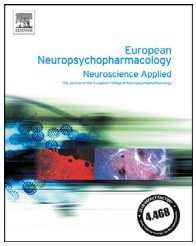
European Neuropsychopharmacology (2019) 29, 1169–1184

www.elsevier.com/locate/euroneuro



REVIEW

The effects of perinatal SSRI exposure on anxious behavior and neurobiology in rodent and human offspring

Z.A. Grieb[a,*], **C.M. Ragan**[b]

[a] *Neuroscience Institute, 880 Petit Science Center, Georgia State University, Atlanta, GA 30303, United States*
[b] *Department of Psychology, Library Student Faculty Building, Room 63, Purdue University Northwest, Westville, IN 46391, United States*

Received 8 April 2019; received in revised form 10 July 2019; accepted 27 July 2019

KEYWORDS
SSRI;
Anxiety;
Fluoxetine;
Prenatal;
Postnatal;
Development

Abstract
While the postpartum period is typically associated with increased positive affect, many women will develop a depressive- or anxiety-related disorder during this time, which can degrade the mother-infant bond and lead to detrimental consequences for the infant. Given the potential for negative consequences, effective treatments have been critical, with selective serotonin reuptake inhibitors (SSRIs) being the most commonly-prescribed pharmaceutical agents to treat postpartum depression and anxiety. However, SSRIs can readily cross the placenta and are present in breast milk, so they might, therefore, unintentionally interact with the developing fetus/infant. There is already experimental evidence that perinatal SSRI exposure has a number of long-term effects on offspring, but this review focuses on the current literature examining the timing and consequences of perinatal SSRI exposure specifically on anxiety-like behaviors in rodents and humans, with an emphasis on the anxiety-related brain regions of the amygdala and hippocampus. This review also discusses discrepancies between the rodent and human literatures and how they might inform future studies. Finally, some key factors to consider when examining the role of perinatal SSRIs on offspring anxiety will be discussed, such as the duration of SSRI exposure and the potential neuroprotective effects of SSRIs. Given the extensive prescribing of SSRIs, the potential health consequences of perinatal SSRI exposure, and the discrepancies in the literature, it will be necessary to critically examine the factors underlying offspring anxiety outcomes.

* Corresponding author.
E-mail address: zgrieb1@gsu.edu (Z.A. Grieb).

https://doi.org/10.1016/j.euroneuro.2019.07.239
0924-977X/

1. Introduction

For many women, pregnancy and the postpartum period are associated with increased positive affect. However, a notable amount of women (~10%-20%) will develop a depressive or anxiety disorder during these times (Dennis et al., 2017; Fairbrother et al., 2016; Pawluski et al., 2017). The consequences of a postpartum depressive or anxiety disorder on mothers and their offspring can be severe and can result in insecurely attached mother-infant dyads and a decrease in maternal sensitivity to their infant's needs (Goecke et al., 2012; Lovejoy et al., 2000; Manassis et al., 1994; Murray et al., 1996). In their most severe forms, postpartum depression and anxiety disorders can lead to child neglect, which itself can then lead to deficits in affective and cognitive development in infants (Barnett and Parker, 1986; Galler et al., 2000), with long-lasting effects into adulthood (Brown et al., 1999; Hildyard and Wolfe, 2002; Mills et al., 2011). Given these consequences of postpartum depression and anxiety on offspring, it has been crucial to find effective treatments. As of early 2019, the most commonly-prescribed pharmaceutical treatment of postpartum depression and anxiety disorders are the selective-serotonin reuptake inhibitors (SSRIs) (Cooper et al., 2007; Hayes et al., 2012). However, concerns about SSRI use during pregnancy and the postpartum period have arisen because SSRIs can readily cross the placenta, are present in breast milk, and fetuses and infants may experience difficulty metabolizing SSRIs effectively (Kim et al., 2006; Kristensen et al., 1999; Rampono et al., 2009). This presence of drug in the perinatal environment suggests an ability of perinatal SSRI exposure to unintentionally influence serotonin signaling in the offspring and has thrown into question whether prescribing SSRIs in pregnant and postpartum women is safe for long-term offspring outcomes. Indeed, there is a growing body of work suggesting that there are developmental consequences from perinatal SSRI exposure on offspring outcomes in both rodents and humans (Gemmel et al., 2017a; Glover and Clinton, 2016; Kaplan et al., 2016; Malm et al., 2016; Millard et al., 2017; Oberlander et al., 2005, 2007). When considering that in the United States, an estimated 5 - 13% of pregnant and postpartum women are prescribed SSRIs annually (Cooper et al., 2007; Gemmel et al., 2017a; Hayes et al., 2012), and that there are approximately 4 million births annually (Hamilton et al., 2018), upwards of 200,000 - 400,000 fetuses and infants are exposed to SSRIs perinatally each year. Therefore, any negative consequences of perinatal SSRI exposure could have a major public health impact. One potentially major consequence of perinatal SSRI exposure could be the potentiation of offspring anxiety disorders. There is already a large literature linking serotonin with anxiety (Gordon and Hen, 2004; Żmudzka et al., 2018), which makes any long-term perturbations in the serotonin system likely to influence anxiety. There have already been thorough reviews recently published on the effects of perinatal SSRI exposure on offspring behavioral development (Millard et al., 2017) and offspring social development (Gemmel et al., 2017a). However, this review will focus on the current literature examining the timing and consequences of perinatal SSRI exposure specifically on anxiety-like behaviors in laboratory rodents and humans, with an emphasis on the anxiety-related brain regions of the amygdala and hippocampus. This review will also discuss discrepancies between the laboratory rodent and human literatures on the effects of SSRI exposure on offspring anxiety-related disorders. Finally, this review will examine how discrepancies in the current literature might be addressed in future research, along with other important factors to consider when investigating the role of perinatal SSRIs on offspring anxiety.

2. Serotonin and neural development

To determine the potential behavioral effects of perinatal SSRI treatment on offspring anxiety-like behaviors, it is first necessary to examine the early-life development of the serotonin system. The serotonergic system develops in three main stages (timepoints listed in reference to rats, which have a 21-22 days gestational period): 1) differentiation of serotonergic neurons: embryonic days 10-14; 2) initial axonal elongation: embryonic days 13-16, and axonal growth: embryonic days 15-19; and 3) serotonergic maturation and modification of target regions: embryonic day 19 - postnatal day 21 (Deneris and Gaspar, 2018; Lauder, 1990; Lidov and Molliver, 1982). This section will be a general overview of these stages, with emphasis placed on systems key to anxiety-like behaviors. For a more complete review, readers are referred to (Deneris and Gaspar, 2018).

2.1. Differentiation of serotonergic neurons

Serotonergic neuronal differentiation occurs during mid-gestation in rodents (e.g. serotonin neurons present by embryonic days 10-14 in rats) (Lauder and Bloom, 1974; Olson and Seiger, 1972; Wallace and Lauder, 1983). In contrast to rodents, serotonergic neurons in humans are seen earlier in gestation, being present by gestational weeks 5-10 (Kinney et al., 2011; Olson et al., 1973; Shen et al., 1989). Considering the comparative developmental stages at these points when serotonin neurons appear, with humans in their first trimester and rats in the human equivalent of the second trimester (Romijn et al., 1991), this could suggest that human infants could be more vulnerable to early SSRI treatment compared to rodents.

2.2. Initial axonal elongation

After differentiation of serotonergic neurons, there is an initial axonal elongation and growth that matures through the prenatal period (Lauder, 1990; Lidov and Molliver, 1982). Growth of serotonergic fibers is at least partially guided by serotonergic signaling itself, which is released from newly born serotonergic neurons, and both induces growth factor release and inhibits its own axonal growth. Regarding the induction of growth factors, serotonin, through a *postsynaptic* serotonin 1A receptor-mediated mechanism, can increase astrocytic production and release of the growth factor, s100β (Azmitia et al., 1990; Eriksen et al., 2002; Whitaker-Azmitia et al., 1990). Therefore, depletion of

serotonin content with para-chlorophenylalanine, which inhibits the rate-limiting enzyme in serotonin synthesis, tryptophan hydroxylase, decreases the expression of s100β (Haring et al., 1993). Conversely, increasing serotonin content with the SSRI, fluoxetine, increases s100β expression and release (Haring et al., 1993), although, this might be through a serotonin-independent mechanism (Tramontina et al., 2008). Developmentally, this postsynaptic serotonin 1A receptor-mediated mechanism of axonal growth, while present throughout the lifespan to maintain serotonin fiber density (Wilson et al., 1998), is crucial in early neurobehavioral development. For example, in the hippocampus, serotonin 1A receptor expression is highest during the early postnatal period in rats (Patel and Zhou, 2005), and knocking out serotonin 1A receptors in the early postnatal period causes long-lasting increases in anxiety-like behavior, even if receptor expression is returned in adulthood (Gross et al., 2002). These serotonin-related outcomes raise the possibility of a critical period during early development when perinatal SSRI exposure might permanently alter the serotonergic system and behaviors influenced by serotonergic signaling.

As mentioned above, serotonin can also negatively influence its own axonal growth, and does so through a *presynaptic* serotonin 1A receptor-mediated mechanism. Indeed, perinatal SSRI exposure, which causes a transient increase in serotonin release, ultimately results in decreased serotonergic signaling in typically serotonin-rich areas, such as the amygdala (Cabrera-Vera and Battaglia, 1998) and hippocampus (Simpson et al., 2011; Weaver et al., 2010). While these effects appear contrary to serotonin's positive influence on axonal growth, they are largely attributed to decreases in serotonin release as a result of presynaptic serotonin 1A autoreceptor activation. This suggests that a balance of serotonin release is key to normal development, such that developmentally-typical, transient serotonin release might direct serotonergic fiber growth, while chronically high serotonin from perinatal SSRI exposure might decrease serotonin fiber growth through autoinhibition of serotonin release (da Silva et al., 2010; Maciag et al., 2006; Simpson et al., 2011; Weaver et al., 2010).

