Published in final edited form as:

Birth Defects Res. 2017 July 17; 109(12): 924–932. doi:10.1002/bdr2.1085.

New Insights into How Serotonin Selective Reuptake Inhibitors Shape the Developing Brain

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Abstract

Development passes through sensitive periods, during which plasticity allows for genetic and environmental factors to exert indelible influence on the maturation of the organism. In the context of central nervous system (CNS) development, such sensitive periods shape the formation of neuro-circuits that mediate, regulate, and control behavior. This general mechanism allows for development to be guided by both the genetic blueprint, as well as the environmental context. While allowing for adaptation, such sensitive periods are also windows of vulnerability during which external and internal factors can confer risk to brain disorders by derailing adaptive developmental programs. Our group has been particularly interested in developmental periods that are sensitive to serotonin (5-HT) signaling, and impact behavior and cognition relevant to psychiatry. Specifically, we review a 5-HT-sensitive period that impacts fronto-limbic system development, resulting in cognitive, anxiety, and depression-related behaviors. We discuss preclinical data to establish biological plausibility and mechanistic insights. We also summarize epidemiological findings that underscore the potential public health implications resulting from the current practice of prescribing 5-HT reuptake inhibiting antidepressants during pregnancy. These medications enter the fetal circulation, likely perturb 5-HT signaling in the brain, and may be affecting circuit maturation in ways that parallel our findings in the developing rodent brain. More research is needed to better disambiguate the dual effects of maternal symptoms on fetal and child development from the effects of 5-HT reuptake inhibitors on clinical outcomes in the offspring.

Keywords

SSRI; Pregnancy; Depression; Limbic System; Critical Period; Sensitive Period; Mice; Human

Introduction

Neuronal activity during development critically shapes functional connectivity between neurons, and thus determines the wiring of the mammalian brain. As best described for the development of sensory systems, such plasticity is often restricted to specific developmental periods, so called “sensitive periods”. The best-studied example is the sensitive period for the formation of ocular dominance columns, during which retinal activity determines

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columnar size (Hensch, 2005; Espinosa and Stryker, 2012). Such sensitive period plasticity allows for circuit maturation to respond/adapt to external (environmental) and internal (genetic) factors. Heightened plasticity during sensitive periods also permits environmental and genetic factors to shift developmental pathways and confer risk for disorders.

Preclinical Effects of Developmental Exposure to Serotonin Reuptake Inhibitors (SSRIS)

The serotonergic (5-HTergic) system is among the earliest bioamine systems to appear during brain development. In the human, serotonin (5-HT) neurons are first detected when the embryo is 5 weeks old (Sundstrom et al., 1993), with rapid growth and proliferation until at least the 10th week of development (Levallois et al., 1997). After 15 weeks of development, 5-HT cell bodies cluster in the raphe nuclei (Takahashi et al., 1986). In rodents, this dynamic maturation of the 5-HT system is also present. The first 5-HT neurons appear at the 12th day of rodent gestation (Lauder and Bloom, 1974). 5-HTergic neurons start releasing 5-HT on embryonic day 13 (E13) (Lidov and Molliver, 1982; Lambe et al., 2000), and levels of 5-HT peak within the first postnatal week, after which they decline, reaching adult levels at around postnatal day 15 (P15) (Hohmann et al., 1988). 5-HTergic neurons continue to elaborate their innervation patterns throughout the embryonic and early postnatal life, until approximately P21 (Lauder, 1990).

An additional aspect of presynaptic 5-HTergic system maturation is the transient adoption of a 5-HTergic phenotype by non-5-HTergic neuron populations during late embryonic and early postnatal development (Lebrand et al., 1996, 1998; Salichon et al., 2001; Gaspar et al., 2003). Lastly, 5-HT receptors are expressed early in embryonic development, even before 5-HTergic afferents reach their innervation targets (Hellendall et al., 1993; Bonnin et al., 2006). During these early developmental stages, 5-HT arising from placental sources acts on 5-HT heteroreceptors, enabling developmental 5-HT signaling even before 5-HTergic axons have reached their targets (Bonnin et al., 2011). Although 5-HT is taken up and packaged into vesicles by nonserotonergic neurons during this transient phase of development, it remains unclear whether the packaged 5-HT in these neurons is released or simply sequestered.

