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The effects of maternal antidepressant use on offspring behaviour and brain development: implications for risk of neurodevelopmental disorders

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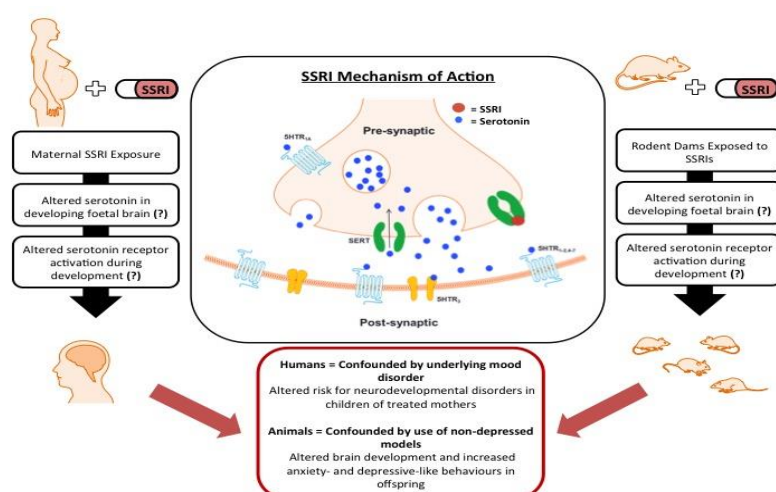
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Graphical Abstract



Highlights:

- 10% of pregnant women are prescribed Selective Serotonin Reuptake Inhibitors
- Serotonin is critical to brain development and behaviour
- SSRI exposure in-utero may influence brain development and offspring behaviour
- We reviewed the effects of SSRI exposure on offspring development and behaviour

Abstract

Approximately 10% of pregnant women are prescribed antidepressant drugs (ADDs), with selective serotonin reuptake inhibitors (SSRIs) the most widely prescribed. SSRIs bind to the serotonin transporter (SERT), blocking the reabsorption of serotonin by the presynaptic neuron and increasing serotonin levels in the synaptic cleft. The serotonergic system regulates a range of brain development processes including neuronal proliferation, migration, differentiation and synaptogenesis. Given the presence of SERT in early brain development, coupled with the ability of SSRIs to cross the placenta and also enter breast milk, concerns have been raised regarding the effects of SSRI exposure on the developing foetus and newborns. In this review, we evaluate preclinical and clinical studies that have examined the effects of maternal SSRI exposure and the risk for altered neurodevelopment and associated behaviours in offspring. While the current body of evidence suggests that maternal SSRI treatment may cause perturbations to the neurobiology, behaviour and ultimately risk for neurodevelopmental disorders in exposed offspring, conflicting findings do exist and the evidence is not conclusive. However given the increasing incidence of depression and number of women prescribed ADDs during pregnancy, further investigation into this area is warranted.

Abbreviations: ADD = Antidepressant Drug; ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism Spectrum Disorders; BSID = Bayley Scales of Infant and Toddler Development instrument; HR = Hazards Ratio; MDD = Major Depressive Disorder; OR = Odds Ratio; SNRI = Serotonin and Norepinephrine Reuptake Inhibitors; SSRI = Selective Serotonin Reuptake Inhibitors; TCA = Tricyclic Antidepressants.

Keywords: Serotonin; SSRI; Brain development; Neurodevelopmental Disorder; Rodent Model; Fluoxetine; Depression; Pregnancy; Antidepressant

1.1 Introduction. Antidepressant drugs (ADDs) are currently one of the most widely prescribed drug classes worldwide, administered to over 10% of the population for the treatment of clinical depression and anxiety-related disorders (Moore et al., 2009; Olfson and Marcus, 2009). Similarly, 8-10% of pregnant women are prescribed ADDs for the treatment of depression (Cooper et al., 2007; Huybrechts et al., 2013). With the overall incidence of depression significantly rising over the last several decades, this value may continue to increase (Huybrechts et al., 2013; Kessler, 2003). While various classes of ADDs exist, selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed to pregnant women (in ~80% of cases) (Huybrechts et al., 2013; Mitchell et al., 2011) and have been considered moderately safe for antenatal use (Oberlander et al., 2009). However, recent analyses indicate that maternal use of SSRIs, particularly paroxetine, is associated with greater risk of structural neuroteratogenic effects (Reefhuis et al., 2015). SSRIs, such as fluoxetine, sertraline, and citalopram (the most commonly prescribed SSRIs during pregnancy (Patil et al., 2011) bind to the serotonin transporter (SERT), blocking the reabsorption of serotonin by the presynaptic neuron and increasing serotonin levels in the synaptic cleft (Hiemke and Härtter, 2000) (Figure 1). While SSRIs cause acute elevations in serotonin concentrations, the antidepressant properties of SSRIs are largely thought to be elicited by downstream mechanisms, such as increases in brain derived neurotrophic factor (BDNF) and subsequent neurogenesis in the prefrontal cortex (PFC) and hippocampus (Martinowich and Lu, 2007). The serotonergic system and other downstream effectors, such as BDNF, are also critical for normal neurodevelopment. This raises concerns about exposure of the developing foetus and newborns to SSRIs as it has been shown that SSRIs administered during pregnancy cross the placenta (Heikkinen et al., 2002) and are excreted in breast milk (Hendrick et al., 2001; Kim et al., 2006). This concern is accentuated by studies demonstrating associations between abnormal neurodevelopment of the serotonergic system and several psychiatric and behavioural disorders, such as Autism Spectrum Disorder (ASD) (Hranilovic et al., 2007; Mulder et al., 2004; Schain and Freedman, 1961), Attention-Deficit Hyperactivity Disorder (ADHD) (Banerjee et al., 2006; Oades et al., 2002; Retz et al., 2008), anxiety and depression (Caspi et al., 2003; Olivier et al., 2011) and schizophrenia (Bleich et al., 1988; Ikeda et al., 2005).

1.2 Development of the Serotonergic System

The serotonergic system plays an important role in early brain development and is critical to a range of processes, including neuronal proliferation, migration, differentiation and synaptogenesis (Vitalis and Parnavelas, 2003; Whitaker-Azmitia, 2001). Serotonergic neurons and receptors appear in the human brain by gestational week 5 (Figure 2); it is one of the earliest monoaminergic systems generated during development (Gaspar et al., 2003; Lambe et al., 2011; Sundström et al., 1993; Whitaker-Azmitia, 2001). By gestational week 15, serotonin cell bodies are in their typical organisation in the raphe nuclei, comprised of nine distinct cell groups spanning from the medulla oblongata through to the midbrain. The caudal division of cell bodies (B1-B5) project serotonergic fibres to the spinal cord, whilst the rostral division (B6-B9) provides the major ascending serotonergic fibres to areas throughout the forebrain, including the cerebral cortex, hippocampus and basal ganglia, and account for 85% of all serotonergic neurons (Glover and Clinton, 2016; Hornung, 2003; Törk, 1990; Sodhi and Sanders-Bush, 2004). Serotonin signals through 7 receptor families, 5-HT₁₋₇, most of which are G-protein coupled, except the ionotropic 5HT₃ receptor subtype (Figure 1). The action of serotonin in the synaptic cleft is terminated by its reuptake by presynaptic SERT and subsequent metabolism by monoamine oxidase A (MAO-A) to 5-hydroxyindoleacetic acid (5-HIAA).

(Insert figure 1 in colour)

In the human brain, SERT expression begins in parallel with the emergence of serotonergic neurons; SERT positive fibres originating from the raphe nucleus reach the telencephalon at gestational week 8, the subplate at gestational week 10 and the cortical plate at gestational week 13 (Verney et al., 2002). A similar neurodevelopmental pattern has been demonstrated in rodents (Figure 2); SERT expression arises in the serotonergic neurons of the raphe nuclei at mid-gestation (embryonic day 13) (Hansson et al., 1998; Rubenstein, 1998) and serotonin fibers project into the telencephalon by embryonic day 17, passing through the septal areas and spreading throughout the cerebral cortex (Sodhi and Sanders-Bush, 2004).

(Insert figure 2 In colour)

While SERT is largely expressed on serotonergic neurons throughout neurodevelopment and maturity, it is also transiently expressed on non-serotonergic neurons. In the rodent brain, SERT expression has been shown to appear on non-serotonergic neurons, including

glutamatergic neurons of thalamocortical pathways, pyramidal neurons in the prefrontal cortex and hippocampus (Chen et al., 2016, 2015), and also projection neurons of the somatosensory and corticolimbic systems, from approximately embryonic day 17 (Homberg et al., 2010; Narboux-Nême et al., 2008). Developmental SERT expression on non-serotonergic neurons in the rodent brain ceases in the first two weeks of postnatal life (equivalent to birth in humans (Semple et al., 2013), and is localised to serotonergic neurons in the mature brain (Narboux-Nême et al., 2008). Likewise in the human brain, an anatomically distinct set of non-serotonergic thalamocortical axons (i.e. internal capsule and corona radiata) have been observed to transiently express SERT between gestational weeks 12 and 14 (Verney et al., 2002). Whether this transient expression of SERT on non-serotonergic corticolimbic and somatosensory neurons also occurs in the human brain has not yet been determined.

The presence of SERT on non-serotonergic neurons and their ability to transiently capture serotonin during this early time period alludes to the possible involvement of serotonin in key neurodevelopmental processes of non-serotonergic systems. Studies have shown that serotonin plays a key role in the development of the neocortex by modulating the migration of cortical neurons (Riccio et al., 2011), and the formation of dendritic spines and branches, as well as dendritic length, in the hippocampus and cerebral cortex (Sodhi and Sanders-Bush, 2004; Vitalis and Parnavelas, 2003). During telencephalic development, monoaminergic afferents and SERT-expressing thalamocortical axons are in close proximity along the internal capsule. These SERT-expressing thalamocortical axons have been shown to take up serotonin, and have been implicated in the migration and proliferation of developing glutamatergic neurons, potentially through subsequent serotonin release (Edgar and Price, 2001; Vitalis and Parnavelas, 2003; Whitworth et al., 2002). In addition, serotonin has been shown to modulate the response of developing thalamocortical axons to guidance cues, such as Netrin-1, via the serotonin receptor (5HTR_{1B/1D}) (Bonnin et al., 2007). The serotonin 5HT_{1A} receptor is highly expressed in the telencephalic proliferative zone in early development, where it modulates cell division and proliferation (Hillion et al., 1994; Lidow and Rakic, 1995; Varrault et al., 1992; Vitalis and Parnavelas, 2003). Recently, studies have shown that serotonin influences the speed and trajectory of migrating GABAergic cortical interneurons via activation of 5HT_{3A} receptors (Murthy et al., 2014), and also encourages the differentiation of early progenitor

cells into glutamatergic neurons in the developing cerebral cortex (Lavdas et al., 1997). Taken together, these findings clearly implicate the serotonergic system as a key regulator of neurodevelopment, of which potential alterations caused by SSRI-exposure are summarized in Figure 3.

Considering the critical role of the serotonergic system in neurodevelopment, it is feasible that manipulation of the serotonergic system during early development has the potential to cause broader disruptions in brain structure and circuitry and lead to associated disturbances in brain function and behaviour. Indeed, increased levels of serotonin during early development, modelled utilising SERT-knockout mice, was found to cause abnormal development of thalamocortical axons and underdevelopment of the somatosensory cortical barrels (Gaspar et al., 2003; Persico et al., 2001), as well as increases in anxiety- and depressive-like behaviours (Ansorge et al., 2004). Behavioural and biological alterations in other serotonergic system knockout models have also been reported with mutants showing increased (5HT_{1A} receptor knockout) and decreased (5HT_{2C} and 5A receptor knockout) anxiety levels, reductions in GABA_A receptor binding and hippocampal neurogenesis (5HT_{1A} receptor knockout), as well as increased aggression in MAO-A (the enzyme responsible for 5HT degradation) knockout mice (for review see Gaspar et al., 2003). Therefore, altering the normal function of the serotonergic system can have broad implications on behavioural and biological phenotypes.