In humans, as with differentiation of serotonin neurons, serotonin fiber growth occurs earlier in relative development than in rats. Initial axonal elongation is present by gestational week 8, and axonal growth is completed by gestational week 13, when the serotonin fibers reach the cortical plate (Verney et al., 2002). Given the earlier developmental stages at which humans complete both neuronal differentiation and axon growth, this again would suggest that humans might be more vulnerable than rodents to perinatal SSRI treatment.

2.3. Serotonergic maturation and modification of target regions

Once serotonergic fibers reach their targets, these fibers mature and modify the target sites (Lauder, 1990; Lidov and Molliver, 1982). While many brain regions receive serotonergic innervation and are modified at this stage of development (Bannerman et al., 2004; Davis, 1992); here, we will focus on serotonin's role in the maturation of two anxiety-related brain regions, the amygdala and hippocampus. To start, it is important to discuss how the expression of serotonin transporters, which are present on serotonergic fibers and target regions, changes across perinatal development. Serotonin transporters regulate the length of serotonin's actions in the synapse by removing serotonin from the synapse, with more serotonin transporters resulting in less serotonergic signaling and vice versa. SSRIs work by blocking these transporters, resulting in increased serotonin in the synapse and serotonergic signaling (at least transiently). Therefore, any normative changes in serotonin transporter content across the perinatal period could lead to more, or less, potential consequences of SSRI exposure across developmental timepoints. Indeed, serotonin transporter expression in rodents is dynamic throughout early development (Fig. 1). For example, serotonin transporter expression in the amygdala is very low until birth, after which serotonin transporters rise through the postnatal period, peak at three weeks of age, and then decline until they plateau at adult levels at four weeks of age (Galineau et al., 2004; Narboux-Nême et al., 2008). Alternatively, the hippocampus starts to express serotonin transporters in the late prenatal period (e.g. embryonic days 15–17), which rise during late gestation into the postnatal period, and then starts to decline to low/adult levels after three weeks of age (Hansson et al., 1998; Lebrand et al., 1998; Narboux-Nême et al., 2008). In humans, there is no work tracking serotonin transporter expression in the amygdala

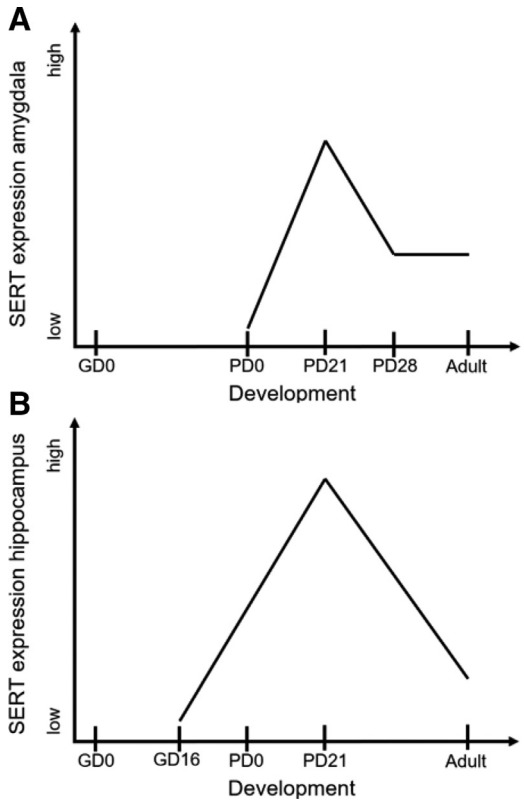


Fig. 1 Relative expression of serotonin transporters (SERT) in the (A) amygdala and (B) hippocampus across development in rats.

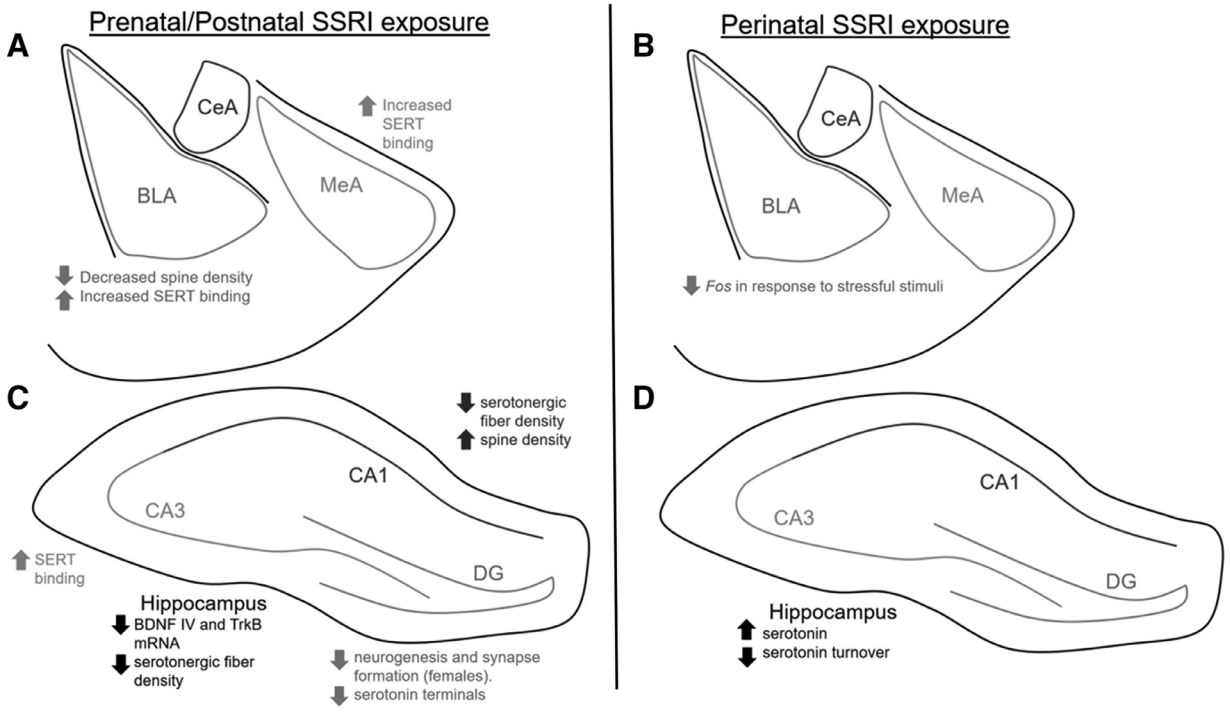


Fig. 2 Regional effects of prenatal/postnatal SSRI exposure on the (A) amygdala and (C) hippocampus versus perinatal SSRI exposure on the (B) amygdala and (D) hippocampus in laboratory rodents.

or the hippocampus across development. Given the dynamic and transient nature of serotonin transporter expression in the amygdala and hippocampus in laboratory rodents, it will be crucial to examine serotonin transporter expression across perinatal development in humans to fully understand the potential impact of perinatal SSRI exposure.

Perinatal SSRI exposure can lead to long-term changes in specific serotonin target regions. For example, prenatal and postnatal SSRI exposure increases serotonin transporter autoradiographic binding (Cabrera-Vera and Battaglia, 1998) and decreases serotonergic fiber density in the adult hippocampus (da Silva et al., 2010; Maciag et al., 2006; Simpson et al., 2011; Weaver et al., 2010), suggesting decreased serotonergic signaling in adulthood (Fig. 2). Serotonergic action in the hippocampus is associated with decreased anxiety (Tu et al., 2014), potentially through activating 5-HT1A receptors (Carli et al., 1993; Guimaraes et al., 1993; Kostowski et al., 1989; Stefański et al., 1993; However, see Andrews et al., 1994; Kenny et al., 2000; Hogg et al., 1994). Therefore, decreased serotonergic signaling in the hippocampus as a result of prenatal or postnatal SSRI exposure would be expected to be anxiogenic.

Overall, it is clear that numerous aspects of the serotonin system and its targets are changing across perinatal development. Therefore, the perinatal period is primed to be a critical time when SSRI exposure might cause long-term structural changes in the serotonin system and its targets (e.g., the amygdala and hippocampus; Fig. 2). It is these long-term changes in innervation and signaling that likely underlie many behavioral outcomes, such as long-term changes in anxious behaviors in offspring.

3. Perinatal SSRI exposure and anxiety-like behaviors in rodents; effects of timing of SSRI exposure

3.1. Prenatal SSRI exposure and anxiety-like behaviors in rodents

One of the most pronounced behavioral changes caused by prenatal (i.e., gestational day 1 until parturition) SSRI exposure in laboratory mice and rats is an increased prevalence of anxiety-like behaviors in peri-adolescence and adulthood (Table 1). Prenatal treatment with the SSRI, fluoxetine, decreases time spent in the open arm of the elevated-plus maze, an indicator of increased anxiety-like behavior (Noorlander et al., 2008; Olivier et al., 2011). Similarly, prenatal treatment with fluoxetine decreases exploration and time spent in the center of the open-field test (Boulle et al., 2016; Noorlander et al., 2008; Olivier et al., 2011), increases the latency to eat in the novelty-suppressed feeding task (Noorlander et al., 2008; Olivier et al., 2011), and increases neophobia to a novel object (Simpson et al., 2011).

3.2. Early postnatal SSRI exposure and anxiety-like behaviors in rodents

Like prenatal exposure to SSRIs, early postnatal (i.e., birth to weaning) exposure to SSRIs also increases anxiety-like behaviors in rodents (Table 1). For example, in many studies postnatal treatment with fluoxetine decreases exploration

Table 1 Effects of perinatal SSRI exposure on anxiety-like behaviors in rodents and humans.

