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Review article

Perinatal selective serotonin reuptake inhibitor exposure and behavioral outcomes: A systematic review and meta-analyses of animal studies

A.S. Ramsteijn[a], L. Van de Wijer[b], J. Rando[c], J. van Luijk[d], J.R. Homberg[c,*,1], J.D.A. Olivier[a,1]

[a] Department of Neurobiology, Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, the Netherlands
[b] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands
[d] SYRCLE, Department for Health Evidence, Radboud University Medical Center, Nijmegen, the Netherlands

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ABSTRACT

In the Western world, 2–5 % of pregnant women use selective serotonin reuptake inhibitor (SSRI) antidepressants. There is no consensus on the potential long-term neurodevelopmental outcomes of early SSRI exposure. Our aim was to determine whether there is an overall effect of perinatal SSRI exposure in animals on a spectrum of behavioral domains. After a comprehensive database search in PubMed, PsycINFO, and Web of Science, we included 99 publications. We performed nine meta-analyses and two qualitative syntheses corresponding to different behavioral categories, aggregating data from thousands of animals. We found evidence for reduced activity and exploration behavior (standardized mean difference (SMD) −0.28 [−0.38, −0.18]), more passive stress coping (SMD −0.37 [−0.52, −0.23]), and less efficient sensory processing (SMD −0.37 [−0.69, −0.06]) in SSRI- *versus* vehicle-exposed animals. No differences were found for anxiety (p = 0.06), social behavior, learning and memory, ingestive- and reward behavior, motoric behavior, or reflex and pain sensitivity. Exposure in the period equivalent to the human third trimester was associated with the strongest effects.

1. Introduction

Depression during pregnancy is common, and carries risks for both mother and child . Antidepressant medication is prescribed for moderate and severe perinatal depression (Vigod et al., 2016). The most popular antidepressants are selective serotonin reuptake inhibitors (SSRIs), and their use during pregnancy has increased tremendously over the past decades (Bakker et al., 2008; Jimenez-Solem et al., 2013; Cooper et al., 2007; Andrade et al., 2008). Recent estimates of SSRI exposure in large population-based studies range from 2.5 to 3.3 % of pregnancies in Europe (Zoega et al., 2015; Jordan et al., 2016) to 2.7–5.4 % in the US (Hayes et al., 2012; Huybrechts et al., 2015). These numbers imply that every year, in these regions alone, hundreds of thousands of newborns have been exposed to SSRIs. Although major teratogenic effects are absent, *in utero* SSRI exposure has been associated with increased risk of neonatal complications such as premature birth (Alwan et al., 2016). SSRIs reach the developing fetus by crossing the placental barrier (Rampono et al., 2009). During fetal development, the serotonin transporter (SERT), the target of SSRIs, is much more diffusely expressed in the brain than during adulthood (Gaspar et al., 2003). In fact, the entire serotonergic neurotransmitter system functions differently in adulthood than during development. In adulthood, serotonin is involved in fundamental brain functions such as the regulation of mood, sleep and wake rhythms, aggression, appetite, learning

* Corresponding author at: Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Kapittelweg 29, 6525 EN Nijmegen, the Netherlands.
E-mail address: Judith.Homberg@radboudumc.nl (J.R. Homberg).
[1] Shared last authorship.

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and memory, and reward (Muller and Jacobs, 2009), while during early development, serotonin serves as a neurotrophic factor mediating basic processes such as neurogenesis, cell migration, axon guidance, dendritogenesis and synaptogenesis (Teissier et al., 2017). Consequently, by reaching the brain and modulating serotonin regulation at crucial neurodevelopmental stages, SSRIs could interfere with brain circuit formation and lifelong mental health (Brummelte et al., 2017).

This is the rationale for the "SSRI paradox": the phenomenon in which adult SSRI exposure decreases symptoms of anxiety and depression, while *in utero* SSRI exposure increases the risk of developing anxiety and depression (Homberg et al., 2010). There is mixed evidence for this theory from human studies, which do not always identify long-lasting neurodevelopmental effects of perinatal SSRI exposure. On the one hand, studies have reported higher levels of anxiety (Hanley et al., 2015) and lower scores on motor-, social-emotional- and adaptive behavioral tests (Hanley et al., 2013) after prenatal SSRI exposure. On the other hand, other studies found no association between *in utero* SSRI exposure and intellectual disability (Viktorin et al., 2017), executive functioning (Hutchison et al., 2019), and emotional or social problems (Lupattelli et al., 2018). Most of the evidence is obtained from studies in infants and children, likely due to the practical challenges of examining the effects of *in utero* exposure to SSRIs on behavioral outcomes in adulthood (Oberlander et al., 2009). Interestingly, some of the reported associations are modulated by behavioral outcome domain (Johnson et al., 2016; Brown et al., 2016), timing of exposure (Lupattelli et al., 2018), and sex (Brown et al., 2016; Smearman et al., 2019). Summarizing the available evidence, a recent meta-analysis reported significant positive associations between SSRI exposure during pregnancy and the development of mental and behavioral disorders such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and mental disability (Halvorsen et al., 2019). However, a number of other studies found no significant relationship between SSRI exposure and ASD (Sujan et al., 2017; Brown et al., 2017) and ADHD (Sujan et al., 2017) after correcting for possible confounding factors. This suggests that genetic and shared environmental factors, rather than SSRI exposure, are responsible for the reported associations (Oberlander and Zwaigenbaum, 2017). Indeed, it is known that maternal mental health issues during pregnancy are linked to long-term neurodevelopmental outcomes in children (Gentile, 2017). Since associations with SSRI exposure may be confounded by factors such as the severity of mental health problems, it remains difficult to draw conclusions on causality (Halvorsen et al., 2019).

In contrast to human studies, experimental studies in laboratory animals allow for investigation of the causal relationship between perinatal SSRI exposure and long-term neurodevelopmental outcomes (Zucker, 2017). From human studies, in which SSRI exposure only occurs in depressed mothers, it is not clear whether any effects of SSRI exposure are due to direct effects of the drug on the developing fetus, or indirect effects on the mother's mental health status, or a combination of both. In animals, we have the ability to study the developmental effects of SSRI treatment during a healthy pregnancy to obtain insight in the developmental effects of SSRIs per se, although it should be noted that treatment in the context of maternal stress bears more translational value. Our knowledge on how serotonergic alterations during development affect behavioral outcomes is still limited, and animals provide great value in unraveling mechanisms underlying such alterations. Animal experiments have several advantages over human research, such as a high degree of control over drug dosing and period of exposure. Laboratory rodents mature much faster than humans, yet the sequence of brain developmental milestones is remarkably similar (Semple et al., 2013). In addition, placental transfer of SSRIs is similar between humans and mice (Noorlander et al., 2008) and rats (Olivier et al., 2011). The last decade especially has witnessed a major surge in animal studies examining various neurobiological outcomes of perinatal SSRI exposure, which have been described in numerous narrative reviews (Brummelte et al., 2017; Gingrich et al., 2017; Glover and Clinton, 2016; Grieb and Ragan, 2019; Bourke et al., 2014; Millard et al., 2017; Ornoy, 2017). To maximize the translational value of animal studies, and in line with efforts to reduce the use of animals in research, it is imperative to comprehensively bundle all available preclinical evidence. Our aim is to systematically review and analyze preclinical studies in order to determine whether there is an overall effect of perinatal SSRI exposure on later-life behavior in animal models, and if so, under what conditions. We focus particularly on potential sex differences, interactions with stress exposure, and the timing of SSRI exposure. The results of this review and accompanying meta-analyses may assist in understanding the mixed results of perinatal SSRI exposure in human studies and inform future study design.

2. Methods

The review protocol was registered at the SYRCLE website (www.syrcle.nl) in 2016. The reporting in this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Search strategy

Three databases were searched systematically from inception to February 27th 2018: PubMed, PsycINFO, and Web of Science. The initial search was performed by JR on April 19th 2016. An updated search was performed by AR on February 27th 2018. We searched for the following concepts, using both controlled terms (*i.e.* MeSH) and free text words: (i) perinatal exposure; (ii) selective serotonin reuptake inhibitor (SSRI); (iii) animal (Supplementary File 1). The SYRCLE animal filter (Hooijmans et al., 2010) was used for PubMed and adapted for PsycINFO and Web of Science. The bibliographic records retrieved were imported and de-duplicated in Mendeley.

2.2. Eligibility screening

Studies were eligible for inclusion if they compared behavioral outcomes of animals perinatally exposed to SSRIs to those of animals exposed to a vehicle treatment. Two reviewers independently screened all identified records for eligibility in two stages using EROS 3.0 (Early Review Organizing Software, Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina). JR and LW performed the screening for the articles identified in the initial search, and AR and LW for those identified in the updated search. Disagreements were resolved by discussion.

The first screening stage involved screening only the title and abstract of the articles. Articles were excluded for one or more of the following reasons: (i) not an original primary study (*e.g.* review, editorial, conference abstract without full data available) or correction to an original primary study; (ii) not an *in vivo* mammalian (non-human) study; (iii) no SSRI treatment.

In the second stage, the full text of all articles passing the first stage was consulted. Articles were excluded at this stage for one or more of the following reasons: (i) not an original primary study (*e.g.*, review, editorial, conference abstract without full data available or data published in duplicate) or correction to an original primary study; (ii) not an *in vivo* mammalian (non-human) study; (iii) no SSRI treatment; (iv) no exposure on or before the developmental day equivalent to human birth in terms of neurogenesis, GABA cortex development, and axon extension, calculated using the Translating Time tool developed by Workman et al. (2013): PND11 in mice and PND10 in rats; (v) no behavior analyses; (vi) no control population; (vii) animals subjected to other factors (*e.g.*, genetic mutation, repeated exposure to additional drug), but studies in which animals or their mothers were exposed to stress were included because these studies are translationally relevant; (viii) no repeated exposure; (ix) no English full text or translation available.

2.3. Extraction of study characteristics and data

The following study characteristics were extracted: (i) study ID: authors, year, title; (ii) study design characteristics: no. of groups, no. of animals per group, no. of litters per group, litter size, repeated measures *vs*. comparison between groups; (iii) animal model characteristics: species, strain, sex, age at testing, presence/absence of stress exposure; (iv) intervention characteristics: type of control, type of SSRI, age and duration of exposure, administration method, dosage (concentration, volume of administration); (v) outcome measures: behavioral test used, test outcome; (vi) other: no. of animals excluded from statistical analysis, reason for excluding animals.

