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Review article

Long-lasting effects of prenatal stress on HPA axis and inflammation: A systematic review and multilevel meta-analysis in rodent studies

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ABSTRACT

Exposure to prenatal stress (PNS) can lead to long-lasting neurobiological and behavioral consequences for the offspring, which may enhance the susceptibility for mental disorders. The hypothalamus-pituitary-adrenal (HPA) axis and the immune system are two major factors involved in the stress response. Here, we performed a systematic review and meta-analysis of rodent studies that investigated the effects of PNS exposure on the HPA axis and inflammatory cytokines in adult offspring. Our analysis shows that animals exposed to PNS display a consistent increase in peripheral corticosterone (CORT) levels and central corticotrophin-releasing hormone (CRH), while decreased levels of its receptor 2 (CRHR2). Meta-regression revealed that sex and duration of PNS protocol are covariates that moderate these results. There was no significant effect of PNS in glucocorticoid receptor (GR), CRH receptor 1 (CRHR1), pro- and anti-inflammatory cytokines. Our findings suggest that PNS exposure elicits long-lasting effects on the HPA axis function, providing an important tool to investigate in preclinical settings key pathological aspects related to early-life stress exposure. Furthermore, researchers should be aware of the mixed outcomes of PNS on inflammatory markers in the adult brain.

1. Introduction

The prenatal period is an extremely important and sensitive stage for the life of each individual since the organism is rapidly evolving and can undergo the influence of positive and negative stimuli from the environment of the womb (Marco et al., 2011). Indeed, during this period, the fetus is directly influenced by the mother's physiological changes, which can be transferred through the placenta in the form of hormones, immune mediators, or nutrients. With this respect, exposure to stress, which is known to be a major risk factor for neuropsychiatric diseases, can alter the normal trajectories of brain maturation thus leading to long-lasting neurobiological and behavioral consequences for the offspring (Abbott et al., 2018; Babenko et al., 2015).

Animal models are extremely valuable to better understand the complex mechanisms underlying the stress response, potentially helping to elucidate the neurobiological bases of psychiatric disorders that represent a long-lasting consequence of the exposure to early life adversities (Scharf and Schmidt, 2012). For instance, exposure to prenatal stress (PNS) may lead to the onset of behavioral alterations, during adolescence and at adulthood, and represents a consistent model used in rodents to mimic key etiological aspects of several mental disorders (Cao-Lei et al., 2017; Weinstock, 2008). Many studies using both rats and mice reported that PNS increases anxiety and depressive-like behavior and impairs cognition in the offspring of stressed dams (Cattaneo et al., 2019; Gur et al., 2017; Welberg et al., 2000; Zhang et al., 2016). However, it is already known that each individual may respond differently to stress exposure and that, next to stress, genetic predisposition represents a major risk factor for the development of psychiatry disorders (Boersma and Tamashiro, 2015; Bosch et al., 2006). With this respect, there is increasing evidence of the behavioral and molecular impact of PNS in transgenic animals targeting different genes and mechanisms (for review see Abbott et al., 2018).

Exposure to stressful events during pregnancy may lead to the maternal release of stress hormones, such as cortisol in humans and

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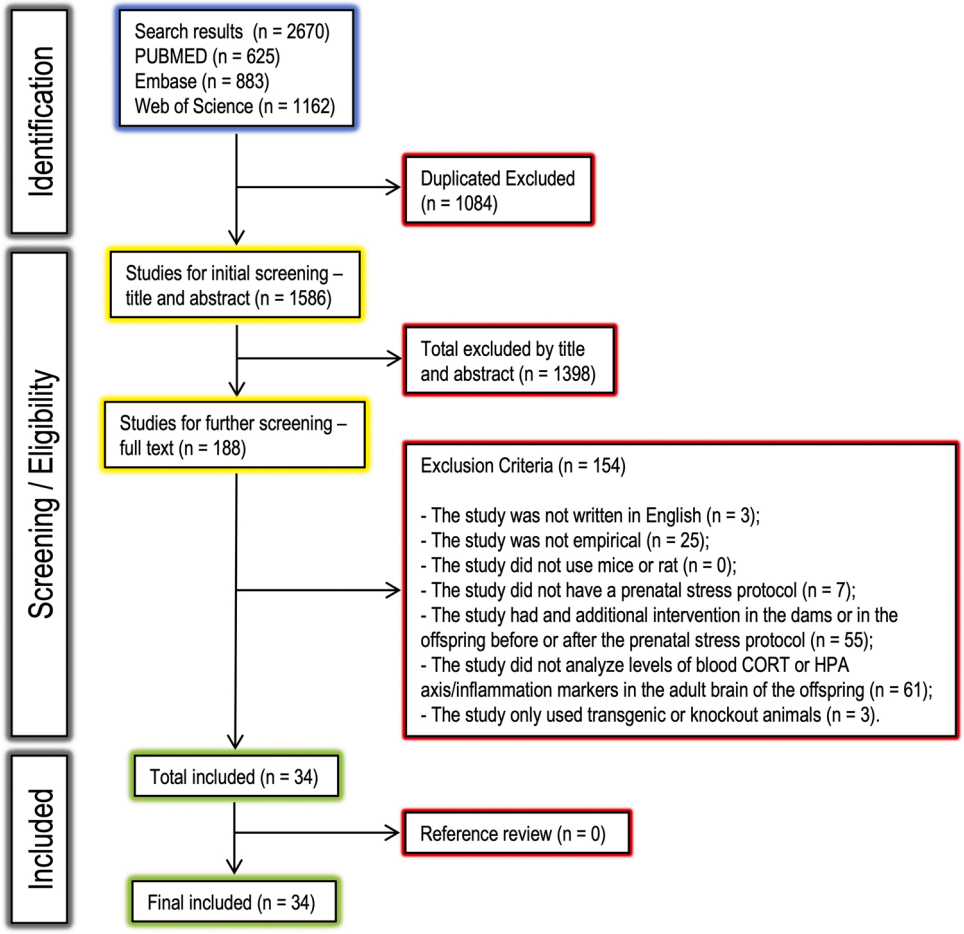

Fig. 1. Flow chart of the systematic review.

corticosterone (CORT) in rodents. Moreover, exposure to stressful situations during pregnancy can trigger the sympathetic nervous system through the increase of adrenaline and noradrenaline secretion (Douglas, 2011) and can alter a range of circulating metabolites (Lian et al., 2020). Regarding the mechanisms underlying the stress response, it is essential to highlight the hypothalamic-pituitary-adrenal (HPA) axis that is activated by the corticotrophin-releasing hormone (CRH) which is released by neuronal projections of neurons of the paraventricular nucleus of the hypothalamus (PVN). The HPA axis is the main system involved in stress responsiveness and it is linked to the above-mentioned neurobiological and behavioral changes. Briefly, the release of CRH from the CRH neurons of the PVN starts the HPA axis cascade and stimulates the anterior pituitary gland to produce and secrete the adrenocorticotropic hormone (ACTH) which will further induce the synthesis of glucocorticoids within the adrenal glands (Stephens and Wand, 2012). In rodents the main glucocorticoid is CORT that is able to reach the fetus through the placenta (Weinstock, 2008): CORT levels are increased following stress exposure during pregnancy in dams, as well as in its offspring (Anacker et al., 2013; Fan et al., 2009; Lan et al., 2017; Ward et al., 2000).