SSRI (dose*)	Exposure	Authors	Species	Anxiety outcome
Prenatal SSRI exposure			**Rodents**	
Prenatal fluoxetine (0.3, 0.6, or 0.7 mg/kg/day: IP) or fluvoxamine (4.2 mg/kg/day: IP)	GD8-GD18	Noorlander et al. (2008)	C57BL/6-Jlco mice	↑ Anxiety on open field and novelty suppressed feeding task in adulthood (fluoxetine) = Anxiety on open field and novelty suppressed feeding task in adulthood (fluvoxamine) ↑ Anxiety on elevated plus maze (more time in closed arms) in adulthood (fluoxetine and fluoxamine)
Prenatal fluoxetine (0.6 mg/kg/day: IP)	GD8-GD18	Smit-Rigter et al. (2012)	C57BL/6 mice	↑ Anxiety in the novelty-suppressed feeding task
Prenatal fluoxetine (12 mg/kg/day: Oral injection)	GD11-Parturition	Olivier et al. (2011)	Wistar rats	↑ Anxiety on novelty-suppressed feeding task Open field test and elevated plus maze in adulthood in adulthood
Prenatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	GD11-GD19	Simpson et al. (2011)	Long-Evans rats	↑ Neophobia: more freezing to a tone and less exploration of a novel object
Postnatal SSRI exposure			**Rodents**	
Postnatal fluoxetine (10 mg/kg/day: IP)	PD4-PD21	Karpova et al. (2009)	C57BL/6 mice	↑ Anxiety in light-dark box and open field test in adulthood
Postnatal fluoxetine (10 mg/kg/day: IP) or fluvoxamine (10 mg/kg/day: IP)	PD4-PD21	Zheng et al. (2011)	C57BL/6 mice	↑ Anxiety (less exploration) in open field in adulthood
Postnatal fluoxetine (10 mg/kg/day: IP)	PD4-PD21	Ansorge et al. (2004)	129S6/SvEv mice	↑ Anxiety in the open field (less exploration) and elevated plus maze (fewer rears) in adulthood
Postnatal fluoxetine (10 mg/kg/day: IP) or citalopram (10 mg/kg/day: IP)	PD4-PD21	Ansorge et al. (2008)	129S6/SvEv mice	↑ Anxiety in open field (less exploration) and elevated plus maze (fewer rears) in adulthood
Postnatal fluoxetine (10 mg/kg: IP)	PD2-PD11	Rebello et al. (2014)	129S6/SvEvTac mice	↑ Anxiety on open field test and novelty suppressed feeding tests
Postnatal fluoxetine (10 mg/kg/day: IP)	PD2-PD21	Yu et al. (2014)	129S6/SvEv mice	↑ Neophobia: novel open field (less exploration) and Novelty-suppressed feeding paradigm in adulthood
Postnatal citalopram (10 mg/kg/day: SC)	PD5-PD19	Popa et al. (2008)	CD1 mice	↑ Anxiety in the elevated pluz maze (fewer rears) = Anxiety in the light/dark box
Postnatal fluoxetine (5 mg/kg/day: Osmotic minipumps)	PD1-Weaning	Rayen et al. (2011)	Sprague-Dawley rats	= Anxiety in the open field test in adolescence

(*continued on next page*)

Table 1 (*continued*)

SSRI (dose*)	Exposure	Authors	Species	Anxiety outcome
Postnatal fluoxetine (10/mg/kg/twice daily: IP)	PD2-PD23	Gobinath et al. (2016)	Sprague-Dawley Rats	↑ Anxiety in the elevated plus maze and novelty-suppressed feeding paradigm in adulthood (males only)
Postnatal fluoxetine (5 mg/kg/day: osmotic minipump dam)	PD1 – Weaning	Boulle et al. (2016)	Sprague-Dawley rats	↑ Anxiety on open field in unstressed males in adulthood; ↓ Anxiety on open field in stressed males in adulthood
Postnatal fluoxetine (10 mg/kg/day: SC)	PD0-PD6	Lee (2009)	Wistar rats	↑ Anxiety in open field (less exploration) in adolescence
Postnatal fluoxetine (20 mg/kg/day: SC)	PD0-PD4	Lee and Lee (2012)	Wistar rats	↑ Anxiety in open field (less exploration) in adolescence
Postnatal fluoxetine (10 mg/kg/day: SC)	PD1-PD21	Ribas et al. (2008)	Wistar rats	= Anxiety in the elevated plus maze in adulthood
Postnatal fluoxetine (20 mg/kg/day: SC)	PD0-PD4	Ko et al. (2014)	Wistar rats	↑ Anxiety in the open field in adulthood; = Anxiety in the elevated plus maze in adulthood
Postnatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	PD8-PD18	Simpson et al. (2011)	Long-Evans rats	↑ Neophobia: more freezing to a novel tone and less exploration of a novel object
Postnatal fluoxetine (5 mg/kg/twice daily: SC) or citalopram (10 mg/kg/twice daily: SC)	PD8-PD28	Rodriguez-Porcel et al. (2011)	Long-Evans rats	↑ Males: Neophobia: lessexploration of a novel object in adolescence; = Females: no effects on neophobia in adolescence
Postnatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	PD8-PD21	Harris et al. (2012)	Long-Evans rats	= Anxiety in the elevated plus maze in adulthood
Perinatal SSRI exposure			**Rodents**	
Perinatal fluoxetine (25 mg/kg/day: Drinking water)	GD15-PD12	McAllister et al. (2012)	C57BL/6 mice	↓ Anxiety on elevated plus maze in adulthood; = Anxiety on open field in adulthood
Perinatal fluoxetine (25 mg/kg/day: Drinking water)	GD15-PD12	Kiryanova and Dyck (2014)	C57BL/6 mice	↓ Anxiety in the elevated pluz maze in adulthood; = Anxiety in the open field in adulthood
Perinatal fluoxetine (25 mg/kg/day: Drinking water)	GD15-PD12	Kiryanova et al. (2016)	C57BL/6 mice	↓ Anxiety on elevated plus maze in adulthood; = Anxiety on open field and light/dark box in adulthood
Perinatal fluoxetine (8 mg/kg/day: Drinking water)	GD10-PD20	Salari et al. (2016)	NMRI mice	↓ Anxiety on zero maze in adulthood; = Anxiety on open field in adulthood

(*continued on next page*)

Table 1 (*continued*)

SSRI (dose*)	Exposure	Authors	Species	Anxiety outcome	
Perinatal fluoxetine (7.5 mg/kg/day: oral gavage)	GD0-PD21	Lisboa et al. (2007)	Swiss mice	=	Anxiety on open field and elevated plus maze
Perinatal citalopram (10 mg/kg/twice daily: SC)	GD6-PD20	Sprowles et al. (2016)	Sprague-Dawley rats	↑ =	Females: Anxiety on open field in aulthood Anxiety in the elevated zero maze
Perinatal citalopram (5 mg/kg/twice daily: SC) or fluoxetine (5 mg/kg/twice daily: SC)	GD6-PD20	Sprowles et al. (2017)	Sprague-Dawley rats	↑ =	Females: Anxiety on open field (less exploration) in adulthood Anxiety in the elevated zero maze
Perinatal venlafaxine (7.5, 37.5, and 75 mg/kg: Oral gavage to dam)	GD15-PD20	Bogi et al. (2018)	Wistar rats	↓	Anxiety on elevated plus maze and light/dark box in adulthood
Perinatal fluoxetine (5 mg/kg/day: Oral gavage)	GD0-PD21	Francis-Oliveira et al. (2013)	Wistar rats	↓	Anxiety in the novelty suppressed feeding paradigm in adolesence
Perinatal SSRI exposure			**Humans**		
Perinatal (?) drug: Fluoxetine (18 mg): $n = 5$ Paroxetine (24 mg): $n = 14$ Sertaline (92 mg): $n = 3$	Pregnancy: confirmed Postpartum: Unspecified	Misri et al. (2006)	Humans	=	No effect on internalizing problems subsection (e.g. depression, anxiety, withdrawal) of the Child Behavior Checklist at 4 - 5 years of age
Perinatal (?) drug: Fluoxetine (30 mg): $n = 4$ Paroxetine (20 mg): $n = 15$ Sertraline (50 mg): $n = 5$ Citalopram (25 mg): $n = 6$ Venlafaxine (75 mg): $n = 3$	Prenancy: Confirmed Postpartum: Unspecified	Oberlander et al. (2010)	Humans	=	No effect on anxious/depressed subscale of the internalizing subsection of Child Behavior Checklist at 3 years of age
Perinatal (?) drug: Fluoxetine: $n = 17$ Paroxetine: $n = 38$ Sertraline: $n = 11$ Fluvoxamine: $n = 6$ Citalopram: $n = 4$	$n = 35$: mothers who used SSRIs exclusively in 1st trimester $n = 34$: Mothers who used SSRIs in the 1st, 2nd, and/or 3rd trimesters (unspecified if used in postpartum)	El Marroun et al. (2014)	Humans	=	No effect on affective disorders on the Child Behavior Checklist at 1.5, 3, or 6 years of age
Perinatal (?) drug: Fluoxetine: $n = 5$ Paroxetine: $n = 16$ Sertraline: $n = 7$ Citalopram: $n = 6$ Venlafaxine: $n = 10$	Pregnancy: Confirmed Postpartum: Unspecified	Hanley et al. (2015)	Humans	↑ =	Internalizing and anxiety problems subsections of the Child Behavior Checklist at 3 years old No effect on anxiety behaviors on the Health and Behavior Questionnaire at 6 years old

(*continued on next page*)

Table 1 (*continued*)

SSRI (dose*)	Exposure	Authors	Species	Anxiety outcome	
Perinatal (?) drug: Unspecified: $n = 28$	Pregnancy: Confirmed Postpartum: Unspecified	Hermansen et al. (2016)	Humans	↑	Internalizing problems subsection of the Child Behavior Checklist at 6 years old
Perinatal (?) drug: Assortment of SSRIs ($n = 15{,}729$): Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine	Pregnancy: Confirmed Postpartum: Unspecified	Malm et al. (2016)	Humans	↑	Marginal increase in the age-related rise in the incidence rate of anxiety disorders

Effects of pre-, post-, or perinatal SSRI exposure on anxiety-like behaviors in laboratory rodents and anxiety in humans. Arrows indicate significant differences between SSRI exposed and control subjects.