During embryonic and postnatal development, monoamines modulate neurodevelopmental processes, such as cell division, migration, and differentiation, axonal and dendritic elaboration and connectivity, and myelination and apoptosis (Haydon et al., 1984, 1987; Lauder 1990; Teicher et al., 1995; Tarazi et al., 1998; Gaspar et al., 2003; Popolo et al., 2004; McCarthy et al., 2007). 5-HT, for example, exerts prominent autoregulatory control in dorsal and median raphe nuclei formation during embryonic development by acting on 5-HT_{1A} and 5-HT_{1B} autoreceptors, to limit the number of 5-HTergic neurons (Rumajogee et al., 2004). An example for heteroregulation of fundamental developmental processes is its modulatory effect on axonal guidance factors. Through 5-HT_{1B/1D} heteroreceptors, 5-HT reverses the attraction exerted by netrin-1 on the developing posterior dorsal thalamic axons into repulsion, thereby contributing to patterning of thalamocortical connections in the developing brain (Bonnin et al., 2007).

Findings from rodent somatosensory and visual system development demonstrate that high levels of 5-HT cause permanent anatomical defects during a sensitive perinatal period. The mechanisms through which 5-HT modulates somatosensory and visual system development are likely to apply to other systems as well, because the transient ectopic expression of *5-HT transporter* during development is also observed in other sensory, thalamic, hippocampal, hypothalamic, and prefrontal cortical neurons throughout development in rodents (Lebrand et al., 1996, 1998; Narboux-Neme et al., 2008). Transient, ectopic 5-HT transporter expression during development is also observed in nonhuman primates, for example, in sensory neurons of the common marmoset (Lebrand et al., 2006). In human 12- to 14-week-old fetuses, 5-HT-immunolabeled fibers have been identified in the rostral and caudal limbs of the internal capsule, including putative thalamocortical fibers that project from the mediodorsal thalamus to the frontal cortex (Verney et al., 2002). This demonstration of ectopic *5-HT transporter* expression in human fetal tissue suggests that humans and rodents may share a similar role for 5-HT and buffering of 5-HT levels, by means of uptake into non-5-HT neurons during cortical development. The phylogenetic conservation of ectopic *5-HT transporter* expression from rodents to humans suggests that humans and other higher order primates use similar strategies to buffer 5-HT signaling during fetal brain development.

Many psychiatric and neurodevelopmental disorders, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental coordination disorder, and schizophrenia display sensory and/or motor deficits (Butler et al., 2001; Doniger et al., 2002; Piek and Dyck, 2004; Rogers and Ozonoff, 2005; Dewey et al., 2007; Crane et al., 2009). Symptoms vary broadly, manifesting as sensory hypo- or hyper-responsiveness, or problems with sensory filtering. The presence of sensory symptoms in these disorders that are primarily characterized by emotional and cognitive dysfunction supports the hypothesis of common mechanisms underlying sensory/motor and emotional/cognitive phenotypes.

Patterns of adult emotional behavior result from a complex interaction of multiple limbic systems whose underlying neuronal circuit properties determine their function. Although these limbic circuits retain some plasticity in adult life, their formation and interconnectivity is predominantly set during embryonic and postnatal development. Heightened plasticity during circuit development bestows malleable potential to external factors (Hensch, 2004; Knudsen, 2004). This has given credence to the hypothesis that, much like the maturation of sensory systems, limbic circuit formation may also pass through sensitive and critical developmental periods, during which external factors can impact and modulate circuit formation, and consequently emotional behaviors encoded by them. Indeed, environmental perturbations that temporally overlap with the first few weeks of postnatal life exert life-long influences on the emotional behavior of different species (Ladd et al., 2000). Furthermore, multiple emotional behaviors, such as anxiety, depression, and fear have their roots in early postnatal developmental periods (Baram et al., 2012; Quinn et al., 2014), and mood disorders likewise often have their origins in early life (Kendler et al., 1992; Caspi et al., 2003; Wals and Verhulst, 2005; Moffitt et al., 2007; Pietrek et al., 2013). However, only recently has there emerged an understanding of the molecular factors that play a crucial role in defining maturing limbic circuit properties that sculpt adult emotional behavior.

