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Review article

Effects of early life stress on brain cytokines: A systematic review and meta-analysis of rodent studies

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ABSTRACT

Exposure to early life stress (ELS) may lead to long-lasting neurobiological and behavioral impairments. Alterations in the immune system and neuroinflammatory state induced by ELS exposure are considered risk factors for developing psychiatric disorders. Here, we performed a systematic review and meta-analysis of rodent studies investigating the short and long-term effects of ELS exposure on anti and pro-inflammatory cytokines in brain tissues. Our analysis shows that animals exposed to ELS present an increase in pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. On the other hand, no alteration was observed in the anti-inflammatory cytokine IL-10. Meta-regression revealed that alterations were more prominent in the hippocampus of adult animals that were exposed to more extended periods of ELS. These inflammatory effects were not permanent since few alterations were identified in aged animals. Our findings suggest that ELS exposure alters pro-inflammatory cytokines expression and may act as a primer for a secondary challenge that may induce lifelong immune alterations. Moreover, the actual evidence is insufficient to comprehend the relationship between anti-inflammatory cytokines and ELS fully.

1. Introduction

Stress in the early stages of life has been suggested to impact the neurodevelopment of infants through biological and behavioral alterations (Provençal and Binder, 2015). Previous studies have shown that early life stress (ELS) exposure may impair brain structure and function, especially in sensitive regions, such as the prefrontal cortex, amygdala, and hippocampus (Aleksić et al., 2016; de Azeredo et al., 2017; Hanson et al., 2015; Teissier et al., 2020; van Bodegom et al., 2017). Moreover, alterations in the inflammatory state and immune system are often observed in individuals exposed to ELS (Agorastos et al., 2019; Brenhouse et al., 2019; Massart et al., 2016). These alterations are considered risk factors for the emergence of psychiatric disorders, including anxiety, depression, and drug addiction (Danese and J Lewis, 2017; Lo Iacono et al., 2018; Park et al., 2021; Tannous et al., 2020). For example, chronic exposure to parental neglect, physical abuse, or abandonment induces overstimulation of the hypothalamus-pituitary-adrenal (HPA) axis, the central system responsible for regulating stress. The hormones released during the activation of the HPA axis have been linked to an increase in the levels of proinflammatory cytokines (Grassi-Oliveira et al., 2016; Reed and Raison, 2016). Therefore, alterations in the levels of inflammatory cytokines and neuroimmune signaling induced by ELS may play a critical role in developing dysfunctions associated with HPA axis function (Diaz-Chávez et al., 2020; Kuhlman et al., 2020).

Cytokines are signaling proteins secreted by immune cells that can trigger protective and damaging responses (Dugue et al., 2017). They

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contribute to modulating the neuroinflammatory state, neurogenesis, and synaptic processes (Pei et al., 2021). ELS may prime brain microglia to stimulate proinflammatory cytokines and chemokines released in response to chronic stress exposure (Weber et al., 2015). Higher stress reactivity induces an increase of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which stimulate neuronal apoptosis and serotonin reuptake (Fabbri et al., 2017). Therefore, it is possible that together these inflammatory-induced changes contribute to a vulnerability factor for the development of psychiatric disorders (Bauer and Teixeira, 2019; Druzhkova et al., 2019; Pace et al., 2006).

Considering the prominent role of inflammatory cytokines in regulating immunological and stress-related systems, it is critical to comprehend the potential relationship of such biomarkers on the brain and its phenotypic expression. For this reason, the use of animal models represents an essential tool to investigate the changes promoted by ELS at different levels (Pfau and Russo, 2015). For example, clinical studies face limitations in accessing specific biological materials and providing adequate control of variables to evaluate stress effects over different periods of development. ELS animal models commonly reproduce adverse postnatal conditions to induce exposure to stressful environments. For example, in the maternal separation (MS) model, pups are separated from the dam for a predetermined period, increasing stress response due to an unfamiliar environment and disrupting the maternal care pattern of the dams after reuniting with the pups (Orso et al., 2019; White and Kaffman, 2019). In the limited bedding (LB) model, the dams have reduced access to bedding material and nest building resources, both necessary for offspring thermoregulation and adequate maternal care (McLaughlin et al., 2014; Rice et al., 2008). A combination of both models (MS and LB) was proposed to induce more robust ELS-induced effects and reduce the previously reported variability observed in studies that utilized MS or LB (Orso et al., 2020; Peña et al., 2017).

A recent review reported that MS exposure might alter the levels of pro-inflammatory cytokines. Still, significant modifications in the immune system were observed after a secondary hit later in life (Dutcher et al., 2020). Nevertheless, no meta-analysis compiled data regarding how ELS exposure may influence multiple inflammatory cytokine levels in rodents. Considering that there are still inconsistencies in the findings of studies utilizing MS and LB models and that the effects of methodological variables have not been previously explored, a meta-analysis is now required to provide further statistical support. Thus, this study aimed to perform a systematic review and meta-analysis with findings from rodent studies that investigated the impact of ELS on inflammatory cytokines in the brain. Moreover, we explored sources of heterogeneity between studies using meta-regression models and investigated the methodological quality of the included studies.

2. Methods

2.1. Search strategy

The search was performed on September 17th, 2019, and updated on January 11th, 2022. Three databases were used: PubMed, Web of Science, and PsycInfo. The following terms were used for the search: [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 AND Rattus OR "mus musculus" OR rat OR mice OR rodent AND "maternal separation" OR "maternal deprivation" OR "neonatal stress" OR "postnatal stress" OR "limited bedding" OR "maternal stress" OR "early life stress" OR "early handling" OR "unpredictable stress." This study followed the Cochrane recommendations for developing a search strategy (Cochrane Infectious Diseases Group, 2007).

2.2. Selection and eligibility

The selection of the articles was performed in two phases. For the first phase, only the titles and abstracts were screened. The second phase consisted in reading the full text for possible inclusion. The following exclusion criteria were applied to select the studies for this review: (1) the study was not written in English; (2) the study was not empirical; (3) the study did not use mice or rats; (4) the study did not have an early life stress protocol; (5) the study did not analyze cytokines in the brains of the offspring; (6) the study only used transgenic or knock-out animals. Both phases were performed blindly by two independent authors (FSL and EKF) using the Rayyan QCRI website (Ouzzani et al., 2016). Two senior authors (RGO and TWV) resolved any disagreement regarding the selection of studies.

2.3. Data extraction

Two independent authors (FSL and EKF) extracted the following data from all included studies: 'first author,' 'publication year,' 'species,' 'strain,' 'early life stress protocol,' 'early life stress period,' 'sex,' 'age,' 'analyzed cytokines,' 'analyzed tissues,' 'biological material,' 'secondary manipulations,' and 'outcome data.' For both the stressed and control groups, the mean, the standard deviation (SD), and the number of animals per group were collected for the outcome data. When only the standard error (SE) was reported, it was used to calculate the SD. When a study reported the number of animals per group as a range, we utilized the smallest number for the meta-analysis. WebPlotDigitizer extracted the necessary information when data was only reported in graphs.

2.4. Coding procedure and potential moderators

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

- Species, coded as: (0) rat; and (1) mice.
- Early life stress protocol, coded as (0) maternal separation; (1) maternal separation + heat or cold stress; (2) limited bedding; (3) maternal deprivation.
- Early life stress period, coded as: (0) 1 day; (1) 2–7 days; (2) 8–14 days; (3) 15–21 days.
- Sex, coded as: (0) male, (1) female, (2) unspecified.
- Age, coded as: (0) post-natal day 0–21; (1) post-natal day 22–45; (2) post-natal day 46–60; (3) post-natal day 61–90; (4) post-natal day 91 or more.
- Tissue, coded as: (0) hippocampus; (1) cortex; (2); cerebrospinal fluid; (3) striatum; (4) nucleus accumbens; (5) brain stem; (6) hypothalamus.
- Biological material, coded as: (0) protein; (1) RNA.
- Secondary manipulations, coded as (0) no manipulation; (1) sham surgery or vehicle injection; (2) behavior; (3) sham surgery or vehicle injection + behavior.

2.5. Analysis of methodological quality

To evaluate the methodological quality of the included studies, we utilized an adapted version of the Gold Standard Publication Checklist (GSPC) (Hooijmans et al., 2011) and the ARRIVE Guidelines for Reporting Animal Research (Kilkenny et al., 2010), which was used by Tractenberg et al. (2016). The checklist consisted of 26 items, and 0.5 points were given when specific data was presented in the article, while 0 points were given when the information was missing. Two authors (FSL and EKF) independently performed the analysis.

2.6. Data analysis

Considering that the independence assumption between outcomes

was violated because some studies contributed with more than one sample, we conducted the meta-analysis using the random-effects model (RE Model) and a multilevel approach to generate the forest plots. A 2-level hierarchical data structure was modeled, with samples within studies nested with samples between studies. The estimated effect size of each cytokine investigated on different brain regions was determined using the standardized mean difference (SMD), which was calculated using Cohen's d. Influence analysis was performed to detect possible outliers for all targets. Q statistic was used to verify possible heterogeneity, and I^2 to assess the proportion of total variability due to heterogeneity. Univariate meta-regression models with potential moderators were used to explore the sources of heterogeneity of all meta-analyses. Publication bias was identified using funnel plots' asymmetry and then statistically confirmed by Egger's regression test. All statistical analyses were performed using the package 'metaphor' (version 2.4–0) from the statistical software R (version 4.0.0).

3. Results

3.1. Included studies

The first database search yielded 828 studies, of which 244 were extracted from PUBMED, 280 from PsycInfo, and 304 from Web of Science. After exclusion of 450 duplicate studies, we evaluated the title and abstract of 378 studies, which resulted in 173 studies selected for full-text screening ($n = 205$ excluded). The full-text analysis resulted in additional 153 exclusions: $n = 6$ studies were not written in English; $n = 7$ were not empirical; $n = 81$ did not use ELS protocols; $n = 59$ did not analyze cytokines in the brain. The search update provided 133 new studies for screening, of which 122 were excluded considering the criteria previously used. The final number of included studies for analysis was 31 (Abelaira et al., 2022, 2021; Amini-Khoei et al., 2017; Arabi et al., 2021; Banqueri et al., 2019; Burke et al., 2013; Ganguly et al., 2019; Giridharan et al., 2019; Hoeijmakers et al., 2017; Hohmann et al., 2017; Lajud et al., 2021; Lorigooini et al., 2021; Nicolas et al., 2022; Nouri et al., 2020; Oliveira et al., 2020; Park et al., 2014; Pinheiro et al., 2015; Réus et al., 2013, 2017, 2015; Romeo et al., 2004; Roque et al., 2016; Saavedra et al., 2017; Ströher et al., 2020; Tang et al., 2017; Viola et al., 2019; Viviani et al., 2014; Wang et al., 2020; Ye et al., 2019; Zhu et al., 2017; Zolfaghari et al., 2021). A flowchart with a detailed description of all stages can be viewed in Fig. 1.