* Note that average dose is reported in the human studies. The anxious/depressed subscale of the internalizing subsection of the Child Behavior Checklist measures: Child crying, feeling of worthlessness, nervousness, fearfulness, guilt, self-consciousness, suicidal thoughts, and worrying.

in the open-field test (Ansorge et al., 2008, 2004; Boulle et al., 2016; Karpova et al., 2009; Ko et al., 2014; Lee, 2009; Lee and Lee, 2012; Rebello et al., 2014; Zheng et al., 2011; however, see Harris et al., 2012; Rayen et al., 2011). Similarly, postnatal fluoxetine treatment increases neophobia to a novel object and novel tone (Rodriguez-Porcel et al., 2011; Simpson et al., 2011; Yu et al., 2014), increases anxiety-like behaviors in the elevated plus maze and light-dark box (Ansorge et al., 2008, 2004; Karpova et al., 2009; Popa et al., 2008: however see Harris et al., 2012; Ko et al., 2014; Ribas et al., 2008), and increases the latency to eat in the novelty-suppressed feeding paradigm (Gobinath et al., 2016; Rebello et al., 2014). Therefore, similar to *prenatal* SSRI exposure, early *postnatal* SSRI exposure also increases anxiety-like behaviors.

3.3. Perinatal SSRI exposure and anxiety-like behaviors in rodents

It is important to note that not all rodent studies that have analyzed the effects of perinatal SSRI exposure show elevated anxiety-like behaviors. Six separate studies found that prolonged *perinatal* (i.e., gestational day 1 – weaning) SSRI exposure *decreased* anxiety-like behavior (Table 1). Three of these studies found that fluoxetine treatment from gestational day 15 to postnatal day 12 increased the percent of time spent in the open arms of the elevated-plus maze in adult mice (Kiryanova and Dyck, 2014; Kiryanova et al., 2016; McAllister et al., 2012; however see Meyer et al., 2018), while another study found that treatment with fluoxetine from gestational day 1 to postnatal day 21 decreased the latency to eat in the novelty-suppressed feeding task in adolescent rats (Francis-Oliveira et al., 2013), and yet another study found fluoxetine treatment from gestational day 10 to postnatal day 20 increased time in the open areas on the elevated zero maze in adult mice (Salari et al., 2016). Furthermore, perinatal treatment (gestational day 15 to postnatal day 20) with the serotonin-norepinephrine reuptake inhibitor, venlafaxine, also led to lower anxiety-like behaviors in adult rats (Bogi et al., 2018). Interestingly, these effects might be specific to particular SSRIs, as perinatal exposure to citalopram increased anxiety-like behaviors, as seen as less time spent in the center of the open-field test (Sprowles et al., 2016, 2017).

3.4. Effects of the timing of SSRI exposure on anxiety-like behaviors

The apparent discrepancies among prenatal, postnatal, and perinatal SSRI exposure on anxiety-like behaviors might be explained by the timing of the SSRI exposure. Almost all studies that exposed offspring to SSRIs during *either* the pre- or postnatal period reported increased anxiety-like behavior (Ansorge et al., 2008, 2004; Boulle et al., 2016; Gobinath et al., 2016; Karpova et al., 2009; Ko et al., 2014; Lee, 2009; Lee and Lee, 2012; Noorlander et al., 2008; Olivier et al., 2011; Popa et al., 2008; Rebello et al., 2014; Rodriguez-Porcel et al., 2011; Simpson et al., 2011; Smit-Rigter et al., 2012; Yu et al., 2014; Zheng et al., 2011), while those that treated *across* the perinatal period show decreased anxiety-like behavior (Bogi et al., 2018; Francis-Oliveira et al., 2013; Kiryanova and Dyck, 2014; Kiryanova et al., 2016; McAllister et al., 2012; Salari et al., 2016). This suggests either a time-dependent or total exposure dependent effect of SSRI exposure on later anxiety-like behavior in rodents, with cumulative SSRI treatment decreasing anxiety-like behaviors. This would be similar to other bio behavioral effects of cumulative perinatal SSRI exposure, in which the duration of SSRI exposure is negatively associated with infant admittance to the neonatal intensive care unit (Casper et al., 2011).

The total duration of SSRI exposure might be particularly relevant because of the transient serotonin transporter expression in the amygdala and hippocampus during perinatal development (Galineau et al., 2004; Hansson et al., 1998; Lebrand et al., 1998; Narboux-Nême et al., 2008), which would lead to abnormally high levels of serotonin in these regions during critical periods of serotonergic system devel-

opment. This increase in serotonin content in the perinatal brain might also be exacerbated by the fact that presynaptic and postsynaptic serotonin 1A receptors are differentially sensitive to prolonged serotonin exposure. For example, *presynaptic* serotonin 1A autoreceptors are desensitized in response to serotonin more so than *postsynaptic* serotonin 1A heteroreceptors (Riad et al., 2001). Therefore, long-term increases in serotonin that occur under perinatal SSRI exposure would be expected to more dramatically increase serotonin output to target regions than either prenatal or postnatal SSRI exposure. Given the importance of balanced, transient, serotonin release for proper serotonergic system development (discussed above), short-term serotonin transporter blockade would be predicted to decrease serotonergic tone by overactivating *presynaptic* serotonin 1A autoreceptors, while long-term serotonin transporter blockade would be predicted to increase serotonergic tone by overactivating *postsynaptic* serotonin 1A heteroreceptors. Consistent with this idea, prenatal and postnatal SSRI exposure decreases serotonergic tone in the amygdala and hippocampus in adulthood (da Silva et al., 2010; Maciag et al., 2006; Simpson et al., 2011; Weaver et al., 2010), while perinatal SSRI exposure increases serotonergic tone in the hippocampus (Gemmel et al., 2017b). It will be crucial for future studies to further examine whether prenatal or postnatal SSRI exposure causes different changes in the amygdala and hippocampus than perinatal SSRI exposure.

4. Perinatal SSRI exposure and anxiety-like behaviors in humans

When examining the effects of perinatal SSRI exposure on anxiety in humans, the relationship is much less clear. Two studies found that perinatal SSRI exposure was not associated with any later affective behaviors, as measured by the Child Behavior Checklist, at 1.5, 3, or 6 years of age (El Marroun et al., 2014) or at 4 - 5 years of age (Misri et al., 2006). However, three other studies examining the role of perinatal SSRI exposure on childhood anxiety found increased internalizing (anxiety, depressive, and over controlled) behavior as measured by the Child Behavior Checklist at 3 and 6 years of age (Hanley et al., 2015; Hermansen et al., 2016; Oberlander et al., 2010). One study found that perinatal SSRI exposure predicted the somatic complaint and sleep disturbance subfields of internalizing behavior in children at 3 years of age (Oberlander et al., 2010). Finally, in a study examining adolescents exposed perinatally to SSRIs, a trend was found for a higher incidence of anxiety-related disorders over time in SSRI exposed adolescents compared to adolescents not exposed (Malm et al., 2016). Taken together, these studies suggest that the relationship between perinatal SSRI exposure and anxiety is not as straightforward in humans compared to laboratory rodents.

5. Important considerations

While studies examining the effects of perinatal SSRI exposure on anxiety in humans have not found robust effects, there are a few caveats to this conclusion. Multiple studies did not control for the potential mediating effects of maternal mood disorder (Misri et al., 2006; Oberlander et al., 2010), which can itself affect child anxious behavior (Cummings and Davies, 1994). Additionally, and perhaps most crucially, all of these studies analyzed toddlers (El Marroun et al., 2014; Hanley et al., 2015; Oberlander et al., 2010) and young children (i.e., 3–6 years old) (El Marroun et al., 2014; Hanley et al., 2015; Hermansen et al., 2016; Misri et al., 2006). Given that the onset of many anxiety-related disorders emerge during adolescence and into young adulthood (Paus et al., 2008), the possibility arises that these timepoints might be too early to observe any anxiety-related effects. Consistent with this idea, one study of perinatal SSRI exposure and later *adolescent* anxiety disorders found a trend for a higher incidence of anxiety-related disorders over time in SSRI exposed adolescents compared to adolescents not exposed (Malm et al., 2016). Interestingly, long-term modifications in serotonergic tone from perinatal SSRI exposure (discussed above) might be important in the peri-adolescent neural changes that are concurrent with the onset of anxiety disorders, such as increased formation of white matter (i.e. myelation of axons), and a corresponding decrease in gray matter (i.e. apoptosis; neuronal death) (Paus et al., 2008). For example, adults with anxiety disorders show impaired connectivity between the amygdala and other cortical regions important for anxiety regulation (Phan et al., 2009; Westlye et al., 2011), and the s/s serotonin transporter polymorphism, which transiently increases synaptic serotonin, can decrease the integrity of these pathways (Pacheco et al., 2009; Pezawas et al., 2005). Similarly, the s/s serotonin transporter polymorphism can also lead to reductions in amygdala and hippocampus volume (Eker et al., 2011; Everaerd et al., 2012; Kobiella et al., 2011; Pezawas et al., 2005), which is associated with increased amygdala activity (Bertolino et al., 2005; Dannlowski et al., 2010; Kobiella et al., 2011). Therefore, the long-term downregulation of serotonergic tone due to prenatal or postnatal SSRI exposure (Simpson et al., 2011; Weaver et al., 2010) could result in long-term changes in neural connectivity and cell composition in circuits important for the display of anxiety behavior that only emerge in adolescence or young adulthood.

Another important distinction that might explain some of the discrepancies between the rodent and human literatures is that the exposure route and dose can be very different between the rodent and human literatures, particularly when examining the “third” trimester of development. In rodents, the comparative third trimester of development occurs during the postnatal period (Romijn et al., 1991). Therefore, many studies investigate the role of late gestational SSRI exposure by directly injecting SSRIs into early postnatal pups, either subcutaneously (Lee, 2009; Lee and Lee, 2012; Rodriguez-Porcel et al., 2011) or into the peritoneum (Ansorge et al., 2008; Karpova et al., 2009; Zheng et al., 2011). This is a caveat if translating to humans, though, as infants would never receive a direct dose of SSRI under typical conditions. This is even more critical when taking into consideration that only an estimated 50% of SSRIs, and 25% of its metabolites, cross the placenta in humans (Ewing et al., 2015). Therefore, administration of SSRIs directly into pups could result in an almost *doubling* of the working dose in rodents compared to humans, which might limit the translatability of rodent work to humans. A

Table 2 Effects of perinatal SSRI exposure on hippocampal and amygdala neurobiology.