Then, the data from all behavioral outcomes were extracted: means, standard deviation (SD) or standard error of the mean (SEM) and number of animals (N). The methods for extraction were, in order of priority, (i) extract data from text or tables; (ii) extract data from figures using digital image analysis software (ImageJ v. 1.52a (Schneider et al., 2012)); (iii) contact authors for missing data. When SDs/SEMs were not clearly distinguishable in a figure, we extracted the most conservative estimate. JR performed the data extraction for all eligible articles retrieved in the initial search, and AR for those in the updated search. LW checked the extraction process for all studies.

2.4. Data analysis

2.4.1. Categorization of behavioral tests

After the data extraction, all behavioral tests found were categorized by AR in consultation with JH and JO and other members of the Behavioral Neuroscience group at the University of Groningen. Ten categories were defined – in order of number of comparisons: (i) activity & exploration; (ii) anxiety; (iii) stress coping; (iv) social behavior; (v) learning & memory; (vi) ingestive & reward; (vii) motoric; (viii) sensory processing; (ix) reflex & pain sensitivity; (x) sleep & circadian activity. Every category had a number of behavioral tests associated with it (Supplementary File 2). For every behavioral category we performed a meta-analysis. An exception was the category sleep & circadian activity, which was deemed too heterogeneous and more suitable for a qualitative synthesis. There was an eleventh category of behavioral tests, in which the animals were challenged with an acute injection of a drug or LPS right before the test. To ensure the analyses for the above-mentioned behavioral categories were not confounded by the effects of an acute injection, we decided not to include these results in any of the 10 categories, and to create a separate qualitative synthesis for them.

2.4.2. Selection of comparisons

If a study reported separate comparisons for males and females, or animals exposed to different SSRIs, we analyzed these comparisons as if they were separate studies. Per meta-analysis, one unique animal can only be used once. If the same animal was exposed to different behavioral tests within the same category, we used the data from the test that was performed first (but when data was available from both during and after SSRI exposure, we used the data from the test performed after SSRI exposure). If the same animal was exposed to the same behavioral tests multiple times, we also used the data from the first time it was administered, unless the test contained an important learning or habituation component. For that reason, the data from the *last* time of test administration was used for the following behavioral tests: alcohol consumption, cocaine conditioning, forced swim test, Morris water maze, sexual behavior, sucrose preference test, and tube runway. In the prepulse inhibition test, usually a range of pulse intensities was tested, in which case we used the data from the middle intensity. For every behavioral test, we only used one outcome measure according to the priority outcome measures we defined (Supplemental File 2). We did not include non-treated or non-handled controls; only vehicle-treated controls.

2.4.3. Meta-analyses

We performed the meta-analyses using Review Manager (RevMan v.5.3., The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen 2014). When a range was reported for N, instead of a specific number per treatment group (for instance N = 11–13), we used the most conservative estimate of N. In practice, this meant we used the maximum value of N (in this case N_{max} = 13) to calculate the SD (SD = SEM*√N), and the minimum value of N (in this case N_{min} = 11) in the actual meta-analysis. We used random effects models using standardized mean differences (SMDs). The individual SMDs were pooled to obtain an overall SMD and 95 % confidence interval (CI). I^2 was used as a measure of heterogeneity. A *p*-value lower than 0.05 was considered significant.

To examine potential sources of heterogeneity within the data, we performed subgroup analyses using a Chi^2 test for subgroup differences based on sex, presence/absence of stress exposure, and period of SSRI exposure for every meta-analysis. For the subgroup analysis for sex there were three subgroups (male, mixed-sex, and female), for presence/absence of stress exposure there were two (no stress and stress) and for period of SSRI exposure three (prenatal, pre- and postnatal, and postnatal). A subgroup analysis was only performed when there was at least one independent comparison. Although there were six subgroup analyses defined in the initial published protocol, we decided to only perform three in order to constrain the scope of this review. We decided not to perform subgroup analyses based on animal species, timing of behavioral test, type of SSRI, and specific behavioral test used. Of the three subgroup analyses we performed, two were included in the original protocol (sex and presence/absence of stress exposure) and one was added (period of SSRI exposure).

2.5. Risk of bias assessment

The risk of bias is important to evaluate, since the presence of randomization, allocation concealment, and blinding affects the reported effect sizes of animal studies, in particular in the case of subjective outcome measures (Hirst et al., 2014). To assess the methodological quality of each included study, we used the SYRCLE risk of bias tool for animal studies (Hooijmans et al., 2014). We added three questions on reporting of randomization, blinding, and a power- or sample size calculation (question 1–3). For these questions, a “Yes” score indicates that it was reported, and a “No” score indicates that it was not reported. The other questions (question 4–14) addressed risk of bias, where “Yes” indicates low risk of bias, “?” indicates unclear risk of bias, and “No” indicates high risk of bias.

2.6. Publication bias assessment

To assess publication bias, funnel plots were produced for each of the nine meta-analyses using the package “metafor” v2.1-0 (Viechtbauer, 2010) in R v3.5. Each funnel plot displays all studies in one plot with SMD as the x-value and 1/√N as the y-value. We used this method because it was shown that plotting the SMD against the SE can lead to false-positive results, especially when the included studies have small sample sizes (Zwetsloot et al., 2017). In the funnel plot, larger studies with high precision and power will be displayed towards the top of the graph, around the average SMD. In the absence of publication bias, smaller studies with lower precision and power will spread evenly on both sides of the average near the bottom of the graph. If the plot is asymmetrical, for example when smaller studies predominantly have SMDs larger than the average, this is an indication of small-study bias, potentially related to publication bias. To test and adjust for funnel plot asymmetry, we used the trim and fill method (Duval and Tweedie, 2000) in the “metafor” package.

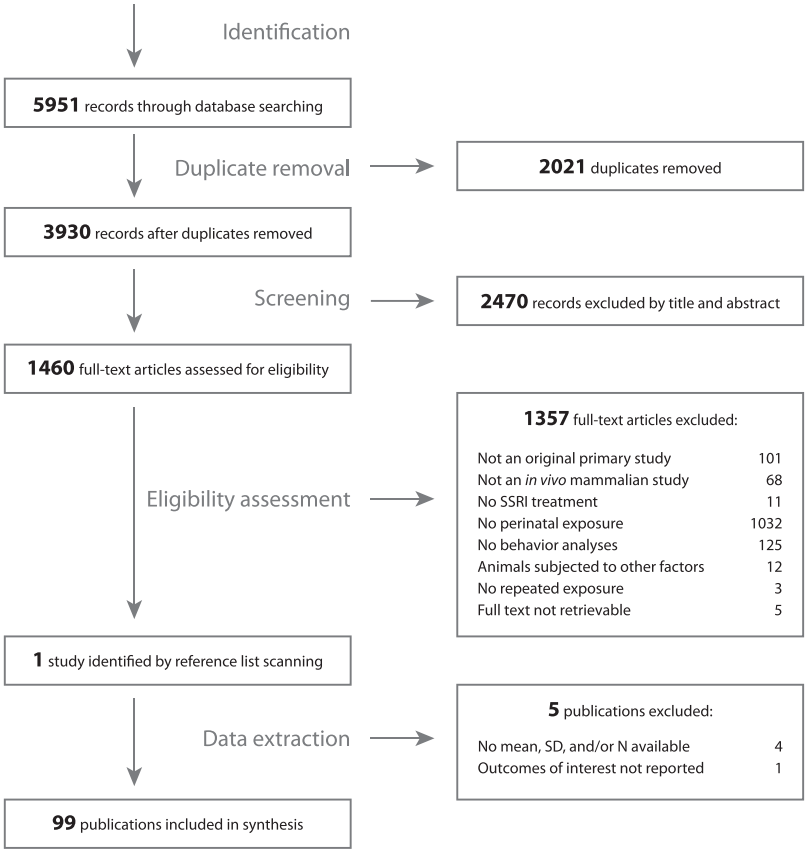

Fig. 1. Study flowchart.

3. Results

3.1. Search results

Through database searching, 5951 records were retrieved, leaving 3930 records after removal of duplicates (Fig. 1). After screening by title and abstract, 1460 full-text articles were assessed for eligibility, from which 103 were deemed eligible. After adding one extra article identified by scanning of the reference lists of the included articles, and excluding five publications because they did not contain usable data, we finally included 99 publications in this synthesis of evidence (Fig. 1).

3.2. Study characteristics

From the 99 included publications, 63 studied rats, 35 mice and one guinea pigs (Table 1). The majority of studies treated animals with fluoxetine (67 studies), followed by citalopram (15 studies), zimelidine (eight studies), escitalopram (five studies), sertraline (four studies), fluvoxamine (three studies), paroxetine (three studies), and LU 10-134-C (one study) (Fig. 2A). SSRI exposure was prenatal in 18 studies, both prenatal and postnatal in 23 studies, and postnatal in 59 studies. From the studies where SSRIs were administered postnatally (either exclusively, or also prenatally), 54 reported injecting the drug directly into the pups, and 28 reported exposure through the mother. The method of SSRI administration was subcutaneous in 43 studies, oral in 31 studies, and intraperitoneal in 25 studies. Forty-seven studies tested male rats, seven studies female, and 45 studies examined both sexes (Fig. 2B). Please note that study numbers might add up to more than 99, because the same study could use multiple SSRIs or exposure periods (Table 1).

Twenty studies used ways to mimic symptoms associated with maternal depression in laboratory animals (Table 2). In 19 studies, the dam was exposed to some form of stress, and in one study the pups were stressed by means of maternal separation. The most common way to apply stress to the mother was using repeated restraint stress (10 studies), followed by chronic unpredictable mild stress (seven studies), and injections of corticosterone or dexamethasone (one study each).

3.3. Study quality

Forty-eight studies mentioned the experiment was randomized at some level, 31 reported blinding, and three included a power or sample size calculation (Supplementary File 3). Overall risk of bias was unclear. Only 68 studies reported all outcome measures that were described in the methods section.