3.2. Studies characteristics

The included studies in the analysis are listed in Table 1. 70.97% of eligible studies were performed with rats (n = 22) and 29.03% with mice (n = 9). Regarding ELS protocols, MS was the most used, which corresponded to 87.10% of studies (n = 27). Both LB (n = 1) and MS

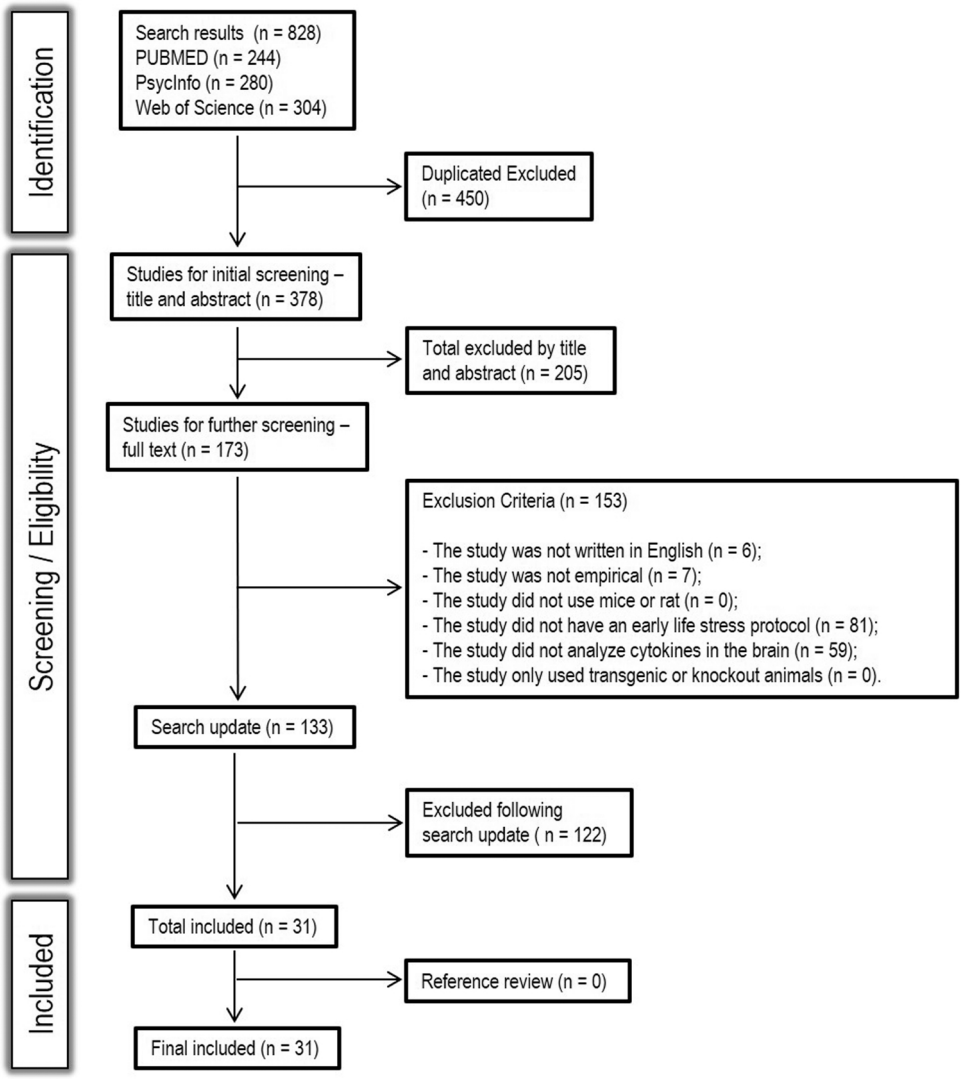

Fig. 1. Flowchart of the systematic review.

Table 1
Descriptive characteristics, summary and main findings of included studies.

Author (year)	Species	Strain	ELS protocol	ELS period	ELS duration	Sex of tested offspring	Behavioral testing	Age of euthanasia	Collected tissue	Targets	Biological Material	Significant findings (vs Controls)	**Quality Score (out of 13)**
Abelaira et al. (2021)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male Female	Yes	PND 61	Hippocampus Prefrontal Cortex	IL-6	Protein	↑ Male Hippocampus IL-6	9
Abelaira et al. (2022)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male Female	Yes	PND 82	Hippocampus Prefrontal Cortex	IL-1β IL-6 TNF-α IL-10	Protein	↑ Male Prefrontal Cortex IL-1β ↑ Male Hippocampus IL-6 ↑ Male Prefrontal Cortex IL-6 ↑ Male Prefrontal Cortex TNF-α ↓ Male Prefrontal Cortex IL-10 ↓ Male Hippocampus Cortex IL-10 ↑ Female Prefrontal Cortex IL-1β ↑ Female HippocampusIL-1β ↑ Female Hippocampus IL-6 ↑ Female Prefrontal Cortex IL-6 ↑ Female Prefrontal Cortex TNF-α ↓ Female Prefrontal Cortex IL-10 ↓ Female Hippocampus Cortex IL-10	10
Amini-Khoei et al. (2017)	Mouse	NMRI	Maternal Separation	PND 2–14	3 h	Male	Yes	PND 60	Hippocampus	IL-1β TNF-α	RNA	↑ IL-1β ↑ TNF-α	10
Arabi et al. (2021)	Mouse	NMRI	Maternal Separation	PND 2–14	3 h	NR	Yes	PND 60	Hippocampus	IL-1β TLR4	RNA	↑ IL-1β ↑ TLR4	9
Banqueri et al. (2019)	Rat	Wistar	Maternal Separation	PND 1–21	4 h	Male	No	PND 100	Dorsal Striatum Hippocampus Prefrontal Cortex	IL-6 TNF-α	RNA	↑ Hippocampus IL-6	11
Burke et al. (2013)	Rat	Albino Wistar	Maternal Separation	PND 9–10	24 h	Male Female	Yes	PND 103	Hippocampus Prefrontal Cortex	IL-1β IL-6 TNF-α	RNA	↑ Female Prefrontal Cortex IL-1β	9
Ganguly et al. (2019)	Rat	Sprague-Dawley	Maternal Separation	PND 2–20	4 h	Male Female	No	PND 40	Nucleus Accumbens Prefrontal Cortex	TNF-α TNFR1	RNA Protein	↑ Male Nucleus Accumbens TNF-α ↑ Male Prefrontal Cortex TNF-α	9.5
Giridharan, et al. (2019)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male	No	PND 10	Hippocampus Prefrontal Cortex	IL1-α IL1-β IL-5 IL-6 IL-7 IL-10 IL-12 TNF-α INF-γ 6-CSF	Protein	↑ Prefrontal Cortex IL-5 ↑ Prefrontal Cortex IL-6 ↑ Prefrontal Cortex IL-7 ↑ Prefrontal Cortex IL-10 ↑ Prefrontal Cortex TNF-α ↑ Prefrontal Cortex INF-γ ↓ Prefrontal Cortex MIP-	7.5

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Table 1 (*continued*)

Author (year)	Species	Strain	ELS protocol	ELS period	ELS duration	Sex of tested offspring	Behavioral testing	Age of euthanasia	Collected tissue	Targets	Biological Material	Significant findings (vs Controls)	**Quality Score (out of 13)**
										M-CSF MIP-1a VEGF GRO-KC MCP-1 Rantes		1a ↑ Hippocampus TNF-α ↑ Hippocampus INF-γ	
Hoeijmakers (2017)	Mice	C57BL/6 J	Limited bedding	PN2–9	24 h	Male	No	PND 9 PND 120 PND 300	Hippocampus	IL-6 IL1-β IL-10 TNF- α	RNA	↑ PND 9 IL-1β ↓ PND 120 IL-1β ↓ PND 120 IL-6	11
Hohmann et al. (2017)	Mice	Balb/CByJ	Maternal Separation (+ heat or cold stress)	PND 2–7	1 h	Male Female	No	NR	Cerebral cortex	IL-1β IL-2 IL-6 TNF-α	Protein	No difference between groups	8.5
Lajud (2021)	Rat	Sprague-Dawley	Maternal Separation	PND 1–21	3 h	Male	Yes	PND 42	Hippocampus Prefrontal Cortex	IL-1β IL-6 TNF-α	RNA	No difference between groups	11
Lorigooini et al. (2021)	Mouse	NMRI	Maternal Separation	PND 2–14	3 h	Male	Yes	PND 60	Hippocampus	IL-1β TNF-α	RNA	↑ IL-1β ↑ TNF-α	10.5
Nicolas et al. (2022)	Rat	Sprague-Dawley	Maternal Separation	PND 2–12	3 h	Female	No	PND 22	Dorsal hippocampus Ventral hippocampus	IL-1β IL-6 TNF-α	RNA	↑ Ventral Hippocampus IL-6 ↑ Dorsal Hippocampus TNF-α ↑ Ventral Hippocampus TNF-α	8
Nouri et al. (2020)	Mouse	NMRI	Maternal Separation	PND 2–14	3 h	Male	Yes	PND 60	Hippocampus	IL-1β TNF-α TLR4 NLRP3	RNA	↑ IL-1β ↑ TNF-α ↑ TLR4 ↑ NLRP3	9.5
Oliveira et al. (2020)	Rat	NR	Maternal Separation	PND 1–10	3 h	Male	Yes	PND 16 PND 30 PND 60	Brainstem Cerebral Cortex	IL-1β IL-4	Protein	↓ PND 30 Brainstem IL-1β ↑ PND 60 Brainstem IL-1β ↑ PND 16 Brainstem IL-4 ↓ PND 30Brainstem IL-4 ↑ PND 60 Brainstem IL-4 ↑ PND Cerebral Cortex IL-1β ↓ PND 60 Cerebral Cortex IL-1β ↑ PND 16 Cerebral Cortex IL-4 ↑ PND 30 Cerebral Cortex IL-4 ↓ 60 PND Cerebral Cortex IL-6	9
Park et al. (2014)	Rat	Sprague-Dawley	Maternal Separation	PND 14–28	14 days	NR	Yes	PND 28	Hippocampus	CCL2 IL-6 CXCL10	RNA Protein	↑ Protein CCL2 ↑ Protein IL-6 ↑ Protein CXCL10 ↑ Protein CCL19	7

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Table 1 (*continued*)

Author (year)	Species	Strain	ELS protocol	ELS period	ELS duration	Sex of tested offspring	Behavioral testing	Age of euthanasia	Collected tissue	Targets	Biological Material	Significant findings (vs Controls)	**Quality Score (out of 13)**
										CCL19 IL1RL1		↑ Protein IL1RL1 ↑ RNA CCL2 ↑ RNA IL-6	
Pinheiro et al. (2015)	Rat	Wistar	Maternal Separation	PND 1–14	3 h	Male	Yes	NR	Hippocampus Prefrontal Cortex	IL-10 TNF-α	Protein	↑ Hippocampus IL-10 ↑ Hippocampus TNF-α ↑ Prefrontal Cortex TNF-α	9
Réus et al. (2013)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male	Yes	PND 104	Cerebrospinal Fluid	IL-1β IL-10 TNF-α	Protein	↑ IL-1β ↑ TNF-α	11.5
Réus et al. (2015)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male	Yes	PND 104	Cerebrospinal Fluid	IL-1β IL-6 TNF-α	Protein	↑ IL-6	10
Réus et al. (2017)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male	Yes	PND 21 PND 31 PND 41 PND 61	Hippocampus Prefrontal Cortex	IL-1β IL-6 IL-10 TNF-α	Protein	↑ PND 21 Hippocampus IL-1β ↑ PND 31 Hippocampus IL-1β ↓ PND 61 Hippocampus IL-1β ↓ PND 21 Prefrontal Cortex IL-1β ↑ PND 31 Prefrontal Cortex IL-1β ↑ PND 21 Hippocampus IL-6 ↑ PND 31 Hippocampus IL-6 ↑ PND 41 Hippocampus IL-6 ↑ PND 61 Hippocampus IL-6 ↑ PND 41 Prefrontal Cortex IL-6 ↑ PND 61 Prefrontal Cortex IL-6 ↓ PND 21 Hippocampus IL-10 ↓ PND 31 Hippocampus IL-10 ↓ PND 41 Hippocampus IL-10 ↓ PND 61 Hippocampus IL-10 ↓ PND 21 Prefrontal Cortex IL-10 ↓ PND 31 Prefrontal Cortex IL-10 ↑ PND 21 Hippocampus TNF-α ↑ PND 31 Hippocampus TNF-α ↑ PND 41 Hippocampus TNF-α	9.5

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Table 1 (*continued*)

