) specifically investigated the degree of methylation in *NR3C1* in umbilical cord blood, but were not able to replicate the abovementioned findings. However, they observe a marginally increased level of methylation at another CpG site within the *NR3C1* gene associated with non-medicated maternal depression or anxiety. Of note, none of the genome-wide array-based approaches referred to above found

differences in the degree of methylation at any CpG sites related to this gene (Non et al., 2014). Two other studies investigated the degree of methylation at the *BDNF* gene, a well-known epigenetically regulated candidate gene and biomarker in mood and anxiety disorders (Bouille et al., 2012). However, both Non and colleagues (2014), and a study by Devlin et al. (2010), found no significant associations of *BDNF* methylation levels with antenatal mood scores or prenatal SSRI exposure. However, that same study showed that genetic variation in *MTHFR*, encoding for methylenetetrahydro-folate reductase, an important enzyme in the generation of methyl groups for DNA methylation, was associated with 2nd trimester depressed mood (Devlin et al., 2010). A study by Soubry et al. (2011) highlighted two imprinted differentially methylated regions (DMRs) of the *IGF2* and *H19* gene, the latter of which requires promotor hypermethylation of the paternal allele to allow expression of the paternal allele of *IGF2*. Although Soubry and colleagues did not find differences in mean methylation levels when comparing umbilical cord blood of women with or without depression during pregnancy, they did observe that antidepressant exposure in African-American women was associated with a higher methylation at the *H19* locus (Soubry et al., 2011). Another well-known candidate gene is *SLC6A4*, encoding the serotonin transporter (SERT or 5-HTT). Non and colleagues (2014) showed that SSRI exposure was associated with a slight decrease in methylation in one CpG site at the *SLC6A4* locus. In addition, Devlin et al. (2010) showed that the degree of methylation at two CpG sites within the *SLC6A4* promoter was lower in newborn cord blood from mothers with increased depressed mood symptoms at 26 weeks of gestation, however, this methylation had no association with SSRI exposure during pregnancy. The study by Non et al. further identified significant differential methylation in response to SSRI exposure at the *NFKB2* and *DNMT3a* genes, while no changes were observed for *CRHR1*, *CRHR2*, *DNMT1*, *FKBP5*, *NFKB1*, or *NFKB2*.

A recent study by Gurnot and colleagues (2015) using an array-based approach followed by a detailed candidate gene pyrosequencing approach examined neonatal DNA methylation in relation to differences in birth outcomes. They showed that lower 3rd trimester maternal depressed mood symptoms only in SSRI-exposed neonates was associated with increased cord blood DNA methylation status at *CYP2E1*, indicating a maternal mood and SSRI exposure interaction. In addition, higher DNA methylation levels at several CpG sites within the interrogated *CYP2E1* region were associated with increased birth weight independently of prenatal maternal mood, SSRI drug exposure, and gestational age at birth (Gurnot et al., 2015).

#### **4.3. Animal Models**

Neonatal exposure to fluoxetine increased hippocampal expression of histone deacetylase 4 (HDAC4) from weaning through 18 months of age, concomitant with increased H3 and H4 acetylation at the rat *HDAC4* promoter (Sarkar et al., 2014a). Interestingly, overexpression of *HDAC4* was associated with increased depressive-like behaviors in postnally fluoxetine exposure offspring. This effect was reversed if HDAC4 overexpression was prevented (Sarkar et al., 2014a). reversed the behavioral effects of perinatal fluoxetine exposure in the forced swim test. Perinatal fluoxetine exposure also affects methylation, decreasing global DNA methylation in the hippocampus around weaning (Toffoli et al., 2014). Furthermore, early life exposure to paroxetine downregulated the expression of DNMT3a and the methyl-binding domain protein (MeCP) and reduced global DNA methylation in the hippocampus, but not in the amygdala, septum, nor mPFC, during the second week of life (Glover et al., 2015). As a well-known target of epigenetic regulation and a biomarker for mood-related disorders, *BDNF* is an interesting target of investigation in these studies. Indeed, adult female Sprague-Dawley rat offspring neonatally exposed to fluoxetine and maternal stress showed altered hippocampal epigenetic

regulation of *BDNF* associated with increased behavioral despair (Boulle et al., 2016). More specifically, developmental SSRI exposure significantly increased behavioral despair measures on the forced swim test and decreased hippocampal *BDNF* exon IV mRNA levels, concomitant with increased levels of the repressive histone 3 lysine 27 tri-methylation mark at the corresponding promoter.