3.4. Activity and exploration

The meta-analysis for activity and exploration comprised 52 studies and 134 comparisons (Supplementary File 4). The most used behavioral test in this category was the open field test with outcome measures such as total distance moved (121 comparisons), followed by the novel object exploration test (six comparisons), running wheel activity (three comparisons), elevated plus maze (two comparisons), home cage activity (one comparison), and object-directed behavior/novel object recognition test (one comparison). In total, 2646 SSRI-exposed animals and 1627 vehicle-treated animals were included in this analysis.

Overall pooled analysis revealed significantly lower activity scores in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3A; Supplementary Fig. 1A, SMD −0.28 [−0.38, −0.18], $p < 0.00001$). Subgroup analysis showed that the effect was different depending on sex (Fig. 3A; Supplementary Fig. 1B, $Chi^2 = 13.89$, $p < 0.01$). More specifically, while activity scores were

Table 1
Study characteristics.

Study ID	Species	Strain	Stress	Control	SSRI	Exposure period	Dose per day	Recipient	Administration method	Sex studied
Grimm and Frieder, 1987	rat	Wistar	no	untreated; saline	zimelidine	G10-G20; P4-P8	5 mg/kg	dam	SC	both
Hilakivi et al., 1987a	rat	Long-Evans; Wistar	no	saline	zimelidine	P6-P19	25 mg/kg	pup	SC	male
Hilakivi and Hilakivi, 1987	rat	Wistar	no	saline	zimelidine	P7-P18	25 mg/kg	pup	IP	male
Hilakivi et al., 1987b	rat	Long-Evans; Wistar	no	control	zimelidine	P7-P18	25 mg/kg	pup	SC	male
Hilakivi et al., 1988a	rat	Wistar	no	saline	zimelidine	P7-P18	25 mg/kg	pup	IP	male
Hilakivi et al., 1988b	rat	Wistar	no	saline	zimelidine	P7-P21	25 mg/kg	pup	IP	male
Hilakivi, 1994	rat	Wistar	no	saline	zimelidine	P6-P22	25 mg/kg	pup	SC	male
Vorhees et al., 1994	rat	Sprague Dawley	no	water; pair-fed	fluoxetine	G7-G20	1; 5; 12 mg/kg	dam	oral: gavage	both
Frank and Heller, 1997	rat	Long-Evans	no	dimethyl sulphoxide (DMSO)	zimelidine	P8-P21	25 mg/kg	pup	IP	male
Hansen et al., 1997	rat	Wistar WU	no	saline	LU 10-134-C	P8-P21	5; 10; 20; 30 mg/kg	pup	IP b.i.d.	male
Singh et al., 1998	rat	Charles Foster	no	saline	fluoxetine	G13-G21	10 mg/kg	dam	IP	both
Stewart et al., 1998	rat	Sprague Dawley	no	saline	fluoxetine	G8-G20	12.5 mg/kg	dam	oral (saline SC)	both
Coleman et al., 1999	mouse	CD-1	no	placebo	paroxetine	G0-G16.5	30 mg/kg	dam	oral: food bar	both
Christensen et al., 2000	mouse	CD-1	no	placebo	paroxetine	G0-P1	30 mg/kg	dam	oral: food bar	both
Mendes-da-Silva et al., 2002	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Ansorge et al., 2004	mouse	129SvEv 5-HTT$^{+/+}$	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	both
Ishiwata et al., 2005	mouse	C57BL/6	yes	sucrose	fluoxetine	P7-P28	5 mg/kg	pup	oral: pipettor	male
Vartazarmian et al., 2005	guinea pig	Hartley	no	untreated; DMSO	fluoxetine	G1-P1	7 mg/kg	dam	SC: osmotic pump	both
Deiro et al., 2006	rat	Wistar	no	water	sertraline	P1-P21	5; 10; 15 mg/kg	pup	SC	male
Maciag et al., 2006a	rat	Long-Evans	no	saline	citalopram	P8-P21	10 mg/kg	pup	SC b.i.d.	male
Maciag et al., 2006b	rat	Long-Evans	no	saline	citalopram	P8-P21	10 mg/kg	pup	SC b.i.d.	male
Maciag et al., 2006c	rat	Long-Evans	no	saline	citalopram	P8-P21	10 mg/kg	pup	SC b.i.d.	male
Bairy et al., 2007	rat	Wistar	no	water	fluoxetine	G6-G20	8; 12 mg/kg	dam	oral	both
Lisboa et al., 2007	mouse	Swiss	no	water	fluoxetine	G0-P21	~7.5 mg/kg	dam	oral: gavage	both
Ansorge et al., 2008	mouse	129SvEv 5-HTT$^{+/+}$	no	untreated; saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	both
					citalopram	P4-P21	10 mg/kg	pup	IP	both
Cagiano, 2008	rat	Wistar	no	saline	fluoxetine	G13-G20	5; 10 mg/kg	dam	SC	male
Deiró et al., 2008	rat	Wistar	no	saline	citalopram	P1-P21	5; 10 mg/kg	pup	SC	male
Favaro et al., 2008	mouse	Swiss	no	water	fluoxetine	G0-P21	5.7–7.5 mg/kg	dam	oral: gavage	both
Forcelli and Heinrichs, 2008	rat	Wistar	no	ethanol	fluoxetine	G14-P7	10 mg/kg	dam	SC: osmotic minipump	both
Gouvêa et al., 2008	mouse	Swiss	no	water	fluoxetine	G0-P21	7.5 mg/kg	dam	oral: gavage	male
Noorlander et al., 2008	mouse	C57BL/6	no	saline	fluoxetine	G8-G18	0.3; 0.6; 0.8 mg/kg	dam	IP	both
					fluvoxamine	G8-G18	4.2 mg/kg	dam	IP	both
Popa et al., 2008	mouse	CD-1	no	saline	escitalopram	P5-P19	10 mg/kg	pup	SC	female
Jiang et al., 2009	mouse	Kunming	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Karpova et al., 2009	mouse	C57BL/6		saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Lee, 2009	rat	Wistar	no	saline	fluoxetine	P0-P6	10 mg/kg	pup	SC	both
Capello et al., 2011	rat	Long-Evans	no	saline + polyethylene glycol	fluoxetine	G12-P1	8; 11 − 12 mg/kg	dam	SC: osmotic minipump	both
Mnie-Filali et al., 2011	rat	Sprague Dawley	no	saline	fluoxetine	P8-P21	10 mg/kg	pup	IP	male
Olivier et al., 2011	rat	Wistar	no	methylcellulose	fluoxetine	G11-P1	12 mg/kg	dam	oral: gavage	both
Pivina et al., 2011	rat	Sprague Dawley	yes	saline	fluoxetine	P1-P14	5 mg/kg	pup	oral	male
					paroxetine	P1-P14	5 mg/kg	pup	oral	male
Rayen et al., 2011	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	both
Rodriguez-Porcel et al., 2011	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
					fluoxetine	P8-P21	10 mg/kg	pup	SC b.i.d.	both
Simpson et al., 2011	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
Zheng et al., 2011	mouse	C57BL/6	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Harris et al., 2012; Swilley-Harris, 2010	rat	Long-Evans	no	saline	citalopram	P8-P21	5; 10; 20 mg/kg	pup	SC b.i.d.	male
Kummet et al., 2012	mouse	C57BL/6	no	saline	sertraline	P1-P14	5 mg/kg	pup	IP	both
Lee and Lee, 2012	rat	Wistar	no	saline	fluoxetine	P0-P4	20 mg/kg	pup	SC	male
McAllister et al., 2012	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	female
Nagano et al., 2012	rat	Sprague Dawley	yes	saccharine + saline G16-G23	fluoxetine	P2-P21	17.2 ± 0.6 mg/kg	dam	oral: drinking water	male
Rebello, 2012	mouse	129SvEv	no	saline	fluoxetine	P2-P21; P2-P11	10 mg/kg	pup	IP	both

(*continued on next page*)

Table 1 (*continued*)