Author (year)	Species	Strain	ELS protocol	ELS period	ELS duration	Sex of tested offspring	Behavioral testing	Age of euthanasia	Collected tissue	Targets	Biological Material	Significant findings (vs Controls)	**Quality Score (out of 13)**
												↑ PND 21 Prefrontal Cortex TNF-α ↑ PND 31 Prefrontal Cortex TNF-α ↑ PND 41 Prefrontal Cortex TNF-α	
Romeo et al. (2004)	Mouse	C57BL/6	Maternal Separation	PND 1–7	3 h	Male	No	PND 7	Hippocampus (CA1, CA2, CA3, Dentate Gyrus) Prefrontal Cortex (Infralimbic, prelimbic cortex)	TGF-α	RNA	↓ Male PFC (Prelimbic Cortex) ↓ Female PFC (Prelimbic Cortex) ↓ Male PFC (Infralimbic Cortex) ↓ Female PFC (Infralimbic Cortex)	10.5
Roque et al. (2016)	Rat	Sprague-Dawley	Maternal Separation	PND 1–14	3 h	Male	No	PND 15	Hippocampus Hypothalamus	IL-1β IL-6 TNF-α	RNA	↑ Hippocampus IL-1β ↑ Hippocampus TNF-α	9
Saavedra et al. (2017)	Rat	Sprague-Dawley	Maternal Separation	PND 1–14	3 h	Male	No	PND 15	Hippocampus	IL-1β	Protein	No difference between groups	10.5
Ströher et al. (2020)	Rat	Wistar	Maternal Separation	PND 1–10	3 h	Male Female	No	PND 44	Hippocampus Hypothalamus Cerebral Cortex	IL-6 TNF-α IL-10	Protein	↑ Male Cerebral Cortex IL-6 ↑ Female Cerebral Cortex IL-6 ↑ Male Cerebral Cortex TNF-α ↓ Male Cerebral Cortex IL-10 ↓ Male Hippocampus TNF-α ↓ Male Hypothalamus IL-6	11.5
Tang et al. (2017)	Mouse	C57BL/10JNju	Maternal Separation	PND 1–15	6 h	Male	Yes	NR	Paraventricular Nucleus	IL-1β IL-6 TNF-α	Protein	↑ IL-1β ↑ TNF-α	8
Viola et al. (2019)	Mouse	BALB/C	Maternal Separation	PND 1–15	3 h	Male	Yes	PND 45	Medial Prefrontal Cortex	IL-6 TNF-α TLR3 NFKB1	RNA	No difference between groups	9
Viviani et al. (2014)	Rat	Albino Wistar	Maternal Separation	PND 9–10	24 h	Male Female	Yes	PND 10 PND 45	Hippocampus Prefrontal Cortex	IL-1β IL-1R1	Protein	↓ PND 45 Male Prefrontal Cortex IL-1βR1	9.5
Wang et al. (2020)	Rat	Wistar	Maternal Separation	PND 2–20	4 h	Male	Yes	PND 27 PND 76	Hippocampus Prefrontal Cortex	IL-1β IL-6 TNF-α	Protein	↑ PND 27 Hippocampus IL-1β ↑ PND 27 Hippocampus IL-6 ↑ PND 27 Prefrontal Cortex IL-1β ↑ PND 27 Prefrontal Cortex IL-6 ↑ PND 27 Prefrontal Cortex TNF-α ↑ PND 76 Hippocampus IL-1β	10.5

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Table 1 (*continued*)

Author (year)	Species	Strain	ELS protocol	ELS period	ELS duration	Sex of tested offspring	Behavioral testing	Age of euthanasia	Collected tissue	Targets	Biological Material	Significant findings (vs Controls)	**Quality Score (out of 13)**
												↑ PND 76 Hippocampus IL-6 ↑ PND 76 Hippocampus TNF-α ↑ PND 76 Prefrontal Cortex IL-6 ↑ PND 76 Prefrontal Cortex TNF-α	
Ye et al. (2019)	Rat	Sprague-Dawley	Maternal Separation	PND 2–21	3 h	Female	Yes	PND 51	Hippocampus Prefrontal Cortex	IL-1β IL-6 TNF-α	Protein	↑ Prefrontal Cortex IL-1β ↑ Prefrontal Cortex IL-6 ↑ Prefrontal Cortex TNF-α ↑ Hippocampus IL-1β ↑ Hippocampus IL-6	8
Zhu et al.,(2017)	Rat	Wistar	Maternal Separation	PND 1–21	6 h	Male	No	PND 88–90	Hippocampus	IL-1β IL-6 TNF-α	Protein	No difference between groups	9
Zolfaghari et al. (2021)	Rat	Albino Wistar	Maternal Separation	PND 2–14	3 h	Male	Yes	PND 67	Hippocampus Prefrontal Cortex	IL-1β IL-6	RNA	↑ Hippocampus IL-1β ↑ Prefrontal Cortex IL-1β ↑ Hippocampus IL-6 ↑ Prefrontal Cortex IL-6	9

Note: Strain: NR = Not Reported; PND = Postnatal Day.

combined with heat or cold stress (n = 1) corresponded to 3.22% and maternal deprivation was performed in 2 studies (6.45%). Most studies utilized an ELS period of 8–14 days (61.3%, n = 19), followed by 25.8% of studies using 15–21 days (n = 8). The use of a single day of stress (n = 2), or 2–7 days (n = 2) composed 6.45% of each. 64.5% of studies utilized only males (n = 20), while only 6.45% used only females (n = 2). 22.6% included both male and female animals (n = 7) and 6.45% did not report the sex of the animals (n = 2). Hippocampus was the predominantly brain tissue analyzed (77.4%, n = 24), followed by the prefrontal cortex (n = 15) that was analyzed in 48.4% of studies. The cerebral cortex (n = 3) and hypothalamus (n = 3) were analyzed in 9.67% of studies each, while 6.45% analyzed the cerebrospinal fluid (n = 2). The striatum (n = 1), nucleus accumbens (n = 1), and Brainstem (n = 1), were the least analyzed regions (3.23% of studies each). 25.8% of studies evaluated cytokines between postnatal day (PND) 0–21 (n = 8), 35.48% between PND 22–45 (n = 11), 19.35% between PND 46–60 (n = 6), 19.35% between PND 61–90 (n = 6), 19.35% from PND 91 or more (n = 6), and 9.67% did not report the age (n = 3). Furthermore, 15 studies (48.38%) were performed using RNA samples, and 18 studies (58.06%) were performed using protein samples. There is a discrepancy between the total number of studies since some of them have evaluated more than one variable.

3.3. Methodological quality assessment

Among all studies, the maximum methodological quality score achieved was 11.5, the minimum score was 7, and the average score between studies was 9.5. The methodological quality score for each study is presented in the last column of Table 1.

Considering each methodological aspect evaluated, we highlight the following features present in 100% of studies: housing conditions, ethical statement, light conditions, number of groups, ELS description, ELS duration, ELS time, and description of the method for biological sampling. Interestingly, only 39% of studies reported the total number of animals used, 29% reported breeding procedures, 26% reported a description of the cages, 19% reported blinding procedures, and only 6% provided information about lost samples. A detailed description of the methodological quality assessment can be viewed in Fig. 2.

3.4. Impact of early life stress on inflammatory cytokines

The meta-analysis was performed in 30 studies previously included in the systematic review. Four cytokines (IL-1β, IL-6, TNF-α, and IL-10) were used for meta-analysis due to insufficient studies analyzing the remaining cytokines. Twenty-two studies analyzed IL-1β (58 effect sizes), and the results indicated that ELS exposure increases brain levels of IL-1β (SMD 0.94; 95% CI 0.45, 1.41; $p = 0.0001$) (Fig. 3). Similarly, 23 studies analyzed TNF-α (57 effect sizes), and the analysis revealed increased levels in the brain after ELS exposure (SMD 0.89; 95% CI 0.46, 1.32; $p < 0.0001$) (Fig. 4). Regarding IL-6, 20 studies reported data regarding this cytokine (55 effect sizes), and there was also a significant increase after ELS exposure (SMD 0.93; 95% CI 0.27, 1.58; $p = 0.0054$) (Fig. 5). The anti-inflammatory cytokine IL-10 was analyzed only by seven studies (24 effect sizes), and no significant effect of ELS was detected (SMD −0.70; 95% CI −1.79, 0.40; $p = 0.2155$) (Fig. 6).

The heterogeneity between studies in IL-1β, IL-6, IL-10 and TNF-α was significant ($I^2 = 84.87\%$, $p < 0.0001$; $I^2 = 88.74\%$, $p < 0.0001$; $I^2 = 81.22\%$, $p < 0.0001$; $I^2 = 79.66\%$, $p < 0.0001$, respectively). Therefore, we explored sources of heterogeneity using meta-regression analysis, including the following seven potential moderators: (1) species, (2) ELS period, (3) sex, (4) age, (5) tissue, (6) biological material, and (7) secondary manipulations. Unfortunately, it was not possible to perform a comparison of the ELS protocols utilized due to insufficient number of studies.

The first applied moderator (species) was significantly associated with the estimates of heterogeneity only in the IL-6 meta-analysis ($p < 0.0001$; variance explained = 13.21%), indicating that mice had lower levels of IL-6 assessments following ELS when compared to rats. At the same time, the ELS period was significantly associated with the estimates of heterogeneity of IL-1β, IL-6, and TNF-α meta-analysis. In

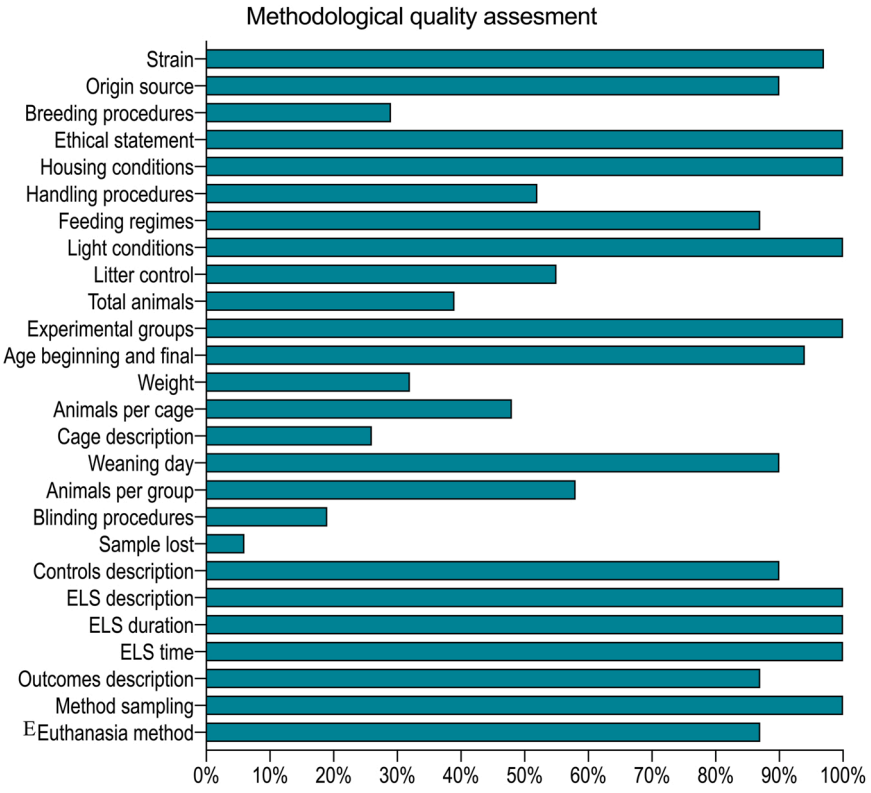

Fig. 2. Methodological quality assessment. Percentage of studies that reported each item of the checklist.