SSRI (dose)	Exposure	Authors	Species	Neurobiological outcome (Hippocampus/amygdala)
Prenatal SSRI exposure			**Rodents**	
Prenatal Fluoxetine (10 mg/kg. SC)	GD13-GD20	Cabrera-Vera and Battaglia (1998)	Sprague-Dawley rats	↑ SERT autoradiographic binding in the CA2 (+47%), CA3 (+38%), basolateral amygdala (+32%), medial amygdala (+44%) of adolescents
Prenatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	GD11-GD19	Simpson et al. (2011)	Long-Evans rats	↓ Density of serotonergic fibers in CA1 region of hippocampus
Postnatal SSRI exposure			**Rodents**	
Postnatal fluoxetine (10 mg/kg/day: IP)	PD4-PD21	Karpova et al. (2009)	C57BL/6 mice	↑ BDNF IV mRNA in hippocampus (adult male mice) ↓ TrkB.T1 mRNA in hippocampus (adult male mice)
Postnatal fluoxetine (10 mg/kg/day: IP) or fluvoxamine (10 mg/kg/day: IP)	PD4-PD21	Zheng et al. (2011)	C57BL/6 mice	↑ Apical dendrite spine density in adult CA1 region of hippocampus (fluoxetine) ↑ Basal dendritic spine density in adult CA1 region of hippocampus (fluoxetine and fluvoxamine)
Postnatal fluoxetine (5 mg/kg/day: Osmotic minipumps)	PD1 - Weaning	Rayen et al. (2011)	Sprague-Dawley rats	↓ Cell proliferation in hippocampus (fluoxetine only) ↑ Neurogenesis in the hippocampus (fluoxetine and maternal stress)
Postnatal fluoxetine (5 mg/kg/day: Osmotic minipumps)	PD1-PD21	Rayen et al. (2015)	Sprague-Dawley rats	↑ Males: hippocampal neurogenesis maternal stress and fluoxetine Tx ↑ Females: cell survival in hippocampus with fluoxetine Tx ↓ Females: synapse formation in dentate gyrus with fluoxetine Tx
Postnatal fluoxetine (10/mg/kg/twice daily: IP)	PD2-PD23	Gobinath et al. (2016)	Sprague-Dawley Rats	↑ Males: hippocampal neurogenesis maternal stress and fluoxetine Tx ↓ Females: hippocampal neurogenesis with fluoxetine Tx
Postnatal fluoxetine (5 mg/kg/day: osmotic minipump dam)	PD1-Weaning	Boulle et al. (2016)	Sprague-Dawley rats	↓ BDNF IV and TrkB mRNA in hippocampus as adults
Postnatal fluoxetine (10 mg/kg/day: SC)	PD1-PD21	da Silva et al. (2010)	Wistar rats	↓ Serotonin terminals in the hippocampus (dentate gyrus)
Postnatal fluoxetine (20 mg/kg/day: SC)	PD0-PD4	Ko et al. (2014)	Wistar rats	↓ Spine density in the basolateral amygdala in adulthood
Postnatal citalopram (5 mg/kg/day: SC)	PD8-PD21	Maciag et al. (2006)	Long-Evans rats	↓ SERT fiber density in the hippocampus in adulthood

(*continued on next page*)

Table 2 (*continued*)

SSRI (dose)	Exposure	Authors	Species	Neurobiological outcome (Hippocampus/amygdala)
Postnatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	PD8-PD21	Weaver et al. (2010)	Long-Evans rats	↓ SERT fiber density in the hippocampus in adulthood (bigger effect at higher doses).
Postnatal citalopram (2.5, 5, or 10 mg/kg/twice daily: SC)	PD8-PD21	Simpson et al. (2011)	Long-Evans rats	↓ Density of serotonergic fibers in CA1 region of hippocampus
Perinatal SSRI exposure			**Rodents**	
Perinatal fluoxetine (5 mg/kg/twice daily: biscuit (Oral))	GD10-PD21	Gemmel et al. (2017a)	Sprague-Dawley rats	↑ Serotonin in the hippocampus ↓ Serotonin metabolism in hippocampus
Perinatal fluoxetine (5 mg/kg/day: Oral gavage)	GD0-PD21	Francis-Oliveira et al. (2013)	Wistar rats	↓ Fos in the basolateral amygdala and medial amygdala in response to stress.

Effects of pre-, post-, or perinatal SSRI exposure on hippocampal and amygdala physiology in laboratory rodents. Arrows indicate significant differences between SSRI exposed and control subjects.

dose-dependent effect might not be surprising, given that serotonin regulates its own development and future serotonin release (Homberg et al., 2010; Shemer et al., 1991; Simpson et al., 2011; Weaver et al., 2010). Additionally, when considering that typical doses of prescribed SSRIs in humans can range up to 8-fold in difference from the lowest to the highest dose, depending on the SSRI (Gemmel et al., 2017a), this could explain the lack of clarity in the human literature as to the role of perinatal SSRI exposure on infant anxiety outcomes.

Perhaps most crucially, is that *prenatal* or *postnatal* SSRI treatments in rodents increase offspring anxiety-like behavior, while *perinatal* SSRI treatments decreases offspring anxiety-like behavior in laboratory rodents (Table 1). Given that ~50% of women discontinue SSRI use by the end of pregnancy (El Marroun et al., 2014; Ververs et al., 2006; Zoega et al., 2015), this could explain why the effects of perinatal SSRI use on offspring anxiety in humans have remained inconclusive. It is important to note that while studies report prenatal SSRI exposure, it is not clear what the mother's SSRI use is like in the early postpartum period when breastfeeding would likely be occurring (Hanley et al., 2015; Hermansen et al., 2016; Malm et al., 2016; Misri et al., 2006; Oberlander et al., 2010). Future human studies might benefit from separating mothers into "SSRIs used exclusively during early pregnancy", "SSRIs used throughout pregnancy", "SSRIs used exclusively during the postpartum period", and "SSRIs used throughout pregnancy and the postpartum period" to determine the specific effects the timing of SSRI exposure may have on child outcomes.

Finally, it is important to consider that SSRIs under certain conditions might, in fact, be protective for the offspring. For example, while prenatal and postnatal SSRI exposure can decrease hippocampal neurogenesis (Gobinath et al., 2016; Rayen et al., 2011), this effect appears to be sex- and/or stress-specific, as postnatal SSRI exposure under stressful conditions (i.e., corticosterone injections or daily restraint stress) decreases neuron density in the hippocampus of adult female rodents (Gobinath et al., 2016; Rayen et al., 2015), while increasing the neuron density in adult male rodents (Gobinath et al., 2016). Perinatal SSRI exposure can also normalize changes in hippocampal circuitry under stressful conditions (Ishiwata et al., 2005; Nagano et al., 2012; Rayen et al., 2015, 2011), suggesting that perinatal SSRI exposure might be neuroprotective in the hippocampus if administered under stressful conditions. These findings might be particularly relevant given that many studies analyzing the effects of perinatal SSRI exposure on anxiety-like behaviors were not conducted under stressful conditions, and thus may not mimic the state of anxious or depressed mothers prescribed SSRIs.

SSRIs might also be neuroprotective by enhancing maternal caregiving. Decreasing serotonergic function in maternal rodents decreases aspects of mothering, including licking, nursing, and pup retrievals (Alenina et al., 2009; Holschbach et al., 2018; Lerch-Haner et al., 2008), while SSRIs can enhance pup licking and nursing behaviors (Johns et al., 2005; Pawluski et al., 2012; however, see Rayen et al., 2011). In humans, there are relatively few studies that assess caregiving behaviors in mothers who were prescribed SSRIs during the perinatal period. SSRIs improve scores on assessments of depression and maternal role functioning (i.e. Global Assessment Scale (GAS); and Gratification in Maternal Role, GRAT, respectively) but not scores of maternal self-efficacy or mother-infant interactions (Logsdon et al., 2011). Conversely, in a small study of women who took SSRIs during pregnancy, 4 out of 5 mother-infant dyads showed disorganized attachment (Troutman et al., 2012). Additional studies examining the effects of SSRI exposure on mothering and mother-infant relationships

are necessary to determine the potentially broad spectrum of perinatal behaviors SSRIs could influence.

6. Conclusions

Taken together, the serotonin system develops extremely early in gestation, regulates its own neurodevelopment, and is necessary for future anxious behavior expression with specific effects on the amygdala and hippocampus (Table 2). Therefore, the perinatal period is primed to be a critical time when perturbations, such as SSRI exposure, might result in long-term behavioral changes including in anxiety (Table 1). While there are strong indications from the rodent literature that perinatal SSRI treatment modifies later anxiety-like behavior, the evidence in human literature is not as clear. In both rodents and humans, though, some of these discrepancies within and across the literature can be accounted for in the developmental timepoints in which the SSRI exposure occurs, the duration of SSRI exposure, the administration route, and the working dose to which the perinatal offspring are exposed. Based on the rodent literature and the limited human literature, this review urges future rodent and human studies to address three major research questions. First, for humans, what are the behavioral and neurobiological effects (i.e., amygdala and hippocampal changes) of perinatal SSRI exposure on late adolescent and adult anxiety-related behaviors? Second, for humans, if prescribed dose of SSRI is included as its own independent variable (or covariate), what is the relationship between SSRI exposure and child, teen, or adult anxiety-related behaviors? Finally, for both rodents and humans, what are the effects of pre- vs. post- vs. perinatal SSRI exposure on anxiety-related behaviors and amygdala/hippocampus neurobiology? Given the incredible costs of anxiety-related disorders, both socially (Kessler et al., 1997, 1995) and economically (Greenberg et al., 1999), it is critical to examine these specific variables to truly understand any effects of perinatal SSRI exposure on later anxiety-related disorders and its associated neurocircuitry.

Role of funding source

This review was not funded by any internal or external funding source.