2.1 The behavioural and biological effects of maternal SSRI treatment on exposed offspring: Evidence from human studies

Taking into account the significant neurodevelopmental role that the serotonergic system plays and the widespread expression of SERT during gestation, manipulation to the serotonergic system could have major implications for human neurodevelopment and associated disorders. SSRIs administered during pregnancy are transferred across the placenta, resulting in prenatal SSRI exposure to the foetus; however, the extent and consequences of this exposure on the developing brain are unclear (Hendrick et al., 2001; Kim et al., 2006). Studies examining SSRI concentrations in foetal cord blood from treated mothers have reported concentrations of at least 50% compared to maternal levels (for review see Ewing et al., 2015). Additionally, two enzymes responsible for the metabolism of SSRIs in humans, cytochrome P450 2C and 2D6 (CYP2C and CYP2D6), are low or undetectable in the

foetal liver but increase progressively during early life (Hines and McCarver, 2002; Sadler et al., 2016). Therefore, the foetus and neonate may be particularly sensitive to maternal SSRI exposure due to an inability to eliminate drugs through metabolism by the liver (Hiemke and Härtter, 2000; Kim et al., 2006).

Several studies observing birth outcomes of infants exposed to SSRIs in-utero (as early as the 1st trimester and throughout pregnancy) have identified an increased risk for preterm delivery (Davis et al., 2007; Huang et al., 2014; Maschi et al., 2008; Reis and Källén, 2010), low Apgar scores (Casper et al., 2011, 2003; Jensen et al., 2013; Källén, 2004), increased risk for low birth weight (Huang et al., 2014; Oberlander et al., 2006; Reis and Källén, 2010), frequent intensive care unit admissions (Casper et al., 2011; Galbally et al., 2009), neonatal abstinence syndrome (i.e. effects of withdrawal caused by the cessation of SSRI exposure) (Levinson-Castiel et al., 2006; Nordeng et al., 2001) and risk for cardiac defects (Källén and Otterblad Olausson, 2007; Kornum et al., 2010; Pedersen et al., 2009). Whilst other studies report no significant association between prenatal SSRI exposure and cardiovascular anomalies (Davis et al., 2007) and pre-term birth (Hendrick et al., 2003), a recent study by Reefhuis et al., (2015), suggested that the potential teratogenicity of SSRIs was drug-specific. Using a Bayesian analysis approach, combining results from independent published studies together with data from a multicentre population-based case-control study of birth defects, the authors concluded that only fluoxetine and paroxetine were associated with increased risk of cardiac defects, while paroxetine alone was associated with an increased risk for anencephaly and atrial septal defects (Reefhuis et al., 2015).

While traditional assessments of drug safety during pregnancy have focused on structural or teratogenic defects to exposed offspring, more recent research has focused on the possible long-term effects on brain function, behaviour and the development of neurodevelopmental disorders. Several studies have examined the effects of maternal antidepressant drug treatment on offspring behaviour and risk of neurodevelopmental and psychiatric disorders, with a primary focus on ADHD and ASD (Table 1). These studies exhibit an apparent division into longitudinal studies that track the development of offspring from antidepressant-treated mothers and studies that track the familial history of offspring with ADHD and ASD. While the results of these studies are varied, there is evidence to suggest a possible association between maternal antidepressant drug use and ASD and/or ADHD and their associated behaviours in

exposed offspring. Four out of eight retrospective studies reported significant increases in the risk of ASD following prenatal exposure to antidepressant (primarily SSRI) treatment (Boukhris et al., 2016; Croen et al., 2011; Gidaya et al., 2014; Harrington et al., 2014). Of these studies, two found that maternal SSRI treatment was associated with a 2- fold increased risk in the development of ASD in offspring, with a three-fold increase in risk observed when exposure occurred in the first trimester (Croen et al., 2011; Harrington et al., 2014). Moreover, Croen et al., (2011) found no increase in the risk of ASD in offspring of mothers with a history of depression or any other health disorder in absence of prenatal SSRI treatment, suggesting that SSRI exposure plays an influential role (Croen et al., 2011). Conversely, another study reported that maternal history of depression was associated with a greater risk for ASD in offspring, with an even greater risk observed when combined with maternal SSRI treatment (Rai et al., 2013). While these studies are somewhat conflicting, SSRI treatment could be an indicator of maternal depressive symptom severity that could also contribute to the greater risk of ASD reported in these studies. Interestingly, one study reported that SSRI exposure prior to, but not during pregnancy, increased the risk for ASD in offspring (Clements et al., 2015), further suggesting that the observed risk for ASD as the result of prenatal SSRI exposure is possibly confounded by severity of maternal mental illness. Unfortunately, the measure in severity of maternal mental illness in these studies was based on measures such as frequency of past hospital admissions, which may be insufficient to truly capture symptom severity differences between participants. Nonetheless, Croen et al (2011) did report an increase in risk of ASD in offspring exposed to SSRIs in pregnancy, despite taking into consideration maternal mental health symptom severity and history (Croen et al., 2011) suggesting that symptom severity and history alone may not influence the risks.

Of the retrospective studies that investigated cases of ADHD, two reported a significantly increased risk associated with SSRI exposure and this behavioural disorder (Clements et al., 2015; Figueroa, 2010). One study reported that SSRI treatment during, but not prior to pregnancy was associated with an increased risk for ADHD in offspring (Clements et al., 2015), suggesting that exposure plays an influential role. In comparison to these findings, another study reported an increased risk of ADHD in children of women exposed to SSRIs postnatally only, proposing greater emphasis on the influence that maternal mood disorders play during pregnancy; however, the influence of SSRI-exposure through breast milk on offspring cannot

be ruled out (Figueroa, 2010). Differences in sample sizes, ages and methodology may have contributed to the conflicting findings. For example Clements et al., (2015) recruited data from cases of ADHD ($n=2,243$) in offspring aged 2-19 years, then identified those exposed to maternal SSRIs ($n=62$), whilst Figueroa et al., (2010) recruited data from pregnancies with SSRI exposure ($n=916$) and aligned with cases of ADHD ($n=23$) in offspring aged 0-5 years.

Collectively, with the exception of Malm et al., (2016), who reported an increased risk for depression in adolescent offspring exposed prenatally to SSRIs, the retrospective studies largely neglect the assessment of symptoms specific to anxiety and depressive disorders or later adolescent ages, and focus instead on ASD, ADHD and the juvenile ages, making it difficult to posit the potential longer term effects of maternal SSRI exposure. In addition, though the majority of the retrospective studies indicate that maternal SSRI exposure may increase the risk for developmental disorders in offspring, it is obvious that the exposure period that confers the greatest risk is much deliberated.

While retrospective studies provide the opportunity for large sample sizes and relative ease in data collection, they are limited by their inability to confirm SSRI use/compliance or symptom severity of maternal mood disorders during pregnancies. In comparison, despite lower samples sizes, longitudinal studies have the added benefit of examining more specific subject behaviours and measures of neurodevelopment and associated disorders. Of the ten published longitudinal studies, five reported no significant effects of SSRI exposure on behavioural parameters, as measured using the Bayley Scales of Infant and Toddler Development Instrument (BSID) administered by trained clinicians (Austin et al., 2013; Casper et al., 2003; Galbally et al., 2011) and the Child Behaviour Checklist (CBCL), a subjective, observational questionnaire completed by subject parents or caregivers (Misri et al., 2006; Nulman et al., 2012). The BSID assesses motor, language and cognitive development of infants and toddlers aged 0-3.5, whilst the CBCL aims to measure problem behaviour in children characterized by internalizing, such as withdrawal and anxiety, and/or externalising, such as delinquent or aggressive behaviours (Nøvik, 1999). These studies include small sample sizes ($n=13-35$) that may have limited statistical power to detect any associations. Conversely, five studies with larger sample sizes ($n=28-5,531$) have reported significant associations between maternal SSRI exposure and behavioural disturbances in offspring, including autistic traits, anxiety and externalizing behaviours. These studies were conducted in cohorts of slightly

older children (up to 6 years of age) assessed using the CBCL (Hanley et al., 2015; Hermansen et al., 2016; Marroun et al., 2014; Oberlander et al., 2010) and BSID (Hanley et al., 2013). The question of whether the conflicting nature of these findings is due to the different methodology employed, or other factors such as sample size and age of subjects, needs further investigation. Furthermore, it must be acknowledged that several longitudinal studies lack effective comparison groups that enable separation of the effects of SSRI exposure from the effects of maternal depression (Austin et al., 2013; Galbally et al., 2011; Hanley et al., 2013; Misri et al., 2006; Oberlander et al., 2010). In addition, the longitudinal studies only examine the juvenile years and as such emotional disturbances, such as depression and anxiety, that commonly emerge during adolescent years, were not measured (Paus et al., 2008). Therefore, further studies examining later time periods would help provide a complete spectrum of potential neurobehavioural alterations associated with developmental SSRI exposure.

(Insert table 1 here)

While there has been minimal investigation of the neuro-biological consequences of foetal SSRI exposure, the limited studies that have been conducted (Bellissima et al., 2015; Davidson et al., 2009; Laine et al., 2003; Oberlander et al., 2008; Pawluski et al., 2012, 2009) have focused primarily on aspects of the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter metabolites in cord blood samples, with an absence of studies focusing on longer term changes. One study reported significantly decreased serotonin and its main metabolite, 5HIAA, by as much as 67% in the cord blood of SSRI exposed infants compared to controls (Laine et al., 2003). However, given that sources of foetal serotonin are dynamic and switch progressively during development from exogenous (placental) to endogenous (foetal raphe neurons) sources (Bonnin et al., 2011), caution needs to be taken when interpreting levels of serotonin in cord blood. Furthermore, another study reported a reduction in the dopamine metabolite, homovanillic acid (HVA), and a borderline reduction in cord blood noradrenaline (Laine et al., 2003), suggesting that SSRI exposure can influence neurotransmission systems beyond serotonin. The serotonergic system is a key regulator of the HPA axis and corticotropin releasing hormone (CRH) release is mediated by serotonergic transmission (Heisler et al., 2007b, 2007a). Accordingly, SSRI exposed infants have exhibited significantly

decreased levels of cortisol in cord blood (Davidson et al., 2009) and in salivary samples at three months of age (Oberlander et al., 2008).

Recent studies have investigated other potential markers of neurobiological alterations caused by maternal SSRI exposure in human samples (Table 2). S100 calcium-binding protein β (S100 β) is an astroglial-derived neurotrophic factor used as a marker of CNS cellular damage when detected at elevated biological concentrations (Kleindienst et al., 2007). One study reported significantly increased S100 β levels in maternal blood, amniotic fluid, cord blood and neonatal peripheral blood throughout pregnancy, at birth and 24hours postnatal following maternal treatment with the SSRI paroxetine compared to untreated controls (Bellissima et al., 2015). In addition, infants showing major neurological symptoms (i.e. hypotonia and seizures) at postnatal day 7 exhibited the highest blood S100 β levels (Bellissima et al., 2015). Separating these findings in SSRI-treated mothers from the effects of innate maternal depression are difficult given that no control group for maternal depression was used (Bellissima et al., 2015), particularly when other studies suggest that untreated depressed subjects display higher levels of S100 β (Arolt et al., 2003; Grabe et al., 2001). On the other hand, another study reported decreased S100 β levels in cord blood following SSRI exposure, even after controlling for maternal mood disorder, but reported significantly higher maternal S100 β levels in SSRI treated subjects compared with non-treated (Pawluski et al., 2009). The conflicting findings regarding neonatal S100 β levels between these two studies may be attributed to the specific SSRIs tested with Pawluski et al., (2009) collectively examining a range of SSRIs, whereas Bellissima et al., (2015) included data from those mothers treated with paroxetine only.

Finally, although levels of biological markers taken from blood provide some insight into the potential peripheral neurochemical perturbations occurring as the result of SSRI exposure, there is no guarantee that these peripheral measures accurately reflect changes in the brain. One recent study assessed the brain neurobiology of SSRI-exposed preterm neonates directly via MRI, MRSI and DTI imaging, reporting impaired brain microstructural development and cerebral metabolism in infants exposed to SSRIs (Podrebarac et al., 2017). Although the study provides clear evidence of neurobiological perturbations in SSRI-exposed offspring, further studies investigating the long-term effects of SSRI exposure on central neurotransmitter systems and their metabolites are required to elucidate the potential for these drugs to

manipulate the developing brain. This last point is compounded given the purported role of the serotonergic system in the development of other systems, including glutamate and GABA (refer to section 1.2) and its relationship with neurotrophic markers such as BDNF, and their role in neurogenesis.

(Insert table 2 here)

2.2 Considerations for Human Studies

Human studies are invaluable to clarify the risks associated with maternal SSRI exposure; yet they are confounded by the underlying maternal psychopathology and maternal stress or adversities. Furthermore, human studies often omit or report difficulties measuring the severity of maternal mood disorders, which may be phenotypically masked due to SSRI treatment, and could represent a considerable influence over the observed effects of SSRI exposure on offspring. As iterated by Petersen et al., (2014), SSRI use may be a marker of severity of underlying mental illness and that may confound the interpretation of these clinical findings. Therefore, careful consideration must be given to the interpretation of clinical studies and their implications for the broader population, especially when inherent difficulties in separating the effects of maternal SSRI exposure from confounding factors, such as maternal depression, are often overlooked.