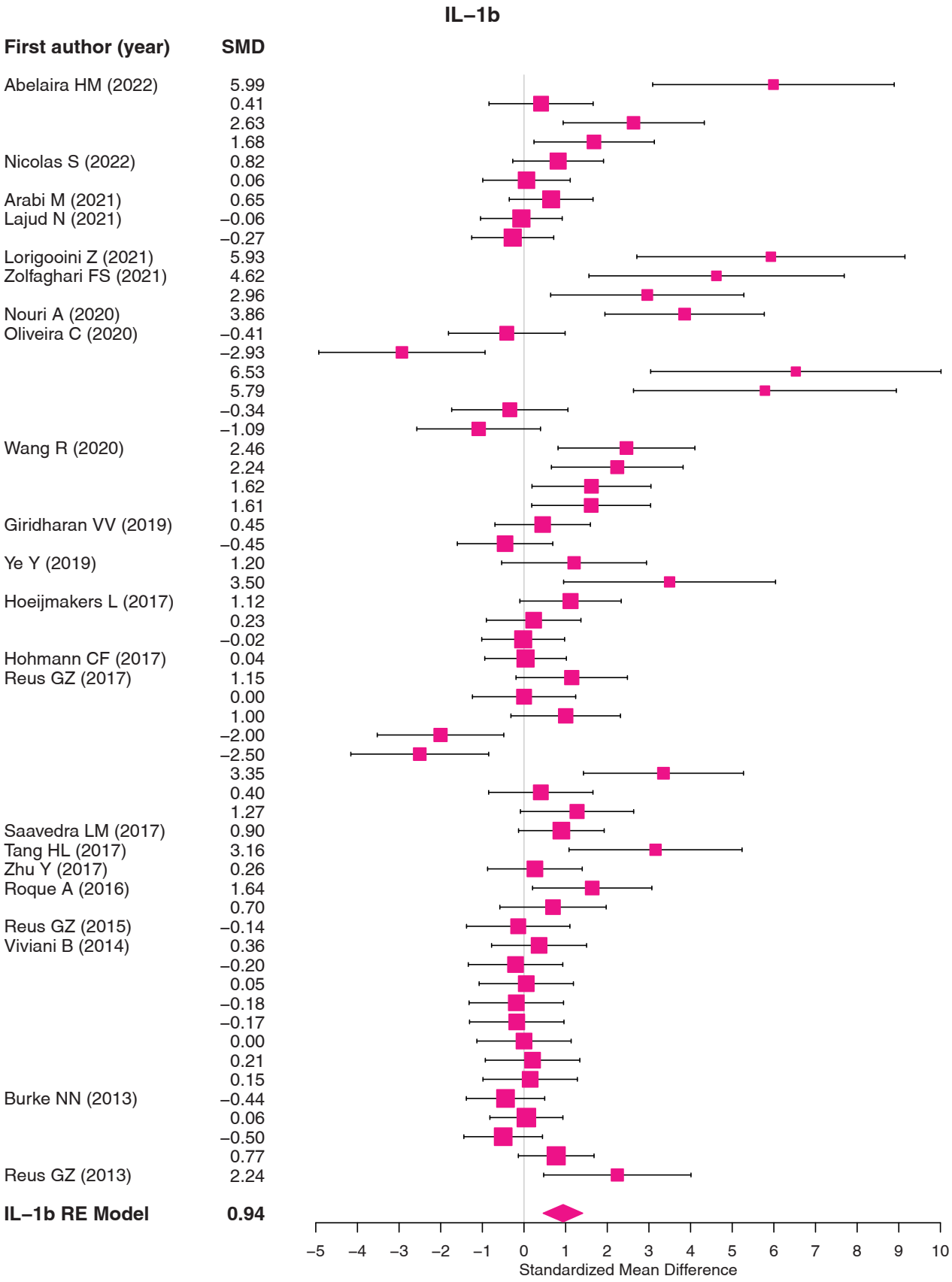

Fig. 3. Forest plot showing the effect size of IL-1β. SMD = Standardized Mean Difference; RE Model = Random Effects Model; 95% CI.

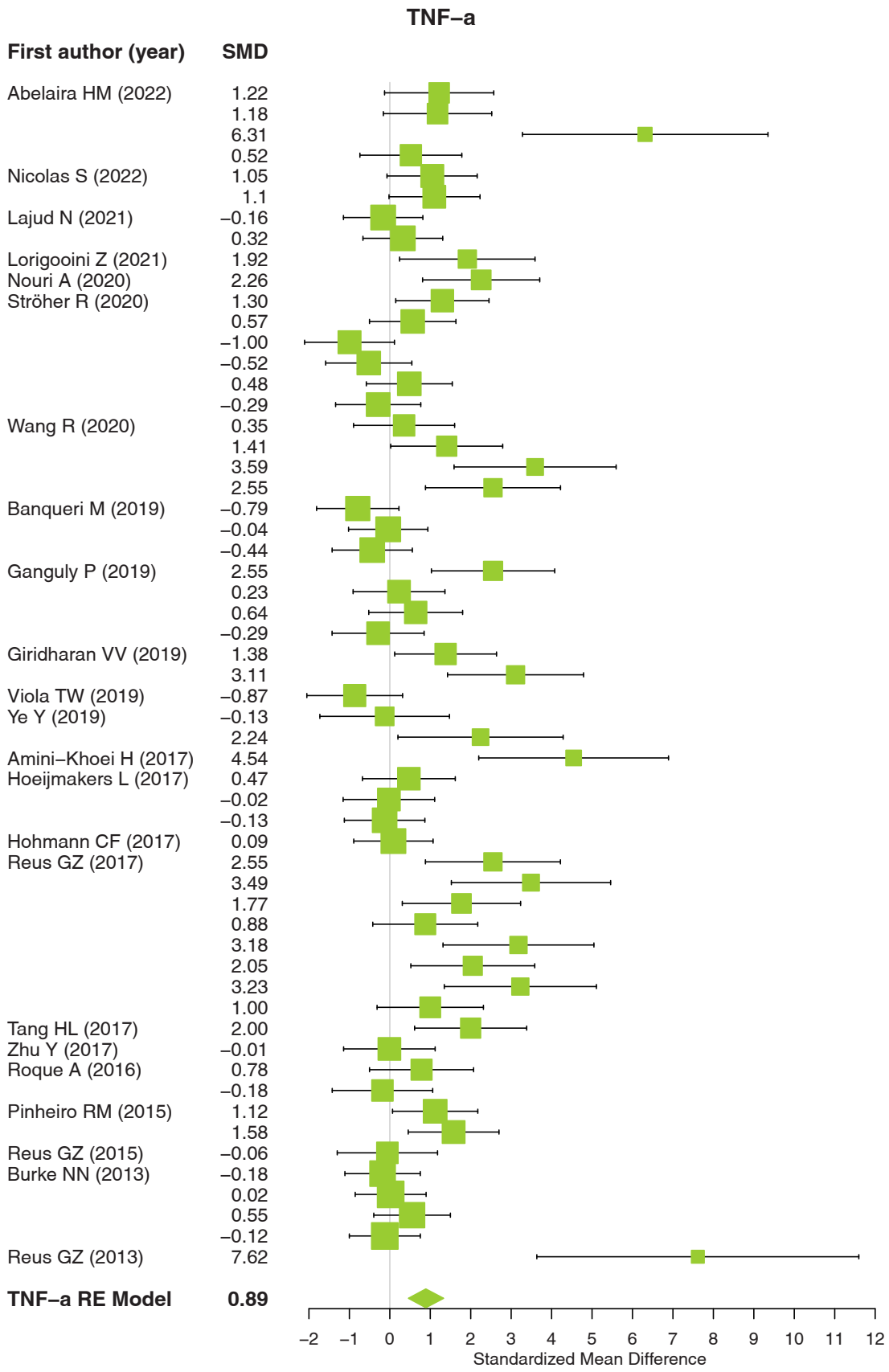

Fig. 4. Forest plot showing the effect size of TNF-α. SMD = Standardized Mean Difference; RE Model = Random Effects Model; 95% CI.

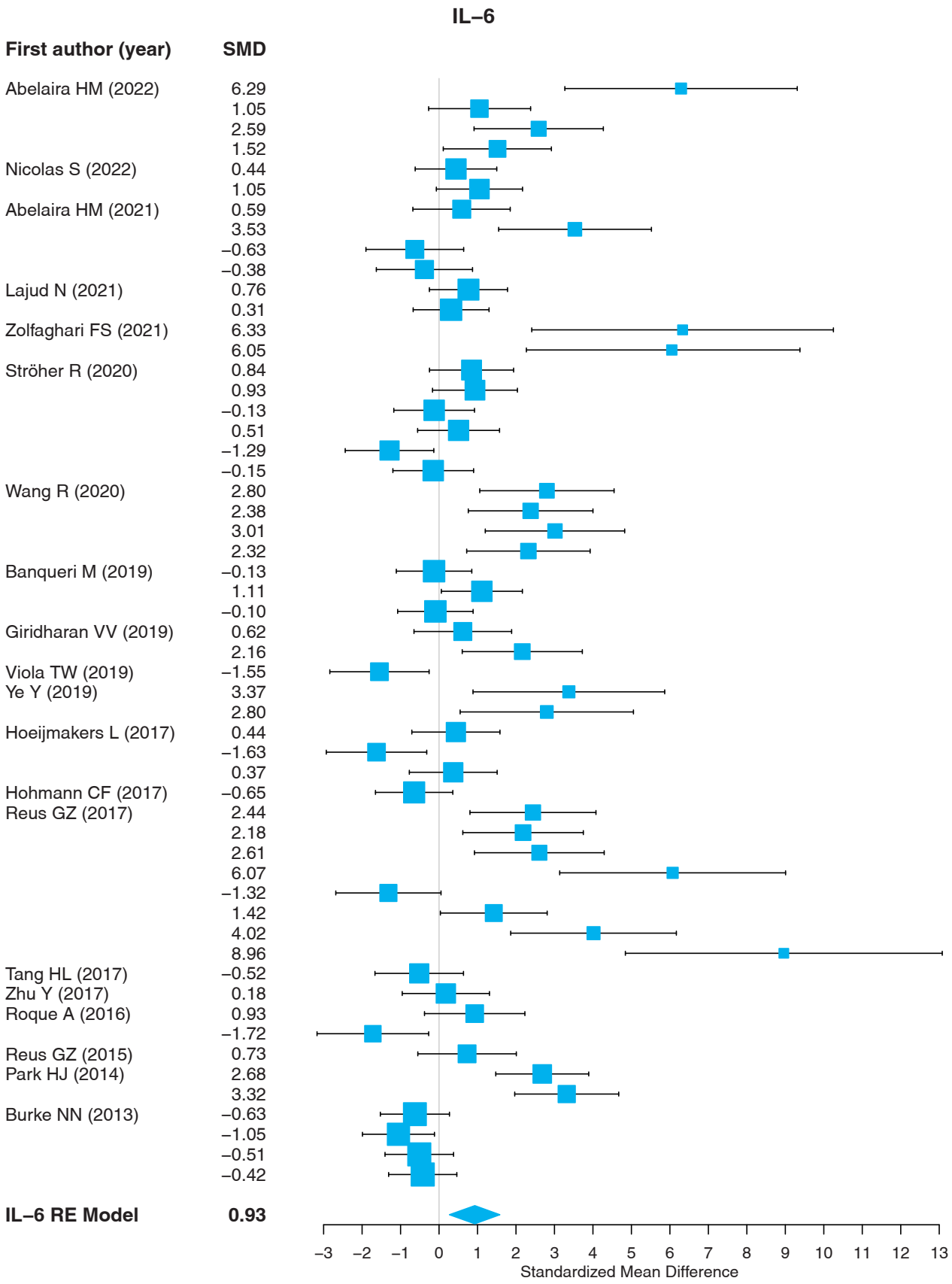

Fig. 5. Forest plot showing the effect size of IL-6. SMD = Standardized Mean Difference; RE Model = Random Effects Model; 95% CI.