Contributors

Z.A. Grieb and C.M. Ragan contributed equally to the ideas and writing in this review.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

CRediT authorship contribution statement

Z.A. Grieb: Writing - review & editing. **C.M. Ragan:** Writing - review & editing.

Acknowledgments

The authors would like to thank Dr. Joseph S. Lonstein for his valuable feedback on this review.

References

Alenina, N., Kikic, D., Todiras, M., Mosienko, V., Qadri, F., Plehm, R., Tenner, K., 2009. Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc. Natl. Acad. Sci. USA 106 (25), 10332–10337.

Andrews, N., Hogg, S., Gonzalez, L.E., File, S.E., 1994. 5-HT1A receptors in the median raphe nucleus and dorsal hippocampus may mediate anxiolytic and anxiogenic behaviours respectively. Eur. J. Pharmacol. 264 (3), 259–264.

Ansorge, M.S., Morelli, E., Gingrich, J.A., 2008. Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. J. Neurosci. 28 (1), 199–207.

Ansorge, M.S., Zhou, M., Lira, A., Hen, R., Gingrich, J.A., 2004. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306 (5697), 879–881.

Azmitia, E., Dolan, K., Whitaker-Azmitia, P., 1990. S-100 b but not NGF, EGF, insulin or calmodulin is a CNS serotonergic growth factor. Brain Res. 516 (2), 354–356.

Bannerman, D., Rawlins, J., McHugh, S., Deacon, R., Yee, B., Bast, T., Feldon, J., 2004. Regional dissociations within the hippocampus—memory and anxiety. Neurosci. Biobehav. Rev. 28 (3), 273–283.

Barnett, B., Parker, G., 1986. Possible determinants, correlates and consequences of high levels of anxiety in primiparous mothers. Psychol. Med. 16 (01), 177–185.

Bertolino, A., Arciero, G., Rubino, V., Latorre, V., De Candia, M., Mazzola, V., Kolachana, B.J., 2005. Variation of human amygdala response during threatening stimuli as a function of 5′ HTTLPR genotype and personality style. Biol. Psychiatry 57 (12), 1517–1525.

Bogi, E., Belovicová, K., Ujhazy, E., Mach, M., Koprdova, R., Zilava, L., Dubovicky, M., 2018. Perinatal exposure to venlafaxine leads to lower anxiety and depression-like behavior in the adult rat offspring. Behav. Pharmacol. 29 (5), 445–452.

Boulle, F., Pawluski, J.L., Homberg, J.R., Machiels, B., Kroeze, Y., Kumar, N., Daniel, L., 2016. Prenatal stress and early-life exposure to fluoxetine have enduring effects on anxiety and hippocampal BDNF gene expression in adult male offspring. Dev. Psychobiol. 58 (4), 427–438.

Brown, J., Cohen, P., Johnson, J.G., Smailes, E.M., 1999. Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. J. Am. Acad. Child Adolesc. Psychiatry 38 (12), 1490–1496.

Cabrera-Vera, T.M., Battaglia, G., 1998. Prenatal exposure to fluoxetine (Prozac) produces site-specific and age-dependent alterations in brain serotonin transporters in rat progeny: evidence from autoradiographic studies. J. Pharmacol. Exp. Ther. 286 (3), 1474–1481.

Carli, M., Tatarczynska, E., Cervo, L., Samanin, R., 1993. Stimulation of hippocampal 5-HT1A receptors causes amnesia and anxiolytic-like but not antidepressant-like effects in the rat. Eur. J. Pharmacol. 234 (2-3), 215–221.

Casper, R.C., Gilles, A.A., Fleisher, B.E., Baran, J., Enns, G., Lazzeroni, L.C., 2011. Length of prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants: effects on neonatal adaptation and psychomotor development. Psychopharmacology 217 (2), 211–219.

Cooper, W.O., Willy, M.E., Pont, S.J., Ray, W.A., 2007. Increasing use of antidepressants in pregnancy. Am. J. Obstet. Gynecol. 196 (6), 544.e541–544.e545.

Cummings, E.M., Davies, P.T., 1994. Maternal depression and child development. J. Child Psychol. Psychiatry 35 (1), 73–122.

da Silva, C.M., Gonçalves, L., Manhaes-de-Castro, R., Nogueira, M.I., 2010. Postnatal fluoxetine treatment affects the development of serotonergic neurons in rats. Neurosci. Lett. 483 (3), 179–183.

Dannlowski, U., Konrad, C., Kugel, H., Zwitserlood, P., Domschke, K., Schöning, S., Hohoff, C.J.N., 2010. Emotion specific modulation of automatic amygdala responses by 5-HTTLPR genotype. Neuroimage 53 (3), 893–898.

Davis, M., 1992. The role of the amygdala in fear and anxiety. Annu. Rev. Neurosci. 15 (1), 353–375.

Deneris, E., Gaspar, P., 2018. Serotonin neuron development: shaping molecular and structural identities. Wiley Interdiscipl. Rev. Dev. Biol. 7 (1), e301.

Dennis, C.-L., Falah-Hassani, K., Shiri, R., 2017. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. Br. J. Psychiatry 210 (5), 315–323.

Eker, M.C., Kitis, O., Okur, H., Eker, O.D., Ozan, E., Isikli, S., Gonul, A.S.J.N., 2011. Smaller hippocampus volume is associated with short variant of 5-HTTLPR polymorphism in medication-free major depressive disorder patients. Neuropsychobiology 63 (1), 22–28.

El Marroun, H., White, T.J., Van Der Knaap, N.J., Homberg, J.R., Fernández, G., Schoemaker, N.K., Hudziak, J.J., 2014. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. Br. J. Psychiatry 205 (2), 95–102.

Eriksen, J.L., Gillespie, R., Druse, M.J., 2002. Effects of ethanol and 5-HT 1A agonists on astroglial S100B. Dev. Brain Res. 139 (2), 97–105.

Everaerd, D., Gerritsen, L., Rijpkema, M., Frodl, T., Van Oostrom, I., Franke, B., Tendolkar, I.J.N., 2012. Sex modulates the interactive effect of the serotonin transporter gene polymorphism and childhood adversity on hippocampal volume. Neuropsychopharmacology 37 (8), 1848.

Ewing, G., Tatarchuk, Y., Appleby, D., Schwartz, N., Kim, D., 2015. Placental transfer of antidepressant medications: implications for postnatal adaptation syndrome. Clin. Pharmacokinet. 54 (4), 359–370.

Fairbrother, N., Janssen, P., Antony, M.M., Tucker, E., Young, A.H., 2016. Perinatal anxiety disorder prevalence and incidence. J. Affect Disord. 200, 148–155.

Francis-Oliveira, J., Ponte, B., Barbosa, A.P.M., Veríssimo, L.F., Gomes, M.V., Pelosi, G.G., Moreira, E.G., 2013. Fluoxetine exposure during pregnancy and lactation: Effects on acute stress response and behavior in the novelty-suppressed feeding are age and gender-dependent in rats. Behav Brain Res 252, 195–203.

Galineau, L., Kodas, E., Guilloteau, D., Vilar, M.-P., Chalon, S., 2004. Ontogeny of the dopamine and serotonin transporters in the rat brain: an autoradiographic study. Neurosci. Lett. 363 (3), 266–271.

Galler, J.R., Harrison, R.H., Ramsey, F., Forde, V., Butler, S.C., 2000. Maternal depressive symptoms affect infant cognitive development in barbados. J. Child Psychol. Psychiatry 41 (6), 747–757.

Gemmel, M., Bögi, E., Ragan, C., Hazlett, M., Dubovicky, M., van den Hove, D.L., Pawluski, J.L., 2017a. Perinatal selective serotonin reuptake inhibitor medication (SSRI) effects on social behaviors, neurodevelopment and the epigenome. Neurosci. Biobehav. Rev 85, 102–116.

Gemmel, M., Hazlett, M., Bögi, E., De Lacalle, S., Hill, L.A., Kokras, N., Pawluski, J.L., 2017b. 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.

Glover, M.E., Clinton, S.M., 2016. Of rodents and humans: A comparative review of the neurobehavioral effects of early life SSRI exposure in preclinical and clinical research. Int. J. Dev. Neurosci. 51, 50–72.

Gobinath, A.R., Workman, J.L., Chow, C., Lieblich, S.E., Galea, L.A., 2016. Maternal postpartum corticosterone and fluoxetine differentially affect adult male and female offspring on anxiety-like behavior, stress reactivity, and hippocampal neurogenesis. Neuropharmacology 101, 165–178.

Goecke, T., Voigt, F., Faschingbauer, F., Spangler, G., Beckmann, M., Beetz, A.J., 2012. The association of prenatal attachment and perinatal factors with pre-and postpartum depression in first-time mothers. Achieves of Gynecology and Obstetrics 286, 309–316.

Gordon, J.A., Hen, R., 2004. The serotonergic system and anxiety. NeuroMol. Med. 5 (1), 27–40.

Greenberg, P.E., Sisitsky, T., Kessler, R.C., Finkelstein, S.N., Berndt, E.R., Davidson, J.R., Fyer, A.J., 1999. The economic burden of anxiety disorders in the 1990s. J. Clin. Psychiatry 60, 4327–4435.

Gross, C., Zhuang, X., Stark, K., Ramboz, S., Oosting, R., Kirby, L., Hen, R., 2002. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 416 (6879), 396–400.

Guimaraes, F., Del Bel, E., Padovan, C., Netto, S.M., De Almeida, R.T., 1993. Hippocampal 5-HT receptors and consolidation of stressful memories. Behav. Brain Res. 58 (1-2), 133–139.

Hamilton, B.E., Osterman, M.J., Driscoll, A.K., Rossen, L.M., 2018. Births: provisional data for 2017. National vital statistics reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System 2018.

Hanley, G.E., Brain, U., Oberlander, T.F., 2015. Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior. Pediatr. Res. 78 (2), 174–180.

Hansson, S., Mezey, E., Hoffman, B., 1998. Serotonin transporter messenger RNA in the developing rat brain: early expression in serotonergic neurons and transient expression in non-serotonergic neurons. Neuroscience 83 (4), 1185–1201.

