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

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#### Highlights

- Perinatal SSRI exposure in rodents alters outcomes in three behavioral domains.
- It leads to reduced activity, passive stress coping, and weaker sensory processing.
- Females are understudied but seem to be less vulnerable than males.
- Early postnatal exposure in rodents leads to the largest effects on behavior.
- This is equivalent to the third trimester of pregnancy in humans.

# 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.

# Keywords

Activity and exploration; Animal studies; Antidepressants; Anxiety; Behavior; Developmental exposure; Ingestive and reward behavior; Learning and memory; Meta-analysis; Motoric behavior; Offspring; Pregnancy; Reflex and pain sensitivity; Selective serotonin reuptake inhibitors (SSRIs); Sensory processing; Sleep and circadian activity; Social behavior; Stress coping; Systematic review; Translational, Teratogenic effects

#### 1. Introduction

Selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy has increased tremendously over the past decades<sup>1-4</sup>. Recent estimates of SSRI exposure in large population-based studies range from 2.5-3.3% of pregnancies in Europe<sup>5,6</sup> to 2.7-5.4% in the US<sup>7,8</sup>. These numbers imply that every year, in these regions alone, hundreds of thousands of babies are born after exposure to SSRIs. Although major teratogenic effects are absent, *in utero* SSRI exposure has been associated with increased risk of neonatal complications such as preterm birth<sup>9</sup>. SSRIs reach the developing fetus by crossing the placental barrier<sup>10</sup>. During fetal development, the serotonin transporter (SERT), the target of SSRIs, is much more diffusely expressed in the brain than during adulthood<sup>11</sup>. 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 and memory, and reward<sup>12</sup>, while during early development, serotonin serves as a neurotrophic factor mediating basic processes such as neurogenesis, cell migration, axon guidance, dendritogenesis and synaptogenesis<sup>13</sup>. Consequently, by reaching the brain and modulating serotonin regulation at crucial neurodevelopmental stages, SSRIs could interfere with brain circuit formation and lifelong mental health<sup>14</sup>.

This is the rationale for the "SSRI paradox", which refers to 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<sup>15</sup>. 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<sup>16</sup> and lower scores on motor-, social- emotionaland adaptive behavioral tests<sup>17</sup> after prenatal SSRI exposure. On the other hand, other studies found no association between in utero SSRI exposure and intellectual disability<sup>18</sup>, executive functioning<sup>19</sup>, and emotional or social problems<sup>20</sup>. 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<sup>21</sup>. Interestingly, some of the reported associations are modulated by behavioral outcome domain<sup>22,23</sup>, timing of exposure<sup>20</sup>, and sex<sup>23,24</sup>. 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), attentiondeficit/hyperactivity disorder (ADHD), and mental disability<sup>25</sup>. As these results may be confounded by factors such as the severity of mental health problems, it remains difficult to draw conclusions on causality<sup>25</sup>. Indeed, it is known that maternal mental health issues during pregnancy are associated with long-term neurodevelopmental outcomes in children as well<sup>26</sup>.

Laboratory rodents mature much faster than humans, yet the sequence of brain developmental milestones is remarkably similar<sup>27</sup>. 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<sup>28</sup>. Animal experiments have several other advantages, such as the ability to study the developmental effects of SSRI treatment during a healthy pregnancy and a high degree of control over drug dosing and period of exposure. 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<sup>14,29–34</sup>. 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 particularly focused 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 help inform future study design.

# 2. Methods

The review protocol was registered at the SYRCLE website (<u>www.syrcle.nl</u>) in 2016. The reporting in this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>35</sup>.

# 2.1. Search strategy

Three databases were searched systematically from inception to February 27<sup>th</sup> 2018: PubMed, PsycINFO, and Web of Science. The initial search was performed by JR on April 19<sup>th</sup> 2016. An updated search was performed by AR on February 27<sup>th</sup> 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<sup>36</sup> 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<sup>37</sup>: 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<sup>38</sup>); (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 vehicletreated 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<sub>max</sub>=13) to calculate the SD (SD=SEM\*vN), and the minimum value of N (in this case N<sub>min</sub>=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<sup>2</sup> 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<sup>2</sup> 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

To assess the methodological quality of each included study, we used the SYRCLE risk of bias tool for animal studies<sup>39</sup>. 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<sup>40</sup> in R v3.5. Each funnel plot displays all studies in one plot with SMD as the x-value and 1/VN 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<sup>41</sup>. 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<sup>42</sup> in the "metafor" package.

# 3. Results

#### 3.1. Search results

Through database searching, 5951 records were retrieved, leaving 3930 records after removal of duplicates (Figure 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 (Figure 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) (Supplementary Figure 1A). 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 (Supplementary Figure 1B). 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 (Table 3). Overall risk of bias was unclear. Only 68 studies reported all outcome measures that were described in the methods section.

# Table 1: study characteristics

Study ID	Species	Strain	Stress	Control	SSRI	Exposure period	Dose per day	Recipient	Administration method	
Grimm et al. 1987 <sup>43</sup>	rat	Wistar	no	untreated; saline	zimelidine	G10-G20; P4-P8	5 mg/kg	dam	SC	both
Hilakivi et al. 1987a44	rat	Long-Evans; Wistar	no	saline	zimelidine	P6-P19	25 mg/kg	pup	SC	male
Hilakivi et al. 1987b <sup>45</sup>	rat	Wistar	no	saline	zimelidine	P7-P18	25 mg/kg	pup	IP	male
Hilakivi et al. 1987c <sup>46</sup>	rat	Long-Evans; Wistar	no	control	zimelidine	P7-P18	25 mg/kg	pup	SC	male
Hilakivi et al. 1988a <sup>47</sup>	rat	Wistar	no	saline	zim elidin e	P7-P18	25 mg/kg	pup	IP	male
Hilakivi et al. 1988b <sup>48</sup>	rat	Wistar	no	saline	zimelidine	P7-P21	25 mg/kg	pup	IP	male
Hilakivi et al. 1994 <sup>49</sup>	rat	Wistar	no	saline	zimelidine	P6-P22	25 mg/kg	pup	SC	male
Vorhees et al. 1994 <sup>50</sup>	rat	Sprague Dawley	no	water; pair-fed	fluoxetine	G7-G20	1; 5; 12 mg/kg	dam	oral:gavage	both
Frank et al. 1997 <sup>51</sup>	rat	Long-Evans	no	dimethyl sulphoxide (DMSO)	zimelidine	P8-P21	25 mg/kg	pup	IP	male
Hansen et al. 1997 <sup>52</sup>	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 <sup>53</sup>	rat	Charles Foster	no	saline	fluoxetine	G13-G21	10 mg/kg	dam	IP	both
Stewart et al. 1998 <sup>54</sup>	rat	Sprague Dawley	no	saline	fluoxetine	G8-G20	12.5 mg/kg	dam	oral (saline SC)	both
Coleman et al. 1999 <sup>55</sup>	mouse	CD-1	no	placebo	paroxetine	G0-G16.5	30 mg/kg	dam	oral: food bar	both
Christensen et al. 2000 <sup>56</sup>	mouse	CD-1	no	placebo	paroxetine	G0-P1	30 mg/kg	dam	oral: food bar	both
Mendes da Silva et al. 2002 <sup>57</sup>	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Ansorge et al. 2004 <sup>58</sup>	mouse	129SvEv 5-HTT <sup>+/+</sup>	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	both
Ishiwata et al. 2005 <sup>59</sup>	mouse	C57BL/6	yes	sucrose	fluoxetine	P7-P28	5 mg/kg	pup	oral: pipettor	male
Vartazarmian et al. 2005	guinea pig			untreated; DMSO	fluoxetine	G1-P1	7 mg/kg	dam	SC: osmotic pump	both
Deiro et al. 2006 <sup>61</sup>	rat	Wistar	no no	water	sertraline	P1-P21	5; 10; 15 mg/kg		SC SC SC SC	male
Maciag et al. 2006a <sup>62</sup>		Long-Evans		saline		P8-P21		pup pup	SC b.i.d.	male
Maciag et al. 2006b <sup>63</sup>	rat	-	no		citalopram		10 mg/kg			
	rat	Long-Evans	no	saline	citalopram	P8-P21	10 mg/kg	pup	SC b.i.d.	male
Maciag et al. 2006c <sup>64</sup> Bairy et al. 2007 <sup>65</sup>	rat	Long-Evans	no	saline	citalopram	P8-P21	10 mg/kg	pup	SC b.i.d.	male
	rat	Wistar	no	water	fluoxetine	G6-G20	8; 12 mg/kg	dam	oral	both
Lisboa et al. 2007 <sup>66</sup>	mouse	Swiss	no	water	fluoxetine	G0-P21	~7.5 mg/kg	dam	oral:gavage	both
Ansorge et al. 2008 <sup>67</sup>	mouse	129SvEv 5-HTT* <sup>/+</sup>	no	untreated; saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	both
					citalopram	P4-P21	10 mg/kg	pup	IP	both
Cagiano et al. 2008 <sup>68</sup>	rat	Wistar	no	saline	fluoxetine	G13-G20	5; 10 mg/kg	dam	SC	male
Deiró et al. 2008 <sup>69</sup>	rat	Wistar	no	saline	citalopram	P1-P21	5; 10 mg/kg	pup	SC	male
Favaro et al. 2008'0	mouse	Swiss	no	water	fluoxetine	G0-P21	5.7-7.5 mg/kg	dam	oral: gavage	both
Forcelli et al. 2008 <sup>71</sup>	rat	Wistar	no	ethanol	fluoxetine	G14-P7	10 mg/kg	dam	SC: osmotic minipump	both
Gouvêa et al. 200872	mouse	Swiss	no	water	fluoxetine	G0-P21	7.5 mg/kg	dam	oral: gavage	male
Noorlander et al. 2008 <sup>73</sup>	mouse	C57BL/6	no	saline	fluoxetine	G8-G18	0.3; 0.6; 0.8 mg/kg	dam	IP	both
					fluvoxamine		4.2 mg/kg	dam	IP	both
Popa et al. 2008 <sup>74</sup>	mouse	CD-1	no	saline	escitalopram	P5-P19	10 mg/kg	pup	SC	female
Jiang et al. 2009 <sup>75</sup>	mouse	Kunming	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Karpova et al. 2009 <sup>76</sup>	mouse	C57BL/6		saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Lee 2009 <sup>77</sup>	rat	Wistar	no	saline	fluoxetine	P0-P6	10 mg/kg	pup	SC	both
Capello et al. 2011 <sup>78</sup>	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 <sup>79</sup>	rat	Sprague Dawley	no	saline	fluoxetine	P8-P21	10 mg/kg	pup	IP	male
Olivier et al. 2011 <sup>80</sup>	rat	Wistar	no	methylcellulose	fluoxetine	G11-P1	12 mg/kg	dam	oral:gavage	both
Pivina et al. 2011 <sup>81</sup>	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 <sup>82</sup>	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	both
Rodriguez-Porcel et al. 2011 <sup>83</sup>	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
5		5			fluoxetine	P8-P21	10 mg/kg	pup	SC b.i.d.	both
Simpson et al. 2011 <sup>84</sup>	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
Zheng et al. 2011 <sup>85</sup>	mouse	C57BL/6	no	saline	fluoxetine	P4-P21	10 mg/kg	pup	IP	male
Harris et al. 2012 <sup>86,87</sup>	rat	Long-Evans	no	saline	citalopram	P8-P21	5; 10; 20 mg/kg	pup	SC b.i.d.	male
Kummet et al. 2012 <sup>88</sup>	mouse	C57BL/6	no	saline	sertraline	P1-P14	5 mg/kg	pup	IP	both
Lee et al. 2012	rat	Wistar	no	saline	fluoxetine	PO-P4	20 mg/kg	pup	SC	male
McAllister et al. 2012 <sup>90</sup>	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	female
Nagano et al. 2012 <sup>91</sup>				saccharine + saline G16-G23		P2-P21	17.2 ± 0.6 mg/kg	dam	oral: drinking water	male
Rebello 2012 <sup>92</sup>	rat mouse	Sprague Dawley 129SvEv	yes no	saline	fluoxetine fluoxetine	P2-P21; P2-P11	10 mg/kg		IP	both
Smit-Rigter et al. 2012								pup	IP	
Smit-Rigter et al. 2012 Soga et al. 2012 <sup>94</sup>	mouse	C57BL/6	no	saline	fluoxetine	G8-G18	0.6 mg/kg	dam		both
	mouse	C57BL/6 129SvEv Htr2a <sup>+/+</sup>	no	water	citalopram	P8-P22	10 mg/kg	pup	SC	male
Yu et al. 2012 <sup>95</sup>	mouse		no	saline	fluoxetine	P2-P11	10 mg/kg	pup	IP CC competie estationer	both
Bourke et al. 201396	rat	Sprague Dawley	yes	saline	escitalopram		12.2-17.3 mg/kg	dam	SC: osmotic minipump	male
Francis-Oliveira et al. 201397	rat	Wistar	no	water	fluoxetine	G0-P21	5 mg/kg	dam	oral: oral gavage	both
Freund et al. 2013 <sup>98</sup> Kiryanova et al. 2013 <sup>99</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	P2-P9	10 mg/kg	pup	IP	both
	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male

Knaepen et al. 2013 <sup>100</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	G21-P21	10 mg/kg	dam	oral: wafer b.i.d.	male
Rayen et al. 2013 <sup>101</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	male
Schaefer et al. 2013 <sup>102</sup>	rat	Sprague Dawley	no	saline	citalopram	P11-P20	10; 15 mg/kg	pup	SC b.i.d.	male
Vieira et al. 2013 <sup>103</sup>	rat	Wistar	no	water	fluoxetine	G0-P21	7.5 mg/kg	dam	oral:gavage	male
da Silva et al. 2014 <sup>104</sup>	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Glazova et al. 2014 <sup>105</sup>	rat	Outbred white		untreated; water	fluvoxamine	P1-P14	10 mg/kg	pup	IP	both
Khatri et al. 2014 <sup>106,107</sup>	rat	Long-Evans	no	saline	citalopram	P8-P21	20 mg/kg	pup	SC b.i.d.	both
Kiryanova et al. 2014 <sup>108</sup>	mouse	C57BL/6	no	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Ko et al. 2014 <sup>109</sup>	rat	Wistar	no	saline	fluoxetine	P0-P4	20 mg/kg	pup	SC b.i.d.	male
Rayen et al. 2014 <sup>110</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	female
Rebello 2014 et al. <sup>111</sup>	mouse	129SvEv	no	saline	fluoxetine	P2-P21; P2-P11; P12-P21	10 mg/kg	pup	IP	both
Sarkar et al. 2014a <sup>112</sup>	rat	Sprague Dawley	no	sucrose	fluoxetine	P2-P21	10 mg/kg	pup	oral: gavage	male
Sarkar et al. 2014b <sup>113</sup>	rat	Sprague Dawley	no	sucrose	fluoxetine	P2-P21	10 mg/kg	pup	oral: gavage	male
Toffoli et al. 2014 <sup>114</sup>	rat	Wistar	no	water	fluoxetine	G0-P21	5 mg/kg	dam	oral: gavage	male
Volodina et al. 2014 <sup>115</sup>	rat	Outbred white	no	water + intranasal water P15-P28			10 mg/kg	pup	IP	both
Yu et al. 2014 Yu et al. 2014	mouse	129SvEv	no	saline	fluoxetine	P2-P21	10 mg/kg		IP	both
Altieri et al. 2015 <sup>117</sup>	mouse	CD-1 x 129SvEv 5-HTT*/*			fluoxetine	P5-P21	10 mg/kg	pup	SC	
Aitien et al. 2015	mouse	CD-1 X 1293VEV 5-H11	no	untreated; saline	escitalopram		0, 0	pup	SC	both
Avitsur et al. 2015 <sup>118</sup>		6D 1		11			10 mg/kg	pup	SC	both
da Silva et al. 2015	m ouse	CD-1	no	saline	fluoxetine	G1-P0	10 mg/kg	dam	SC	both
da Silva et al. 2015 Ehrlich et al. 2015 <sup>120</sup>	rat	Wistar	no	saline	fluoxetine	P2-P21	10 mg/kg	pup		male
	rat	Sprague Dawley	yes	saline	escitalopram		12.2-17.3 mg/kg	dam	SC: osmotic minipump	female
Galindo et al. 2015 <sup>121</sup>	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Zhou et al. 2015 <sup>122</sup>	rat	Sprague Dawley	no	saline	citalopram	P1-P10	20 mg/kg	pup	SC b.i.d.	both
Boulle et al. 2016a <sup>123</sup>	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	male
Boulle et al. 2016b <sup>124</sup>	rat	Sprague Dawley	yes	saline + propylene glycol	fluoxetine	P1-P21	5 mg/kg	dam	SC: osmotic minipump	female
Dos Santos et al. 2016 <sup>125</sup>	rat	Wistar	no	water	fluoxetine	G1-P21	5 mg/kg	dam	oral: gavage	female
Gobinath et al. 2016 <sup>126</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	P2-P23	10 mg/kg	dam	IP	both
Kiryanova et al. 2016 <sup>127</sup>	mouse	C57BL/6	yes	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Kroeze et al. 2016 <sup>128</sup>	rat	Wistar	no	methylcellulose	fluoxetine	G11-P7	12 mg/kg	dam	oral:gavage	male
Matsumoto et al. 2016 <sup>129</sup>	rat	Wistar	no	water	fluoxetine	G1-P21	5 mg/kg	dam	oral: gavage	both
Salari et al. 2016 <sup>130</sup>	mouse	NMRI	yes	water	fluoxetine	G10-P20	8 mg/kg	dam	oral: drinking water	male
Sprowles et al. 2016 <sup>131</sup>	rat	Sprague Dawley	no	saline	citalopram	G6-G21 + P1-P20	20 mg/kg	dam + pup	SC b.i.d.	both
Svirsky et al. 2016 <sup>132</sup>	mouse	CD-1	no	saline	fluoxetine	G1-P1	10 mg/kg	dam	SC	both
Zohar et al. 2016 <sup>133</sup>	rat	Wistar	yes	water	citalopram	G7-P21	10 mg/kg	dam	oral: drinking water	both
Avitsur 2017 <sup>134</sup>	mouse	CD-1	yes	saline + food/water deprived	fluoxetine	G1-delivery	10 mg/kg	dam	SC	both
Gemmel et al. 2017 <sup>135</sup>	rat	Sprague Dawley	yes	saline	fluoxetine	G10-P21	10 mg/kg	dam	oral: wafer b.i.d.	both
Haskell et al. 2017 <sup>136</sup>	mouse	C57BL/6	no	saline	sertraline	G1-delivery + P1-P14	dam 5 + pup 1.5 mg/kg	dam + pup	IP	both
lshikawa et al. 2017 <sup>137</sup>	mouse	BALB/c	no	sucrose	fluoxetine	P1-P21	5 mg/kg	pup	oral:gavage	male
Kiryanova et al. 2017a <sup>138</sup>	mouse	C57BL/6	yes	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	male
Kiryanova et al. 2017b <sup>139</sup>	mouse	C57BL/6	y es	water	fluoxetine	G15-P12	25 mg/kg	dam	oral: drinking water	female
Nagano et al. 2017 <sup>140</sup>	mouse	C57BL/6	no	saline + sham surgery G16	fluoxetine	P3-P21	50 μg/kg (pup)	pup	SC	both
	moute	00,02,0			escitalopram		50 μg/kg (pup)	pup	SC	both
Pinheiro et al. 2017 <sup>141</sup>	rat	Wistar	no	saline	fluoxetine	P1-P21	10 mg/kg	pup	SC	male
Sprowles et al. 2017 <sup>142</sup>	rat	Sprague Dawley	no	saline	citalopram	G6-G21 + P1-P20	10 mg/kg	dam + pup	SC b.i.d.	both
oprovinci et ul. 2017		Spidgue Duwicy	110	Same	fluoxetine	G6-G21 + P1-P20	10 mg/kg	dam + pup dam + pup	SC b.i.d.	both
Meyer et al. 2018 <sup>143</sup>	mouse	C57BL/6	no	saline	sertraline	G1-delivery + P1-P14	dam 5 + pup 1.5 mg/kg	dam + pup dam + pup	IP	both
Abbreviations and notes		C378L/0	110	301110	sertrainte	GI-Genvery Tri-r14	uam of hub To mg/kg	uani – pup	IF	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

	Table 2: characteristics o	f studie	s combining	(maternal	) stress with SSRI treatment
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Study ID	Dam or pup?	Control	Stressor	Duration	Frequency	Intervention period	SSRI exposure
shiwata et al. 2005 <sup>59</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Pivina et al. 2011 <sup>81</sup>	dam	undisturbed	restraint stress	20 min	daily	G15-G18	before
Rayen et al. 2011 <sup>82</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Nagano et al. 2012 <sup>91</sup>	dam	saline (SC)	dexamethasone (50 μg/kg SC)	N/A	daily	G16-G21	before
Bourke et al. 201396	dam	undisturbed	chronic unpredictable mild stress	various	various	G15-G20	during
Freund et al. 2013 <sup>98</sup>	pup	handled	maternal separation (individual isolation)	4 hr	daily	P2-P9	during
Knaepen et al. 2013 <sup>100</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G14-G20	before
Rayen et al. 2013 <sup>101</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Rayen et al. 2014 <sup>110</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Ehrlich et al. 2015 <sup>120</sup>	dam	undisturbed	chronic unpredictable mild stress	various	various	G9-G20	during
Boulle et al. 2016a <sup>123</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Boulle et al. 2016b <sup>124</sup>	dam	undisturbed	restraint stress	45 min	3 times/day	G15-G21	before
Gobinath et al. 2016 <sup>126</sup>	dam	sesame oil (1 ml/kg SC)	corticosterone (40 mg/kg SC)	N/A	2 times/day	P2-P23	during
Kiryanova et al. 2016 <sup>127</sup>	dam	undisturbed	chronic unpredictable mild stress	various	daily	G4-G18	before+during
Salari et al. 2016 <sup>130</sup>	dam	undisturbed	restraint stress	40 min	3 times/day	G5-G19	before+during
Zohar et al. 2016 <sup>133</sup>	dam	undisturbed	chronic unpredictable mild stress	various	daily	G13-G21	during
Avitsur 2017 <sup>134</sup>	dam	food and water deprived	restraint stress	45 min	3 times/day	G14-G18	during
Gemmel et al. 2017 <sup>135</sup>	dam	undisturbed	chronic unpredictable mild stress	various	0-2 times/day	G1-G21	before+during
Kiryanova et al. 2017a <sup>138</sup>	dam	undisturbed	chronic unpredictable mild stress	various	daily	G7-G18	before+during
Kiryanova et al. 2017b <sup>139</sup>	dam	undisturbed	chronic unpredictable mild stress	various	daily	G4-G18	before+during

	1. Is it mentioned that the experiment Was	2. Is it mentioned that the experiment	3. Is a power- or sample size calculation	4. Was the allocation sequence adequately generated	5. Were the maternal groups similar at baseline or adjusted for confounders? Species,	distribution),	7. Was the allocation adequately	8. Were the animals randomly housed during the	9. Were the caregivers or in vestigators during the course of the experiment adequately	10. Were animals selected at random during outcome	11. Was the outcome assessment adequately	12. Were incomplete outcome data adequately	reported in	free of other problems that could cause a high risk of bias? one pup/litter OR correct for litter size in
Study ID 40		was blinded?	shown?		strain, weight	litter size	concealed?	experiment?	blinded?	assessment?	blinded?	addressed?	results?	stats?
Grimm et al. 1987 <sup>43</sup>	Y	N	N	?	?	Y	?	?	?	?	?	?	Y	N
Hilakivi et al. 1987a44	Y	N	N	?	Y	Y	?	Y	?	?	?	Y	Y	N
Hilakivi et al. 1987b <sup>45</sup>	N	Y	N	?	Y	Y	?	?	Y	?	Y	?	Y	N
Hilakivi et al. 1987c <sup>46</sup>	N	N	N	?	?	?	?	?	?	?	?	Y	Y	?
Hilakivi et al. 1988a <sup>47</sup>	Y	N	N	?	Y	Y	?	?	?	?	?	?	Y	?
Hilakivi et al. 1988b <sup>48</sup>	N	Y	N	?	Y	Y	?	?	?	?	Y	Y	Y	Y
Hilakivi et al. 1994 <sup>49</sup>	N	N	N	?	?	?	?	?	?	?	?	Y	N	?
Vorhees et al. 1994 <sup>50</sup>	Ν	Y	N	?	Y	?	Y	?	?	?	?	?	Ν	Y
Frank et al. 1997 <sup>51</sup>	Y	Ν	N	?	?	Y	?	?	?	?	?	Y	Y	?
Hansen et al. 1997 <sup>52</sup>	Y	Ν	Ν	?	Y	Y	?	?	?	?	?	Y	Y	?
Singh et al. $1998^{53}$	Ν	Ν	Ν	?	?	?	?	?	?	?	?	?	Y	?
Stewart et al. 1998 <sup>54</sup>	Ν	Y	Ν	?	Y	Y	?	?	?	Y	Y	Y	Ν	Ν
Coleman et al. 1999 <sup>55</sup>	Ŷ	Y	Y	?	?	Y	2	2	2	2	Y	Ν	Ν	Y
Christensen et al. 2000 <sup>56</sup>	Ŷ	N	Ŷ	?	?	Ŷ	?	?	?	?	?	?	N	Ŷ
Mendes da Silva et al. 2002 <sup>57</sup>	v	N	N	?	?	2	?	?	?	?	?	· v	Ŷ	N
Ansorge et al. 2004 <sup>58</sup>	v	N	N	?	?	v	?	?	?	?	2	Ý	Ý	?
Ishiwata et al. 2005 <sup>59</sup>	N	N	N	?	?	י ר	?	?	?	?	?	Ŷ	Ý	?
Vartazarmian et al. 2005	N	N	N	?	Ŷ	Y	י ?	2	?	?	י י	2	Ŷ	?
Deiró et al. 2006 <sup>61</sup>	N Y	Y	N Y		т ?	t V	r ?	r ?	r ?	r ?	r ?	r Y	r Y	
				?	-	ř	•	•	-	•	-			?
Maciag et al. 2006a <sup>62</sup>	N	N	N	?	Y	Ŷ	?	?	?	?	?	?	N	?
Maciag et al. 2006b <sup>63</sup>	N	N	N	?	Y	Ŷ	?	?	?	?	?	N	N	?
Maciag et al. 2006c <sup>64</sup>	N	Y	N	?	Y	Y	?	?	?	?	Y	?	N	?
Bairy et al. 2007 <sup>65</sup>	Y	N	N	?	?	Y	?	?	?	?	?	Y	Y	Y
Lisboa et al. 2007 <sup>66</sup>	N	Y	N	?	Y	Y	?	?	?	?	Y	N	Y	Y
Ansorge et al. 2008 <sup>67</sup>	Y	N	N	?	Y	Y	?	Y	?	?	?	?	N	Y
Cagiano et al. 200868	Y	N	N	?	?	Y	?	?	?	?	?	N	N	Y
Deiró et al. 2008 <sup>69</sup>	Y	Y	N	?	?	Y	?	?	?	?	?	Y	Y	?
Favaro et al. 2008 <sup>70</sup>	Ν	Y	Ν	?	Y	Y	?	?	?	?	Y	Ν	Y	Y
Forcelli et al. 2008 <sup>/1</sup>	Ν	Y	N	?	?	Y	?	?	?	?	Y	Y	Y	Ν
Gouvêa et al. 2008 <sup>72</sup>	Ν	Ν	Ν	?	?	Y	?	?	?	?	?	?	Y	Y
Noorlander et al. 2008 <sup>73</sup>	Ν	Ν	Ν	?	?	?	?	?	?	?	?	?	N	?
Popa et al. 2008 <sup>74</sup>	Y	Ν	Ν	?	Y	Y	?	?	?	?	?	?	Ν	?
Jiang et al. 2009 <sup>75</sup>	Ν	Ν	N	?	?	?	?	?	?	?	?	?	Y	?
Karpova et al. 2009 <sup>76</sup>	Ŷ	N	N	?	?	?	?	?	?	?	?	Ŷ	Ŷ	?
Lee 2009 <sup>77</sup>	N	N	N	?	?	?	?	?	?	?	?	?	Ŷ	?
Capello et al. 2011 <sup>78</sup>	Ŷ	Y	N	?	?	?	?	?	?	?	Ŷ	?	Ŷ	N
Mnie-Filali et al. 2011 <sup>79</sup>	Ŷ	N	N	?	?	Ŷ	?	?	?	?	, ,	N	Ŷ	?
Olivier et al. 2011 <sup>80</sup>	N	N	N	?	?	N	?	2	?	?	?	2	N	?
Pivina et al. 2011 <sup>81</sup>	N	N	N	י ?	: ?	2	?	2	; ?	?	2	?	Y	, N
Rayen et al. 2011 <sup>82</sup>	v	N	N	r ?	r ?	· V	r ?	7	?	?	r ?	r ?	Ŷ	N
Rodriguez-Porcel et al. 2011	N	Y	N	?	r Y	v	r ?	r ?	r ?	r ?	r ?	r ?	N	?
Cimpson et al. 2011 <sup>84</sup>			N		ř ?	T D	r P	?	r ?	? ?		r ?	N ?	r ?
Simpson et al. 2011 <sup>84</sup>	N	N		?	-	? 					?		-	
Zheng et al. 2011 <sup>85</sup>	Y	N	N	?	Y	Ŷ	?	?	?	?	?	?	Y	?
Harris et al. 2012 <sup>86,87</sup>	N	Y	N	?	Y	Y	?	?	?	?	?	?	N	N
Kummet et al. 2012 <sup>88</sup>	Y	N	N	?	Y	Y	?	?	?	?	?	?	Y	N
Lee et al. 2012 <sup>89</sup>	N	N	N	?	?	?	?	?	?	?	?	Y	Y	?
McAllister et al. 2012 <sup>90</sup> Nagano et al. 2012 <sup>91</sup>	N	N	N	?	?	Y	?	?	?	?	?	Y	Y	Y
	Ŷ	Ν	Ν	?	Ŷ							Ν	Y	?

	Ν	Ν	Ν	?	?	?	2	Y	?	?	2	?	Y	ъ	
Rebello 2012 <sup>92</sup> Smit-Rigter et al. 2012 <sup>93</sup>	N	N	N	?	?	?	?	?	?	?	r ?	?	Y	?	
Soga et al. 2012 <sup>94</sup>	N	N	N	, ?	, ?	Ŷ	; ?	?	?	, ?	?	Ŷ	Ý	N	-
Yu et al. 2012 <sup>95</sup>	N	N	N	; ?	?	?	, 2	: ?	?	2	, 2	?	Ý	?	D Dic
Bourke et al. 2013 <sup>96</sup>	N	N	N	r 7	r ?	Y	r 2	r ?	r ?	r ?	r 2	-	N	r N	ਹੈ ਹੋ
Francis-Oliveira et al. 2013				r	r Y	Y	r	r	-	r	r	N	Y		ë, €
Francis-Oliveira et al. 2013	N	N	N	r	-		r	r 2	?	r	r	?	-	Y	fip
Freund et al. 2013 <sup>98</sup>	Y	N	N	?	?	Y	2	?	?	2	2	Ŷ	Y	Y	bioRxiv prepr not certified b
Kiryanova et al. 2013 <sup>99</sup>	N	N	N	?	?	Y	?	?	?	?	?	Y	N	N	by peer
Knaepen et al. 2013 <sup>100</sup>	Ŷ	Y	N	?	?	Y	?	?	?	?	7	?	Y	N	- p m
Rayen et al. 2013 <sup>101</sup>	Y	Y	N	?	Y	Y	?	?	?	?	Ŷ	?	Y	N	t doi: peer
Schaefer et al. 2013 <sup>102</sup>	N	N	N	?	Y	Y	7	7	?	7	7	?	N	Y	
Vieira et al. 2013 <sup>103</sup>	N	N	N	?	?	Y	?	?	?	?	?	?	Y	Y	https://doi. r review) is
da Silva et al. 2014 <sup>104</sup>	N	N	N	?	?	?	?	?	?	?	?	N	Y	?	ie s:
Glazova et al. 2014 <sup>105</sup>	N	N	Ν	?	Y	Y	?	?	?	?	?	?	N	N	2
Khatri et al. 2014 <sup>106,107</sup>	N	N	N	?	Y	Y	?	?	?	?	?	N	N	?	<u>s</u> . <u>o</u> .
Kiryanova et al. 2014 <sup>108</sup>	N	N	N	?	?	Y	?	?	?	?	?	Y	N	Y	59
Ko et al. 2014	Y	N	N	?	Y	Y	?	?	?	?	?	?	Y	?	e Q
Raven et al. 2014 <sup>110</sup>	Y	Y	Ν	?	?	Y	?	?	?	?	Y	?	Y	N	the aut
Rebello 2014 et al. <sup>111</sup>	Ν	Ν	Ν	?	?	N	?	Y	?	?	?	?	Y	N	
Sarkar et al. 2014a <sup>112</sup>	Ν	Y	Ν	?	?	?	?	?	?	?	?	?	Ν	?	110.1101/868265; this author/funder, who ha under aCC
Sarkar et al. 2014b <sup>113</sup>	Y	Y	Ν	?	?	?	?	?	?	?	?	Ν	Y	N	un 🖌
Toffoli et al. 2014 <sup>114</sup>	Ν	Ν	Ν	?	?	Y	?	?	?	?	?	?	Y	?	L De S
Volodina et al. 2014 <sup>115</sup>	Ν	Ν	Ν	?	Y	Y	?	?	?	?	?	?	Y	Ν	inde
Yu et al. 2014 <sup>95,116</sup>	Y	Ν	Ν	?	Y	Y	?	?	?	?	?	?	Ν	?	let ₹ 0
Altieri et al. 2015 <sup>117</sup>	Y	Y	Ν	?	Y	Y	?	?	Ν	?	Y	?	Y	?	a 0 <del>4</del>
Avitsur et al. 2015 <sup>118</sup>	N	N	N	,	2	Ŷ	2	?	?	2	2	,	Ŷ	N	Chanis
da Silva et al. 2015 <sup>119</sup>	N	N	N	?	?	, ,	, ,	?	?	, ,	?	?	Ŷ	?	÷ s ≤
Ehrlich et al. 2015 <sup>120</sup>	N	Ŷ	N	?	?	Y	ว		?	ว	· v	ว	N	v	BY ers
Galindo et al. 2015 <sup>121</sup>	N	N	N	, ?	Ŷ	Ý	: ว	2	?	: ว	2	v	Y	N	version p s grante -BY-NC
Zhou et al. 2015 <sup>122</sup>	N	N	N	, ?	2	Ŷ	: ว	2	2	: ว	2	2	Ý	?	ط ق <mark>ہ</mark>
Boulle et al. 2016a <sup>123</sup>	Y	N	N	, ?	: ว	Ý	2	2	?	2	2	2	Ý	N	Z – Š
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Dos Santos et al. 2016 <sup>125</sup>	I V	N	N	?	?	Y	r 2	י ר	r ?	r 2	r 2	r N	Y	Ŷ	- 20 G
Gobinath et al. 2016	t Y	Y		r ?	r ?	т ?	r 2	r 7	r ?	r 7	r ?	או ?	•	r N	Dece 0 Inte
Kiryanova et al. 2016 <sup>127</sup>	r Y	r Y	N	r ?	r ?	r Y	r	r ?	r ?	r ?	r	r ?	N	N Y	iter ali
Kroeze et al. 2016	•	-	N		-	-	r	-		-	r		N		embe licen ernatii
Kroeze et al. 2016	Y	Ŷ	N	?	?	?	2	?	N	?	Y	Y	Y	N	ember license ernatio
Matsumoto et al. 2016 <sup>129</sup>	N	Y	N	?	?	Y	?	?	?	?	Ŷ	?	Y	Ŷ	
Salari et al. 2016 <sup>130</sup>	Y	Y	N	?	?	Y	?	?	?	?	Y	?	Y	Ŷ	<sup>≞</sup> ਰੋ <sub>N</sub>
Sprowles et al. 2016 <sup>131</sup>	Y	Y	N	N	?	Y	Y	?	?	?	Ŷ	?	Y	Y	2019. o displ Hicens
Svirsky et al. 2016 <sup>132</sup>	N	N	N	?	?	Y	?	?	?	?	?	?	N	N	ည်း ရှိနှ
Zohar et al. 2016 <sup>133</sup>	Y	Y	N	?	?	Y	?	?	?	?	Y	?	Y	N	<sup>8</sup> ay T
Avitsur 2017 <sup>134</sup>	Y	N	N	?	?	?	?	?	?	?	?	?	Y	N	. The copyright h lay the preprint i se.
Gemmel et al. 2017 <sup>135</sup>	Y	Y	N	?	?	Y	?	?	?	?	Y	Y	Y	?	<u>ē</u> 8
Haskell et al. 2017 <sup>136</sup>	Y	N	N	?	Y	Y	?	?	?	?	?	?	N	?	prepy
lshikawa et al. 2017 <sup>137</sup>	Y	N	Ν	?	?	?	?	?	?	?	?	?	Y	?	pi (ric
Kiryanova et al. 2017a <sup>138</sup>	Y	Ν	Ν	?	?	Y	?	?	?	?	?	Y	Y	N	n jit
Kiryanova et al. 2017b <sup>139</sup>	Y	N	N	?	Y	Y	?	?	?	?	?	?	N	?	t in perp
Nagano et al. 2017 <sup>140</sup>	Ν	N	N	?	?	?	?	?	?	?	?	N	N	N	d r
Pinhaira at al. 2017 <sup>141</sup>	Y	Ν	Ν	?	Y	Y	?	?	?	?	?	?	Y	?	erier
Finnen olet al. 2017	Y	Y	Ν	?	?	Y	Y	?	Y	?	Y	Ν	Y	Y	perpetuity.
Pinheiro et al. 2017 <sup>141</sup> Sprowles et al. 2017 <sup>142</sup> Meyer et al. 2018 <sup>143</sup>		Y	Ν	?	Y	Y	?	?	?	?	?	?	Y	?	É T

# 3.4. Activity and exploration

The meta-analysis for activity and exploration comprised 52 studies and 134 comparisons. 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 (Figure 2A; Supplementary Figure 2A, SMD -0.28 [-0.38, -0.18], p<0.00001). Subgroup analysis showed that the effect was different depending on sex (Figure 2A; Supplementary Figure 2B, Chi<sup>2</sup>=13.89, p<0.01). More specifically, while activity scores were 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<0.0001) developmentally exposed to SSRIs versus those exposed to vehicle, they were not for females (SMD -0.12 [-0.29, 0.04], p=0.14) (Figure 2A; Supplementary Figure 2B). Subgroup analysis based on stress exposure did not reveal significantly different effects of developmental SSRI exposure depending on stress exposure (Figure 2A; Supplementary Figure 2C, Chi<sup>2</sup>=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 (Figure 2A; Supplementary Figure 2D, Chi<sup>2</sup>=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 (Figure 2A; Supplementary Figure 2D).