Study ID	Species	Strain	Stress	Control	SSRI	Exposure period	Dose per day	Recipient	Administration method	Sex studied
Smit-Rigter et al., 2012	mouse	C57BL/6	no	saline	fluoxetine	G8-G18	0.6 mg/kg	dam	IP	both
Soga et al., 2012	mouse	C57BL/6	no	water	citalopram	P8-P22	10 mg/kg	pup	SC	male
Yu, 2012	mouse	129SvEv Htr2a$^{+/+}$	no	saline	fluoxetine	P2-P11	10 mg/kg	pup	IP	both
Bourke et al., 2013	rat	Sprague Dawley	yes	saline	escitalopram	G0-P1	12.2–17.3 mg/kg	dam	SC: osmotic minipump	male
Francis-Oliveira et al., 2013	rat	Wistar	no	water	fluoxetine	G0-P21	5 mg/kg	dam	oral: oral gavage	both
Freund et al., 2013	rat	Sprague Dawley	yes	saline	fluoxetine	P2-P9	10 mg/kg	pup	IP	both
Kiryanova et al., 2013	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Knaepen et al., 2013	rat	Sprague Dawley	yes	saline	fluoxetine	G21-P21	10 mg/kg	dam	oral: wafer b.i.d.	male
Rayen et al., 2013	rat	Sprague Dawley	yes	saline	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	male
Schaefer et al., 2013	rat	Sprague Dawley	no	saline	citalopram	P11-P20	10; 15 mg/kg	pup	SC b.i.d.	male
Vieira et al., 2013	rat	Wistar	no	water	fluoxetine	G0-P21	7.5 mg/kg	dam	oral: gavage	male
da Silva et al., 2014	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Glazova et al., 2014	rat	Outbred white		untreated; water	fluvoxamine	P1-P14	10 mg/kg	pup	IP	both
Khatri et al., 2014; Khatri, 2013	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
Kiryanova and Dyck, 2014	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Ko et al., 2014	rat	Wistar	no	saline	fluoxetine	P0-P4	20 mg/kg	pup	SC b.i.d.	male
Rayen et al., 2014	rat	Sprague Dawley	yes	saline	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	female
Rebello et al., 2014	mouse	129SvEv	no	saline	fluoxetine	P2-P21; P2-P11; P12-P21	10 mg/kg	pup	IP	both
Sarkar et al., 2014a	rat	Sprague Dawley	no	sucrose	fluoxetine	P2-P21	10 mg/kg	pup	oral: gavage	male
Sarkar et al., 2014b	rat	Sprague Dawley	no	sucrose	fluoxetine	P2-P21	10 mg/kg	pup	oral: gavage	male
Toffoli et al., 2014	rat	Wistar	no	water	fluoxetine	G0-P21	5 mg/kg	dam	oral: gavage	male
Volodina et al., 2014	rat	Outbred white	no	water + intranasal water P15-P28	fluvoxamine	P1-P14	10 mg/kg	pup	IP	both
Yu, 2012; Yu et al., 2014	mouse	129SvEv	no	saline	fluoxetine	P2-P21	10 mg/kg	pup	IP	both
Altieri et al., 2015	mouse	CD-1 × 129SvEv 5-HTT$^{+/+}$	no	untreated; saline	fluoxetine	P5-P21	10 mg/kg	pup	SC	both
					escitalopram	P5-P21	10 mg/kg	pup	SC	both
Avitsur et al., 2015	mouse	CD-1	no	saline	fluoxetine	G1-P0	10 mg/kg	dam	SC	both
da Silva et al., 2015	rat	Wistar	no	saline	fluoxetine	P2-P21	10 mg/kg	pup	SC	male
Ehrlich et al., 2015	rat	Sprague Dawley	yes	saline	escitalopram	G0-P1	12.2–17.3 mg/kg	dam	SC: osmotic minipump	female
Galindo et al., 2015	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Zhou et al., 2015	rat	Sprague Dawley	no	saline	citalopram	P1-P10	20 mg/kg	pup	SC b.i.d.	both
Boulle et al., 2016a	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	male
Boulle et al., 2016b	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	female
Dos Santos et al., 2016	rat	Wistar	no	water	fluoxetine	G1-P21	5 mg/kg	dam	oral: gavage	female
Gobinath et al., 2016	rat	Sprague Dawley	yes	saline	fluoxetine	P2-P23	10 mg/kg	dam	IP	both
Kiryanova et al., 2016	mouse	C57BL/6	yes	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Kroeze et al., 2016	rat	Wistar	no	methylcellulose	fluoxetine	G11-P7	12 mg/kg	dam	oral: gavage	male
Matsumoto et al., 2016	rat	Wistar	no	water	fluoxetine	G1-P21	5 mg/kg	dam	oral: gavage	both
Salari et al., 2016	mouse	NMRI	yes	water	fluoxetine	G10-P20	8 mg/kg	dam	oral: drinking water	male
Sprowles et al., 2016	rat	Sprague Dawley	no	saline	citalopram	G6-G21 + P1-P20	20 mg/kg	dam + pup	SC b.i.d.	both
Svirsky et al., 2016	mouse	CD-1	no	saline	fluoxetine	G1-P1	10 mg/kg	dam	SC	both
Zohar et al., 2016	rat	Wistar	yes	water	citalopram	G7-P21	10 mg/kg	dam	oral: drinking water	both
Avitsur, 2017	mouse	CD-1	yes	saline + food/water deprived	fluoxetine	G1-delivery	10 mg/kg	dam	SC	both
Gemmel et al., 2017	rat	Sprague Dawley	yes	saline	fluoxetine	G10-P21	10 mg/kg	dam	oral: wafer b.i.d.	both
Haskell et al., 2017	mouse	C57BL/6	no	saline	sertraline	G1-delivery + P1-P14	dam 5 + pup 1.5 mg/kg	dam + pup	IP	both
Ishikawa and Shiga, 2017	mouse	BALB/c	no	sucrose	fluoxetine	P1-P21	5 mg/kg	pup	oral: gavage	male
Kiryanova et al., 2017a	mouse	C57BL/6	yes	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Kiryanova et al., 2017b	mouse	C57BL/6	yes	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	female
Nagano et al., 2017	mouse	C57BL/6	no	saline + sham surgery G16	fluoxetine	P3-P21	50 μg/kg (pup)	pup	SC	both
					escitalopram	P3-P21	50 μg/kg (pup)	pup	SC	both
Pinheiro et al., 2019	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Sprowles et al., 2017	rat	Sprague Dawley	no	saline	citalopram	G6-G21 + P1-P20	10 mg/kg	dam + pup	SC b.i.d.	both

(*continued on next page*)

Table 1 (*continued*)

Study ID	Species	Strain	Stress	Control	SSRI	Exposure period	Dose per day	Recipient	Administration method	Sex studied
Meyer et al., 2018	mouse	C57BL/6	no	saline	fluoxetine sertraline	G6-G21 + P1-P20 G1-delivery + P1-P14	10 mg/kg dam 5 + pup 1.5 mg/kg	dam + pup dam + pup	SC b.i.d. IP	both both

Abbreviations and notes.
Stress means the use of any experimental paradigm aimed at mimicking aspects of maternal depression, see Table 2.
SC: subcutaneous.
IP: intraperitoneal.
b.i.d.: twice a day.
; indicates multiple groups.
+ indicates in the same group.

significantly lower for males (SMD −0.28 [−0.41, −0.15], $p < 0.0001$) and mixed-sex groups (SMD −0.62 [−0.82, −0.42], $p < 0.00001$) developmentally exposed to SSRIs *versus* those exposed to vehicle, they were not for females (SMD −0.12 [−0.29, 0.04], $p = 0.14$) (Fig. 3A; Supplementary Fig. 1B). Subgroup analysis based on stress exposure did not reveal significantly different effects of developmental SSRI exposure depending on stress exposure (Fig. 3A; Supplementary Fig. 1C, $Chi^2 = 1.76$, $p = 0.18$). Subgroup analysis based on the period of SSRI exposure showed that the effect of developmental SSRI exposure on later-life activity and exploration was different depending on exposure timing (Fig. 3A; Supplementary Fig. 1D, $Chi^2 = 11.60$, $p < 0.01$). More specifically, while activity scores were not different for those exposed only prenatally (SMD −0.01 [−0.21, 0.19], $p = 0.93$), they were significantly lower for animals exposed pre- and postnatally (SMD −0.40 [−0.59, −0.22], $p < 0.0001$), and postnatally (SMD −0.39 [−0.51, −0.27], $p < 0.00001$) *versus* those exposed to vehicle (Fig. 3A; Supplementary Fig. 1D).

The heterogeneity (I^2) of the overall analysis was 49 %. Subgroup analyses based on sex decreased the heterogeneity to 44 % for males, 39 % for mixed-sex, and 46 % for females. The subgroups based on stress exposure and SSRI exposure timing did not lower the heterogeneity.

3.5. Anxiety

The meta-analysis for anxiety comprised 55 studies and 133 comparisons (Supplementary File 4). The most used behavioral test in this category was the open field test with outcome measures such as time spent in center (55 comparisons), followed by the elevated plus maze (46 comparisons), the novelty-suppressed feeding test (11 comparisons), fear during tone (nine comparisons), the defensive withdrawal test (six comparisons), the elevated zero maze (four comparisons), and the light-dark test (two comparisons). In total, 1816 SSRI-exposed animals and 1522 vehicle-treated animals were included in this analysis.

Overall pooled analysis did not show significantly different anxiety scores in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3B; Supplementary Fig. 2A, SMD 0.10 [−0.00, 0.21], $p = 0.06$). Subgroup analyses did not reveal significantly different effects of developmental SSRI exposure depending on sex (Fig. 3B; Supplementary Fig. 2B, $Chi^2 = 4.44$, $p = 0.11$), stress exposure (Fig. 3B; Supplementary Fig. 2C, $Chi^2 = 2.73$, $p = 0.10$), or period of SSRI exposure (Fig. 3B; Supplementary Fig. 2D, $Chi^2 = 4.95$, $p = 0.08$).

The heterogeneity (I^2) of the overall analysis was 51 %. The subgroups based on sex, stress exposure and SSRI exposure timing did not lower the heterogeneity.

3.6. Stress coping

The meta-analysis for stress coping comprised 30 studies and 90 comparisons (Supplementary File 4). The most used behavioral test in this category was the forced swim test (55 comparisons), followed by shock avoidance (30 comparisons), the open field test after stress and the tail suspension test (two comparisons each), and the elevated plus maze after stress (one comparison). In total, 955 SSRI-exposed animals and 806 vehicle-treated animals were included in this analysis.

Overall pooled analysis showed a significantly more passive coping style in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3C; Supplementary Fig. 3A, SMD −0.37 [−0.52, −0.23], $p < 0.00001$). Subgroup analyses did not reveal significantly different effects of developmental SSRI exposure depending on sex (Fig. 3C; Supplementary Fig. 3B, $Chi^2 = 1.61$, $p = 0.45$), stress exposure (Fig. 3C; Supplementary Fig. 3C, $Chi^2 = 1.32$, $p = 0.25$), or period of SSRI exposure (Fig. 3C; Supplementary Fig. 3D, $Chi^2 = 2.72$, $p = 0.26$).

The heterogeneity (I^2) of the overall analysis was 48 %. The subgroups based on sex, stress exposure and SSRI exposure timing did not

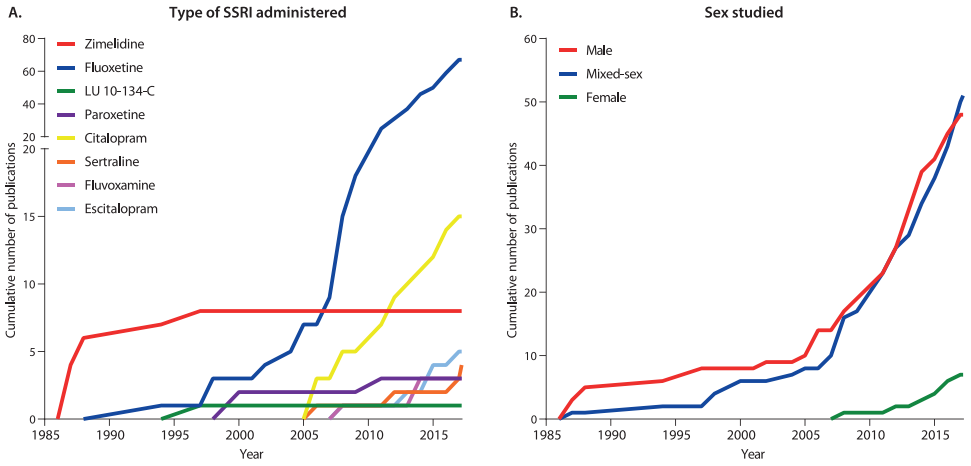

Fig. 2. Historical perspective of study characteristics. The cumulative number of publications published each year on behavioral outcomes after perinatal SSRI exposure in animals, with a focus on (A) the type of SSRI administered and (B) the sex studied.