Haring, J.H., Hagan, A., Olson, J., Rodgers, B., 1993. Hippocampal serotonin levels influence the expression of S100β detected by immunocytochemistry. Brain Res. 631 (1), 119–123.

Harris, S.S., Maciag, D., Simpson, K.L., Lin, R.C., Paul, I.A., 2012. Dose-dependent effects of neonatal SSRI exposure on adult behavior in the rat. Brain Res. 1429, 52–60.

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 (1), 49.e41–49.e49.

Hermansen, T.K., Røysamb, E., Augusti, E.-M., Melinder, A., 2016. Behavior and inhibitory control in children with prenatal exposure to antidepressants and medically untreated depression. Psychopharmacology (Berl.) 233 (8), 1523–1535.

Hildyard, K.L., Wolfe, D.A., 2002. Child neglect: developmental issues and outcomes. Child Abuse Neglect 26 (6), 679–695.

Hogg, S., Andrews, N., File, S., 1994. Contrasting behavioural effects of 8-OH DPAT in the dorsal raphénucleus and ventral hippocampus. Neuropharmacology 33 (3-4), 343–348.

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 (2), 60–65.
Ishiwata, H., Shiga, T., Okado, N., 2005. Selective serotonin reuptake inhibitor treatment of early postnatal mice reverses their prenatal stress-induced brain dysfunction. Neuroscience 133 (4), 893–901.
Johns, J., Joyner, P., McMurray, M., Elliott, D., Hofler, V., Middleton, C., 2005. The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. Pharmacol. Biochem. Behav. 81 (4), 769–785.
Kaplan, Y.C., Keskin-Arslan, E., Acar, S., Sozmen, K., 2016. Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: a systematic review and meta-analysis. Reprod. Toxicol. 66, 31–43.
Karpova, N.N., Lindholm, J., Pruunsild, P., Timmusk, T., Castrén, E., 2009. Long-lasting behavioural and molecular alterations induced by early postnatal fluoxetine exposure are restored by chronic fluoxetine treatment in adult mice. Eur. Neuropsychopharmacol. 19 (2), 97–108.
Kenny, P.J., Cheeta, S., File, S.E., 2000. Anxiogenic effects of nicotine in the dorsal hippocampus are mediated by 5-HT1A and not by muscarinic M1 receptors. Neuropharmacology 39 (2), 300–307.
Kessler, R.C., Berglund, P.A., Foster, C.L., Saunders, W.B., Stang, P.E., Walters, E.E., 1997. Social consequences of psychiatric disorders, II: Teenage parenthood. Am. J. Psychiatry 154 (10), 1405–1411.
Kessler, R.C., Foster, C.L., Saunders, W.B., Stang, P.E., 1995. Social consequences of psychiatric disorders, I: educational attainment. Am. J. Psychiatry 152 (7), 1026.
Kim, J., Riggs, K.W., Misri, S., Kent, N., Oberlander, T.F., Grunau, R.E., Rurak, D.W., 2006. Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and breast-feeding. Br. J. Clin. Pharmacol. 61 (2), 155–163.
Kinney, H.C., Broadbelt, K.G., Haynes, R.L., Rognum, I.J., Paterson, D.S., 2011. The serotonergic anatomy of the developing human medulla oblongata: implications for pediatric disorders of homeostasis. J. Chem. Neuroanat. 41 (4), 182–199.
Kiryanova, V., Dyck, R.H., 2014. Increased aggression, improved spatial memory, and reduced anxiety-like behaviour in adult male mice exposed to fluoxetine early in life. Dev. Neurosci. 36 (5), 396–408.
Kiryanova, V., Meunier, S., Vecchiarelli, H., Hill, M., Dyck, R., 2016. Effects of maternal stress and perinatal fluoxetine exposure on behavioral outcomes of adult male offspring. Neuroscience 320, 281–296.
Ko, M.C., Lee, L.J.H., Li, Y., Lee, L.J., 2014. Long-term consequences of neonatal fluoxetine exposure in adult rats. Dev. Neurobiol. 74 (10), 1038–1051.
Kobiella, A., Reimold, M., Ulshöfer, D., Ikonomidou, V., Vollmert, C., Vollstädt-Klein, S., Smolka, M.J.T.P., 2011. How the serotonin transporter 5-HTTLPR polymorphism influences amygdala function: the roles of in vivo serotonin transporter expression and amygdala structure. Transl. Psychiatry 1, e37.
Kostowski, W., Płaźnik, A., Stefański, R., 1989. Intra-hippocampal buspirone in animal models of anxiety. Eur. J. Pharmacol. 168 (3), 393–396.
Kristensen, J., Ilett, K., Hackett, L., Yapp, P., Paech, M., Begg, E., 1999. Distribution and excretion of fluoxetine and norfluoxetine in human milk. Br. J. Clin. Pharmacol. 48, 521–527.
Lauder, J.M., 1990. Ontogeny of the serotonergic system in the rat: serotonin as a developmental signal. Ann. N Y Acad. Sci. 600 (1), 297–313.
Lauder, J.M., Bloom, F.E., 1974. Ontogeny of monoamine neurons in the locus coeruleus, raphe nuclei and substantia nigra of the rat. I. Cell differentiation. J. Comp. Neurol. 155 (4), 469–481.
Lebrand, C., Cases, O., Wehrlé, R., Blakely, R.D., Edwards, R.H., Gaspar, P., 1998. Transient developmental expression of monoamine transporters in the rodent forebrain. J. Comp. Neurol. 401 (4), 506–524.
Lee, L.J., 2009. Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats. Neurotox. Res. 15 (3), 212–223.
Lee, L.J., Lee, L.J.H., 2012. Neonatal fluoxetine exposure alters motor performances of adolescent rats. Dev. Neurobiol. 72 (8), 1122–1132.
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. Nature Neuroscience 11, 1001–1003.
Lidov, H.G., Molliver, M.E., 1982. Immunohistochemical study of the development of serotonergic neurons in the rat CNS. Brain Res. Bull. 9 (1), 559–604.
Lisboa, S.F., Oliveira, P.E., Costa, L.C., Venâncio, E.J., Moreira, E.G., 2007. Behavioral evaluation of male and female mice pups exposed to fluoxetine during pregnancy and lactation. Pharmacology 80 (1), 49–56.
Logsdon, M.C., Wisner, K., Sit, D., Luther, J.F., Wisniewski, S.R.J.D., 2011. Depression treatment and maternal functioning. Depress Anxiety 28 (11), 1020–1026.
Lovejoy, M.C., Graczyk, P.A., O'Hare, E., Neuman, G., 2000. Maternal depression and parenting behavior: a meta-analytic review. Clin. Psychol. Rev. 20 (5), 561–592.
Maciag, D., Simpson, K.L., Coppinger, D., Lu, Y., Wang, Y., Lin, R.C., Paul, I.A., 2006. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology 31 (1), 47.
Malm, H., Brown, A.S., Gissler, M., Gyllenberg, D., Hinkka-Yli-Salomäki, S., McKeague, I.W., Psychiatry, A., 2016. Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J. Am. Acad. Child Adolesc. Psychiatry 55, 359–366.
Manassis, K., Bradley, S., Goldberg, S., Hood, J., Swinson, R.P., 1994. Attachment in mothers with anxiety disorders and their children. J. Am. Acad. Child Adoles. Psychiatry 33 (8), 1106–1113.
McAllister, B., Kiryanova, V., Dyck, R., 2012. Behavioural outcomes of perinatal maternal fluoxetine treatment. Neuroscience 226, 356–366.
Meyer, L.R., Dexter, B., Lo, C., Kenkel, E., Hirai, T., Roghair, R.D., Haskell, S.E., 2018. Perinatal SSRI exposure permanently alters cerebral serotonin receptor mRNA in mice but does not impact adult behaviors. J. Mater.-Fetal Neonatal Med. 31 (11), 1393–1401.
Millard, S.J., Weston-Green, K., Newell, K.A., 2017. The effects of maternal antidepressant use on offspring behaviour and brain development: implications for risk of neurodevelopmental disorders. Neurosci. Biobehav. Rev 80, 743–765.
Mills, R., Alati, R., O'Callaghan, M., Najman, J.M., Williams, G.M., Bor, W., Strathearn, L., 2011. Child abuse and neglect and cognitive function at 14 years of age: Findings from a birth cohort. Pediatrics 127 (1), 4–10.
Misri, S., Reebye, P., Kendrick, K., Carter, D., Ryan, D., Grunau, R.E., Oberlander, T.F., 2006. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am. J. Psychiatry 163 (6), 1026–1032.
Murray, L., Fiori-Cowley, A., Hooper, R., Cooper, P., 1996. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child Dev. 67 (5), 2512–2526.
Nagano, M., Liu, M., Inagaki, H., Kawada, T., Suzuki, H., 2012. Early intervention with fluoxetine reverses abnormalities in the serotonergic system and behavior of rats exposed prenatally to dexamethasone. Neuropharmacology 63 (2), 292–300.
Narboux-Nême, N., Pavone, L.M., Avallone, L., Zhuang, X., Gas-