The heterogeneity (I<sup>2</sup>) 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. 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 (Figure 2B; Supplementary Figure 3A, 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 (Figure 2B; Supplementary Figure 3B, Chi<sup>2</sup> = 4.44, p=0.11), stress exposure (Figure 2B; Supplementary Figure 3C, Chi<sup>2</sup> = 2.73, p=0.10), or period of SSRI exposure (Figure 2B; Supplementary Figure 3D, Chi<sup>2</sup> = 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. 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 (Figure 2C; Supplementary Figure 4A, 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 (Figure 2C; Supplementary Figure 4B, Chi<sup>2</sup> = 1.61, p=0.45), stress exposure (Figure 2C; Supplementary Figure 4D, Chi<sup>2</sup> = 2.72, p=0.25), or period of SSRI exposure (Figure 2C; Supplementary Figure 4D, Chi<sup>2</sup> = 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 lower the heterogeneity.

#### 3.7. Social behavior

The meta-analysis for social behavior comprised 30 studies with 53 comparisons. 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 (Figure 2D; Supplementary Figure 5A, 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 (Figure 2D; Supplementary Figure 5B, Chi<sup>2</sup> = 5.12, p=0.08) and stress exposure (Figure 2D; Supplementary Figure 5C, Chi<sup>2</sup> = 0.41, p=0.52), the effect was different depending on period of SSRI exposure (Figure 2D; Supplementary Figure 5D, Chi<sup>2</sup> = 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) (Figure 2D; Supplementary Figure 5D).

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. 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.

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 (Figure 2E; Supplementary Figure 6A, SMD -0.04 [-0.20, 0.11], p=0.57). Subgroup analyses revealed significantly different effects of developmental SSRI exposure depending on sex (Figure 2E; Supplementary Figure 6B, Chi<sup>2</sup> = 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) (Figure 2E; Supplementary Figure 6B). There was no different effect of developmental SSRI exposure on learning and memory outcomes depending on stress exposure (Figure 2E; Supplementary Figure 6C, Chi<sup>2</sup> = 0.13, p=0.72). In contrast, the effect was different depending on period of SSRI exposure (Figure 2E; Supplementary Figure 6D, Chi<sup>2</sup> = 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) (Figure 2E; Supplementary Figure 6D).

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. 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 (Figure 2F; Supplementary Figure 7A, 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 (Figure 2F; Supplementary Figure 7B, Chi<sup>2</sup> = 1.98, p=0.37), stress exposure (Figure 2F; Supplementary Figure 7C, Chi<sup>2</sup> = 1.65, p=0.20), or period of SSRI exposure (Figure 2F; Supplementary Figure 7D, Chi<sup>2</sup> = 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. 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 (Figure 2G; Supplementary Figure 8A, 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 (Figure 2G; Supplementary Figure 8B, Chi<sup>2</sup> = 1.40, p=0.50) or period of SSRI exposure (Figure 2G; Supplementary Figure 8C, Chi<sup>2</sup> = 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. 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 (Figure 2H; Supplementary Figure 9A, 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 (Figure 2H; Supplementary Figure 9B, Chi<sup>2</sup> = 1.71, p=0.42) and stress exposure (Figure 2H; Supplementary Figure 9C, Chi<sup>2</sup> = 0.23, p=0.63), the effect was different depending on period of SSRI exposure (Figure 2H; Supplementary Figure 9D, Chi<sup>2</sup> = 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) (Figure 2H; Supplementary Figure 9D).

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. 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 (Figure 2I; Supplementary Figure 10A, 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 (Figure 2I; Supplementary Figure 10B, Chi<sup>2</sup> = 1.33, p=0.51), stress exposure (Figure 2I; Supplementary Figure 10C, Chi<sup>2</sup> = 0.02, p=0.88), or period of SSRI exposure (Figure 2I; Supplementary Figure 10D, Chi<sup>2</sup> = 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 Figure 11A), stress coping (Supplementary Figure 11C), social behavior (Supplementary Figure 11D), motoric behavior (Supplementary Figure 11G), sensory processing (Supplementary Figure 11H), and reflex and pain sensitivity (Supplementary Figure 11I).

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 Figure 11B). 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 Figure 11E). 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 eight extra data points and an adjusted estimated effect size of SMD -0.12 [-0.49, 0.25] (Supplementary Figure 11F).

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<sup>144</sup>. 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 Figure 11B) and few extra data points for learning and memory (Supplementary Figure 11E). 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 4).

Table 4: study outcomes for sleep & circadian activity

Study ID	Measure	Summary of outcome
Hilakivi et al. 1987a <sup>44</sup>	Sleep-wake behavior measured with a	Less active sleep and more wakefulness during neonatal SSRI treatment
46	movement sensitive mattress	
Hilakivi et al. 1987c <sup>46</sup>	Sleep-wake behavior measured with a movement sensitive mattress	Less active sleep during neonatal SSRI treatment
Hilakivi et al. 1988a <sup>47</sup>	Sleep-wake behavior measured with a movement sensitive mattress	Less active sleep during neonatal SSRI treatment
Frank et al. 1997 <sup>51</sup>	Sleep architecture using EEG and EMG	More non-REM-REM transitions*. No differences in sleep and wake amount.
Popa et al. 2008 <sup>74</sup>	Sleep architecture using EEG and EMG	Total REM sleep duration and frequency is higher*. No differences in non REM sleep.
Kiryanova et al. 2013 <sup>99</sup>	Running wheel activity during LD, DD (baseline and after short light pulse),	Baseline: free-running period in DD was shorter*. Otherwise no differences.
	and LL (baseline and after long dark pulse)	Light pulse: larger phase advance by light pulse at CT22*, but not at CT16 No difference in phase advance after dark pulse.
Kiryanova et al. 2017a <sup>138</sup>	Running wheel activity during LD, after	No baseline differences. It took longer to re-entrain to the new LD cycle*
	LD advance, during DD (baseline and after short light pulse), and LL	Interaction with maternal stress in the phase shift to light pulses at CT22* but not at CT16.
Abbreviations and notes		* in adult animals developmentally exposed to SSRIs versus vehicle
EEG = electroencephalogra	am	

EMG = electromyogram REM = rapid eye movement LD = light/dark cycle

DD = constant darkness

LL = constant light CT = circadian time

# 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 5).

Challenge	Measure	Summary of outcome	Study ID
Central depressants			
Alcohol	Open field test	Stronger inhibitory effect on ambulation*	Hilakivi et al. 1987a <sup>44</sup>
Baclofen	Forced swim test	No different response*	Hilakivi et al. 1988b <sup>48</sup>
Diazepam	Elevated plus maze	No different response in males or females*	Favaro et al. 2008 <sup>70</sup>
Dizocilpine/MK-801 (NMDA antagonist)	Open field test	No different response*	Sprowles et al. 2016 <sup>131</sup>
	Open field test	No different response*	Sprowles et al. 2017 <sup>142</sup>
Progabide (GABA receptor agonist)	Forced swim test	Reduced enhancing effect on immobility time*	Hilakivi et al. 1988b <sup>48</sup>
Propyleneglycol	Elevated plus maze	No different response in males or females*	Favaro et al. 2008 <sup>70</sup>
Dopamine system			
Apomorphine (D2/D3 agonist)	Prepulse inhibition	No different response*	Vorhees et al. 1994 <sup>50</sup>
	Stereotyped behavior	No different response*	Hilakivi et al. 1994 <sup>49</sup>
	Stereotyped behavior	Somewhat reduced stereotypy in females*	Favaro et al. 2008 <sup>70</sup>
Quinpirole ( $D_2/D_3$ agonist)	Open field test	No different response*	Stewart et al. 1998 <sup>54</sup>
	Stereotyped behavior	No different response*	Stewart et al. 1998 <sup>54</sup>
lmmune response			
Lipopolysacchari de	Food consumption	Reduced food consumption in the first 24hrs in males*, not females	Avitsur et al. 2015 <sup>118</sup>
	Food consumption	No different response*	Avitsur 2017 <sup>134</sup>
	Sucrose consumption	Reduced inhibitory effect in the first 60hrs* in males, not females	Avitsur et al. 2015 <sup>118</sup>
	Sucrose consumption	Reduced inhibitory effect in females*, not in males	Avitsur 2017 <sup>134</sup>
Norepinephrine system			
Amphetamine	Open field test	No different response*	Sprowles et al. 2016 <sup>131</sup>
	Open fieldtest	Reduced stimulant effect	Sprowles et al. 2017 <sup>142</sup>
Diethylpropion (NE-releasing)	Open field test	Reduced stimulant effect in females*, not males	Favaro et al. 2008 <sup>70</sup>
	Stereotyped behavior	Reduced stereotypy in females*, not in males	Favaro et al. 2008 <sup>70</sup>
Salbutamol (β2-adrenergic agonist)	Forced swim test	Reduced enhancing effect on immobility time* at	Hilakivi et al. 1988b <sup>48</sup>
		two months of age, increased enhancing effect at five months of age	
Serotonin system			
8-OH-DPAT (5-HT1A agonist)	Forced swim test	No different response in males or females*	Favaro et al. 2008 <sup>70</sup>
(0	Open field test	No different response in males or females*	Favaro et al. 2008 <sup>70</sup>
	Phase shift	Smaller phase advance*	Kiryanova et al. 2013 <sup>99</sup>
	Phase shift	Smaller phase advance*	Kiryanova et al. 2017a <sup>13</sup>
Fluoxetine (SSRI)	Food intake	Smaller reduction (none) in food intake*	Pinheiro et al. 2017 <sup>141</sup>
indoxedire (SSNI)	Prepulse inhibition	No different response in males or females*	Vorhees et al. 1994 <sup>50</sup>

Table 5: behavioral outcomes after shall

\*... in adult animals developmentally exposed to SSRIs versus vehicle

#### 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, 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<sup>37</sup> – 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<sup>37</sup> – 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<sup>14</sup> and postnatal maternal care<sup>145</sup>. The serotonin system consists of 15 different receptors that are key players at crucial neurodevelopmental stages, regulating neurogenesis, apoptosis, axon branching and dendritogenesis<sup>11</sup>. 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<sup>74,81,96,100,123,124,126,130,135</sup>, brain structure and connectivity<sup>71,77,84,93,101,110,122</sup>, health<sup>59,82,85,89,104,109,111,126,135</sup>. monoamine concentrations neuronal in the brain<sup>43,44,46,59,105,116,117,133,135,140,141</sup>, protein expression in the brain – mainly related to the serotonergic system and neurogenesis<sup>62,71,78,88,91,97,127,129,141</sup>, gene expression<sup>76,94,96,112,113,120,121,123,137,141,143</sup>, and epigenetic modifications<sup>76,112,114,124</sup>

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<sup>15</sup>. 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<sup>146,147</sup> and affect the development of the somatosensory cortex<sup>77,148</sup>. 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<sup>32</sup>. 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<sup>149</sup>. Early SSRI-exposure may affect males and females differently because of the sex-specific maturation of the serotonin system<sup>14</sup>. 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<sup>150</sup>.

#### 4.3. Clinical implications

The neurodevelopmental pattern of the serotonin system is remarkably conserved across species<sup>29,32,33</sup>. 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<sup>151</sup> 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<sup>152</sup>. 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<sup>153</sup>. Similarly, disruptions in sensory processing like those associated with early SSRI exposure in animals are present in a spectrum of neuropsychiatric disorders for those prenatally exposed to SSRIs, as indicated in some studies<sup>25</sup>, might be mediated by differences in stress coping, sensory processing and perhaps anxiety<sup>25,155</sup>.

A major challenge in human studies is to properly control for the confounding factor of maternal psychiatric condition<sup>33</sup>. 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<sup>156</sup>. 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 at least partially independently from maternal psychiatric condition. As maternal psychiatric disorder might interact with SSRI use to influence offspring outcomes<sup>14,32</sup>, 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<sup>14</sup>. 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.

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<sup>29</sup>. In terms of brain development, this period is approximately equivalent to the third trimester of human gestation<sup>37</sup>. 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<sup>20</sup>, whereas a meta-analysis found that exposure to SSRIs during the *first* trimester was most consistently associated with later diagnosis of mental disorders<sup>25</sup>. Perhaps for good reasons, many women discontinue SSRI use over the course of pregnancy, with the least users in the third trimester<sup>5</sup>, 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.

# 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<sup>157,158</sup>. 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<sup>32</sup>. In addition, dosing and route of administration varied widely<sup>33</sup>.

Additional limitations of this study originate from the choices that we had to make during data analysis. 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<sup>1–4</sup> and the uncertainties about their long-term effects on the developing neurobiology of the child<sup>159</sup>, 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., <u>www.preclinicaltrials.eu</u>) should become common practice<sup>160</sup>. In addition, reporting of animal studies should be improved by adherence to guidelines such as the ARRIVE guidelines<sup>161,162</sup>. 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<sup>163</sup>. 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<sup>164</sup>.

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<sup>159</sup>, especially considering that phenotypic differences may emerge only after adolescence<sup>30</sup>. 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. 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.

#### **Declarations of interest**

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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.

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# References

- 1. Bakker, M. K., Kölling, P., van den Berg, P. B., de Walle, H. E. K. & de Jong van den Berg, L. T. W. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br. J. Clin. Pharmacol.* **65**, 600–606 (2008).
- 2. Jimenez-Solem, E. *et al.* Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. *PLoS One* **8**, e63034 (2013).
- 3. Cooper, W. O., Willy, M. E., Pont, S. J. & Ray, W. A. Increasing use of antidepressants in pregnancy. *Am. J. Obstet. Gynecol.* **196**, 544.e1-544.e5 (2007).
- 4. Andrade, S. E. *et al.* Use of antidepressant medications during pregnancy: a multisite study. *Am. J. Obstet. Gynecol.* **198**, 194.e1–5 (2008).
- 5. Zoega, H. *et al.* Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden. *PLoS One* **10**, e0144474 (2015).
- 6. Jordan, S. *et al.* Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark. *PLoS One* **11**, e0165122 (2016).
- 7. Hayes, R. M. *et al.* Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. *Am. J. Obstet. Gynecol.* **207**, 49.e1-49.e9 (2012).
- 8. Huybrechts, K. F. *et al.* Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn. *JAMA* **313**, 2142 (2015).
- 9. Alwan, S., Friedman, J. M. & Chambers, C. Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy: A Review of Current Evidence. *CNS Drugs* **30**, 499–515 (2016).
- 10. Rampono, J. *et al.* Placental Transfer of SSRI and SNRI Antidepressants and Effects on the Neonate. *Pharmacopsychiatry* **42**, 95–100 (2009).
- 11. Gaspar, P., Cases, O. & Maroteaux, L. The developmental role of serotonin: news from mouse molecular genetics. *Nat. Rev. Neurosci.* **4**, 1002–1012 (2003).
- 12. Muller, C. P. & Jacobs, B. *Handbook of the behavioral neurobiology of serotonin. 2009* **21**, (Academic Press).
- 13. Teissier, A., Soiza-Reilly, M. & Gaspar, P. Refining the Role of 5-HT in Postnatal Development of Brain Circuits. *Front. Cell. Neurosci.* **11**, 139 (2017).

- 14. Brummelte, S., Mc Glanaghy, E., Bonnin, A. & Oberlander, T. F. Developmental changes in serotonin signaling: Implications for early brain function, behavior and adaptation. *Neuroscience* **342**, 212–231 (2017).
- 15. Homberg, J. R., Schubert, D. & Gaspar, P. New perspectives on the neurodevelopmental effects of SSRIs. *Trends Pharmacol. Sci.* **31**, 60–65 (2010).
- 16. Hanley, G. E., Brain, U. & Oberlander, T. F. Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior. *Pediatr. Res.* **78**, 174–180 (2015).
- Hanley, G. E., Brain, U. & Oberlander, T. F. Infant developmental outcomes following prenatal exposure to antidepressants, and maternal depressed mood and positive affect. *Early Hum. Dev.* 89, 519–524 (2013).
- 18. Viktorin, A. *et al.* Association of Antidepressant Medication Use During Pregnancy With Intellectual Disability in Offspring. *JAMA Psychiatry* **74**, 1031 (2017).
- 19. Hutchison, S. M., Mâsse, L. C., Brain, U. & Oberlander, T. F. A 6-year longitudinal study: Are maternal depressive symptoms and Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant treatment during pregnancy associated with everyday measures of executive function in young children? *Early Hum. Dev.* **128**, 21–26 (2019).
- 20. Lupattelli, A. *et al.* Effect of Time-Dependent Selective Serotonin Reuptake Inhibitor Antidepressants During Pregnancy on Behavioral, Emotional, and Social Development in Preschool-Aged Children. *J. Am. Acad. Child Adolesc. Psychiatry* **57**, 200–208 (2018).
- 21. Oberlander, T. F., Gingrich, J. A. & Ansorge, M. S. Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. *Clin. Pharmacol. Ther.* **86**, 672–677 (2009).
- 22. Johnson, K. C., Smith, A. K., Stowe, Z. N., Newport, D. J. & Brennan, P. A. Preschool outcomes following prenatal serotonin reuptake inhibitor exposure: differences in language and behavior, but not cognitive function. *J. Clin. Psychiatry* **77**, e176-82 (2016).
- 23. Brown, A. S. *et al.* Association of Selective Serotonin Reuptake Inhibitor Exposure During Pregnancy With Speech, Scholastic, and Motor Disorders in Offspring. *JAMA Psychiatry* **73**, 1163 (2016).
- 24. Smearman, E. L. *et al.* School-age social behavior and pragmatic language ability in children with prenatal serotonin reuptake inhibitor exposure. *Dev. Psychopathol.* 1–10 (2019). doi:10.1017/S0954579418001372
- 25. Halvorsen, A., Hesel, B., Østergaard, S. D. & Danielsen, A. A. In utero exposure to selective serotonin reuptake inhibitors and development of mental disorders: a systematic review and meta-analysis. *Acta Psychiatr. Scand.* **139**, 493–507 (2019).
- 26. Gentile, S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience* **342**, 154–166 (2017).

- 27. Semple, B. D., Blomgren, K., Gimlin, K., Ferriero, D. M. & Noble-Haeusslein, L. J. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Prog. Neurobiol.* **106–107**, 1–16 (2013).
- 28. Zucker, I. Risk mitigation for children exposed to drugs during gestation: A critical role for animal preclinical behavioral testing. *Neurosci. Biobehav. Rev.* **77**, 107–121 (2017).
- 29. Gingrich, J. A. *et al.* New Insights into How Serotonin Selective Reuptake Inhibitors Shape the Developing Brain. *Birth Defects Res.* **109**, 924–932 (2017).
- 30. Glover, M. E. & Clinton, S. M. Of rodents and humans: A comparative review of the neurobehavioral effects of early life SSRI exposure in preclinical and clinical research. *Int. J. Dev. Neurosci.* **51**, 50–72 (2016).
- 31. Grieb, Z. A. & Ragan, C. M. The effects of perinatal SSRI exposure on anxious behavior and neurobiology in rodent and human offspring. *Eur. Neuropsychopharmacol.* 1–16 (2019). doi:10.1016/j.euroneuro.2019.07.239
- 32. Bourke, C. H., Stowe, Z. N. & Owens, M. J. Prenatal Antidepressant Exposure: Clinical and Preclinical Findings. *Pharmacol. Rev.* **66**, 435–465 (2014).
- 33. Millard, S. J., Weston-Green, K. & Newell, K. A. The effects of maternal antidepressant use on offspring behaviour and brain development: Implications for risk of neurodevelopmental disorders. *Neurosci. Biobehav. Rev.* **80**, 743–765 (2017).
- 34. Ornoy, A. Neurobehavioral risks of SSRIs in pregnancy: Comparing human and animal data. *Reprod. Toxicol.* **72**, 191–200 (2017).
- 35. Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **6**, e1000097 (2009).
- Hooijmans, C. R., Tillema, A., Leenaars, M. & Ritskes-Hoitinga, M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. *Lab. Anim.* 44, 170–175 (2010).
- 37. Workman, A. D., Charvet, C. J., Clancy, B., Darlington, R. B. & Finlay, B. L. Modeling Transformations of Neurodevelopmental Sequences across Mammalian Species. *J. Neurosci.* **33**, 7368–7383 (2013).
- 38. Schneider, C. A., Rasband, W. S. & Eliceiri, K. W. NIH Image to ImageJ: 25 years of image analysis. *Nat. Methods* **9**, 671–5 (2012).
- Hooijmans, C. R. *et al.* SYRCLE's risk of bias tool for animal studies. *BMC Med. Res. Methodol.* 14, 43 (2014).
- 40. Viechtbauer, W. Conducting Meta-Analyses in R with the metafor Package. *J. Stat. Softw.* **36**, 1–48 (2010).
- 41. Zwetsloot, P.-P. et al. Standardized mean differences cause funnel plot distortion in publication

bias assessments. *Elife* **6**, 1–20 (2017).

- 42. Duval, S. & Tweedie, R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455–63 (2000).
- 43. Grimm, V. E. & Frieder, B. Prenatal and early postnatal exposure to zimelidine: behavioral, neurochemical and histological findings in rats. *Int. J. Neurosci.* **33**, 225–235 (1987).
- 44. Hilakivi, L. A., Stenberg, D., Sinclair, J. D. & Kiianmaa, K. Neonatal desipramine or zimeldine treatment causes long-lasting changes in brain monoaminergic systems and alcohol related behavior in rats. *Psychopharmacology (Berl)*. **91**, 403–409 (1987).
- 45. Hilakivi, L. A. & Hilakivi, I. Increased adult behavioral 'despair' in rats neonatally exposed to desipramine or zimeldine: An animal model of depression? *Pharmacol. Biochem. Behav.* **28**, 367–369 (1987).
- 46. Hilakivi, L. A., Hilakivi, I. & Kiianmaa, K. Neonatal antidepressant administration suppresses concurrent active (REM) sleep and increases adult alcohol consumption in rats. *Alcohol Alcohol Suppl.* **1**, 339–43 (1987).
- Hilakivi, L. A., Taira, T. & Hilakivi, I. Early postnatal deprivation of active sleep with desipramine or zimeldine impairs later behavioural reactivity to auditory stimuli in rats. *Acta Physiol. Scand.* 132, 191–8 (1988).
- 48. Hilakivi, L. A., Taira, T., Hilakivi, I. & Loikas, P. Neonatal treatment with monoamine uptake inhibitors alters later response in behavioural 'despair' test to beta and GABA-B receptor agonists. *Pharmacol. Toxicol.* **63**, 57–61 (1988).
- 49. Hilakivi, I. Early postnatal antidepressant treatment and juvenile stereotyped behaviour in rats. *Eur. J. Pharmacol.* **271**, 223–226 (1994).
- 50. Vorhees, C. V *et al.* A developmental neurotoxicity evaluation of the effects of prenatal exposure to fluoxetine in rats. *Fundam. Appl. Toxicol.* **23**, 194–205 (1994).
- 51. Frank, M. G. & Heller, H. C. Neonatal treatments with the serotonin uptake inhibitors clomipramine and zimelidine, but not the noradrenaline uptake inhibitor desipramine, disrupt sleep patterns in adult rats. *Brain Res.* **768**, 287–293 (1997).
- 52. Hansen, H. H., Sanchez, C. & Meier, E. Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: a putative animal model of depression? *J. Pharmacol. Exp. Ther.* **283**, 1333–1341 (1997).
- 53. Singh, Y., Jaiswal, A. K., Singh, M. & Bhattacharya, S. K. Effect of prenatal diazepam, phenobarbital, haloperidol and fluoxetine exposure on foot shock induced aggression in rats. *Indian J. Exp. Biol.* **36**, 1023–1024 (1998).
- 54. Stewart, C. W. *et al.* Gestational exposure to cocaine or pharmacologically related compounds: effects on behavior and striatal dopamine receptors. *Life Sci.* **63**, 2015–2022 (1998).

- 55. Coleman, F. H., Christensen, H. D., Gonzalez, C. L. & Rayburn, W. F. Behavioral changes in developing mice after prenatal exposure to paroxetine (Paxil). *Am. J. Obstet. Gynecol.* **181**, 1166–1171 (1999).
- 56. Christensen, H. D., Rayburn, W. F. & Gonzalez, C. L. Chronic prenatal exposure to paroxetine (Paxil) and cognitive development of mice offspring. *Neurotoxicol. Teratol.* **22**, 733–739 (2000).
- 57. Mendes-da-Silva, C. *et al.* Neonatal treatment with fluoxetine reduces depressive behavior induced by forced swim in adult rats. *Arg. Neuropsiquiatr.* **60**, 928–31 (2002).
- 58. Ansorge, M. S., Zhou, M., Lira, A., Hen, R. & Gingrich, J. A. Early-Life Blockade of the 5-HT Transporter Alters Emotional Behavior in Adult Mice. *Science (80-. ).* **306**, 879–881 (2004).
- 59. Ishiwata, H., Shiga, T. & Okado, N. Selective serotonin reuptake inhibitor treatment of early postnatal mice reverses their prenatal stress-induced brain dysfunction. *Neuroscience* **133**, 893–901 (2005).
- 60. Vartazarmian, R., Malik, S., Baker, G. B. & Boksa, P. Long-term effects of fluoxetine or vehicle administration during pregnancy on behavioral outcomes in guinea pig offspring. *Psychopharmacology (Berl).* **178**, 328–338 (2005).
- 61. Deiro, T. C. B. J. *et al.* Sertraline delays the somatic growth and reflex ontogeny in neonate rats. *Physiol. Behav.* **87**, 338–344 (2006).
- 62. Maciag, D. *et al.* Neonatal Antidepressant Exposure has Lasting Effects on Behavior and Serotonin Circuitry. *Neuropsychopharmacology* **31**, 47–57 (2006).
- 63. Maciag, D., Williams, L., Coppinger, D. & Paul, I. A. Neonatal citalopram exposure produces lasting changes in behavior which are reversed by adult imipramine treatment. *Eur. J. Pharmacol.* **532**, 265–269 (2006).
- 64. Maciag, D., Coppinger, D. & Paul, I. A. Evidence that the deficit in sexual behavior in adult rats neonatally exposed to citalopram is a consequence of 5-HT1 receptor stimulation during development. *BRAIN Res.* **1125**, 171–175 (2006).
- 65. Bairy, K. L., Madhyastha, S., Ashok, K. P., Bairy, I. & Malini, S. Developmental and behavioral consequences of prenatal fluoxetine. *Pharmacology* **79**, 1–11 (2007).
- Lisboa, S. F. S., Oliveira, P. E., Costa, L. C., Venancio, E. J. & Moreira, E. G. Behavioral evaluation of male and female mice pups exposed to fluoxetine during pregnancy and lactation. *Pharmacology* 80, 49–56 (2007).
- 67. Ansorge, M. S., Morelli, E. & Gingrich, J. A. Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. *J. Neurosci.* **28**, 199–207 (2008).
- 68. Cagiano, R. Neurofunctional effects in rats prenatally exposed to fluoxetine. *Eur. Rev. Med. Pharmacol. Sci.* **12**, 137–148 (2008).

- 69. Deiró, T. C. B. D. J. *et al.* Neonatal exposure to citalopram, a serotonin selective reuptake inhibitor, programs a delay in the reflex ontogeny in rats. *Arg. Neuropsiquiatr.* **66**, 736–40 (2008).
- 70. Favaro, P. das N., Costa, L. C. & Moreira, E. G. Maternal fluoxetine treatment decreases behavioral response to dopaminergic drugs in female pups. *Neurotoxicol. Teratol.* **30**, 487–494 (2008).
- 71. Forcelli, P. A. & Heinrichs, S. C. Teratogenic effects of maternal antidepressant exposure on neural substrates of drug-seeking behavior in offspring. *Addict. Biol.* **13**, 52–62 (2008).
- 72. Gouvêa, T. S., Morimoto, H. K., de Faria, M. J. S. S., Moreira, E. G. & Gerardin, D. C. C. Maternal exposure to the antidepressant fluoxetine impairs sexual motivation in adult male mice. *Pharmacol. Biochem. Behav.* **90**, 416–9 (2008).
- 73. Noorlander, C. W. *et al.* Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. *PLoS One* **3**, e2782 (2008).
- 74. Popa, D., Léna, C., Alexandre, C. & Adrien, J. Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. *J. Neurosci.* **28**, 3546–54 (2008).
- 75. Jiang, X.-Z. *et al.* [Neonatal fluoxetine exposure induced depression-like behaviors in adult Kunming mice and the antidepressant-like effect of agmatine]. *Yao Xue Xue Bao* **44**, 716–21 (2009).
- 76. Karpova, N. N., Lindholm, J., Pruunsild, P., Timmusk, T. & Castren, E. Long-lasting behavioural and molecular alterations induced by early postnatal fluoxetine exposure are restored by chronic fluoxetine treatment in adult mice. *Eur. Neuropsychopharmacol.* **19**, 97–108 (2009).
- 77. Lee, L.-J. Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats. *Neurotox. Res.* **15**, 212–23 (2009).
- 78. Capello, C. F. *et al.* Serotonin transporter occupancy in rats exposed to serotonin reuptake inhibitors in utero or via breast milk. *J. Pharmacol. Exp. Ther.* **339**, 275–85 (2011).
- 79. Mnie-Filali, O. *et al.* Pharmacological blockade of 5-HT7 receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology* **36**, 1275–1288 (2011).
- 80. Olivier, J. D. A. A. *et al.* Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring. *Psychopharmacology (Berl).* **217**, 419–432 (2011).
- 81. Pivina, S. G., Fedotova, Y. O., Akulova, V. K. & Ordyan, N. E. Effects of selective inhibitors of serotonin reuptake on the anxiety behavior and activity of the pituitary-adrenal system in prenatally stressed male rats. *Neurochem. J.* **5**, 47–51 (2011).
- 82. Rayen, I., van den Hove, D. L., Prickaerts, J., Steinbusch, H. W. & Pawluski, J. L. Fluoxetine during Development Reverses the Effects of Prenatal Stress on Depressive-Like Behavior and Hippocampal Neurogenesis in Adolescence. *PLoS One* **6**, e24003 (2011).

- 83. Rodriguez-Porcel, F. *et al.* Neonatal exposure of rats to antidepressants affects behavioral reactions to novelty and social interactions in a manner analogous to autistic spectrum disorders. *Anat. Rec. (Hoboken).* **294**, 1726–35 (2011).
- 84. Simpson, K. L. *et al.* Perinatal antidepressant exposure alters cortical network function in rodents. *Proc. Natl. Acad. Sci.* **108**, 18465–18470 (2011).
- 85. Zheng, J. *et al.* Neonatal exposure to fluoxetine and fluvoxamine alteres spine density in mouse hippocampal CA1 pyramidal neurons. *Int. J. Clin. Exp. Pathol.* **4**, 162–8 (2011).
- 86. Harris, S. S., Maciag, D., Simpson, K. L., Lin, R. C. S. S. & Paul, I. A. Dose-dependent effects of neonatal SSRI exposure on adult behavior in the rat. *Brain Res.* **1429**, 52–60 (2012).
- 87. Swilley-Harris, S. Dose-dependent Effects of Neonatal SSRI Exposure on Behavior and Brain Serotonin Turnover In the Adult Rat. (The University of Mississippi Medical Center, 2010).
- 88. Kummet, G. J. *et al.* Neonatal SSRI Exposure Programs a Hypermetabolic State in Adult Mice. *J. Nutr. Metab.* **2012**, 1–8 (2012).
- 89. Lee, L.-J. & Lee, L. J.-H. Neonatal fluoxetine exposure alters motor performances of adolescent rats. *Dev. Neurobiol.* **72**, 1122–32 (2012).
- 90. McAllister, B. B., Kiryanova, V. & Dyck, R. H. Behavioural outcomes of perinatal maternal fluoxetine treatment. *Neuroscience* **226**, 356–66 (2012).
- 91. Nagano, M., Liu, M., Inagaki, H., Kawada, T. & Suzuki, H. Early intervention with fluoxetine reverses abnormalities in the serotonergic system and behavior of rats exposed prenatally to dexamethasone. *Neuropharmacology* **63**, 292–300 (2012).
- 92. Rebello, T. J. Serotonin Modulates the Maturation of the Medial Prefrontal Cortex and Hippocampus: Relevance to the Etiology of Emotional and Cognitive Behaviors. (Columbia University, 2012).
- 93. Smit-Rigter, L. A. *et al.* Prenatal fluoxetine exposure induces life-long serotonin 5-HT<sub>3</sub> receptordependent cortical abnormalities and anxiety-like behaviour. *Neuropharmacology* **62**, 865–70 (2012).
- 94. Soga, T., Wong, D. W., Putteeraj, M., Song, K. P. & Parhar, I. S. Early-life citalopram-induced impairments in sexual behavior and the role of androgen receptor. *Neuroscience* **225**, 172–184 (2012).
- 95. Yu, Q. Developmental monoamine signaling impacts adult affective and aggressive behaviors. (Columbia University, 2012).
- 96. Bourke, C. H., Stowe, Z. N., Neigh, G. N., Olson, D. E. & Owens, M. J. Prenatal exposure to escitalopram and/or stress in rats produces limited effects on endocrine, behavioral, or gene expression measures in adult male rats. *Neurotoxicol. Teratol.* **39**, 100–109 (2013).
- 97. Francis-Oliveira, J. et al. Fluoxetine exposure during pregnancy and lactation: Effects on acute

stress response and behavior in the novelty-suppressed feeding are age and gender-dependent in rats. *Behav. Brain Res.* **252**, 195–203 (2013).

- 98. Freund, N., Thompson, B. S., DeNormandie, J., Vaccarro, K. & Andersen, S. L. Windows of vulnerability: Maternal separation, age, and fluoxetine on adolescent depressive-like behavior in rats. *Neuroscience* **249**, 88–97 (2013).
- 99. Kiryanova, V., Smith, V. M., Dyck, R. H. & Antle, M. C. The effects of perinatal fluoxetine treatment on the circadian system of the adult mouse. *Psychopharmacology (Berl).* **225**, 743–51 (2013).
- Knaepen, L. *et al.* Developmental Fluoxetine Exposure Normalizes the Long-Term Effects of Maternal Stress on Post-Operative Pain in Sprague-Dawley Rat Offspring. *PLoS One* 8, e57608 (2013).
- 101. Rayen, I., Steinbusch, H. W. M., Charlier, T. D. & Pawluski, J. L. Developmental fluoxetine exposure and prenatal stress alter sexual differentiation of the brain and reproductive behavior in male rat offspring. *Psychoneuroendocrinology* **38**, 1618–29 (2013).
- 102. Schaefer, T. L. *et al.* Cognitive impairments from developmental exposure to serotonergic drugs: citalopram and MDMA. *Int. J. Neuropsychopharmacol.* **16**, 1383–94 (2013).
- 103. Vieira, M. L. *et al.* Could maternal exposure to the antidepressants fluoxetine and St. John's Wort induce long-term reproductive effects on male rats? *Reprod. Toxicol.* **35**, 102–7 (2013).
- 104. da Silva, A. I. *et al.* Fluoxetine treatment of rat neonates significantly reduces oxidative stress in the hippocampus and in behavioral indicators of anxiety later in postnatal life. *Can. J. Physiol. Pharmacol.* **92**, 330–7 (2014).
- 105. Glazova, N. Y. *et al.* Effects of neonatal fluvoxamine administration on the physical development and activity of the serotoninergic system in white rats. *Acta Naturae* **6**, 98–105 (2014).
- 106. Khatri, N., Simpson, K. L., Lin, R. C. S. & Paul, I. A. Lasting neurobehavioral abnormalities in rats after neonatal activation of serotonin 1A and 1B receptors: possible mechanisms for serotonin dysfunction in autistic spectrum disorders. *Psychopharmacology (Berl).* **231**, 1191–200 (2014).
- 107. Khatri, N. Role of Early Life Stimulation of Serotonin 1A and 1B (5-HT1A and 5-HT1B) Receptors in the Lasting Neurobehavioral Effects of neonatal SSRI Exposure. (The University of Mississippi Medical Center, 2013).
- 108. Kiryanova, V. & Dyck, R. H. Increased Aggression, Improved Spatial Memory, and Reduced Anxiety-Like Behaviour in Adult Male Mice Exposed to Fluoxetine Early in Life. *Dev. Neurosci.* **36**, 396–408 (2014).
- 109. Ko, M.-C., Lee, L. J.-H., Li, Y. & Lee, L.-J. Long-term consequences of neonatal fluoxetine exposure in adult rats. *Dev. Neurobiol.* **74**, 1038–1051 (2014).
- 110. Rayen, I., Steinbusch, H. W. M., Charlier, T. D. & Pawluski, J. L. Developmental fluoxetine exposure facilitates sexual behavior in female offspring. *Psychopharmacology (Berl).* **231**, 123–133 (2014).