Table 2
Characteristics of studies combining (maternal) stress with SSRI treatment.

Study ID	Dam or pup?	Control	Stressor	Duration	Frequency	Intervention period	… SSRI exposure
Ishiwata et al., 2005	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Pivina et al., 2011	dam	undisturbed	restraint stress	20 min	daily	G15-G18	before
Rayen et al., 2011	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Nagano et al., 2012	dam	saline (SC)	dexamethasone (50 µg/kg SC)	N/A	daily	G16-G21	before
Bourke et al., 2013	dam	undisturbed	chronic unpredictable mild stress	various	various	G15-G20	during
Freund et al., 2013	pup	handled	maternal separation (individual isolation)	4 h	daily	P2-P9	during
Knaepen et al., 2013	dam	undisturbed	restraint stress	45 min	3 times/day	G14-G20	before
Rayen et al., 2013	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Rayen et al., 2014	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Ehrlich et al., 2015	dam	undisturbed	chronic unpredictable mild stress	various	various	G9-G20	during
Boulle et al., 2016a	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Boulle et al., 2016b	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Gobinath et al., 2016	dam	sesame oil (1 ml/kg SC)	corticosterone (40 mg/kg SC)	N/A	2 times/day	P2-P23	during
Kiryanova et al., 2016	dam	undisturbed	chronic unpredictable mild stress	various	daily	G4-G18	before + during
Salari et al., 2016	dam	undisturbed	restraint stress	40 min	3 times/day	G5-G19	before + during
Zohar et al., 2016	dam	undisturbed	chronic unpredictable mild stress	various	daily	G13-G21	during
Avitsur, 2017	dam	food and water deprived	restraint stress	45 min	3 times/day	G14-G18	during
Gemmel et al., 2017	dam	undisturbed	chronic unpredictable mild stress	various	0-2 times/day	G1-G21	before + during
Kiryanova et al., 2017a	dam	undisturbed	chronic unpredictable mild stress	various	daily	G7-G18	before + during
Kiryanova et al., 2017b	dam	undisturbed	chronic unpredictable mild stress	various	daily	G4-G18	before + during

lower the heterogeneity.

3.7. Social behavior

The meta-analysis for social behavior comprised 30 studies with 53 comparisons (Supplementary File 4). The most used behavioral tests in this category were sexual behavior and social play behavior (14 comparisons each), followed by the social interaction test (10 comparisons), the social preference test (five comparisons), the resident-intruder test (four comparisons), ultrasonic vocalizations (three comparisons), aggressive behavior (two comparisons) and maternal behavior (one comparison). In total, 749 SSRI-exposed animals and 645 vehicle-treated animals were included in this analysis.

Overall pooled analysis did not show significantly different social behavior in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3D; Supplementary Fig. 4A, SMD −0.07 [−0.27, 0.13], $p = 0.47$). Whereas subgroup analyses did not show significantly different effects of developmental SSRI exposure depending on sex (Fig. 3D; Supplementary Fig. 4B, $Chi^2 = 5.12$, $p = 0.08$) and stress exposure (Fig. 3D; Supplementary Fig. 4C, $Chi^2 = 0.41$, $p = 0.52$), the effect was different depending on period of SSRI exposure (Fig. 3D; Supplementary Fig. 4D, $Chi^2 = 6.20$, $p < 0.05$). More specifically, while SSRI-exposed offspring did not differ in social behavior in those exposed prenatally (SMD 0.34 [−0.16, 0.84], $p = 0.18$) and pre- and postnatally (SMD 0.03 [−0.29, 0.35], $p = 0.85$), animals exposed to SSRIs postnatally were significantly less pro-social than those exposed to vehicle (SMD −0.32 [−0.58, −0.05], $p < 0.05$) (Fig. 3D; Supplementary Fig. 4D).

The heterogeneity (I^2) of the overall analysis was 65 %. The subgroups based on sex, stress exposure and SSRI exposure timing did not lower the heterogeneity.

3.8. Learning and memory

The meta-analysis for learning and memory comprised 23 studies with 47 comparisons (Supplementary File 4). The most used behavioral test in this category was the Morris water maze (18 comparisons), followed by the passive avoidance test (eight comparisons), novel object recognition (seven comparisons), the Cincinnati water maze (five comparisons), contextual fear conditioning (three comparisons), the radial water maze (two comparisons) and the Barnes maze, complex maze, cued fear conditioning and novel scent recognition (one comparison each). In total, 982 SSRI-exposed animals and 679 vehicle-treated animals were included in this analysis.

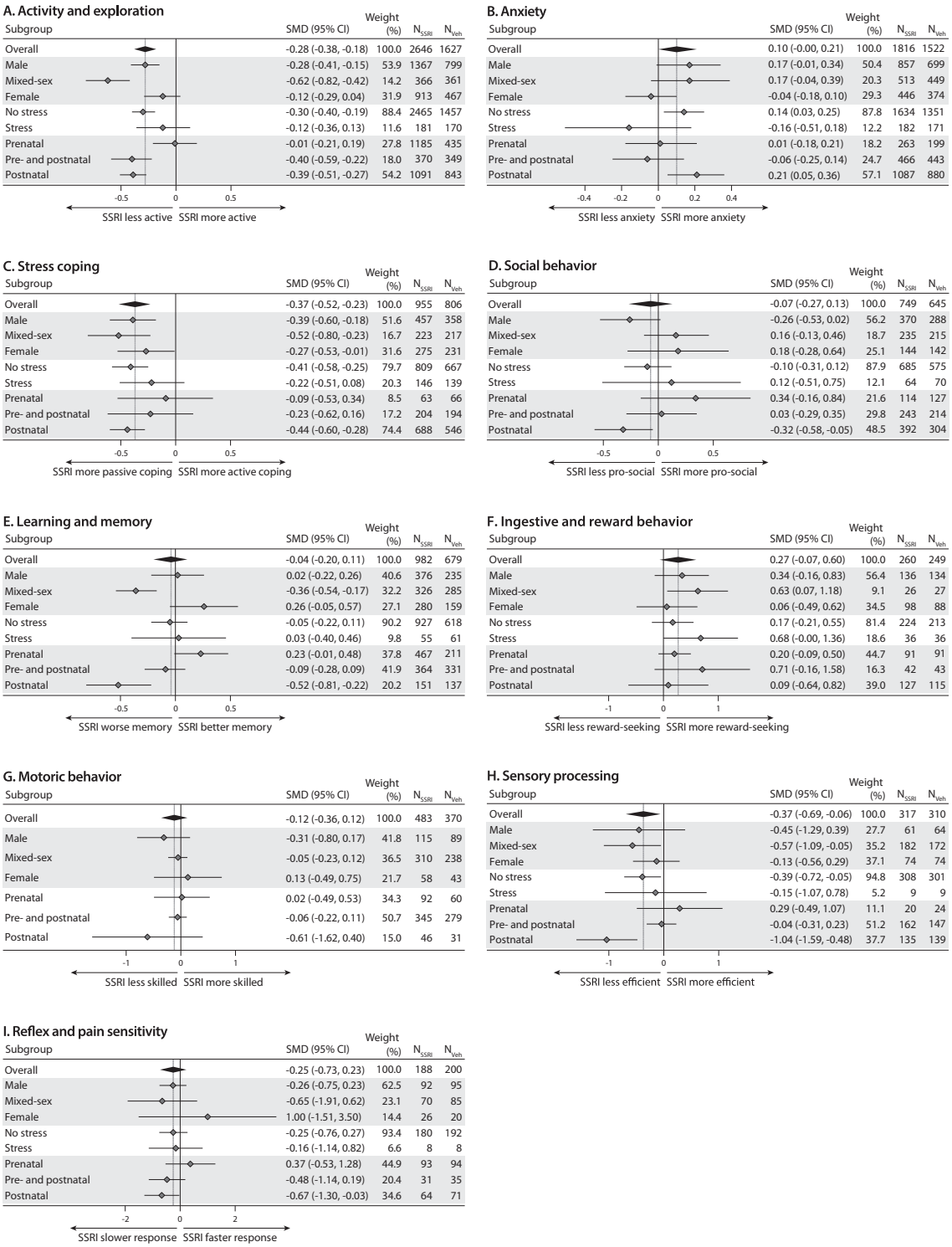

Fig. 3. Summary forest plots from all meta-analyses comparing animals perinatally exposed to SSRIs to those exposed to vehicle. (A) Activity and exploration. (B) Anxiety. (C) Stress coping. (D) Social behavior. (E) Learning and memory. (F) Ingestive and reward. (G) Motoric behavior. (H) Sensory processing. (I) Reflex and pain sensitivity.

Overall pooled analysis did not show significantly different learning and memory in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3E; Supplementary Fig. 5A, SMD −0.04 [−0.20, 0.11], $p = 0.57$). Subgroup analyses revealed significantly different effects of developmental SSRI exposure depending on sex (Fig. 3E; Supplementary Fig. 5B, $Chi^2 = 13.54$, $p < 0.01$). More specifically, the mixed-sex subgroup showed a significantly lower score on learning and memory tests (SMD −0.36 [−0.54, −0.17], $p < 0.001$), but this was not the case for the groups consisting of only males (SMD 0.02 [−0.22, 0.26], $p = 0.86$) or females (SMD 0.26 [−0.05, 0.57], $p = 0.10$) (Fig. 3E; Supplementary Fig. 5B). There was no different effect of developmental SSRI exposure on learning and memory outcomes depending on stress exposure (Fig. 3E; Supplementary Fig. 5C, $Chi^2 = 0.13$, $p = 0.72$). In contrast, the effect was different depending on period of SSRI exposure (Fig. 3E; Supplementary Fig. 5D, $Chi^2 = 14.79$, $p < 0.001$). More specifically, while SSRI-exposed

offspring did not differ significantly in learning and memory outcomes in the groups exposed prenatally (SMD 0.23 [−0.01, 0.48], $p = 0.06$) and pre- and postnatally (SMD −0.09 [−0.28, 0.09], $p = 0.33$), animals exposed to SSRIs postnatally scored significantly lower on learning and memory tests than those exposed to vehicle (SMD −0.52 [−0.81, −0.22], $p < 0.001$) (Fig. 3E; Supplementary Fig. 5D).