Future larger-sampled studies, correcting for e.g. the level of maternal depression and/or other maternal illness, and maternal use of other types of medication, could use whole genome-based sequencing to identify possible new differentially methylated sites. Understanding the role of epigenetics in mediating the effects of early-life stress and exposure to SSRIs will be of pivotal importance for development of novel therapeutic approaches.

### **5. Additional Considerations**

Many of the conclusions about the effects of perinatal exposure to SSRIs have been made from studies in animal models where healthy dams and offspring were used. However, over the past few years a growing body of research has shown that perinatal SSRI effects on offspring neurobehavioral outcomes can differ when using a model of maternal stress or depression (Gemmel et al., 2015; Gemmel et al., 2016; Gobinath et al., 2016; Ishiwata et al., 2005; Ko et al., 2014; Pawluski et al., 2012b; Pawluski et al., 2015; Pawluski et al., 2012c; Pawluski et al., 2011; Rayen et al., 2015; Rayen et al., 2013b, 2014; Rayen et al., 2011). This interaction between perinatal SSRIs and maternal stress is perhaps not surprising as we know that exposure to maternal stress alone can alter the developing serotonergic system with prenatal stress increasing TPH-ir cells in the dorsal raphe nucleus (Miyagawa et al., 2011; Miyagawa et al., 2015) and increasing 5HT synthesis in the fetal brain (Peters, 1982, 1990). Thus, it is important that appropriate models of aspects of maternal mental illness be used when animal work explores

perinatal SSRI effects on development. In this regard, it is also important that clinical research control for levels of maternal depression and anxiety in study participants prescribed, and not prescribed, SSRIs; particularly as SSRI medications often do not alleviate all aspects of maternal mental illness (Molyneaux et al., 2014) and both exposure to maternal depression and anxiety can have long-term effects on child development (Marcus, 2009; Olivier et al., 2013; Talge et al., 2007).

It is also worthwhile to consider that women are increasingly likely to continue SSRI treatment during the perinatal period if they have previously suffered from stress, anxiety and depression (which serves as one of the major risk factors for developing perinatal depression) (Pawluski et al., 2017). Therefore, future animal studies investigating the pre-gestational effects of maternal depression and SSRI exposure would be valuable to understanding the extent to which SSRIs may impact offspring development.

### **Conclusions**

One of the strongest predictors of mental illness and behavioral disorders is early-life stress (Eiland and Romeo, 2013). However, both clinical and pre-clinical work demonstrate that offspring exposed perinatally to SSRIs, used to treat maternal stress-related disorders, may also be at risk for altered development of a host of social affiliative behaviors (Homberg et al., 2010; Man et al., 2015; Misri et al., 2006; Oberlander et al., 2010; Oberlander et al., 2007; Pawluski et al., 2012b; Rayen et al., 2013b, 2014) on a behavioral, neural and epigenetic level; these effects can be altered by maternal care as well as maternal stress and depression (Figure 1). It may be that perinatal SSRIs protect against some aspects of maternal mental illness, but also independently affect the development of social behavior-mediating neural circuitry in the hippocampus, PFC, amygdala, and hypothalamus, at a physiological, cellular, and epigenetic

level. One of the more recently studied examples of how early-life alterations in the serotonergic environment may impact the development of social behaviors and relevant neurobiology is observed in the reported link between prenatal SSRIs and increased risk of autistic-like behaviors. More than 25% of individuals diagnosed with ASD display hyperserotonemia, which was one of the first classified clinical biomarkers indicative of the disorder (Muller et al., 2016). Individuals with ASD, as with perinatal SSRI exposure, show neurobiological and epigenetic abnormalities in all the above mentioned brain regions (Lotspeich and Ciaranello, 1993; Muller et al., 2016), as well as demonstrate increased aggressive traits which are, interestingly, often treated with medications to regulate serotonergic system functioning (Fitzpatrick et al., 2016). Therefore, it is clear that serotonin plays a critical role in regulating neurobehavioral outcomes, and in some cases may be a risk factor for the development of neurodevelopmental disorders.

Given the vital role of the serotonergic system throughout development and adulthood on a host of neurobehavioral outcomes, it is not surprising that perinatal SSRIs, which can increase serotonin levels in offspring, can have a long-term impact on neurobehavioral development. However, it should not be forgotten that exposure to maternal stress-related disorders can also alter the developing serotonergic system (Miyagawa et al., 2011; Miyagawa et al., 2015; Peters, 1982, 1990; Zohar et al., 2014) and thus more research is needed to determine the complexity of early life exposure to maternal mental illness and perinatal SSRIs on mother and child. The risks and benefits of SSRIs, as well as additional treatments for maternal affective disorders, such as psychotherapy, diet, and exercise, need further investigation and will aid in developing safe and effective treatments for both mother and child (Pawluski et al., 2017).