Nevertheless, during pregnancy, the dam's organism adopts different strategies to cope with stressful situations to protect the fetus. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) within the placenta can inactivate CORT thus minimizing the fetal exposure to glucocorticoids, however, it does not completely block the mother-to-fetus transmission (van Bodegom et al., 2017; Welberg et al., 2000). This early exposure to glucocorticoids may be responsible for the long-term alterations in stress responsiveness. Additionally, evidence suggests that 11β-HSD2 expression is reduced and glucocorticoid receptor (GR) is increased in the placenta under PNS conditions (Panetta et al., 2017). However, dams from a low anxiety-related behavior line showed to have higher activity of placental 11β-HSD2 when compared to dams from a high anxiety-related behavior line, suggesting that the mother's genetic background can influence the degree of protection from maternal glucocorticoid exposure (Lucassen et al., 2009). Besides the levels of 11β-HSD2, it is also known that the HPA axis is hyporesponsive in late pregnancy in humans and rodents (for review see Brunton et al., 2008), evidenced by an attenuation on the levels of CORT and ACTH after stress exposure (Douglas et al., 2003; Neumann et al., 1998). Different studies suggest that this reduced responsiveness of the HPA may be due to altered levels of endogenous opioids and oxytocin in the pregnant dam (Brunton et al., 2008; Douglas et al., 2005; Neumann et al., 2000). The altered HPA axis regulation is evident from the significant functional variance of CRH and its receptors (CRHR1 and CRHR2), as well as of GR and CORT in animals exposed to PNS (Stephens and Wand, 2012).

Nevertheless, the changes on the HPA axis within the offspring represent only one of the long-term consequences produced by PNS exposure. The immune system is also potentially modified by adverse experiences during the fetal period, since there is a strong link between stress, glucocorticoid function and neuroinflammation, which may also represent a key element for the susceptibility to mental disorders (Dowell et al., 2019; Zhang et al., 2016). There is a bidirectional communication between the immune system and the central nervous system, which is enabled by cytokines that can cross the blood-brain barrier and are involved in a range of processes, including the stimulation of the HPA axis (Eskandari et al., 2003). Exposure to PNS has been associated with alterations in the levels of pro- and anti-inflammatory

Table 1
List of included studies sorted by temporal order.

First Author	Year
Luft et al.	2020
Niu et al.	2020
Mazzelli et al.	2020
Liao et al.	2020
Enayati et al.	2020
Chen et al.	2020
Gur et al.	2019
Cattaneo et al.	2018
Pascuan et al.	2017
Luoni et al.	2016
Pivina et al.	2016
Ratajczak et al.	2015
Zohar et al.	2015
Wang et al.	2013
Bolton et al.	2013
Anacker et al.	2013
Brunton et al.	2011
Zohar & Weinstock	2011
Green et al.	2011
García-Cáceres et al.	2010
Brunton & Russell	2010
Fan et al.	2009
Mueller & Bale	2008
Nagano et al.	2008
Sliwowska et al.	2008
Mandyam et al.	2008
Jezová et al.	2002
Page et al.	2001
Welberg et al.	2001
Ward et al.	2000
Szuran et al.	2000
Welberg et al.	2000
Smythe et al.	1996
Cratty et al.	1995

cytokines (Brunton and Russell, 2011; Dowell et al., 2019) in the placenta (Gur et al., 2017; Mueller and Bale, 2008), as well as in the offspring's brain (Enayati et al., 2020; Gur et al., 2019).

Despite the strong scientific background, studies using PNS models in rodents that have investigated the HPA axis and inflammatory markers have yielded mixed results. These inconsistent findings might be attributable to a number of variables, including the timing and the length of stress exposure, the rodent species, the brain region assessed, as well as potential sex differences. Therefore, the aim of this study was to perform a systematic review and meta-analysis with the findings of rodent studies that investigated the effects of PNS exposure on the HPA axis and on inflammatory cytokines within the adult offspring. We also explored sources of heterogeneity between studies using meta-regression models.

2. Methods

2.1. Search strategy

The search was performed on April 6th, 2020, and updated on October 26th, in three online databases, PubMed, EMBASE, and Web of Science. The following MeSH terms were used: ["prenatal stress" OR "gestational stress" OR "perinatal stress" OR "antenatal stress" OR "pregnancy stress" OR "maternal stress"] AND [rattus OR rat OR "mus musculus" OR mice OR rodent] AND [HPA OR "HPA axis" OR "HPA activity" OR "HPA function" OR "hypothalamic pituitary adrenal" OR CRH OR "corticotropin releasing hormone" OR CRF OR "corticotropin releasing factor" OR ACTH OR "adrenocorticotropic hormone" OR CORT OR corticosterone OR GR OR glucocorticoid OR cytokine OR "proinflammatory cytokine" OR chemokine OR inflammation OR "tumor necrosis factor alpha" OR "interferon gamma" OR "granulocyte macrophage colony stimulating factor" OR "transforming growth factor" OR "C reactive protein" OR "macrophage inflammatory protein-1 alpha" OR eotaxin-1 OR IL-1 OR IL-1β OR IL-2 OR IL-4 OR IL-5 OR IL-6 OR IL-8 OR IL-10 OR IL-12 OR IL-17 OR IL-18]. The recommendations of Cochrane for developing a search strategy (Cochrane Review, 2007) were followed in this study.

2.2. Selection and eligibility

The selection was done in two phases. The first phase consisted of the screening of titles and abstracts. While in the second phase the screening of full texts was performed. The article was excluded if met one of the following exclusion criteria: (1) the study was not written in English; (2) the study was not empirical; (3) the study did not use mice or rat; (4) the study did not have a prenatal stress protocol; (5) the study had an additional intervention in the dams or in the offspring, such as surgery, injections or stress protocols before or after the prenatal stress protocol; (6) the study did not analyze levels of blood CORT or HPA axis/inflammation markers in the adult brain of the offspring; (7) the study only used transgenic or knockout animals. Both selection phases were performed independently by two authors (AS and KCC) using the Rayyan Software (Ouzzani et al., 2016). Any disagreements about study inclusion or exclusion during this process were resolved in consensus discussions.

2.3. Data extraction

The following data were extracted from all included articles by two independent authors (AS and KCC): 'first author', 'publication year', 'species', 'strain', 'prenatal stress protocol', 'prenatal stress period', 'prenatal stress duration', 'sex of tested animals', 'postnatal day of euthanasia', 'analyzed tissues', 'targets of the molecular analysis', 'molecular technique', and 'outcome data'. The mean, the standard deviation (SD) and, the number of animals per group were collected as the outcome data from the stressed group and its respective control group. If the article reported only standard error (SE), the SD was recalculated. When the number of animals per group was reported as a range, the smallest number was used for meta-analysis. Moreover, if the article presented its data using only graphs and not as text or in a table the data was extracted using WebPlotDigitizer (Rohatgi).