Maternal mood disorders and adversity themselves are factors associated with a greater risk for obstetric complications, impaired pre- and post-natal care and the development of psychopathologies in children (Ashman et al., 2002; Davalos et al., 2012; Glover, 2014; Hammen and Brennan, 2003; Nulman et al., 2002; O'Connor et al., 2002). Systematic reviews have shown that untreated maternal depression is associated with increased markers of infant morbidity, including preterm birth, low birth weight, childhood emotional and behavioural problems and poor cognitive development (Davalos et al., 2012; Gentile, 2015; Steer et al., 1992). Studies have also noted neurobehavioural consequences of untreated maternal depression or maternal adversity on children, with some showing an increased risk for internalizing behaviours (Ashman et al., 2002), decreased cognitive and language development (Nulman et al., 2002), developmental delay (Deave et al., 2008) and an increased risk for depression, anxiety, ADHD and ASD symptomology (Glover, 2014; Hammen and Brennan, 2003; O'Connor et al., 2003, 2002; Rice et al., 2010; Rodriguez and Bohlin, 2005;

Ronald et al., 2011; Van den Bergh and Marcoen, 2004). Untreated maternal depression can also have indirect effects on the offspring through means of unhealthy maternal behaviours, for example studies have found a significant association with pregnant women suffering from depression and cigarette, alcohol and cocaine use in some people (Zuckerman et al., 1989); all well-known to detrimentally affect pregnancy outcomes (Cnattingius, 2004; Eyler et al., 1998; Ornoy and Ergaz, 2010). Finally, prenatal depression remains one of the strongest risk factors for postnatal depression (Robertson et al., 2004); a disorder linked to developmental problems and increased risk of depression in children (Murray et al., 2011; Talge et al., 2007). Severe untreated depression, can also result in suicide, which is a major cause of maternal death (Oates, 2003). Therefore, SSRIs continue to be critically important to the health and well-being of mothers with depression and accordingly, current clinical guidelines from the American Psychiatric Association advise against the discontinuation of SSRI use in pregnancy (though switching from paroxetine may be advised in some instances), particularly if the chance of psychopathological relapse is high (Yonkers et al., 2009). Despite reports of increased risk associated with third trimester SSRI exposure and teratogenic effects or neonatal abstinence syndrome, tapering of SSRI dosage has also been recommended over discontinuation (Yonkers et al., 2009). In addition, although there is some evidence to suggest that nutritional interventions, such as omega-3 supplementation, may improve maternal depression; further research including large-scale clinical trials are required to substantiate alternatives to antidepressant treatment (Kaviani et al., 2014; Larqué et al., 2012). Finally, although some clinical studies report ~2-3x fold increases in risks for neurodevelopmental disorders in offspring exposed to SSRIs (Boukhris et al., 2016; Clements et al., 2015; Croen et al., 2011; Gidaya et al., 2014; Harrington et al., 2014), the fact remains that the overall incidence/prevalence of these disorders in the population is relatively low (incident rate of 38.6 per 100,000 and prevalence of 6 per 1000 for ASD (Jensen et al., 2014; Newschaffer et al., 2007); and incidence rate of 9.9 per 100,000 and prevalence of 1 per 1000 for ADHD (Holden et al., 2013)). The low incidence of behavioural disorders in the general population warrants careful consideration in light of the consequences associated with untreated maternal depression and the risks this pathology poses for the health and wellbeing of the mother and child. Ultimately, this is clearly an area that requires further research with an emphasis on discerning the effects of maternal SSRI treatment from maternal psychopathology on the neurodevelopment and risk for associated disorders in offspring.

3.1 The behavioural and biological effects of maternal SSRI treatment on exposed offspring: Evidence from animal studies

Given the inherent difficulties in assessing the effects of developmental SSRI exposure in humans, researchers have turned to animal models to gain a deeper understanding of the effects of maternal SSRI treatment on exposed offspring. To begin translation of the findings from animal models to the clinic, emphasis needs to be placed on the timeline of SSRI-exposure, and the equivalent neurodevelopmental milestones reached compared to humans. In humans, the blood brain barrier is established at 23-32 weeks gestation, whilst gliogenesis, synaptogenesis and myelination contribute to the peak brain growth occurring at 36-40 weeks gestation (reviewed in Semple et al., (2013)). In rodents, these same milestones are reached at PN1 – 3 and PN7 – 10, respectively (Semple et al., 2013). Indeed, it has been estimated based on neurodevelopmental comparisons that rodent PN7 is equivalent to birth in humans (Clancy et al., 2007). Typically, rodent studies are divided into those that deliver SSRIs to dams during gestation (+/- lactation) and others that deliver SSRIs directly to pups in the early postnatal period. Despite wide variance in other methodological considerations, including drug dosage, administration method and treatment duration, it is clear that SSRI exposure in rodent models can alter neurodevelopment in ways that impact behavioural characteristics of offspring, including increases in anxiety- and depressive-like behaviours, as well as abnormalities in social interaction and exploratory behaviours (Table 3). With the exception of a few studies (Boulle et al., 2016a, 2016b; Glover et al., 2015; Kiryanova et al., 2016; Rayen et al., 2011), the current body of animal literature, does not assess the effects of SSRIs in a depression or anxiety model, overshadowing the clinical relevance of results. Considering depression and anxiety are associated with altered serotonergic development in their own right (Nulman et al., 2012), modelling SSRI exposure in a model of depression or anxiety that mimics the underlying serotonergic pathology may influence the effects of SSRIs on the serotonergic system.

Of the 13 studies assessing maternally administered SSRIs, 12 report significant increases in anxiety- or depressive-like behaviour and/or deficits in cognition in offspring ranging in age from PN8 to PN140 (Table 3). Specifically, seven of these studies demonstrated an increase in anxiety-like behaviours following doses ranging from 0.3 – 25mg/kg Fluoxetine (Bairry et al., 2006; Boulle et al., 2016b; Lisboa et al., 2007; Noorlander et al., 2008; Olivier et al., 2011;

Smit-Rigter et al., 2012) and 10mg/kg citalopram (Sprowles et al., 2016), with exposure durations from GD0 to PN21. Six studies reported increases in depressive-like behaviour measured by the forced swim test, shock escape test and novelty-suppressed feeding test (Boulle et al., 2016a; Glover et al., 2015; Lisboa et al., 2007; Noorlander et al., 2008; Rayen et al., 2011; Sprowles et al., 2016). Conversely, six studies found either no differences (Glover et al., 2015; Rayen et al., 2011), or decreases in anxiety-like behaviour (Francis-Oliveira et al., 2013; Kiryanova et al., 2016; McAllister et al., 2012), and no changes (Francis-Oliveira et al., 2013; Olivier et al., 2011) or decreases in depressive-like behaviour (Francis-Oliveira et al., 2013; McAllister et al., 2012). In addition, five studies assessed cognition, with one noting significant deficits in the passive avoidance test (Bairy et al., 2006), and another reporting reduced performance in the Morris water maze in SSRI-exposed offspring; the latter study also reported increased prepulse inhibition (Sprowles et al., 2016). On the contrary, other studies reported no changes (Kiryanova et al., 2016; McAllister et al., 2012; Olivier et al., 2011), or increases in cognition (spatial memory) in the Morris water maze (Bairy et al., 2006). The differences in findings may be attributable to differences in drug dosages, subject sex and behavioural test protocols (Table 3). For example, one study reported a decrease in ambulation during the OFT in males only, but not females, and an increase in immobility time in the forced swim test specifically in females, following maternal fluoxetine exposure (Lisboa et al., 2007). Another study reported negligible alterations in the behaviour of female rodents exposed to a high dose of fluoxetine (McAllister et al., 2012), excluding males from the study. Further studies are required to assess the dose effects of SSRI exposure on offspring behaviour of both sexes.

Studies examining the effects of postnatal SSRI exposure (ranging from PN0 – PN21) on offspring behaviour provided the greatest consistency in findings (Table 3). All studies reported significant increases in anxiety-like behaviour evident through decreases in exploration and/or increases in anxiogenic parameters in the open field test, elevated plus maze, light-dark test, novelty-induced hypophagia and novelty-suppressed feeding tests (Ansorge et al., 2008, 2004; Karpova et al., 2009; Lee, 2009; Lee and Lee, 2012; Rodriguez-Porcel et al., 2011; Zheng et al., 2011). Three studies assessed the effects of postnatal exposure on offspring depressive-like behaviour. Of those, two reported increases in learned helplessness in the shock escape test (Ansorge et al., 2008, 2004) and one reported decreased immobility

time in the forced swim test (Karpova et al., 2009). The conflicting findings of the three latter studies are likely to be attributable to the different behavioural tests used to measure depressive-like behaviour, given that the drug dose and administration methods were similar. Indeed, although the forced swim test has been validated as an effective measure of antidepressant efficacy and depressive-like behaviour in rodents (Slattery and Cryan, 2012), others have suggested that in some cases immobility behaviour may resemble a survival mechanism rather than behavioural despair (Nishimura et al., 1988). Despite the relative consistency in findings of these studies exposing offspring to SSRIs postnatally, translation of the results must be taken with caution. In the clinical scenario, SSRIs are transferred via the mother in utero or through breast milk, which has been shown to influence the pharmacokinetics of SSRIs (Heikkinen et al., 2002; Velasquez and Bonnin, 2016). Therefore, directly exposing offspring to SSRIs postnatally could have an exaggerated influence on their behaviour and neurobiology. Nonetheless, these consistent findings suggest that the first 14 days of postnatal development in rodents, (third trimester in humans (Clancy et al., 2007)), a period marked by peak brain growth (Semple et al., 2013), represents a time period perhaps more vulnerable to the effects of developmental SSRI exposure.

As previously mentioned, the majority of animal studies assess the effects of developmental SSRI exposure in naïve rodents. A limited number assess the effects in models of maternal depression (Boulle et al., 2016a, 2016b; Glover et al., 2015; Kiryanova et al., 2016; Rayen et al., 2011), which arguably represents the clinical scenario more closely. Several studies have modelled SSRI exposure in dams exposed to environmental stress (as a model of maternal depression) through restraint, intense light exposure, confinement or other stressors (Table 3) (Boulle et al., 2016b, 2016a; Kiryanova et al., 2016; Rayen et al., 2011). Of those studies, two reported increased depressive-like behaviour in the forced swim test in SSRI-exposed offspring of maternally stressed dams (Boulle et al., 2016a; Rayen et al., 2011). Boulle et al., (2016a) reported an increase in immobility in the forced swim test in fluoxetine exposed female (but not male) Boulle et al., (2016b)) offspring regardless of maternal stress, whilst Rayen et al., (2011) reported increased immobility time in fluoxetine-exposed offspring of maternally stressed dams only. Another reported that SSRI-exposed offspring born of dams subjected to stress have decreased anxiety-like behaviour compared to SSRI-exposed offspring born of dams naïve to stress (Boulle et al., 2016b). Similarly, Kiryanova et al., (2016)

reported a reduction in anxiety-like behaviour in male offspring of maternally stressed dams exposed to fluoxetine, suggesting that exposure could be beneficial in ameliorating the effects of maternal mood on offspring, at least in relation to anxiety-related behaviour. In comparison to these studies, another study investigated the effects of maternal SSRI exposure in selectively bred rats to determine whether innate disturbances in emotional behaviour altered susceptibility (or resistance) to the effects of paroxetine treatment in offspring (Glover et al., 2015). Using selectively bred Sprague-Dawley rats that exhibited decreased anxiety-like behaviour (high responders) or increased anxiety-like behaviour (low responders), Glover et al., (2015) showed significantly greater immobility times (depressive-like behaviour) in the forced swim test in offspring of paroxetine-treated low responder dams, but no other differences in any parameters of the open field test, forced swim test and elevated plus maze (Glover et al., 2015). Taken together these findings suggest that the effects of developmental SSRI exposure can differ substantially in models of maternal adversity and depression (which appears to reflect the findings observed in the clinic). Furthermore, animal studies have highlighted an influence of sex on the effects of SSRI exposure in offspring that warrants further investigation.

(Insert table 3 here)

There is mounting evidence from human and animal studies to suggest neurobehavioural alterations in offspring exposed to SSRIs (Tables 1 and 3). Understanding the biological foundations of such exposure might help elucidate causative mechanisms underlying behavioural alterations and increased risk profiles, and assists in the development of appropriate preventative strategies.