5-HT has been hypothesized to guide the maturation of brain regions associated with emotional and cognitive behaviors, based on its neurotrophic factor-like consequences on basic neurodevelopmental processes, and because of its impact on sensory system development. Supporting this hypothesis, the maturation of multiple limbic circuits, such as the amygdala, prefrontal cortex (PFC), and the hippocampus (HPC) (Morys et al., 1998; Koss et al., 2014), and the emergence of anxiety to novel environments (Ba and Seri, 1993), temporally coincide with the rise of 5-HT levels in the postnatal brain (Loizou, 1972; Hohmann et al., 1988).

For example, mice administered SSRIs or 5-HTT blocking tricyclic antidepressants during the first 3 weeks of postnatal life (P4–P21), but not in adulthood (P90–P107 or P56–P70), mimic the pro-depressive and anxiogenic phenotype observed in transgenic models with constitutively enhanced 5-HTergic tone (Ansorge et al., 2004, 2008; Popa et al., 2008). We have recently refined this SSRI-sensitive period to P2 to P11, and extended the behavioral characterization, finding impaired hippocampal-dependent spatial learning and contextual fear learning, as well as diminished amygdala and PFC-dependent fear extinction and extinction recall. Of interest, this P2 to P11 period not only lies within the maturation-period of both 5-HTergic afferents and cortical circuits (Lidov and Molliver, 1982; Kiyasova and Gaspar, 2011; Vitalis et al., 2013), but also coincides with the peak of cortical 5-HT and 5-HT metabolite levels (Hohmann et al., 1988).

Likewise, while in mice, 5-HTT blockade between P2 and P11 impairs cognitive behavior (Rebello et al., 2014). pharmacological perturbations that enhance levels of 5-HT from P11 to P20 but not from P1 to P10 result in dose-related impairments of sequential learning and spatial learning and memory in rats (Broening et al., 2001; Morford et al., 2002). Furthermore, specific behavioral phenotypes resulting from postnatal SSRI treatment appear to exhibit differential sensitivity to the timing of SSRI treatment. Interestingly, both rat and mouse studies have revealed timing-dependent bidirectional effects of chronic 5-HTT blockade.

Overall, even with species and target effects taken into account, the convergence of behavioral malleability when interfering with 5-HT signaling during early postnatal periods highlights the importance of this time window for circuit maturation and circuit plasticity. Elevated levels of postnatal 5-HT may exert their effects by impinging on the normal developmental trajectory of both its target limbic neuro-circuits, as well as the 5-HTergic system itself. For example, 5-HT autoreceptors inhibit 5-HTergic differentiation in cell culture, with a loss of either 5-HT_{1A} or 5-HT_{1B} receptors increasing, and a loss of 5-HT transporter reducing the 5-HT neuronal number in raphe cultures (Rumajogee et al., 2004). Likewise, *5-HTT*^{−/−} mice exhibit a 50% reduction in 5-HTergic cell number (Lira et al., 2003). Although these changes might carry their own behavioral consequences, they likely dissociate from the effects produced by increased early postnatal 5-HT signaling, because 5-HTergic cell numbers are set at that time point.

However, additional aspects of 5-HTergic function are still malleable during postnatal periods. 5-HTergic neurons of the dorsal raphe fire at a fourfold lower rate in *5-HTT*^{−/−} mice, when compared with controls (Lira et al., 2003). Likewise, rats exposed to

clomipramine from P8 to P21 and mice exposed to FLX from P4 to P21 also have reduced 5-HTergic neuronal activity when compared with vehicle treated controls in adulthood (Kinney et al., 1997) (personal communication, Mark Ansorge). Such blunted 5-HTergic tone could contribute to the dysregulated emotional and cognitive behavior in these mice. Furthermore, 5-HTergic fiber density in the HPC and medial PFC of rats treated with citalopram (Maciag et al., 2006; Weaver et al., 2010) or mice treated with FLX (personal communication, Mark Ansorge) during postnatal development is reduced. These anatomical abnormalities might synergize with hypo-5-HTergic tone to weaken functional connectivity, and thus 5-HTergic modulation of the HPC and medial PFC, which in turn could underlie increased anxiety/depression and impaired cognition. Testing of such direct causal relationships between circuit-specific 5-HTergic input and behavior are underway in many labs that are applying optogenetic and pharmacogenetic tools to decipher the 5-HTergic code in vivo. For example, a recent study has uncovered a role for 5-HT in encoding reward, wherein enhanced activity of dorsal raphe neurons is observed in reward-associated tasks, and optogenetic manipulation of 5-HTergic neuronal activity strongly biases reward-associated behaviors (Liu et al., 2014).