par, P., 2008. Serotonin transporter transgenic (SERT cre) mouse line reveals developmental targets of serotonin specific reuptake inhibitors (SSRIs). Neuropharmacology 55 (6), 994–1005.
Noorlander, C.W., Ververs, F.F., Nikkels, P.G., van Echteld, C.J., Visser, G.H., Smidt, M.P., 2008. Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. PLoS One 3 (7), e2782.
Oberlander, T.F., Grunau, R.E., Fitzgerald, C., Papsdorf, M., Rurak, D., Riggs, W., 2005. Pain reactivity in 2-month-old infants after prenatal and postnatal selective serotonin reuptake inhibitor medication exposure. Pediatrics 115 (2), 411–425.
Oberlander, T.F., Papsdorf, M., Brain, U.M., Misri, S., Ross, C., Grunau, R.E., 2010. Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age. Arch. Pediatr. Adoles. Med. 164 (5), 444–451.
Oberlander, T.F., Reebye, P., Misri, S., Papsdorf, M., Kim, J., Grunau, R.E., 2007. Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. Arch. Pediatr. Adoles. Med. 161 (1), 22–29.
Olivier, J.D., Valles, A., van Heesch, F., Afrasiab-Middelman, A., Roelofs, J.J., Jonkers, M., . . . Kiliaan, A.J., 2011. Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring. Psychopharmacology (Berl.) 217 (3), 419.
Olson, L., Boreus, L., Seiger, Å, 1973. Histochemical demonstration and mapping of 5-hydroxytryptamine-and catecholamine-containing neuron systems in the human fetal brain. Anat. Embryol. (Berl.) 139 (3), 259–282.
Olson, L., Seiger, Å, 1972. Early prenatal ontogeny of central monoamine neurons in the rat: fluorescence histochemical observations. Zeitschrift für Anatomie und Entwicklungsgeschichte 137 (3), 301–316.
Pacheco, J., Beevers, C.G., Benavides, C., McGeary, J., Stice, E., Schnyer, D.M., 2009. Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. J. Neurosci. 29 (19), 6229–6233.
Patel, T.D., Zhou, F.C., 2005. Ontogeny of 5-HT 1A receptor expression in the developing hippocampus. Dev. Brain Res. 157 (1), 42–57.
Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9, 947–957.
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. 228(1), 159–168.
Pawluski, J.L., Lonstein, J.S., Fleming, A.S., 2017. The neurobiology of postpartum anxiety and depression. Trends Neurosci 40, 106–120.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., ..., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 8 (6), 828–834.
Phan, K.L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E.F., Liberzon, I., Arfanakis, K., 2009. Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. Biol. Psychiatry 66 (7), 691–694.
Popa, D., Léna, C., Alexandre, C., Adrien, J., 2008. Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. The Journal of Neuroscience 28 (14), 3546–3554.
Rampono, J., Simmer, K., Ilett, K., Hackett, L., Doherty, D., Elliot, R., Forman, T., 2009. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. Pharmacopsychiatry 42 (03), 95–100.
Rayen, I., Gemmel, M., Pauley, G., Steinbusch, H.W., Pawluski, J.L., 2015. Developmental exposure to SSRIs, in addition to maternal stress, has long-term sex-dependent effects on hippocampal plasticity. Psychopharmacology 232 (7), 1231–1244.
Rayen, I., Van Den Hove, D.L., Prickaerts, J., Steinbusch, H.W., Pawluski, J.L., 2011. Fluoxetine during development reverses the effects of prenatal stress on depressive-like behavior and hippocampal neurogenesis in adolescence. PLoS One 6 (9), e24003.
Rebello, T.J., Yu, Q., Goodfellow, N.M., Cagliostro, M.K.C., Teissier, A., Morelli, E., Dwork, A.J., 2014. Postnatal day 2 to 11 constitutes a 5-HT-sensitive period impacting adult mPFC function. J. Neurosci. 34 (37), 12379–12393.
Riad, M., Watkins, K.C., Doucet, E., Hamon, M., Descarries, L., 2001. Agonist-induced internalization of serotonin-1a receptors in the dorsal raphe nucleus (autoreceptors) but not hippocampus (heteroreceptors). J. Neurosci. 21 (21), 8378–8386.
Ribas, V.R., Aniceto, H.K.R., Martins, H.A.d.L., Ribas, K.H.d.S., Guerra-Ribas, R.d.M., Fraga, S.d.N., Manhaes-de-Castro, R., 2008. Neonatal administration of fluoxetine did not alter the anxiety indicators, but decreased the locomotor activity in adult rats in the elevated plus-maze. Arq. Neuropsiquiatr. 66 (4), 844–847.
Rodriguez-Porcel, F., Green, D., Khatri, N., Harris, S.S., May, W.L., Lin, R., Paul, I.A., 2011. Neonatal exposure of rats to antidepressants affects behavioral reactions to novelty and social interactions in a manner analogous to autistic spectrum disorders. Anat. Rec. 294 (10), 1726–1735.
Romijn, H.J., Hofman, M.A., Gramsbergen, A., 1991. At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby? Early Hum. Dev. 26 (1), 61–67.
Salari, A.-A., Fatehi-Gharehlar, L., Motayagheni, N., Homberg, J.R., 2016. Fluoxetine normalizes the effects of prenatal maternal stress on depression-and anxiety-like behaviors in mouse dams and male offspring. Behav. Brain Res. 311, 354–367.
Shemer, A., Azmitia, E., Whitaker-Azmitia, P., 1991. Dose-related effects of prenatal 5-methoxytryptamine (5-MT) on development of serotonin terminal density and behavior. Dev. Brain Res. 59 (1), 59–63.
Shen, W., Luo, Z., Zheng, D., Yew, D., 1989. Immunohistochemical studies on the development of 5-HT (serotonin) neurons in the nuclei of the reticular formations of human fetuses. Pediatr. Neurosurg. 15 (6), 291–295.
Simpson, K.L., Weaver, K.J., de Villers-Sidani, E., Lu, J.Y.-F., Cai, Z., Pang, Y., Lin, R.C., 2011. Perinatal antidepressant exposure alters cortical network function in rodents. Proc. Natl. Acad. Sci. 108 (45), 18465–18470.
Smit-Rigter, L.A., Noorlander, C.W., von Oerthel, L., Chameau, P., Smidt, M.P., van Hooft, J.A., 2012. Prenatal fluoxetine exposure induces life-long serotonin 5-HT 3 receptor-dependent cortical abnormalities and anxiety-like behaviour. Neuropharmacology 62 (2), 865–870.
Sprowles, J.L., Hufgard, J.R., Gutierrez, A., Bailey, R.A., Jablonski, S.A., Williams, M.T., Vorhees, C.V., 2016. Perinatal exposure to the selective serotonin reuptake inhibitor citalopram alters spatial learning and memory, anxiety, depression, and startle in sprague-dawley rats. Int. J. Dev. Neurosci. 54, 39–52.
Sprowles, J.L., Hufgard, J.R., Gutierrez, A., Bailey, R.A., Jablonski, S.A., Williams, M.T., Vorhees, C.V., 2017. Differential effects of perinatal exposure to antidepressants on learning and memory, acoustic startle, anxiety, and open-field activity in sprague-dawley rats. Int. J. Dev. Neurosci. 61, 92–111.
Stefański, R., Bidziński, A., Kostowski, W., Plaźnik, A., 1993. Serotonergic innervation of the hippocampus and nucleus accumbens

septi and the anxiolytic-like action of midazolam and 5-HT1A a receptor agonists. Neuropharmacology 32 (10), 977–985.
Tramontina, A.C., Tramontina, F., Bobermin, L.D., Zanotto, C., Souza, D.F., Leite, M.C., Gonçalves, C.-A., 2008. Secretion of S100B, an astrocyte-derived neurotrophic protein, is stimulated by fluoxetine via a mechanism independent of serotonin. Prog. Neuropsychopharmacol. Biol. Psychiatry 32 (6), 1580–1583.
Troutman, B.R., Momany, A.M., 2012. Use of selective serotonin reuptake inhibitors during pregnancy and disorganised infant—mother attachment. Journal of Reproductive and Infant Psychology 30, 261–277.
Tu, W., Cook, A., Scholl, J.L., Mears, M., Watt, M.J., Renner, K.J., Forster, G.L., 2014. Serotonin in the ventral hippocampus modulates anxiety-like behavior during amphetamine withdrawal. Neuroscience 281, 35–43.
Verney, C., Lebrand, C., Gaspar, P., 2002. Changing distribution of monoaminergic markers in the developing human cerebral cortex with special emphasis on the serotonin transporter. Anat. Rec. 267 (2), 87–93.
Ververs, T., Kaasenbrood, H., Visser, G., Schobben, F., de Jong-van den Berg, L., Egberts, T., 2006. Prevalence and patterns of antidepressant drug use during pregnancy. Eur. J. Clin. Pharmacol. 62 (10), 863–870.
Wallace, J.A., Lauder, J.M., 1983. Development of the serotonergic system in the rat embryo: an immunocytochemical study. Brain Res. Bull. 10 (4), 459–479.
Weaver, K.J., Paul, I.A., Lin, R., Simpson, K.L., 2010. Neonatal exposure to citalopram selectively alters the expression of the serotonin transporter in the hippocampus: dose-dependent effects. Anat. Rec. 293 (11), 1920–1932.
Westlye, L.T., Bjørnebekk, A., Grydeland, H., Fjell, A.M., Walhovd, K.B., 2011. Linking an anxiety-related personality trait to brain white matter microstructure: diffusion tensor imaging and harm avoidance. Arch. Gen. Psychiatry 68 (4), 369–377.
Whitaker-Azmitia, P.M., Murphy, R., Azmitia, E.C., 1990. Stimulation of astroglial 5-HT 1A receptors releases the serotonergic growth factor, protein S-100, and alters astroglial morphology. Brain Res. 528 (1), 155–158.
Wilson, C.C., Faber, K.M., Haring, J.H., 1998. Serotonin regulates synaptic connections in the dentate molecular layer of adult rats via 5-HT 1a receptors: evidence for a glial mechanism. Brain Res. 782 (1), 235–239.
Yu, Q., Teixeira, C.M., Mahadevia, D., Huang, Y., Balsam, D., Mann, J.J., Ansorge, M.S., 2014. Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. Mol. Psychiatry 19 (6), 688.
Zheng, J., Xu, D.-F., Li, K., Wang, H.-T., Shen, P.-C., Lin, M., Wang, R., 2011. Neonatal exposure to fluoxetine and fluvoxamine alteres spine density in mouse hippocampal CA1 pyramidal neurons. Int. J. Clin. Exp. Pathol. 4 (2), 162.
Żmudzka, E., Sałaciak, K., Sapa, J., Pytka, K., 2018. Serotonin receptors in depression and anxiety: Insights from animal studies. Life Sci 210, 106–124.
Zoega, H., Kieler, H., Nørgaard, 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 (12), e0144474.