As SSRIs bind to and inhibit SERT, resulting in increased synaptic levels of serotonin, it is reasonable to hypothesise that SSRI exposure could lead to altered development of aspects of the serotonin system. Several studies have focused on the effect of developmental SSRI exposure on the developmental expression of SERT. Specifically, it was reported that SERT densities at adolescence (PN28) were significantly increased in the hippocampus, amygdala and lateral hypothalamus, decreased in the dorsomedial hypothalamus and substantia nigra, and unchanged in the raphe nuclei, of fluoxetine-exposed rodent offspring (Cabrera-Vera and Battaglia, 1998). The findings indicated brain region specific changes and a particular vulnerability of the limbic system (Cabrera-Vera and Battaglia, 1998). Interestingly, the same

study noted no significant differences in SERT densities between exposed and control groups at adulthood (PN70), suggesting that the effects of developmental SSRI exposure on SERT are transient in nature and become negligible in later life (Cabrera-Vera and Battaglia, 1998). On the contrary another study reported *reductions* in SERT expression in the raphe nucleus that persisted during adolescence (PN20) and adulthood (PN90) following exposure to fluoxetine (Noorlander et al., 2008). The same study also reported increases in anxiety- and depressive-like behaviour at both PN20 and PN90 in offspring exposed to SSRIs in-utero, providing a potential behavioural translation to the alterations in SERT expression (Noorlander et al., 2008). Another study assessing serotonergic neurons in the raphe nucleus of offspring at PN56 reported marked reductions in neuronal number and axonal terminals as a result of SSRI exposure (Silva et al., 2010). The contrast in findings in the raphe nucleus between these studies (Cabrera-Vera and Battaglia, 1998 and Noorlander et al., 2008) may be attributed to the use of different species (rat vs. mouse) as well as different drug doses and administration methods (10mg/kg s.c. vs. 0.8mg/kg i.p. fluoxetine). Interestingly, a high maternal fluoxetine dosage did not produce longer lasting changes in SERT expression in the brain of offspring (Cabrera-Vera and Battaglia, 1998), which seems paradoxical but may allude to a greater influence of the drug administration method used in these studies. Accordingly, unlike subcutaneous, the pharmacokinetics of intraperitoneal injections parallels those administered orally given that they are absorbed through the mesenteric vessels and undergo first pass metabolism by the liver (Turner et al., 2011), and could result in a greater ratio of active metabolite to parent drug.

Taken together, it may be suggested that SERT expression is altered through a) decreased serotonergic neurons at their origin (raphe nucleus) and hence decreased SERT expression, and/or b) alterations in serotonergic projections to areas including the hippocampus and the subsequent altered expression of SERT, or c) the down/up-regulation of SERT in response to increased extracellular serotonin. Surprisingly, given the effect of SSRIs on the serotonergic system, few studies to-date have assessed the potential alterations to serotonergic receptors or associated signalling. Recently, two studies have reported alterations in serotonergic signalling in offspring as the result of SSRI-exposure (King et al., 2017; Meyer et al., 2017). One study, reported a significant decrease in P11, a trafficking protein that regulates cell surface expression of the 5HT_{1b/d} receptor, in offspring exposed to maternal citalopram

treatment (King et al., 2017). Another reported significant increases in the mRNA of several serotonin receptors (5HT_{1a}, 5HT_{2a}, 5HT_c), SERT and Tryptophan Hydroxylase-2 in adult offspring as the result of developmental SSRI exposure (Meyer et al., 2017). These findings from recent studies, compounded with reports from SERT knock-out (KO) rodents showing reduced 5HT_{1A} receptor binding in the raphe, hypothalamus, amygdala and septum (Li et al., 2000), and increased 5HT_{2A/2C} receptor binding in the hypothalamus and amygdala (Li et al., 2003) highlight an area that clearly warrants further investigation.

Given the neurotrophic role of serotonin during neurodevelopment (Gaspar et al., 2003), animal studies have also focused on the effects of developmental SSRI exposure on dendritic and neuronal mapping, and markers of neurogenesis, growth and development in offspring (Table 4). All studies report significant cellular alterations to some extent with varying SSRI exposure duration, dosage and exposure time points (Lee, 2009; Lee and Lee, 2012; Silva et al., 2010; Smit-Rigter et al., 2012; Swerts et al., 2010; Zheng et al., 2011). Exposing embryos to SSRIs during gestation induced significant morphological alterations, such as a decrease in neuronal number in the foetal frontal lobe at GD21 following 10mg/kg fluoxetine treatment on GD9, 10 and 11 (Swerts et al., 2010). This study provides clear evidence of neuronal alterations in exposed offspring; however, examination of any potentially permanent alterations from birth to adulthood is required. Another study assessed pyramidal neuronal complexity (quantified by measuring dendritic branching and length) throughout adolescence to adulthood and reported a significant reduction in complexity following administration of 0.6mg/kg/day fluoxetine to dams during GD8 – GD18 (Smit-Rigter et al., 2012). The study provided evidence to suggest alterations caused by SSRI exposure persist to adulthood.

As discussed previously, a limited number of animal studies assess the effects of developmental SSRI exposure in clinically relevant models. Several recent studies have assessed the effects of SSRI exposure on the neurobiology of offspring using a model of maternal adversity by subjecting dams to stress (Boulle et al., 2016b, 2016a; Rayen et al., 2011). Although varied in methodology, these studies collectively show significant influences of SSRI exposure in animal models of stress (Table 4). One study reported a decrease in hippocampal neurogenesis and proliferation, and increase in depressive-like behaviour in adolescent offspring exposed to maternal stress (Rayen et al., 2011). The same study noted that these findings were corrected when the offspring were also exposed to maternal SSRI

treatment (Rayen et al., 2011), suggesting that SSRI-exposure has the potential to reverse the negative effects of maternal depression on offspring, at least in relation to hippocampal neurogenesis. It has been widely suggested that the anti-depressive characteristics of SSRIs occurs via downstream mechanisms by increasing BDNF expression and subsequent neurogenesis (Martinowich and Lu, 2007). In contrast to this notion, one study assessing SSRI-exposure during development showed reduced levels of hippocampal BDNF mRNA expression in male and female offspring (Boulle et al., 2016a, 2016b). However, when examined in a model of maternal adversity, it was shown that the SSRI exposure corrected an observable increase in hippocampal BDNF induced by maternal stress in female offspring; while in the males, exposure to maternal stress alone or in combination with fluoxetine caused no effect (Boulle et al., 2016b). These sex-specific findings highlight the need for a greater focus on assessing the influence of sex on SSRI exposure and outcomes of maternal adversity.

(Insert table 4 here)

3.2 Considerations for Animal Studies

Animal studies, whilst being a step away from the clinic, have begun to address the question of whether the reported adverse effects of maternal SSRI treatment on offspring are the result of SSRI exposure or a response to innate maternal depression and/or adversity. However, a number of limitations and challenges arise when translating preclinical findings to the clinical scenario. Firstly, with the exception of studies that model maternal depression using environmental stressors, most studies administer SSRIs to healthy dams, which does not represent the clinical scenario. Indeed, the very presence of maternal depression, a disorder characterized by an underlying serotonergic pathology, could influence the effects of maternal SSRI exposure on offspring. One current animal model of depression, the Wistar-Kyoto rat (WKY), exhibits serotonergic and behavioural abnormalities similar to human depressive disorder (Arango et al., 2001; Lemos et al., 2011; Paré, 1994; Pare and Tejani-Butt, 1996; Quan-Bui et al., 1984; Scholl et al., 2010; Sullivan et al., 2006; Zhang et al., 2005) and could provide an invaluable tool for investigating the effects of SSRI exposure in a more clinically relevant setting. For example, the WKY exhibits increased anxiety- and depressive-like behaviour, decreased basal serotonin and 5HIAA concentrations, decreased SERT density in hippocampal and cortical brain regions, decreased 5HT_{1a} receptor density and a reduction in the serotonin rate limiting enzyme, tryptophan hydroxylase; all of which have been

reported in clinical cases of MDD (Arango et al., 2001; Lemos et al., 2011; Paré, 1994; Pare and Tejani-Butt, 1996; Quan-Bui et al., 1984; Scholl et al., 2010; Sullivan et al., 2006; Zhang et al., 2005). Acknowledging that MDD is not characterised by abnormalities in the serotonergic system alone, these serotonergic alterations in both clinical cases of MDD and the WKY rat could underpin significant differences in response to SSRI exposure compared to the response observed in otherwise healthy subjects. Furthermore, the few animal studies modelling maternal adversity have shown that maternal SSRI treatment differentially affects offspring neurodevelopment and behaviour compared to subjects born of dams absent of adversity (Boulle et al., 2016a, 2016b; Kiryanova et al., 2016; Rayen et al., 2011). Overall, further research utilising appropriate models of depression or adversity are required in order to determine the effects of maternal SSRI exposure on offspring in a clinically relevant setting.

The second limitation to consider when interpreting evidence from animal models is the variation in SSRI dosages and treatment duration between studies. Fluoxetine, which appears to be the SSRI of choice for animal studies, ranges in dosages from 0.3mg/kg to 25mg/kg in animal studies whilst in the clinic, daily fluoxetine doses of 20 – 80mg are commonly prescribed (Beasley et al., 2000). Further investigation into the dose range that is clinically relevant for rodent studies is required. The critical neurodevelopmental time period which SSRI exposure confers the greatest changes are also unknown. As such, variance in the timing and duration of SSRI exposure during and after gestation remains a major difference in methods between rodent studies (Tables 3 and 4). As previously discussed animal studies can be divided into those that administer SSRIs maternally, thereby indirectly exposing offspring (similar to the clinical scenario), or those that directly administer SSRIs to offspring in early life. Neurodevelopmental milestones occurring in rodents between PN1 – PN10 are equivalent to those occurring during 23 – 40 weeks gestation in humans (Semple et al., 2013). Thus, postnatal exposure in rodents represents developmental exposure during the third trimester in humans only and should be interpreted as such. It is still unclear from human studies whether there are periods either during pregnancy or after that confer greater risks associated with SSRI exposure. Further animal studies are required to examine the time-dependent effects of developmental SSRI exposure on offspring.

Finally, animal studies have been useful in the assessment of the molecular effects of SSRI exposure on offspring; however, they have largely focused on the serotonergic system and

neuronal topography, with evidence suggesting that SSRI exposure can produce alterations to serotonergic (Raphe) neuronal number, SERT densities and neuronal/dendritic mapping in offspring (see Table 4.). Further examination of other neurotransmitter systems implicated in the neurobiology and pathology of various developmental neuropsychiatric disorders is required. Human studies have suggested an increased risk of ADHD, ASD and depression in SSRI-exposed offspring; disorders which are characterized by gross alterations in glutamatergic, GABAergic and neurotrophic signalling (Brambilla et al., 2003; Castrén and Rantamäki, 2010; Coghlan et al., 2012; Dölen et al., 2007; Duman et al., 2000; Dwivedi et al., 2003; Hashemi et al., 2016; Hashimoto, 2010; Homberg et al., 2014; Kim et al., 1982; Knable et al., 2004; Küçükibrahimoğlu et al., 2009; Lin and Sibille, 2013; Mitani et al., 2006; Sanacora et al., 2012). Indeed, the purported increased risk of inducing developmental disorders associated with maternal SSRI exposure could be related to the perturbed development of a range of systems, not only serotonin itself. Investigation of other neurotransmitter and neurotrophic systems would provide valuable insight into broader alterations caused by maternal SSRI exposure and form a basis for future studies.

4. Concluding Remarks

In conclusion, the current body of evidence suggests that maternal SSRI treatment may cause perturbations to the neurobiology, behaviour and ultimately risk for neurodevelopmental disorders in exposed offspring. However, conflicting findings do persist and the evidence summarised in the current review regarding the safety of SSRI use during pregnancy or whilst breast feeding is far from conclusive. Evidence from human studies suggest that SSRI exposure during neurodevelopment may be associated with an increased risk for neurodevelopmental disorders, such as ADHD and ASD, and mood disorders including depression; however, these studies are often confounded by the presence of the underlying maternal psychopathology. Difficulties in quantifying or accounting for the symptom severity of the maternal psychopathology are often inherent to clinical studies, and since SSRI treatment could be phenotypically masking symptoms, the findings warrant careful consideration. Furthermore, given that untreated maternal depression and adversity themselves are associated with an increased risk for neurodevelopmental disorders; maternal SSRI use could in fact be a marker of symptom severity of the underlying mood disorder, which itself contributes to the reported risk. Contrary to this notion, preclinical studies have

reported alterations in behaviour and neurobiology in offspring as the result of developmental SSRI-exposure in otherwise healthy animals, suggesting that SSRI exposure can cause long lasting perturbations to neurodevelopment, irrespective of the innate maternal mood disorder. Although valuable in assessing the effects of developmental SSRI-exposure in isolation, these studies are limited by the fact that they use healthy or naïve animals otherwise free of any underlying psychopathology. In the clinic, SSRI treatment and an underlying mood disorder occur in combination and it may be that the underlying mood disorder confers a degree of resistance (or exacerbation), or at least influences the effects of SSRI-exposure on offspring. The pervading question that remains unanswered is: if SSRI use does increase the risk of neurodevelopmental disorders in offspring, which of the two factors - the underlying maternal psychopathology or the SSRI treatment – has a greater influence on this risk. Further research utilizing models of depression is required in order to clarify the answer to this question in a manner that truly discerns the effects of SSRI-exposure from the innate maternal mood disorder on offspring neurodevelopment and risk for associated disorders. Considering the number of women prescribed ADDs during pregnancy, further research into this area is warranted.