- 111. Rebello, T. J. *et al.* Postnatal Day 2 to 11 Constitutes a 5-HT-Sensitive Period Impacting Adult mPFC Function. *J. Neurosci.* **34**, 12379–12393 (2014).
- 112. Sarkar, A. *et al.* Hippocampal HDAC4 Contributes to Postnatal Fluoxetine-Evoked Depression-Like Behavior. *Neuropsychopharmacology* **39**, 2221–2232 (2014).
- 113. Sarkar, A., Chachra, P. & Vaidya, V. A. Postnatal fluoxetine-evoked anxiety is prevented by concomitant 5-HT2A/C receptor blockade and mimicked by postnatal 5-HT2A/C receptor stimulation. *Biol. Psychiatry* **76**, 858–68 (2014).
- 114. Toffoli, L. V *et al.* Maternal exposure to fluoxetine during gestation and lactation affects the DNA methylation programming of rat's offspring: modulation by folic acid supplementation. *Behav. Brain Res.* **265**, 142–147 (2014).
- 115. Volodina, M. A. *et al.* [Effects of neonatal fluvoxamine administration to white rats and their correction by semax treatment]. *Izv. Akad. Nauk. Seriia Biol.* 391–7 (2014).
- 116. Yu, Q. *et al.* Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. *Mol. Psychiatry* **19**, 688–698 (2014).
- 117. Altieri, S. C. *et al.* Perinatal vs genetic programming of serotonin states associated with anxiety. *Neuropsychopharmacology* **40**, 1456–70 (2015).
- 118. Avitsur, R. *et al.* Prenatal fluoxetine exposure affects cytokine and behavioral response to an immune challenge. *J. Neuroimmunol.* **284**, 49–56 (2015).
- 119. da Silva, A. I. *et al.* Fluoxetine induces lean phenotype in rat by increasing the brown/white adipose tissue ratio and UCP1 expression. *J. Bioenerg. Biomembr.* **47**, 309–318 (2015).
- 120. Ehrlich, D. E. *et al.* Prenatal stress, regardless of concurrent escitalopram treatment, alters behavior and amygdala gene expression of adolescent female rats. *Neuropharmacology* **97**, 251–258 (2015).
- 121. Galindo, L. C. M. *et al.* Neonatal serotonin reuptake inhibition reduces hypercaloric diet effects on fat mass and hypothalamic gene expression in adult rats. *Int. J. Dev. Neurosci.* **46**, 76–81 (2015).
- 122. Zhou, X. *et al.* Behavioral training reverses global cortical network dysfunction induced by perinatal antidepressant exposure. *Proc. Natl. Acad. Sci.* **112**, 2233–2238 (2015).
- 123. Boulle, F. *et al.* Prenatal stress and early-life exposure to fluoxetine have enduring effects on anxiety and hippocampal BDNF gene expression in adult male offspring. *Dev. Psychobiol.* **58**, 427–438 (2016).
- 124. Boulle, F. *et al.* Developmental fluoxetine exposure increases behavioral despair and alters epigenetic regulation of the hippocampal BDNF gene in adult female offspring. *Horm. Behav.* **80**, 47–57 (2016).
- 125. Dos Santos, A. H. et al. In utero and lactational exposure to fluoxetine delays puberty onset in

female rats offspring. Reprod. Toxicol. 62, 1-8 (2016).

- 126. Gobinath, A. R., Workman, J. L., Chow, C., Lieblich, S. E. & Galea, L. A. M. M. Maternal postpartum corticosterone and fluoxetine differentially affect adult male and female offspring on anxiety-like behavior, stress reactivity, and hippocampal neurogenesis. *Neuropharmacology* **101**, 165–178 (2016).
- 127. Kiryanova, V., Meunier, S. J., Vecchiarelli, H. A., Hill, M. N. & Dyck, R. H. Effects of maternal stress and perinatal fluoxetine exposure on behavioral outcomes of adult male offspring. *Neuroscience* **320**, 281–96 (2016).
- 128. Kroeze, Y. *et al.* Perinatal reduction of functional serotonin transporters results in developmental delay. *Neuropharmacology* **109**, 96–111 (2016).
- 129. Matsumoto, A. K. *et al.* Co-exposure to fish oil or folic acid does not reverse effects in the progeny induced by maternal exposure to fluoxetine. *Neurotoxicol. Teratol.* **56**, 1–8 (2016).
- 130. Salari, A.-A., Fatehi-Gharehlar, L., Motayagheni, N. & Homberg, J. R. Fluoxetine normalizes the effects of prenatal maternal stress on depression- and anxiety-like behaviors in mouse dams and male offspring. *Behav. Brain Res.* **311**, 354–367 (2016).
- 131. Sprowles, J. L. N. *et al.* Perinatal exposure to the selective serotonin reuptake inhibitor citalopram alters spatial learning and memory, anxiety, depression, and startle in Sprague-Dawley rats. *Int. J. Dev. Neurosci.* **54**, 39–52 (2016).
- Svirsky, N., Levy, S. & Avitsur, R. Prenatal exposure to selective serotonin reuptake inhibitors (SSRI) increases aggression and modulates maternal behavior in offspring mice. *Dev. Psychobiol.* 58, 71–82 (2016).
- 133. Zohar, I., Shoham, S. & Weinstock, M. Perinatal citalopram does not prevent the effect of prenatal stress on anxiety, depressive-like behaviour and serotonergic transmission in adult rat offspring. *Eur. J. Neurosci.* **43**, 590–600 (2016).
- 134. Avitsur, R. Increased symptoms of illness following prenatal stress: Can it be prevented by fluoxetine? *Behav. Brain Res.* **317**, 62–70 (2017).
- 135. Gemmel, M. *et al.* Perinatal fluoxetine effects on social play, the HPA system, and hippocampal plasticity in pre-adolescent male and female rats: Interactions with pre-gestational maternal stress. *Psychoneuroendocrinology* **84**, 159–171 (2017).
- 136. Haskell, S. E. *et al.* Cardiac Outcomes After Perinatal Sertraline Exposure in Mice. *J. Cardiovasc. Pharmacol.* **70**, 119–127 (2017).
- 137. Ishikawa, C. & Shiga, T. The postnatal 5-HT1A receptor regulates adult anxiety and depression differently via multiple molecules. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* **78**, 66–74 (2017).
- 138. Kiryanova, V., Smith, V. M., Dyck, R. H. & Antle, M. C. Circadian behavior of adult mice exposed to stress and fluoxetine during development. *Psychopharmacology (Berl).* **234**, 793–804 (2017).

- 139. Kiryanova, V., Meunier, S. J. & Dyck, R. H. Behavioural outcomes of adult female offspring following maternal stress and perinatal fluoxetine exposure. *Behav. Brain Res.* **331**, 84–91 (2017).
- 140. Nagano, R., Nagano, M., Nakai, A., Takeshita, T. & Suzuki, H. Differential effects of neonatal SSRI treatments on hypoxia-induced behavioral changes in male and female offspring. *Neuroscience* **360**, 95–105 (2017).
- 141. Pinheiro, I. L. *et al.* Neonatal fluoxetine exposure modulates serotonergic neurotransmission and disturb inhibitory action of serotonin on food intake. *Behav. Brain Res.* **357–358**, 65–70 (2019).
- 142. Sprowles, J. L. N. *et al.* Differential effects of perinatal exposure to antidepressants on learning and memory, acoustic startle, anxiety, and open-field activity in Sprague-Dawley rats. *Int. J. Dev. Neurosci.* **61**, 92–111 (2017).
- 143. Meyer, L. R. *et al.* Perinatal SSRI exposure permanently alters cerebral serotonin receptor mRNA in mice but does not impact adult behaviors. *J. Matern. Neonatal Med.* **31**, 1393–1401 (2018).
- 144. Sterne, J. A. C. *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* **343**, d4002–d4002 (2011).
- 145. Pawluski, J. L., Li, M. & Lonstein, J. S. Serotonin and motherhood: From molecules to mood. *Front. Neuroendocrinol.* **53**, 100742 (2019).
- 146. Bonnin, A., Torii, M., Wang, L., Rakic, P. & Levitt, P. Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. *Nat. Neurosci.* **10**, 588–597 (2007).
- 147. Bonnin, A. *et al.* A transient placental source of serotonin for the fetal forebrain. *Nature* **472**, 347–350 (2011).
- 148. Xu, Y., Sari, Y. & Zhou, F. C. Selective serotonin reuptake inhibitor disrupts organization of thalamocortical somatosensory barrels during development. *Dev. Brain Res.* **150**, 151–161 (2004).
- 149. Hodes, G. E. & Epperson, C. N. Sex Differences in Vulnerability and Resilience to Stress Across the Life Span. *Biol. Psychiatry* **86**, 421–432 (2019).
- 150. Connell, S., Karikari, C. & Hohmann, C. F. Sex-specific development of cortical monoamine levels in mouse. *Dev. Brain Res.* **151**, 187–191 (2004).
- 151. Slattery, D. A. & Cryan, J. F. Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nat. Protoc.* **7**, 1009–1014 (2012).
- 152. Porsolt, R. D., Le Pichon, M. & Jalfre, M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* **266**, 730–2 (1977).
- Commons, K. G., Cholanians, A. B., Babb, J. A. & Ehlinger, D. G. The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior. ACS Chem. Neurosci. 8, 955–960 (2017).
- 154. Hornix, B. E., Havekes, R. & Kas, M. J. H. Multisensory cortical processing and dysfunction across the neuropsychiatric spectrum. *Neurosci. Biobehav. Rev.* **97**, 138–151 (2019).

- 155. Malm, H. *et al.* Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study. *J. Am. Acad. Child Adolesc. Psychiatry* **55**, 359–366 (2016).
- 156. Sorensen, M. J. *et al.* Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin. Epidemiol.* **5**, 449 (2013).
- 157. Avey, M. T. *et al.* The Devil Is in the Details: Incomplete Reporting in Preclinical Animal Research. *PLoS One* **11**, e0166733 (2016).
- 158. Kilkenny, C. *et al.* Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals. *PLoS One* **4**, (2009).
- 159. Rotem-Kohavi, N. & Oberlander, T. F. Variations in Neurodevelopmental Outcomes in Children with Prenatal SSRI Antidepressant Exposure. *Birth Defects Res.* **109**, 909–923 (2017).
- 160. Jansen of Lorkeers, S. J., Doevendans, P. A. & Chamuleau, S. A. J. All preclinical trials should be registered in advance in an online registry. *Eur. J. Clin. Invest.* **44**, 891–892 (2014).
- 161. Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M. & Altman, D. G. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PLoS Biol.* **8**, e1000412 (2010).
- 162. Muhlhausler, B. S., Bloomfield, F. H. & Gillman, M. W. Whole Animal Experiments Should Be More Like Human Randomized Controlled Trials. *PLoS Biol.* **11**, e1001481 (2013).
- 163. Clayton, J. A. & Collins, F. S. Policy: NIH to balance sex in cell and animal studies. *Nature* **509**, 282–283 (2014).
- 164. Glover, M. E. *et al.* Early-life exposure to the SSRI paroxetine exacerbates depression-like behavior in anxiety/depression-prone rats. *Neuroscience* **284**, 775–797 (2015).

# **Figure captions**

# Figure 1: Study flowchart.

Figure 2: 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.

Supplementary Figure 1: 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.

Supplementary Figure 2: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome activity and exploration. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 3: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome anxiety. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 4: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome stress coping. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 5: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome social behavior. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 6: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome learning and memory. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 7: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome ingestive- and reward behavior. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 8: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome motoric behavior. (A) Overall analysis. (B) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 9: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome sensory processing. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

Supplementary Figure 10: Forest plots of meta-analysis comparing animals perinatally exposed to SSRIs to those exposed to vehicle on the behavioral outcome reflex and pain sensitivity. (A) Overall analysis. (B) Subgroup analysis based on sex. (C) Subgroup analysis based on presence/absence of stress exposure. (D) Subgroup analysis based on SSRI exposure timing.

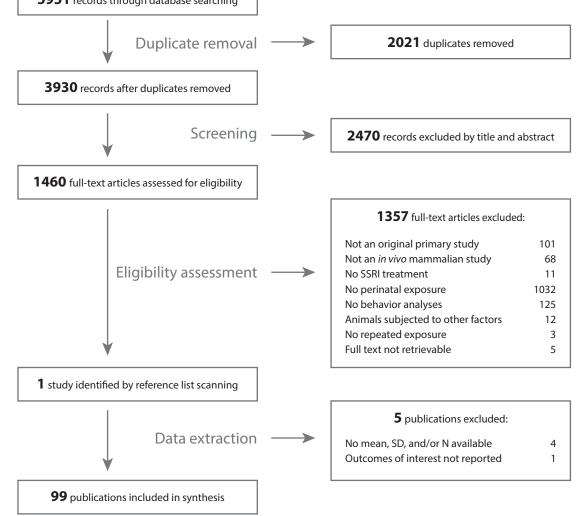
Supplementary Figure 11: Funnel plots of behavioral outcomes in animals perinatally exposed to SSRIs to those exposed to vehicle on the with imputed extra data points by trim and fill analysis. (A) Activity and exploration. (B) Anxiety. In the gray box the same data separate for each exposure period. (C) Stress coping. (D) Social behavior. (E) Learning and memory. In the gray box the same data separate for each exposure period. (F) Ingestive and reward. (G) Motoric behavior. (H) Sensory processing. (I) Reflex and pain sensitivity.

Supplementary File 1: Systematic search strategy for PubMed, PsycINFO and Web of Science.

Supplementary File 2: Behavioral domains and test prioritization.

# Identification

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A. Activity and exploration	Weight	B. Anxiety	Weight	
Subgroup	SMD (95% CI) (%) N <sub>SSRI</sub> N <sub>Veh</sub>	Subgroup	SMD (95% CI) (%)	
Overall 🔶	-0.28 (-0.38, -0.18) 100.0 2646 1627	Overall	0.10 (-0.00, 0.21) 100.0	) 1816 1522
Male	-0.28 (-0.41, -0.15) 53.9 1367 799	Male	0.17 (-0.01, 0.34) 50.4	857 699
Mixed-sex	g/10,1101,868265; this version pos	ed December 6, 2019. The copyright holder for the	his preprint (which wa	<b>S</b> 513 449
Female	-0.12 (-0.29, 014) der 3 CBY -NC -NC	oRxiv a ličense to display the preprint in perpetui 4.0771 demaission of the preprint in perpetui	.y. 1015 111aue availabit -0.04 (-0.18, 0.10) 29.3	446 374
No stress —	-0.30 (-0.40, -0.19) 88.4 2465 1457	No stress	0.14 (0.03, 0.25) 87.8	3 1634 1351
Stress	-0.12 (-0.36, 0.13) 11.6 181 170	Stress	-0.16 (-0.51, 0.18) 12.2	2 182 171
Prenatal —	-0.01 (-0.21, 0.19) 27.8 1185 435	Prenatal —	0.01 (-0.18, 0.21) 18.2	2 263 199
Pre- and postnatal	-0.40 (-0.59, -0.22) 18.0 370 349	Pre- and postnatal	-0.06 (-0.25, 0.14) 24.7	466 443
Postnatal 🔶	-0.39 (-0.51, -0.27) 54.2 1091 843	Postnatal	0.21 (0.05, 0.36) 57.1	1087 880
-0.5 0 0.5 SSRI less active SSRI more active	<b>→</b>	-0.4 -0.2 0 0.2 0.4 SSRI less anxiety SSRI more anxiety	<b>→</b>	

C. Stress coping			v	Veight		
Subgroup			SMD (95% CI)	(%)	$N_{_{SSRI}}$	$N_{Veh}$
Overall	-		-0.37 (-0.52, -0.23)	100.0	955	806
Male			-0.39 (-0.60, -0.18)	51.6	457	358
Mixed-sex —			-0.52 (-0.80, -0.23)	16.7	223	217
Female			-0.27 (-0.53, -0.01)	31.6	275	231
No stress			-0.41 (-0.58, -0.25)	79.7	809	667
Stress		_	-0.22 (-0.51, 0.08)	20.3	146	139
Prenatal			-0.09 (-0.53, 0.34)	8.5	63	66
Pre- and postnatal		<u> </u>	-0.23 (-0.62, 0.16)	17.2	204	194
Postnatal			-0.44 (-0.60, -0.28)	74.4	688	546
	-0.5 0	) 05				

S

SRI more passive coping	SSRI more active coping

E. Learning and Subgroup	memory	W SMD (95% CI)	/eight (%)	N	N <sub>veh</sub>
Subgroup	1	. ,	()		
Overall		-0.04 (-0.20, 0.11)	100.0	982	679
Male		0.02 (-0.22, 0.26)	40.6	376	235
Mixed-sex	<b>→</b>	-0.36 (-0.54, -0.17)	32.2	326	285
Female	<b>↓</b>	0.26 (-0.05, 0.57)	27.1	280	159
No stress		-0.05 (-0.22, 0.11)	90.2	927	618
Stress		0.03 (-0.40, 0.46)	9.8	55	61
Prenatal	<b>↓</b>	0.23 (-0.01, 0.48)	37.8	467	211
Pre- and postnatal		-0.09 (-0.28, 0.09)	41.9	364	331
Postnatal —	<b>→</b>	-0.52 (-0.81, -0.22)	20.2	151	137

SSRI worse memory SSRI better memory

### G. Motoric behavior

G. Motoric beha	vior	v	Veight		
Subgroup		SMD (95% CI)	(%)	$N_{_{\mathrm{SSRI}}}$	$N_{Veh}$
Overall	-	-0.12 (-0.36, 0.12)	100.0	483	370
Male		-0.31 (-0.80, 0.17)	41.8	115	89
Mixed-sex		-0.05 (-0.23, 0.12)	36.5	310	238
Female		0.13 (-0.49, 0.75)	21.7	58	43
Prenatal	<b>þ</b>	0.02 (-0.49, 0.53)	34.3	92	60
Pre- and postnatal	-	-0.06 (-0.22, 0.11)	50.7	345	279
Postnatal –		-0.61 (-1.62, 0.40)	15.0	46	31
	-1 0 1				
<b>←</b>	SSRI less skilled SSRI more skilled	<b>→</b>			

### I. Reflex and pain sensitivity

I. Reflex and pain	sensitivity				1	Neight		
Subgroup				SME	O (95% CI)	(%)	$N_{_{SSRI}}$	N <sub>Veh</sub>
Overall				-0.2	5 (-0.73, 0.23)	100.0	188	200
Male		+		-0.2	6 (-0.75, 0.23)	62.5	92	95
Mixed-sex				-0.6	5 (-1.91, 0.62)	23.1	70	85
Female		+		1.00	) (-1.51, 3.50)	14.4	26	20
No stress		┣—		-0.2	5 (-0.76, 0.27)	93.4	180	192
Stress		<u>ه                                    </u>		-0.1	6 (-1.14, 0.82)	6.6	8	8
Prenatal	-	+		0.37	7 (-0.53, 1.28)	44.9	93	94
Pre- and postnatal				-0.4	8 (-1.14, 0.19)	20.4	31	35
Postnatal				-0.6	7 (-1.30, -0.03)	34.6	64	71
	-2	0	2					

SSRI slower response SSRI faster response

D. Social behavi	or		W	/eight		
Subgroup			SMD (95% CI)	(%)	$N_{SSRI}$	$N_{Veh}$
Overall			-0.07 (-0.27, 0.13)	100.0	749	645
Male			-0.26 (-0.53, 0.02)	56.2	370	288
Mixed-sex	++-+		0.16 (-0.13, 0.46)	18.7	235	215
Female		<b></b>	0.18 (-0.28, 0.64)	25.1	144	142
No stress			-0.10 (-0.31, 0.12)	87.9	685	575
Stress			— 0.12 (-0.51, 0.75)	12.1	64	70
Prenatal		•	0.34 (-0.16, 0.84)	21.6	114	127
Pre- and postnatal			0.03 (-0.29, 0.35)	29.8	243	214
Postnatal			-0.32 (-0.58, -0.05)	48.5	392	304
	-0.5 0	0.5				

SSRI less pro-social SSRI more pro-social

# F. Ingestive and reward behavior

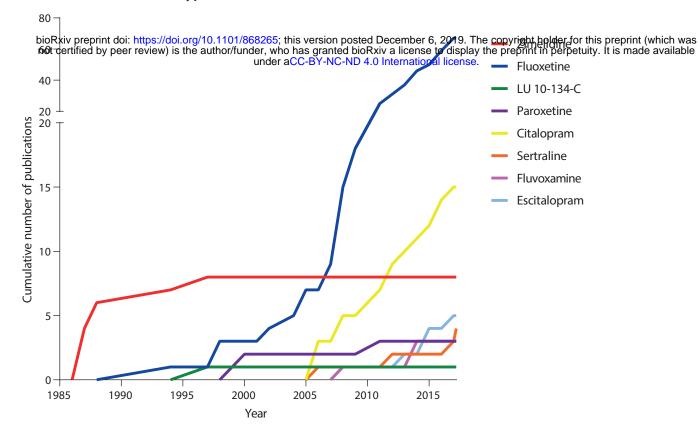
Subgroup	reward behavior	SMD (95% CI)	Veight (%)	N	N <sub>Veh</sub>
Overall	-	0.27 (-0.07, 0.60)	100.0	260	249
Male		0.34 (-0.16, 0.83)	56.4	136	134
Mixed-sex	<b>↓</b>	0.63 (0.07, 1.18)	9.1	26	27
Female		0.06 (-0.49, 0.62)	34.5	98	88
No stress		0.17 (-0.21, 0.55)	81.4	224	213
Stress	<b></b>	0.68 (-0.00, 1.36)	18.6	36	36
Prenatal	++	0.20 (-0.09, 0.50)	44.7	91	91
Pre- and postnatal		0.71 (-0.16, 1.58)	16.3	42	43
Postnatal		0.09 (-0.64, 0.82)	39.0	127	115

SSRI less reward-seeking SSRI more reward-seeking

H. Sensory processing			/eight		
Subgroup		SMD (95% CI)	(%)	N <sub>ssri</sub>	N <sub>veh</sub>
Overall 🔶		-0.37 (-0.69, -0.06)	100.0	317	310
Male		-0.45 (-1.29, 0.39)	27.7	61	64
Mixed-sex		-0.57 (-1.09, -0.05)	35.2	182	172
Female		-0.13 (-0.56, 0.29)	37.1	74	74
No stress		-0.39 (-0.72, -0.05)	94.8	308	301
Stress 🔶		-0.15 (-1.07, 0.78)	5.2	9	9
Prenatal 🔶		0.29 (-0.49, 1.07)	11.1	20	24
Pre- and postnatal —		-0.04 (-0.31, 0.23)	51.2	162	147
Postnatal		-1.04 (-1.59, -0.48)	37.7	135	139
-1 0	1				

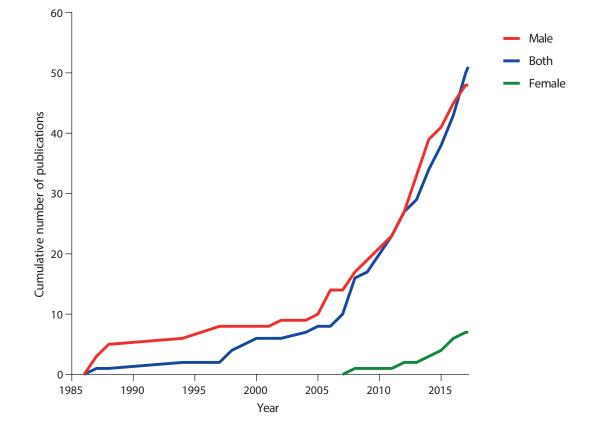
SSRI less efficient SSRI more efficient

# Type of SSRI administered



Β.

Sex studied



# A. Activity and exploration

Comparison Bairy 2007 Male cohort 2 12 mg/kg —	i1		SMD (95% CI) -2.56 (-4.29, -0.83	(%)
Bairy 2007 Male conort 2 12 mg/kg Bairy 2007 Female cohort 2 12 mg/kg Zheng 2011 FLX			-2.56 (-4.29, -0.83, -2.14 (-3.73, -0.55) -1.71 (-3.18, -0.25)	) 0.3
Simpson 2011 Male		needed December 0, 0010	-1.34 (-2.14, -0.53	) 0.78
/ Phephilith 4005,00000010. rtified by peernewiew) is the aut	nor/funder, who has arante	ed bioRxiv a license to displ	The copyright holder for this private the preprint in perpetuitive.	eprinst (whi simade av
Altieri 2015 Male cohort 2 FLX Zheng 2011 FLV	under aCC-BY-NC	-ND 4.0 International licens	Se. -1.11 (-2.03, -0.18) -1.1 (-2.42, 0.21)	) 0.66 0.41
Pivina 2011 FLX Olivier 2011 Female			-1.02 (-2.09, 0.05) -1 (-1.94, -0.06)	0.55 0.65
Sprowles 2017 Female cohort 2 CIT Harris 2012 20 mg/kg			-0.96 (-1.73, -0.2) -0.95 (-1.87, -0.02)	0.82
Sprowles 2017 Cohort 1 CIT Rebello 2014 Exposure P2-P21			-0.93 (-1.45, -0.41) -0.89 (-1.54, -0.24)	) 1.13
Lee 2009 Sarkar 2014b Cohort 1			-0.88 (-1.68, -0.08) -0.86 (-1.83, 0.12)	) 0.78
Karpova 2009 Sprowles 2017 Cohort 1 FLX			-0.85 (-1.83, 0.12) -0.85 (-1.77, 0.06) -0.85 (-1.37, -0.32)	0.68
Sprowles 2016 Cohort 1			-0.85 (-1.43, -0.26)	) 1.04
Harris 2012 10 mg/kg Yu 2014			-0.81 (-1.71, 0.09) -0.81 (-1.51, -0.1)	0.89
Ansorge 2004 Jiang 2009 Samuda 2017 Samula salasit 2 SLX			-0.76 (-1.49, -0.02) -0.75 (-1.19, -0.32)	) 1.24
Sprowles 2017 Female cohort 2 FLX Khatri 2014 Cohort 1			-0.75 (-1.52, 0.01) -0.73 (-1.12, -0.34)	) 1.32
Gobinath 2016 Female stress Lee 2012			-0.72 (-1.8, 0.35) -0.72 (-1.48, 0.03)	0.55 0.83
da Silva 2015 Soga 2012			-0.71 (-1.89, 0.48) -0.7 (-1.62, 0.21)	0.48 0.67
Pivina 2011 PRX Ansorge 2008			-0.7 (-1.73, 0.33) -0.7 (-1.26, -0.14)	0.58 1.08
Rodriguez-Porcel 2011 Male CIT Sarkar 2014b Cohort 3			-0.7 (-1.53, 0.13) -0.68 (-1.64, 0.27)	
Altieri 2015 Female cohort 2 FLX Lisboa 2007 Male			-0.68 (-1.44, 0.09) -0.65 (-1.35, 0.06)	0.82 0.89
Harris 2012 5 mg/kg Rayen 2011 Female stress			-0.64 (-1.49, 0.21) -0.64 (-1.54, 0.26)	0.68
Sarkar 2014a Cohort 1 Rayen 2013 No stress			-0.64 (-1.59, 0.32) -0.63 (-1.54, 0.27)	0.64 0.68
Gobinath 2016 Male stress McAllister 2012			-0.62 (-1.67, 0.42) -0.59 (-1.28, 0.11)	0.57 0.89
Altieri 2015 Female cohort 2 ESC Kiryanova 2016 No stress			-0.57 (-1.33, 0.2) -0.52 (-1.2, 0.15)	0.82
Boulle 2016b No stress Altieri 2015 Female cohort 3 ESC			-0.52 (-1.2, 0.13) -0.52 (-1.33, 0.3) -0.51 (-1.41, 0.39)	0.77 0.69
Sarkar 2014a Cohort 2 Rayen 2014 Stress			-0.5 (-1.57, 0.57) -0.49 (-1.39, 0.4)	0.55 0.69
Altieri 2015 Female cohort 1 Nagano 2017 Male FLX			-0.49 (-1.39, 0.4) -0.47 (-1.47, 0.53) -0.47 (-1.56, 0.62)	0.6
Ehrlich 2015 Stress cohort 1 Kroeze 2016			-0.47 (-1.36, 0.62) -0.46 (-1.46, 0.53) -0.43 (-1.19, 0.33)	0.6 0.83
Nagano 2017 Female ESC Grimm 1987 Exposure P4-P8			-0.41 (-1.52, 0.7) -0.41 (-0.94, 0.12)	0.53
Olivier 2011 Male Yu 2012			-0.4 (-1.21, 0.41) -0.4 (-1.13, 0.32)	0.77
Kiryanova 2014 Kiryanova 2017a Stress			-0.39 (-1.13, 0.32) -0.39 (-1.09, 0.31) -0.39 (-1.45, 0.68)	0.89 0.56
Altieri 2015 Male cohort 2 ESC Vieira 2013			-0.38 (-1.23, 0.47)	0.73
Sprowles 2016 Cohort 2			-0.38 (-1.26, 0.51) -0.37 (-0.93, 0.19) 0.37 (1.36, 0.62)	0.7
Altieri 2015 Male cohort 1 Nagano 2017 Female FLX Ebrlick 2015 No strong schort 1			-0.37 (-1.36, 0.62) -0.36 (-1.4, 0.68) 0.36 (-1.4, 0.68)	0.61
Ehrlich 2015 No stress cohort 1 Altieri 2015 Male cohort 3 ESC Altieri 2015 Male cohort 3 FLX			-0.36 (-1.35, 0.63) -0.34 (-1.21, 0.52)	0.61
Rayen 2013 Stress			-0.34 (-1.23, 0.55) -0.34 (-1.23, 0.54)	0.7
Rayen 2014 No stress Boulle 2016a No stress			-0.31 (-1.2, 0.57) -0.31 (-1.09, 0.46)	0.7 0.81
Sprowles 2017 Male cohort 2 CIT Rodriguez-Porcel 2011 Female FLX			-0.29 (-1.01, 0.42) -0.29 (-1.15, 0.57)	
Coleman 1999 Male Rayen 2011 Male no stress			-0.28 (-1.1, 0.54) -0.27 (-1.15, 0.62)	0.76 0.7
Hansen 1997 5 mg/kg Kiryanova 2016 Stress			-0.23 (-1.17, 0.71) -0.19 (-0.87, 0.5)	0.91
Vorhees 1994 Male cohort 1 5 mg/kg Sprowles 2017 Male cohort 2 FLX			-0.15 (-0.71, 0.4) -0.14 (-0.85, 0.56)	1.09 0.89
Hansen 1997 30 mg/kg Knaepen 2013 Stress			-0.14 (-1.14, 0.86) -0.13 (-1.12, 0.85)	0.6 0.62
Vorhees 1994 Male cohort 3 5 mg/kg Hansen 1997 20 mg/kg			-0.13 (-0.68, 0.42) -0.13 (-1.09, 0.83)	1.09 0.64
Nagano 2012 No stress Vorhees 1994 Female cohort 3 5 mg/kg			-0.1 (-0.78, 0.57) -0.1 (-0.65, 0.45)	0.93 1.09
Gobinath 2016 Male no stress Vorhees 1994 Male cohort 3 1 mg/kg			-0.1 (-1.16, 0.96) -0.09 (-0.64, 0.46)	0.56 1.09
Vorhees 1994 Female cohort 3 1 mg/kg Vorhees 1994 Female cohort 2 1 mg/kg			-0.08 (-0.63, 0.47) -0.08 (-0.63, 0.47)	1.09
Bairy 2007 Female cohort 2 8 mg/kg Grimm 1987 Exposure G10-G20			-0.08 (-0.03, 0.47) -0.08 (-1.28, 1.12) -0.06 (-1.04, 0.92)	0.47
Vorhees 1994 Male cohort 3 12 mg/kg Coleman 1999 Female			-0.06 (-1.04, 0.92) -0.06 (-0.59, 0.47) -0.04 (-0.85, 0.78)	
Vorhees 1994 Male cohort 1 1 mg/kg Vorhees 1994 Female cohort 3 12 mg/kg			-0.03 (-0.58, 0.52)	1.09
Vorhees 1994 Female cohort 2 12 mg/kg	÷.		-0.02 (-0.55, 0.51) -0.01 (-0.54, 0.51) -0.01 (-0.56, 0.54)	1.12
Vorhees 1994 Male cohort 2 5 mg/kg Bairy 2007 Male cohort 2 8 mg/kg Vorhoos 1994 Fomalo cohort 2 5 mg/kg			-0.01 (-0.56, 0.54) 0 (-1.2, 1.2)	1.09 0.47
Vorhees 1994 Female cohort 2 5 mg/kg Altieri 2015 Female cohort 3 FLX Simpson 2011 Famale			0.01 (-0.54, 0.56) 0.01 (-0.84, 0.87)	1.09 0.72
Simpson 2011 Female Vorhees 1994 Male cohort 2 12 mg/kg			0.04 (-0.67, 0.76) 0.05 (-0.48, 0.58)	0.87
Vorhees 1994 Male cohort 2 1 mg/kg Hansen 1997 10 mg/kg			0.08 (-0.47, 0.63) 0.08 (-0.87, 1.04)	1.09 0.64
Khatri 2014 Cohort 2 Rodriguez-Porcel 2011 Female CIT	+ <del>0</del>		0.09 (-0.45, 0.63) 0.09 (-0.77, 0.95)	1.1 0.72
Vorhees 1994 Female cohort 1 5 mg/kg Kiryanova 2017b No stress	+ <b>\</b>		0.1 (-0.45, 0.65) 0.11 (-0.81, 1.04)	1.09 0.66
Haskell 2017 Rebello 2014 Exposure P12-P21			0.11 (-0.95, 1.17) 0.14 (-0.48, 0.76)	0.56 0.99
Vorhees 1994 Female cohort 1 12 mg/kg Vorhees 1994 Male cohort 1 12 mg/kg			0.15 (-0.38, 0.68) 0.2 (-0.33, 0.73)	1.12 1.12
Nagano 2017 Male ESC Vorhees 1994 Female cohort 1 1 mg/kg			0.22 (-0.93, 1.38) 0.24 (-0.31, 0.79)	0.5
Boulle 2016b Stress Lisboa 2007 Female			0.24 (-0.56, 1.05) 0.26 (-0.6, 1.12)	0.78
Ehrlich 2015 Stress cohort 2 Rayen 2011 Male stress			0.27 (-0.54, 1.07) 0.28 (-0.61, 1.16)	0.78
Nagano 2012 Stress Knaepen 2013 No stress			0.33 (-0.35, 1.01) 0.37 (-0.62, 1.36)	0.92 0.61
Kiryanova 2017a No stress Kiryanova 2013			0.42 (-0.64, 1.49)	0.55
Sarkar 2014b Cohort 2			0.47 (-0.69, 1.62) 0.48 (-0.41, 1.37) 0.51 (.0.38, 1.41)	0.69
Rayen 2011 Female no stress Boulle 2016a Stress Cobiesth 2016 Female no stress			0.51 (-0.38, 1.41) 0.64 (-0.15, 1.43)	0.69 0.79
Gobinath 2016 Female no stress Sarkar 2014b Cohort 4			0.66 (-0.41, 1.73) 0.74 (-0.45, 1.93)	0.55
Ehrlich 2015 No stress cohort 2 Kiryanova 2017b Stress Hilakiri 1989a			0.82 (-0.04, 1.68) 0.89 (-0.09, 1.87) 1.25 (-0.02, 2.54)	0.72
Hilakivi 1988a Maciag 2006b Maciae 2006			1.25 (-0.03, 2.54) 1.32 (-0.12, 2.77)	0.42
Maciag 2006a Bairy 2007 Female cohort 1 12 mg/kg			1.99 (0.41, 3.56) 5.79 (2.72, 8.86)	0.31 0.09
Bairy 2007 Male cohort 1 12 mg/kg Bairy 2007 Female cohort 1 8 mg/kg			6.5 (3.1, 9.89) 7.06 (3.41, 10.71)	0.08 0.07
Bairy 2007 Male cohort 1 8 mg/kg			→ 9.9 (4.92, 14.88)	0.04