Postnatal FLX treatment reduces the arborization of apical dendrites of layer 2/3 infralimbic (IL) but not prelimbic pyramidal neurons in mice (Rebello et al., 2014). This finding demonstrates that the structural development of the PFC is sensitive to SSRI exposure in the early postnatal period. A similar 5-HT sensitivity has been reported for layer 2/3 pyramidal neurons in the SSC, where increased 5-HT signaling from embryonic day 8 to 18 decreases apical dendritic arborization (Chameau et al., 2009; Smit-Rigter et al., 2012). This latter effect is mediated by 5-HT_{3A} receptors present on reelin-secreting Cajal-Retzius cells (Smit-Rigter et al., 2012), key regulators of cortical development, including neural migration, neural positioning, and dendritic arborization (Super et al., 2000; Soriano and Del Rio, 2005; Lakatosova and Ostatnikova, 2012).

Embryonic 5-HT acting by means of 5-HT_{3A} receptors stimulates the release of reelin, which in turn limits cortical neuron apical dendritic elaboration (Chameau et al., 2009). Genetic loss or pharmacologic inhibition of 5-HT_{3A} receptors, or anti-reelin antibody administration, all result in hyper-complexity of cortical neurons (Chameau et al., 2009). Conversely, increased activation of the 5-HT_{3A} receptor results in reduced complexity of apical arbors (Smit-Rigter et al., 2011). Because Cajal-Retzius cells are still present and active in the first 2 postnatal weeks, a similar mechanism involving hyperactivation of the 5-HT_{3A} receptors can be postulated for the cytoarchitectural changes observed following postnatal fluoxetine treatment. Differential activity or sensitivity of this pathway as a function of time and region might underlie the restriction of postnatal SSRI consequences to the apical arbors of IL and not prelimbic neurons. Together, these data suggest that developmental excess of 5-HT can increase reelin secretion by over-activating 5-HT_{3A} receptors present on Cajal-Retzius cells, consequently inhibiting dendritic growth of layer 2/3 IL pyramidal neurons. An interesting, yet un-studied, aspect in that regard is whether developmental 5-HT signaling permanently impacts the cytoarchitecture and consequently function of Cajal-Retzius cells themselves, and/or other *HTR3A* expressing inter-neurons such as neurogliaform cells.

Antidepressant use During Pregnancy and Offspring Outcomes

The 5-HT sensitive murine P2 to P11 period roughly corresponds to the 3rd trimester of human gestation, and because the 5HT system is highly conserved across phylogeny, outcome studies of offspring receiving exposure to SSRIs during gestation is warranted. Up to 8% of pregnant women are reported to use SSRIs, and their use during pregnancy has been increasing (Andrade et al., 2008; Bakker et al., 2008). SSRIs cross the placental barrier (Hendrick et al., 2003; Rampono et al., 2004) and can be measured in amniotic fluid (Loughhead et al., 2006). SSRIs do not cause any overt developmental abnormalities in the neonates (Pastuszak et al., 1993; Chambers et al., 1996; Simon et al., 2002), and contrary to previous research (Oberlander et al., 2006; El Marroun et al., 2012; Grzeskowiak et al., 2012), SSRI use may even have a protective role on preterm birth (Malm et al., 2015).

However, an association between use of SSRIs during pregnancy and neonatal maladaptation (Malm et al., 2015), persistent pulmonary hypertension (Chambers et al., 2006; Kieler et al., 2012), congenital cardiac defects (Berard et al., 2007; Diav-Citrin et al., 2008; Pedersen et al., 2009), and a delay in motor development (Casper et al., 2003; de Vries et al., 2013; Hanley et al., 2013) have been noted in the neonates. Exposed infants also display indications of central nervous system stress at 3 weeks after birth (Salisbury et al., 2011), and affected neurological functioning as measured by general movement at 3 to 4 months postpartum (de Vries et al., 2013). To date, little is known about the long-term impact of in utero SSRI exposure on brain development, adult behavior, and the prevalence of emotional disorders later in life (see Rotem-Kohavi and Oberlander, and Ornoy and Koren reviews this issue).