The heterogeneity (I^2) of the overall analysis was 49 %. Subgroup analyses based on sex lowered the heterogeneity to 43 % for males, 15 % for mixed-sex, and 48 % for females. The subgroups based on stress exposure did not lower the heterogeneity. Subgroup analyses based on SSRI exposure timing lowered the heterogeneity to 42 % for those exposed prenatally, 27 % for those exposed pre- and postnatally, and 28 % for those exposed postnatally.

3.9. Ingestive- and reward behavior

The meta-analysis for ingestive- and reward behavior comprised 14 studies with 24 comparisons (Supplementary File 4). The most used behavioral test in this category was food consumption (13 comparisons), followed by the sucrose preference test (four comparisons), alcohol consumption, cocaine place preference, and the tube runway (two comparisons each), and cocaine self-administration (one comparison). In total, SSRI-exposed animals and vehicle-treated animals were included in this analysis.

Overall pooled analysis did not show significantly different ingestive- and reward behavior in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3F; Supplementary Fig. 6A, SMD 0.27 [-0.07, 0.60], $p = 0.12$). Subgroup analyses did not show significantly different effects of developmental SSRI exposure depending on sex (Fig. 3F; Supplementary Fig. 6B, $Chi^2 = 1.98$, $p = 0.37$), stress exposure (Fig. 3F; Supplementary Fig. 6C, $Chi^2 = 1.65$, $p = 0.20$), or period of SSRI exposure (Fig. 3F; Supplementary Fig. 6D, $Chi^2 = 1.33$, $p = 0.52$).

The heterogeneity (I^2) of the overall analysis was 69 %. The subgroups based on sex, stress exposure and SSRI exposure timing did not lower the heterogeneity.

3.10. Motoric behavior

The meta-analysis for motoric behavior comprised 11 studies with 20 comparisons (Supplementary File 4). The most used behavioral test in this category was swimming (seven comparisons), followed by beam traversing and the rotarod test (five comparisons each), the horizontal ladder test (two comparisons), and walking (one comparison). In total, 483 SSRI-exposed animals and 370 vehicle-treated animals were included in this analysis.

Overall pooled analysis did not show significantly different motoric behavior in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3G; Supplementary Fig. 7A, SMD −0.12 [−0.36, 0.12], $p = 0.50$). Subgroup analyses did not show significantly different effects of developmental SSRI exposure depending on sex (Fig. 3G; Supplementary Fig. 7B, $Chi^2 = 1.40$, $p = 0.50$) or period of SSRI exposure (Fig. 3G; Supplementary Fig. 7C, $Chi^2 = 1.24$, $p = 0.54$). Subgroup analysis based on stress exposure could not be done because there were no studies with stress exposure in this category.

The heterogeneity (I^2) of the overall analysis was 49 %. The subgroups based on sex and SSRI exposure timing did not lower the heterogeneity.

3.11. Sensory processing

The meta-analysis for sensory processing comprised 12 studies with 17 comparisons (Supplementary File 4). The most used behavioral test in this category was prepulse inhibition (13 comparisons), followed by auditory temporal rate discrimination (two comparisons), and gap crossing and olfactory investigation (one comparison each). In total, 317 SSRI-exposed animals and 310 vehicle-treated animals were included in this analysis.

Overall pooled analysis showed significantly less efficient sensory processing in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3H; Supplementary Fig. 8A, SMD −0.37 [−0.69, −0.06], $p < 0.05$). Whereas subgroup analyses did not show significantly different effects of developmental SSRI exposure depending on sex (Fig. 3H; Supplementary Fig. 8B, $Chi^2 = 1.71$, $p = 0.42$) and stress exposure (Fig. 3H; Supplementary Fig. 8C, $Chi^2 = 0.23$, $p = 0.63$), the effect was different depending on period of SSRI exposure (Fig. 3H; Supplementary Fig. 8D, $Chi^2 = 11.67$, $p < 0.01$). More specifically, while SSRI-exposed offspring did not differ in sensory processing in those exposed prenatally (SMD 0.29 [-0.49, 1.07], $p = 0.47$) and pre- and postnatally (SMD -0.04 [−0.31, 0.23], $p = 0.77$), animals exposed to SSRIs postnatally showed significantly less efficient sensory processing than those exposed to vehicle (SMD −1.04 [−1.59, −0.48], $p < 0.001$) (Fig. 3H; Supplementary Fig. 8D).

The heterogeneity (I^2) of the overall analysis was 68 %. The subgroups based on sex and stress exposure did not lower the heterogeneity. Subgroup analyses based on SSRI exposure timing lowered the heterogeneity to 40 % for those exposed prenatally, 21 % for those exposed pre- and postnatally, and 68 % for those exposed postnatally.

3.12. Reflex and pain sensitivity

The meta-analysis for reflex and pain sensitivity comprised 11 studies with 16 comparisons (Supplementary File 4). The most used behavioral tests in this category were the hot plate test and negative geotaxis (six comparisons each), followed by mechanical sensitivity and righting reflex (two comparisons each). In total, 188 SSRI-exposed animals and 200 vehicle-treated animals were included in this analysis.

Overall pooled analysis did not show significantly different reflex and pain sensitivity in animals that were developmentally exposed to SSRIs than in those exposed to vehicle (Fig. 3I; Supplementary Fig. 9A, SMD −0.25 [−0.73, 0.23], $p = 0.31$). Subgroup analyses did not show significantly different effects of developmental SSRI exposure depending on sex (Fig. 3I; Supplementary Fig. 9B, $Chi^2 = 1.33$, $p = 0.51$), stress exposure (Fig. 3I; Supplementary Fig. 9C, $Chi^2 = 0.02$, $p = 0.88$), or period of SSRI exposure (Fig. 3I; Supplementary Fig. 9D, $Chi^2 = 3.54$, $p = 0.17$).

The heterogeneity (I^2) of the overall analysis was 77 %. The subgroups based on sex, stress exposure and SSRI exposure timing did not lower the heterogeneity.

3.13. Publication bias

Publication bias was assessed using funnel plots. Inspection of the funnel plots supplemented with trim and fill analysis revealed no asymmetry for activity and exploration (Supplementary Fig. 10A), stress coping (Supplementary Fig. 10C), social behavior (Supplementary Fig. 10D), motoric behavior (Supplementary Fig. 10G), sensory processing (Supplementary Fig. 10H), and reflex and pain sensitivity (Supplementary Fig. 10I).

Using trim and fill analysis, we found an indication for funnel plot asymmetry for three behavioral categories. First, for anxiety, studies with moderate and low precision showing increased anxiety as a result of perinatal SSRI exposure were underrepresented, resulting in 20 extra data points and an adjusted estimated effect size SMD 0.26 [0.14, 0.37] (Supplementary Fig. 10B). Second, for learning and memory behavior, studies showing worse test scores as a result of perinatal SSRI exposure were underrepresented, resulting in 10 extra data points and an adjusted estimated effect size of SMD −0.21 [−0.40, −0.02] (Supplementary Fig. 10E). Finally, for ingestive and reward behavior, studies showing lower scores of ingestive and reward behavior as a result of perinatal SSRI exposure were underrepresented, resulting in

Table 3
Study outcomes for sleep & circadian activity.

Study ID	Measure	Summary of outcome
Hilakivi et al., 1987a	Sleep-wake behavior measured with a movement sensitive mattress	Less active sleep and more wakefulness during neonatal SSRI treatment
Hilakivi et al., 1987b	Sleep-wake behavior measured with a movement sensitive mattress	Less active sleep during neonatal SSRI treatment
Hilakivi et al., 1988a	Sleep-wake behavior measured with a movement sensitive mattress	Less active sleep during neonatal SSRI treatment
Frank and Heller, 1997	Sleep architecture using EEG and EMG	More non-REM-REM transitions[a]. No differences in sleep and wake amount.
Popa et al., 2008	Sleep architecture using EEG and EMG	Total REM sleep duration and frequency is higher[a]. No differences in non-REM sleep.
Kiryanova et al., 2013	Running wheel activity during LD, DD (baseline and after short light pulse), and LL (baseline and after long dark pulse)	Baseline: free-running period in DD was shorter[a]. Otherwise no differences. Light pulse: larger phase advance by light pulse at CT22[a], but not at CT16. No difference in phase advance after dark pulse.
Kiryanova et al., 2017a	Running wheel activity during LD, after LD advance, during DD (baseline and after short light pulse), and LL	No baseline differences. It took longer to re-entrain to the new LD cycle[a]. Interaction with maternal stress in the phase shift to light pulses at CT22[a], but not at CT16.

Abbreviations and notes.
EEG = electroencephalogram.
EMG = electromyogram.
REM = rapid eye movement.
LD = light/dark cycle.
DD = constant darkness.
LL = constant light.
CT = circadian time.
[a] In adult animals developmentally exposed to SSRIs *versus* vehicle.

eight extra data points and an adjusted estimated effect size of SMD −0.12 [−0.49, 0.25] (Supplementary Fig. 10F).

For anxiety and learning and memory, the trim and fill analysis suggested publication bias might be at play and that the effect size we found might have underestimated the true effect. However, publication bias is only one possible explanation for funnel plot asymmetry (Sterne et al., 2011). Considering strong indications that period of drug exposure mediates the relationship between perinatal SSRI exposure and later-life behavioral outcomes, we further examined this alternative explanation. Separate funnel plots and subsequent trim and fill analysis per exposure period produced no extra data points for anxiety (Supplementary Fig. 10B) and few extra data points for learning and memory (Supplementary Fig. 10E). This suggests that the funnel plot asymmetry for these categories can largely be explained by subgroup heterogeneity.

3.14. Sleep & circadian activity

Seven studies examined the effects of perinatal SSRI exposure on outcome measures related to sleep and circadian activity (Table 3).