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## Figure Captions

Figure 1. Schematic representation of key factors influencing the development of social behavior after SSRI exposure. Present in the figure are links between maternal mood, maternal care, and SSRI medications that can all act to alter social behaviors. In addition, the age and sex/gender of the offspring are key factors mediating these effects.

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**Table 1. Summary of individual SRI medications prescribed during the perinatal period to women.** <sup>1</sup>Bakker et al. 2007 (The Netherlands), <sup>2</sup>Zoega et al. 2015 (Nordic countries), <sup>3</sup>Oberlander et al. 2008 (British Columbia, Canada; % of total prescriptions in pregnancy women), <sup>4</sup>Alwan et al. 2011 (United States). Common dose information from www.cms.gov.

SRI	Trade Name	FDA Rating During Pregnancy	Prescription Rate (% total pregnancies)	Prescription Rate (% total prescriptions during pregnancy)	Common Starting Dose in Adults <sup>5</sup>	Common Maximum Dose in Adults <sup>5</sup>
<b>Selective Serotonin Reuptake Inhibitor (SSRI)</b>						
Fluoxetine	Prozac	C	0.45 <sup>1</sup> 0.22-1.8 <sup>2</sup> 1.1 <sup>4</sup>	5.2 <sup>3</sup>	20 mg/day	80 mg/day
Sertraline	Zoloft	C	0.07 <sup>1</sup> 0.3-3.32 <sup>2</sup> 1.6 <sup>4</sup>	4.8 <sup>3</sup>	25 mg/day	200 mg/day
Paroxetine	Paxil	D	1.2 <sup>1</sup> 0.08-0.59 <sup>2</sup> 0.8 <sup>4</sup>	8.2 <sup>3</sup>	20 mg/day	60 mg/day
Citalopram	Celexa	C	0.18 <sup>1</sup> 0.24-1.88 <sup>2</sup> 0.2 <sup>4</sup>	0.57 <sup>3</sup>	20 mg/day	40 mg/day
Escitalopram	Lexapro	C	0.36-1.53 <sup>2</sup> 0.2 <sup>4</sup>	-	10 mg/day	20 mg/day
Fluvoxamine	Luvox	C	0.26 <sup>1</sup>	0.95 <sup>3</sup>	50 mg/day	300 mg/day
<b>Serotonin Norepinephrine Reuptake Inhibitor (SNRI)</b>						
Venlafaxine	Effexor	C	0.27-0.61 <sup>2</sup> 0.2 <sup>4</sup>	1.4 <sup>3</sup>	75 mg/day	375 mg/day
Duloxetine	Cymbalta	C	0.02-0.15 <sup>2</sup>		40-60 mg/day	120 mg/day

<sup>5</sup><https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ad-adult-dosingchart.pdf>

**Table 2. Summary of laboratory rodent research investigating how perinatal SSRIs affect offspring social behaviors. P=postnatal day, G=gestation day, s.c.=subcutaneous**

Age investigated	Sex	Species	SSRI (dose/day)	SSRI admin	Results	Comments	Reference
<b>Play Behavior</b>							
P28-35, P87	Male/Female	Wistar rat	Fluoxetine (12mg/kg)	G11-P0	Fluoxetine reduces pinning, boxing/wrestling and social exploration frequency at P28-35. Fluoxetine reduces self-grooming and exploration at P87.	Oral injection to dam.	Olivier et al. 2011
P24-28	Male/Female	Long Evans rat	Citalopram (20mg/kg)	P8-21	Citalopram reduces boxing/wrestling, following/chasing and exploration (rearing) and increases self-grooming (stereotypic behavior).	s.c. injections to offspring	Khatri et al. 2014
P32-34	Male/Female	Long Evans rat	Citalopram (10mg/kg) Fluoxetine (5mg/kg)	P8-21	Citalopram reduces male and female boxing and male pinning while increasing male stereotypic behaviors.	s.c. injections to offspring	Rodriguez-Porcel et al. 2011
P32-34	Male/Female	Long Evans rat	Citalopram (20mg/kg)	P8-21	Citalopram reduces juvenile play in male, not female, offspring.	s.c. injections to offspring	Simpson et al, 2011
P>56	Male	Wistar rat	Fluoxetine (20mg/kg)	P0-4	Fluoxetine increases sniffing, contact behaviors, and total social interaction time.	s.c. injections to offspring	Ko et al, 2014
<b>Social Interaction &amp; Social Preference</b>							
P30-40 P>60	Male/Female	Long Evans rat	Citalopram (20mg/kg)	P8-21	Citalopram reduces conspecific/object contacts at P30-40 and P>60.	s.c. injections to offspring	Simpson et al. 2011
P78 P101	Male/Female	Long Evans rat	Citalopram (10mg/kg) Fluoxetine (5mg/kg)	P8-21	Citalopram and fluoxetine reduces male and female conspecific/object contacts at P78 and P101.	s.c. injections to offspring	Rodriguez-Porcel et al. 2011