# B. Activity and exploration - Sex

Comparison Bairy 2007 Male cohort 2 12 mg/kg			-2.56 (-4.29, -0.83) 0.26
Zheng 2011 FLX Simpson 2011 Male			-1.71 (-3.18, -0.25) 0.35 -1.34 (-2.14, -0.53) 0.78
Ko 2014		an another Deservice to 2010. The service to be	-1.32 (-2.44, -0.21) 0.52
preprint <u>an</u> : <u>chttps://doi.org/10.1</u>	or/funder who has ara	on posted December 6, 2019. The copyright honten the properties of	n perpetuity at is made av
Pivina 2011 FLX Harris 2012 20 mg/kg	under aCC-BY-	NC-ND 4.0 International license.	-1.02 (-2.09, 0.05) 0.55 -0.95 (-1.87, -0.02) 0.66
Sarkar 2014b Cohort 1 Karpova 2009			-0.86 (-1.83, 0.12) 0.62 -0.85 (-1.77, 0.06) 0.68
Harris 2012 10 mg/kg			-0.81 (-1.71, 0.09) 0.69
Jiang 2009 Lee 2012			-0.72 (-1.48, 0.03) 0.83
da Silva 2015 Soga 2012			-0.71 (-1.89, 0.48) 0.48 -0.7 (-1.62, 0.21) 0.67
Pivina 2011 PRX Ansorge 2008			-0.7 (-1.73, 0.33) 0.58 -0.7 (-1.26, -0.14) 1.08
Rodriguez-Porcel 2011 Male CIT Sarkar 2014b Cohort 3			-0.7 (-1.53, 0.13) 0.76 -0.68 (-1.64, 0.27) 0.64
Lisboa 2007 Male Harris 2012 5 mg/kg			-0.65 (-1.35, 0.06) 0.89 -0.64 (-1.49, 0.21) 0.73
Sarkar 2014a Cohort 1 Rayen 2013 No stress			-0.64 (-1.59, 0.32) 0.64 -0.63 (-1.54, 0.27) 0.68
Gobinath 2016 Male stress Kiryanova 2016 No stress			-0.62 (-1.67, 0.42) 0.57 -0.52 (-1.2, 0.15) 0.92
Sarkar 2014a Cohort 2			-0.5 (-1.57, 0.57) 0.55
Nagano 2017 Male FLX Kroeze 2016			-0.47 (-1.56, 0.62) 0.54 -0.43 (-1.19, 0.33) 0.83
Olivier 2011 Male Kiryanova 2014			-0.4 (-1.21, 0.41) 0.77 -0.39 (-1.09, 0.31) 0.89
Kiryanova 2017a Stress Altieri 2015 Male cohort 2 ESC			-0.39 (-1.45, 0.68) 0.56 -0.38 (-1.23, 0.47) 0.73
Vieira 2013 Altieri 2015 Male cohort 1			-0.38 (-1.26, 0.51) 0.7 -0.37 (-1.36, 0.62) 0.61
Altieri 2015 Male cohort 3 ESC Altieri 2015 Male cohort 3 FLX			-0.34 (-1.21, 0.52) 0.72 -0.34 (-1.23, 0.55) 0.7
Rayen 2013 Stress Boulle 2016a No stress			-0.34 (-1.23, 0.54) 0.7 -0.31 (-1.09, 0.46) 0.81
Sprowles 2017 Male cohort 2 CIT Coleman 1999 Male			-0.29 (-1.01, 0.42) 0.88
Rayen 2011 Male no stress			-0.27 (-1.15, 0.62) 0.7
Hansen 1997 5 mg/kg Kiryanova 2016 Stress			-0.23 (-1.17, 0.71) 0.65 -0.19 (-0.87, 0.5) 0.91
Vorhees 1994 Male cohort 1 5 mg/kg Sprowles 2017 Male cohort 2 FLX			-0.15 (-0.71, 0.4) 1.09 -0.14 (-0.85, 0.56) 0.89
Hansen 1997 30 mg/kg Knaepen 2013 Stress			-0.14 (-1.14, 0.86) 0.6 -0.13 (-1.12, 0.85) 0.62
Vorhees 1994 Male cohort 3 5 mg/kg Hansen 1997 20 mg/kg			-0.13 (-0.68, 0.42) 1.09 -0.13 (-1.09, 0.83) 0.64
Nagano 2012 No stress Gobinath 2016 Male no stress			-0.1 (-0.78, 0.57) 0.93 -0.1 (-1.16, 0.96) 0.56
Vorhees 1994 Male cohort 3 1 mg/kg Grimm 1987 Exposure G10-G20			-0.09 (-0.64, 0.46) 1.09 -0.06 (-1.04, 0.92) 0.62
Vorhees 1994 Male cohort 3 12 mg/kg			-0.06 (-0.59, 0.47) 1.12
Vorhees 1994 Male cohort 1 1 mg/kg Vorhees 1994 Male cohort 2 5 mg/kg Pains 2007 Male cohort 2 8 mg/kg			-0.01 (-0.56, 0.54) 1.09
Bairy 2007 Male cohort 2 8 mg/kg Vorhees 1994 Male cohort 2 12 mg/kg			0 (-1.2, 1.2) 0.47 0.05 (-0.48, 0.58) 1.12
Vorhees 1994 Male cohort 2 1 mg/kg Hansen 1997 10 mg/kg	+ <b>&gt;</b>		0.08 (-0.47, 0.63) 1.09 0.08 (-0.87, 1.04) 0.64
Haskell 2017 Vorhees 1994 Male cohort 1 12 mg/kg			0.11 (-0.95, 1.17) 0.56 0.2 (-0.33, 0.73) 1.12
Nagano 2017 Male ESC Rayen 2011 Male stress			0.22 (-0.93, 1.38) 0.5 0.28 (-0.61, 1.16) 0.7
Nagano 2012 Stress Knaepen 2013 No stress			0.33 (-0.35, 1.01) 0.92 0.37 (-0.62, 1.36) 0.61
Kiryanova 2017a No stress Kiryanova 2013			0.42 (-0.64, 1.49) 0.55 0.47 (-0.69, 1.62) 0.5
Sarkar 2014b Cohort 2 Boulle 2016a Stress			0.47 (-0.09, 1.02) 0.5 0.48 (-0.41, 1.37) 0.69 0.64 (-0.15, 1.43) 0.79
Sarkar 2014b Cohort 4		_	0.74 (-0.45, 1.93) 0.48
Hilakivi 1988a Maciag 2006b	$\rightarrow$		1.25 (-0.03, 2.54) 0.42 1.32 (-0.12, 2.77) 0.35
Maciag 2006a Bairy 2007 Male cohort 1 12 mg/kg			1.99 (0.41, 3.56) 0.31 6.5 (3.1, 9.89) 0.08
Bairy 2007 Male cohort 1 8 mg/kg Male	•		
Rebello 2014 Exposure P2-P11 Sprowles 2017 Cohort 1 CIT			-1.18 (-1.85, -0.51) 0.93 -0.93 (-1.45, -0.41) 1.13
Rebello 2014 Exposure P2-P21 Lee 2009			-0.89 (-1.54, -0.24) 0.95 -0.88 (-1.68, -0.08) 0.78
Sprowles 2017 Cohort 1 FLX Sprowles 2016 Cohort 1			-0.85 (-1.37, -0.32) 1.12 -0.85 (-1.43, -0.26) 1.04
Yu 2014 Ansorge 2004			-0.81 (-1.51, -0.1) 0.89 -0.76 (-1.49, -0.02) 0.86
Khatri 2014 Cohort 1	->		-0.73 (-1.12, -0.34) 1.32
Grimm 1987 Exposure P4-P8 Yu 2012			-0.41 (-0.94, 0.12) 1.11 -0.4 (-1.13, 0.32) 0.86
Sprowles 2016 Cohort 2 Khatri 2014 Cohort 2			-0.37 (-0.93, 0.19) 1.07 0.09 (-0.45, 0.63) 1.1
Rebello 2014 Exposure P12-P21 Mixed-sex	•		0.14 (-0.48, 0.76) 0.99 -0.62 (-0.82, -0.42) 14.17
Bairy 2007 Female cohort 2 12 mg/kg — Olivier 2011 Female			-2.14 (-3.73, -0.55) 0.3 -1 (-1.94, -0.06) 0.65
Sprowles 2017 Female cohort 2 CIT Sprowles 2017 Female cohort 2 FLX			-0.96 (-1.73, -0.2) 0.82 -0.75 (-1.52, 0.01) 0.82
Gobinath 2016 Female stress Altieri 2015 Female cohort 2 FLX			-0.72 (-1.8, 0.35) 0.55 -0.68 (-1.44, 0.09) 0.82
Rayen 2011 Female stress McAllister 2012			-0.64 (-1.54, 0.26) 0.68
Altieri 2015 Female cohort 2 ESC			-0.57 (-1.33, 0.2) 0.82
Boulle 2016b No stress Altieri 2015 Female cohort 3 ESC			-0.52 (-1.33, 0.3) 0.77 -0.51 (-1.41, 0.39) 0.69
Rayen 2014 Stress Altieri 2015 Female cohort 1			-0.49 (-1.39, 0.4) 0.69 -0.47 (-1.47, 0.53) 0.6
Ehrlich 2015 Stress cohort 1 Nagano 2017 Female ESC			-0.46 (-1.46, 0.53) 0.6 -0.41 (-1.52, 0.7) 0.53
Nagano 2017 Female FLX Ehrlich 2015 No stress cohort 1			-0.36 (-1.4, 0.68) 0.57 -0.36 (-1.35, 0.63) 0.61
Rayen 2014 No stress Rodriguez-Porcel 2011 Female FLX			-0.31 (-1.2, 0.57) 0.7 -0.29 (-1.15, 0.57) 0.72
Vorhees 1994 Female cohort 3 5 mg/kg			-0.1 (-0.65, 0.45) 1.09
Vorhees 1994 Female cohort 3 1 mg/kg Vorhees 1994 Female cohort 2 1 mg/kg Pain: 2007 Famale schort 2 8 mg/kg			-0.08 (-0.63, 0.47) 1.09
Bairy 2007 Female cohort 2 8 mg/kg Coleman 1999 Female			-0.08 (-1.28, 1.12) 0.47 -0.04 (-0.85, 0.78) 0.76
Vorhees 1994 Female cohort 3 12 mg/kg Vorhees 1994 Female cohort 2 12 mg/kg			-0.02 (-0.55, 0.51) 1.12 -0.01 (-0.54, 0.51) 1.12
Vorhees 1994 Female cohort 2 5 mg/kg Altieri 2015 Female cohort 3 FLX			0.01 (-0.54, 0.56) 1.09 0.01 (-0.84, 0.87) 0.72
Simpson 2011 Female Rodriguez-Porcel 2011 Female CIT			0.04 (-0.67, 0.76) 0.87 0.09 (-0.77, 0.95) 0.72
Vorhees 1994 Female cohort 1 5 mg/kg Kiryanova 2017b No stress			0.1 (-0.45, 0.65) 1.09 0.11 (-0.81, 1.04) 0.66
Vorhees 1994 Female cohort 1 12 mg/kg			0.15 (-0.38, 0.68) 1.12
Vorhees 1994 Female cohort 1 1 mg/kg Boulle 2016b Stress			0.24 (-0.31, 0.79) 1.08 0.24 (-0.56, 1.05) 0.78
Lisboa 2007 Female Ehrlich 2015 Stress cohort 2			0.26 (-0.6, 1.12) 0.72 0.27 (-0.54, 1.07) 0.78
Rayen 2011 Female no stress Gobinath 2016 Female no stress			0.51 (-0.38, 1.41) 0.69 0.66 (-0.41, 1.73) 0.55
Ehrlich 2015 No stress cohort 2 Kiryanova 2017b Stress			0.82 (-0.04, 1.68) 0.72 0.89 (-0.09, 1.87) 0.62
Bairy 2007 Female cohort 1 12 mg/kg Bairy 2007 Female cohort 1 8 mg/kg		<del></del>	5.79 (2.72, 8.86) 0.09 7.06 (3.41, 10.71) 0.07
, ,, ,, ,, , , , , , , ,		·	-0.12 (-0.29, 0.04) 31.93

Weight SMD (95% Cl) (%)

-2.56 (-4.29, -0.83)	0.26
-2.14 (-3.73, -0.55)	0.3
-1.71 (-3.18, -0.25)	0.35

C	Comparison	-	-			SM	/ID (95% CI)	(%)	
	Bairy 2007 Male cohort 2 12 mg/kg Bairy 2007 Female cohort 2 12 mg/kg						56 (-4.29, -0.83) 14 (-3.73, -0.55)	0.26 0.3	
Z	heng 2011 FLX					-1.	71 (-3.18, -0.25)	0.35	
	impson 2011 Male		this version	nosted December 6	2019 The c	-1. opyright holder fr	34 (-2.14, -0.53) 32 (+p.14 -0.21)	0.78	(which was
not certific	edioy peer review) is th	e author/funder wh	o has grante	ed bioRxiv a license	to display the	preprint in perpe	18 (4.85, 451) tuitiva liteis	mad	le available
A	Altieri 2015 Male cohort 2 FLX Cheng 2011 FLV	under	aCC-BY-NC	-ND 4.0 Internationa	al license.	-1.	11 (-2.03, -0.18) 1 (-2.42, 0.21)	0.66 0.41	
C	Dlivier 2011 Female	$\rightarrow$				-1	(-1.94, -0.06)	0.65	
	prowles 2017 Female cohort 2 CIT Iarris 2012 20 mg/kg		-				96 (-1.73, -0.2) 95 (-1.87, -0.02)	0.82 0.66	
S	prowles 2017 Cohort 1 CIT Rebello 2014 Exposure P2-P21	->				-0.	93 (-1.45, -0.41) 89 (-1.54, -0.24)	1.13 0.95	
L	ee 2009					-0.	88 (-1.68, -0.08)	0.78	
	arkar 2014b Cohort 1 Carpova 2009		ţ				86 (-1.83, 0.12) 85 (-1.77, 0.06)	0.62 0.68	
	prowles 2017 Cohort 1 FLX prowles 2016 Cohort 1					-0.	85 (-1.37, -0.32) 85 (-1.43, -0.26)	1.12 1.04	
н	larris 2012 10 mg/kg		+			-0.	81 (-1.71, 0.09)	0.69	
A	'u 2014 Ansorge 2004		-				81 (-1.51, -0.1) 76 (-1.49, -0.02)	0.89 0.86	
	iang 2009 prowles 2017 Female cohort 2 FLX						75 (-1.19, -0.32) 75 (-1.52, 0.01)	1.24 0.82	
K	íhatri 2014 Cohort 1 .ee 2012					-0.	73 (-1.12, -0.34) 72 (-1.48, 0.03)	1.32 0.83	
d	la Silva 2015		<u> </u>			-0.	71 (-1.89, 0.48)	0.48	
A	ioga 2012 Ansorge 2008		Ť				7 (-1.62, 0.21) 7 (-1.26, -0.14)	0.67 1.08	
	odriguez-Porcel 2011 Male CIT arkar 2014b Cohort 3		+				7 (-1.53, 0.13) 68 (-1.64, 0.27)	0.76 0.64	
A	Altieri 2015 Female cohort 2 FLX		ł			-0.	68 (-1.44, 0.09)	0.82	
H	isboa 2007 Male Iarris 2012 5 mg/kg		F			-0.	65 (-1.35, 0.06) 64 (-1.49, 0.21)	0.89 0.73	
	arkar 2014a Cohort 1 Rayen 2013 No stress		<u> </u>				64 (-1.59, 0.32) 63 (-1.54, 0.27)	0.64 0.68	
	AcAllister 2012 Altieri 2015 Female cohort 2 ESC		Ł			-0.	59 (-1.28, 0.11) 57 (-1.33, 0.2)	0.89 0.82	
K	(iryanova 2016 No stress		ł			-0.	52 (-1.2, 0.15)	0.92	
A	Boulle 2016b No stress Altieri 2015 Female cohort 3 ESC		F			-0.	52 (-1.33, 0.3) 51 (-1.41, 0.39)	0.77 0.69	
	arkar 2014a Cohort 2 Altieri 2015 Female cohort 1		t				5 (-1.57, 0.57) 47 (-1.47, 0.53)	0.55 0.6	
N	lagano 2017 Male FLX Groeze 2016		F			-0.	47 (-1.56, 0.62)	0.54	
N	lagano 2017 Female ESC		Ë-			-0.	43 (-1.19, 0.33) 41 (-1.52, 0.7)	0.83 0.53	
	Grimm 1987 Exposure P4-P8 Divier 2011 Male		Į.				41 (-0.94, 0.12) 4 (-1.21, 0.41)	1.11 0.77	
Y	íryanova 2014		t			-0.	4 (-1.13, 0.32) 39 (-1.09, 0.31)	0.86	
A	Altieri 2015 Male cohort 2 ESC		+			-0.	38 (-1.23, 0.47)	0.73	
S	/ieira 2013 iprowles 2016 Cohort 2		F			-0.	38 (-1.26, 0.51) 37 (-0.93, 0.19)	0.7 1.07	
	Altieri 2015 Male cohort 1 Jagano 2017 Female FLX						37 (-1.36, 0.62) 36 (-1.4, 0.68)	0.61 0.57	
E	hrlich 2015 No stress cohort 1		<u> </u>			-0.	36 (-1.35, 0.63)	0.61	
A	Altieri 2015 Male cohort 3 ESC Altieri 2015 Male cohort 3 FLX		F			-0.	34 (-1.21, 0.52) 34 (-1.23, 0.55)	0.72 0.7	
	Rayen 2014 No stress Boulle 2016a No stress		<b></b>				31 (-1.2, 0.57) 31 (-1.09, 0.46)	0.7 0.81	
	prowles 2017 Male cohort 2 CIT Rodriguez-Porcel 2011 Female FLX		E				29 (-1.01, 0.42) 29 (-1.15, 0.57)	0.88 0.72	
C	oleman 1999 Male	¥	<u> </u>			-0.	28 (-1.1, 0.54)	0.76	
H	Rayen 2011 Male no stress Hansen 1997 5 mg/kg	$\rightarrow$	<b>—</b>				27 (-1.15, 0.62) 23 (-1.17, 0.71)	0.7 0.65	
	/orhees 1994 Male cohort 1 5 mg/kg prowles 2017 Male cohort 2 FLX	 	<u>↓</u>				15 (-0.71, 0.4) 14 (-0.85, 0.56)	1.09 0.89	
н	lansen 1997 30 mg/kg /orhees 1994 Male cohort 3 5 mg/kg		<u>}</u>			-0.	14 (-1.14, 0.86)	0.6	
H	lansen 1997 20 mg/kg		<b>_</b>			-0.	13 (-0.68, 0.42) 13 (-1.09, 0.83)	0.64	
	lagano 2012 No stress /orhees 1994 Female cohort 3 5 mg/kg						1 (-0.78, 0.57) 1 (-0.65, 0.45)	0.93 1.09	
	Sobinath 2016 Male no stress /orhees 1994 Male cohort 3 1 mg/kg					-0.	1 (-1.16, 0.96) 09 (-0.64, 0.46)	0.56 1.09	
V	/orhees 1994 Female cohort 3 1 mg/kg		-			-0.	08 (-0.63, 0.47)	1.09	
В	/orhees 1994 Female cohort 2 1 mg/kg Bairy 2007 Female cohort 2 8 mg/kg		<u> </u>				08 (-0.63, 0.47) 08 (-1.28, 1.12)	1.09 0.47	
	Frimm 1987 Exposure G10-G20 /orhees 1994 Male cohort 3 12 mg/kg		<u></u>				06 (-1.04, 0.92) 06 (-0.59, 0.47)	0.62 1.12	
C	Coleman 1999 Female /orhees 1994 Male cohort 1 1 mg/kg		<u> </u>			-0.	04 (-0.85, 0.78) 03 (-0.58, 0.52)	0.76 1.09	
V	/orhees 1994 Female cohort 3 12 mg/kg		F			-0.	02 (-0.55, 0.51)	1.12	
	/orhees 1994 Female cohort 2 12 mg/kg /orhees 1994 Male cohort 2 5 mg/kg		t i				01 (-0.54, 0.51) 01 (-0.56, 0.54)	1.12 1.09	
	Bairy 2007 Male cohort 2 8 mg/kg /orhees 1994 Female cohort 2 5 mg/kg		<u> </u>				-1.2, 1.2) 11 (-0.54, 0.56)	0.47 1.09	
A	Altieri 2015 Female cohort 3 FLX	-	<b>↓</b>			0.0	1 (-0.84, 0.87)	0.72	
V	impson 2011 Female /orhees 1994 Male cohort 2 12 mg/kg	+	F			0.0	14 (-0.67, 0.76) 15 (-0.48, 0.58)	0.87 1.12	
	/orhees 1994 Male cohort 2 1 mg/kg lansen 1997 10 mg/kg		<b>⊳</b>				8 (-0.47, 0.63) 8 (-0.87, 1.04)	1.09 0.64	
K	Chatri 2014 Cohort 2 Rodriguez-Porcel 2011 Female CIT		è			0.0	9 (-0.45, 0.63) 9 (-0.77, 0.95)	1.1 0.72	
V	/orhees 1994 Female cohort 1 5 mg/kg	+	è			0.1	(-0.45, 0.65)	1.09	
н	íiryanova 2017b No stress Iaskell 2017		è			0.1	1 (-0.81, 1.04) 1 (-0.95, 1.17)	0.66 0.56	
V	Rebello 2014 Exposure P12-P21 /orhees 1994 Female cohort 1 12 mg/kg					0.1	4 (-0.48, 0.76) 5 (-0.38, 0.68)	0.99 1.12	
V	/orhees 1994 Male cohort 1 12 mg/kg Jagano 2017 Male ESC	_	<b>◇</b>			0.2	(-0.33, 0.73) (2 (-0.93, 1.38)	1.12	
V	/orhees 1994 Female cohort 1 1 mg/kg		-			0.2	4 (-0.31, 0.79)	1.08	
K	isboa 2007 Female (naepen 2013 No stress		i →			0.3	6 (-0.6, 1.12) 7 (-0.62, 1.36)	0.72 0.61	
K	(iryanova 2017a No stress (iryanova 2013	<u> </u>	<b>↓</b>			0.4	2 (-0.64, 1.49) 7 (-0.69, 1.62)	0.55 0.5	
S	arkar 2014b Cohort 2 Rayen 2011 Female no stress	+				0.4	8 (-0.41, 1.37) 1 (-0.38, 1.41)	0.69	
G	obinath 2016 Female no stress		<b>→</b>			0.6	6 (-0.41, 1.73)	0.55	
E	arkar 2014b Cohort 4 hrlich 2015 No stress cohort 2	1	→ →			0.8	4 (-0.45, 1.93) 2 (-0.04, 1.68)	0.48 0.72	
H	lilakivi 1988a Aaciaq 2006b		÷			1.2	5 (-0.03, 2.54) 2 (-0.12, 2.77)	0.42	
N	Naciag 2006a		— → —	<u> </u>		1.9	9 (0.41, 3.56)	0.31	
В	Bairy 2007 Female cohort 1 12 mg/kg Bairy 2007 Male cohort 1 12 mg/kg		-			6.5	9 (2.72, 8.86) (3.1, 9.89)	0.09 0.08	
B	Bairy 2007 Female cohort 1 8 mg/kg Bairy 2007 Male cohort 1 8 mg/kg					7.0	6 (3.41, 10.71) (4.92, 14.88)	0.07 0.04	
N	lo stress Pivina 2011 FLX	- ^			•	-0.	<b>3 (-0.4, -0.19)</b> 02 (-2.09, 0.05)	88.41 0.55	
G	Sobinath 2016 Female stress		+			-0.	72 (-1.8, 0.35)	0.55	
R	Pivina 2011 PRX Rayen 2011 Female stress		F			-0.	7 (-1.73, 0.33) 64 (-1.54, 0.26)	0.58 0.68	
G	Gobinath 2016 Male stress Rayen 2014 Stress		F			-0.	62 (-1.67, 0.42) 49 (-1.39, 0.4)	0.57	
E	hrlich 2015 Stress cohort 1		+			-0.	46 (-1.46, 0.53)	0.6	
R	(iryanova 2017a Stress Rayen 2013 Stress	¢	F			-0.	39 (-1.45, 0.68) 34 (-1.23, 0.54)	0.56 0.7	
	(iryanova 2016 Stress (naepen 2013 Stress	¢	<u> </u>				19 (-0.87, 0.5) 13 (-1.12, 0.85)	0.91 0.62	
В	Boulle 2016b Stress Brilich 2015 Stress cohort 2	+	<b>♦</b>			0.2	4 (-0.56, 1.05) 7 (-0.54, 1.07)	0.78	
R	ayen 2011 Male stress	+				0.2	8 (-0.61, 1.16)	0.7	
B	lagano 2012 Stress Boulle 2016a Stress	+	<b>↓</b>			0.6	3 (-0.35, 1.01) 4 (-0.15, 1.43)	0.92 0.79	
K	iryanova 2017b Stress i <b>tress</b>		<b>→</b>				9 (-0.09, 1.87) 12 (-0.36, 0.13)	0.62 11.59	
	Activity and exploration - Overall	+					28 (-0.38, -0.18)		

 Stress
 -0.12 (0.36, 0.13)
 11.59

 Activity and exploration - Overall
 -0.28 (-0.38, -0.18)
 100

 -5
 -4
 -3
 -2
 -1
 0
 1
 2
 3
 4
 5
 6
 7
 8
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 10
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 12
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 -5
 -4
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 14

 SSRI less active
 SSRI more active
 SSRI more active
 SSRI more active
 11
 12
 13
 14

# D. Activity and exploration - SSRI exposure timing

Bairy 2007 Male cohort 2 12 mg/kg	→		-2.56 (-4.29, -0.83)	0.26
Bairy 2007 Female cohort 2 12 mg/kg – Olivier 2011 Female			-2.14 (-3.73, -0.55) -1 (-1.94, -0.06)	0.3 0.65
Ehrlich 2015 Stress cohort 1 Olivier 2011 Male			-0.46 (-1.46, 0.53)	0.6
fied by see review) is the auth	or/funder_who has are	on posted December 6, 2019. The cop nted bioRxiv a license to display the p	preprint noider tor this pre-	print (wn made a'
Vorhees 1994 Male cohort 1 5 mg/kg	under aCC-BY-	NC-ND 4.0 International license.	-0.15 (-0.71, 0.4) -0.13 (-0.68, 0.42)	1.09 1.09
Vorhees 1994 Male cohort 3 5 mg/kg Vorhees 1994 Female cohort 3 5 mg/kg			-0.1 (-0.65, 0.45)	1.09
Vorhees 1994 Male cohort 3 1 mg/kg Vorhees 1994 Female cohort 3 1 mg/kg			-0.09 (-0.64, 0.46) -0.08 (-0.63, 0.47)	1.09 1.09
Vorhees 1994 Female cohort 2 1 mg/kg Bairy 2007 Female cohort 2 8 mg/kg			-0.08 (-0.63, 0.47) -0.08 (-1.28, 1.12)	1.09 0.47
Grimm 1987 Exposure G10-G20 Vorhees 1994 Male cohort 3 12 mg/kg			-0.06 (-1.04, 0.92) -0.06 (-0.59, 0.47)	0.62 1.12
Coleman 1999 Female Vorhees 1994 Male cohort 1 1 mg/kg			-0.04 (-0.85, 0.78) -0.03 (-0.58, 0.52)	0.76
Vorhees 1994 Female cohort 3 12 mg/kg Vorhees 1994 Female cohort 2 12 mg/kg			-0.02 (-0.55, 0.51)	1.12
Vorhees 1994 Male cohort 2 5 mg/kg			-0.01 (-0.54, 0.51) -0.01 (-0.56, 0.54)	1.09
Bairy 2007 Male cohort 2 8 mg/kg Vorhees 1994 Female cohort 2 5 mg/kg			0 (-1.2, 1.2) 0.01 (-0.54, 0.56)	0.47 1.09
Vorhees 1994 Male cohort 2 12 mg/kg Vorhees 1994 Male cohort 2 1 mg/kg	+		0.05 (-0.48, 0.58) 0.08 (-0.47, 0.63)	1.12 1.09
Vorhees 1994 Female cohort 1 5 mg/kg Vorhees 1994 Female cohort 1 12 mg/kg			0.1 (-0.45, 0.65) 0.15 (-0.38, 0.68)	1.09 1.12
Vorhees 1994 Male cohort 1 12 mg/kg Vorhees 1994 Female cohort 1 1 mg/kg			0.2 (-0.33, 0.73) 0.24 (-0.31, 0.79)	1.12
Ehrlich 2015 Stress cohort 2 Ehrlich 2015 No stress cohort 2			0.27 (-0.54, 1.07)	0.78
Bairy 2007 Female cohort 1 12 mg/kg			0.82 (-0.04, 1.68) 5.79 (2.72, 8.86)	0.09
Bairy 2007 Male cohort 1 12 mg/kg Bairy 2007 Female cohort 1 8 mg/kg		<del>`</del>	6.5 (3.1, 9.89) 7.06 (3.41, 10.71)	0.08 0.07
Bairy 2007 Male cohort 1 8 mg/kg Prenatal	+		9.9 (4.92, 14.88) -0.01 (-0.21, 0.19)	0.04 27.78
Sprowles 2017 Female cohort 2 CIT Sprowles 2017 Cohort 1 CIT			-0.96 (-1.73, -0.2) -0.93 (-1.45, -0.41)	0.82 1.13
Sprowles 2017 Cohort 1 FLX			-0.85 (-1.37, -0.32) -0.85 (-1.43, -0.26)	1.12
Sprowles 2016 Cohort 1 Sprowles 2017 Female cohort 2 FLX			-0.75 (-1.52, 0.01)	0.82
Lisboa 2007 Male McAllister 2012			-0.65 (-1.35, 0.06) -0.59 (-1.28, 0.11)	0.89 0.89
Kiryanova 2016 No stress Kroeze 2016			-0.52 (-1.2, 0.15) -0.43 (-1.19, 0.33)	0.92 0.83
Kiryanova 2014 Kiryanova 2017a Stress			-0.39 (-1.09, 0.31) -0.39 (-1.45, 0.68)	0.89 0.56
Vieira 2013 Sprowles 2016 Cohort 2			-0.38 (-1.26, 0.51) -0.37 (-0.93, 0.19)	0.7
Sprowles 2017 Male cohort 2 CIT			-0.29 (-1.01, 0.42)	0.88
Kiryanova 2016 Stress Sprowles 2017 Male cohort 2 FLX			-0.19 (-0.87, 0.5) -0.14 (-0.85, 0.56)	0.91 0.89
Kiryanova 2017b No stress Haskell 2017			0.11 (-0.81, 1.04) 0.11 (-0.95, 1.17)	0.66 0.56
Lisboa 2007 Female Kiryanova 2017a No stress			0.26 (-0.6, 1.12) 0.42 (-0.64, 1.49)	0.72 0.55
Kiryanova 2013 Kiryanova 2017b Stress			0.47 (-0.69, 1.62) 0.89 (-0.09, 1.87)	0.5 0.62
Pre- and postnatal Zheng 2011 FLX	•			17.98 0.35
Simpson 2011 Male	<u> </u>		-1.34 (-2.14, -0.53)	0.78
Ko 2014 Rebello 2014 Exposure P2-P11			-1.32 (-2.44, -0.21) -1.18 (-1.85, -0.51)	0.52 0.93
Rodriguez-Porcel 2011 Male FLX Altieri 2015 Male cohort 2 FLX			-1.16 (-2.03, -0.29) -1.11 (-2.03, -0.18)	0.72 0.66
Zheng 2011 FLV Pivina 2011 FLX			-1.1 (-2.42, 0.21) -1.02 (-2.09, 0.05)	0.41 0.55
Harris 2012 20 mg/kg Rebello 2014 Exposure P2-P21			-0.95 (-1.87, -0.02) -0.89 (-1.54, -0.24)	0.66 0.95
Lee 2009 Sarkar 2014b Cohort 1			-0.88 (-1.68, -0.08) -0.86 (-1.83, 0.12)	0.78
Karpova 2009 Harris 2012 10 mg/kg			-0.85 (-1.77, 0.06)	0.68
Yu 2014			-0.81 (-1.71, 0.09) -0.81 (-1.51, -0.1) 0.76 (1.40, 0.02)	0.69 0.89
Ansorge 2004 Jiang 2009			-0.76 (-1.49, -0.02) -0.75 (-1.19, -0.32)	0.86 1.24
Khatri 2014 Cohort 1 Gobinath 2016 Female stress			-0.73 (-1.12, -0.34) -0.72 (-1.8, 0.35)	1.32 0.55
Lee 2012 da Silva 2015			-0.72 (-1.48, 0.03) -0.71 (-1.89, 0.48)	0.83 0.48
Soga 2012 Pivina 2011 PRX			-0.7 (-1.62, 0.21) -0.7 (-1.73, 0.33)	0.67
Ansorge 2008			-0.7 (-1.26, -0.14)	1.08
Rodriguez-Porcel 2011 Male CIT Sarkar 2014b Cohort 3			-0.7 (-1.53, 0.13) -0.68 (-1.64, 0.27)	0.76 0.64
Altieri 2015 Female cohort 2 FLX Harris 2012 5 mg/kg			-0.68 (-1.44, 0.09) -0.64 (-1.49, 0.21)	0.82 0.73
Rayen 2011 Female stress Sarkar 2014a Cohort 1			-0.64 (-1.54, 0.26) -0.64 (-1.59, 0.32)	0.68 0.64
Rayen 2013 No stress Gobinath 2016 Male stress	 		-0.63 (-1.54, 0.27) -0.62 (-1.67, 0.42)	0.68 0.57
Altieri 2015 Female cohort 2 ESC Boulle 2016b No stress			-0.57 (-1.33, 0.2) -0.52 (-1.33, 0.3)	0.82
Altieri 2015 Female cohort 3 ESC Sarkar 2014a Cohort 2			-0.52 (-1.55, 0.5) -0.51 (-1.41, 0.39) -0.5 (-1.57, 0.57)	0.69
Rayen 2014 Stress			-0.49 (-1.39, 0.4)	0.69
Altieri 2015 Female cohort 1 Nagano 2017 Male FLX			-0.47 (-1.47, 0.53) -0.47 (-1.56, 0.62)	0.6 0.54
Nagano 2017 Female ESC Grimm 1987 Exposure P4-P8			-0.41 (-1.52, 0.7) -0.41 (-0.94, 0.12)	0.53 1.11
Yu 2012 Altieri 2015 Male cohort 2 ESC			-0.4 (-1.13, 0.32) -0.38 (-1.23, 0.47)	0.86 0.73
Altieri 2015 Male cohort 1 Nagano 2017 Female FLX			-0.37 (-1.36, 0.62) -0.36 (-1.4, 0.68)	0.61 0.57
Altieri 2015 Male cohort 3 ESC Altieri 2015 Male cohort 3 FLX			-0.30 (-1.4, 0.08) -0.34 (-1.21, 0.52) -0.34 (-1.23, 0.55)	0.72
Rayen 2013 Stress	$\rightarrow$		-0.34 (-1.23, 0.54)	0.7
Rayen 2014 No stress Boulle 2016a No stress			-0.31 (-1.2, 0.57) -0.31 (-1.09, 0.46)	0.7 0.81
Rodriguez-Porcel 2011 Female FLX Rayen 2011 Male no stress			-0.29 (-1.15, 0.57) -0.27 (-1.15, 0.62)	0.72 0.7
Hansen 1997 5 mg/kg Hansen 1997 30 mg/kg			-0.23 (-1.17, 0.71) -0.14 (-1.14, 0.86)	0.65 0.6
Knaepen 2013 Stress Hansen 1997 20 mg/kg			-0.13 (-1.12, 0.85) -0.13 (-1.09, 0.83)	0.62 0.64
Nagano 2012 No stress Gobinath 2016 Male no stress			-0.1 (-0.78, 0.57) -0.1 (-1.16, 0.96)	0.93
Altieri 2015 Female cohort 3 FLX			0.01 (-0.84, 0.87)	0.72
Simpson 2011 Female Hansen 1997 10 mg/kg			0.04 (-0.67, 0.76) 0.08 (-0.87, 1.04)	0.87 0.64
Khatri 2014 Cohort 2 Rodriguez-Porcel 2011 Female CIT	+ <del>\</del>		0.09 (-0.45, 0.63) 0.09 (-0.77, 0.95)	1.1 0.72
Rebello 2014 Exposure P12-P21 Nagano 2017 Male ESC			0.14 (-0.48, 0.76) 0.22 (-0.93, 1.38)	0.99
Boulle 2016b Stress Rayen 2011 Male stress			0.22 (0.05, 1.05) 0.24 (-0.56, 1.05) 0.28 (-0.61, 1.16)	0.78
Nagano 2012 Stress			0.33 (-0.35, 1.01)	0.92
Knaepen 2013 No stress Sarkar 2014b Cohort 2	 + -◆		0.37 (-0.62, 1.36) 0.48 (-0.41, 1.37)	0.61 0.69
Rayen 2011 Female no stress Boulle 2016a Stress			0.51 (-0.38, 1.41) 0.64 (-0.15, 1.43)	0.69 0.79
Gobinath 2016 Female no stress Sarkar 2014b Cohort 4			0.66 (-0.41, 1.73) 0.74 (-0.45, 1.93)	0.55 0.48
Hilakivi 1988a Maciag 2006b			1.25 (-0.03, 2.54) 1.32 (-0.12, 2.77)	0.42 0.35
macial 20000				11.2.2