Conflict of Interest:

The authors have no conflicting financial interests to declare.

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Figure Captions

Figure 1. Selective serotonin reuptake inhibitors (SSRIs) block the serotonergic transporter (SERT), which inhibits the reuptake of serotonin, raising synaptic serotonin concentrations that causes prolonged and exaggerated serotonin receptor activation. Serotonin exerts its effects via a myriad of g-protein coupled receptors (5HTR_{1-2, 4-7}) and ionotropic receptor (5HTR₃) subclasses. **(a)** Serotonin-containing vesicles fuse with the pre-synaptic membrane; **(b)** spilling their contents into the synaptic cleft. **(c)** SERT removes serotonin from the synaptic cleft, modulating the action of serotonin on its receptors. **(d)** SSRIs bind to SERT and inhibit removal of serotonin from the cleft. **(e)** Activation of presynaptic and **(f)** **(g)** postsynaptic serotonin receptors exerts varying inhibitory and excitatory effects depending on the subclass and location, and regulates synaptic transmission and associated signaling cascades.

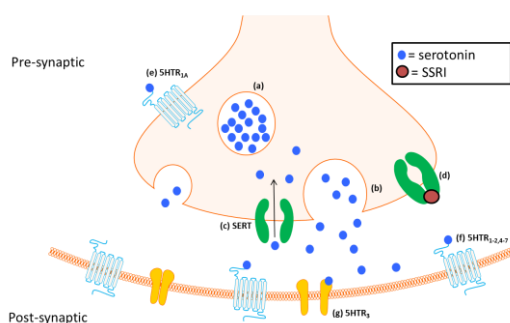


Figure 1

Figure 2. Schematic of SERT expression in rodents and humans from early gestation to adulthood. (a) In rodents, SERT expression follows a similar neurodevelopmental pattern as humans, beginning in the raphe neurons at Embryonic Day (ED) 13 then extending to non-serotonergic neurons at ED17; SERT expression on non-serotonergic neurons ceases in the rat brain by postnatal day (PN)12. **(b)** In humans, SERT expression arises in raphe neurons corresponding with the development of the serotonergic system at gestational week (GW) 5, and remains through to adulthood. At ~GW12, SERT expression arises in non-serotonergic thalamocortical neurons. Whether transient SERT expression occurs in other non-serotonergic neurons in humans, similar to the rodent brain, remains to be determined. Figure adapted from Homberg et al., (2009).

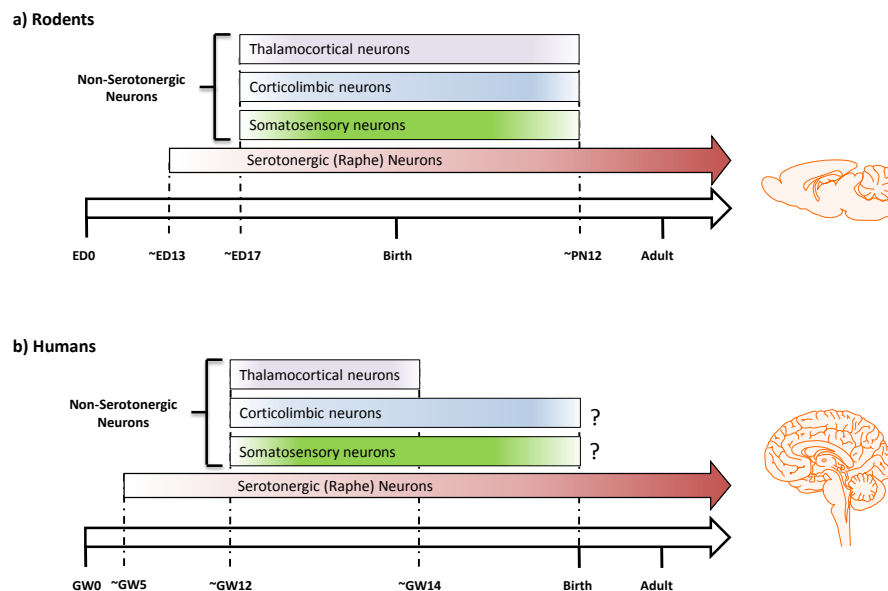


Figure 2

Table 1: Effects of maternal SSRI exposure on offspring neurodevelopmental disorders: evidence from human studies.

Study	Antidepressants	Participants (n) with or without symptomology of Major Depressive Disorder (+/- MDD)	Age of offspring studied	Findings
Longitudinal Studies				
Austin et al., (2013)	SSRIs (Fluoxetine, Sertraline, Citalopram, Escitalopram, Paroxetine, Fluvoxamine) SNRI (venlafaxine) TCA (Dothiepin)	n = 35 treated/exposed + MDD n = 23 controls untreated - MDD	17-24 months	Nil significant effects of in-utero SSRI exposure on motor, language or cognitive development – assessed using the Bayley Scales of Infant and Toddler Development instrument (BSID-III).
Casper et al., (2003)	SSRIs (Fluoxetine, Sertraline, Paroxetine, Fluvoxamine)	n = 31 treated/exposed + MDD n = 13 controls untreated + MDD	6-40 months	Nil significant effects of in-utero SSRI exposure on infant neurodevelopmental outcomes measuring motor, language and cognitive development - assessed using BSID-II.
Misri et al., (2006)	SSRIs (Fluoxetine, Sertraline, Paroxetine)	n = 22 treated/exposed + MDD n = 14 controls untreated -MDD	4-5 years	Nil significant differences between groups in internalizing behaviours , based on parental/teacher self-report using the Child Behaviour Checklist (CBCL) (which is designed to screen for psychological disorders and associated behaviours, including anxiety, depression, social interaction, aggressiveness, attention and cognition)(Mazefsky et al., 2011)
Oberlander et al., (2010)	SSRIs (fluoxetine, paroxetine, sertraline, venlafaxine, Citalopram)	n = 33 treated/exposed + MDD n = 42 controls untreated - MDD	3 years	Children exposed to SSRIs and maternal depressed mood had significantly increased internalizing behaviours reported using the CBCL.

Galbally et al., (2011)	SSRIs (sertraline, venlafaxine, citalopram)	n = 22 treated/exposed + MDD n = 19 controls untreated - MDD	19-35 months	Children exposed to SSRIs scored lower on motor subscales , particularly fine motor and gross motor, using the BSID-II. Nil significant effects on infant language and cognitive development.
Hermansen et al., (2016)	SSRIs (Fluoxetine, Paroxetine, Sertraline, Escitalopram and citalopram) SNRI (Venlafaxine) Mirtazapine	n = 28 treated/exposed + MDD n = 42 controls untreated + MDD n = 33 controls untreated - MDD	5-6 years	Children exposed to SSRIs had significantly increased internalizing and externalizing behaviour measured by the CBCL.
Hanley et al., (2015)	SSRIs (Fluoxetine, Paroxetine, Sertraline, Venlafaxine, Citalopram)	n = 44 treated/exposed + MDD n = 66 controls untreated, of which n = 10 +MDD	3 – 6 years	Children exposed had significantly increased anxiety and internalizing behaviours at 3 and 6 years of age , measured using the CBCL.
El Marroun et al., (2014)	SSRI (paroxetine, fluoxetine, sertraline, fluvoxamine and citalopram)	n = 69 treated/exposed + MDD n = 376 controls untreated + MDD n = 5,531 controls untreated - MDD	1.5-6 years	Prenatal SSRI exposed offspring showed higher risk for autistic traits and development of pervasive developmental problems compared to those exposed to maternal depression only – measured by the CBCL and the Social Responsiveness Scale, which focuses specifically on dimensions that relate to that of autism spectrum disorders, such as social cognition, communication and autistic mannerism (Constantino et al., 2003).

Hanley et al., (2013)	SSRIs (paroxetine, fluoxetine, sertraline, venlafaxine, citalopram)	n = 31 treated/exposed + MDD n = 52 controls untreated - MDD	10 months	Children exposed to SSRIs scored significantly lower on gross motor, social-emotional and adaptive behaviour using the BSID-III, and after controlling for MDD.
Nulman et al., (2012)	SSRIs (sertraline, paroxetine, citalopram, fluoxetine, fluvoxamine). SNRIs (venlafaxine)	n = 62 treated/exposed (SSRI) + MDD n = 62 treated/exposed (SNRI) + MDD n = 54 controls untreated + MDD n = 62 controls untreated - MDD	3-6 years	IQs of children exposed to venlafaxine and SSRIs were significantly lower compared to children of mothers with untreated MDD and controls with no history of MDD or ADD treatment. Nil significant differences in cognitive or behavioural abnormalities of exposed groups assessed using the Child Behaviour Checklist.
Retrospective Studies				
Hviid et al., (2013)	SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine)	n = 6,068 SSRI exposed of which n= 835 mothers + MDD n= 52 offspring + ASD n = 620,807 control of which 2647 mothers + MDD	0 – 10 years	SSRI use during pregnancy was not associated with an altered risk of ASD.
Sorensen et al., (2013)	SSRIs, SNRI, TCA	n = 8,833 ADD exposed, of which n= 1,756 mothers + MDD n= 104 + ASD Of those exposed to ADD; n = 7,506 SSRI exposed n = 673 SNRI exposed n = 642 TCA exposed	5-9 years	Prenatal exposure to SSRIs was not associated with a significantly altered risk for ASD in offspring.

		n = 646,782 controls, of which; n= 4,324 mothers + MDD n= 5,333 + ASD		
Boukhris et al., (2016)	SSRIs, SNRIs, TCA, Monoamine Oxidase Inhibitors (MAOI)	n = 4724 ADD exposed, of which; n = 46 + ASD n = 3290 mothers + MDD n = 140,732 controls, of which; n = 1008 + ASD n = 14,651 mothers + MDD	0 – 11 years	SSRI use was associated with increased risk of ASD in offspring, when exposed in the second and/or third trimester only (HR 1.87), after accounting for confounders.
Brown et al., (2017)	SSRIs	n = 2837 pregnancies ADD exposed, of which; n = 1176 + Bipolar or MDD n = 2364 other depressive/anxiety disorder n = 58 offspring +ASD n = 33069 pregnancies without ADD exposure, of which; n = 3175 + Bipolar or MDD n = 13589 other depressive/anxiety disorder n = 335 offspring +ASD	4 – 12 years	In-utero SSRI exposure was not associated with increased risk of ASD in offspring.
Figuerola (2010)	SSRIs, Bupropion, TCA	n = 1030 ADD exposed, of which; n = 28 +ADHD n = 3532 children of mothers +MDD, of which; n = 88 +ADHD n = 29, 329 children of mothers –MDD, of	0 – 5 years	Significant increase in ADHD in offspring exposed to SSRIs postnatally, and not before/during pregnancy (OR 2.04). Significant increase in ADHD in offspring exposed to Bupropion during pregnancy, and not before/after (OR 3.63).