2.4. Coding procedure of potential moderators

The following variables and codes were used as potential moderators for meta-analysis:

- Species, coded as: (0) rat; and (1) mice.
- Prenatal stress protocol, coded as: (0) restraint; (1) combination of two or more protocols; (2) hypoxia; (3) social defeat; (4) diet protocols; (5) drug injection protocols; and (6) other protocols.
- Duration of prenatal stress, coded as: (0) 1−7 days; (1) 8−14 days; and (2) more than 14 days.
- Sex, coded as: (0) male; (1) female; and (2) male and female analyzed together.
- Tissue, coded as: (0) hippocampus; (1) cortex; (2) amygdala; (3) hypothalamus; (4) striatum; (5) more than one region analyzed together; and (6) blood.
- Biological material, coded as: (0) RNA; (1) protein.
- Behavior, coded as: (0) the study did not have behavioral tests; (1) the study did have behavioral tests.

2.5. Risk of bias assessment

To assess the risk of bias of the included studies, the Risk of Bias (RoB) tool for animal studies from the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) (Hooijmans et al., 2014) was used. The RoB tool consists of 10 items that detect bias related to

Table 2
Descriptive characteristics, summary and significative findings of included studies.

Author (year)	Rat/ Mice	Strain	Stress Protocol	Stress Period	Stress Duration	Sex of tested offspring	PND of Euthanasia	Collected tissue	Targets	Molecular Technique	Significant Findings (vs CT group)
Luft et al. (2020)	Mice	Balb/C	Restraint Stress	GD 8 to delivery, in intercalated days	30 min; 1x/day	Male and Female	PND 74	PFC and Blood	GR, CRHR1 and CORT	RT-qPCR; ELISA	GR: decreased in males. CRHR1: increased in females.
Niu et al. (2020)	Rat	SPF Sprague-Dawley	Restraint Stress + Cold Exposure + Food Deprivation + Forced Swim + Continuous Light Exposure	Last week of pregnancy	120 min; 360 min; overnight; 15 min; 1 day	Male and Female	PND 72	PFC	GR	ELISA	No significant differences between PNS and CT animals.
Mazzelli et al. (2020)	Rat	Sprague-Dawley	Restraint Stress with light (6500 lx)	Last week of pregnancy	45 min; 3x/day	Male	PND 62	Hippocampus	TNF-α	RT-qPCR	No significant differences between PNS and CT animals.
Liao et al. (2020)	Rat	Sprague-Dawley	Restraint Stress	Last week of pregnancy	15 min; 3x day	Female	PND 60	Hippocampus	GR	WB	GR: increased in females.
Enayati et al. (2020)	Rat and Mice	Wistar, Lewis, NMRI and C57/Bl6	Restraint Stress with light (60 W)	GD 5-19	30 min; 3x/day	Male and Female	PND 150	Whole brain and Blood	IL-1β, TNF-α and CORT	ELISA	IL-1β: increased in NMRI males. TNF-α: increased in Wistar females and in NMRI males. CORT (blood): increased in Wistar females, in Lewis males and females, in NMRI males and in C57/Bl6 females.
Chen et al. (2020)	Rat	SPF Sprague-Dawley	Restraint Stress with light (6500 lx)	GD 8-14 or GD 15-21	45 min; 3x/day	Male and Female (analyzed together)	PND 87	Dorsal and Ventral Hippocampus	IL-18	ELISA and WB	IL-18 (dorsal hippocampus): increased in early and late animals. IL-18 (ventral hippocampus): increased in early and late animals.
Gur et al. (2019)	Mice	C57/Bl6	Restraint Stress	GD 10-16	120 min; 1x/day	Male	R PND 60-70	Cortex and Blood	CRH, IL-1β, IL-6 and CORT	qPCR and ELISA	CRH: increased in males. IL-1β: increased in males. IL-6: increased in males. CORT: increased in males.
Cattaneo et al. (2018)	Rat	Sprague-Dawley	Restraint Stress with light (6500 lx)	Last week of pregnancy	45 min; 3x/day	Male	PND 62	Hippocampus	CRHR1	Transcriptome	CRHR1: decreased in males.
Pascuan et al. (2017)	Mice	Balc/C	Restraint Stress	GD 15 to delivery	120 min; 1x/day	Male and Female	NR	Hippocampus and Blood	GR, INF-γ, IL-2, IL-4, IL-10 and CORT	RT-qPCR, WB and RIA	GR: increased in males and females. INF-γ: increased in males and decreased in females. IL-4: increased in females.
Luoni et al. (2016)	Rat	Sprague-Dawley	Restraint Stress	Last week of pregnancy	45 min; 3x/day	Male and Female	PND 62	Hippocampus and PFC	GR	RT-qPCR	GR (hippocampus): decreased in males and females. GR (PFC): decreased in males and females.
Pivina et al. (2016)	Rat	Wistar	Restraint Stress with light (60 W)	GD 15-19	NR	Male	NR	Hypothalamus and Blood	CRH and CORT	IHC and RIA	CRH: increased in males.
	Rat	Wistar				Male	PND 61	Blood	CORT	ELISA	

(*continued on next page*)

Table 2 (*continued*)

Author (year)	Rat/ Mice	Strain	Stress Protocol	Stress Period	Stress Duration	Sex of tested offspring	PND of Euthanasia	Collected tissue	Targets	Molecular Technique	Significant Findings (vs CT group)
Ratajczak et al. (2015)			Restraint Stress + Cold Exposure + Food Deprivation + Forced Swim + Continuous Light Exposure + Overcrowding or Methylazoxymethanol acetate (22 mg/kg) Injection	GD 14-21 or GD 17	120 min; 360 min; overnight; 15 min; 1 day or one injection						CORT: increased in males (regardless of stress protocol).
Zohar et al. (2015)	Rat	SPF Wistar	Restraint Stress + Forced Swim + Elevated Platform	GD 13-21, stress protocols intercalated	45 min; 1x/day, NR, 30 min; 1x/day	Male and Female	PND 60	mPFC	CRHR2	RT-qPCR and IHC	CRHR2: decreased in females.
Wang et al. (2013)	Rat	SPF Sprague-Dawley	Hypoxia	GD 1-21	240 min; 1x/day	Male and Female	PND 90	PVN and CeA	CRH, CRHR1 and CRHR2	RT-qPCR	CRH (PVN): increased in males. CRH (CeA): increased in males. CRHR1 (PVN): increased in males and decreased in females. CRHR2 (PVN): decreased in males and females.
Bolton et al. (2013)	Mice	C57/Bl6	Diesel exhaust particles exposure	GD 2-17, every 3 days	NR	Male and Female	PND 100	PFC, Hippocampus, PCX, Hypothalamus (analyzed together)	IL-1β and IL-10	ELISA	IL-1β (pool of all regions): increased in males. IL-10 (pool of all regions): decreased in males.
Anacker et al. (2013)	Rat	Sprague-Dawley	Restraint Stress with light (6500 lx)	Last week of pregnancy	45 min; 3x/day	Male	PND 62	Hippocampus and Blood	GR, IL-6 and CORT	Transcriptome and RIA	GR: decreased in males. CORT: increased in males.
Brunton et al. (2011)	Rat	Sprague-Dawley	Social Defeat	GD 16-20	10 min; 1x/day	Male and Female	R PND 91-98	BLA, BMA, MeA and CeA	CRHR1 and CRHR2	ISH	CRHR1 (BLA): increased in males. CRHR1 (MeA): increased in females. CRHR1 (CeA): increased in males. CRHR2 (BMA): decreased in males and increased in females.
Zohar and Weinstock (2011)	Rat	SPF Wistar	Restraint Stress + Forced Swim + Elevated Platform	GD 13-21, stress protocols intercalated	45 min; 1x/day, 15 min 1x/day, 30 min; 1x/day	Male and Female	R PND 56-63	PVN, CeA and Amygdala	CRH, CRHR1 and CRHR2	RT-qPCR and ISH	CRH (ISH – PVN): increased in females. CRH (ISH – CeA): increased in females. CRH (PVN): increased in females. CRHR2 (PVN): decreased in females. CRH (amygdala): increased in females. CRHR1 (amygdala): decreased in males. CRHR2 (amygdala): decreased in males and females.
Green et al. (2011)	Rat	Sprague-Dawley	Restraint Stress	GD 14 to delivery	60 min; 1x/day	Male	R PND 59-64	PFC, Hippocampus and Blood	GR and CORT	ELISA and RIA	GR (PFC): decreased in males.