	A. Anxiety				ight	B. Anxiety -	- Sex				Neight
	Comparison				(%)	Comparison			1		
	Francis-Oliveira 2013 Female P35		-1.5	1 (-2.66, -0.36)	0.56	da Silva 2014				-1.5 (-2.85, -0.15)	0.45
	Noorlander 2008 FLX 0.8 mg/kg cohort 1		-15	(-2 77 -0 22)	0.49	Francis-Oliveira 2013 Male I	P35			-0.85 (-1.89, 0.18)	) 0.64
	Ishikawa 2017 Nagano 2017 Female ESC bioRxiv prep	rint doi: https://doi.	.org/10.1101/868265; th	is versior	n₿ĝost		2019. The copyright	holder	for this preprint (which v	Nas (-1.31, -0.08)	0.77
	Noorlander 2008 FLX 0.8 mp of coertified	by peer review) is	-the author/funder, who	has_grant	ted bio	ORixivoa license to	o display the preprint	in perp	etuity. It is made availa	-0.58 (-1.74, 0.59)	0.66
	Noorlander 2008 FLV			9 (-1.86, 0.28)	0.62	Rayen 2011 Male No stress	license.	`		-0.55 (-1.5, 0.39)	0.71 0.42
	Altieri 2015 Female P50		-0.7	3 (-1.56, 0.1)	0.82	Altieri 2015 Male P90 ESC	ig/kg	÷		-0.53 (-1.38, 0.33)	) 0.79
	Altieri 2015 Male P300 ESC Kiryanova 2014					Nagano 2012 Stress				-0.46 (-1.14, 0.22)	) 0.97
	Altieri 2015 Male P50 Grimm 1987 Exposure G10-G20							<b>↔</b>		-0.43 (-1.46, 0.6)	0.65
	Hilakivi 1988a OF		0.5	8 (-1.74, 0.59)	0.55					-0.31 (-1.31, 0.69)	
	Capello 2011 Male 11-12 mg/kg		-0.5	3 (-1.95, 0.9)	0.42	Matsumoto 2016 Male NSF	P75				0.81
	Noorlander 2008 FLX 0.3 mg/kg		-0.5	3 (-1.57, 0.52)	0.63	Gobinath 2016 Male Stress				-0.28 (-1.3, 0.74)	0.66
	McAllister 2012 Zohar 2016 Male Stress		-0.4 -0.4			Capello 2011 Male 8 mg/kg	I			-0.26 (-1.57, 1.05)	) 0.47
	Nagano 2012 Stress Noorlander 2008 ELX 0.6 mg/kg		-0.4	6 (-1.14, 0.22)	0.97	Nagano 2017 Male FLX				-0.21 (-1.28, 0.87)	) 0.61
	Harris 2012 10 mg/kg		0.4	3 (-1.49, 0.62)	0.63					-0.18 (-1, 0.64)	0.83
	Harris 2012 5 mg/kg		-0.4	3 (-1.46, 0.6)	0.65	Ansorge 2008			<u>≯</u> ≯		1.14
	Karpova 2009		0.4 -0.3			Gobinath 2016 Male No stre	ess		di		0.63
	Pivina 2011 PRX Matsumoto 2016 Male NSF		0.3			Kiryanova 2016 No stress				-0.05 (-0.71, 0.62)	) 1.00
	Gobinath 2016 Female Stress Matsumoto 2016 Female NSE		-0.2	9 (-1.33, 0.75)	0.64	Bourke 2013 Stress				-0.02 (-1.16, 1.11)	) 0.58
	Francis-Oliveira 2013 Male P75		0.2	9 (-1.17, 0.59)	0.77	Bairy 2007 Male P30 8 mg/k				0 (-1.2, 1.2)	0.53
	Altieri 2015 Female P300 ESC		-0.2	7 (-1.16, 0.61)	0.77	Altieri 2015 Male P300 FLX	/kg		<b>◆</b>	0.05 (-0.83, 0.93)	0.77
	Hansen 1997 20 mg/kg			6 (-1.22, 0.7)	0.70				¢ ∲	0.07 (-0.66, 0.8)	0.92
	Capello 2011 Male 8 mg/kg Ehrlich 2015 Stress P90		-0.2			Altieri 2015 Male P90 FLX		_	<b>♦</b>		0.93
	Coleman 1999 Female Rayen 2011 Male Stress		0.2	6 (-1.08, 0.57)	0.83	Sprowles 2016 Male		_	è	0.17 (-0.59, 0.94)	
	Nagano 2017 Male FLX		-0.2	1 (-1.28, 0.87)	0.61	Salari 2016 No stress		_	Ě	0.2 (-0.79, 1.18)	0.68
	Hansen 1997 30 mg/kg			9 (-1.19, 0.81)	0.67	Olivier 2011 Male OF		_	÷	0.27 (-0.54, 1.07)	0.84
am         am         am         am         bit         bit<	Coleman 1999 Male					Bourke 2013 No stress			+ <u></u>	0.37 (-0.77, 1.52)	0.57
Some 2.00         Some 2.00 <t< td=""><td>Ehrlich 2015 No stress P90 Harris 2012 20 mg/kg</td><td></td><td></td><td></td><td></td><td></td><td>kg</td><td></td><td></td><td></td><td>0.52 1.11</td></t<>	Ehrlich 2015 No stress P90 Harris 2012 20 mg/kg						kg				0.52 1.11
Description         Output         Output        Output         Outpu         Outp	Ansorge 2008		-0.1	(-0.64, 0.44)			1	-			
abade Sing Sing Sing Sing Sing Sing Sing Sing	Sprowles 2017 FLX		-0.0	9 (-0.61, 0.43)	1.17	Toffoli 2014		-		0.66 (-0.25, 1.56)	0.75
Biosocial Displace         BiosociaDisplace         BiosociaD	Gobinath 2016 Male No stress		-0.0	6 (-1.11, 1)	0.63	Rodriguez-Porcel 2011 Male	e FLX		l →	0.67 (-0.16, 1.49)	0.83
manuage base         manuage base<	Boulle 2016a Stress Kiryanova 2016 No stress					Bairy 2007 Male P56 12 mg	/kg	_		0.85 (-0.42, 2.12)	0.49
bak 2014 M 2 mg	Kiryanova 2016 Stress Ansorge 2004					Simpson 2011 Male				1.05 (0.28, 1.82)	0.88
Bases Mar Jong         Inc. Act of Jong <td>Bourke 2013 Stress Bairy 2007 Male P30.8 mg/kg</td> <td></td> <td>-0.0</td> <td>02 (-1.16, 1.11)</td> <td></td> <td></td> <td>e CIT</td> <td></td> <td></td> <td></td> <td>0.78 0.65</td>	Bourke 2013 Stress Bairy 2007 Male P30.8 mg/kg		-0.0	02 (-1.16, 1.11)			e CIT				0.78 0.65
Date:         Dot:         Dot: <thdo:< th="">         Dot:         Dot:         <thd< td=""><td>Hansen 1997 5 mg/kg</td><td></td><td> 0 (-0</td><td>0.94, 0.94)</td><td>0.72</td><td></td><td></td><td></td><td></td><td></td><td>0.61 0.64</td></thd<></thdo:<>	Hansen 1997 5 mg/kg		0 (-0	0.94, 0.94)	0.72						0.61 0.64
amb         amb         bits         b	Boulle 2016b Stress		- 0 (-0	0.8, 0.8)	0.85					1.32 (0.4, 2.23)	0.74 0.63
mail         mail <td< td=""><td>Lisboa 2007 Female</td><td></td><td></td><td></td><td></td><td>Hilakivi 1988a FT</td><td></td><td></td><td>÷</td><td>1.37 (0.05, 2.68)</td><td>0.47</td></td<>	Lisboa 2007 Female					Hilakivi 1988a FT			÷	1.37 (0.05, 2.68)	0.47
000000000000000000000000000000000000	Olivier 2011 Female Popa 2008					Sarkar 2014b Cohort 2				1.45 (0.44, 2.47)	0.66
Bale         Outer Add 20.00         Dist         Dist <thdis< th=""> <thdis< th="">         Dist</thdis<></thdis<>	Bairy 2007 Male P30 12 mg/kg Raven 2011 Female No stress					Ko 2014				2.74 (1.27, 4.21)	0.40
Name         Open Set 20, 20, 20, 20, 20, 20, 20, 20, 20, 20,	Rebello 2014 Exposure P2-P21		- 0.04	4 (-0.58, 0.66)	1.05	Male			•	0.17 (-0.01, 0.34)	) 50.36
Buck 2016 hosters         Obsector         Obsector <td>Altieri 2015 Female P90 FLX</td> <td></td> <td>- 0.05</td> <td>5 (-0.7, 0.79)</td> <td>0.91</td> <td>Noorlander 2008 FLX 0.8 m</td> <td></td> <td><u>→</u></td> <td></td> <td>-0.87 (-2.42, 0.68)</td> <td>) 0.37</td>	Altieri 2015 Female P90 FLX		- 0.05	5 (-0.7, 0.79)	0.91	Noorlander 2008 FLX 0.8 m		<u>→</u>		-0.87 (-2.42, 0.68)	) 0.37
Party 2011 PL         Both and 2011 PL 20	Boulle 2016b No stress		- 0.06	5 (-0.74, 0.86)	0.85	Noorlander 2008 FLV					
G4 002         007 (45,0,0,0)<	Meyer 2018									-0.53 (-1.57, 0.52)	) 0.63
byen 2011 Francis Stress	Lee 2012 Altieri 2015 Male P90 FLX					Rebello 2014 Exposure P12	-P21			-0.43 (-1.06, 0.2)	1.04
minutes         011 (col. 18.0 )         04         Mayer 2010         011 (col. 18.0 )         011 (col. 18	Rayen 2011 Female Stress			9 (-0.84, 1.01)	0.73	Ansorge 2004				-0.04 (-0.74, 0.66)	) 0.95
pionete 2010 fm. 1007 F2 proves P4P3	Simpson 2011 Female		- 0.11	1 (-0.61, 0.82)	0.94	Meyer 2018	P21	_	<b>◆</b>	0.07 (-0.5, 0.64)	1.10
digment 2017 Bless         Option 2017 Bless	Sprowles 2017 CIT		- 0.13	3 (-0.39, 0.64)	1.17	Forcelli 2008			<u>♦</u>	0.2 (-0.14, 0.55)	1.38
slal 2016 bastres	Kiryanova 2017b Stress						28				0.86
Greell 2006         0.2 (21,42,53)         1.38         Path 2014 Cohort 2         0.7 (0,12,13)	Zheng 2011 FLX Salari 2016 No stress							-			0.88 0.97
Jinker 2011 Mark 06       0.27 (= 54, 1/27)       0.24       0.24 (= 54, 1/27)       0.24       0.24 (= 54, 1/27)       0.24       0.24 (= 54, 1/27)       0.24 (= 17, 1/28)       0.24 (	Forcelli 2008		- 0.2	(-0.14, 0.55)	1.38	Khatri 2014 Cohort 2				0.73 (0.12, 1.33)	1.06
htthch.2015 Stress P32       0       029 (4,7,1,28)       0.60       02 (4,7,1,28)       0.60       0.71 (7,1,10)       0.60         applie 3011 Frends (0)       0.81 (4,7,1,50) <td>Olivier 2011 Male OF</td> <td></td> <td> 0.27</td> <td>7 (-0.54, 1.07)</td> <td>0.84</td> <td>Rebello 2014 Exposure P2-F</td> <td>P11</td> <td></td> <td></td> <td>0.85 (0.21, 1.5)</td> <td>1.02</td>	Olivier 2011 Male OF		0.27	7 (-0.54, 1.07)	0.84	Rebello 2014 Exposure P2-F	P11			0.85 (0.21, 1.5)	1.02
roladina 2014       -       <	Ehrlich 2015 Stress P32		0.29	9 (-0.7, 1.28)	0.68	Yu 2012				0.94 (0.18, 1.7)	0.89
japello 2011 Female Sing/Ag <ul> <li>Algano 2017 Female SC</li> <li>Contro 2013 Female Sc</li> <li>Contro 2014 Female Sc</li> <li>Contro</li></ul>	Volodina 2014		- 0.31	1 (-0.15, 0.78)	1.23	Francis-Oliveira 2013 Femal	le P35			-1.51 (-2.66, -0.36	6) 0.56
Darbe 2013 No stress         0.37 (0.27, 152)         257         Aller 2015 Female F50         0.47 (1.52, 0.29)         0.47 (1.52, 0.52)         0.47 (1.52, 0.52)         0	Capello 2011 Female 8 mg/kg Nagano 2012 No stress		0.33	3 (-0.98, 1.65)		Zohar 2016 Female Stress	-		† †	-0.73 (-1.56, 0.1)	
Diag 2012         Control (1, 28, 0, 49)         Out (1, 28,	Bourke 2013 No stress Bairy 2007 Male P56 8 mg/kg		0.37	7 (-0.77, 1.52)	0.57	McAllister 2012				-0.47 (-1.17, 0.22)	) 0.96
min b a construction         0.5 (12.8, 11.9)         0.9         Alter 2015 Fernale NS Fer         -0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.22 (1.13, 0.55)         0.23 (1.04, 0.5)         0.23 (1.04, 0.5) <td>Soga 2012</td> <td></td> <td>- 0.42</td> <td>2 (-0.15, 0.99)</td> <td>1.11</td> <td>Rodriguez-Porcel 2011 Fem</td> <td></td> <td></td> <td></td> <td>-0.41 (-1.28, 0.46)</td> <td>) 0.78</td>	Soga 2012		- 0.42	2 (-0.15, 0.99)	1.11	Rodriguez-Porcel 2011 Fem				-0.41 (-1.28, 0.46)	) 0.78
Community D10 Fermale PLX         Output	Lee 2009		→ 0.5	(-0.28, 1.27)	0.88	Matsumoto 2016 Female N	ISF			-0.29 (-1.13, 0.55)	) 0.81
Attack Dep Marke EPM       0.05 (10.00 - 0.07 0.00 - 0.00 0.07 0.00 0.07 0.00 0.00	Gobinath 2016 Female No stress		♦─── 0.63	3 (-0.44, 1.7)	0.62	Nagano 2017 Female FLX				-0.27 (-1.31, 0.77)	) 0.64
iording 2014       0.66 (-0.25, 1.56)       0.75       Alteriz 2015 Female P300 FLX       0.21 (-107, 0.66)       0.20 (-107, 0.76)       0.20 (-107, 0.76)       0.20 (-1	Bairy 2007 Female P56 12 mg/kg Matsumoto 2016 Male EPM		→ 0.65	5 (-0.26, 1.55)	0.75	Coleman 1999 Female		$\rightarrow$		-0.26 (-1.08, 0.57)	) 0.83
bodriguez-Porcel 2011 Male FLX       0.67 (c.0.6, 1,49)       0.88       Enrich 2015 No stress PPO       -0.13 (0.95, 0.09 0.65         francis Oliviera 2013 Female P75       0.07 (c.0.6, 1,60       0.7       -0.07 (0.98, 0.80       0.55         francis Oliviera 2013 Female P75       0.07 (c.0.6, 1,59)       0.81       Bolle 2016 Stress       -0.07 (0.98, 0.80       0.55         francis Oliviera 2013 Female P30 ESC       0.07 (c.0.6, 1,59)       0.81       Bolle 2016 Stress       0.06 (0.80, 0.80       0.55         francis Oliviera 2013 Female P30 Brg/kg       0.07 (c.0.6, 1,59)       0.81       Balry 2007 Female P30 Brg/kg       0.01 (c.1.2, 1.2)       0.55         francis Oliviera 2011 Female P55       0.07 (c.0.6, 1,59)       0.81       Balry 2007 Female P30 Brg/kg       0.01 (c.6.7, 0.72)       0.55         francis Oliviera 2011 Female P55 L2 mg/kg       0.081 (c.0.2, 1.21)       0.05       0.03 (c.6.7, 0.72)       0.55         francis Oliviera 2011 Female No stress       0.00 (c.6.7, 0.72)       0.55       0.03 (c.6.7, 0.72)       0.55         francis Oliviera 2011 Female P30 L2 mg/kg       0.04 (c.0.8, 0.96)       0.05 (c.7, 0.72)       0.55       0.004 (c.0.8, 0.96)       0.03 (c.6.7, 0.72)       0.55         francis Oliviera 2011 Female P30 L2 mg/kg       0.04 (c.0.8, 0.96)       0.03 (c.6.7, 0.72)       0.55       0.03 (c.6.7, 0.72) <td>Toffoli 2014 Zohar 2016 Male No stress</td> <td></td> <td>-♦ 0.66</td> <td>5 (-0.25, 1.56)</td> <td>0.75</td> <td>Zohar 2016 Female No stres</td> <td></td> <td></td> <td></td> <td>-0.18 (-0.99, 0.62)</td> <td>) 0.85</td>	Toffoli 2014 Zohar 2016 Male No stress		-♦ 0.66	5 (-0.25, 1.56)	0.75	Zohar 2016 Female No stres				-0.18 (-0.99, 0.62)	) 0.85
hydrod 201/0 No Stess       0.7 (-0.26, 1.69)       0.7 (-0.26, 1.69)       0.7 (-0.26, 0.68)       0.6         pipowles 2016 Female       0.7 (-0.26, 0.68)       0.7 (-0.26, 0.68)       0.8       0.6	Rodriguez-Porcel 2011 Male FLX		-> 0.67	7 (-0.16, 1.49)	0.83	Francis-Oliveira 2013 Femal		$\square$	<del>}</del>	-0.1 (-0.98, 0.78)	0.77
Difference         Difference         Difference         Difference         Part of the second se	Khatri 2014 Cohort 2		→ 0.73	3 (0.12, 1.33)	1.06	Altieri 2015 Female P90 ESC			₩ <u> </u>	-0.07 (-0.83, 0.68)	
MaskUndo 2010 Female       0.03 (-0.76, 0.82)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.04 (-0.98, 0.03)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-0.76, 0.82)       0.06 (-	Khatri 2014 Cohort 1	-	→ 0.76	5 (0.44, 1.09)	1.40	Bairy 2007 Female P30 8 mg	g/kg na/ka		<u></u>	0 (-1.2, 1.2)	0.53
Sainy 2007 Male PS6 12 mg/kg       088 (-0.42, 2.12)       0.49       Olivier 2011 Female       003 (-0.85, 0.02)       0.5         Rebello 2014 Exposure P2-P11       0.86 (-0.42, 2.12)       0.49       Olivier 2011 Female No stress       0.04 (-0.88, 0.96)       0.7         SimP.Signer D212       0.86 (0.01, 7)       0.80       0.04       0.86 (-0.01, 7)       0.80       0.04 (-0.88, 0.96)       0.7         Simp 2007 Female PS6 8 mg/kg       0.86 (-0.39, 2.16)       0.49       0.416, 7)       0.89       0.04 (-0.48, 0.49, 0.22)       0.46 (-0.49, 1.02)       0.46 (-0.49, 1.02)       0.46 (-0.49, 1.02)       0.46 (-0.49, 1.02)       0.46 (-0.49, 1.02)       0.46 (-0.49, 1.02)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.46 (-0.49, 1.02)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.46 (-0.49, 1.02)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.46 (-0.49, 1.02)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.46 (-0.44, 1.01)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.46 (-0.44, 1.01)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.87 (-0.44, 1.01)       0.66 (-0.74, 0.86)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12)       0.86 (-0.42, 2.12) <td< td=""><td>Matsumoto 2016 Female EPM Nagano 2017 Male ESC</td><td></td><td></td><td></td><td></td><td>Lisboa 2007 Female</td><td></td><td></td><td><u>}</u></td><td>0.03 (-0.76, 0.82)</td><td>0.86</td></td<>	Matsumoto 2016 Female EPM Nagano 2017 Male ESC					Lisboa 2007 Female			<u>}</u>	0.03 (-0.76, 0.82)	0.86
imit-figure 2012       086 (001, 1.7)       080       halve 2011 Female No stress       0.04 (0.28, 0.39)       0.05 (0.27, 0.27)       0.05 (0.27, 0.27)       0.05 (0.27, 0.27)       0.05 (0.27, 0.27)       0.05 (0.27, 0.27)       0.05 (0.27, 0.27)       0.04 (0.28, 0.39)       0.04 (0.28, 0.39)       0.04 (0.28, 0.39)       0.04 (0.28, 0.39)       0.04 (0.28, 0.39)       0.04 (0.28, 0.39)       0.04 (0.21, 0.27)       0.04 (0.21, 0.27)       0.04 (0.21, 0.27)       0.01 (0.02, 0.27)       0.01 (0.02	Bairy 2007 Male P56 12 mg/kg Rebello 2014 Exposure P2-P11			5 (-0.42, 2.12)	0.49	Popa 2008		_	<b>—</b>	0.03 (-0.67, 0.72)	
Yu 2012       →       0.94 (0.18, 1.7)       0.89       Boulle 2016 bh o stress       0.06 (0.7, 0.39)       0.55         Jimps 2009       →       1.05 (0.28, 1.82)       0.88       Boulle 2016 bh o stress       0.06 (0.7, 0.39)       0.55         Kodriguez-Porcel 2011 Male CTT       →       1.05 (0.28, 1.82)       0.88       Simpson 2011 Female Stress       0.01 (0.6, 0.82)       0.65         Jihier 2011 Male CTT       →       1.21 (0.2, 2.40)       0.78       Capello 2011 Female Stress       0.01 (0.7, 0.39)       0.51 (0.82)       0.61 (0.7, 0.39)       0.53         Jihier 2011 Male CTT       →       1.17 (0.3, 2.04)       0.78       Capello 2011 Female Stress       0.01 (0.7, 0.37)       0.01 (0.7, 0.37)       0.01 (0.62)       0.05         Jihier 2011 Male NSF       →       1.23 (0.2, 2.37)       0.61       Boulle 2017 Stress Stress       0.01 (0.7, 1.28)       0.01 (0.7, 1.28)       0.01 (0.7, 1.28)       0.01 (0.7, 1.28)       0.01 (0.7, 1.28)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.28)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01 (0.7, 0.27)       0.01	Smit-Rigter 2012		0.86	5 (0.01, 1.7)	0.80	Ehrlich 2015 No stress P32			-	0.04 (-0.94, 1.02)	0.69
iang 2009       impson 2011 Male       impson 2011 Male Stress       009 (-094, 101)       0.7         ibngson 2011 Male       impson 2011 Male       impson 2011 Kemale Stress       0.11 (-061, 0.82)       0.85         ibngson 2011 Male       impson 2011 Male       impson 2011 Kemale       0.11 (-061, 0.82)       0.55         ibngson 2011 Male       impson 2011 Male       impson 2011 Female Stress       0.11 (-061, 0.82)       0.55         ibne 2014 Male NSF       impson 2017 Stress S12       0.11 (-061, 0.82)       0.55       0.55       0.11 (-061, 0.82)       0.55         ibne Filal 2011       impson 2017 Stress S12       0.11 (-061, 0.82)       0.57       0.11 (-061, 0.82)       0.57         ibne Filal 2011       impson 2017 Stress S12       0.11 (-061, 0.82)       0.29 (-07, 1.28)       0.63       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       0.64       0.29 (-07, 1.28)       <	Yu 2012			4 (0.18, 1.7)	0.89	Boulle 2016b No stress	K	_	<b>←</b>		0.91 0.85
todriguez-Porcel 2011 Male CIT       Image: Constraint 2014b Cohort 3       I	Jiang 2009 Simpson 2011 Male				0.88	Rayen 2011 Female Stress			<b>↓</b>	0.09 (-0.84, 1.01)	0.73
Divier 2011 Male NSF <ul> <li>128 (0.2, 2.37)</li> <li>0.61</li> <li>131 (0.27, 2.35)</li> <li>0.61</li> <li>6.7, 126</li> <li>0.61</li> <li>0.62</li> <li>0.61</li> <li>0.62</li> <li>0.61</li> <li>0.62</li> <li>0.62</li> <li>0.61</li> <l< td=""><td>Rodriguez-Porcel 2011 Male CIT Sarkar 2014b Cohort 3</td><td></td><td></td><td>7 (0.3, 2.04)</td><td>0.78</td><td>Capello 2011 Female 11-12</td><td>mg/kg</td><td></td><td><u>k</u></td><td>0.11 (-1.28, 1.5)</td><td>0.44</td></l<></ul>	Rodriguez-Porcel 2011 Male CIT Sarkar 2014b Cohort 3			7 (0.3, 2.04)	0.78	Capello 2011 Female 11-12	mg/kg		<u>k</u>	0.11 (-1.28, 1.5)	0.44
Antie-Filial 2011       Image: 1 a 2 (0,4,2.23)       0,74       Capello 2011 Female 8 mg/kg       0,31 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,43 (0,98, 165)       0,44 (1,7)       0,63 (0,44, 17)       0,64 (0,6) (1,60, 17)       0,63 (0,44, 17)       0,63 (0,44, 17)       0,63 (0,44, 17)       0,63 (0,44, 17)       0,64 (0,6) (1,60, 17)       0,74 (0,61,88)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,80, 01)       0,74 (0,61,17)       0,74 (0,61,17)       0,74 (0,61,17)       0,76 (0,61,17)       0,76 (0,61,17)       0,74 (0,61,17)       0,74 (0,61,17)       0,74 (0,61,17)       0,74 (0,61,17)	Olivier 2011 Male NSF			8 (0.2, 2.37)	0.61	Ehrlich 2015 Stress P32	aala CIT	_		0.29 (-0.7, 1.28)	0.68
iardar 2014b Cohort 1       i i i i i i i i i i i i i i i i i i i	Mnie-Filali 2011	-		2 (0.4, 2.23)	0.74	Capello 2011 Female 8 mg/	/kg			0.33 (-0.98, 1.65)	
iarkar 2014b Cohort 4       -       1.37 (0.06, 2.69)       0.47       Kiryanova 2017b No stress       0.7 (-0.26, 1.66)       0.7         iarkar 2014b Cohort 2       -       1.45 (0.44, 2.47)       0.66       Sprowles 2015 Female       0.7 (-0.26, 1.66)       0.7         iarkar 2014b Cohort 2       -       1.78 (0.47, 3.0)       0.48       Matsumoto 2016 Female EPM       0.76 (-0.08, 1.59)       0.88 (-0.33, 2.16)       0.47         iarkar 2014b Cohort 2       -       2.74 (1.27, 4.21)       0.40       Baity 2007 Female P56 8 mg/kg       0.79 (-0.26, 1.66)       0.77       0.79 (-0.31, 1.77)       0.77         iarkar 2014 Cohort 2       -       2.74 (1.27, 4.21)       0.40       Baity 2007 Female P56 8 mg/kg       0.79 (-0.61, 8.01) 29.3       0.88 (-0.39, 2.16)       0.4         ivina 2011 FLX       -       3.92 (2.12, 5.72)       0.29       Female       -0.04 (-0.18, 0.1) 29.3       -0.04 (-0.18, 0.1) 29.3         ivinity - Overall       0.1 (0, 0.21)       100.00       Anxiety - Overall       0.1 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0.01 (0, 0.21)       0	Hilakivi 1988a FT			7 (0.05, 2.68)	0.47	Gobinath 2016 Female No s Bairy 2007 Female P56 12 m	stress	_		0.63 (-0.44, 1.7)	0.62 0.51
instar	Sarkar 2014b Cohort 4 Sarkar 2014b Cohort 2			7 (0.06, 2.69)	0.47	Kiryanova 2017b No stress	-	-		0.7 (-0.26, 1.66)	0.70
Pivina 2011 FLX	Sarkar 2014a Cohort 2	-		8 (0.47, 3.08)	0.48	Matsumoto 2016 Female EF				0.79 (-0.13, 1.7)	0.74
	Pivina 2011 FLX			2 (2.12, 5.72)	0.29	Female	əə		•	-0.04 (-0.18, 0.1)	29.30
	-	4 -3 -2 -1 0		(0, 0.21) 1(	00.00	- malety - Overall	-5 -4 -3	2 -1		0.1(0,0.21)	100.00

 $\stackrel{1}{\leftarrow} \stackrel{1}{\leftarrow} \stackrel{1}{\leftarrow} \stackrel{1}{\phantom{\leftarrow}} \stackrel{1}\phantom{\phantom}} \stackrel{1}{\phantom{\leftarrow}} \stackrel{1}\phantom{\phantom}} \stackrel{1}\phantom{\phantom}} \stackrel{1}\phantom{\phantom}} \stackrel{1}\phantom{\phantom}} \stackrel$ 

	Stress exposure	e			eight	D. Anxiety -	SSRI exp	osure peri	iod		eight
Comparison Francis-Oliveira 2013 Female P	235			(95% CI)		Comparison Noorlander 2008 FLX 0.8 mg	/kg cohort 1		1	SMD (95% CI) -1.5 (-2.77, -0.22)	(%)
da Silva 2014			-1.5 (-2	.85, -0.15)	0.45	Noorlander 2008 FLX 0.8 mg, Noorlander 2008 FLX 0.8 mg,			1 2 1	-0.87 (-2.42, 0.68)	0.37
Noorlander 2008 FLX 0.8 mg/k Ishikawa 2017	-	←	1 10 /	.77, -0.22) -2.02, -0.36)	0.49 0.82	Grimm 1987 Exposure G10-G	520	~	1	-0.79 (-1.86, 0.28) -0.59 (-1.6, 0.42)	0.62 0.66
Nagano 2017 Female ESC Noorlander 2008 FLX 0.8 mg/k	Rxiv, preprint doi: http	o <mark>ŝ;//do</mark> i.	org/10.1101/868265; this: the author/funder, who has under a	versior	n þjós	teo December 0.6mg	19. The cor	oyright holder	or this preprint (which w	Vas (-1.95, 0.9)	0.42 0.63
Francis-Oliveira 2013 Male	t certified by peer rev	iew) is	the author/funder, who ha	S801200			display the p	preprint in perp	etuity. It is made availa	0.26 (-1.53, 0.65)	0.60 0.47
Altieri 2015 Female P50 Altieri 2015 Male P300 ESC	_	$\rightarrow$		1.75, 0.29)	0.65	Ehrlich 2015 Stress P90 Coleman 1999 Female	license.		0 0	-0.26 (-1.06, 0.55) -0.26 (-1.08, 0.57)	0.84 0.83
Kiryanova 2014	_		-0.7 (-1	-1.6, 0.17) .31, -0.08)	1.05	Coleman 1999 Male		$\rightarrow$	0 0 0	-0.18 (-1, 0.64)	0.83
Altieri 2015 Male P50 Grimm 1987 Exposure G10-G20	.0 —	$\rightarrow$		1.6, 0.42) 1.6, 0.42)	0.66 0.66	Ehrlich 2015 No stress P90 Bourke 2013 Stress			<u>+</u>	-0.13 (-0.95, 0.69) -0.02 (-1.16, 1.11)	0.83 0.58
Hilakivi 1988a OF Rayen 2011 Male No stress		$\rightarrow$		1.74, 0.59) 1.5, 0.39)	0.55 0.71	Bairy 2007 Female P30 12 mg Bairy 2007 Male P30 8 mg/kg				0 (-1.2, 1.2) 0 (-1.2, 1.2)	0.53 0.53
Capello 2011 Male 11-12 mg/k Altieri 2015 Male P90 ESC	۰		-0.53 (-	1.95, 0.9) 1.38, 0.33)	0.42 0.79	Bairy 2007 Female P30 8 mg/ Olivier 2011 Female			<u> </u>	0 (-1.2, 1.2) 0.03 (-0.85, 0.9)	0.53 0.77
Noorlander 2008 FLX 0.3 mg/kg	kg —		-0.53 (-	1.57, 0.52)	0.63	Bairy 2007 Male P30 12 mg/k Ehrlich 2015 No stress P32	٨g		<u> </u>	0.04 (-1.16, 1.24) 0.04 (-0.94, 1.02)	0.53
McAllister 2012 Noorlander 2008 FLX 0.6 mg/k	kg –		-0.47 (-	1.17, 0.22) 1.53, 0.65)	0.96 0.60	Capello 2011 Female 11-12 n	ng/kg		\$	0.11 (-1.28, 1.5)	0.44
Harris 2012 10 mg/kg Rebello 2014 Exposure P12-P2	-	$\rightarrow$	-0.43 (- -0.43 (-	1.49, 0.62) 1.06, 0.2)	0.63 1.04	Olivier 2011 Male OF Ehrlich 2015 Stress P32				0.27 (-0.54, 1.07) 0.29 (-0.7, 1.28)	0.84 0.68
Harris 2012 5 mg/kg Rodriguez-Porcel 2011 Female		<u></u>	-0.43 (-	1.46, 0.6) 1.28, 0.46)	0.65 0.78	Capello 2011 Female 8 mg/k Bourke 2013 No stress	g			0.33 (-0.98, 1.65) 0.37 (-0.77, 1.52)	0.47 0.57
Karpova 2009			-0.34 (-	1.21, 0.54)	0.78	Bairy 2007 Male P56 8 mg/kg Bairy 2007 Female P56 12 mg				0.4 (-0.82, 1.61) 0.64 (-0.6, 1.88)	0.52
Matsumoto 2016 Male NSF Matsumoto 2016 Female NSF		$\rightarrow$	-0.3 (-1	.14, 0.55) 1.13, 0.55)	0.81 0.81	Bairy 2007 Male P56 12 mg/k		_		0.85 (-0.42, 2.12)	0.49
Francis-Oliveira 2013 Male P75 Altieri 2015 Female P300 ESC	5			1.17, 0.59) 1.16, 0.61)	0.77 0.77	Smit-Rigter 2012 Bairy 2007 Female P56 8 mg/	/kg	_		0.86 (0.01, 1.7) 0.88 (-0.39, 2.16)	0.80 0.49
Nagano 2017 Female FLX Hansen 1997 20 mg/kg			-0.27 (-	1.31, 0.77) 1.22, 0.7)	0.64 0.70	Olivier 2011 Male NSF Prenatal				1.28 (0.2, 2.37) 0.01 (-0.18, 0.21)	0.61 18.19
Capello 2011 Male 8 mg/kg	-		-0.26 (-	1.57, 1.05)	0.47	Salari 2016 Stress Francis-Oliveira 2013 Female	P35			-3.02 (-4.57, -1.46) -1.51 (-2.66, -0.36)	
Coleman 1999 Female Nagano 2017 Male FLX			-0.21 (-	1.08, 0.57) 1.28, 0.87)	0.61	Francis-Oliveira 2013 Male P Zohar 2016 Female Stress			- 	-0.85 (-1.89, 0.18)	0.64
Altieri 2015 Female P300 FLX Hansen 1997 30 mg/kg			-0.19 (-	1.07, 0.66) 1.19, 0.81)	0.79 0.67	Kiryanova 2014		 		-0.73 (-1.56, 0.1) -0.7 (-1.31, -0.08)	0.82
Zohar 2016 Female No stress Coleman 1999 Male			-0.18 (-	0.99, 0.62)	0.85 0.83	McAllister 2012 Zohar 2016 Male Stress		 	1 1 1	-0.47 (-1.17, 0.22) -0.46 (-1.27, 0.35)	0.96 0.84
Ehrlich 2015 No stress P90 Harris 2012 20 mg/kg			-0.13 (-	-0.95, 0.69) -1.17, 0.92)	0.83	Matsumoto 2016 Male NSF Matsumoto 2016 Female NSF	F			-0.3 (-1.14, 0.55) -0.29 (-1.13, 0.55)	0.81 0.81
Ansorge 2008	26		0.1 (-0	.64, 0.44)	1.14	Francis-Oliveira 2013 Male P7 Zohar 2016 Female No stress	75		8 8	-0.29 (-1.17, 0.59) -0.18 (-0.99, 0.62)	0.77
Francis-Oliveira 2013 Female P Sprowles 2017 FLX	//5			0.98, 0.78) -0.61, 0.43)	0.77 1.17	Francis-Oliveira 2013 Female			0 0 0	-0.1 (-0.98, 0.78)	0.77
Altieri 2015 Female P90 ESC Gobinath 2016 Male No stress			-0.07 (-	0.83, 0.68) 1.11, 1)	0.90 0.63	Sprowles 2017 FLX Kiryanova 2016 No stress		 	+	-0.09 (-0.61, 0.43) -0.05 (-0.71, 0.62)	1.17 1.00
Kiryanova 2016 No stress Ansorge 2004		_}	-0.05 (-	0.71, 0.62)	1.00	Kiryanova 2016 Stress Lisboa 2007 Female			<u> </u>	-0.04 (-0.73, 0.64) 0.03 (-0.76, 0.82)	0.97 0.86
Bairy 2007 Female P30 8 mg/kg			0 (-1.2,	1.2)	0.53	Meyer 2018 Lisboa 2007 Male			Ģ	0.07 (-0.5, 0.64) 0.11 (-0.61, 0.83)	1.10 0.93
Bairy 2007 Female P30 12 mg/l Bairy 2007 Male P30 8 mg/kg	кg		0 (-1.2, 0 (-1.2, 0 (-1.2,	1.2)	0.53 0.53	Sprowles 2017 CIT		_	<u> </u>	0.13 (-0.39, 0.64)	1.17
Hansen 1997 5 mg/kg Lisboa 2007 Female			0 (-0.94 0.03 (-0	4, 0.94) 0.76, 0.82)	0.72 0.86	Sprowles 2016 Male Kiryanova 2017b Stress				0.17 (-0.59, 0.94) 0.19 (-0.73, 1.12)	0.88
Olivier 2011 Female Popa 2008			0.03 (-0	0.85, 0.9) 0.67, 0.72)	0.77	Salari 2016 No stress Forcelli 2008			¢	0.2 (-0.79, 1.18) 0.2 (-0.14, 0.55)	0.68 1.38
Bairy 2007 Male P30 12 mg/kg			0.04 (-1	1.16, 1.24)	0.53	Matsumoto 2016 Male EPM Toffoli 2014		=		0.65 (-0.26, 1.55) 0.66 (-0.25, 1.56)	0.75 0.75
Rayen 2011 Female No stress Rebello 2014 Exposure P2-P21		$\rightarrow$	0.04 (-0	0.88, 0.96) 0.58, 0.66)	0.73 1.05	Zohar 2016 Male No stress Kiryanova 2017b No stress		=		0.66 (-0.16, 1.49) 0.7 (-0.26, 1.66)	0.82 0.70
Ehrlich 2015 No stress P32 Altieri 2015 Female P90 FLX				0.94, 1.02) 0.7, 0.79)	0.69 0.91	Sprowles 2016 Female				0.76 (-0.08, 1.59)	0.81
Altieri 2015 Male P300 FLX Boulle 2016b No stress				0.83, 0.93) 0.74, 0.86)	0.77 0.85	Matsumoto 2016 Female EPA Pre- and postnatal	vi	•		0.79 (-0.13, 1.7) -0.06 (-0.25, 0.14)	
Zheng 2011 FLV			0.07 (-1	1.13, 1.27) 0.5, 0.64)	0.53	da Silva 2014 Ishikawa 2017				-1.5 (-2.85, -0.15) -1.19 (-2.02, -0.36)	0.45 0.82
Meyer 2018 Lee 2012		$\rightarrow$	0.07 (-0	0.66, 0.8)	0.92	Nagano 2017 Female ESC Altieri 2015 Female P50			0 0 0	-1 (-2.19, 0.18) -0.73 (-1.75, 0.29)	0.54 0.65
Altieri 2015 Male P90 FLX Lisboa 2007 Male		¢	0.11 (-0	0.78, 0.93) 0.61, 0.83)	0.79 0.93	Altieri 2015 Male P300 ESC Altieri 2015 Male P50				-0.72 (-1.6, 0.17) -0.59 (-1.6, 0.42)	0.77
Simpson 2011 Female Capello 2011 Female 11-12 mg	g/kg			0.61, 0.82) 1.28, 1.5)	0.94 0.44	Hilakivi 1988a OF		`		-0.58 (-1.74, 0.59)	0.55
Sprowles 2017 CIT Sprowles 2016 Male		-	- 0.13 (-0	0.39, 0.64) 0.59, 0.94)	1.17	Rayen 2011 Male No stress Altieri 2015 Male P90 ESC		$\rightarrow$		-0.55 (-1.5, 0.39) -0.53 (-1.38, 0.33)	0.71 0.79
Zheng 2011 FLX Salari 2016 No stress			0.2 (-1.	01, 1.4)	0.53	Nagano 2012 Stress Harris 2012 10 mg/kg				-0.46 (-1.14, 0.22) -0.43 (-1.49, 0.62)	0.97 0.63
Forcelli 2008		-0	- 0.2 (-0.	79, 1.18) 14, 0.55)	0.68 1.38	Rebello 2014 Exposure P12-P Harris 2012 5 mg/kg	21			-0.43 (-1.06, 0.2) -0.43 (-1.46, 0.6)	1.04 0.65
Hansen 1997 10 mg/kg Olivier 2011 Male OF		*		0.73, 1.19) 0.54, 1.07)	0.70 0.84	Rodriguez-Porcel 2011 Fema Karpova 2009	ale FLX		0 0 0	-0.41 (-1.28, 0.46) -0.34 (-1.21, 0.54)	0.78
Grimm 1987 Exposure P4-P8 Rodriguez-Porcel 2011 Female	• СП			0.5, 1.08) 57, 1.16)	0.86 0.79	Pivina 2011 PRX		~		-0.31 (-1.31, 0.69)	0.67
Volodina 2014 Capello 2011 Female 8 mg/kg		+0	→ 0.31 (-0	0.15, 0.78) 0.98, 1.65)	1.23 0.47	Gobinath 2016 Female Stress Gobinath 2016 Male Stress			1 1 1	-0.29 (-1.33, 0.75) -0.28 (-1.3, 0.74)	0.64 0.66
Nagano 2012 No stress			>→ 0.36 (-0	0.32, 1.04)	0.98	Altieri 2015 Female P300 ESC Nagano 2017 Female FLX	2			-0.27 (-1.16, 0.61) -0.27 (-1.31, 0.77)	0.77 0.64
Bourke 2013 No stress Bairy 2007 Male P56 8 mg/kg				0.77, 1.52) 82, 1.61)	0.57 0.52	Hansen 1997 20 mg/kg Rayen 2011 Male Stress			5 5 7	-0.26 (-1.22, 0.7) -0.24 (-1.17, 0.68)	0.70 0.73
Soga 2012 Boulle 2016a No stress		+		0.15, 0.99) 0.31, 1.26)	1.11 0.87	Nagano 2017 Male FLX Altieri 2015 Female P300 FLX	,		0 0 0	-0.21 (-1.28, 0.87) -0.21 (-1.07, 0.66)	0.61 0.79
Lee 2009 Yu 2014		+		28, 1.27) 18, 1.19)	0.88 0.97	Hansen 1997 30 mg/kg	,			-0.19 (-1.19, 0.81)	0.67
Gobinath 2016 Female No stre		-		0.44, 1.7)	0.62	Harris 2012 20 mg/kg Ansorge 2008				-0.12 (-1.17, 0.92) -0.1 (-0.64, 0.44)	0.64 1.14
Bairy 2007 Female P56 12 mg/l Matsumoto 2016 Male EPM	ny			0.6, 1.88) 0.26, 1.55)	0.51	Altieri 2015 Female P90 ESC Gobinath 2016 Male No stres	ss		<u>;</u>	-0.07 (-0.83, 0.68) -0.06 (-1.11, 1)	0.90 0.63
Toffoli 2014 Zohar 2016 Male No stress				0.25, 1.56) 0.16, 1.49)	0.75 0.82	Boulle 2016a Stress Ansorge 2004				-0.05 (-0.82, 0.72) -0.04 (-0.74, 0.66)	0.88
Rodriguez-Porcel 2011 Male FL Kiryanova 2017b No stress	LX	+		0.16, 1.49) 26, 1.66)	0.83 0.70	Boulle 2016b Stress Hansen 1997 5 mg/kg			<u> </u>	0 (-0.8, 0.8) 0 (-0.94, 0.94)	0.95
Khatri 2014 Cohort 2 Sprowles 2016 Female				.12, 1.33) 0.08, 1.59)	1.06 0.81	Popa 2008			<u>}</u>	0.03 (-0.67, 0.72)	0.96
Khatri 2014 Cohort 1 Matsumoto 2016 Female EPM		8	-\$ 0.76 (0	.44, 1.09)	1.40	Rayen 2011 Female No stress Rebello 2014 Exposure P2-P2				0.04 (-0.88, 0.96) 0.04 (-0.58, 0.66)	0.73 1.05
Nagano 2017 Male ESC		-		0.13, 1.7) 0.4, 2.03)	0.74	Altieri 2015 Female P90 FLX Altieri 2015 Male P300 FLX			¢	0.05 (-0.7, 0.79) 0.05 (-0.83, 0.93)	0.91 0.77
Bairy 2007 Male P56 12 mg/kg Rebello 2014 Exposure P2-P11		-		0.42, 2.12) .21, 1.5)	0.49 1.02	Boulle 2016b No stress Zheng 2011 FLV			5 6	0.06 (-0.74, 0.86) 0.07 (-1.13, 1.27)	0.85 0.53
Smit-Rigter 2012 Bairy 2007 Female P56 8 mg/kg		-		.01, 1.7) 0.39, 2.16)	0.80 0.49	Lee 2012 Altieri 2015 Male P90 FLX			<u></u>	0.07 (-0.66, 0.8) 0.08 (-0.78, 0.93)	0.92
Yu 2012 Jiang 2009	-	-		.18, 1.7)	0.89	Rayen 2011 Female Stress			¥	0.09 (-0.84, 1.01)	0.73
Simpson 2011 Male	п	-	\$ 1.05 (0	.28, 1.82)	0.88	Simpson 2011 Female Zheng 2011 FLX			<b>∲</b>	0.11 (-0.61, 0.82) 0.2 (-1.01, 1.4)	0.94 0.53
Rodriguez-Porcel 2011 Male CI Sarkar 2014b Cohort 3		-		.3, 2.04) .2, 2.26)	0.78 0.65	Hansen 1997 10 mg/kg Grimm 1987 Exposure P4-P8			     →	0.23 (-0.73, 1.19) 0.29 (-0.5, 1.08)	0.70 0.86
Olivier 2011 Male NSF Sarkar 2014a Cohort 1		-		.2, 2.37) .27, 2.35)	0.61 0.64	Rodriguez-Porcel 2011 Fema Volodina 2014			<b>♦</b>	0.3 (-0.57, 1.16) 0.31 (-0.15, 0.78)	0.79 1.23
Mnie-Filali 2011 Sarkar 2014b Cohort 1		-		.4, 2.23) .29, 2.39)	0.74 0.63	Nagano 2012 No stress Soga 2012			+ <b>~</b>	0.36 (-0.32, 1.04) 0.42 (-0.15, 0.99)	0.98
Hilakivi 1988a FT Sarkar 2014b Cohort 4		0 0 0		.05, 2.68) .06, 2.69)	0.47	Boulle 2016a No stress		-		0.48 (-0.31, 1.26)	0.87
Sarkar 2014b Cohort 2		8		.44, 2.47)	0.66	Lee 2009 Yu 2014		-		0.5 (-0.28, 1.27) 0.5 (-0.18, 1.19)	0.88 0.97
Sarkar 2014a Cohort 2 Ko 2014		1	\$ 2.74 (1	.47, 3.08) .27, 4.21)	0.48	Gobinath 2016 Female No str Rodriguez-Porcel 2011 Male			<u>→</u>	0.63 (-0.44, 1.7) 0.67 (-0.16, 1.49)	0.62 0.83
No stress Salari 2016 Stress		•	-3.02 (-	4.57, -1.46)		Khatri 2014 Cohort 2 Khatri 2014 Cohort 1			 -→	0.73 (0.12, 1.33) 0.76 (0.44, 1.09)	1.06 1.40
Zohar 2016 Female Stress Zohar 2016 Male Stress	-		-0.73 (-	1.56, 0.1) 1.27, 0.35)	0.82 0.84	Nagano 2017 Male ESC Rebello 2014 Exposure P2-P1	11	_		0.81 (-0.4, 2.03) 0.85 (0.21, 1.5)	0.52
Nagano 2012 Stress			-0.46 (-	1.14, 0.22)	0.97	Yu 2012				0.94 (0.18, 1.7)	0.89
Pivina 2011 PRX Gobinath 2016 Female Stress			-0.29 (-	1.31, 0.69) 1.33, 0.75)	0.67	Jiang 2009 Simpson 2011 Male	<b>CIT</b>			1 (0.55, 1.45) 1.05 (0.28, 1.82)	1.25 0.88
Gobinath 2016 Male Stress Ehrlich 2015 Stress P90			0.26 (-	1.3, 0.74) 1.06, 0.55)	0.66 0.84	Rodriguez-Porcel 2011 Male Sarkar 2014b Cohort 3	ui			1.17 (0.3, 2.04) 1.23 (0.2, 2.26)	0.78 0.65
Rayen 2011 Male Stress Boulle 2016a Stress				1.17, 0.68) 0.82, 0.72)	0.73 0.88	Sarkar 2014a Cohort 1 Mnie-Filali 2011				1.31 (0.27, 2.35) 1.32 (0.4, 2.23)	0.64 0.74
Kiryanova 2016 Stress Bourke 2013 Stress			-0.04 (-	0.73, 0.64)	0.97	Sarkar 2014b Cohort 1 Hilakivi 1988a FT				1.34 (0.29, 2.39) 1.37 (0.05, 2.68)	0.63 0.47
Boulle 2016 Stress Rayen 2011 Female Stress					0.85	Sarkar 2014b Cohort 4 Sarkar 2014b Cohort 2				1.37 (0.06, 2.69)	0.47
Kiryanova 2017b Stress		-	0.19 (-0	0.73, 1.12)	0.73	Sarkar 2014a Cohort 2				1.45 (0.44, 2.47) 1.78 (0.47, 3.08)	0.66
Ehrlich 2015 Stress P32 Pivina 2011 FLX		-		0.7, 1.28) .12, 5.72)	0.68 0.29	Ko 2014 Pivina 2011 FLX			<u>→</u>	2.74 (1.27, 4.21) 3.92 (2.12, 5.72)	0.40 0.29
Stress Anxiety - Overall		-		-0.51, 0.18) 0.21) 1		Postnatal Anxiety - Overall			<ul> <li>◆</li> <li>◆</li> </ul>		57.13 100.00
	-5 -4 -3 -2	-1 0					-5 -4	-3 -2 -1 (			
	SSRI less ar	nxiety S	SRI more anxiety				←	SSRI less anxiety	SSRI more anxiety		