Recent studies have suggested enhanced internalizing behavior in childhood (Oberlander et al., 2010), and an increased risk of ASDs in prenatally SSRI exposed offspring (Croen et al., 2011; Rai et al., 2013). Still, further research is needed to determine whether associations with SSRI exposure are causal, and to disentangle the effects of maternal depression versus maternal SSRI use on infant and childhood emotional behavior (Misri et al., 2006; Oberlander et al., 2007, 2010; Salisbury et al., 2011). While small, nonpopulation based cohort studies observed no excess risk by age three to seven (Nulman et al., 1997, 2002), more longitudinal studies are required to assess the long term effects of postnatal SSRI exposure on the development of psychiatric disorders (Malm et al., 2012).

We sought to address the question of whether prenatal SSRI exposure enhances vulnerability to later life disorders in a recent study of a large national birth cohort in Finland (Malm et al., 2016). The issue of whether SSRIs augment offspring risk of depression and anxiety diagnoses is confounded by heritable contributions from maternal and paternal mental illness that would increase risk of neuropsychiatric diagnoses in these children. To disambiguate these confounds we used several comparison groups. To control for maternal psychopathology, we first compared offspring of mothers using SSRIs during pregnancy (SSRI exposed, $n = 15,729$) to offspring of mothers with a diagnosis of a psychiatric disorder related to depression but no antidepressant use during pregnancy (psychiatric disorder, no medication group, $n = 9651$). Next, we reasoned that by comparing offspring outcomes born to mothers who were prescribed SSRIs before but not during pregnancy

(SSRI discontinued group, $n = 7980$) we could test whether maternal SSRI use was an important factor, or whether the exposure was required to be during gestation to influence offspring outcomes.

Similar to the delayed onset of depressive-type phenotypes observed in rodent studies, children exposed to SSRI during gestation were increasingly diagnosed with depression-related disorders from age 12 onward, compared with the control groups that were not exposed, reaching a cumulative incidence of 8.2% by age 14.9, compared with 1.9% in the psychiatric disorder, no medication group, 2.8% in the SSRI discontinued group, and 1.6% in the unexposed. The adjusted hazard ratio (HR) for depression in SSRI exposed offspring was 1.78 (95% confidence interval, 1.12–2.82; $p = 0.02$), compared with the psychiatric disorder, no medication group, and 1.84 (95% confidence interval, 1.14–2.97; $p = 0.01$) compared with the SSRI discontinued group. The age-specific incidence rate per 10,000 person-years of offspring depression in the oldest age group, 12 to 14 years, was 180.7 in the SSRI-exposed group, compared with 35.1 in the psychiatric disorder, no medication group, 84.8 in the SSRI discontinued group, and 58.4 in unexposed.

Although gestational SSRI exposure was associated with higher rates of depressive illness in adolescent offspring, only a modest, nonsignificant increase in diagnosed anxiety disorders was observed in this cohort. Likewise, the age-specific incidence rate of anxiety in the oldest age group differed only marginally between the SSRI exposed, the psychiatric disorder, no medication group, and the SSRI discontinued group. Rates of ASD and ADHD diagnoses in the SSRI exposed group of this cohort were comparable to rates in offspring of mothers with a psychiatric disorder who did not use SSRIs during pregnancy, and to rates in offspring of mothers who discontinued SSRIs before pregnancy. Comparing the SSRI exposed to the unexposed, the HRs were significantly elevated for each outcome. No significant HRs were observed for any of the outcomes when comparing the psychiatric disorder, no medication group to the SSRI discontinued group, whereas compared with unexposed, the HRs were increased for ASD and ADHD. However, maternal exposure to SSRIs, compared with the psychiatric disorder, no medication group was also associated with an increased rate of speech and language disorders in the same cohort (Brown et al., 2016).

Antenatal depression itself has been associated with an increased risk of emotional disorders in offspring (Pearson et al., 2013), suggesting by extension that maternal depression severity impacts offspring risk. Hence, we controlled for potential depression severity differences between the SSRI exposed and the psychiatric diagnosis, no medication groups. Prior studies have shown that the severity of maternal psychiatric symptoms was not related to the choice to continue or discontinue medication use during pregnancy (Cohen et al., 2006), allowing use of the SSRI discontinued group as a depression severity control. Furthermore, we excluded women using multiple psychotropic medications (a proxy for severity) and restricted our exposure to SSRI monotherapy ($n = 12,121$). This refined SSRI exposure group still yielded increased HRs for offspring depression, when compared with the psychiatric disorder, no medication group (HR, 1.85) and to the SSRI discontinued group (HR, 2.12). Following adjustment for other possible indicators of maternal illness severity, including previous depression episodes or diagnoses related to suicidal behavior, the HR for offspring depression remained significantly elevated in the SSRI exposed, compared with all

comparison groups. Hence, when both main comparison groups were adjusted for these “severity proxies,” the significance of SSRI exposure as the principal variable did not diminish.