3.15. Behavior after challenges

Thirteen studies examined the effects of perinatal SSRI exposure on behavioral responses to pharmacological- and immune challenges in adulthood (Table 4).

4. Discussion

Our main aim was to systematically review and analyze animal studies to determine whether there is an overall effect of perinatal SSRI exposure on later-life behavior in a spectrum of behavioral domains. We included 99 publications and performed nine separate meta-analyses for different behavioral domains. We found evidence for reduced activity and exploration behavior in SSRI-exposed (N = 2646) relative to vehicle-treated (N = 1627) animals. In addition, we found evidence for a more passive stress coping style in SSRI-exposed (N = 955) compared to vehicle-treated (N = 806) animals. Lastly, we found evidence for less efficient sensory processing in SSRI-exposed (N = 317) *versus* vehicle-treated (N = 310) animals. All effect sizes were small to medium. We found a tendency for increased anxiety ($p = 0.06$), while no differences were found in social behavior, learning and memory, ingestive- and reward behavior, motoric behavior, and reflex and pain sensitivity as a result of developmental SSRI exposure in animals.

4.1. Modulating role of sex, stress exposure, and timing of SSRI exposure

Our secondary aim was to examine the conditions under which a potential effect of developmental SSRI exposure on later-life behavior would manifest itself. We selected three moderators to examine using subgroup analyses: animal sex, presence of perinatal stress exposure (reflecting efforts to mimic aspects of a maternal depressed mood in animal models), and timing of SSRI exposure.

The sex of the animal tested explained part of the heterogeneity in the data for two behavioral categories. The male- and the mixed-sex subgroups showed significantly lower scores for activity and exploration in SSRI-exposed offspring relative to vehicle-exposed offspring, whereas in females there was no significant difference. Interestingly, most other behavioral categories also showed larger effect sizes in males than in females, although these were not statistically significant effects. For learning and memory, we found a significant effect of SSRI exposure in the mixed-sex subgroup, but not in the male or female subgroups. These results may be explained by confounding effects of other moderators such as the timing of SSRI exposure. In general, it is important to realize that subgroup analyses are observational in nature, as they are not based on randomized grouping. To enable more reliable and informative analyses of potential sex effects in the future, researchers should make their data available separately for males and females in a supplementary file.

We found no evidence for a modulatory role of stress exposure on the effects of developmental SSRI exposure on behavior. This could be a reflection of a true absence of an interaction between perinatal stress- and SSRI exposure. It could also be due to the large heterogeneity and wide confidence interval in the stress-exposed group, as a result of the relatively low number of comparisons and the variation in the nature, timing and intensity of the stress protocols used. A selective meta-analysis including only those studies reporting on both stress-unexposed and stress-exposed offspring would yield more insight into the effects of stress exposure, but is beyond the scope of the current review.

The specific period the animal was exposed to an SSRI (prenatal,

Table 4
behavioral outcomes after challenges.

Challenge	Measure	Summary of outcome	Study ID
Central depressants			
Alcohol	Open field test	Stronger inhibitory effect on ambulation[a]	Hilakivi et al., 1987a
Baclofen	Forced swim test	No different response[a]	Hilakivi et al., 1988b
Diazepam	Elevated plus maze	No different response in males or females[a]	Favaro et al., 2008
Dizocilpine/MK-801 (NMDA antagonist)	Open field test	No different response[a]	Sprowles et al., 2016
	Open field test	No different response[a]	Sprowles et al., 2017
Progabide (GABA receptor agonist)	Forced swim test	Reduced enhancing effect on immobility time[a]	Hilakivi et al., 1988b
Propyleneglycol	Elevated plus maze	No different response in males or females[a]	Favaro et al., 2008
Dopamine system			
Apomorphine (D_2/D_3 agonist)	Prepulse inhibition	No different response[a]	Vorhees et al., 1994
	Stereotyped behavior	No different response[a]	Hilakivi, 1994
	Stereotyped behavior	Somewhat reduced stereotypy in females[a]	Favaro et al., 2008
Quinpirole (D_2/D_3 agonist)	Open field test	No different response[a]	Stewart et al., 1998
	Stereotyped behavior	No different response[a]	Stewart et al., 1998
Immune response			
Lipopolysaccharide	Food consumption	Reduced food consumption in the first 24 h in males[a], not females	Avitsur et al., 2015
	Food consumption	No different response[a]	Avitsur, 2017
	Sucrose consumption	Reduced inhibitory effect in the first 60h[a] in males, not females	Avitsur et al., 2015
	Sucrose consumption	Reduced inhibitory effect in females[a], not in males	Avitsur, 2017
Norepinephrine system			
Amphetamine	Open field test	No different response[a]	Sprowles et al., 2016
	Open field test	Reduced stimulant effect	Sprowles et al., 2017
Diethylpropion (NE-releasing)	Open field test	Reduced stimulant effect in females[a], not males	Favaro et al., 2008
	Stereotyped behavior	Reduced stereotypy in females[a], not in males	Favaro et al., 2008
Salbutamol (β2-adrenergic agonist)	Forced swim test	Reduced enhancing effect on immobility time[a] at two months of age, increased enhancing effect at five months of age	Hilakivi et al., 1988b
Serotonin system			
8-OH-DPAT (5-HT1A agonist)	Forced swim test	No different response in males or females[a]	Favaro et al., 2008
	Open field test	No different response in males or females[a]	Favaro et al., 2008
	Phase shift	Smaller phase advance[a]	Kiryanova et al., 2013
	Phase shift	Smaller phase advance[a]	Kiryanova et al., 2017a
Fluoxetine (SSRI)	Food intake	Smaller reduction (none) in food intake[a]	Pinheiro et al., 2019
	Prepulse inhibition	No different response in males or females[a]	Vorhees et al., 1994

[a] In adult animals developmentally exposed to SSRIs *versus* vehicle.

postnatal, or both) explained the most heterogeneity in the data out of the 3 subgroup analyses we performed. Animals exposed to SSRIs postnatally – this roughly corresponds to the third trimester in humans (Workman et al., 2013) – showed reductions in activity and exploration, social behavior, learning and memory, and sensory processing scores, while animals exposed prenatally – roughly corresponding to the first two trimesters in humans (Workman et al., 2013) – did not.

4.2. Potential mechanisms

The effects of developmental SSRI exposure on later-life behavioral outcomes are the result of a combination of direct effects on the developing brain and indirect effects, for example through changes in placental and maternal homeostasis (Brummelte et al., 2017) and postnatal maternal care (Pawluski et al., 2019). The serotonin system consists of 15 different receptors that are key players at crucial neurodevelopmental stages, regulating neurogenesis, apoptosis, axon branching and dendritogenesis (Gaspar et al., 2003). Many of the studies included in the synthesis of evidence in the current review, which have been selected on the presence of behavioral outcomes, also include outcomes reflecting brain health from the global to the molecular level: the corticosterone response to stress (Popa et al., 2008; Pivina et al., 2011; Bourke et al., 2013; Knaepen et al., 2013; Boulle et al., 2016a, b; Gobinath et al., 2016; Salari et al., 2016; Gemmel et al., 2017), brain structure and connectivity (Forcelli and Heinrichs, 2008; Lee, 2009; Simpson et al., 2011; Smit-Rigter et al., 2012; Rayen et al., 2013, 2014; Zhou et al., 2015), neuronal health (Ishiwata et al., 2005; Rayen et al., 2011; Zheng et al., 2011; Lee and Lee, 2012; da Silva et al., 2014; Ko et al., 2014; Rebello et al., 2014; Gobinath et al., 2016; Gemmel et al., 2017), monoamine concentrations in the brain (Grimm and Frieder, 1987; Hilakivi et al., 1987a; Pinheiro et al., 2019; Hilakivi et al., 1987b; Ishiwata et al., 2005; Glazova et al., 2014; Yu et al., 2014; Altieri et al., 2015; Zohar et al., 2016; Gemmel et al., 2017; Nagano et al., 2017), protein expression in the brain – mainly related to the serotonergic system and neurogenesis (Maciag et al., 2006a; Forcelli and Heinrichs, 2008; Capello et al., 2011; Kummet et al., 2012; Nagano et al., 2012; Francis-Oliveira et al., 2013; Kiryanova et al., 2016; Matsumoto et al., 2016; Pinheiro et al., 2019), gene expression (Karpova et al., 2009; Soga et al., 2012; Meyer et al., 2018; Bourke et al., 2013; Sarkar et al., 2014a, b; Ehrlich et al., 2015; Galindo et al., 2015; Boulle et al., 2016a; Ishikawa and Shiga, 2017; Pinheiro et al., 2019), and epigenetic modifications (Karpova et al., 2009; Sarkar et al., 2014a; Toffoli et al., 2014; Boulle et al., 2016b).

Several mechanisms may underlie our current findings. Earlier work in serotonin transporter (SERT) knockout rodents, which lack the SERT and thereby mimic SSRI exposure from conception onwards, showed that 2 main neural networks were changed compared to wildtype rodents: the somatosensory cortex and the corticolimbic circuit (Homberg et al., 2010). The first network is likely related to the sensory processing deficits we found in SSRI-exposed animals. Axons extending from the thalamus to the cortex transiently express SERT during development, and disruption of serotonin availability cause them to form aberrant trajectories (Bonnin et al., 2007, 2011) and affect the development of the somatosensory cortex (Lee, 2009; Xu et al., 2004). The second network could be responsible for the effects seen on activity and exploration and stress coping behaviors. In addition, changes in

neuroendocrine function could play a role in the development of a more passive stress coping style in SSRI-exposed animals (Bourke et al., 2014). It is unclear whether the effects of early SSRI exposure on activity and exploration behavior and stress coping behavior have overlapping brain correlates.

Lastly, we found higher effect sizes in males (relative to females). In general, male offspring seem more vulnerable to various types of stressors during pregnancy than female offspring (Hodes and Epperson, 2019). Early SSRI-exposure may affect males and females differently because of the sex-specific maturation of the serotonin system (Brummelte et al., 2017). For instance, serotonin levels in early postnatal life in rodents are different in males and females: male pups show a peak of serotonin at PND3, while female pups show more stable serotonin levels with a later peak (Connell et al., 2004). In addition, it has been known for a long time that serotonin plays a pivotal role in sexual differentiation through the hypothalamic-pituitary-gonadal axis (Ladosky and Gaziri, 1970; Jarzab and Döhler, 1984). Recent evidence suggests that perinatal SSRI exposure may indeed affect sexual differentiation of the brain and behavior (Rayen et al., 2013). This might be related to the differential susceptibility of males and females to developmental exposure to SSRIs.