# A. Stress coping

A. Stress coping	Weight
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Zohar 2016 Female No stress under a CC-BY-NC-ND 4.0 In	ternational license1.74 (-2.75, -0.73) 1.13

iarkar 2014b Cohort 2 Hilakivi 1987b Hansen 1997 30 mg/kg sarkar 2014a Cohort 2 Sarkar 2014b Cohort 3 Jarkar 2014a Cohort 1 Opa 2008 Lisboa 2007 Female Hansen 1997 10 mg/kg				-1.69 (-2.87, -0.5) -1.67 (-3.06, -0.27) -1.63 (-3.09, -0.16) -1.45 (-2.6, -0.31)	0.9 0.7 0.7 0.7
Hansen 1997 30 mg/kg Sarkar 2014a Cohort 2 Sarkar 2014b Cohort 3 Sarkar 2014a Cohort 1 Yopa 2008 Lisboa 2007 Female				-1.63 (-3.09, -0.16) -1.45 (-2.6, -0.31)	0.7
Sarkar 2014a Cohort 2 Sarkar 2014b Cohort 3 Sarkar 2014a Cohort 1 Yoopa 2008 Lisboa 2007 Female				-1.45 (-2.6, -0.31)	
arkar 2014b Cohort 3 arkar 2014a Cohort 1 20pa 2008 .isboa 2007 Female					0.9
Sarkar 2014a Cohort 1 20pa 2008 Lisboa 2007 Female					0.9
<sup>2</sup> opa 2008 .isboa 2007 Female				-1.45 (-2.59, -0.31) -1.41 (-2.47, -0.35)	1.0
isboa 2007 Female					
Jisboa 2007 Female Japsen 1997 10 mg/kg				-1.36 (-2.13, -0.59)	1.4
				-1.35 (-2.37, -0.33)	1.1
				-1.29 (-2.63, 0.05)	0.
Zohar 2016 Male No stress				-1.22 (-2.14, -0.29)	1.2
Vagano 2017 FLX				-1.18 (-2.36, 0)	0.9
Sarkar 2014b Cohort 1				-1.17 (-2.26, -0.09)	1.0
Ko 2014				-1.11 (-2.19, -0.04)	1.0
Rebello 2014 FS		+		-1.1 (-1.96, -0.23)	1.3
Dlivier 2011 Male EPM after stress				-1.05 (-2, -0.1)	1.2
Rebello 2014 Exposure P2-P11 SE				-1.04 (-1.67, -0.41)	1.7
Boulle 2016b Stress				-1.03 (-1.9, -0.17)	1.3
Vinie-Filali 2011				-1 (-2.01, 0.02)	1.1
Rebello 2014 Exposure P2-P21 SE		<del>`</del>		-0.93 (-1.6, -0.27)	1.6
Rayen 2011 Male Stress				-0.91 (-1.89, 0.07)	1.1
Ansorge 2004				-0.89 (-1.64, -0.15)	1.5
lansen 1997 20 mg/kg			_	-0.89 (-2.18, 0.41)	0.8
Altieri 2015 Male cohort 3 FLX				-0.81 (-1.73, 0.1)	1.2
/u 2014		$\rightarrow$ +		-0.8 (-1.51, -0.1)	1.5
Sobinath 2016 Female Stress			_	-0.77 (-1.85, 0.31)	1.0
alari 2016 No stress			_	-0.73 (-1.75, 0.3)	1.1
3oulle 2016a Stress		+		-0.7 (-1.49, 0.1)	1.4
Dlivier 2011 Female FS			_	-0.66 (-1.59, 0.27)	1.2
Altieri 2015 Male cohort 1			_	-0.65 (-1.66, 0.36)	1.1
Altieri 2015 Male cohort 3 ESC			_	-0.65 (-1.53, 0.23)	1.
Boulle 2016b No stress			-	-0.64 (-1.46, 0.19)	1.3
reund 2013 Female stress Exp. P2-F	9 inescap.			-0.62 (-2.07, 0.83)	0.7
lansen 1997 5 mg/kg				-0.61 (-1.87, 0.64)	0.8
Rayen 2011 Female Stress			_	-0.57 (-1.52, 0.37)	1.2
(u 2012			_	-0.55 (-1.29, 0.18)	1.5
reund 2013 Female stress Exp. P9-F	16 no shock			-0.52 (-1.95, 0.91)	0.7
reund 2013 Male no stress Exp. P2-				-0.51 (-1.94, 0.92)	0.7
reund 2013 Male stress Exp. P9-P16	no shock			-0.51 (-1.94, 0.92)	0.7
reund 2013 Female no stress Exp. F				-0.42 (-1.84, 1)	0.7
reund 2013 Male no stress Exp. P9-	P16 no shock	è		-0.41 (-1.82, 1.01)	0.7
reund 2013 Female no stress Exp. F	9-P16 no shock			-0.39 (-1.8, 1.02)	0.7
prowles 2016			-	-0.38 (-0.95, 0.18)	1.8
reund 2013 Female stress Exp. P2-F	9 no shock	è		-0.37 (-1.78, 1.04)	0.7
reund 2013 Male no stress Exp. P2-	P9 no shock			-0.34 (-1.75, 1.06)	0.7
reund 2013 Male no stress Exp. P2-		Y		-0.33 (-1.73, 1.08)	0.7
Altieri 2015 Female cohort 1	i sineseup.	`		-0.32 (-1.31, 0.67)	1.1
Vagano 2017 ESC		¢		-0.29 (-1.45, 0.87)	0.9
reund 2013 Male stress Exp. P2-P9	no shock			-0.24 (-1.64, 1.15)	0.7
reund 2013 Female stress Exp. P2-F		č		-0.24 (-1.64, 1.15)	0.7
Divier 2011 Male FS	s escup.	è		-0.2 (-1.08, 0.68)	1.
shikawa 2017		`		-0.19 (-0.94, 0.57)	1.4
Sobinath 2016 Male Stress				-0.14 (-1.15, 0.88)	1.1
Freund 2013 Female no stress Exp. F	2-PQ inescan	``		-0.12 (-1.51, 1.27)	0.7
Rayen 2011 Male No Stress	2 i 5 meseup.			-0.07 (-1, 0.85)	1.2
prowles 2017 CIT				-0.03 (-0.54, 0.47)	1.2
Zohar 2016 Male Stress			_	0 (-0.84, 0.84)	1.3
Rebello 2014 Exposure P12-P21 SE				0 (-0.62, 0.62)	1.7
Freund 2013 Female no stress Exp. F	0. P16 occan			0.02 (-1.37, 1.41)	0.7
Sprowles 2017 FLX	54 TO escap.			0.02 (-1.37, 1.41)	1.9
			<u> </u>		
Altieri 2015 Female cohort 3 ESC	Inoscon		<u> </u>	0.13 (-0.75, 1.01)	1.
reund 2013 Male stress Exp. P9-P16			· · · · · · · · · · · · · · · · · · ·	0.13 (-1.26, 1.52)	0.7
Freund 2013 Male stress Exp. P2-P9	mescap.		~	0.14 (-1.25, 1.53)	0.7
Coleman 1999 Male			<u> </u>	0.14 (-0.68, 0.96)	1.3
Boulle 2016a No stress		+	\$ <u> </u>	0.18 (-0.59, 0.95)	1.4
Zohar 2016 Female Stress			\$	0.18 (-0.65, 1.02)	1.3
Altieri 2015 Female cohort 2 ESC		+	\$	0.19 (-0.56, 0.95)	1.4
Bourke 2013 No stress				0.25 (-0.89, 1.38)	0.9
reund 2013 Female no stress Exp. F	2-P9 no shock		->	0.25 (-1.15, 1.65)	0.7
Altieri 2015 Female cohort 2 FLX		+		0.25 (-0.49, 1)	1.5
reund 2013 Female no stress Exp. F			-↔	0.28 (-1.12, 1.68)	0.7
Freund 2013 Female stress Exp. P9-F	'16 escap.		->	0.28 (-1.12, 1.68)	0.7
McAllister 2012		-		0.29 (-0.42, 1)	1.5
reund 2013 Male no stress Exp. P9-	P16 inescap.		->	0.31 (-1.09, 1.71)	0.7
isboa 2007 Male		H		0.33 (-0.36, 1.02)	1.6
Bourke 2013 Stress			->	0.35 (-0.79, 1.5)	0.9
Altieri 2015 Female cohort 3 FLX		-		0.36 (-0.51, 1.22)	1.3
Altieri 2015 Male cohort 2 FLX		-		0.55 (-0.33, 1.42)	1.3
Coleman 1999 Female		-		0.55 (-0.28, 1.39)	1.3
Altieri 2015 Male cohort 2 ESC		-		0.56 (-0.29, 1.42)	1.3
Rayen 2011 Female No stress		H		0.58 (-0.36, 1.53)	1.2
Gobinath 2016 Female No stress		-		0.64 (-0.43, 1.71)	1.0
reund 2013 Male no stress Exp. P9-	P16 escap.			0.64 (-0.81, 2.09)	0.7
reund 2013 Male stress Exp. P9-P16				0.66 (-0.8, 2.12)	0.7
reund 2013 Male stress Exp. P2-P9				0.67 (-0.79, 2.13)	0.7
Gobinath 2016 Male No stress	· · · · F.	L		0.75 (-0.35, 1.86)	1.0
(arpova 2009				0.89 (-0.03, 1.8)	1.2
			-	- 1.44 (0.31, 2.58)	0.9
Salari 2016 Stress					

SSRI more passive coping SSRI more active coping

# **B. Stress coping - Sex**

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Hansen 1997 30 mg/kg		D 4.0 International license.	-1.67 (-3.06, -0.27) -1.63 (-3.09, -0.16)	0.75
Sarkar 2014a Cohort 2			-1.45 (-2.6, -0.31)	0.98
Sarkar 2014b Cohort 3			-1.45 (-2.59, -0.31)	0.98
Sarkar 2014a Cohort 1			-1.41 (-2.47, -0.35)	1.07
Hansen 1997 10 mg/kg			-1.29 (-2.63, 0.05)	0.8
Zohar 2016 Male No stress			-1.22 (-2.14, -0.29)	1.24
Nagano 2017 FLX			-1.18 (-2.36, 0)	0.94
Sarkar 2014b Cohort 1			-1.17 (-2.26, -0.09)	1.04
Ko 2014		<del></del>	-1.11 (-2.19, -0.04)	1.05
Olivier 2011 Male EPM after stress			-1.05 (-2, -0.1)	1.21
Mnie-Filali 2011			-1 (-2.01, 0.02)	1.12
Rayen 2011 Male Stress			-0.91 (-1.89, 0.07)	1.16
Hansen 1997 20 mg/kg			-0.89 (-2.18, 0.41)	0.84
Altieri 2015 Male cohort 3 FLX			-0.81 (-1.73, 0.1)	1.25
Salari 2016 No stress			-0.73 (-1.75, 0.3)	1.12
Boulle 2016a Stress			-0.7 (-1.49, 0.1)	1.43
Altieri 2015 Male cohort 1			-0.65 (-1.66, 0.36)	1.13
Altieri 2015 Male cohort 3 ESC			-0.65 (-1.53, 0.23)	1.3
Hansen 1997 5 mg/kg			-0.61 (-1.87, 0.64)	0.87
Freund 2013 Male no stress Exp. P2-	P9 escap.		-0.51 (-1.94, 0.92)	0.73
Freund 2013 Male stress Exp. P9-P10			-0.51 (-1.94, 0.92)	0.73
Freund 2013 Male no stress Exp. P9-	P16 no shock		-0.41 (-1.82, 1.01)	0.74
Freund 2013 Male no stress Exp. P2			-0.34 (-1.75, 1.06)	0.74
Freund 2013 Male no stress Exp. P2-	P9 inescap.		-0.33 (-1.73, 1.08)	0.75
Nagano 2017 ESC			-0.29 (-1.45, 0.87)	0.96
Freund 2013 Male stress Exp. P2-P9	no shock		-0.24 (-1.64, 1.15)	0.75
Olivier 2011 Male FS			-0.2 (-1.08, 0.68)	1.3
Ishikawa 2017			-0.19 (-0.94, 0.57)	1.49
Gobinath 2016 Male Stress			-0.14 (-1.15, 0.88)	1.13
Rayen 2011 Male No Stress			-0.07 (-1, 0.85)	1.24
Zohar 2016 Male Stress Fround 2012 Male stress Exp. PO P1	inorcan		0 (-0.84, 0.84)	1.37
Freund 2013 Male stress Exp. P9-P10			0.13 (-1.26, 1.52)	0.76
Freund 2013 Male stress Exp. P2-P9 Coleman 1999 Male	шезсар.		0.14 (-1.25, 1.53) 0.14 (-0.68, 0.96)	0.76
Coleman 1999 Male Boulle 2016a No stress			0.14 (-0.68, 0.96) 0.18 (-0.59, 0.95)	1.39
Boulle 2016a No stress Bourke 2013 No stress			0.18 (-0.59, 0.95) 0.25 (-0.89, 1.38)	1.4/
Bourke 2013 No stress Freund 2013 Male no stress Exp. P9-	P16 iporcap		0.25 (-0.89, 1.38) 0.31 (-1.09, 1.71)	0.98
Lisboa 2007 Male	r to mescap.		0.33 (-0.36, 1.02)	1.61
Bourke 2013 Stress			0.35 (-0.79, 1.5)	0.98
Altieri 2015 Male cohort 2 FLX			0.55 (-0.33, 1.42)	1.31
Altieri 2015 Male cohort 2 ESC			0.56 (-0.29, 1.42)	1.34
Freund 2013 Male no stress Exp. P9-	Pléescap		0.64 (-0.81, 2.09)	0.71
Freund 2013 Male stress Exp. P9-P10	Sescan		0.66 (-0.8, 2.12)	0.71
Freund 2013 Male stress Exp. P2-P9	escan		0.67 (-0.79, 2.13)	0.71
Gobinath 2016 Male No stress	escap.	, i li contra la	0.75 (-0.35, 1.86)	1.02
Karpova 2009			0.89 (-0.03, 1.8)	1.26
Salari 2016 Stress		· · · · · · · · · · · · · · · · · · ·	- 1.44 (0.31, 2.58)	0.99
Male		•	-0.39 (-0.6, -0.18)	51.65
Rebello 2014 FS			-1.1 (-1.96, -0.23)	1.32
Rebello 2014 Exposure P2-P11 SE			-1.04 (-1.67, -0.41)	1.71
Rebello 2014 Exposure P2-P21 SE		<del></del> +	-0.93 (-1.6, -0.27)	1.65
Ansorge 2004		+	-0.89 (-1.64, -0.15)	1.51
Yu 2014			-0.8 (-1.51, -0.1)	1.58
Yu 2012			-0.55 (-1.29, 0.18)	1.53
Sprowles 2016			-0.38 (-0.95, 0.18)	1.83
Sprowles 2017 CIT		+	-0.03 (-0.54, 0.47)	1.93
Rebello 2014 Exposure P12-P21 SE		÷+	0 (-0.62, 0.62)	1.73
Sprowles 2017 FLX			0.05 (-0.46, 0.55)	1.92
Mixed-sex		*	-0.52 (-0.8, -0.23)	16.72
Freund 2013 Female stress Exp. P9-I	716 inescap.		-4.58 (-8.03, -1.14)	0.16
Zohar 2016 Female No stress			-1.74 (-2.75, -0.73)	1.13
Popa 2008			-1.36 (-2.13, -0.59)	1.47
Lisboa 2007 Female			-1.35 (-2.37, -0.33)	1.12
Boulle 2016b Stress Gobinath 2016 Female Stress			-1.03 (-1.9, -0.17)	1.33
			-0.77 (-1.85, 0.31)	1.05
Olivier 2011 Female FS Roullo 2016b No stross			-0.66 (-1.59, 0.27)	1.23
Boulle 2016b No stress	20 inorcan		-0.64 (-1.46, 0.19) -0.62 (-2.07, 0.83)	0.71
Freund 2013 Female stress Exp. P2-I Raven 2011 Female Stress	-9 mescap.			0./1
	216 po shock		-0.57 (-1.52, 0.37) -0.52 (-1.95, 0.91)	0.73
	TO TIO STIUCK	•	-0.52 (-1.95, 0.91) -0.42 (-1.84, 1)	0.73
Freund 2013 Female stress Exp. P9-I	0 D16 inorcan		-0.42 (-1.04, 1)	0.74
Freund 2013 Female stress Exp. P9-I Freund 2013 Female no stress Exp. I	9-P16 inescap.			
Freund 2013 Female stress Exp. P9-I Freund 2013 Female no stress Exp. I Freund 2013 Female no stress Exp. I	P9-P16 inescap. P9-P16 no shock		-0.39 (-1.8, 1.02)	
Freund 2013 Female stress Exp. P9- Freund 2013 Female no stress Exp. I Freund 2013 Female no stress Exp. I Freund 2013 Female stress Exp. P2-I	P9-P16 inescap. P9-P16 no shock		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04)	0.74
Fréund 2013 Female stress Exp. P9- Freund 2013 Female no stress Exp. I Freund 2013 Female no stress Exp. I Freund 2013 Female stress Exp. P2-I Altieri 2015 Female cohort 1	29-P16 inescap. 29-P16 no shock 29 no shock		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67)	0.74 1.16
Fréund 2013 Female stress Exp. P9- Freund 2013 Female no stress Exp. I Freund 2013 Female no stress Exp. I Freund 2013 Female stress Exp. P2- Altieri 2015 Female cohort 1 Freund 2013 Female stress Exp. P2-I	99-P16 inescap. 99-P16 no shock 99 no shock 99 escap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15)	0.74 1.16 0.75
Fréund 2013 Female stress Exp. P9- Freund 2013 Female no stress Exp. I Freund 2013 Female no stress Exp. J. Freund 2013 Female stress Exp. P2- Altieri 2015 Female cohort 1 Freund 2013 Female stress Exp. P2- Freund 2013 Female no stress Exp. P3-	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27)	0.74 1.16 0.75 0.76
Fréund 2013 Female stress Exp. P-9 Freund 2013 Female no stress Exp. F Freund 2013 Female no stress Exp. J Freund 2013 Female constress Exp. P-2-4 Miteri 2015 Female cohort 1 Freund 2013 Female stress Exp. P-2- Freund 2013 Female no stress Exp. J	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41)	0.74 1.16 0.75 0.76 0.76
Fréund 2013 Female nostress Exp. P-9- Freund 2013 Female no stress Exp. Freund 2013 Female no stress Exp. P-2- Ritlein 2015 Female cohort 1 Freund 2013 Female cohort 1 Freund 2013 Female nostress Exp. P-2- Freund 2013 Female nostress Exp. Freund 2013 Female nostress Exp. P-2- Ritlein 2013 Female nostress Exp. P-2- Freund 2013 Female nostress Exp. P-2- Freund 2013 Female nostress Exp. P-2- Ritlein 2015 Female cohort 3 ESC	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41) 0.13 (-0.75, 1.01)	0.74 1.16 0.75 0.76 0.76 1.3
Fréund 2013 Female stress Exp, P3- Freund 2013 Female no stress Exp, 1 Freund 2013 Female no stress Exp, 1 Freund 2013 Female stress Exp, P2- Miteri 2015 Female cohort 1 Freund 2013 Female no stress Exp, P4- Freund 2013 Female no stress Exp, 1 Freund 2013 Female no stress Exp, 1 Miteri 2015 Female cohort 3 ESC Johan 2016 Female Stress	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41) 0.13 (-0.75, 1.01) 0.18 (-0.65, 1.02)	0.74 1.16 0.75 0.76 0.76 1.3 1.37
Fréund 2013 Female totress Exp. P9- Freund 2013 Female no stress Exp. Freund 2013 Female no stress Exp. Freund 2013 Female stress Exp. P2- Mitieri 2015 Female cohort 1 Freund 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1 Mitieri 2015 Female cohort 3 ESC Zohar 2016 Female Stress Miteri 2015 Female cohort 2 ESC	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap. 99-P16 escap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41) 0.13 (-0.75, 1.01) 0.18 (-0.65, 1.02) 0.19 (-0.56, 0.95)	0.74 1.16 0.75 0.76 0.76 1.3 1.37 1.49
Fréund 2013 Female stress Exp, P3- Freund 2013 Female no stress Exp, P Freund 2013 Female no stress Exp, P2- Altien 2015 Female stress Exp, P2- Altien 2015 Female cohort 1 Freund 2013 Female no stress Exp, P3- Altieri 2013 Female no stress Exp, P3- Altieri 2013 Female cohort 3 ESC Cohar 2016 Female Stress Altien 2015 Female Cohort 3 ESC Altieri 2015 Female Cohort 2 ESC Freund 2013 Female no stress Exp, P3- Altieri 2015 Female Cohort 2 ESC Freund 2013 Female no stress Exp, P3- Altieri 2015 Female cohort 2 ESC Freund 2013 Female no stress Exp, P3- Altieri 2015 Female Cohort 2 ESC Freund 2013 Female no stress Exp, P3- Altieri 2015 Female Notice	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap. 99-P16 escap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41) 0.13 (-0.75, 1.01) 0.18 (-0.65, 1.02) 0.19 (-0.56, 0.95) 0.25 (-1.15, 1.65)	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75
refund 2013 Female stress top, P9- rereund 2013 Female no stress Exp. 1 rereund 2013 Female stress Exp. P2- Altieri 2015 Female stress Exp. P2- Altieri 2015 Female stress Exp. P2- rereund 2013 Female no stress Exp. 1 rereund 2013 Female no stress Exp. 1 Miteri 2015 Female cohort 3 Miteri 2015 Female cohort 3 Miteri 2015 Female cohort 3 EXO Target 2015 Female Stress Miteri 2015 Female S	99-P16 inescap. 99-P16 no shock 99 no shock 29 escap. 22-P9 inescap. 99-P16 escap.		-0.39 (-1.8, 1.02) -0.37 (-1.78, 1.04) -0.32 (-1.31, 0.67) -0.24 (-1.64, 1.15) -0.12 (-1.51, 1.27) 0.02 (-1.37, 1.41) 0.13 (-0.65, 1.02) 0.19 (-0.56, 0.95) 0.25 (-0.49, 1) 0.25 (-0.49, 1)	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75 1.51
Fréund 2013 Female stress Exp. P3- Freund 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 2 Hulen 2015 Female extress Exp. P2-1 Mulen 2015 Female cohort 1 Freund 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1 Hulen 2015 Female cohort 3 ESC Zohar 2016 Female cohort 3 ESC Altier 2015 Female cohort 2 ESC Freund 2015 Female no stress Exp. 1 Mulen 2015 Female no stress Exp. 1	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.32 \ (-1.31, 0.67) \\ -0.24 \ (-1.64, 1.15) \\ -0.12 \ (-1.37, 1.41) \\ 0.13 \ (-0.75, 1.01) \\ 0.18 \ (-0.65, 1.02) \\ 0.19 \ (-0.56, 0.95) \\ 0.25 \ (-1.15, 1.65) \\ 0.25 \ (-0.49, 1) \\ 0.28 \ (-1.12, 1.68) \end{array}$	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75 1.51 0.75
réund 2013 Female totres top, P9- rereund 2013 Female no stress Exp. 1 rereund 2013 Female no stress Exp. 1 rereund 2013 Female stress Exp. P2- Altieri 2013 Female no stress Exp. 1 rereund 2013 Female no stress Exp. 1 rereund 2013 Female no stress Exp. 1 Miteri 2015 Female cohort 3 ESC Zohar 2016 Female Stress Miteri 2015 Female cohort 3 ESC Zohar 2016 Female Stress Miteri 2015 Female cohort 2 ESC Freund 2013 Female no stress Exp. 1 Miteri 2015 Female cohort 2 EXC Freund 2013 Female no stress Exp. 1 Freund 2013 Female stress Exp. P9-	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.22 \ (-1.31, 0.67) \\ -0.24 \ (-1.64, 1.15) \\ -0.12 \ (-1.51, 1.27) \\ 0.02 \ (-1.37, 1.41) \\ 0.13 \ (-0.65, 1.02) \\ 0.19 \ (-0.56, 0.95) \\ 0.25 \ (-1.15, 1.65) \\ 0.25 \ (-1.51, 1.65) \\ 0.26 \ (-1.12, 1.68) \\ 0.28 \ (-1.12, 1.68) \\ 0.28 \ (-1.12, 1.68) \end{array}$	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75 1.51 0.75 0.75
Fréund 2013 Female estress Exp. P3- Freund 2013 Female en ostress Exp. I Freund 2013 Female en ostress Exp. 2 Hilteri 2015 Female estress Exp. P2- Hilteri 2015 Female cohort 1 Freund 2013 Female estress Exp. P2- Hilteri 2013 Female en ostress Exp. 1 Freund 2013 Female en ostress Exp. 1 Hilteri 2015 Female cohort 2 FLX Freund 2013 Female en ostress Exp. 1 Hilteri 2015 Female cohort 2 FLX Freund 2015 Female no stress Exp. 1 Hilteri 2015 Female cohort 2 FLX Freund 2015 Female no stress Exp. 1 Hilteri 2015 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1 Hilteri 2015 Female no stress Exp. 1 Hilteri 2015 Female no stress Exp. 1 Kullisteri 2013 Female no stress Exp. 1 Freund 2013 Female no stress Exp. 1	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \left(-1.8, 1.02\right)\\ -0.37 \left(-1.78, 1.04\right)\\ -0.32 \left(-1.37, 1.04\right)\\ -0.32 \left(-1.31, 0.67\right)\\ -0.24 \left(-1.64, 1.15\right)\\ -0.12 \left(-1.51, 1.27\right)\\ 0.02 \left(-1.37, 1.41\right)\\ 0.18 \left(-0.65, 1.02\right)\\ 0.19 \left(-0.56, 0.95\right)\\ 0.25 \left(-1.04, 91\right)\\ 0.28 \left(-1.12, 1.68\right)\\ 0.28 \left(-1.12, 1.68\right)\\ 0.29 \left(-0.42, 1\right)\end{array}$	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75 1.51 0.75 0.75 1.57
Fréund 2013 Female stress Exp, P3- Freund 2013 Female no stress Exp, P3- Freund 2013 Female no stress Exp, P4- Altien 2015 Female cohort 9 Freund 2013 Female stress Exp, P2- Altien 2013 Female no stress Exp, P3- Altien 2013 Female no stress Exp, P3- Altien 2013 Female no stress Exp, P3- Altien 2013 Female stress Exp Altien 2015 Female Stress Exp Altien 2015 Female Nort 2 ESC Altien 2015 Female no stress Exp, P3- Altien 2013 Female no stress Exp, P3- McAllister 2012 Altien 2013 Female stress Exp, P3- McAllister 2012	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.32 \ (-1.31, 0.67) \\ -0.24 \ (-1.64, 1.15) \\ -0.12 \ (-1.51, 1.27) \\ 0.02 \ (-1.37, 1.41) \\ 0.13 \ (-0.75, 1.01) \\ 0.18 \ (-0.65, 1.02) \\ 0.19 \ (-0.56, 0.95) \\ 0.25 \ (-1.15, 1.65) \\ 0.25 \ (-1.15, 1.65) \\ 0.25 \ (-1.12, 1.68) \\ 0.28 \ (-1.12, 1.68) \\ 0.29 \ (-0.42, 1) \\ 0.36 \ (-0.51, 1.22) \end{array}$	0.74 1.16 0.75 0.76 1.3 1.37 1.49 0.75 1.51 0.75 0.75 1.57 1.32
Fréund 2013 Female estress Exp. P-9- Freund 2013 Female no stress Exp. J- Freund 2013 Female no stress Exp. J- Alteir 2015 Female cohort 1 Freund 2013 Female estress Exp. J-2 Freund 2013 Female no stress Exp. J-2 Alteir 2015 Female no stress Exp. J-2 Alteir 2015 Female cohort 2 ESC Zohar 2016 Female Stress Altieri 2015 Female no stress Exp. J- Altieri 2015 Female no stress Exp. J- Altieri 2015 Female no stress Exp. J- Altieri 2015 Female no stress Exp. J- Kreund 2013 Female stress Exp. J- Altieri 2015 Female cohort 2 FLX Freund 2013 Female stress Exp. P-9- McAllister 2012 Altieri 2015 Female cohort 3 FLX Goleman 1999 Female	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.32 \ (-1.78, 1.04) \\ -0.32 \ (-1.31, 0.67) \\ -0.24 \ (-1.61, 1.15) \\ -0.12 \ (-1.51, 1.27) \\ 0.02 \ (-1.51, 1.27) \\ 0.02 \ (-1.51, 1.27) \\ 0.019 \ (-0.56, 0.95) \\ 0.25 \ (-0.49, 1) \\ 0.28 \ (-1.12, 1.68) \\ 0.28 \ (-1.12, 1.68) \\ 0.29 \ (-0.42, 1) \\ 0.36 \ (-0.51, 1.22) \\ 0.55 \ (-0.28, 1.39) \end{array}$	0.74 1.16 0.75 0.76 0.76 1.3 1.37 1.49 0.75 1.51 0.75 1.57 1.57 1.32 1.37
Fréund 2013 Female stress Exp, PJ- Freund 2013 Female no stress Exp, J Freund 2013 Female no stress Exp, I Freund 2013 Female stress Exp, P2- Altien 2015 Female cohort 3 Freund 2013 Female no stress Exp, I- Altien 2015 Female no stress Exp, I- Altien 2013 Female no stress Exp, I- Altien 2013 Female cohort 3 ESC Johar 2016 Female Stress Altien 2015 Female cohort 3 Ferund 2013 Female no stress Exp, I- Altien 2015 Female no stress Exp, I- McAlister 2012 Altien 2015 Female cohort 3 FLX Coleman 1999 Female Royne 2011 Female No stress	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.32 \ (-1.37, 1.04) \\ -0.24 \ (-1.64, 1.15) \\ -0.12 \ (-1.64, 1.15) \\ -0.12 \ (-1.57, 1.02) \\ -0.12 \ (-1.57, 1.02) \\ -0.12 \ (-1.57, 1.02) \\ -0.18 \ (-0.65, 1.02) \\ -0.18 \ (-0.65, 1.02) \\ -0.25 \ (-0.49, 1) \\ -0.28 \ (-1.12, 1.68) \\ -0.28 \ (-1.12, 1.68) \\ -0.28 \ (-1.12, 1.68) \\ -0.29 \ (-0.42, 1) \\ -0.36 \ (-0.57, 1.22) \\ -0.58 \ (-0.38, 1.53) \end{array}$	0.74 1.16 0.75 0.76 0.76 1.3 1.37 1.49 0.75 1.51 0.75 1.57 1.32 1.37 1.32 1.37 1.21
Fréund 2013 Female rotress Exp. P3- Freund 2013 Female no stress Exp. Freund 2013 Female no stress Exp. Freund 2013 Female to stress Exp. P3- Freund 2013 Female cohort 1 Freund 2013 Female no stress Exp. P3- Freund 2013 Female no stress Exp. Freund 2013 Female no stress Exp. Miteri 2015 Female cohort 3 ESC Zohar 2016 Female cohort 2 FSC Freund 2013 Female no stress Exp. Freund 2013 Female no stress Exp. Adlister 2015 Female Cohort 3 FLX Coleman 1999 Female	99-P16 in escap. 99 Pto An obock 99 no shock 99 escap. 29-P16 escap. 92-P19 no shock 92-P9 no shock 92-P9 escap.		$\begin{array}{c} -0.39 \ (-1.8, 1.02) \\ -0.37 \ (-1.78, 1.04) \\ -0.32 \ (-1.78, 1.04) \\ -0.32 \ (-1.31, 0.67) \\ -0.24 \ (-1.61, 1.15) \\ -0.12 \ (-1.51, 1.27) \\ 0.02 \ (-1.51, 1.27) \\ 0.02 \ (-1.51, 1.27) \\ 0.019 \ (-0.56, 0.95) \\ 0.25 \ (-0.49, 1) \\ 0.28 \ (-1.12, 1.68) \\ 0.28 \ (-1.12, 1.68) \\ 0.29 \ (-0.42, 1) \\ 0.36 \ (-0.51, 1.22) \\ 0.55 \ (-0.28, 1.39) \end{array}$	0.74 1.16 0.75 0.76 0.76 1.3 1.37 1.49 0.75 1.51 0.75 1.57 1.57 1.32 1.37