The issue of maternal illness severity has proven to be of critical importance in other studies examining offspring effects of in utero SSRI exposure. Recent studies found that increased rates of ASD associated with in utero exposure to SSRIs, became nonsignificant when controlled for maternal psychiatric illness (Sorensen et al., 2013). Our findings show similar effects of maternal illness on rates of ASD, ADHD, and anxiety, insofar as SSRI exposure added no additional risk over and above mothers with depression and no SSRI use. Yet offspring of both groups (SSRI exposed and psychiatric disorder, no medication group) had higher risks of ASD and ADHD than offspring of mothers with no diagnosis and no psychotropic medication use. Likewise, the use of SSRI medications before pregnancy did not increase the rates of these disorders over and above the rates seen with maternal illness alone and no gestational SSRI use. These observations lend further support to the notion that our main comparison groups (SSRI exposed, psychiatric disorder, no medication group, and SSRI discontinued group) were not biased by increased severity of illness in mothers using SSRIs during pregnancy. Moreover, the specific impact of SSRI exposure on offspring depression, but not on other neuropsychiatric diagnoses, mitigates the possible confound of surveillance bias, namely, the likelihood that parents, teachers, or physicians would be more vigilant about reporting, referring, or diagnosing possible problems in these children. We have no reason to suspect that parents or caregivers would be more likely to report depressive symptoms in SSRI-exposed children than problems related to ASD, ADHD, or anxiety.

Because of studies showing a detrimental impact of antenatal and postnatal maternal depression on offspring development and emotional functioning, the current practice recommends treatment of maternal depression with antidepressants in the SSRI class (Stewart, 2011). Our observation that SSRIs prescribed to mitigate maternal symptoms lead to increased risk of adolescent depression (above and beyond the risk posed by maternal depression) may appear paradoxical. However, our findings here comport with experimental research in rodents. Mice with genetic inactivation of the 5-HT transporter exhibit several depression- and anxiety-related phenotypes and these behavioral abnormalities can be completely recapitulated with brief exposures to SSRIs during sensitive windows of development. Moreover, mouse studies have shown that early-life SSRI exposure produces long-lasting changes to limbic circuitry, morphology, and physiology, which may have explanatory value for understanding the risk for adolescent depression seen in this study. A phylogenetically-conserved mechanism of 5-HT signaling on early limbic system maturation may prove to be a powerful tool to gain insight into at least one developmental pathway to major depression, a common, chronic, and potentially devastating disorder that remains poorly understood.

Taken together, our findings have potential implications for how maternal psychopathology during pregnancy is managed. The clinical rationale that SSRI treatment during pregnancy helps both mother and the developing child by reducing antenatal and postnatal symptoms may require modification. If SSRI exposure during gestation was delayed, but significant

effects on offspring risk for depression, considerations regarding timing of exposure, antidepressant mechanism of action, and increased use of validated psychotherapies may be needed to maximize maternal benefits while minimizing risk to the long-term health of the developing fetus. Clearly, further research is required to achieve these therapeutic goals and better inform treatment decisions during pregnancy.

Outlook

Our findings from rodent studies that there are “sensitive periods” of brain maturation, where SSRI-disruption of 5-HT sequestration into nonserotonergic neurons alters brain circuitry, suggest that similar “sensitive periods” exist in human brain development. In rodents, these SSRI-induced circuit alterations appear to predispose the animals to depression and anxiety-related phenotypes that emerge after adolescence. Strikingly, we observed in our Finnish cohort, that an excess of depression diagnoses was seen during puberty only in the SSRI-exposed group. Further study is required to replicate these findings in other populations, and to better disambiguate the role of maternal symptoms during early childhood versus the effects of gestational SSRI exposure on offspring outcomes.

Acknowledgments

Funding and Disclosure: The authors declare no conflict of interest.

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