4.3. Clinical implications

The neurodevelopmental pattern of the serotonin system is remarkably conserved across species (Gingrich et al., 2017; Bourke et al., 2014; Millard et al., 2017). Therefore, rodent studies of early SSRI exposure can yield important insights and circumvent some of the difficulties of studying this phenomenon in humans. Preclinical and clinical studies on this topic should ideally continuously inform and supplement each other.

The finding that early SSRI exposure is linked to a passive coping style in adult animals is an interesting manifestation of the “SSRI paradox”. Treatment with antidepressants in adulthood generates a more active coping style in animals (Slattery and Cryan, 2012) and alleviates symptoms of depression in humans. Conversely, SSRI treatment in the *perinatal* period leads to a more *passive* coping style in animals later in life. The most common behavioral test in this category is the forced swim test (Porsolt et al., 1977). The basic premise of this test is that, confronted with an inescapable situation in a cylinder of water, rodents can either actively try to escape, or go into a state of passive floating. This passive behavioral response may be analogous to maladaptive responses to stress as seen in humans with neuropsychiatric disorders (Commons et al., 2017). Similarly, disruptions in sensory processing like those associated with early SSRI exposure in animals are present in a spectrum of neuropsychiatric diseases in humans (Hornix et al., 2019). Our results suggest that the increased risk of symptoms of neuropsychiatric disorders for those prenatally exposed to SSRIs, as indicated in some studies (Halvorsen et al., 2019), might be mediated by differences in stress coping, sensory processing and perhaps anxiety (Halvorsen et al., 2019; Malm et al., 2016).

A major challenge in human studies is to properly control for the confounding factor of maternal psychiatric condition (Millard et al., 2017). Statistical methods aim to approximate this, illustrated by the finding that the association between *in utero* SSRI exposure and risk of ASD was not significant when controlled for maternal psychiatric diagnosis (Sorensen et al., 2013). However, a clean comparison between children from SSRI- and vehicle-treated mothers without any psychiatric history is not available. Our results suggest that perinatal SSRI exposure exerts effects on neurodevelopmental outcomes in animal studies. As maternal psychiatric disorder might interact with SSRI use to influence offspring outcomes (Brummelte et al., 2017; Bourke et al., 2014), researchers and clinicians have questioned how clinically relevant rodent studies are. To address this, animal models have been developed aiming to study SSRI exposure in light of maternal (pre)gestational stress (Brummelte et al., 2017). Our current results do not support the notion of an interaction effect of maternal stress exposure and perinatal SSRI exposure on behavioral outcomes in offspring, although the number of studies that examine this is still limited. This is therefore an important question for future experimental studies and meta-analyses to focus on.

The first few postnatal weeks in rodents are instrumental in the maturation of both the serotonin system and cortical circuit wiring, and also show the highest levels of serotonin and its metabolites in the brain (Gingrich et al., 2017). In terms of brain development, this period is approximately equivalent to the third trimester of human gestation (Workman et al., 2013). Our finding that SSRI exposure in the first postnatal weeks has the largest effect on later-life behavior in animals therefore implies that SSRI treatment during the last months of pregnancy should have the largest effect on human outcomes. Clinical studies investigating the effect of timing of SSRI exposure are limited and inconsistent. In line with current results, a recent study found that late-pregnancy SSRI exposure was associated with greater depressed and anxious symptoms in children (Lupattelli et al., 2018), whereas a meta-analysis found that exposure to SSRIs during the *first* trimester was most consistently associated with later diagnosis of mental disorders (Halvorsen et al., 2019). A Scandinavian study found that SSRI use is lowest in the third trimester (Zoega et al., 2015), making this the most challenging trimester to study. Our results suggest, however, that the timing of SSRI exposure should be a key variable of interest in future human studies.

Any potential effects of SSRI use on child development notwithstanding, we want to emphasize that perinatal depression is a serious illness that needs to be treated. SSRI discontinuation during pregnancy increases the chance of relapse into depression, with potential harmful consequences for both mother and child (Chisolm and Payne, 2016). Therefore, decisions about treatment need to be carefully weighed by the clinician and their patient.

4.4. Limitations and strengths

One of the limitations of this study is that the quality of the pooled analyses is only as high as the quality of the individual studies that it consists of, which is hard to determine. Basic characteristics of best practices in experimental studies, such as blinding and randomization, were sparsely reported. This is often the case with animal studies (Avey et al., 2016; Kilkenny et al., 2009). Especially problematic is the high percentage of studies not reporting all outcome measures that were described in their respective methods section, potentially introducing bias. However, inspection and analysis of funnel plots in search of indications for publication bias was mostly reassuring. Funnel plot asymmetry was largely accounted for by subgroup heterogeneity and therefore likely not a sign of publication bias. Other limitations stem from the features of the animal studies we included, which might not make them optimally suitable for translation to the human situation. For instance, many studies employed bolus daily injections that might lead to transient high serum concentrations of the compounds and their metabolites because of their relatively short half-life in rodents. In humans, SSRI use leads to more stable concentrations over the course of the day (Bourke et al., 2014). In addition, dosing and route of administration varied widely (Millard et al., 2017). SSRI plasma levels and placental transfer are sparsely measured.

Additional limitations of this study originate from the choices that we made regarding data analysis. Since this is the first systematic review of its kind, we took a broad and explorative approach. Before analyzing the data, 11 behavioral categories were created in consultation with experts. It is certainly possible that some categories are too broad in order to find subtle effects. Moreover, many behavioral tests in the studies that we included have a complex temporal design where, for instance, reflex development or learning is assessed over several days or sexual behavior over several weeks. For lack of an overall score of performance in these tests, we opted to include one time-point in our

analyses, thereby reducing these often elegant study designs to a snap shot. Comparison between studies is further complicated by the fact that not all studies report on similar time-points. In addition, besides the subgroup analyses we performed, there are other mediators that may be of interest. These analyses were outside the scope of the current review, but we do think that comparisons between the different SSRIs, the different dosages, animal species, timing of behavioral testing, and the specific test used within each category would be interesting for future studies and meta-analyses. For example, preliminary data exploration along these lines suggests that it is mainly the elevated plus maze that does not show a net effect of perinatal SSRI exposure within the category anxiety. It would be interesting to explore this further.

The strength of this review is that it is the first effort to comprehensively summarize and quantitatively analyze all available evidence on developmental SSRI exposure on behavioral outcomes in animals. The sheer number of animals included in our analyses – hundreds to thousands depending on behavioral category – gives us statistical power that far exceeds the standard in animal studies. Considering the increasing use of SSRIs during pregnancy (Bakker et al., 2008; Jimenez-Solem et al., 2013; Cooper et al., 2007; Andrade et al., 2008) and the uncertainties about their long-term effects on the developing neurobiology of the child (Rotem-Kohavi and Oberlander, 2017), studies of this phenomenon are necessary. We think this review could be valuable to the field, as we were able to concisely summarize the available animal evidence in order to inform design of future preclinical- as well as clinical studies.

4.5. Recommendations and future perspectives

Animal studies will continue to play an important role in this field because of their experimental nature and the ability to mechanistically study the developmental effects of SSRIs. To improve their transparency, quality, and utility, pre-registration of animal experiments (*e.g.*, www.preclinicaltrials.eu) should become common practice (Jansen of Lorkeers et al., 2014). In addition, reporting of animal studies should be improved by adherence to guidelines such as the ARRIVE guidelines (Kilkenny et al., 2010; Muhlhausler et al., 2013). Animal studies should be expected to adhere to a high standard of reporting for various reasons: substantial public funds are used to support this work, animals are sacrificed, and the research informs clinical study design, decision making, and policy. We would like to emphasize that, although those responsible for making (all) research results available to the scientific and wider community are the researchers themselves, other people and organizations such as funding agencies, universities, collaborating companies, journal editors and peer reviewers should all use their influence to make this the norm.

As to future animal study design, we encourage recent trends and requirements to study both males and females (Clayton and Collins, 2014). Females are understudied, and considering that we found indications of sex effects, it is clearly of interest to study both sexes. Additionally, the potential interactions of SSRI use with features of maternal depression remain underinvestigated in animals but are of high translational value. Further mechanistic studies are required to elucidate the neurobiological underpinnings of behavioral symptoms affected by early SSRI exposure. In particular, it remains to be understood whether the effects found on activity and exploration behavior can be traced back to the same neurodevelopmental processes as those found on stress coping behavior. Shifting perspectives slightly, one might wonder why early SSRI exposure does not seem to lead to stronger and more aberrant behavioral alterations than it does, considering the ubiquitous role of serotonin in the brain. Animal studies shed light on individual differences in susceptibility and resilience to the effects of early SSRI exposure, for example using strains of rats differing in their novelty seeking traits (Glover et al., 2015).

Implications for future clinical study design appear noteworthy as well: there is a clear need for studies on the effects of early SSRI exposure on mental health and behavior extending into adulthood (Rotem-Kohavi and Oberlander, 2017), especially considering that phenotypic differences may emerge only after adolescence (Glover and Clinton, 2016). In addition, while examining the risk for developing mental disorders is important, it could be equally or perhaps more informative to focus on their shared symptoms. Changes in activity and exploration, stress coping, and sensory processing are relevant to people's quality of life, even if they are not necessarily tied to the diagnosis of a mental disorder. Although subgroup analyses are observational by nature, our results suggest a strong effect of the timing of exposure to SSRIs on their long-term effect, with exposure in the period corresponding to the third trimester in humans conferring the biggest effects. Future studies in human populations should therefore seek to include timing of exposure as a key variable of interest, since this knowledge, if confirmed in humans, bears great interest for clinicians and pregnant women suffering from depression.

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Contributors

JH and JO conceived the study. AR and JR performed the systematic search. AR, LW and JR performed the screening and data extraction process. AR analyzed the data. JL advised on methodology. AR wrote the manuscript, which was revised critically by the other authors LW, JR, JL, JH and JO.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.04.010.

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