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Table 2 (*continued*)

Author (year)	Rat/ Mice	Strain	Stress Protocol	Stress Period	Stress Duration	Sex of tested offspring	PND of Euthanasia	Collected tissue	Targets	Molecular Technique	Significant Findings (vs CT group)
García-Cáceres et al. (2010)	Rat	Wistar	Restraint Stress with light	Last week of pregnancy	45 min; 1x/day	Male and Female	PND 180	Hypothalamus and Blood	CRH and CORT	RT-qPCR and RIA	GR (hippocampus): decreased in males. CRH: increased in females.
Brunton and Russell (2010)	Rat	Sprague-Dawley	Social Defeat	GD 16-20	10 min; 1x/day	Male and Female	R PND 77-84	Hippocampus (CA1, CA2, CA3, DG) and CeA	GR and CRH	ISH	GR (CA2): decreased in females. GR (CeA): increased in males and females. CRH (CeA): increased in males and females.
Fan et al. (2009)	Rat	Sprague-Dawley	Hypoxia or Restraint Stress or Both	GD 1-21	240 min; 1x/day	Male	PND 120	PVN and Blood	CRH, CRHR1, CRHR2 and CORT	IHC, ISH and RIA	CRH: increased in males (regardless of stress protocol). CRHR1: increased in males (regardless of stress protocol). CRHR2: decreased in males (regardless of stress protocol). CORT: increased in males (regardless of stress protocol).
Mueller and Bale (2008)	Mice	C57/ Bl6:129	Chronic Variable Stress	GD 1-7 (early), GD 8-14 (mid) or GD 15-21 (late)	15 min; 1x/day, 36 h or overnight (depending on the stress)	Male and Female	NR	Hippocampus (CA1, CA2, CA3, DG), CeA and Blood	GR, CRH and CORT	ISH	GR (CA3): decreased in early males. GR (DG): decreased in early males. CRH (CeA): increased in early males.
Nagano et al. (2008)	Rat	Sprague-Dawley	Dexamethasone 21-phosphate (50ug/kg) Injection	GD 16-21	One daily injection	Male and Female (analyzed together)	NR	CeA, MeA, Hypothalamus and Blood	GR, CRH and CORT	IHC and RIA	GR (CeA): decreased in offspring. GR (MeA): decreased in offspring. CRH (hypothalamus): decreased in offspring. CORT (estrous phase): decreased in females (regardless of stress protocol).
Sliwowska et al. (2008)	Rat	Sprague-Dawley	Ethanol diet or Liquid diet	GD 1-21	Intermittent (24 h/day)	Female	R PND 90-120	Hippocampus and Blood	GR and CORT	ISH and RIA	CORT (proestrus phase): increased in females (regardless of stress protocol).
Mandyam et al. (2008)	Rat	Crl:CD (SD)	Restraint Stress with light (2 × 150 W) or Randomized Stressors (Restraint, Foot Shock or Saline Injection)	GD 14-21	45 min; 3x/day, 30 min; 1x/day, and one daily injection	Male and Female	R 21-23 weeks	DG	IL-1β	Densitometry	IL-1β: decreased in males (regardless of stress protocol).
Jezová et al. (2002)	Rat	Wistar	Food Restriction (powder diet)	GD 13-20	21 h/day of restriction	Male and Female	NR	PVN	CRH	ISH	No significant differences between PNS and CT animals.
Page et al. (2001)	Rat	Sprague-Dawley	Dexamethasone (100ug/kg) Injection	GD 14-19	One daily injection	Male	PND 90	Blood	CORT	RIA	CORT: increased in males.
Welberg et al. (2001)	Rat	Wistar	Dexamethasone (100ug/kg) Injection	GD 0 to delivery or GD 14 to delivery	One daily injection	Male	6 months	Hippocampus (CA1, CA2, CA3, CA4, DG) and PVN	GR and CRH	ISH	GR (CA1): decreased in males (last week DEX only).

(*continued on next page*)

Table 2 (*continued*)

Author (year)	Rat/ Mice	Strain	Stress Protocol	Stress Period	Stress Duration	Sex of tested offspring	PND of Euthanasia	Collected tissue	Targets	Molecular Technique	Significant Findings (vs CT group)
Ward et al. (2000)	Rat	Sprague-Dawley	Handling, Exposure to Novel Cage and Saline Injection	GD 14-21	1x/day, 5 min; 1x/day and one daily injection	Male	R PND 90-120	Amygdala and Blood	CRH and CORT	Protein assay and RIA	GR (DG): decreased in males (last week DEX only). CRH (PVN): increased in males (last week DEX only). CRH: increased in males. CORT: increased in males.
Szuran et al. (2000)	Rat	Wistar-HAN	Restraint Stress	GD 15-19	30 min; 3x/day	Male and Female	12 months	Hippocampus and Blood	GR and CORT	Protein assay and RIA	GR: decreased in females. CORT: increased in females.
Welberg et al. (2000)	Rat	Wistar	Carbenoxolone (12.5 mg/200 μL) Injection	Throughout pregnancy	One daily injection	Male	6 months	Hippocampus (CA1, CA2, CA3, CA4, DG), PVN, BLA, CeA, MeA and Blood	GR, CRH and CORT	ISH and RIA	GR (PVN): decreased in males. GR (BLA): increased in males. GR (CeA): increased in males. GR (MeA): increased in males. CRH (PVN): increased in males. CORT (8am): increased in males.
Smythe et al. (1996)	Rat	Long-Evans Hooded	Restraint Stress	GD 13-17	25 min; 1x/day	Male	4 months	Hypothalamus and Blood	CRH and CORT	RIA	CORT: decreased in males.
Cratty et al. (1995)	Rat	Sprague-Dawley	Handling and Saline Injection	GD 14-21	NR and one daily injection	Male	R 8-16 weeks	Amygdala	CRH	RIA	CRH: increased in males.

Note: GD = Gestational Day; PND = Postnatal Day; R = Range; NR = Not Reported; PNS = Prenatal Stress; CT = Control. Strain: SPF = Specific Pathogen Free. Collected Tissue: PFC = Pre-frontal cortex; PCX = Adjacent parietal cortex; PVN = Paraventricular nucleus of the hypothalamus; BLA = Basolateral amygdala; BMA = Basomedial amygdala; CeA = Central nucleus of the amygdala; MeA = Medial amygdala; DG = Dentate gyrus. Molecular Technique: RT-qPCR = Real Time quantitative Polymerase Chain Reaction; WB = Western Blot; RIA = Radioimmunoassay; IHC = Immunohistochemistry; ISH = In Situ Hybridization.