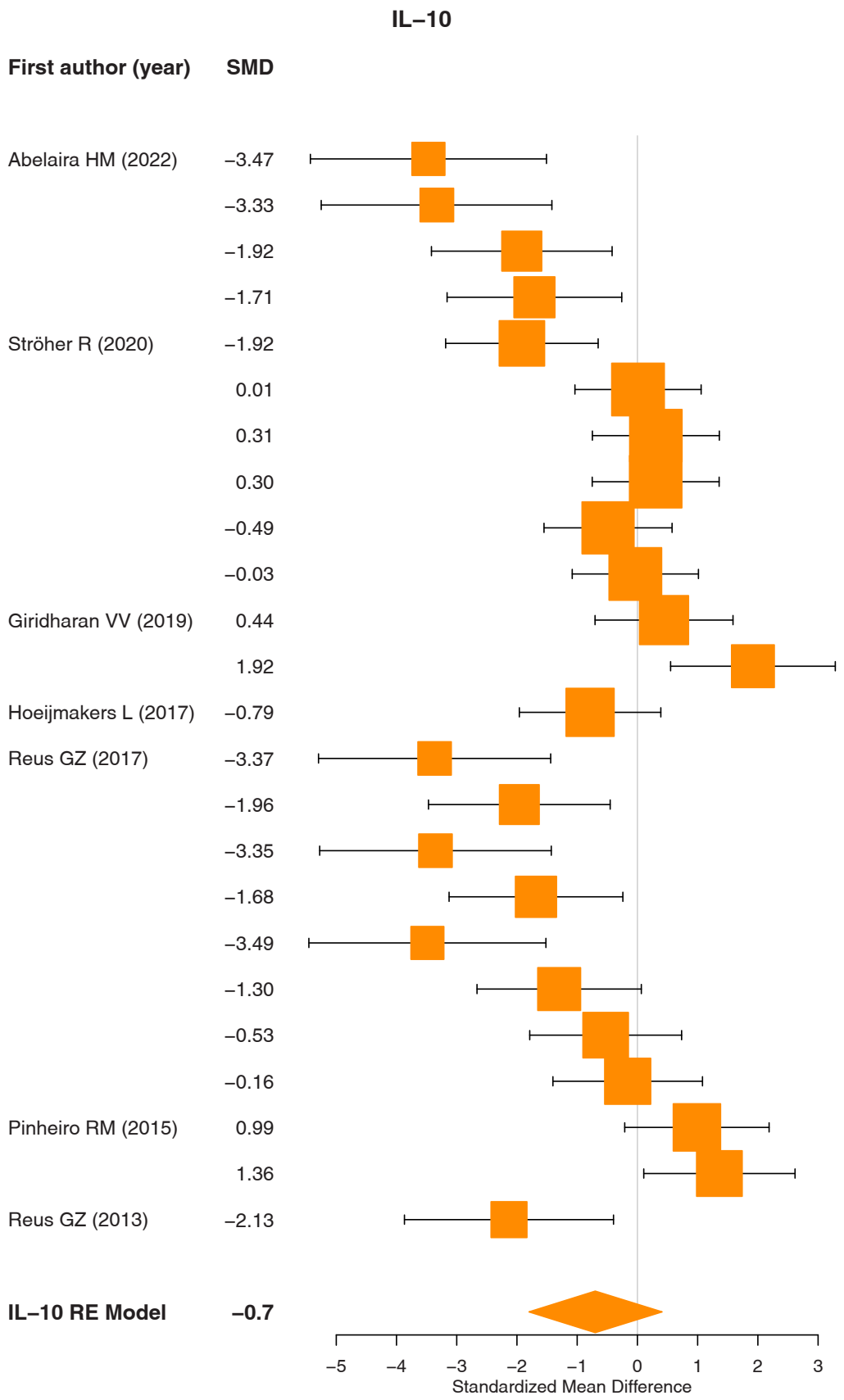

Fig. 6. Forest plot showing the effect size of IL-10. SMD = Standardized Mean Difference; RE Model = Random Effects Model; 95% CI.

detail, animals that were exposed for 8–14 days or 15–21 days had higher IL-1β and IL-6 levels following ELS when compared to levels of animals exposed to only one day of ELS (IL-1β: $p = 0.0017$ and $p = 0.0007$, respectively; variance explained = 6.69%; IL-6: $p < 0.0001$ for both periods; variance explained = 9.17%). For TNF-α, this increase was only observed in animals exposed from 8 to 14 days of ELS ($p = 0.0007$; variance explained = 6.97%). The sex of the animals was significantly associated with the estimates of heterogeneity only in the TNF-α meta-analysis ($p = 0.024$; variance explained = 0%), indicating that female animals had lower estimates of this cytokine following ELS when compared to male animals.

Regarding the age of the animals, this moderator was significantly associated with the estimates of heterogeneity of the meta-analysis of all targets. In detail, animals analyzed from PND 46–60 and PND 61–90 had higher IL-1β estimates following ELS when compared to estimates of animals analyzed between PND 0 and 21 ($p = 0.007$ and $p = 0.039$, respectively; variance explained = 14.8%). Moreover, animals from PND 61–90 had higher IL-6 estimates, while animals analyzed on PND 91 or later had lower estimates of this cytokine ($p = 0.003$ and $p = 0.028$, respectively; variance explained = 17.03%). Furthermore, animals analyzed from PND 22–45 and PND 91 or later had lower TNF-α estimates following ELS ($p = 0.015$ and $p < 0.0001$, respectively; variance explained = 38.85%). Finally, animals analyzed from PND 60–91 presented lower IL-10 estimates ($p = 0.003$; variance explained = 1.44%). The analyzed tissue was significantly associated with heterogeneity estimates for IL-6 and TNF-α meta-analysis. Indicating that analysis performed in the hypothalamus had lower IL-6 estimates ($p < 0.0001$; variance explained = 4.76%) and the striatum had lower TNF-α estimates ($p = 0.010$; variance explained = 0%) following ELS when compared to the hippocampus.

Furthermore, the biological material analyzed was associated with the heterogeneity of IL-6 and TNF-α meta-analysis, indicating that RNA analysis presented lower estimates of both cytokines following ELS when compared to protein analysis estimates ($p < 0.0001$ for both targets; variance explained = 15.52% and 18.51%, respectively). Finally, secondary manipulations were significantly associated with the estimates of heterogeneity of IL-10 and TNF-α. In detail, animals that experienced behavioral testing or both sham surgery or vehicle injection and behavioral testing had lower IL-10 estimates ($p = 0.003$ and $p = 0.007$, respectively; variance explained = 5.63%). Regarding the TNF-α estimates, animals exposed to sham surgery or vehicle injection, or behavioral testing or both sham surgery or vehicle injection and behavioral testing showed higher estimates of this cytokine ($p = 0.039$, $p = 0.001$, and $p = 0.008$, respectively; variance explained = 1.89%) following ELS exposure when compared to estimates of animals not exposed to secondary manipulations. Detailed information regarding IL-1β, IL-6, IL-10, and TNF-α heterogeneity sources are respectively displayed in Supplementary Tables 1 to 4.

Funnel plots were created to evaluate the publication bias, revealing an asymmetry in all targets (Fig. 7). Egger's regression test confirmed if the asymmetry was statistically significant. As we predicted, the test evidenced publication bias in IL-1β, IL-6, IL-10, and TNF-α ($z = 7.330$, $p < 0.0001$; $z = 9.494$, $p < 0.0001$; $z = -6.220$, $p < 0.0001$; $z = 10.929$, $p < 0.0001$, respectively). The existence of publication bias may indicate an overestimation of the effect size.

4. Discussion

In this study, we sought to analyze the effects of ELS exposure on the levels of inflammatory cytokines in the brain. To our knowledge, this is the first meta-analytic investigation of such outcomes in rodents. The evidence analyzed in our study indicated that ELS induced a significant increase in the proinflammatory cytokines IL-1β, IL-6, and TNF-α in the brain, especially in the hippocampus. Our meta-regression analysis showed that extended ELS protocols induce more pronounced alterations in the investigated cytokines. ELS effects appear to diminish when

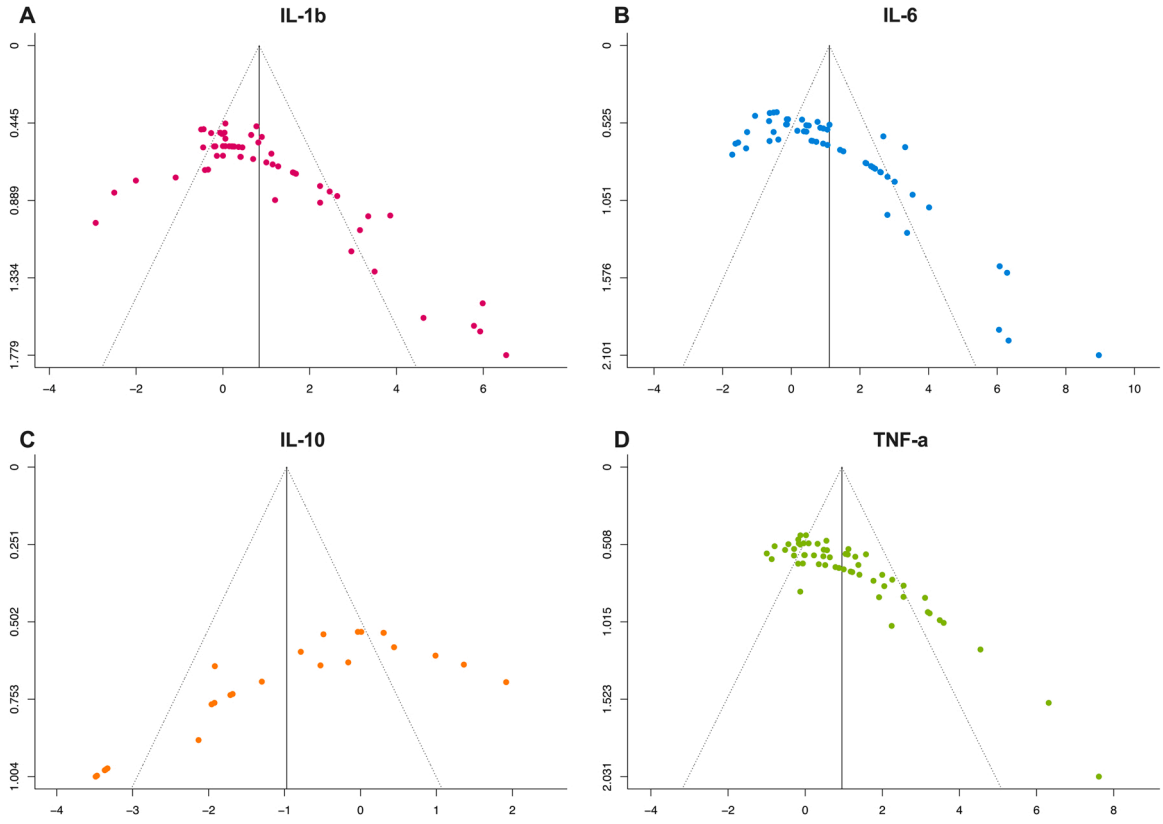

Fig. 7. Funnel plots indicating publication bias of included studies. A) IL-1β; B) IL-6; C) IL-10; D) TNF-α.

the analysis is performed in older animals. Furthermore, publication bias was evidenced in all meta-analyses, which indicates that negative results might not have been reported in the studies.

Cytokines are critical modulators of neuroinflammatory processes, which are directly related to protecting neural integrity. However, increased pro-inflammatory cytokines expression is harmful when uncontrolled, leading to chronic changes in the patterns of inflammation and aggravating neuronal damage (Kim et al., 2016) S0278584615001359?via%3Dihub. Chronic stress exposure may induce changes in the immune system, which could lead to alterations on the HPA axis (Jia et al., 2019; Walker et al., 2019),30844940/ and trigger a chronic neuroinflammatory state that has been associated with multiple psychiatric conditions (Kim et al., 2016; Na et al., 2014). Our study observed that ELS increased TNF-α and IL-1β, which is an interesting finding considering that both cytokines have similar pro-inflammatory properties. TNF-α and IL-1β are capable of inducing inflammatory damage by regulating a series of cellular activities in the endothelium through similar mechanisms (Feghali and Wright, 1997; Marafini et al., 2019; Wojdasiewicz et al., 2014). However, a key function of these cytokines is the ability to stimulate IL-6 synthesis in various cell types during the TNF-α and IL-1β activation (Feghali and Wright, 1997), which promotes a cascade of intracellular events that perpetuate the inflammatory response through the release of several cytokines with culminating effects (Feghali and Wright, 1997; Marafini et al., 2019; Warren, 1990). This scenario may favor the development of a chronic inflammatory state that may significantly impact sensitive regions of the brain.

A similar long-term increase induced by ELS was observed regarding IL-6 data. Even though recent studies have reported alterations in IL-6 levels only within 24 h after the end of the ELS protocol, our data suggest a chronic increase related to this interleukin after ELS exposure (Giridharan et al., 2019; Roque et al., 2016). Furthermore, IL-6 induces alterations in hepatocytes and lymphocytes, which are currently detected in chronic inflammatory diseases (Tanaka et al., 2014). Moreover, past studies have linked alterations in IL-6 levels with the mechanisms of depressive-like behavior. Monje et al. (2011) showed that IL-6 knockout mice became resistant to developing depressive-like behavior after exposure to chronic darkness compared to wild-type animals. Chourbaji et al. (2006) reported that IL-6-deficient mice were reduced to despair in the forced swim test, tail suspension test, and enhanced hedonic behavior. This data set reinforces that IL-6 plays a significant role in the biomolecular mechanisms associated with psychiatric conditions.