P45 P85	Male/Female	Long Evans rat	Citalopram (20mg/kg)	P8-21	Citalopram reduces male and female conspecific/object contacts at P45 and 85.	s.c. injections to offspring	Khatri et al. 2014
P34 P76	Male/Female	Norway High/Low lines	Fluoxetine (10mg/kg)	P2-7	Fluoxetine reduces time spent with a novel conspecific at P34 and 76.	Oral gavage to offspring	Zimmerberg et al. 2015
P28-31 P49-52	Male/Female	ICR (CD1) mice	Fluoxetine (10mg/kg)	G1-P0	Adult animals spend more time with social conspecific, particularly males. Fluoxetine increases female conspecific interaction at P28-31. Fluoxetine increases number and duration of aggressive attacks in males at P49-52.	s.c. injections to dams	Svirsky et al. 2016
P>60	Male	C57BL/6 mice	Fluoxetine (25mg/kg)	G15-P12	Fluoxetine increases aggressive attacks and time spent in aggressive behaviors. Fluoxetine did not affect time spent in social behavior with a resident intruder.	Administration via drinking water to dams.	Kiryanova et al. 2014
P90-120	Males	Wistar rat	Citalopram (20mg/kg/3days)	P1-19	Citalopram reduces duration of aggressive attacks on a resident intruder.	s.c. injections to offspring	Manhaes de Castro et al. 2001

### Reproductive Behavior

P103-111	Female	Sprague-Dawley rat	Fluoxetine (5 mg/kg)	P1-21	Fluoxetine facilitates sexual behaviors, regardless of maternal stress exposure, and does not affect SDN-POA, ACPv and pBST brain areas, or estrous cyclicity.	Osmotic minipump to the dam; model of maternal stress	Rayen et al. 2014
P80-88	Male	Sprague-Dawley rat	Fluoxetine (5mg/kg)	P1-21	Fluoxetine exposure inhibits sexual behavior. Fluoxetine after maternal stress decreases the area of the SDN-POA.	Osmotic minipump to the dam; model of maternal stress	Rayen et al. 2013
P>100	Male	Long Evans rat	Citalopram (5, 10 or 20mg/kg)	P8-21	Citalopram exposure results in dose-dependent reductions mounting,	s.c. injections to offspring	Harris et al. 2012

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intromissions, and ejaculations

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P133	Male	Wistar rat	Fluoxetine (12mg/kg)	G11-21	Fluoxetine does not affect male sexual behavior	s.c. injections to dam	Oliver et al. 2011
P153-184	Male	Long Evans rat	Fluoxetine (5mg/kg)	P8-21	Fluoxetine disrupts male sexual behavior: fewer mounts, intromissions and ejaculations	s.c. injections to offspring	Rodriguez Porcel et al. 2011
P80	Male	Wistar rat	Fluoxetine (5 and 10 mg/kg)	G13-20	Fluoxetine has no effect on male sex behavior	s.c. injections to dam	Cagliano et al. 2008
P>90	Male	Swiss mice	Fluoxetine (7.5mg/kg)	G0-P21	Fluoxetine impairs sexual motivation	Oral gavage to dam	Gouvea et al. 2008
P90	Male	Long Evans rat	Citalopram (5mg/kg)	P8-21	Citalopram decreases sexual activity: fewer mounts, intromissions and ejaculations	s.c. injections to offspring	Maciag et al. 2006

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#### **Maternal Behavior**

P>60	Female (F1)	ICR (CD1) mice	Fluoxetine (10mg/kg)	G1-P0	Fluoxetine reduces maternal behavior on PD1 via reduced nest quality and delayed pup retrieval. Fluoxetine exposed females showed more adaptability in maternal behaviors, with greater improvements in maternal care on PD 2 and 3.	s.c. injections to dams (F0)	Svirsky et al. 2016
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### **Highlights**

- Serotonin and SSRIs are mediators of maternal care-giving behaviors
- Perinatal SSRIs affect development of play, social, and reproductive behaviors
- Perinatal SSRIs and maternal stress alter the developing serotonergic system
- Perinatal SSRIs alter neuroplasticity and epigenetic profiles in offspring

Revised manuscript