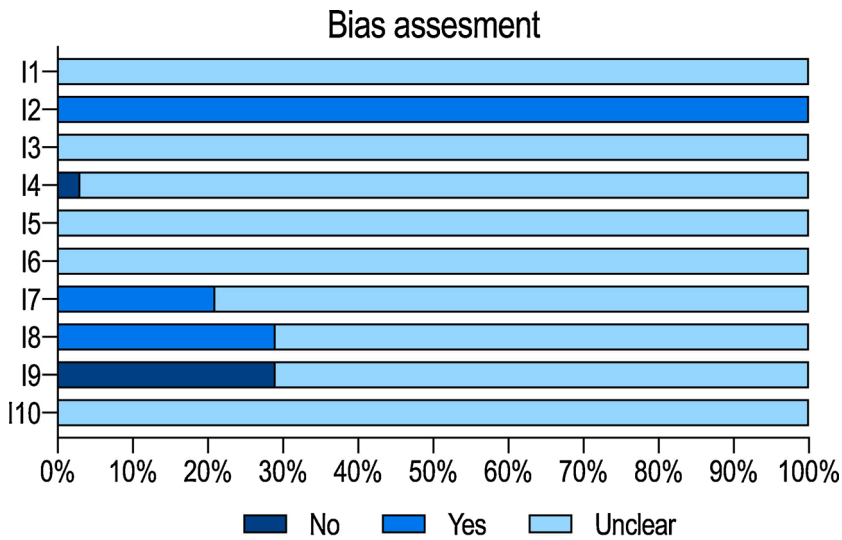

Fig. 2. Risk of bias assessment. The 10 items detect bias related to selection, performance, detection, attrition and reporting. Yes: demonstrates a low risk of bias; No: indicates a high risk of bias; Unclear: the risk of bias is unknown.

selection, performance, detection, attrition, and reporting. If the item is scored with "yes" it demonstrates a low risk of bias while if it is scored with "no" it indicates a high risk. When the item was not reported or explicitly stated it was marked as "unclear" and its risk of bias was unknown.

2.6. Data analysis

Meta-analysis was conducted using the random effects model (RE Model) and a multilevel approach to generate forest plots. The multilevel approach was chosen since the assumption of independence between outcomes was violated since some studies could contribute with more than one sample. A 2-level hierarchical data structure was modeled, with samples within studies nested with samples between studies. The estimated effect size of GR, CRH, CRHR1, CRHR2, pro-inflammatory and anti-inflammatory cytokines on different brain regions and blood CORT was determined using the standardized mean difference (SMD), calculated by use of Cohen's d. Q statistic was used to test the existence of heterogeneity and I^2 to assess the proportion of total variability due to heterogeneity. Sources of heterogeneity in statistically significant meta-analyses were explored by means of univariate meta-regression models with the inclusion of potential moderators. Publication bias was detected using funnel plots' asymmetry and further statistically proven by Egger's regression test. All statistical analyses were performed using the package 'metafor' (version 2.4-0) from the open-source statistical software R (version 4.0.0).

3. Results

The database search yielded 2670 studies, after excluding duplicate records (n = 1084), 1586 studies went through initial screening, that consisted of the review of title and abstract. 1398 studies were excluded and the remained (n = 188) were full text reviewed applying the exclusion criteria. Following the application of these criteria, a total of 34 studies were included in this review. Fig. 1 displays the flowchart of this systematic review. Moreover, 1 study was excluded from meta-analysis due to the impossibility to calculate its SMD.

3.1. Included studies

The included studies in the analysis are listed in Table 1 sorted by temporal order, from the most recent to the oldest.

3.2. Characteristics of studies

Of the 34 included studies, 82.85 % (n = 29) were performed with rats and 17.15 % (n = 6) with mice. Regarding the prenatal stress protocol, 13 different protocols were identified. The most used was restraint stress that was applied in 44.75 % of the studies (n = 17). The other protocols were: the combination of two or more stress protocols (23.65 %; n = 9), dams exposition to an hypoxic environment (5.25 %; n = 2), a social defeat protocol (5.25 %; n = 2), subcutaneous injection of dexamethasone (7.85 %; n = 3), subcutaneous injection of carbenoxolone (2.65 %; n = 1), subcutaneous injection of methylazoxymethanol acetate (2.65 %; n = 1), exposition to diesel exhaust particles (2.65 %; n = 1), a food restriction protocol (2.65 %; n = 1), and exposition to ethanol and liquid diet (2.65 %; n = 1). Stress protocol duration varied from 1 to 21 days of pregnancy. The majority of studies used a protocol of 7 days (50 %; n = 18), followed by 5 studies that had a protocol of 5 days (13.9 %) and another 5 studies that had 21 days of stress (13.9 %). In relation to the stress exposure period, 55.5 % of the studies applied the protocol during the third week of pregnancy (n = 20), while 19.5 % used a stress protocol during the whole pregnancy (n = 7) and 16.5 % exposed the dams to stress during the second and third week of pregnancy (n = 6).

Forty seven percent of the studies (n = 16) used male and female offspring for the analysis, while 41.2 % performed their investigation only in males (n = 14). Two studies used exclusively females (5.9 %), while 2 studies (5.9 %) did not differentiate males and females and plotted the results with both sexes together. In relation to the analyzed brain tissues, the majority of the studies focused on the hippocampus (25.4 %; n = 15), hypothalamus (16.95 %; n = 10) and, amygdala (15.25 %; n = 9), whereas six studies (10.15 %) investigated the cortex and two studies (3.4 %) used the whole brain or a pool of multiple regions. Moreover, 28.85 % of the included studies (n = 17) performed blood analysis.

Furthermore, the identified targets were divided in three main groups: HPA axis-related targets (75 %; n = 30), pro-inflammatory cytokines (20 %; n = 8) and anti-inflammatory cytokines (5 %; n = 2). The following targets were considered for the HPA axis sub-group: GR (19.7 %; n = 14), CRH (21.1 %; n = 15) and its receptors, CRHR1 8.5 %; n = 6) and CRHR2 (7 %; n = 5) and blood CORT (24 %; n = 17). The studies on pro-inflammatory cytokines focused on different interleukins (1β, 2, 6, 18), TNF-α and IFN-γ, which together represented 15.5 % of the analyses (n = 11). Finally, the studies on anti-inflammatory cytokines were primarily related to interleukin 4 and interleukin 10, which were analyzed 3 times (4.2 %). Additionally, different molecular techniques were used