No alteration was observed regarding IL-10 levels, which agrees with a recent review that reported inconsistencies in studies that investigated IL-10 levels after ELS exposure (Dutcher et al., 2020). Considering that IL-10 has a robust action to counteract an inflammatory response (Feghali and Wright, 1997; Pedersen et al., 2018), it is possible that the stress protocols used by the studies included in our review were not sufficient to induce long-lasting alterations in the levels of this cytokine. In addition, according to Walker et al. (2019), IL-10 expression varies significantly among brain tissues, being more expressed in the hypothalamus and pituitary when compared to the hippocampus. Our review found that the hippocampus was the predominantly analyzed tissue. In contrast, the hypothalamus was analyzed only in 11,11% of the studies, highlighting that the focus of analysis of IL-10 levels should expand to other brain regions to complement this research gap.

Regarding the specific moderators investigated in our meta-analysis, we observed that multiple moderators impacted analysis estimates. For instance, we identified that extended ELS protocols induced higher estimates of IL-1β, IL-6, and TNF-α when compared to shorter protocols. This interpretation can be seen in the studies by Burke et al. (2013), in which one day of maternal deprivation resulted in an IL-1β increase only in females. Furthermore, Hohmann et al. (2017) used a six-day MS protocol, and no difference was observed in any of the cytokines investigated in our meta-analysis. On the other hand, Wang et al. (2020) exposed rats to 19 days of MS and reported increased levels of IL-1β, IL-6, and TNF-α in both the PFC and hippocampus. Additionally, we identified an overexpression of TNF-α in female animals compared to males, which can support the hypothesis that females are more prone to a pro-inflammatory state following stressful events, and might be related to the development of later in life psychiatric disorders (Bekhbat and Neigh, 2018; Engler et al., 2016).

Even though overexpression of pro-inflammatory cytokines was observed during adolescence and early adulthood in animals previously exposed to ELS (Fagundes and Way, 2014; Majcher-Maślanka et al., 2019), we identified a transitory effect of ELS in older animals. When analyzing animals past PND 90, ELS-induced cytokine alterations were hardly present. For example, Hoeijmakers et al. (2017) reported no effect of ELS on animals at ten months of age. Moreover, Banqueri et al. (2019) utilized a robust MS protocol of 21 days and 4 h per day of separation and only reported a single increase in IL-6 levels in the hippocampus at PND 100. This data set goes in line with a recent systematic review, in which Dutcher et al. (2020) showed no central alteration in IL-1β, IL-6, and TNF-α in animals past PND 85 exposed to MS. However, after a secondary exposure to stress later in life, a robust and long-lasting effect was observed. For this reason, it is possible to hypothesize that ELS indeed primes a neuroinflammatory response, but it cannot ensure long-lasting alterations in cytokine levels. Previous evidence has shown that secondary stress exposure, especially during adolescence, could be the critical factor in triggering an irreversible neuroinflammatory malfunction (Dutcher et al., 2020; Kiank et al., 2009; Wohleb et al., 2012).

Another critical factor that must be considered for interpreting our data is tissue specificity. A previous systematic review has shown no long-term alteration in IL-1β, IL-6, and TNF-α levels after MS exposure in the peripherical tissues (Dutcher et al., 2020). Our analysis is strictly related to brain regions, which could in part be responsible for this data discrepancy. Moreover, this could also be associated with the fact that central regions are susceptible to disruptions during early development and could be more prone to long-term alterations in cytokine levels. Therefore, our data add to the comprehensive work by Dutcher et al. (2020) that highlighted the effects of early life stress and the combination of early-life and later-life stress. Nevertheless, our analysis was restricted to the brain and a single stress period to increase power and decrease heterogeneity.

Considering that RNA transcripts do not necessarily correlate with protein levels, our meta-analysis sought to deepen the knowledge about the differences between cytokines RNA and protein levels (Koussounadis et al., 2015). We observed that protein analysis presented higher estimates when compared to studies that investigated only RNA expression. We suggest that future studies investigate both protein and RNA levels of cytokines since only RNA might not give a proper estimative of how these alterations may influence the immune state of the brain (Vogel and Marcotte, 2012). For example, Lajud et al. (2021) performed MS protocol on rats and investigated RNA expression, but no difference was observed in the cytokines analyzed. On the other hand, Reus et al. (2017) performed a similar MS protocol but analyzed protein levels of cytokines and saw multiple alterations in the targets. Considering the brain regions analyzed in the included studies, we observed that the hippocampus was the region with the most significant effects. The high number of studies in our meta-analysis that investigated this region and also the substantial relationship in the hippocampus with neuroinflammatory function could be in part associated with those results (Calcia et al., 2016; Çalışkan et al., 2020; Frank et al., 2014; González-Pardo et al., 2020; Wohleb et al., 2012).

We must consider some limitations of the present study. First, we identified publication bias in all the analyzed targets included in this study, suggesting that some of the effect sizes of these cytokines could be overestimated. In addition, pro-inflammatory cytokines analysis gathered 46 effect sizes or even more, while few studies analyzed anti-inflammatory cytokines; hence only IL-10 could be included in the meta-analysis, but still not being present in many studies and having only 20 effect sizes, which is less than half when compared to other

cytokines. We know that the included studies have different methodological approaches and aim for a range of brain regions. To overcome this issue, we applied meta-regression analysis with other moderators. Unfortunately, we could not investigate specific differences between ELS protocols due to the predominance of MS, so model-to-model singularities could not be identified.

In conclusion, our analysis revealed that ELS exposure could alter the expression of pro-inflammatory cytokines, especially regarding protein levels of IL-1β, IL-6, and TNF-α. The study also suggests that these alterations were more apparent in the hippocampus of adult animals that were exposed to at least eight days of ELS protocol. Moreover, the meta-regression results indicate that these inflammatory changes might not be long-lasting, and we hypothesize that a further stressful challenge could trigger a robust long-term effect. Finally, it would be necessary for future studies to focus on the impact of ELS exposure on anti-inflammatory cytokines because the actual evidence is still not sufficient to comprehend the relationship between these targets and ELS fully.

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Conflict of interest

All authors declare no conflicts of interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104746.

References

Abelaira, H.M., Veron, D.C., de Moura, A.B., Carlessi, A.S., Borba, L.A., Botelho, M.E.M., Andrade, N.M., Martinello, N.S., Zabot, G.C., Joaquim, L., Biehl, E., Bonfante, S., Budni, J., Petronilho, F., Quevedo, J., Réus, G.Z., 2021. Sex differences on the behavior and oxidative stress after ketamine treatment in adult rats subjected to early life stress. Brain Res. Bull. 172, 129–138. https://doi.org/10.1016/j.brainresbull.2021.04.021.

Abelaira, H.M., Rosa, T., de Moura, A.B., Andrade, N.M., Martinello, N.S., Maciel, L.R., Botelho, M.E.M., Borba, L.A., Chede, B.C., Arent, C.O., Joaquim, L., Bonfante, S., Danielski, L.G., Tuon, T., Petronilho, F., Quevedo, J., Réus, G.Z., 2022. Combination of electroconvulsive stimulation with ketamine or escitalopram protects the brain against inflammation and oxidative stress induced by maternal deprivation and is critical for associated behaviors in male and female rats. Mol. Neurobiol. https://doi.org/10.1007/s12035-021-02718-x.

Agorastos, A., Pervanidou, P., Chrousos, G.P., Baker, D.G., 2019. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry 10, 118. https://doi.org/10.3389/fpsyt.2019.00118.

Aleksić, D., Aksić, M., Radonjić, N.V., Jovanović, A., Marković, B., Petronijević, N., Radonjić, V., Mališ, M., Filipović, B., 2016. Long-term effects of maternal deprivation on the volume, number and size of neurons in the amygdala and nucleus accumbens of rats. Psychiatr. Danub 28 (3), 211–219. ⟨https://www.ncbi.nlm.nih.gov/pubmed/27658829⟩.

Amini-Khoei, H., Mohammadi-Asl, A., Amiri, S., Hosseini, M.J., Momeny, M., Hassanipour, M., Rastegar, M., Haj-Mirzaian, A., Mirzaian, A.H., Sanjarimoghaddam, H., Mehr, S.E., Dehpour, A.R., 2017. Oxytocin mitigated the depressive-like behaviors of maternal separation stress through modulating mitochondrial function and neuroinflammation. Prog. Neuropsychopharmacol. Biol. Psychiatry 76, 169–178. https://doi.org/10.1016/j.pnpbp.2017.02.022.

Arabi, M., Nasab, S.H., Lorigooini, Z., Boroujeni, S.N., Mortazavi, S.M., Anjomshoa, M., Amini-Khoei, H., 2021. Auraptene exerts protective effects on maternal separation stress-induced changes in behavior, hippocampus, heart and serum of mice. Int Immunopharmacol. 93, 107436 https://doi.org/10.1016/j.intimp.2021.107436.

de Azeredo, L.A., Wearick-Silva, L.E., Viola, T.W., Tractenberg, S.G., Centeno-Silva, A., Orso, R., Schröder, N., Bredy, T.W., Grassi-Oliveira, R., 2017. Maternal separation induces hippocampal changes in cadherin-1 (CDH-1) mRNA and recognition memory impairment in adolescent mice. Neurobiol. Learn Mem. 141, 157–167. https://doi.org/10.1016/j.nlm.2017.04.006.

Banqueri, M., Méndez, M., Gómez-Lázaro, E., Arias, J.L., 2019. Early life stress by repeated maternal separation induces long-term neuroinflammatory response in glial cells of male rats. Stress 22 (5), 563–570. https://doi.org/10.1080/10253890.2019.1604666. Epub 2019 Apr 22. PMID: 31007117.

Bauer, M.E., Teixeira, A.L., 2019. Inflammation in psychiatric disorders: what comes first? Ann. N. Y Acad. Sci. 1437 (1), 57–67. https://doi.org/10.1111/nyas.13712.

Bekhbat, M., Neigh, G.N., 2018. Sex differences in the neuro-immune consequences of stress: focus on depression and anxiety. Brain Behav. Immun. 67, 1–12. https://doi.org/10.1016/j.bbi.2017.02.006.

Brenhouse, H.C., Danese, A., Grassi-Oliveira, R., 2019. Neuroimmune impacts of early-life stress on development and psychopathology. Curr. Top. Behav. Neurosci. 43, 423–447. https://doi.org/10.1007/7854_2018_53.

Burke, N.N., Llorente, R., Marco, E.M., Tong, K., Finn, D.P., Viveros, M.P., Roche, M., 2013. Maternal deprivation is associated with sex-dependent alterations in nociceptive behavior and neuroinflammatory mediators in the rat following peripheral nerve injury. J. Pain. 14 (10), 1173–1184. https://doi.org/10.1016/j.jpain.2013.05.003.

Calcia, M.A., Bonsall, D.R., Bloomfield, P.S., Selvaraj, S., Barichello, T., Howes, O.D., 2016. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacol. (Berl.) 233 (9), 1637–1650. https://doi.org/10.1007/s00213-016-4218-9.

Çalışkan, G., Müller, A., Albrecht, A., 2020. Long-term impact of early-life stress on hippocampal plasticity: spotlight on astrocytes. Int J. Mol. Sci. 21 (14) https://doi.org/10.3390/ijms21144999.

Chourbaji, S., Urani, A., Inta, I., Sanchis-Segura, C., Brandwein, C., Zink, M., Schwaninger, M., Gass, P., 2006. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. Neurobiol. Dis. 23 (3), 587–594. https://doi.org/10.1016/j.nbd.2006.05.001.

Cochrane Infectious Diseases Group, 2007. How to develop a search strategy for a Cochrane Review. The Cochrane Library.

Danese, A., J Lewis, S., 2017. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma. Neuropsychopharmacology 42 (1), 99–114. https://doi.org/10.1038/npp.2016.198.

Diaz-Chávez, A., Lajud, N., Roque, A., Cheng, J.P., Meléndez-Herrera, E., Valdéz-Alarcón, J.J., Bondi, C.O., Kline, A.E., 2020. Early life stress increases vulnerability to the sequelae of pediatric mild traumatic brain injury. Exp. Neurol. 329, 113318 https://doi.org/10.1016/j.expneurol.2020.113318.