		which; n = 239 +ADHD		
Brandlistuen et al., (2015)	SSRIs, TCA, Other	n = 141 ADD exposed, of which; n = 90 +MDD n = 20,039 not exposed, of which; n = 3831 +MDD	0-3 years	Significant increase in anxiety symptoms in offspring exposed to ADDs ($r=0.64$, $p<0.05$ regression analysis) after adjusting for MDD during pregnancy, MDD history, smoking, alcohol and co-medication. Measured using the CBCL.
Clements et al., (2015)	Antidepressants (categorized by their 5-HT transporter affinity – High: fluoxetine, paroxetine, duloxetine, sertraline, escitalopram. Moderate: citalopram, fluvoxamine, venlafaxine. Low: nefazodone, bupropion, mirtazapine).	n = 1,377 ASD, of which n= 128 ASD subjects had a mother with history of + MDD n= 4,022 controls, of which n= 225 subjects had mother + MDD n = 2,243 ADHD, of which n= 184 subjects had mother + MDD n = 5,631 controls, of which n= 214 subjects had mother + MDD	2-19 years	ADD exposure during but not prior to pregnancy was associated with ADHD (OR 1.69) , after adjusting for MDD ADD use prior to pregnancy but not during was associated with ASD (OR 1.91) , after adjusting for MDD
Croen et al., (2011)	SSRI, TCA and DAA (dual action ADD)	n = 298 ASD, of which 10 mothers + MDD n = 1,507 controls, of which 44 mothers + MDD	12 to 16 years	Two-Fold increased risk of ASD associated with SSRI exposure during the year prior to delivery (OR 2.2) (including before and during pregnancy), with the strongest effect associated with treatment in first trimester (OR 3.8). No increase in risk of ASD in children of mothers with a history of mental health treatment and no SSRI use.
Gidaya et al., (2014)	SSRIs (fluoxetine, citalopram, paroxetine, sertraline,	n = 5,215 ASD, of which; n = 76 SSRI exposed n= 55 mothers + MDD	8-17 years	In utero exposure to SSRIs increased risk for ASD (OR 1.8) , after adjusting for maternal depression and any SSRI indication.

	fluvoxamine, escitalopram).	n = 52,150 controls Of which; n = 365 SSRI exposed n = 347 mothers + MDD		
Harrington et al., (2014)	SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram)	n = 492 ASD, of which 122 mothers + MDD n = 154 developmental delay, of which 40 mothers + MDD n = 320 controls, of which 67 mothers + MDD	2 to 5 years	SSRI use associated with greater risk of ASD (OR 2.91), with strongest association occurring with first-trimester exposure (OR 3.22) and developmental delay in boys (OR 3.39) (authors report invalid sample size for girls)
Malm et al., (2016)	SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine)	n = 15,729 SSRI exposed, of which; n = 60 + ASD n = 160 + ADHD n = 60 + Depression n = 65 + Anxiety n = 9,651 maternal psychiatric disorder, no SSRI, of which; n = 79 + ASD n = 137 + ADHD n = 30 + Depression n = 39 + Anxiety n = 31,394 controls, nil SSRI exposure, nil maternal psychiatric disorders, of which; n = 100 + ASD n = 124 + ADHD n = 30 + Depression n = 62 + Anxiety	0 – 14 years	SSRI exposure was associated with increased rates of depression in early adolescence (HR 1.78) but not with ASD or ADHD.
Rai et al., (2013)	SSRI, TCA	n = 4,429 ASD, of which 44 mothers + MDD n = 43,277 control, of which 272 mothers + MDD	0-17 years	Maternal history of depression was associated with a higher risk of ASD in offspring (OR 1.49). Of the subsample with available data on ADD exposure, this association was limited to women reporting ADD use during pregnancy.

Table 2: Effects of maternal antidepressant administration on biological measures in offspring: Evidence from human studies

Study	Antidepressants	Participants (n)	Measurements Taken	Main Findings
Bellissima et al. (2015)	SSRI (Paroxetine n = 75)	n = 75 SSRI exposed + MDD or other mood disorders n = 231 controls untreated - MDD or other mood disorders	S100 β protein concentrations assessed in maternal blood, amniotic fluid, cord blood and neonatal peripheral blood. Samples taken at: -16-20, 27-30 and 35-40 weeks pregnancy (maternal blood). - Birth (amniotic fluid) - 24 hours postnatal (arterial and venous cord blood).	<ul style="list-style-type: none"> • Significant increase in S100β levels in maternal blood, amniotic fluid, and arterial and venous cord blood at all time points. % Difference in median S100β levels 16-20 weeks (+233%) 27-30 weeks (+220%) 35-40 weeks (+157%) Birth (+1425%) 24 hours (+829%)
Davidson et al. (2009)	SSRIs (paroxetine n = 8, fluoxetine n = 7, citalopram n = 6)	n = 21 exposed (details of maternal mood disorders unknown) n = 20 control untreated - MDD or other mood disorders	Birth (cord blood) <ul style="list-style-type: none"> - cortisol - Thyroid Stimulating Hormone (TSH) - Insulin-like growth factor (IGF-1) - Dehydroepiandrosterone (DHEA) Placenta <ul style="list-style-type: none"> - IGF-1 receptor (IGF-1R) Urine (newborn) <ul style="list-style-type: none"> - 5-HIAA 	<ul style="list-style-type: none"> • Significant decrease (-31%) in cord blood cortisol levels in the SSRI exposed group. • Significant increase (+31%) in cord blood TSH levels in SSRI exposed group. • Significantly lower (-70%) IGF-I level in infants exposed to citalopram only. • Significantly elevated (+100%) level of placental (IGF-1R) in SSRI exposed group. • Nil significant difference in DHEA and 5HIAA
Laine et al. (2003)	SSRIs (n=20 Fluoxetine; n=20 Citalopram)	n = 20 SSRI exposed (n=10 + MDD; n=10 + panic disorder) n = 20 control untreated - MDD or other	Birth (cord blood) <ul style="list-style-type: none"> - 5-HT - 5-HIAA - Homovanillic Acid (HVA) (dopamine metabolite) - Noradrenaline - Prolactin 	<ul style="list-style-type: none"> • Significantly decreased cord 5-HT (-67%), 5-HIAA (-18%) and HVA (-23%), serum prolactin (-29%) in the SSRI exposed

		mood disorders		<p>infants compared to control.</p> <ul style="list-style-type: none"> • Borderline significant decrease (-46%; p=0.05) cord Noradrenaline in SSRI exposed.
Oberlander et al. (2008)	SSRIs	<p>n = 31 SSRI exposed (maternal mood disorder history not stated)</p> <p>n = 45 control untreated - MDD or other mood disorders</p>	<p>Cortisol collected at 3 months' age (saliva) at three daily time points, before, during, and after an information processing task.</p> <p>An additional measure of cortisol was taken the next day in the afternoon/evening.</p>	<ul style="list-style-type: none"> • No significant differences in saliva cortisol levels between infants during the time points associated with the information processing task. • Evening cortisol was significantly lower (-65%) in SSRI exposed infants compared to control.
Pawluski et al. (2009)	SSRIs paroxetine n =14, fluoxetine n = 6, sertraline n = 6, citalopram n = 4	<p>n = 36 exposed + MDD or other mood disorders</p> <p>n = 17 controls untreated - MDD or other mood disorders</p>	<p>Birth (cord blood)</p> <p>- S100β pg/ml</p>	<ul style="list-style-type: none"> • Prenatal SSRI exposure significantly lowered (-16%) neonatal serum S100β levels compared to controls.
Pawluski et al., (2012)	SSRIs	<p>36 Weeks (n) n = 47 control untreated - MDD or other mood disorders</p> <p>n = 29 exposed + MDD or other mood disorders</p> <p>Neonate (n) n = 40 control untreated - MDD or other mood disorders</p>	<p>Serum at 36 weeks and neonates (cord blood)</p> <p>- Cortisol-binding globulin (CBG)</p> <p>- Cortisol</p> <p>Saliva (infants 3month old)</p> <p>- cortisol</p>	<ul style="list-style-type: none"> • Significant increases in serum CBG (+33%) of neonates exposed to SSRIs after vaginal delivery. • No significant differences in levels of other measured parameters.

		n = 25 exposed + MDD or other mood disorders		
Podrebarac et al., (2017)	<p>SSRIs (citalopram n = 5, Sertraline n = 1, Paroxetine n = 1, Cipralex n = 1)</p> <p>SNRI (Venlafaxine n = 3)</p> <p>SSRI + NDRI (n = 1)</p> <p>SSRI + Benzodiazepine (n = 1)</p>	<p>Pre-term Neonates</p> <p>n = 14 ADD exposed + MDD</p> <p>n = 163 control untreated – MDD or other mood disorders</p>	<p>MRI, DTI (Diffusion Tensor Imaging) and MRSI (multivoxel chemical shift imaging) at 2x time points to assess white and gray matter development. Imaging measures were taken once within weeks of birth (once clinically stable) and then at term equivalent age.</p> <p>Measures taken (DTI)</p> <ul style="list-style-type: none"> - FA (Fractional Anisotropy) - MD (mean diffusivity) - RD (radial diffusivity) - AD (axial diffusivity) <p>Measures taken (MRSI)</p> <ul style="list-style-type: none"> - N-acetylaspartate (NAA) - Lactate - Total choline (Cho) <p>Bayley-III at 18months of age was used to assess neurobehavioural outcomes.</p>	<ul style="list-style-type: none"> • Significantly increased FA and decreased AD and RD values in cortical white matter (centrum semiovale). • Significantly increased FA values in deep subcortical gray matter in the caudate, lentiform nucleus and thalamus • Significantly higher Lactate/Cho and reduced NAA/Cho levels in the calcarine region in SSRI exposed • Nil significant differences in Bayley-III scores at 18months

Abbreviations: SSRIs = selective serotonin reuptake inhibitors, IGF-I = insulin-like growth factor, IGF-IR = insulin-like growth factor receptor, TSH = thyroid stimulating hormone, 5-HT = 5-hydroxytryptamine, 5-HIAA = 5-hydroxyindoleacetic acid, HVA = homovanillic acid, DHPG = dihydroxyphenylglycine, S100B = S100 calcium-binding protein B.

Table 3: Effects of maternal antidepressant administration on biological measures in exposed offspring: evidence from animal studies.

Study (Shaded studies indicates those implementing models of maternal depression/a diversity).	Species, Strain, Drug Dose, Route and Duration	Test and age performed	Main Findings: (SSRI-exposed offspring compared to control unless otherwise stated. Percentages given are approximations)
Prenatal/maternal exposure			
Baird et al., (2006)	Species/Strain Wistar Rats (n= 16 offspring/group) Dose Fluoxetine 8 and 12mg/kg Route and Duration GD6 – GD20 Oral (dissolved in water)	PN8-49 (pre-adolescence to adolescence) Negative Geotaxis (NG) Open Field Test (OFT) Rotarod Test (RT) Morris Water Maze (MWM) Elevated Plus Maze (EPM) Passive Avoidance (PA)	NG – Flx 8mg/kg increased time to turn 180° at PN10 (+20%) and PN12 (+53%). Flx 12mg/kg decreased time to turn 180° at PN10 (-6%) and increased time at PN12 (+44%) OFT – Increased central, peripheral and total crossings at PN18 (Flx 8mg/kg: +320%, +127% and +133%. Flx 12mg/kg: +136%, +110% and +110%). Decreased central, peripheral and total crossings at PN35 (Flx 8mg/kg: -52%, -15% and -20%. Flx 12mg/kg: -38%, -23% and -25%). No differences on PN56. RT – Increased retention time at PN22 (Flx 12mg/kg: +350%) and PN49 (Flx 8 and 12mg/kg: +70%) MWM – Flx 8mg/kg: Decrease in time to escape at PN24 (-29%). Flx 12mg/kg decrease time to escape at PN24 and PN29 (-32% and -50%). PA – Flx 12mg/kg: increase in latency to enter dark compartment (+96%) EPM – No significant differences Summary – SSRI exposure caused a transient delay in motor development, favourable effect on cognition and learning at higher doses and decreased exploratory behaviour at adolescence.