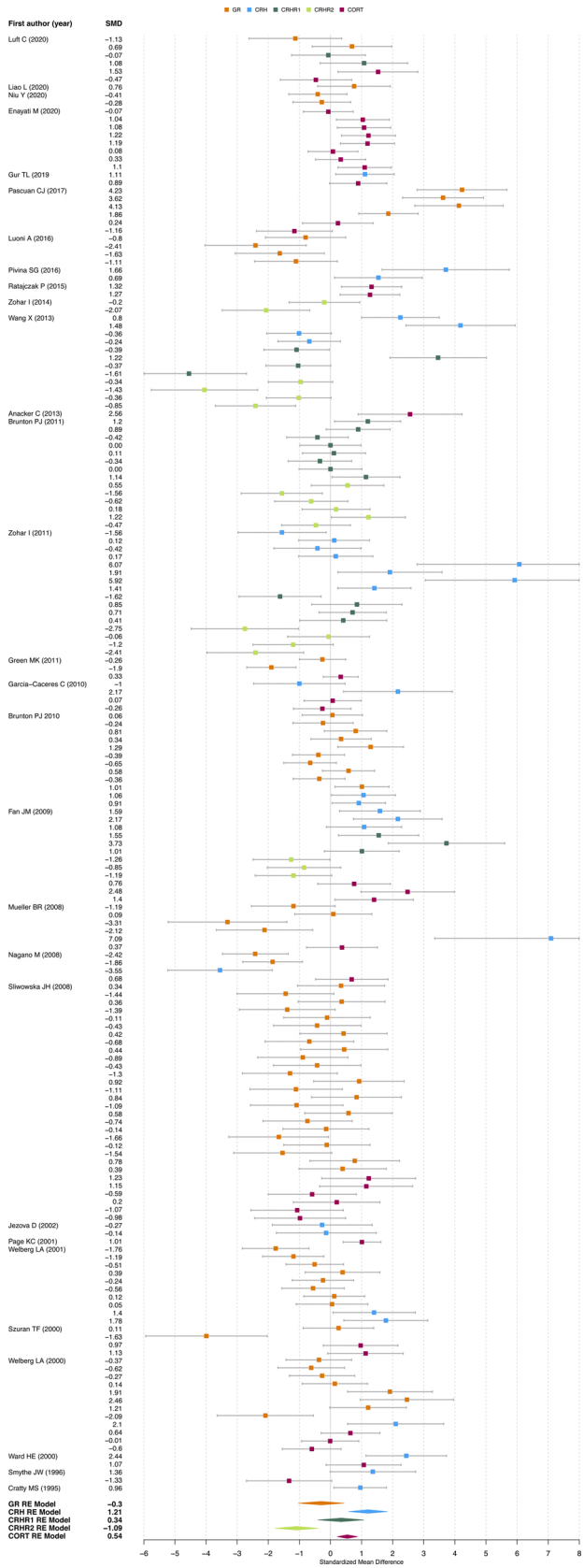

Fig. 3. Effect of size of HPA axis targets. Forest plot demonstrating SMD and 95 % CI. SMD = Standardized Mean Difference; RE Model = Random Effects Model.

to measure the targets. The majority of the studies targeted only protein levels (n = 17; 50 %), while 9 studies (26.5 %) analyzed RNA samples and the remaining studies (n = 8; 23.5 %) analyzed both, RNA and protein samples. The total number of studies can vary since each study may contribute with more than one evidence for each variable. More detailed information is reported in Table 2.

3.3. Risk of bias assessment

Risk of bias was assessed using the SYRCLE Risk of Bias tool. Studies scored "unclear" in most of the items, due to the lack of information or explicitness, what resulted in an unknown risk of bias (Fig. 2). Regarding selection bias (items 1, 2 and 3), only the second item that is related to baseline similarity was scored as "yes" in the included studies (100 %). Even though some studies mentioned that animals were randomly assigned to experimental groups, none of them provided information about the randomization method. In relation to performance bias (items 4 and 5) just one study (3 %) scored "no" in item 4, while the remaining were "unclear". When it comes to detection bias (items 6 and 7), 21 % of the studies (n = 7) reported to have a blinded outcome assessor in item 7, whereas the item 6 was "unclear" in all studies. 30 % of included studies scored "yes" on attrition bias (item 8), since they reported the incomplete outcome data. Moreover, 10 studies (30 %), scored "no" in reporting bias (item 9). Finally, all studies scored "unclear" on item 10, regarding other bias.

3.4. Impact of prenatal stress in the HPA axis

Of the 33 studies included in the meta-analysis, 14 evaluated brain GR levels (73 effect sizes), and there was no significant effect of PNS exposure (SMD −0.29; 95 % CI −1.04, 0.44). Regarding the corticotrophinergic system, 15 studies showed data on brain CRH levels (32 effect sizes), 6 on brain CRHR1 levels (21 effect sizes), and 5 on brain CRHR2 levels (19 effect sizes). Based on these results, CRH levels showed to be increased in animals exposed to PNS (SMD 1.21; 95 % CI 0.58, 1.83), CRHR1 did not show a significative effect of PNS exposure (SMD 0.34; 95 % CI −0.40, 1.07), whereas CRHR2 showed to be decreased in animals exposed to PNS (SMD -1.09; 95 % CI −1.78, −0.40). In relation to CORT levels, 17 studies evaluated its blood levels (38 effect sizes) showing a significant increase in animals exposed to PNS (SMD 0.54; 95 % CI 0.22, 0.87). Fig. 3 summarizes all the SMD of the targets related to the HPA axis.

The heterogeneity between studies in CRH, CRHR2 and CORT meta-analyses was significant ($I^2 = 88.34$ %; $p < 0.0001$, $I^2 = 72.45$ %; $p < 0.0001$; $I^2 = 61.41$ %; $p < 0.0001$, respectively). Therefore, we explored sources of heterogeneity using meta-regression analysis, including the following potential moderators: species, PNS protocol, duration of PNS, sex, tissue, biological material, and behavior. Sex ($p = 0.004$; variance explained = 23.46 %) was a covariate significantly associated with estimates of heterogeneity of CRH meta-analysis, indicating that male animals had higher CRH estimates following PNS when compared to estimates of both sexes grouped into the same category. Duration ($p = 0.008$; variance explained = 36.82 %) of PNS was significantly associated with estimates of heterogeneity of CRHR2 meta-analysis, indicating that longer periods of PNS exposure resulted in larger reductions of CRHR2 estimates. No significant covariates were observed for CORT estimates.

Funnel plots were created to evaluate the publication bias and they revealed an asymmetry in CRH and CRHR2 but not in CORT (Fig. 4). Egger's regression test was used to confirm if the asymmetry was statistically significant. As expected, the test evidenced publication bias in CRH and CRHR2 ($z = 4.1602$, $p < 0.0001$; $z = -4.1837$, $p < 0.0001$, respectively). CORT did not present publication bias ($z = 0.0003$, $p = 0.9997$). The existence of publication bias may indicate an overestimation of the effect size.

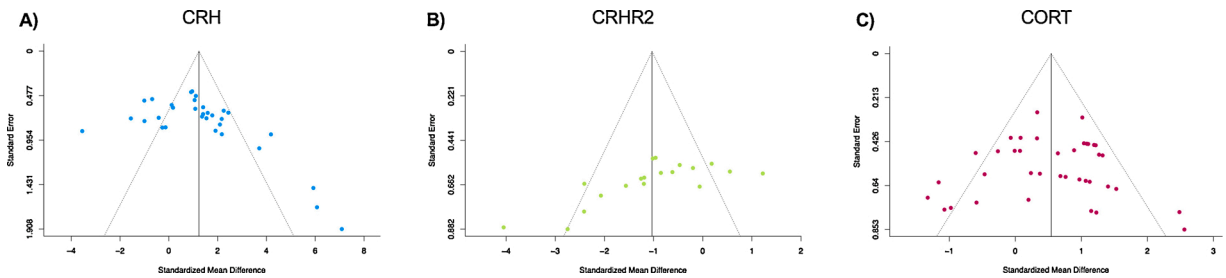

Fig. 4. Funnel plots demonstrating publication bias from included studies. Funnel plots for A) CRH; B) CRHR2 and C) CORT.