Druzhkova, T., Pochigaeva, K., Yakovlev, A., Kazimirova, E., Grishkina, M., Chepelev, A., Guekht, A., Gulyaeva, N., 2019. Acute stress response to a cognitive task in patients with major depressive disorder: potential metabolic and proinflammatory biomarkers. Metab. Brain Dis. 34 (2), 621–629. https://doi.org/10.1007/s11011-018-0367-3.

Dugue, R., Nath, M., Dugue, A., Barone, F.C., 2017. Roles of pro-and anti-inflammatory cytokines in traumatic brain injury and acute ischemic stroke. Mech. Neuroinflamm. 211.

Dutcher, E.G., Pama, E.A.C., Lynall, M.E., Khan, S., Clatworthy, M.R., Robbins, T.W., Bullmore, E.T., Dalley, J.W., 2020. Early-life stress and inflammation: a systematic review of a key experimental approach in rodents. Brain Neurosci. Adv. 4 https://doi.org/10.1177/2398212820978049.

Engler, H., Benson, S., Wegner, A., Spreitzer, I., Schedlowski, M., Elsenbruch, S., 2016. Men and women differ in inflammatory and neuroendocrine responses to endotoxin but not in the severity of sickness symptoms. Brain Behav. Immun. 52, 18–26. https://doi.org/10.1016/j.bbi.2015.08.013.

Fabbri, C., Hosak, L., Mössner, R., Giegling, I., Mandelli, L., Bellivier, F., Claes, S., Collier, D.A., Corrales, A., Delisi, L.E., Gallo, C., Gill, M., Kennedy, J.L., Leboyer, M., Lisoway, A., Maier, W., Marquez, M., Massat, I., Mors, O., Serretti, A., 2017. Consensus paper of the WFSBP Task Force on Genetics: genetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response. World J. Biol. Psychiatry. https://doi.org/10.1080/15622975.2016.1208843.

Fagundes, C.P., Way, B., 2014. Early-life stress and adult inflammation. Curr. Dir. Psychol. Sci. 23 (4), 277–283.

Feghali, C.A., Wright, T.M., 1997. Cytokines in acute and chronic inflammation. Front. Biosci. 2 (1), d12–d26.

Frank, M.G., Hershman, S.A., Weber, M.D., Watkins, L.R., Maier, S.F., 2014. Chronic exposure to exogenous glucocorticoids primes microglia to pro-inflammatory stimuli and induces NLRP3 mRNA in the hippocampus. Psychoneuroendocrinology 40, 191–200. https://doi.org/10.1016/j.psyneuen.2013.11.006.

Ganguly, P., Honeycutt, J.A., Rowe, J.R., Demaestri, C., Brenhouse, H.C., 2019. Effects of early life stress on cocaine conditioning and AMPA receptor composition are sex-specific and driven by TNF. Brain Behav. Immun. 78, 41–51. https://doi.org/10.1016/j.bbi.2019.01.006.

Giridharan, V.V., Réus, G.Z., Selvaraj, S., Scaini, G., Barichello, T., Quevedo, J., 2019. Maternal deprivation increases microglial activation and neuroinflammatory markers in the prefrontal cortex and hippocampus of infant rats. J. Psychiatr. Res 115, 13–20. https://doi.org/10.1016/j.jpsychires.2019.05.001.

González-Pardo, H., Arias, J.L., Gómez-Lázaro, E., López Taboada, I., Conejo, N.M., 2020. Sex-specific effects of early life stress on brain mitochondrial function, monoamine levels and neuroinflammation. Brain Sci. 10 (7) https://doi.org/10.3390/brainsci10070447.

Grassi-Oliveira, R., Honeycutt, J.A., Holland, F.H., Ganguly, P., Brenhouse, H.C., 2016. Cognitive impairment effects of early life stress in adolescents can be predicted with early biomarkers: impacts of sex, experience, and cytokines. Psychoneuroendocrinology 71, 19–30. https://doi.org/10.1016/j.psyneuen.2016.04.016.

Hanson, J.L., Nacewicz, B.M., Sutterer, M.J., Cayo, A.A., Schaefer, S.M., Rudolph, K.D., Shirtcliff, E.A., Pollak, S.D., Davidson, R.J., 2015. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. Biol. Psychiatry 77 (4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020.

Hoeijmakers, L., Ruigrok, S.R., Amelianchik, A., Ivan, D., van Dam, A.M., Lucassen, P.J., Korosi, A., 2017. Early-life stress lastingly alters the neuroinflammatory response to amyloid pathology in an Alzheimer's disease mouse model. Brain Behav. Immun. 63, 160–175. https://doi.org/10.1016/j.bbi.2016.12.023.

Hohmann, C.F., Odebode, G., Naidu, L., Koban, M., 2017. Early life stress alters adult inflammatory responses in a mouse model for depression. Ann. Psychiatry Ment. Health 5 (2). ⟨https://www.ncbi.nlm.nih.gov/pubmed/29657960⟩.

Hooijmans, C.R., de Vries, R., Leenaars, M., Curfs, J., Ritskes-Hoitinga, M., 2011. Improving planning, design, reporting and scientific quality of animal experiments by using the Gold Standard Publication Checklist, in addition to the ARRIVE guidelines. Br. J. Pharm. 162 (6), 1259–1260. https://doi.org/10.1111/j.1476-5381.2010.01128.x.

Jia, Y., Liu, L., Sheng, C., Cheng, Z., Cui, L., Li, M., Zhao, Y., Shi, T., Yau, T.O., Li, F., Chen, L., 2019. Increased serum levels of cortisol and inflammatory cytokines in people with depression. J. Nerv. Ment. Dis. 207 (4), 271–276. https://doi.org/10.1097/NMD.0000000000000957.

Kiank, C., Mundt, A., Schuett, C., 2009. Mild postnatal separation stress reduces repeated stress-induced immunosuppression in adult BALB/c mice. Neuro Endocrinol. Lett. 30 (6), 761–768. ⟨https://www.ncbi.nlm.nih.gov/pubmed/20038927⟩.

Kilkenny, C., Browne, W.J., Cuthill, I.C., Emerson, M., Altman, D.G., 2010. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol. 8 (6), e1000412 https://doi.org/10.1371/journal.pbio.1000412.

Kim, Y.K., Na, K.S., Myint, A.M., Leonard, B.E., 2016. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 277–284. https://doi.org/10.1016/j.pnpbp.2015.06.008.

Koussounadis, A., Langdon, S.P., Um, I.H., Harrison, D.J., Smith, V.A., 2015. Relationship between differentially expressed mRNA and mRNA-protein correlations in a xenograft model system. Sci. Rep. 5, 10775. https://doi.org/10.1038/srep10775.

Kuhlman, K.R., Robles, T.F., Haydon, M.D., Dooley, L., Boyle, C.C., Bower, J.E., 2020. Early life stress sensitizes individuals to the psychological correlates of mild fluctuations in inflammation. Dev. Psychobiol. 62 (3), 400–408. https://doi.org/10.1002/dev.21908.

Lajud, N., Roque, A., Cheng, J.P., Bondi, C.O., Kline, A.E., 2021. Early life stress preceding mild pediatric traumatic brain injury increases neuroinflammation but does not exacerbate impairment of cognitive flexibility during adolescence. J. Neurotrauma 38 (4), 411–421. https://doi.org/10.1089/neu.2020.7354.

Lo Iacono, L., Catale, C., Martini, A., Valzania, A., Viscomi, M.T., Chiurchiù, V., Guatteo, E., Bussone, S., Perrone, F., Di Sabato, P., Aricò, E., D'Argenio, A., Troisi, A., Mercuri, N.B., Maccarrone, M., Puglisi-Allegra, S., Casella, P., Carola, V., 2018. From traumatic childhood to cocaine abuse: the critical function of the immune system. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2018.05.022.

Lorigooini, Z., Boroujeni, S.N., Sayyadi-Shahraki, M., Rahimi-Madiseh, M., Bijad, E., Amini-Khoei, H., 2021. Limonene through attenuation of neuroinflammation and nitrite level exerts antidepressant-like effect on mouse model of maternal separation stress. Behav. Neurol. 2021, 8817309 https://doi.org/10.1155/2021/8817309.

Majcher-Maślanka, I., Solarz, A., Chocyk, A., 2019. Maternal separation disturbs postnatal development of the medial prefrontal cortex and affects the number of neurons and glial cells in adolescent rats. Neuroscience 423, 131–147. https://doi.org/10.1016/j.neuroscience.2019.10.033.

Marafini, I., Sedda, S., Dinallo, V., Monteleone, G., 2019. Inflammatory cytokines: from discoveries to therapies in IBD. Expert Opin. Biol. Ther. 19 (11), 1207–1217. https://doi.org/10.1080/14712598.2019.1652267.

Massart, R., Nemoda, Z., Suderman, M.J., Sutti, S., Ruggiero, A.M., Dettmer, A.M., Suomi, S.J., Szyf, M., 2016. Early life adversity alters normal sex-dependent developmental dynamics of DNA methylation. Dev. Psychopathol. 28 (4pt2), 1259–1272. https://doi.org/10.1017/S0954579416000833.

McLaughlin, K.A., Sheridan, M.A., Lambert, H.K., 2014. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci. Biobehav Rev. 47, 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012.

Monje, F.J., Cabatic, M., Divisch, I., Kim, E.J., Herkner, K.R., Binder, B.R., Pollak, D.D., 2011. Constant darkness induces IL-6-dependent depression-like behavior through the NF-κB signaling pathway. J. Neurosci. 31 (25), 9075–9083. https://doi.org/10.1523/JNEUROSCI.1537-11.2011.

Na, K.S., Jung, H.Y., Kim, Y.K., 2014. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 277–286. https://doi.org/10.1016/j.pnpbp.2012.10.022.

Nicolas, S., McGovern, A.J., Hueston, C.M., O'Mahony, S.M., Cryan, J.F., O'Leary, O.F., Nolan, Y.M., 2022. Prior maternal separation stress alters the dendritic complexity of new hippocampal neurons and neuroinflammation in response to an inflammatory stressor in juvenile female rats. Brain Behav. Immun. 99, 327–338. https://doi.org/10.1016/j.bbi.2021.10.016.

Nouri, A., Hashemzadeh, F., Soltani, A., Saghaei, E., Amini-Khoei, H., 2020. Progesterone exerts antidepressant-like effect in a mouse model of maternal separation stress through mitigation of neuroinflammatory response and oxidative stress. Pharm. Biol. 58 (1), 64–71. https://doi.org/10.1080/13880209.2019.1702704.

Oliveira, C., Toledo, R.S., Scarabelot, V.L., Vercelino, R., da Silva, L.S., Regner, G.G., de Souza, A., Silveira, N.P., Caumo, W., Torres, I.L.S., 2020. Neonatal morphine exposure and maternal deprivation alter nociceptive response and central biomarkers' levels throughout the life of rats. Neurosci. Lett. 738, 135350 https://doi.org/10.1016/j.neulet.2020.135350.

Orso, R., Creutzberg, K.C., Wearick-Silva, L.E., Wendt Viola, T., Tractenberg, S.G., Benetti, F., Grassi-Oliveira, R., 2019. How early life stress impact maternal care: a systematic review of rodent studies. Front Behav. Neurosci. 13, 197. https://doi.org/10.3389/fnbeh.2019.00197.

Orso, R., Creutzberg, K.C., Kestering-Ferreira, E., Wearick-Silva, L.E., Tractenberg, S.G., Grassi-Oliveira, R., 2020. Maternal separation combined with limited bedding increases anxiety-like behavior and alters hypothalamic-pituitary-adrenal axis function of male BALB/cJ mice. Front Behav. Neurosci. 14, 600766 https://doi.org/10.3389/fnbeh.2020.600766.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210. https://doi.org/10.1186/s13643-016-0384-4.

Pace, T.W., Mletzko, T.C., Alagbe, O., Musselman, D.L., Nemeroff, C.B., Miller, A.H., Heim, C.M., 2006. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am. J. Psychiatry 163 (9), 1630–1633.