Glover et al., (2015)	<p>Species/Strain Sprague-Dawley Rats (high responders and low responders, n= 24 offspring/group)</p> <p>Dose Paroxetine 10mg/kg</p> <p>Route and Duration 7 days prior to mating – PN21 Oral (dissolved in water)</p>	<p>PN75 (Adult) Locomotor response to novelty (LRN) EPM Forced Swim Test (FST)</p>	<p>FST – exposed low-responders had increased immobility compare to vehicle low-responders (+50%). LRN and EPM – no differences</p> <p>Summary – SSRI exposure exacerbated low-responder's depressive-like behaviour but had no effect on high responders.</p>
Lisboa et al., (2007)	<p>Species/Strain Swiss Mice (n= 9-17 offspring/group)</p> <p>Dose Fluoxetine 7.5mg/kg</p> <p>Route and Duration GD0 – PN21 Gavage</p>	<p>PN30-40 (Adolescence) and PN70 (Adult) OFT EPM FST Intruder-resistant test (IRT) Hot plate test (HPT)</p>	<p>Male: OFT – Decreased ambulation at PN40 (-16%) IRT – Increased latency to first attack (+65%) EPM, FST and HPT – no differences</p> <p>Summary – Males: SSRI exposure induced decreased exploratory behaviour at adolescence and decreased reactivity/impulsivity in adults.</p> <p>Female: FST – Increased immobility both PN30 (+41%) and PN70 (+22%)</p> <p>OFT, EPM and HPT – no differences</p> <p>Summary - Females: SSRI exposure increased depressive-like behaviour at both adolescence and adulthood.</p>
Kiryanova et al., (2016)	<p>Species/Strain C57BL/6 Mice (n= 16-17 offspring/group)</p> <p>Dose Fluoxetine 25mg/kg</p> <p>Route and Duration GD15 to PN12 Oral (dissolved in drinking water)</p> <p>Stress (maternal depression model) Combination of restricted access to food, continuous lighting, cage tilt, foreign object in cage, paired housing of dams, soiled cage, irregular tones, restraint</p>	<p>PN56 (Adult) OFT EPM Passive Avoidance Test (PAT) MWM Prepulse Inhibition (PPI) IRT Social Behaviour (SB)</p>	<p>EPM – Increase time in open arms in both stressed and non-stressed offspring (+96%). IRT – Increase in time spent (+223%) engaged in aggressive behaviour.</p> <p>OFT, PAT, MWM and PPI – no difference</p> <p>Summary – SSRI exposure caused decreases in anxiety and increases in aggression in adulthood, largely independent of maternal stress.</p>

	and white noise from GD4 – GD18.		
Olivier et al., (2011)	<p>Species/Strain Wistar Rats (n= 7-16 offspring/group)</p> <p>Dose Fluoxetine 12mg/kg</p> <p>Route and Duration GD11 – PN1 Gavage</p>	<p>PN28-35 (Adolescence) and PN65 (Adult)</p> <p>Novelty Suppressed Feeding (NSF) OFT EPM Conditioned Place Aversion (CPA) EPM – After Stress (EPMS) FST Sucrose Preference Test (SPT) Adolescent Social Play (ASP) Adult Social Play (AdSP)</p>	<p>NSF – increased latency to start eating (+110%) CPA – increased freezing time in the shock compartment (+5%) EPMS – decreased time spent in open arms (-45%) AdSP – decreased amount of pinning behaviour (-46%) OFT, EPM, FST, SPT, ASP and SeB – no difference Summary – SSRI exposure caused increases in anxiety-like behaviour. No effect on depressive-like behaviour was observed.</p>
Noorlander et al., (2008)	<p>Species/Strain C57BL/6 Mice (n= 5-13 offspring/group)</p> <p>Dose Fluoxetine 0.3, 0.6 or 0.8mg/kg Fluvoxamine 4.2mg/kg</p> <p>Route and Duration GD8 – 18 Intraperitoneal (IP)</p>	<p>P20 (pre-adolescence) and PN90 (adult)</p> <p>EPM OFT NSF</p>	<p>EPM – increased duration in closed arms at both PN20 (Flx: +23%, Flv: 14%) OFT – decreased distance travelled in the centre arena at adulthood (Flx: -56%) NSF – increased latency to feed at adulthood (Flx: +240%) Summary – SSRI exposure caused increases in anxiety-like and depressive-like behaviour</p>
McAllister et al., (2012)	<p>Species/Strain C57BL/6 Mice (n= 16-17 offspring/group)</p> <p>Dose Fluoxetine 25mg/kg</p> <p>Route and Duration GD15 – PN12 Oral (dissolved in drinking water)</p>	<p>PN73 – 83 (adult)</p> <p>EPM OFT Horizontal Ladder (HL) FST MWM PPI Fear Conditioning (FC)</p>	<p>EPM – reduced time spent in closed arms (-21%) FST – longer latency to first bout of immobility (+25%) OFT, HL, MWM, PPI and FC – no difference Summary – SSRI exposure caused decreases in anxiety- and depressive-like behaviours.</p>
Boulle et al., (2016a)	<p>Species/Strain Sprague-Dawley Rats (n= 13-16 offspring/group)</p>	<p>PN140 (adult)</p> <p>OFT Elevated Zero</p>	<p>Male: OFT – Fluoxetine exposure decreased centre crossing in naïve offspring</p>

Boulle et al., (2016b)	Dose Fluoxetine 5mg/kg Route and Duration PN1 – PN21 Osmotic Minipumps Stress (maternal depression model) Restraint 3x daily under bright light for 45 minutes from GD15 – GD21.	Maze (EZM) FST	compared to maternally stressed offspring (-50%). FST – decreased escape driven behaviour in maternally stressed offspring regardless of treatment (-12%). EZM – no differences Summary – In male offspring SSRI exposure in combination with maternal stress decreased anxiety-like behaviour. Female: FST – increased immobility (+100%) OFT and EZM – no differences Summary - In females, SSRI exposure increased depressive-like behaviour regardless of maternal stress.
Rayen et al., (2011)	Species/Strain Sprague-Dawley Rats (n= 9-11 offspring/group) Dose Fluoxetine 5mg/kg Route and Duration PN1 – PN21 Osmotic Minipumps Stress (maternal depression model) Restraint 3x daily under bright light for 45 minutes from GD15 – GD20.	PN32 (adolescence) OFT FST	FST – Increased immobility in offspring born of maternally stressed dams (+150%). OFT – no difference Summary – SSRI exposure reversed the decrease in depressive-like behaviour observed in unexposed maternally stressed offspring.
Francis-Olivier et al., (2013)	Species/Strain Wistar Rat Dose Fluoxetine 5mg/kg Route and Duration GD0 – PN21 Gavage	PN35 (adolescence) and PN75 (adult) SPT NSF	NSF – decreased latency to feed at adolescence (-30%) SPT – no difference Summary – SSRI exposure caused decreases in anxiety-like and depressive like-behaviour in offspring at adolescence.
Smit-Rigter et al., (2012)	Species/Strain C57BL/6 Mice (n/group not specified) Dose Fluoxetine 0.6mg/kg Route and Duration GD8 – GD18 IP	Unknown age of testing NSF	NSF – Increased latency to feed (+66%) Summary – SSRI exposure caused increases in anxiety-like and depressive like-behaviour in offspring.
Prenatal/maternal exposure and postnatal/pup exposure			

Sprowles et al., (2016b)	<p>Species/Strain Sprague-Dawley Rats (n= 9-23 offspring/group)</p> <p>Dose Citalopram 10mg/kg</p> <p>Route and Duration (Dams) GD6 – GD21 2x daily Subcutaneous Injection (SC)</p> <p>Route and Duration (Offspring) PN1 – PN20 2x daily SC</p>	<p>PN60 (adult) Straight Channel Swimming (SCS) Cincinnati Water Maze (CWM) MWM OFT EZM Marble Burying (MB) PPI SB FST</p>	<p>MWM – Increased latency to reach platform (+40)</p> <p>OFT – decreased centre crossing (-66%, females only)</p> <p>MB – increased burying of marbles (+140%)</p> <p>PPI – increased response amplitudes (day 1, +280%; day 2, +110%)</p> <p>FST – decreased latency to first bout of immobility (-100%)</p> <p>SCS, CWM, EZM and SB – no difference</p> <p>Summary – SSRI exposed offspring had alterations in cognition and increased anxiety- and depressive-like behaviour.</p>
Postnatal/pup exposure			
Lee and Lee (2012)	<p>Species/Strain Wistar Rats (n= 14-15/group)</p> <p>Dose Fluoxetine 20mg/kg</p> <p>Route and Duration PN0 – PN4 SC</p>	<p>PN30 (adolescence) OFT EPM RT</p>	<p>OFT – decreased locomotor activity (-23%)</p> <p>RT – decreased latency to fall (-44%)</p> <p>EPM – no difference</p> <p>Summary – SSRI exposed offspring had increased anxiety-like behaviour, evident through decreased exploratory behaviour and impaired motor function.</p>
Ansorge et al., (2004)	<p>Species/Strain SERT Knockout Mice (+/+)(+/-)(-/-) (n= 13-27/group)</p> <p>Dose Fluoxetine 10mg/kg</p> <p>Route and Duration PN4 – PN21 IP</p>	<p>PN84 (adult) OFT EPM</p>	<p>OFT – decreased distance travelled (-40%), reduced total ambulatory time (-38%) and vertical activity (-75%)</p> <p>EPM – decreased entries into both arms (-30%)</p> <p>NSF – increased latency to feed in (+/-) mice only (+130%)</p> <p>SE – Increased latency to escape (+150%)</p> <p>Summary – SSRI exposure increased anxiety- and depressive-like behaviour evident through reduced exploratory behaviours, increased latency to feed, and increased latency to escape in SERT (+/+) and (+/-) offspring. Had no effect on SERT (-/-) offspring.</p>
Ansorge et al., (2008)	<p>Species/Strain SERT Knockout Mice (+/+)(+/-) (n= 32-65/group)</p>	<p>PN84 (adult) OFT EPM NSF</p>	<p>OFT – reduced ambulatory time (-18 to -30%)</p> <p>EPM – reduced entries into either arms (-10 to -22%)</p>

	Dose Fluoxetine 10mg/kg Desipramine 10mg/kg Citalopram 10mg/kg Clomipramine 20mg/kg Route and Duration PN4 – PN21 IP	Novelty Induced Hypophagia (NIH) Shock Escape (SE)	NSF – increased latency to feed (+60 to +45%) NIH – increased latency to drink (+83 to +100%) SE – increased latency to escape (+25 to +38%) Summary – SSRI exposed had increased anxiety- and depressive-like behaviour and reduced exploratory behaviour.
Zheng et al., (2011)	Species/Strain GFP-transgenic mice and wild-type C57 mice. (n/group not specified) Dose Fluoxetine (10mg/kg) Fluvoxamine (10mg/kg) Route and Duration PN4 – PN21 IP	PN91 (adult) OFT	OFT – decreased distance travelled (-37%) Summary – SSRI exposure increased anxiety-like behaviour evident through decreased exploratory behaviour.
Karpova et al., (2009)	Species/Strain C57BL/6 Mice (n= 9-12/group) Dose Fluoxetine (10mg/kg) Route and Duration PN4 – PN21 IP	PN110 (adult) Light-Dark Test (LDT) OFT FST	LDT – reduction in rearing (-42%) and increased immobility (+11%) OFT – reduced rearing (-30%) increased immobility in central arena (+42%) FST – decreased immobility time (-38%) Summary – SSRI-exposed offspring had increased anxiety-like behaviour but reduced depressive-like behaviour.
Lee, (2009)	Species/Strain Wistar Rats (n = 12 – 15/group) Dose Fluoxetine (10mg/kg) Route and Duration PN0 – PN6 SC	PN30 – 35 (adolescence) HPT Gap-Crossing Test (GCT) OFT	HPT – increased latency to first licking (+110%) GCT – decreased crossable gap distance (-36%) OFT – decreased total (-20%) and central (-37%) ambulation and decreased rearing (-19%) Summary – SSRI-exposed offspring exhibited greater pain thresholds. Impaired environmental perception (gap-crossing test) and increased anxiety-like behaviour.
Rodriguez-Porcel et al., (2011)	Species/Strain Long Evans Rats (n = 12 – 22/group) Dose Fluoxetine (5mg/kg) Citalopram (10mg/kg) Bupropion (15mg/kg)	PN25 – 39 (adolescence) Locomotor Tone (LT) Novel Object Approach (NOA) Juvenile Play (JP)	Adolescence (PN25-39) LT – increased immobility in response to tone (+180%) NOA – reduced time spent investigating the novel object (-33%) in males JP – reduced pinning (-82 to -98%) in

	Route and Duration PN8 – PN21 2x daily SC	PN89 – 184 (adult) Object- Conspecific Preference (OCP) SB	males and boxing in both male (-71 to -80%) and females (-71%). Adult (PN89-184) OCP – reduced time spent investigating conspecific subject (-58%) SB – disrupted mounting behaviour Summary – SSRI-exposure increased anxiety-like behaviour and impaired social and sexual behaviour in offspring.
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Abbreviations: Flx = Fluoxetine; Flv = Fluvoxamine; GD = Gestational Day; PN = Postnatal Day; NG = Negative Geotaxis; OFT = Open Field Test; RT = Rotarod Test; MWM = Morris Water Maze; EPM = Elevated Plus Maze; PA = Passive Avoidance Test; LRN = Locomotor Response to Novelty; FST = Forced Swim Test; IRT = Intruder Resistant Test; HPT = Hot Plate Test; PAT = Passive Avoidance Test; PPI = Prepulse Inhibition Test; SB = Social Behaviour; NSF = Novelty-Suppressed Feeding; CPA = Conditioned Place Aversion; EPMS = Elevated Plus Maze after Stress; SPT = Sucrose Preference Test; ASP = Adolescent Social Play; AdSP = Adult Social Play; SeB = Sexual Behaviour; IP = Intraperitoneal; SC = Subcutaneous; HL = Horizontal Ladder; FC = Fear Conditioning; EZM = Elevated Zero Maze; CWM = Cincinnati Water Maze; MB = Marble Burying Test; SCS = Straight Channel Swimming; NIH = Novelty Induced Hypophagia; SE = Shock Escape Test; LDT = Light-Dark Test; GCT = Gap-Crossing Test; LT = Locomotor Tone; NOA = Novel Object Approach; JP = Juvenile Play; OCP = Object Conspecific Recognition

Table 4: Effects of maternal antidepressant administration on biological measures in exposed offspring: evidence from animal studies.