3.5. Impact of prenatal stress in inflammatory cytokines

Regarding pro-inflammatory cytokines, they were analyzed by 8 of the 33 included studies (35 effect sizes), and there was no significant difference between control and PNS animals (SMD 0.29; 95 % CI −0.39, 0.99). In relation to anti-inflammatory cytokines, only 2 studies reported them (6 effect sizes), and similar to what was observed for the pro-inflammatory cytokines, there were no significant changes in the estimates of PNS animals compared to control animals (SMD 0.19; 95 % CI −1, 1.38). Fig. 5 displays all the SMD related to the inflammatory cytokines.

4. Discussion

In the present study, we analyzed the effects of PNS on the HPA axis and on inflammation-related players in adult offspring. To the best of our knowledge, this is the first systematic review and meta-analysis that investigated these outcomes in rodents. The evidence analyzed in our review exposed altered HPA axis functioning, at both central and peripheral levels, in adult offspring exposed to PNS. This alteration is supported by an increase in peripheral CORT levels, an increase in central CRH levels as well as a reduction of central CRHR2 levels. However, there were no significant differences in inflammatory markers, which was possibly driven by the high heterogeneity of the existing evidence on the levels of these markers in adult animals exposed to PNS.

4.1. PNS exposure leads to alterations of glucocorticoid levels

The activation of the HPA axis results in the release of glucocorticoids: its dysfunction may lead to altered levels and function of these hormones, which may contribute to different pathological domains of psychiatric disorders. The present meta-analysis revealed that exposure to PNS leads to a significant increase of the peripheral levels of CORT in adult offspring, as compared to control animals. However, it should be noted that during pregnancy, maternal and fetus CORT levels increase as a prenatal developmental mechanism. Indeed, fetal exposure to CORT at the third trimester of gestation is necessary to ensure proper maturation of lungs and brain, as well as for the preparation of birth and fetal delivery (Davis and Sandman, 2010). Furthermore, moderate increases in CORT exposure after birth have been associated with beneficial effects on newborns' brain, cognitive, and behavioral development (Kapoor et al., 2006). While a physiological elevation of CORT levels in the fetus and the newborn pups may be required for the maturation of different organs, an excessive exposure to CORT, as a consequence of protracted stressful events (PNS), may lead to a persistent elevation of glucocorticoids in adult animals, which can be extremely harmful for brain function. Indeed, overexposure to stress hormones may lead to altered neural and glial processes and morphology (e.g. reduced dendritic spines and myelination), decreased neurogenesis and synaptogenesis, and altered neurotransmission (Andersen and Teicher, 2009).

Several studies have employed chronic administration of CORT or overexpression of GR to characterize the potential consequences of increased CORT levels on brain function. Chronic exposure to CORT may lead to impaired cognition and reduced sociability (Li et al., 2017; Veenit et al., 2013), and it is also associated with a higher anxiety-like state, as demonstrated by the impaired performance in the open field and in the novelty suppressed feeding test (Dieterich et al., 2019; Li et al., 2017). Additionally, increased levels of CORT in animals exposed to stress are negatively correlated with the number of entries in the open arms on the elevated plus maze, which also suggests that higher CORT levels are associated with an anxiety-like state (Jakovcevski et al., 2008). Similarly, the overexpression of GR also leads to increased anxiety and depressive-like behaviors in the elevated plus maze, in the light/dark box, and in the forced swim tests (Wei et al., 2004).

Glucocorticoids bind and activate GR as well as mineral-glucocorticoid receptor, which are widely distributed in the brain, although their expression is heterogeneous across different brain regions (Reul and de Kloet, 1985). Our analysis revealed a high variance in GR expression following PNS exposure, since there were studies that identified a decrease, an increase, or even no significant differences in the expression levels of this receptor. We hypothesize that such heterogeneity may be explained by the range of different brain regions that were investigated in the studies included in the present meta-analysis. Moreover, the expression of this receptor was evaluated at RNA and protein levels, which may also show opposite changes. Furthermore, with respect to the studies with the analysis of protein levels, it is also likely that, across different studies, the evaluation of GR in the nuclear fraction, as compared to cytoplasm or whole homogenate may affect the type and the magnitude of the observed effects. However, meta-regression analysis failed to identify the causes of the heterogeneity among different studies, suggesting that more research is required to clearly establish a relationship between PNS exposure and GR expression.

4.2. PNS exposure leads to alterations on the corticotrophinergic system

The primary role of CRH is to activate the HPA axis, thus, the corticotrophinergic system can be seen as a starting point to unravel the altered stress responsiveness (Bakshi and Kalin, 2000). In accordance with altered peripheral HPA function (elevation of CORT levels), the analysis also detected alterations in central targets, the CRH itself and its receptor 2 (CRHR2). Our results revealed increased CRH levels in animals exposed to PNS, as compared to controls. Furthermore, the meta-regression analysis with potential moderators revealed that male animals had higher CRH levels compared to both sexes grouped in the same category. The effects of an overexpression of CRH have been extensively investigated in genetically altered rodent models. Indeed, increased levels of CRH are associated with higher basal CORT levels, increased anxiety-like behavior in different tests as well as decreased despair in the forced swim test (Dedic et al., 2012; Stenzel-Poore et al., 1994; van Gaalen et al., 2002). Additionally, these animals show increased adrenal weight and decreased thymus weight (Dedic et al., 2012; Groenink et al., 2002). Accordingly, overexpression of CRH in cynomolgus monkeys produced increased anxious temperament, changes in brain metabolism as well as altered functional connectivity