Park, H.J., Kim, S.K., Kang, W.S., Woo, J.M., Kim, J.W., 2014. Effects of essential oil from Chamaecyparis obtusa on cytokine genes in the hippocampus of maternal separation rats. Can. J. Physiol. Pharm. 92 (2), 95–101. https://doi.org/10.1139/cjpp-2013-0224.

Park, H.J., Kim, S.A., Kang, W.S., Kim, J.W., 2021. Early-life stress modulates gut microbiota and peripheral and central inflammation in a sex-dependent manner. Int J. Mol. Sci. 22 (4) https://doi.org/10.3390/ijms22041899.

Pedersen, J.M., Mortensen, E.L., Christensen, D.S., Rozing, M., Brunsgaard, H., Meincke, R.H., Petersen, G.L., Lund, R., 2018. Prenatal and early postnatal stress and later life inflammation. Psychoneuroendocrinology 88, 158–166. https://doi.org/10.1016/j.psyneuen.2017.12.014.

Pei, X., Jiang, H., Liu, X., Li, L., Li, C., Xiao, X., Li, D., Tang, S., 2021. Targeting HMGB1 inhibits T-2 toxin-induced neurotoxicity via regulation of oxidative stress, neuroinflammation and neuronal apoptosis. Food Chem. Toxicol. 151, 112134 https://doi.org/10.1016/j.fct.2021.112134.

Peña, C.J., Kronman, H.G., Walker, D.M., Cates, H.M., Bagot, R.C., Purushothaman, I., Issler, O., Loh, Y.E., Leong, T., Kiraly, D.D., Goodman, E., Neve, R.L., Shen, L., Nestler, E.J., 2017. Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 356 (6343), 1185–1188. https://doi.org/10.1126/science.aan4491.

Pfau, M.L., Russo, S.J., 2015. Peripheral and central mechanisms of stress resilience. Neurobiol. Stress 1, 66–79. https://doi.org/10.1016/j.ynstr.2014.09.004.

Pinheiro, R.M., de Lima, M.N., Portal, B.C., Busato, S.B., Falavigna, L., Ferreira, R.D., Paz, A.C., de Aguiar, B.W., Kapczinski, F., Schröder, N., 2015. Long-lasting recognition memory impairment and alterations in brain levels of cytokines and BDNF induced by maternal deprivation: effects of valproic acid and topiramate. J. Neural Transm. (Vienna) 122 (5), 709–719. https://doi.org/10.1007/s00702-014-1303-2.

Provençal, N., Binder, E.B., 2015. The effects of early life stress on the epigenome: from the womb to adulthood and even before. Exp. Neurol. 268, 10–20. https://doi.org/10.1016/j.expneurol.2014.09.001.

Reed, R.G., Raison, C.L., 2016. Stress and the immune system. Environmental influences on the immune system. Springer, pp. 97–126.

Réus, G.Z., Dos Santos, M.A., Abelaira, H.M., Ribeiro, K.F., Petronilho, F., Vuolo, F., Colpo, G.D., Pfaffenseller, B., Kapczinski, F., Dal-Pizzol, F., Quevedo, J., 2013. Imipramine reverses alterations in cytokines and BDNF levels induced by maternal deprivation in adult rats. Behav. Brain Res. 242, 40–46. https://doi.org/10.1016/j.bbr.2012.11.044.

Réus, G.Z., Nacif, M.P., Abelaira, H.M., Tomaz, D.B., dos Santos, M.A., Carlessi, A.S., da Luz, J.R., Gonçalves, R.C., Vuolo, F., Dal-Pizzol, F., Carvalho, A.F., Quevedo, J., 2015. Ketamine ameliorates depressive-like behaviors and immune alterations in adult rats following maternal deprivation. Neurosci. Lett. 584, 83–87. https://doi.org/10.1016/j.neulet.2014.10.022.

Réus, G.Z., Fernandes, G.C., de Moura, A.B., Silva, R.H., Darabas, A.C., de Souza, T.G., Abelaira, H.M., Carneiro, C., Wendhausen, D., Michels, M., Pescador, B., Dal-Pizzol, F., Macêdo, D.S., Quevedo, J., 2017. Early life experience contributes to the developmental programming of depressive-like behaviour, neuroinflammation and oxidative stress. J. Psychiatr. Res. 95, 196–207. https://doi.org/10.1016/j.jpsychires.2017.08.020.

Rice, C.J., Sandman, C.A., Lenjavi, M.R., Baram, T.Z., 2008. A novel mouse model for acute and long-lasting consequences of early life stress. Endocrinology 149 (10), 4892–4900. https://doi.org/10.1210/en.2008-0633.

Romeo, R.D., Fossella, J.A., Bateup, H.S., Sisti, H.M., Brake, W.G., McEwen, B.S., 2004. Maternal separation suppresses TGF alpha mRNA expression in the prefrontal cortex of male and female neonatal C57BL/6 mice. Brain Res Dev. Brain Res 152 (1), 73–77. https://doi.org/10.1016/j.devbrainres.2004.05.007.

Roque, A., Ochoa-Zarzosa, A., Torner, L., 2016. Maternal separation activates microglial cells and induces an inflammatory response in the hippocampus of male rat pups,

independently of hypothalamic and peripheral cytokine levels. Brain Behav. Immun. 55, 39–48. https://doi.org/10.1016/j.bbi.2015.09.017.
Saavedra, L.M., Fenton Navarro, B., Torner, L., 2017. Early life stress activates glial cells in the hippocampus but attenuates cytokine secretion in response to an immune challenge in rat pups. Neuroimmunomodulation 24 (4–5), 242–255. https://doi.org/10.1159/000485383.
Ströher, R., de Oliveira, C., Stein, D.J., de Macedo, I.C., Goularte, J.F., da Silva, L.S., Regner, G.G., Medeiros, H.R., Caumo, W., Torres, I.L.S., 2020. Maternal deprivation and sex alter central levels of neurotrophins and inflammatory cytokines in rats exposed to palatable food in adolescence. Neuroscience 428, 122–131. https://doi.org/10.1016/j.neuroscience.2019.12.027.
Tanaka, T., Narazaki, M., Kishimoto, T., 2014. IL-6 in inflammation, immunity, and disease. Cold Spring Harb. Perspect. Biol. 6 (10), a016295 https://doi.org/10.1101/cshperspect.a016295.
Tang, H.L., Zhang, G., Ji, N.N., Du, L., Chen, B.B., Hua, R., Zhang, Y.M., 2017. Toll-like receptor 4 in paraventricular nucleus mediates visceral hypersensitivity induced by maternal separation. Front Pharm. 8, 309. https://doi.org/10.3389/fphar.2017.00309.
Tannous, J., Godlewska, B.R., Tirumalaraju, V., Soares, J.C., Cowen, P.J., Selvaraj, S., 2020. Stress, inflammation and hippocampal subfields in depression: a 7 Tesla MRI Study. Transl. Psychiatry 10 (1), 78. https://doi.org/10.1038/s41398-020-0759-0.
Teissier, A., Le Magueresse, C., Olusakin, J., Andrade da Costa, B.L.S., De Stasi, A.M., Bacci, A., Imamura Kawasawa, Y., Vaidya, V.A., Gaspar, P., 2020. Early-life stress impairs postnatal oligodendrogenesis and adult emotional behaviour through activity-dependent mechanisms. Mol. Psychiatry 25 (6), 1159–1174. https://doi.org/10.1038/s41380-019-0493-2.
Tractenberg, S.G., Levandowski, M.L., de Azeredo, L.A., Orso, R., Roithmann, L.G., Hoffmann, E.S., Brenhouse, H., Grassi-Oliveira, R., 2016. An overview of maternal separation effects on behavioural outcomes in mice: evidence from a four-stage methodological systematic review. Neurosci. Biobehav Rev. 68, 489–503. https://doi.org/10.1016/j.neubiorev.2016.06.021.
van Bodegom, M., Homberg, J.R., Henckens, M.J.A.G., 2017. Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. Front Cell Neurosci. 11, 87. https://doi.org/10.3389/fncel.2017.00087.
Viola, T.W., Creutzberg, K.C., Zaparte, A., Kestering-Ferreira, É., Tractenberg, S.G., Centeno-Silva, A., Orso, R., Lumertz, F.S., Brietzke, E., Wearick-Silva, L.E., Riva, M. A., Grassi-Oliveira, R., 2019. Acute neuroinflammation elicited by TLR-3 systemic activation combined with early life stress induces working memory impairments in male adolescent mice. Behav. Brain Res 376, 112221. https://doi.org/10.1016/j.bbr.2019.112221.
Viviani, B., Boraso, M., Valero, M., Gardoni, F., Marco, E.M., Llorente, R., Corsini, E., Galli, C.L., Di Luca, M., Marinovich, M., López-Gallardo, M., Viveros, M.P., 2014. Early maternal deprivation immunologically primes hippocampal synapses by redistributing interleukin-1 receptor type I in a sex dependent manner. Brain Behav. Immun. 35, 135–143. https://doi.org/10.1016/j.bbi.2013.09.008.
Vogel, C., Marcotte, E.M., 2012. Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. Nat. Rev. Genet 13 (4), 227–232. https://doi.org/10.1038/nrg3185.
Walker, D.J., Zimmer, C., Larriva, M., Healy, S.D., Spencer, K.A., 2019. Early-life adversity programs long-term cytokine and microglia expression within the HPA axis in female Japanese quail. J. Exp. Biol. 222 (Pt 6) https://doi.org/10.1242/jeb.187039.
Wang, R., Wang, W., Xu, J., Liu, D., Wu, H., Qin, X., Jiang, H., Pan, F., 2020. Jmjd3 is involved in the susceptibility to depression induced by maternal separation via enhancing the neuroinflammation in the prefrontal cortex and hippocampus of male rats. Exp. Neurol. 328, 113254 https://doi.org/10.1016/j.expneurol.2020.113254.
Warren, J.S., 1990. Interleukins and tumor necrosis factor in inflammation. Crit. Rev. Clin. Lab Sci. 28 (1), 37–59. https://doi.org/10.3109/10408369009105897.
Weber, M.D., Frank, M.G., Tracey, K.J., Watkins, L.R., Maier, S.F., 2015. Stress induces the danger-associated molecular pattern HMGB-1 in the hippocampus of male Sprague Dawley rats: a priming stimulus of microglia and the NLRP3 inflammasome. J. Neurosci. 35 (1), 316–324. https://doi.org/10.1523/JNEUROSCI.3561-14.2015.
White, J.D., Kaffman, A., 2019. The moderating effects of sex on consequences of childhood maltreatment: from clinical studies to animal models. Front Neurosci. 13, 1082. https://doi.org/10.3389/fnins.2019.01082.
Wohleb, E.S., Fenn, A.M., Pacenta, A.M., Powell, N.D., Sheridan, J.F., Godbout, J.P., 2012. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. Psychoneuroendocrinology 37 (9), 1491–1505. https://doi.org/10.1016/j.psyneuen.2012.02.003.
Wojdasiewicz, P., Poniatowski, Ł., Szukiewicz, D., 2014. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediat. Inflamm. 2014, 561459 https://doi.org/10.1155/2014/561459.
Ye, Y., Yao, S., Wang, R., Fang, Z., Zhong, K., Nie, L., Zhang, Q., 2019. PI3K/Akt/NF-κB signaling pathway regulates behaviors in adolescent female rats following with neonatal maternal deprivation and chronic mild stress. Behav. Brain Res 362, 199–207. https://doi.org/10.1016/j.bbr.2019.01.008.
Zhu, Y., Wang, Y., Yao, R., Hao, T., Cao, J., Huang, H., Wang, L., Wu, Y., 2017. Enhanced neuroinflammation mediated by DNA methylation of the glucocorticoid receptor triggers cognitive dysfunction after sevoflurane anesthesia in adult rats subjected to maternal separation during the neonatal period. J. Neuroinflamm. 14 (1), 6. https://doi.org/10.1186/s12974-016-0782-5.
Zolfaghari, F.S., Pirri, F., Gauvin, E., Peeri, M., Amiri, S., 2021. Exercise and fluoxetine treatment during adolescence protect against early life stress-induced behavioral abnormalities in adult rats. Pharm. Biochem. Behav. 205, 173190 https://doi.org/10.1016/j.pbb.2021.173190.