Study (Shaded studies indicates those implementing models of maternal depression/adversity).	Species, Strain, Drug Dose, Route and Duration	Analyses	Main Findings
Prenatal/maternal exposure			
Fornaro et al., (2007)	Species/Strain Sprague-Dawley rat dams. (n=9 to 11/group) Dose Fluoxetine (10mg/kg) Route and Duration Oral gavage daily to dams from GD11 to GD21	Serotonin concentrations in Placenta and foetal lungs Rat foetuses were collected via caesarean section on GD21	<ul style="list-style-type: none"> • Prenatal FLX exposure significantly reduced (-38%) placental tissue serotonin content. Did not alter lung serotonin content.
Noorlander et al., (2008)	Species/Strain Mice (C57Bl/6-Jlco) (n= 3-6/group) Dose Fluoxetine (0.3, 0.6 or 0.8mg/kg). Route and Duration I.P. injection daily to dams from GD8 to GD18.	Dorsal raphe nucleus examined via autoradiography for SERT binding (PN20 and PN90)	<ul style="list-style-type: none"> • Significant decreases at PN20 (-40%) and PN90 (-53%) in SERT binding in the raphe nucleus after prenatal exposure to FLX compared to controls (dose-dependent exposure).
Cabrera-Vera & Battaglia (1998)	Species/Strain Sprague-Dawley Dams (n= 7/group) Dose Fluoxetine (10mg/kg) Route and Duration S.C. injection daily to dams from GD13 to GD20	PN28 and PN70 Cortex, hippocampus, septum, amygdala, basal ganglia and raphe nucleus – autoradiography for SERT binding.	PN28 Following prenatal FLX exposure <ul style="list-style-type: none"> • Significant increases in SERT densities in the CA2 and CA3 areas of the hippocampus (+47% and +38% respectively). • Significant increases in SERT densities in basolateral (+32%) and medial (+44%) amygdaloid nuclei and lateral hypothalamus (+21%) of offspring compared to controls. • Significant reductions in SERT densities in dorsomedial

			<p>hypothalamus (-21%) and substantia nigra (-19%)</p> <ul style="list-style-type: none"> • Nil significant differences in SERT densities in raphe nucleus <p>PN70 Following prenatal FLX exposure</p> <ul style="list-style-type: none"> • nil significant differences in SERT densities in any examined brain regions compared to control
<p>Female offspring study Boulle et al., (2016a)</p> <p>Male offspring study Boulle et al., (2015b)</p>	<p>Species/Strain Sprague-Dawley Dams (n= 7/group)</p> <p>Groups Prenatal stress + VEH Prenatal stress + FLX Control + VEH Control + FLX</p> <p>Dose Fluoxetine (5mg/kg)</p> <p>Route and Duration Osmotic minipumps from PN1 to PN21.</p> <p>Stress (exposure to confinement and bright light for 45min) induced on GD14 to assigned dams, occurring 3x daily until end of pregnancy.</p>	<p>Offspring (PN168)</p> <p>Hippocampus - Quantitative reverse transcriptase PCR (qRT-PCR), analyses of genes associated with BDNF/TrkB signalling pathway</p> <p>- Chromatin immunoprecipitation (ChIP), quantification of fragments of promoter regions of target genes in BDNF/TrkB signalling pathway</p>	<p>Female</p> <ul style="list-style-type: none"> • Significant decreases in hippocampal BDNF exon IV mRNA levels in FLX-exposed offspring (-10% non-stressed group; -20% stressed group) • Significant negative correlation ($r = -0.33$, $p = 0.02$) between hippocampal BDNF exon IV mRNA levels and immobility in the forced swim test. <p>Male</p> <ul style="list-style-type: none"> • Significant decreases in BDNF IV (-20%) and TrkB (-40%) mRNA expression in the hippocampus of FLX-exposed offspring. • Significant decreases in hippocampal BDNF mRNA (-20%) expression of prenatally stressed subjects regardless of treatment.
King et al., (2017)	<p>Species/Strain CD-1 Mice</p> <p>Dose Citalopram 20mg/kg/daily</p> <p>Route and Duration GD8 – 17 Oral (dissolved in drinking water)</p>	<p>Immunohistochemistry on foetal brains (GD17) was used to measure P11, Netrin-G1, 5HT, and Phospho-Histone H3.</p> <p>Western blot on</p>	<ul style="list-style-type: none"> • Significant decreases in number of stained PH3+ cells in caudal subventricular cortex (~40%), medial hippocampal neuroepithelium (~50%) and lateral (~40%) and medial (~50%) ganglionic eminence compared to controls.

		foetal brains (GD17) was used to measure P11 and 5HT1B/D relative levels, in the cortex, thalamus and hindbrain.	<ul style="list-style-type: none"> • Significant decrease in p11 expression in the thalamus compared to controls (~50%).
Morrison et al., (2004)	Species/Strain Sheep ewe (n=7-8/group) Dose Fluoxetine (98.5µg/kg) Route and Duration Polyvinyl catheters to dam for 8 days, commencement ranged from GD118 – 122 ±4-5 days.	Foetal blood (sampled daily during infusion period, 8 days). - ACTH - Cortisol - FLX	<ul style="list-style-type: none"> • Significant increase (+115%) in FLX exposed foetal plasma cortisol concentrations on infusion day(s) 6, 7 and 8. • Significant increase (+102%) foetal plasma ACTH concentrations on infusion day 7 in FLX exposed
Rayen et al., (2011)	Species/Strain Sprague-Dawley (n=9-11/group) Groups Prenatal stress + VEH Prenatal stress + FLX Control + VEH Control + FLX Dose Fluoxetine (5mg/kg) Route and Duration Osmotic minipumps to dams from PN1 to PN39.	Immunohistochemistry (PN42) - Hippocampus and dentate gyrus number of proliferating cells and immature neurons.	<ul style="list-style-type: none"> • FLX exposure significantly reversed the decrease in hippocampal cell proliferation and hippocampal neurogenesis in prenatally stressed offspring to levels comparable to control.
Smit-Rigter et al., (2012)	Species/Strain Mice (C57/BL6J) Dose Fluoxetine (0.6mg/kg) Route and Duration I.P. injections to dams from GD8 – GD18.	Offspring brains collected to determine complexity of dendritic tree of layer 2/3 pyramidal neurons in the somatosensory cortex at three ages (PN6-9, PN60 and PN>365). Complexity of dendritic tree was quantified using the Dendritic Complexity Index (DCI), which takes	<ul style="list-style-type: none"> • Significant reduction (~50%) in complexity of 2/3 pyramidal neurons of fluoxetine exposed animals. Reduction in complexity was evident at all life stages (PN6-9, PN60, PN>365)

		into consideration dendritic branching and dendritic length.	
Swerts et al., (2010)	Species/Strain Wistar Rats Dose Fluoxetine or Imipramine (10mg/kg) Route and Duration I.P. injections to dam on GD9, GD10 and GD11	Dams euthanized GD21, and fetuses extracted. Foetal brains collected and analysed via optical microscope for visual quantification of frontal lobe nerve cell bodies.	• Significant decreases in the number of frontal lobe neurons in FLX (-6%) and IMIP (-23%) exposed offspring compared to control
Prenatal/maternal exposure and postnatal/pup exposure			
Meyer et al., (2017)	Species/Strain C57BL/6 Dose Sertraline (Dams) 5mg/kg Sertraline (Offspring) 1.5mg/kg Route and Duration GD0 – GD21 I.P. to dams, then PN1 – PN14 I.P. to offspring.	Adult PCR SERT and serotonin receptor expression	PCR – significant increases in cortical 5HT1a (+50%), SERT (+200%), 5HT2a (+60%), 5HT2c (+30%) and TPH2 (+40%) mRNA in SSRI-exposed compared to controls
Postnatal/pup exposure			
Silva et al., (2010)	Species/Strain Wistar Rat pups (n=5/group) Dose Fluoxetine (10mg/kg) Route and Duration S.C. injections daily to pups from PN1 to PN21	2 months of age (~PN56) subject brains collected for morphometric analysis of 5HT neurons in the dorsal (DR) and median (MnR) raphe nuclei, and hippocampal dentate gyrus (DG). Morphometric parameters of serotonergic neurons - Perimeter (PER) - Maximum, minimum and median diameters	• Significant reduction in neuron number of the DR (-26%), and reduced 5HT terminals (-63%) in the DG of FLX exposed compared to vehicles. • Significant reduction in all morphometric parameters of serotonergic neurons. DR - Perikaryal area (-18%), Dmax (-9.6%), Dmin (-17%), Perikaryal perimeter (-9.6%). MnR - Perikaryal area (-23%), Dmax (-13%), Dmin (-10%), Dmed (-14%) Perikaryal perimeter (-13.5%).

		(Dmax, Dmin and Dmed).	
Lee (2009)	Species/Strain Wistar Rat Pups (n=36 to 42/group) Dose Fluoxetine (10mg/kg) Route and Duration S.C. injections daily to pups from PN0 to PN6.	PN7 and PN35 Dil Labelling of Thalamocortical Afferents (somatosensory cortex) Golgi-Cox impregnation (somatosensory cortex)	<ul style="list-style-type: none"> • Significant reduction (-51%) in number of terminal tips of Thalamocortical afferent arbors • Significant reduction in dendritic field (-27%), shorter dendritic length (-20%) and fewer terminal endings (-20%) in FLX exposed compared to vehicle. • Significant reduction in dendritic spines of the 2nd (-43%), 3rd (-42%) and 4th (-40%) dendritic orders.
Lee & Lee (2011)	Species/Strain Wistar Rat Pups (n=7 to 9/group) Dose Fluoxetine (20mg/kg) Dose and Duration S.C. injections daily to pups from PN0 to PN4	PN35 Immunocytochemistry - cerebellum (Purkinje cells) Golgi-Cox Impregnation - Striatum (dendritic structure) - Layer 5 pyramidal neurons of primary motor cortex	<ul style="list-style-type: none"> • Significant reduction in bifurcation nodes (-25%), terminals (-25%) and dendritic length (-38%) of medium spiny striatal neurons and Layer 5 pyramidal M1 neurons. • No significant differences in Purkinje cell density and soma size between treatment groups
Zheng et al., (2011)	Species/Strain Male GFP-Transgenic mice or wild-type C57 mice Dose Fluoxetine or Fluvoxamine (10mg/kg) Route and Duration I.P. injections daily to pups from PN4 to PN21	Confocal imaging of hippocampus neuronal development – spinal densities of CA1 neurons were assessed at PN22 (adolescence) and PN90 (adult) stages.	<ul style="list-style-type: none"> • Significant reduction (-10%) in spine density of basal dendrites at PN22 of SSRI exposed groups • Significant reduction (-16%) in spine density of apical dendrites at PN22 of those exposed to fluvoxamine • Significant increase (+15%) in spine density of basal dendrites at PN90 of SSRI exposed groups • Significant increase (+13%) in spine density of apical dendrites at PN90 of those exposed to fluoxetine.

Abbreviations: FLX = fluoxetine, DA = dopamine, NE = norepinephrine, 5-HT = 5-hydroxytryptamine receptors, DOPAC = 3,4-dihydroxyphenylacetic acid, 5-HIAA = 5-hydroxyindoleacetic acid, HVA = homovanillic acid, s.c. = subcutaneously, SERT = serotonin transporter, GD = gestational day, P_{CO_2} = partial pressure of carbon dioxide, P_{O_2} = partial pressure of oxygen, ACTH = adrenocorticotrophic hormone, i.p. = intraperitoneal, CBG = corticosteroid binding capacity, GR = glucocorticoid receptor, GRIP1 = glucocorticoid receptor interacting protein, MR = mineralcorticoid, DCX = doublecortin, IMIP = imipramine.