SSRI more passive coping SSRI more active coping

# C. Stress coping - Stress exposure

Weight SMD (95% Cl) (%)

Comparison		SMD (95% CI) (%)
hioRxiv preprint doi: https://doi.org/10.1101/	868265 this version posted December 6, 2019 T	he convright holder for this preprint (which was
biorexiv proprint doi: https://doi.org/10.1101/		
not certified by peer review/) is the author/fu	868265; this version posted December 6, 2019. T nder, who has granted bioRxiv_a liçense to display	the preprint in perpetuity. It is made available
Sarkar 2014b Cohort 2	under aCC-BY-NC-ND 4.0 International license	-1.69 (-2.87, -0.5) 0.93
Hilakiyi 1997b		167 (206 027) 075

Sarkar 2014b Cohort 2	under aCC-BY-NC-ND	4.0 International license.	-1.69 (-2.87, -0.5)	0.93
mildkivi 1967D			-1.67 (-3.06, -0.27)	0.75
Hansen 1997 30 mg/kg			-1.63 (-3.09, -0.16)	0.71
Sarkar 2014a Cohort 2			-1.45 (-2.6, -0.31)	0.98
Sarkar 2014b Cohort 3			-1.45 (-2.59, -0.31)	0.98
Sarkar 2014a Cohort 1			-1.41 (-2.47, -0.35)	1.07
Popa 2008 Lisboa 2007 Female			-1.36 (-2.13, -0.59) -1.35 (-2.37, -0.33)	1.47 1.12
Hansen 1997 10 mg/kg			-1.35 (-2.37, -0.33) -1.29 (-2.63, 0.05)	0.8
				1.24
Zohar 2016 Male No stress Nagano 2017 FLX			-1.22 (-2.14, -0.29) -1.18 (-2.36, 0)	0.94
Sarkar 2014b Cohort 1			-1.18 (-2.36, 0) -1.17 (-2.26, -0.09)	1.04
Ko 2014			-1.11 (-2.19, -0.04)	1.04
Rebello 2014 FS				1.32
Olivier 2011 Male EPM after stress			-1.1 (-1.96, -0.23) -1.05 (-2, -0.1)	1.32
Rebello 2014 Exposure P2-P11 SE			-1.04 (-1.67, -0.41)	1.71
Mnie-Filali 2011			-1 (-2.01, 0.02)	1.12
Rebello 2014 Exposure P2-P21 SE			-0.93 (-1.6, -0.27)	1.65
Ansorge 2004			-0.89 (-1.64, -0.15)	1.51
Hansen 1997 20 mg/kg			-0.89 (-2.18, 0.41)	0.84
Altieri 2015 Male cohort 3 FLX			-0.81 (-1.73, 0.1)	1.25
Yu 2014			-0.8 (-1.51, -0.1)	1.58
Salari 2016 No stress			-0.73 (-1.75, 0.3)	1.12
Olivier 2011 Female FS			-0.66 (-1.59, 0.27)	1.23
Altieri 2015 Male cohort 1			-0.65 (-1.66, 0.36)	1.13
Altieri 2015 Male cohort 3 ESC			-0.65 (-1.53, 0.23)	1.3
Boulle 2016b No stress			-0.64 (-1.46, 0.19)	1.39
Hansen 1997 5 mg/kg			-0.61 (-1.87, 0.64)	0.87
Yu 2012			-0.55 (-1.29, 0.18)	1.53
Freund 2013 Male no stress Exp. P2-P9	escap.		-0.51 (-1.94, 0.92)	0.73
Freund 2013 Female no stress Exp. P9-F	P16 inescap.	i	-0.42 (-1.84, 1)	0.74
Freund 2013 Male no stress Exp. P9-P16	5 no shock	i	-0.41 (-1.82, 1.01)	0.74
Freund 2013 Female no stress Exp. P9-F		Ì	-0.39 (-1.8, 1.02)	0.74
Sprowles 2016			-0.38 (-0.95, 0.18)	1.83
Freund 2013 Male no stress Exp. P2-P9	no shock		-0.34 (-1.75, 1.06)	0.74
Freund 2013 Male no stress Exp. P2-P9	inescap.		-0.33 (-1.73, 1.08)	0.75
Altieri 2015 Female cohort 1			-0.32 (-1.31, 0.67)	1.16
Nagano 2017 ESC			-0.29 (-1.45, 0.87)	0.96
Olivier 2011 Male FS		i <b>\</b>	-0.2 (-1.08, 0.68)	1.3
Ishikawa 2017		i	-0.19 (-0.94, 0.57)	1.49
Freund 2013 Female no stress Exp. P2-F	P9 inescap.		-0.12 (-1.51, 1.27)	0.76
Rayen 2011 Male No Stress			-0.07 (-1, 0.85)	1.24
Sprowles 2017 CIT		+++	-0.03 (-0.54, 0.47)	1.93
Rebello 2014 Exposure P12-P21 SE		÷.	0 (-0.62, 0.62)	1.73
Freund 2013 Female no stress Exp. P9-F	P16 escap.		0.02 (-1.37, 1.41)	0.76
Sprowles 2017 FLX			0.05 (-0.46, 0.55)	1.92
Altieri 2015 Female cohort 3 ESC			0.13 (-0.75, 1.01)	1.3
Coleman 1999 Male			0.14 (-0.68, 0.96)	1.39
Boulle 2016a No stress		<u>+</u>	0.18 (-0.59, 0.95)	1.47
Altieri 2015 Female cohort 2 ESC		+++	0.19 (-0.56, 0.95)	1.49
Bourke 2013 No stress			0.25 (-0.89, 1.38)	0.98
Freund 2013 Female no stress Exp. P2-F	P9 no shock		0.25 (-1.15, 1.65)	0.75
Altieri 2015 Female cohort 2 FLX		+++++	0.25 (-0.49, 1)	1.51
Freund 2013 Female no stress Exp. P2-F	P9 escap.		0.28 (-1.12, 1.68)	0.75
McAllister 2012		++++	0.29 (-0.42, 1)	1.57
Freund 2013 Male no stress Exp. P9-P16	б inescap.		0.31 (-1.09, 1.71)	0.75
Lisboa 2007 Male			0.33 (-0.36, 1.02)	1.61
Altieri 2015 Female cohort 3 FLX		<u>+</u> +◆	0.36 (-0.51, 1.22)	1.32
Altieri 2015 Male cohort 2 FLX		<u>i</u> +>	0.55 (-0.33, 1.42)	1.31
Coleman 1999 Female		<b>↓</b> → →	0.55 (-0.28, 1.39)	1.37
Altieri 2015 Male cohort 2 ESC		<b>→</b>	0.56 (-0.29, 1.42)	1.34
Rayen 2011 Female No stress		<b>├├</b>	0.58 (-0.36, 1.53)	1.21
Gobinath 2016 Female No stress		<u>⊢</u>	0.64 (-0.43, 1.71)	1.06
Freund 2013 Male no stress Exp. P9-P16	6 escap.		0.64 (-0.81, 2.09)	0.71
Gobinath 2016 Male No stress		<b>├</b> ─◆──	0.75 (-0.35, 1.86)	1.02
Karpova 2009			0.89 (-0.03, 1.8)	1.26
No stress		+	-0.41 (-0.58, -0.25)	
Freund 2013 Female stress Exp. P9-P16	inescap. 🔶		-4.58 (-8.03, -1.14)	0.16
Boulle 2016b Stress			-1.03 (-1.9, -0.17)	1.33
Rayen 2011 Male Stress			-0.91 (-1.89, 0.07)	1.16
Gobinath 2016 Female Stress			-0.77 (-1.85, 0.31)	1.05
Boulle 2016a Stress			-0.7 (-1.49, 0.1)	1.43
Freund 2013 Female stress Exp. P2-P9 i	nescap.		-0.62 (-2.07, 0.83)	0.71
Rayen 2011 Female Stress			-0.57 (-1.52, 0.37)	1.21
Freund 2013 Female stress Exp. P9-P16	no snock		-0.52 (-1.95, 0.91)	0.73
Freund 2013 Male stress Exp. P9-P16 no	o snock		-0.51 (-1.94, 0.92)	0.73
Freund 2013 Female stress Exp. P2-P9 r			-0.37 (-1.78, 1.04)	0.74
Freund 2013 Male stress Exp. P2-P9 no	no shock	Ť		0.75
Freund 2013 Female stress Exp. P2-P9 e	no shock shock		-0.24 (-1.64, 1.15)	
	no shock shock		-0.24 (-1.64, 1.15)	0.75
Gobinath 2016 Male Stress	no shock shock	i l	-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88)	1.13
Gobinath 2016 Male Stress Zohar 2016 Male Stress	no shock shock escap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84)	1.13 1.37
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in	no shock shock escap. iescap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52)	1.13 1.37 0.76
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine	no shock shock escap. iescap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53)	1.13 1.37 0.76 0.76
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Female Stress	no shock shock escap. rescap. rscap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53) 0.18 (-0.65, 1.02)	1.13 1.37 0.76 0.76 1.37
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Female Stress Freund 2013 Female stress Exp. P9-P16	no shock shock escap. rescap. rscap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53) 0.18 (-0.65, 1.02) 0.28 (-1.12, 1.68)	1.13 1.37 0.76 0.76 1.37 0.75
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Female Stress Freund 2013 Female stress Exp. P9-P16 Bourke 2013 Stress	no shock shock secap. lescap. secap. j: escap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53) 0.18 (-0.65, 1.02) 0.28 (-1.12, 1.68) 0.35 (-0.79, 1.5)	1.13 1.37 0.76 0.76 1.37 0.75 0.98
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Fermale Stress Freund 2013 Female stress Exp. P9-P16 Bourke 2013 Stress Freund 2013 Male stress Exp. P9-P16 es	no shock shock escap. scap. ; escap. scap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53) 0.18 (-0.65, 1.02) 0.28 (-1.12, 1.68) 0.35 (-0.79, 1.5) 0.66 (-0.8, 2.12)	1.13 1.37 0.76 0.76 1.37 0.75 0.98 0.71
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Female Stress Freund 2013 Stress Freund 2013 Male stress Exp. P9-P16 es Freund 2013 Male stress Exp. P2-P9 esc	no shock shock escap. scap. ; escap. scap.		-0.24 (-1.64, 1.15) -0.14 (-1.15, 0.88) 0 (-0.84, 0.84) 0.13 (-1.26, 1.52) 0.14 (-1.25, 1.53) 0.18 (-0.65, 1.02) 0.28 (-1.12, 1.68) 0.35 (-0.79, 1.5) 0.66 (-0.8, 2.12) 0.67 (-0.79, 2.13)	1.13 1.37 0.76 0.76 1.37 0.75 0.98 0.71 0.71
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P9 ine Zohar 2016 Female Stress Freund 2013 Female stress Exp. P9-P16 Bourke 2013 Stress Freund 2013 Male stress Exp. P2-P16 es Freund 2013 Male stress Exp. P2-P9 esc Salan 2016 Stress	no shock shock escap. scap. ; escap. scap.		$\begin{array}{c} -0.24 \left(-1.64, 1.15\right) \\ -0.14 \left(-1.15, 0.88\right) \\ 0 \left(-0.84, 0.84\right) \\ 0.13 \left(-1.26, 1.52\right) \\ 0.14 \left(-1.25, 1.53\right) \\ 0.18 \left(-0.65, 1.02\right) \\ 0.28 \left(-1.12, 1.68\right) \\ 0.35 \left(-0.79, 1.5\right) \\ 0.66 \left(-0.8, 2.12\right) \\ 0.67 \left(-0.79, 2.13\right) \\ -1.44 \left(0.31, 2.58\right) \end{array}$	1.13 1.37 0.76 0.76 1.37 0.75 0.98 0.71 0.71 0.71 0.99
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P3 Pin Zohar 2016 Female Stress Freund 2013 Foress Freund 2013 Male stress Exp. P9-P16 es Freund 2013 Male stress Exp. P2-P9 es Salari 2016 Stress Stress	no shock shock escap. scap. ; escap. scap.		$\begin{array}{r} -0.24 \ (-1.64, 1.15) \\ -0.14 \ (-1.15, 0.88) \\ 0 \ (-0.84, 0.84) \\ 0.13 \ (-1.26, 1.52) \\ 0.14 \ (-1.25, 1.53) \\ 0.18 \ (-0.65, 1.02) \\ 0.28 \ (-1.12, 1.68) \\ 0.35 \ (-0.79, 1.5) \\ 0.66 \ (-0.8, 2.12) \\ 0.67 \ (-0.79, 2.13) \\ -1.44 \ (0.31, 2.58) \\ -0.22 \ (-0.51, 0.08) \end{array}$	1.13 1.37 0.76 1.37 0.75 0.98 0.71 0.71 0.71 0.99 20.26
Gobinath 2016 Male Stress	no shock shock escap. scap. ; escap. scap.		$\begin{array}{c} -0.24 \left(-1.64, 1.15\right) \\ -0.14 \left(-1.15, 0.88\right) \\ 0 \left(-0.84, 0.84\right) \\ 0.13 \left(-1.26, 1.52\right) \\ 0.14 \left(-1.25, 1.53\right) \\ 0.18 \left(-0.65, 1.02\right) \\ 0.28 \left(-1.12, 1.68\right) \\ 0.35 \left(-0.79, 1.5\right) \\ 0.66 \left(-0.8, 2.12\right) \\ 0.67 \left(-0.79, 2.13\right) \\ -1.44 \left(0.31, 2.58\right) \end{array}$	1.13 1.37 0.76 0.76 1.37 0.75 0.98 0.71 0.71 0.71 0.99
Gobinath 2016 Male Stress Zohar 2016 Male Stress Freund 2013 Male stress Exp. P9-P16 in Freund 2013 Male stress Exp. P2-P3 Pin Zohar 2016 Female Stress Freund 2013 Foress Freund 2013 Male stress Exp. P9-P16 es Freund 2013 Male stress Exp. P2-P9 es Salari 2016 Stress Stress	no shock escap. escap. escap. é escap. scap. cap.		$\begin{array}{r} -0.24 \ (-1.64, 1.15) \\ -0.14 \ (-1.15, 0.88) \\ 0 \ (-0.84, 0.84) \\ 0.13 \ (-1.26, 1.52) \\ 0.14 \ (-1.25, 1.53) \\ 0.18 \ (-0.65, 1.02) \\ 0.28 \ (-1.12, 1.68) \\ 0.35 \ (-0.79, 1.5) \\ 0.66 \ (-0.8, 2.12) \\ 0.67 \ (-0.79, 2.13) \\ -1.44 \ (0.31, 2.58) \\ -0.22 \ (-0.51, 0.08) \end{array}$	1.13 1.37 0.76 1.37 0.75 0.98 0.71 0.71 0.71 0.99 20.26

 $\frac{-5}{4} - 3 - 2 - 1 0 \qquad 1 2$ SSRI more passive coping SSRI more active coping

**D. Stress coping - SSRI exposure period** bioRxiv preprint doi: https://doi.org/10.1101/868265; this version posted December 6, 2019. The copyright holder for this preprint (which was not certified by peer review) as the author/funder, who has granted bioRxiv a license to display the preprint/in perpetuity. It is made available Olivier2011/Male 5 under a CC-BX-NC-ND 4.0 International license - 22(108,068) 13

Olivier 2011 Male FS	under aCC-BY-NC-ND 4	4.0 International license	-0.2 (-1.08, 0.68)	•
Coleman 1999 Male			0.14 (-0.68, 0.96)	1. 0.
Bourke 2013 No stress			0.25 (-0.89, 1.38)	0.
Bourke 2013 Stress Coleman 1999 Female			0.35 (-0.79, 1.5) 0.55 (-0.28, 1.39)	1.
Prenatal			-0.09 (-0.53, 0.34)	8.
Zohar 2016 Female No stress		T	-1.74 (-2.75, -0.73)	1.
Lisboa 2007 Female			-1.35 (-2.37, -0.33)	1
Zohar 2016 Male No stress			-1.22 (-2.14, -0.29)	1.
Salari 2016 No stress			-0.73 (-1.75, 0.3)	1.
Sprowles 2016				1.
Sprowles 2016 Sprowles 2017 CIT		-YT	-0.38 (-0.95, 0.18) -0.03 (-0.54, 0.47)	1.
Zohar 2016 Male Stress		TT	0 (-0.84, 0.84)	1.
				1.
Sprowles 2017 FLX			0.05 (-0.46, 0.55)	
Zohar 2016 Female Stress			0.18 (-0.65, 1.02)	1.
McAllister 2012		<u>+</u> +◆	0.29 (-0.42, 1)	1.
Lisboa 2007 Male		<u>⊢</u> +♦—	0.33 (-0.36, 1.02)	1.
Salari 2016 Stress			- 1.44 (0.31, 2.58)	0.
Pre- and postnatal			-0.23 (-0.62, 0.16)	17.
Freund 2013 Female stress Exp. P9-P	6 inescap.		-4.58 (-8.03, -1.14)	0.
Jiang 2009			-1.74 (-2.81, -0.68)	1.
Sarkar 2014b Cohort 2			-1.69 (-2.87, -0.5)	0.
Hilakivi 1987b		+	-1.67 (-3.06, -0.27)	0.
Hansen 1997 30 mg/kg		<del></del>	-1.63 (-3.09, -0.16)	0.
Sarkar 2014a Cohort 2			-1.45 (-2.6, -0.31)	0.
Sarkar 2014b Cohort 3			-1.45 (-2.59, -0.31)	0.
Sarkar 2014a Cohort 1		i	-1.41 (-2.47, -0.35)	1.
Popa 2008			-1.36 (-2.13, -0.59)	1.
Hansen 1997 10 mg/kg		<b>\_</b>	-1.29 (-2.63, 0.05)	
Nagano 2017 FLX			-1.18 (-2.36, 0)	0.
Sarkar 2014b Cohort 1			-1.17 (-2.26, -0.09)	1.
Ko 2014			-1.11 (-2.19, -0.04)	1.
Rebello 2014 FS			-1.1 (-1.96, -0.23)	1.
Rebello 2014 Exposure P2-P11 SE			-1.04 (-1.67, -0.41)	1.
Boulle 2016b Stress		i	-1.03 (-1.9, -0.17)	1.
Mnie-Filali 2011				1.
Rebello 2014 Exposure P2-P21 SE			-1 (-2.01, 0.02) -0.93 (-1.6, -0.27)	1.
Rayen 2011 Male Stress			-0.91 (-1.89, 0.07)	1.
Ansorge 2004			-0.89 (-1.64, -0.15)	1.
Hansen 1997 20 mg/kg			-0.89 (-2.18, 0.41)	0.
Altieri 2015 Male cohort 3 FLX			-0.81 (-1.73, 0.1)	1.
Yu 2014			-0.8 (-1.51, -0.1)	1.
Gobinath 2016 Female Stress			-0.77 (-1.85, 0.31)	1.
Boulle 2016a Stress			-0.7 (-1.49, 0.1)	1.
Altieri 2015 Male cohort 1			-0.65 (-1.66, 0.36)	1.
Altieri 2015 Male cohort 3 ESC			-0.65 (-1.53, 0.23)	
Boulle 2016b No stress			-0.64 (-1.46, 0.19)	1.
Freund 2013 Female stress Exp. P2-P	inescap.		-0.62 (-2.07, 0.83)	0.
Hansen 1997 5 mg/kg			-0.61 (-1.87, 0.64)	0.
Rayen 2011 Female Stress			-0.57 (-1.52, 0.37)	1.
Yu 2012			-0.55 (-1.29, 0.18)	1.
Freund 2013 Female stress Exp. P9-P			-0.52 (-1.95, 0.91)	0.
Freund 2013 Male no stress Exp. P2-F	9 escap.		-0.51 (-1.94, 0.92)	0.
Freund 2013 Male stress Exp. P9-P16	no shock		-0.51 (-1.94, 0.92)	0.
Freund 2013 Female no stress Exp. P	J-P16 inescap.		-0.42 (-1.84, 1)	0.
Freund 2013 Male no stress Exp. P9-F	16 no shock		-0.41 (-1.82, 1.01)	0.
Freund 2013 Female no stress Exp. P	-P16 no shock		-0.39 (-1.8, 1.02)	0.
Freund 2013 Female stress Exp. P2-P			-0.37 (-1.78, 1.04)	0.
Freund 2013 Male no stress Exp. P2-F		è	-0.34 (-1.75, 1.06)	0.
Freund 2013 Male no stress Exp. P2-F			-0.33 (-1.73, 1.08)	0.
Altieri 2015 Female cohort 1	· · · ·	š	-0.32 (-1.31, 0.67)	1.
Nagano 2017 ESC		Ă	-0.29 (-1.45, 0.87)	0.
Freund 2013 Male stress Exp. P2-P9 n	o shock	k	-0.24 (-1.64, 1.15)	0.
Freund 2013 Female stress Exp. P2-P		````	-0.24 (-1.64, 1.15)	0.
Ishikawa 2017	· cocup.			1.
Gobinath 2016 Male Stress			-0.19 (-0.94, 0.57) -0.14 (-1.15, 0.88)	1.
	-P9 inescan			
Freund 2013 Female no stress Exp. P.	. i v mescap.		-0.12 (-1.51, 1.27)	0.
Rayen 2011 Male No Stress			-0.07 (-1, 0.85)	1.
Rebello 2014 Exposure P12-P21 SE		+	0 (-0.62, 0.62)	1.
Freund 2013 Female no stress Exp. P	/-P16 escap.	<u>+</u>	0.02 (-1.37, 1.41)	0.
Altieri 2015 Female cohort 3 ESC			0.13 (-0.75, 1.01)	
Freund 2013 Male stress Exp. P9-P16			0.13 (-1.26, 1.52)	0
Freund 2013 Male stress Exp. P2-P9 in	iescap.		0.14 (-1.25, 1.53)	0.
Boulle 2016a No stress		- <del>!  </del>	0.18 (-0.59, 0.95)	1
Altieri 2015 Female cohort 2 ESC			0.19 (-0.56, 0.95)	1.
Freund 2013 Female no stress Exp. P.	2-P9 no shock		0.25 (-1.15, 1.65)	0.
Altieri 2015 Female cohort 2 FLX		++++++	0.25 (-0.49, 1)	1.
Freund 2013 Female no stress Exp. P.	2-P9 escap.		0.28 (-1.12, 1.68)	0.
Freund 2013 Female stress Exp. P9-P			0.28 (-1.12, 1.68)	0.
Freund 2013 Male no stress Exp. P9-F			0.31 (-1.09, 1.71)	0.
Altieri 2015 Female cohort 3 FLX			0.36 (-0.51, 1.22)	1.
Altieri 2015 Male cohort 2 FLX		L_`	0.55 (-0.33, 1.42)	1
Altieri 2015 Male cohort 2 ESC			0.56 (-0.29, 1.42)	1.
Rayen 2011 Female No stress				1
Gobinath 2016 Female No stress			0.58 (-0.36, 1.53)	1
Gobinath 2016 Female No stress Freund 2013 Male no stress Exp. P9-F	16 occop		0.64 (-0.43, 1.71)	
Freuriu 2013 Male no stress EXD. P9-F			0.64 (-0.81, 2.09)	0
			0.66 (-0.8, 2.12)	0
Freund 2013 Male stress Exp. P9-P16			0.67 (-0.79, 2.13)	0
Freund 2013 Male stress Exp. P9-P16 Freund 2013 Male stress Exp. P2-P9 e	scap.			
Freund 2013 Male stress Exp. P9-P16 Freund 2013 Male stress Exp. P2-P9 e Gobinath 2016 Male No stress	scap.	<b>→</b>	0.75 (-0.35, 1.86)	
Freund 2013 Male stress Exp. P9-P16 Freund 2013 Male stress Exp. P2-P9 e Gobinath 2016 Male No stress Karpova 2009	scap.		0.89 (-0.03, 1.8)	1.
Freund 2013 Male stress Exp. P9-P16 Freund 2013 Male stress Exp. P2-P9 e Gobinath 2016 Male No stress	scap.			1. 74.

SSRI more passive coping SSRI more active coping

omparison			SMD (95% CI)	eight (%)	Comparison		Weig SMD (95% Cl)
		[	-1.44 (-2.84, -0.03)		· · · · · · · · · · · · · · · · · · ·		
aciag 2006a	1 10 1 1 1		-1.44 (-2.84, -0.03)	1.21	Maciag 2006a -		-1.44 (-2.84, -0.03)
rvanova 2016 Stress	it doj: nit	ps://doi.org/10.1101/86		ersion posted i	December 6, 2019. 1 ne	e copyright holder for this prep he preprint in perpetuity. It is r	rint (which was
aciag 2006b not certified by	peĕr re	<u>/i</u> ew) is the author/func	ler, who has	granted bioRx	iwaalcense to display t	he preprint∣in perpetuity. It is r	nade available
arkar 2014a		ł	under alls-	B%-NC-ND 4.0	Soga 2012	· · · · · ·	-0.93 (-1.92, 0.05)
oga 2012		I	-0.93 (-1.69, -0.17)	2.15	Soga 2012		-0.93 (-1.69, -0.17)
arris 2012 10 mg/kg		F	-0.92 (-1.98, 0.14)		Harris 2012 10 mg/kg		-0.92 (-1.98, 0.14)
ivier 2011 SPL		Г	-0.89 (-2.02, 0.24)		Olivier 2011 SPL Rodriguez-Porcel 2011 Male CIT		-0.89 (-2.02, 0.24) -0.83 (-1.7, 0.04)
nrlich 2015 No stress cohort 1		C	-0.89 (-1.93, 0.16)		Maciag 2006c		-0.81 (-1.64, 0.02)
odriguez-Porcel 2011 Female CIT		I	-0.88 (-1.74, -0.02)		Kiryanova 2016 No stress		-0.81 (-1.5, -0.11)
odriguez-Porcel 2011 Male CIT		1	-0.83 (-1.7, 0.04)	1.95	Gemmel 2017 Male no stress		-0.76 (-1.87, 0.35)
aciag 2006c		I	-0.81 (-1.64, 0.02)	2.03 2.26	Rayen 2013 No stress	<del></del>	-0.73 (-1.64, 0.18)
ryanova 2016 No stress		I			Simpson 2011 Male		-0.71 (-1.43, 0.01)
emmel 2017 Male no stress aven 2013 No stress			-0.76 (-1.87, 0.35) -0.73 (-1.64, 0.18)	1.88	Hansen 1997 30 mg/kg		-0.51 (-1.52, 0.51)
npson 2011 Female		Ē	-0.71 (-1.43, 0.01)	2.22	Harris 2012 20 mg/kg		-0.48 (-1.55, 0.59) -0.23 (-1.22, 0.76)
npson 2011 Male		1	-0.71 (-1.43, 0.01)	2.22	Gouvea 2008		-0.23 (-1.22, 0.76) -0.23 (-1.17, 0.72)
atri 2014 Cohort 2		Į.	-0.52 (-1.09, 0.04)	2.5	Hansen 1997 5 mg/kg Lisboa 2007		-0.23 (-1.17, 0.72)
ansen 1997 30 mg/kg		L	-0.51 (-1.52, 0.51)		Vieira 2013		-0.09 (-0.97, 0.78)
rris 2012 20 mg/kg	`	<u> </u>	-0.48 (-1.55, 0.59)	1.63	Rayen 2013 Stress		0.07 (-0.8, 0.95)
driguez-Porcel 2011 Female FLX		<u>—</u>	-0.26 (-1.13, 0.6)	1.95	Olivier 2011 SEX		0.08 (-0.81, 0.96)
mmel 2017 Female no stress		<u> </u>	-0.25 (-1.31, 0.82)	1.64	Harris 2012 5 mg/kg		0.1 (-0.91, 1.1)
lich 2015 Stress cohort 1		<u> </u>	-0.24 (-1.23, 0.74)	1.76	Hansen 1997 10 mg/kg	<del></del>	0.32 (-0.64, 1.29)
gh 1998		<u> </u>	-0.23 (-1.2, 0.74)	1.79	Kiryanova 2014	<u>+</u> ↔	0.34 (-0.37, 1.05)
uvea 2008		<u> </u>	-0.23 (-1.22, 0.76)	1.75	Gemmel 2017 Male stress		0.57 (-0.71, 1.85)
nsen 1997 5 mg/kg	\$i	<u> </u>	-0.23 (-1.17, 0.72)	1.83	Hansen 1997 20 mg/kg Coleman 1999 Male		0.7 (-0.29, 1.69) 0.88 (0.04, 1.71)
boa 2007					Cagiano 2008		0.96 (0.02, 1.89)
eira 2013			-0.09 (-0.97, 0.78)	1.94	Svirsky 2016 Male		1.09 (0.14, 2.04)
rowles 2016		<u> </u>	-0.05 (-0.61, 0.52)		Ko 2014	·	2.54 (1.13, 3.95)
rlich 2015 Stress cohort 2		<u> </u>	0.06 (-0.74, 0.86)	2.07	Male	•	-0.26 (-0.53, 0.02)
yen 2013 Stress		) I.	0.07 (-0.8, 0.95)	1.94	Khatri 2014 Cohort 2		-0.52 (-1.09, 0.04)
ivier 2011 SEX			0.08 (-0.81, 0.96)	1.93 2.88	Singh 1998		-0.23 (-1.2, 0.74)
atri 2014 Cohort 1 rris 2012 5 mg/kg	1	а— Ь	0.09 (-0.25, 0.42) 0.1 (-0.91, 1.1)	1.73	Sprowles 2016		-0.05 (-0.61, 0.52)
leman 1999 Female			0.18 (-0.61, 0.97)	2.09	Khatri 2014 Cohort 1		0.09 (-0.25, 0.42) 0.27 (-0.27, 0.8)
rowles 2017 CIT		LA	0.27 (-0.27, 0.8)	2.56	Sprowles 2017 CIT Sprowles 2017 FLX		0.27 (-0.27, 0.8) 0.3 (-0.24, 0.84)
owles 2017 FLX	1	с <u>к</u>	0.3 (-0.24, 0.84)	2.55	Meyer 2018		0.82 (0.22, 1.41)
lich 2015 No stress cohort 2		Lõ.	0.31 (-0.51, 1.13)	2.03	Yu 2014		1.03 (-0.11, 2.17)
nsen 1997 10 mg/kg		Long and the second sec	0.32 (-0.64, 1.29)	1.8	Mixed-sex	-	0.16 (-0.13, 0.46)
yanova 2014	_	⊢∲——	0.34 (-0.37, 1.05)	2.23	Ehrlich 2015 No stress cohort 1	<u></u>	-0.89 (-1.93, 0.16) -0.88 (-1.74, -0.02)
en 2014 No stress		⊢∻──	0.43 (-0.46, 1.32)	1.92	Rodriguez-Porcel 2011 Female CIT		-0.88 (-1.74, -0.02)
en 2014 Stress		<b>→</b>	0.49 (-0.4, 1.39)	1.91	Simpson 2011 Female	<del></del>	-0.71 (-1.43, 0.01)
s Santos 2016		<b>→</b>	0.55 (-0.37, 1.48)	1.86	Rodriguez-Porcel 2011 Female FLX		-0.26 (-1.13, 0.6)
mmel 2017 Male stress		<b>→</b>	0.57 (-0.71, 1.85)	1.35	Gemmel 2017 Female no stress		-0.25 (-1.31, 0.82)
isen 1997 20 mg/kg	-	<b>→</b>	0.7 (-0.29, 1.69)	1.76	Ehrlich 2015 Stress cohort 1 Ehrlich 2015 Stress cohort 2		-0.24 (-1.23, 0.74) 0.06 (-0.74, 0.86)
yer 2018		<b>→</b>	0.82 (0.22, 1.41)	2.44	Coleman 1999 Female		0.18 (-0.61, 0.97)
eman 1999 Male		<b></b>	0.88 (0.04, 1.71)	2.01	Ehrlich 2015 No stress cohort 2		0.31 (-0.51, 1.13)
jiano 2008		<b>_</b>	0.96 (0.02, 1.89)	1.84	Rayen 2014 No stress		0.43 (-0.46, 1.32)
2014	-	<b>_</b>	1.03 (-0.11, 2.17)	1.53	Rayen 2014 Stress		0.49 (-0.4, 1.39)
rsky 2016 Male		,	1.09 (0.14, 2.04)	1.81	Dos Santos 2016		0.55 (-0.37, 1.48)
mmel 2017 Female stress		↓	2.31 (0.52, 4.11)	0.87	Gemmel 2017 Female stress	→	2.31 (0.52, 4.11)
2014			2.54 (1.13, 3.95)	1.21	Svirsky 2016 Female		3.66 (2.12, 5.19)
rsky 2016 Female			3.66 (2.12, 5.19)	1.08	Female	-	0.18 (-0.28, 0.64)
cial behavior - Overall		f	-0.07 (-0.27, 0.13	) 100	Social behavior - Overall	+	-0.07 (-0.27, 0.13)