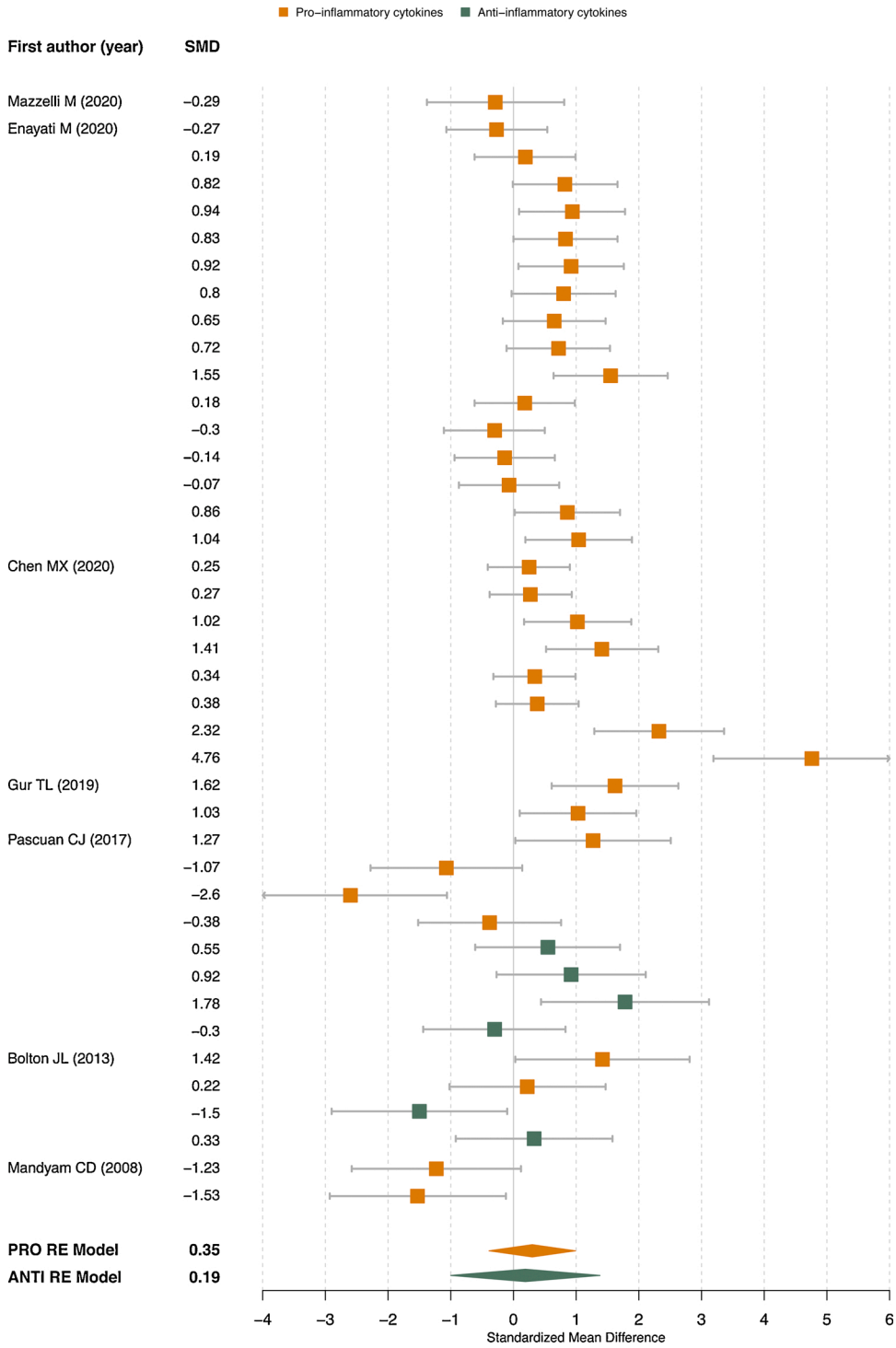

Fig. 5. Effect of size of pro and anti-inflammatory cytokines. Forest plot demonstrating SMD and 95 % CI. SMD = Standardized Mean Difference; RE Model = Random Effects Model.

(Kalin et al., 2016).

Our analysis also revealed a decrease of CRHR2 levels in animals exposed to PNS, as compared to control animals. Moreover, the meta-regression showed that the levels of CRHR2 were related to the duration of PNS, where longer periods of exposition to PNS lead to lower levels of this receptor. Interestingly, CRHR2 deficient mice show increased anxiety- and depression-like behavior, increased expression of CRH levels, and increased levels of stress-induced CORT and adrenocorticotropic hormone (Bale et al., 2000; Bale and Vale, 2003). On the other end, our analysis did not reveal any significant alterations in CRHR1. Different studies suggest that CRHR1 may be modulated by acute stress exposition (Uribe-Mariño et al., 2016; Vagnerová et al., 2019), which could explain why we did not observe significant alterations in our analysis, considering that we only included studies on adult animals exposed to stress in the prenatal period. Overall, these data suggest that stress exposure elevates the levels of central CRH that leads to a hyperactivation of the HPA axis resulting in increased synthesis of glucocorticoids (i.e., CORT). However, the corticotrophinergic system is extremely complex and the link between the abovementioned alterations with the decrease of CRHR2 is still not clear. Differently from the

CRHR1, CRHR2 binds with higher affinity to urocortin (Ucn) instead of CRH. Hence, we may suggest that the decreased levels of the receptor 2 are mediated by the Ucn (for review see Reul and Holsboer, 2002).

4.3. PNS exposure has heterogenous outcomes on inflammatory cytokines

This meta-analysis also aimed to identify the effects of PNS on the expression of pro- and/or anti-inflammatory cytokines. However, the analysis of inflammatory cytokines shows high heterogeneity across the included studies. Nonetheless, beyond the methodological variability, it is important to point out that the overall analysis was carried out on a small number of studies. Indeed, only 8 studies investigated pro-inflammatory cytokines, while only 2 included the investigation of anti-inflammatory targets. We believe that consistent data on the potential modulation of these targets by PNS exposure could only be achieved with a thorough and simultaneous analysis of several inflammatory markers in a large number of studies.

4.4. Translational relevance of the effects produced by PNS exposure

As mentioned above, stress is known to be a major risk factor for the development of neuropsychiatric disorders. Human neurobiological studies are mostly limited to neuroimaging techniques, which provide structural, morphological, and functional measures, or to *postmortem* analysis of brain tissue. Accordingly, most human studies investigate peripheral biological measures as a proxy of brain function. On these bases, animal models represent a crucial tool to better understand the behavioral and neurobiological changes that originate as a consequence of stress exposure, which may predispose to the development of different psychiatric conditions. Accordingly, changes in the levels of cortisol, the major glucocorticoid in humans, have been associated to different psychiatric conditions, including schizophrenia, mood and anxiety disorders (Gerritsen et al., 2019; Høifødt et al., 2019). Moreover, stress exposure during pregnancy leads to altered levels of cortisol and long-lasting consequences in the human fetus, including elevated hair cortisol levels (Fan et al., 2018; Romero-Gonzalez et al., 2018), suggesting that clinical observations corroborate our preclinical meta-analysis findings.

4.5. Study limitations

Certain limitations of the current study must be considered. First, the methodological approaches used in the included studies to measure the levels of peripheral and central targets have high variability. Moreover, the existence of different brain regions makes it difficult to draw a unique conclusion, considering the potential functional heterogeneity of such structures. Furthermore, different PNS protocols may lead to a distinct biological and behavioral response. In order to minimize these existent methodological variations, we applied potential moderators when performing the analysis. Next, the review focused only on the long-term effects produced by PNS exposure in animals, without considering other potential factors that may mediate the functional consequences of the adverse experience. Indeed, we believe that the prenatal manipulation, by altering the HPA axis and the stress system, may create a predisposition toward the negative effects subsequent challenging events at different life stages, which will ultimately lead to an overt pathologic condition. Lastly, it should be noted the existence of a publication bias, particularly regarding CRH and CRHR2 analyses, which suggests that the effect sizes of these markers may be overestimated.

5. Conclusion

In summary, our meta-analysis suggests that PNS exposure elicits long-lasting effects on the HPA axis functioning, including altered CORT, CRH and CRHR2 signaling, providing an important tool to investigate in preclinical settings key pathological aspects related to early-life stress exposure. However, it is important to bear in mind that sex and duration of PNS protocol are important mediators of these consequences. Furthermore, researchers should be aware of the mixed PNS outcomes on inflammatory markers in the adult brain, which may suggest that such experimental paradigm may not lead to an overt 'immunological' phenotype, but rather to a state of vulnerability that could be unmasked by subsequent challenges.

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Declaration of Competing Interest

M.A.R. has received compensation as speaker/consultant from Angelini, Lundbeck, Otzuka, Sumitomo Dainippon Pharma and Sunovion, and he has received research grants from Sumitomo Dainippon Pharma and Sunovion. All the other authors declare no financial interests or potential conflicts of interest.

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