SSRI less pro-social SSRI more pro-social

SSRI less pro-social SSRI more pro-social

# C Social behavior - Stress exposure

Social behavior - Stress exposure	Weight	
Comparison	SMD (95% CI) (%	
1aciag 2006a 🔶 🔶	-1.44 (-2.84, -0.03) 1.2	
odriguez-Porcel 2011 Male FLX	-1.32 (-2.2, -0.43) 1.9	
Aaciag 2006b	-1.02 (-2.39, 0.34) 1.2	
arkar 2014a — 🔶 🕴	-0.93 (-1.92, 0.05) 1.7	
oga 2012 — 🔶 👘	-0.93 (-1.69, -0.17) 2.1	
larris 2012 10 mg/kg	-0.92 (-1.98, 0.14) 1.6	
Divier 2011 SPL	-0.89 (-2.02, 0.24) 1.5	
hrlich 2015 No stress cohort 1	-0.89 (-1.93, 0.16) 1.6	
odriguez-Porcel 2011 Female CIT	-0.88 (-1.74, -0.02) 1.9	
odriguez-Porcel 2011 Male CIT 🛛 🛶 🚽	-0.83 (-1.7, 0.04) 1.9	
laciag 2006c →	-0.81 (-1.64, 0.02) 2.0	
iryanova 2016 No stress —	-0.81 (-1.5, -0.11) 2.2	
iemmel 2017 Male no stress	-0.76 (-1.87, 0.35) 1.5	
ayen 2013 No stress	-0.73 (-1.64, 0.18) 1.8	
impson 2011 Female —	-0.71 (-1.43, 0.01) 2.2	
impson 2011 Male —	-0.71 (-1.43, 0.01) 2.2	
hatri 2014 Cohort 2	-0.52 (-1.09, 0.04) 2	
lansen 1997 30 mg/kg 🛛 🛶	-0.51 (-1.52, 0.51) 1.7	
larris 2012 20 mg/kg	-0.48 (-1.55, 0.59) 1.6	
odriguez-Porcel 2011 Female FLX	-0.26 (-1.13, 0.6) 1.9	
iemmel 2017 Female no stress	-0.25 (-1.31, 0.82) 1.6	
ingh 1998	-0.23 (-1.2, 0.74) 1.7	
iouvea 2008	-0.23 (-1.22, 0.76) 1.7	
lansen 1997 5 mg/kg	-0.23 (-1.17, 0.72) 1.8	
isboa 2007	-0.19 (-0.97, 0.59) 2.1	
ieira 2013	-0.09 (-0.97, 0.78) 1.9	
prowles 2016	-0.05 (-0.61, 0.52) 2.4	
Divier 2011 SEX	0.08 (-0.81, 0.96) 1.9	
hatri 2014 Cohort 1	0.09 (-0.25, 0.42) 2.8	
larris 2012 5 mg/kg	0.1 (-0.91, 1.1) 1.7	
oleman 1999 Female	0.18 (-0.61, 0.97) 2.0	
prowles 2017 CIT +	0.27 (-0.27, 0.8) 2.5	
hrlich 2015 No stress cohort 2	0.3 (-0.24, 0.84) 2.5	
	0.31 (-0.51, 1.13) 2.0	
lansen 1997 10 mg/kg	0.32 (-0.64, 1.29) 1	
ayen 2014 Average a	0.34 (-0.37, 1.05) 2.2	
los Santos 2016	0.43 (-0.46, 1.32) 1.9 0.55 (-0.37, 1.48) 1.8	
lansen 1997 20 mg/kg		
Never 2018	0.7 (-0.29, 1.69) 1.7 0.82 (0.22, 1.41) 2.4	
oleman 1999 Male	0.82 (0.22, 1.41) 2.4	
agiano 2008	0.96 (0.02, 1.89) 1.8	
u 2014	1.03 (-0.11, 2.17) 1.5	
virsky 2016 Male	1.09 (0.14, 2.04) 1.8	
o 2014	2.54 (1.13, 3.95) 1.2	
virsky 2016 Female	- 3.66 (2.12, 5.19) 1.0	
lo stress	-0.1 (-0.31, 0.12) 87.9	
iryanova 2016 Stress — — — —	-1.11 (-1.85, -0.37) 2.1	
hrlich 2015 Stress cohort 1	-0.24 (-1.23, 0.74) 1.7	
hrlich 2015 Stress cohort 2	-0.24 (-1.23, 0.74) 1.7 0.06 (-0.74, 0.86) 2.0	
ayen 2013 Stress	0.07 (-0.8, 0.95) 1.9	
ayen 2013 Stress	0.49 (-0.4, 1.39) 1.9	
iemmel 2017 Male stress	0.57 (-0.71, 1.85) 1.3	
iemmel 2017 Female stress	2.31 (0.52, 4.11) 0.8	
tress	0.12 (-0.51, 0.75) 12.0	
ocial behavior - Overall	-0.07 (-0.27, 0.13) 10	

SSRI less pro-social SSRI more pro-social

# D. Social behavior - SSRI exposure period

D. Social behavior - SSRI expo		eight
Comparison	SMD (95% CI)	(%
Dlivier 2011 SPL	-0.89 (-2.02, 0.24)	1.5
Ehrlich 2015 No stress cohort 1	-0.89 (-1.93, 0.16)	1.68
hrlich 2015 Stress cohort 1	-0.24 (-1.23, 0.74)	1.76
5ingh 1998	-0.23 (-1.2, 0.74)	1.79
hrlich 2015 Stress cohort 2	0.06 (-0.74, 0.86)	2.03
Dlivier 2011 SEX	0.08 (-0.81, 0.96)	1.93
Coleman 1999 Female 🛛 🚽 🔶 🛶	0.18 (-0.61, 0.97)	2.09
hrlich 2015 No stress cohort 2	0.31 (-0.51, 1.13)	2.03
oleman 1999 Male	0.88 (0.04, 1.71)	2.0
Tagiano 2008	0.96 (0.02, 1.89)	1.84
ivirsky 2016 Male	1.09 (0.14, 2.04)	1.8
virsky 2016 Female –	3.66 (2.12, 5.19)	1.0
Prenatal 🔶	0.34 (-0.16, 0.84)	21.6
iryanova 2016 Stress — — 🔶 🚽	-1.11 (-1.85, -0.37)	2.1
iryanova 2016 No stress — — —	-0.81 (-1.5, -0.11)	2.2
iemmel 2017 Male no stress	-0.76 (-1.87, 0.35)	1.5
iemmel 2017 Female no stress	-0.25 (-1.31, 0.82)	1.6
iouvea 2008	-0.23 (-1.22, 0.76)	1.7
isboa 2007	-0.19 (-0.97, 0.59)	2.1
ieira 2013	-0.09 (-0.97, 0.78)	1.9
prowles 2016 —	-0.05 (-0.61, 0.52)	2.4
prowles 2017 CIT + + -	0.27 (-0.27, 0.8)	2.5
prowles 2017 FLX	0.3 (-0.24, 0.84)	2.5
iryanova 2014 🚽 🔶	0.34 (-0.37, 1.05)	2.2
los Santos 2016	0.55 (-0.37, 1.48)	1.8
iemmel 2017 Male stress	0.57 (-0.71, 1.85)	1.3
Neyer 2018	0.82 (0.22, 1.41)	2.4
iemmel 2017 Female stress	2.31 (0.52, 4.11)	0.8
re- and postnatal	0.03 (-0.29, 0.35)	29.8
Aaciag 2006a	-1.44 (-2.84, -0.03)	1.2
	-1.32 (-2.2, -0.43)	1.9 1.2
Aaciag 2006b  arkar 2014a	-1.02 (-2.39, 0.34)	1.7
oga 2012	-0.93 (-1.92, 0.05)	2.1
larris 2012 10 mg/kg	-0.93 (-1.69, -0.17) -0.92 (-1.98, 0.14)	1.6
odriguez-Porcel 2011 Female CIT	-0.92 (-1.98, 0.14) -0.88 (-1.74, -0.02)	1.0
odriguez-Porcel 2011 Male CIT		1.9
laciag 2006c	-0.83 (-1.7, 0.04) -0.81 (-1.64, 0.02)	2.0
ayen 2013 No stress	-0.73 (-1.64, 0.02)	1.8
impson 2011 Female	-0.71 (-1.43, 0.01)	2.2
impson 2011 Male	-0.71 (-1.43, 0.01)	2.2
hatri 2014 Cohort 2	-0.52 (-1.09, 0.04)	2.
ansen 1997 30 mg/kg	-0.51 (-1.52, 0.51)	1.7
arris 2012 20 mg/kg	-0.48 (-1.55, 0.59)	1.6
odriguez-Porcel 2011 Female FLX	-0.26 (-1.13, 0.6)	1.9
lansen 1997 5 mg/kg	-0.23 (-1.17, 0.72)	1.8
ayen 2013 Stress	0.07 (-0.8, 0.95)	1.9
hatri 2014 Cohort 1	0.09 (-0.25, 0.42)	2.8
arris 2012 5 mg/kg	0.1 (-0.91, 1.1)	1.7
lansen 1997 10 mg/kg	0.32 (-0.64, 1.29)	1.
ayen 2014 No stress	0.43 (-0.46, 1.32)	1.9
ayen 2014 Stress	0.49 (-0.4, 1.39)	1.9
lansen 1997 20 mg/kg	0.7 (-0.29, 1.69)	1.7
u 2014	1.03 (-0.11, 2.17)	1.5
o 2014	2.54 (1.13, 3.95)	1.2
ostnatal 🔶	-0.32 (-0.58, -0.05)	48.5
ocial behavior - Overall 🔷 🔶	-0.07 (-0.27, 0.13)	10
-3 -2 -1 0 1 2	3 4 5	

A. Learning and	memory	Weight	B. Learning and	l memory - Sex	Weight
Comparison	•	SMD (95% CI) (%)	Comparison	•	SMD (95% CI) (%)
Rebello 2012 -		-1.26 (-2.12, -0.41) 1.91	Rebello 2012		-1.26 (-2.12, -0.41) 1.91
Rebello 2014	I	-1.07 (-1.67, -0.47) 2.74	Schaefer 2013 15 mg/kg		-0.79 (-1.67, 0.09) 1.84
Sprowles 2017 GT & W Aring proprie	n <del>t dâi bttps://doi</del> /	0, 110, 110, 10, 10, 10, 10, 10, 10, 10,	nocted Dokuwangka-2018 Street 10 The	convright holdor for this pr	00rinf6/13131089
Schaefer 2013 15 mg/kg		JIG/ 10. 110 1/000203, 1115 VEISION	posted December 6 5 2019. The december of display the construction of the construction	copyrigrit thouser for this bi	epinite 48 (wij28, Gi44) wap
Kiryanova 2016 🕅 🖓 Certified D	y peer review) is t	ne author/tunder, who pas grant	ed bioRxiv arlicense to display the	e preprint in perpetuity. It i	s made available
Simpson 2011	<del></del>	-0.57 (-under a CC-BY-NC	C-ND 4.0 Inteinationalmicense.		-0.36 (-1.76, 1.05) 0.95
	<del></del>		Ishiwata 2005 No stress		-0.18 (-1.05, 0.7) 1.85 -0.13 (-0.93, 0.67) 2.06
Volodina 2014		-0.5 (-0.97, -0.03) 3.29	Bairy 2007 Male 8 mg/kg		-0.13 (-0.93, 0.67) 2.06 -0.12 (-1.33, 1.08) 1.21
Sprowles 2016 MWM		-0.43 (-0.97, 0.11) 2.99	Kiryanova 2016 No stress		-0.08 (-0.74, 0.59) 2.51
Sprowles 2017 CIT MWM		-0.43 (-0.94, 0.08) 3.12	Ishiwata 2005 Stress		-0.03 (-0.83, 0.77) 2,06
Schaefer 2013 10 mg/kg		-0.42 (-1.28, 0.44) 1.9	Vorhees 1994 Male 1 mg/kg	<del>\</del>	0.13 (-0.42, 0.68) 2.94
Sarkar 2014a		-0.4 (-1.33, 0.54) 1.71	Kiryanova 2014	<b>\</b>	0.21 (-0.49, 0.9) 2.4
Cagiano 2008 10 mg/kg		-0.36 (-1.76, 1.05) 0.95	Vorhees 1994 Male 5 mg/kg		0.24 (-0.31, 0.79) 2.94
Sprowles 2017 FLX MWM		-0.27 (-0.78, 0.25) 3.1	Christensen 2000 Male		0.28 (-0.54, 1.11) 2
Ehrlich 2015 No stress cohort 2		-0.19 (-1.01, 0.63) 2.01	Kroeze 2016		0.34 (-0.42, 1.09) 2.2
Svirsky 2016 Male		-0.18 (-1.05, 0.7) 1.85	Vorhees 1994 Male 12 mg/kg		0.44 (-0.1, 0.97) 3.02
Meyer 2018 Vorhees 1994 Female 1 mg/kg		-0.17 (-0.75, 0.4) 2.85 -0.16 (-0.71, 0.39) 2.94	Ishikawa 2017 Olivier 2011	^	0.49 (-0.56, 1.54) 1.46 0.91 (-0.02, 1.84) 1.72
Vorhees 1994 Female 5 mg/kg		-0.16 (-0.71, 0.39) 2.94 -0.14 (-0.69, 0.41) 2.94	Cagiano 2008 5 mg/kg		0.99 (-0.53, 2.5) 0.84
Ishiwata 2005 No stress		-0.13 (-0.93, 0.67) 2.06	Bairy 2007 Male 12 mg/kg	<u> </u>	- 2.27 (0.64, 3.91) 0.74
Bairy 2007 Male 8 mg/kg		-0.12 (-1.33, 1.08) 1.21	Male	+	0.02 (-0.22, 0.26) 40.63
Vorhees 1994 Female 12 mg/kg		-0.11 (-0.64, 0.42) 3.03	Rebello 2014	→	-1.07 (-1.67, -0.47) 2.74
Kiryanova 2016 No stress		-0.08 (-0.74, 0.59) 2.51	Sprowles 2017 CIT RWM		-0.85 (-1.66, -0.04) 2.04
Sprowles 2017 FLX CWM		-0.07 (-0.62, 0.48) 2.95	Simpson 2011	<del></del>	-0.57 (-1.73, 0.6) 1.26
Sprowles 2017 CIT CWM		-0.04 (-0.58, 0.5) 3	Sprowles 2017 FLX RWM		-0.51 (-1.35, 0.33) 1.95
Ishiwata 2005 Stress		-0.03 (-0.83, 0.77) 2.06	Volodina 2014		-0.5 (-0.97, -0.03) 3.29
Sprowles 2016 CWM	<b>_</b> _	0.08 (-0.47, 0.62) 2.97	Sprowles 2016 MWM Sprowles 2017 CIT MWM		-0.43 (-0.97, 0.11) 2.99 -0.43 (-0.94, 0.08) 3.12
Ehrlich 2015 No stress cohort 1	<b>&gt;</b> _	0.08 (-0.9, 1.06) 1.61	Sprowles 2017 CT1 MWM		-0.27 (-0.78, 0.25) 3.1
McAllister 2012	<b>&gt;</b>	0.1 (-0.58, 0.79) 2.44	Meyer 2018		-0.17 (-0.75, 0.4) 2.85
Bairy 2007 Female 8 mg/kg	¢	0.1 (-1.1, 1.31) 1.21	Sprowles 2017 FLX CWM		-0.07 (-0.62, 0.48) 2.95
Christensen 2000 Female	<b>\</b>	0.12 (-0.7, 0.94) 2.01	Sprowles 2017 CIT CWM		-0.04 (-0.58, 0.5) 3
Vorhees 1994 Male 1 mg/kg		0.13 (-0.42, 0.68) 2.94	Sprowles 2016 CWM		0.08 (-0.47, 0.62) 2.97
Ehrlich 2015 Stress cohort 2		0.2 (-0.6, 1.01) 2.06	Mixed-sex	+	-0.36 (-0.54, -0.17) 32.25
Kiryanova 2014		0.21 (-0.49, 0.9) 2.4	Ehrlich 2015 No stress cohort 2		-0.19 (-1.01, 0.63) 2.01
Vorhees 1994 Male 5 mg/kg	+	0.24 (-0.31, 0.79) 2.94	Vorhees 1994 Female 1 mg/kg		-0.16 (-0.71, 0.39) 2.94
Christensen 2000 Male		0.28 (-0.54, 1.11) 2	Vorhees 1994 Female 5 mg/kg Vorhees 1994 Female 12 mg/kg		-0.14 (-0.69, 0.41) 2.94 -0.11 (-0.64, 0.42) 3.03
Ehrlich 2015 Stress cohort 1		0.31 (-0.68, 1.3) 1.59	Ehrlich 2015 No stress cohort 1		0.08 (-0.9, 1.06) 1.61
Kroeze 2016		0.34 (-0.42, 1.09) 2.2	McAllister 2012	č	0.1 (-0.58, 0.79) 2.44
Vorhees 1994 Male 12 mg/kg Ishikawa 2017		0.44 (-0.1, 0.97) 3.02 0.49 (-0.56, 1.54) 1.46	Bairy 2007 Female 8 mg/kg	k	0.1 (-1.1, 1.31) 1.21
Kiryanova 2017b Stress		0.65 (-0.31, 1.6) 1.66	Christensen 2000 Female	<b>\</b>	0.12 (-0.7, 0.94) 2.01
Kirvanova 2017b No stress		0.68 (-0.27, 1.64) 1.66	Ehrlich 2015 Stress cohort 2		0.2 (-0.6, 1.01) 2.06
Olivier 2011		0.91 (-0.02, 1.84) 1.72	Ehrlich 2015 Stress cohort 1		0.31 (-0.68, 1.3) 1.59
Cagiano 2008 5 mg/kg		- 0.99 (-0.53, 2.5) 0.84	Kiryanova 2017b Stress		0.65 (-0.31, 1.6) 1.66
Svirsky 2016 Female	Ť	2.18 (1.02, 3.33) 1.28	Kiryanova 2017b No stress Svirsky 2016 Female	^	0.68 (-0.27, 1.64) 1.66 2.18 (1.02, 3.33) 1.28
Bairy 2007 Male 12 mg/kg		2.27 (0.64, 3.91) 0.74	Bairy 2007 Female 12 mg/kg		2.18 (1.02, 3.33) 1.28 2.44 (0.75, 4.13) 0.7
Bairy 2007 Female 12 mg/kg		2.44 (0.75, 4.13) 0.7	Female	· ·	0.26 (-0.05, 0.57) 27.13
Learning and memory - Overall	4	-0.04 (-0.2, 0.11) 100	Learning and memory - Overall		-0.04 (-0.2, 0.11) 100
					1
-3 -;	2 -1 0 1 2	3 4	<	-2 -1 0 1 2 3	<sup>4</sup> →
SSRI worse	memory SSRI better	memory	SSRI wor	rse memory SSRI better memor	у

# C. Learning and memory - Stress exposure

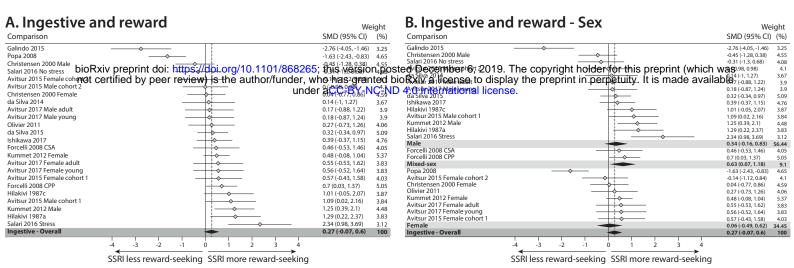
	Ty Sucssexposure	
Comparison	SMD (95% CI)	Weigh
Rebello 2012	-1.26 (-2.12, -0.41)	1.91
Rebello 2014 —	-1.07 (-1.67, -0.47)	2.74
Sprowles 2017 CIT RWM	-0.85 (-1.66, -0.04)	2.04
Schaefer 2013 15 mg/kg	-0.79 (-1.67, 0.09)	1.84
Simpson 2011	-0.57 (-1.73, 0.6)	1.26
Sprowles 2017 FLX RWM	0.51 (-1.35, 0.33)	1.95
Volodina 2014 —	-0.5 (-0.97, -0.03)	3.29
Sprowles 2016 MWM	-0.43 (-0.97, 0.11)	2.99
Sprowles 2017 CIT MWM →	-0.43 (-0.94, 0.08)	3.12
Schaefer 2013 10 mg/kg	-0.42 (-1.28, 0.44)	1.9
Sarkar 2014a	-0.4 (-1.33, 0.54)	1.71
Cagiano 2008 10 mg/kg	-0.36 (-1.76, 1.05)	0.95
Sprowles 2017 FLX MWM	-0.27 (-0.78, 0.25)	3.1
Ehrlich 2015 No stress cohort 2	-0.19 (-1.01, 0.63)	2.01
Svirsky 2016 Male	-0.18 (-1.05, 0.7)	1.85
Meyer 2018 -	0.17 (-0.75, 0.4)	2.85
Vorhees 1994 Female 1 mg/kg	0.16 (-0.71, 0.39)	2.94
Vorhees 1994 Female 5 mg/kg	0.14 (-0.69, 0.41)	2.94
shiwata 2005 No stress		2.06
Bairy 2007 Male 8 mg/kg	-0.12 (-1.33, 1.08)	1.21
/orhees 1994 Female 12 mg/kg	0.12 (-1.33, 1.08)	3.03
Kiryanova 2016 No stress	-0.08 (-0.74, 0.59)	2.51
Sprowles 2017 FLX CWM		
Sprowles 2017 CIT CWM	0.07 (-0.62, 0.48)	2.95
Sprowles 2017 CH CWM		3
Ehrlich 2015 No stress cohort 1		2.97
	0.08 (-0.9, 1.06)	1.61
McAllister 2012		2.44
Bairy 2007 Female 8 mg/kg	0.1 (-1.1, 1.31)	1.21
Christensen 2000 Female	0.12 (-0.7, 0.94)	2.01
/orhees 1994 Male 1 mg/kg	0.13 (-0.42, 0.68)	2.94
Kiryanova 2014	O.21 (-0.49, 0.9)	2.4
/orhees 1994 Male 5 mg/kg	0.24 (-0.31, 0.79)	2.94
Christensen 2000 Male	0.28 (-0.54, 1.11)	2
Kroeze 2016		2.2
/orhees 1994 Male 12 mg/kg	-> 0.44 (-0.1, 0.97)	3.02
shikawa 2017 —		1.46
Kiryanova 2017b No stress		1.66
Dlivier 2011		1.72
Lagiano 2008 5 mg/kg	0.99 (-0.53, 2.5)	0.84
Svirsky 2016 Female	2.18 (1.02, 3.33)	1.28
Bairy 2007 Male 12 mg/kg	2.27 (0.64, 3.91)	0.74
Bairy 2007 Female 12 mg/kg	2.44 (0.75, 4.13)	0.7
No stress	-0.05 (-0.22, 0.11)	90.24
Kiryanova 2016 Stress	-0.61 (-1.31, 0.09)	2.38
shiwata 2005 Stress	-0.03 (-0.83, 0.77)	2.06
Ehrlich 2015 Stress cohort 2	>	2.06
hrlich 2015 Stress cohort 1	♦ 0.31 (-0.68, 1.3)	1.59
Kiryanova 2017b Stress	→ 0.65 (-0.31, 1.6)	1.66
Stress	<ul> <li>0.03 (-0.4, 0.46)</li> </ul>	9.76
Learning and memory - Overall	-0.04 (-0.2, 0.11)	100

SSRI worse memory SSRI better memory

## D. Learning and memory - SSRI exposure period Comparison SMD (95% Cl) Weight (%)

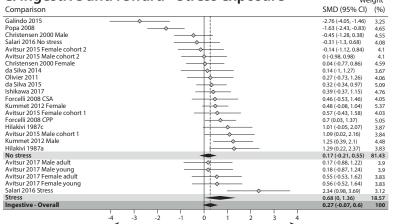
Comparison					SMD (95% CI)	Weigh
Cagiano 2008 10 mg/kg					-0.36 (-1.76, 1.05)	0.95
Ehrlich 2015 No stress coho	rt 2 ·				-0.19 (-1.01, 0.63)	2.01
Svirsky 2016 Male	-				-0.18 (-1.05, 0.7)	1.85
Vorhees 1994 Female 1 mg/	/ka				-0.16 (-0.71, 0.39)	2.94
Vorhees 1994 Female 5 mg/					-0.14 (-0.69, 0.41)	2.94
Bairy 2007 Male 8 mg/kg					-0.12 (-1.33, 1.08)	1.21
Vorhees 1994 Female 12 mg	a/ka				-0.11 (-0.64, 0.42)	3.03
Ehrlich 2015 No stress coho					0.08 (-0.9, 1.06)	1.61
Bairy 2007 Female 8 mg/kg			_		0.1 (-1.1, 1.31)	1.21
Christensen 2000 Female					0.12 (-0.7, 0.94)	2.01
Vorhees 1994 Male 1 mg/kg	1				0.13 (-0.42, 0.68)	2.94
Ehrlich 2015 Stress cohort 2					0.2 (-0.6, 1.01)	2.06
Vorhees 1994 Male 5 mg/kg					0.24 (-0.31, 0.79)	2.94
Christensen 2000 Male					0.28 (-0.54, 1.11)	2
Fhrlich 2015 Stress cohort 1			_		0.31 (-0.68, 1.3)	1.59
Vorhees 1994 Male 12 mg/k	a	L.			0.44 (-0.1, 0.97)	3.02
Cagiano 2008 5 mg/kg	-9	`			0.99 (-0.53, 2.5)	0.84
Svirsky 2016 Female					2.18 (1.02, 3.33)	1.28
Bairy 2007 Male 12 mg/kg				_	2.27 (0.64, 3.91)	0.74
Bairy 2007 Female 12 mg/kg	a		`		2.44 (0.75, 4.13)	0.7
Prenatal	,	-			0.23 (-0.01, 0.48)	37.84
Sprowles 2017 CIT RWM		~~···			-0.85 (-1.66, -0.04)	2.04
Kiryanova 2016 Stress	_	· •			-0.61 (-1.31, 0.09)	2.38
Sprowles 2017 FLX RWM	_				-0.51 (-1.35, 0.33)	1.95
Sprowles 2016 MWM					-0.43 (-0.97, 0.11)	2.99
Sprowles 2017 CIT MWM					-0.43 (-0.94, 0.08)	3.12
Sprowles 2017 FLX MWM					-0.27 (-0.78, 0.25)	3.1
Meyer 2018					-0.17 (-0.75, 0.4)	2.85
Kiryanova 2016 No stress					-0.08 (-0.74, 0.59)	2.51
Sprowles 2017 FLX CWM		-			-0.07 (-0.62, 0.48)	2.95
Sprowles 2017 CIT CWM					-0.04 (-0.58, 0.5)	3
Sprowles 2016 CWM					0.08 (-0.47, 0.62)	2.97
McAllister 2012					0.1 (-0.58, 0.79)	2.44
Kiryanova 2014					0.21 (-0.49, 0.9)	2.4
Króeze 2016		+ <b>↓</b>			0.34 (-0.42, 1.09)	2.2
Kiryanova 2017b Stress					0.65 (-0.31, 1.6)	1.66
Kiryanova 2017b No stress					0.68 (-0.27, 1.64)	1.66
Olivier 2011					0.91 (-0.02, 1.84)	1.72
Pre- and postnatal		+			-0.09 (-0.28, 0.09)	41.93
Rebello 2012		_			-1.26 (-2.12, -0.41)	1.91
Rebello 2014					-1.07 (-1.67, -0.47)	2.74
Schaefer 2013 15 mg/kg		<			-0.79 (-1.67, 0.09)	1.84
Simpson 2011					-0.57 (-1.73, 0.6)	1.26
Volodina 2014		<b>→</b>			-0.5 (-0.97, -0.03)	3.29
Schaefer 2013 10 mg/kg		<b>→</b>			-0.42 (-1.28, 0.44)	1.9
Sarkar 2014a					-0.4 (-1.33, 0.54)	1.71
Ishiwata 2005 No stress					-0.13 (-0.93, 0.67)	2.06
Ishiwata 2005 Stress					-0.03 (-0.83, 0.77)	2.06
Ishikawa 2017		<b>→</b>	_		0.49 (-0.56, 1.54)	1.46
Postnatal		+			-0.52 (-0.81, -0.22)	20.23
Learning and second second second	vorall	-			-0.04 (-0.2, 0.11)	100
Learning and memory - Ov	veran					

SSRI worse memory SSRI better memory



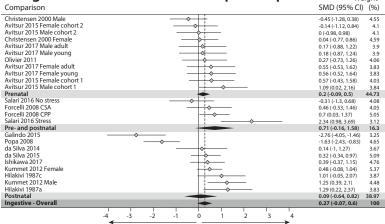
Weight

## C. Ingestive and reward - Stress exposure



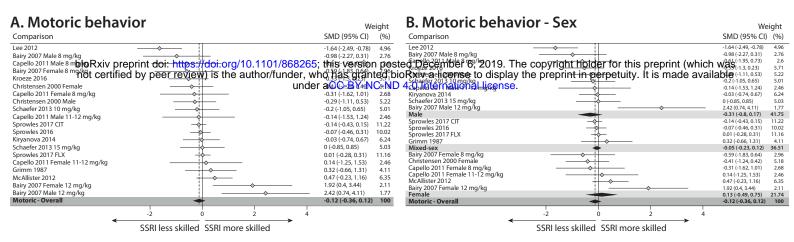
SSRI less reward-seeking SSRI more reward-seeking

# D. Ingestive and reward - SSRI exposure period

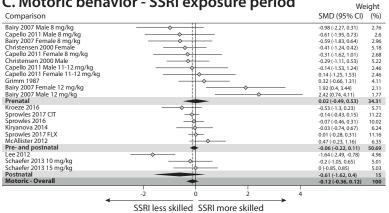


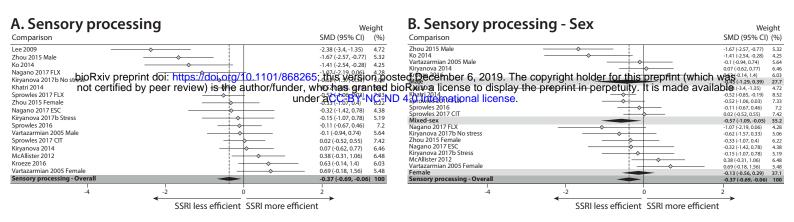
Weight

SSRI less reward-seeking SSRI more reward-seeking



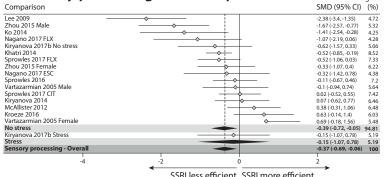
### C. Motoric behavior - SSRI exposure period





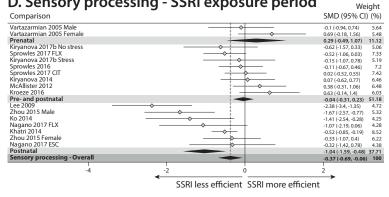
Weight

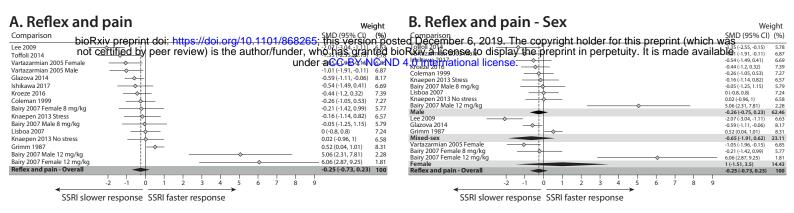
# C. Sensory processing - Stress exposure



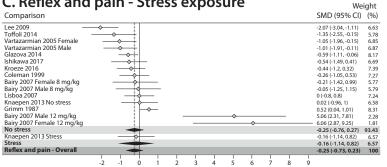
SSRI less efficient SSRI more efficient

# D. Sensory processing - SSRI exposure period



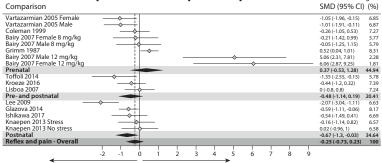


# C. Reflex and pain - Stress exposure



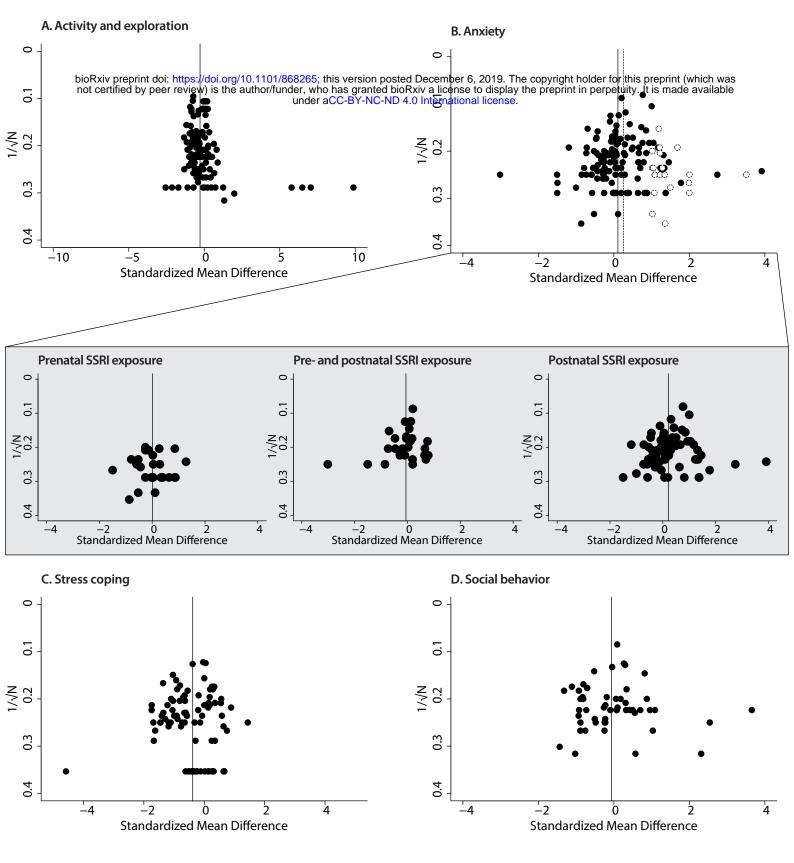
SSRI slower response SSRI faster response

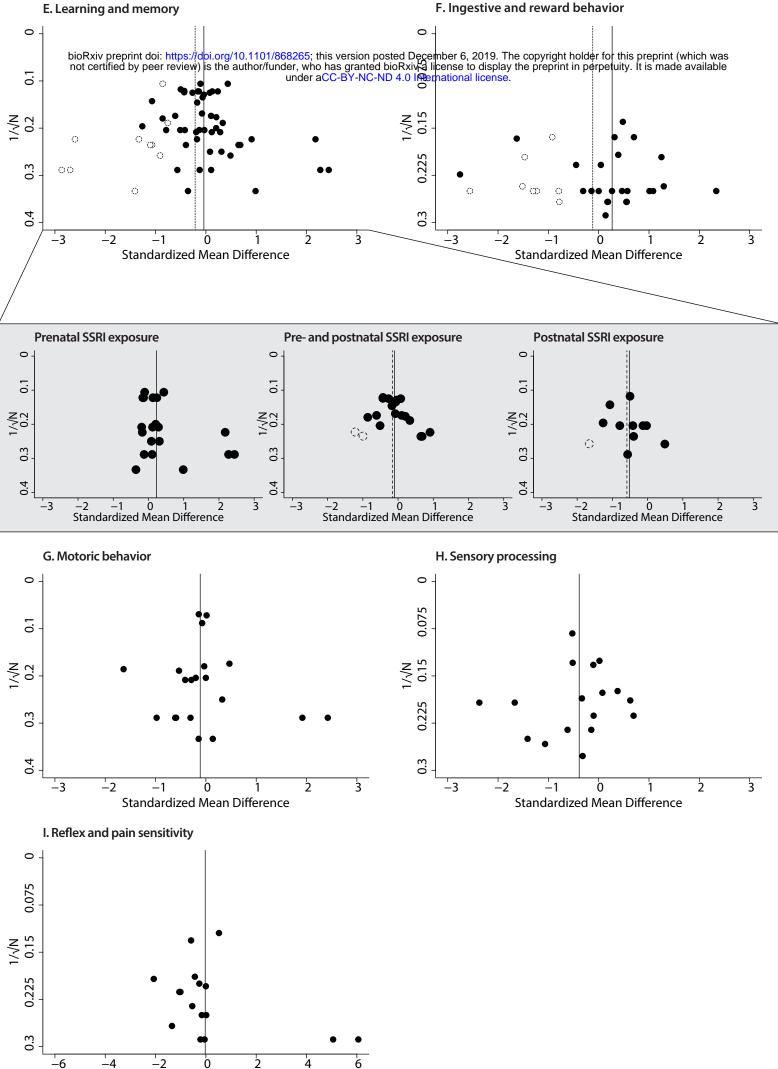
D. Reflex and pain - SSRI exposure period



Weight

SSRI slower response SSRI faster response





-6 -4 -2 0 2 Standardized Mean Difference